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I. Microwave-Influenced Diversity-Oriented Synthesis Of Biologically Relevant Small & Natural-Product-Like Molecules Via Multicomponent Coupling Reactions Ii. Synthetic Studies Toward The Total Synthesis Of The Repeating Tetrasaccharide Unit Of Zwitterionic Polysaccharide Ps A1

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I. MICROWAVE-INFLUENCED DIVERSITY-ORIENTED SYNTHESIS OF BIOLOGICALLY RELEVANT SMALL AND NATURAL-PRODUCT-LIKE MOLECULES VIA MULTICOMPONENT COUPLING REACTIONS

II. SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF THE REPEATING TETRASACCHARIDE UNIT OF ZWITTERIONIC POLYSACCHARIDE PS A1

by

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DISSERTATION

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Advisor **Date**

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DEDICATION

Dedicated To My Parents

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ACS	American chemical society
Ada	adamantyl
Aq	aqueous
BDZ	benzodiazepine
Bn	benzyl
br	broad
n-Bu	*n*-butyl
calcd	calculated
CCR	C-C chemokine receptor
$CDCl_3$	chloroform-*d*
m-CPBA	*meta*-chloroperbenzoic acid
δ	chemical shift
d	doublet
DA	Diels-Alder
DAR	diversity-activity relationship
DBU	1,8-Diazabicycloundec-7-ene
dd	doublet of doublet
ddd	doublet of doublet of doublet
DDQ	2,6-dichloro-5,6-dicyano1,4-benzoquinone
DKP	Diketopiperazine
DMB	dimethoxybenzyl
DMF	*N*, *N*-dimethylformamide

DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
DOS	diversity-oriented synthesis
DPR	dienone-phenol rearrangement
dq	doublet of quartet
ds	diastereoselectivity
dr	diastereomeric ratio
dt	doublet of triplet
E_N	exploratory power
EIMS	electron impact mass spectroscopy
equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate
τ	relaxation time
eV	electron-volt
h	hour(s)
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HTS	high throughput screening
Hz	hertz
IBX	2-iodoxybenzoic acid
IMCR	isocyanide-based multicomponent coupling reaction

i-Pr	isopropyl
IQ	Isoquinolinone
IR	infrared
J	coupling constant
$LiAlH_4$	lithium aluminum hydride
NaH	sodium hydride
$NaBH_4$	sodium borohydride
M^+	molecular ion
m	multiplet
μwave	microwave
MAOS	microwave-assisted organic synthesis
MCCR	multicomponent coupling reaction
Me	methyl
mL	milliliter
Ms	mesylate, methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
MVK	methyl vinyl ketone
NIS	*N*-iodo succinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NMP	*N*-methyl pyrrolidine
PADAM	P-3CCR/amine deprotecion/acyl migration

PCC	pyridinium chloro chromate
PDC	pyridinium dichromate
PDMAB	*para*-*N*,*N*-dimethylaminobenzyl
PEG	poly ethylene glycol
PEP	prolyl endopeptidase
Ph	phenyl
PHB	*p*-hydroxy benzyl
ppm	part(s) per million
PMB	*para*-methoxybenzyl
PMNPAB	*para*-*N*-(methyl-nitrophenyl)aminobenzyl
Pyr	pyridine
q	quartet
qd	quartet of doublet
RB	round bottom
R_f	relative to front
RCM	ring closing metathesis
rt	room temperature
s	singlet
SAR	structure-activity relationship
sat'd	saturated
SIV	simian immunodeficiency virus
t	triplet
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyl-dimethylsilyl
TMSOTf	trimethylsilyl trifluoromethane sulfonate
t-Bu	*tert*-butyl
tert	tertiary
TIPS	triisopropylsilyl
TFA	trifluoroacetic acid
THF	tetrahydofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TOS	target-oriented synthesis
Tf	triflate, trifluoromethanesulfonate
Ts	tosylate, *p*-touenesulfonyl
UMAM	Ugi/Michael/aza-Michael
US EPA	United States Environmental Protection Agency
UV	ultraviolet

CHAPTER 1

BACKGROUND

1.1 Introduction

Therapeutic drugs are crucial in the fight against infectious diseases caused by many viruses, bacteria, parasites and fungi. In recent years, there have been an increasing number of microbial resistances against many commonly used drugs e.g. anti-biotic, anti-malaria, anti-tuberculosis, anti-HIV, anti-retrovials. Although, over the last decade, genetics and molecular biology have advanced at a rapid pace in an attempt to alleviate various drug resistance issues, the number of new antibiotic or antimicrobial drugs that can cure microbial infection has decreased.[1] Diversity-oriented synthesis (DOS) aims to generate structural and skeletal diversity from simple and common starting precursors to provide libraries of compounds that increase the statistical likelihood of finding new drug candidates with improved potency.

Although, many bioactive natural compounds are not assembled with desired pharmacokinetic properties and efficacy, they represent a suitable class of molecules for the discovery of new drugs. Most prescribed drugs are either small, natural products, derivatives thereof, or designer synthetic small molecules. A majority of these drugs are cyclic, often contain "privileged scaffolds" and numerous hetero atoms.[2] Despite recent advancement in combinatorial and synthetic chemistry, heterocyclic building blocks including those that are suitably functionalized, are not easy to access. With all that being said, there is a need to develop new synthetic strategies that can rapidly generate libraries of diverse drug-like molecules in few transformations with column chromatography kept to a minimum.[2] Amongst many strategies employed to generate

molecular diversity, to date, multicomponent coupling reactions (MCCRs) have emerged as a very efficient and powerful strategy that incorporate the new ethos for library development.[3] Hence, there are concerted efforts among the scientific community to develop new MCCRs and design strategies incorporating existing MCCRs to generate skeletal and structural diversity that may or may not contain a "privileged scaffold".[3]

1.1. Multicomponent Coupling Reactions: A Tandem Sequential Reaction

Natural products are an invaluable source of inspiration for the development of new reaction methodologies and strategies. Over the last two decades, modern organic syntheses have advanced dramatically. However, the synthesis of complicated natural products requires multistep, protection-deprotection strategies at times, costly reagents and throughout the endeavor cumbersome purification processes. Although, natural product synthesis is an indispensable part for the advancement of organic chemistry and drug discovery, the encompassing concepts of effective, economical "ideal organic synthesis" have yet to be fully modernized.

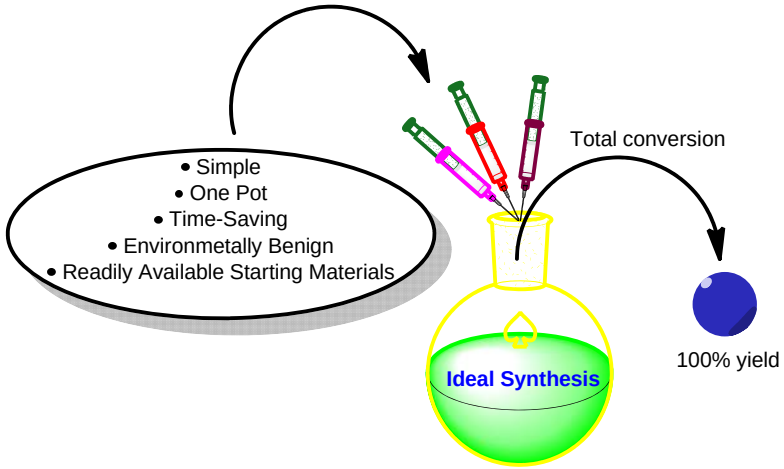
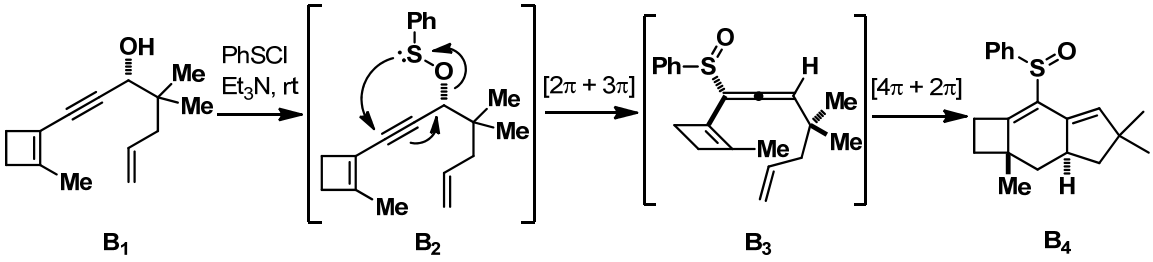


Figure 1. Schematic representation of an ideal organic synthesis (inspired from Wender et al.)[4]

According to Wender, an ideal synthesis (Figure 1) should provide the target compound in fewest possible steps, in high yield, using cheap, environmentally benign reagents and should produce the least amount of waste.[4] In contrast to traditional organic reactions, domino/cascade reactions are more atom-economical and can provide a wide array of complex molecules in an efficient, stereocontrol manner. According to Nicolaou, the classification of tandem, cascade, sequential or domino reactions are not well defined in literature and often indistinguishable from one another.[5]

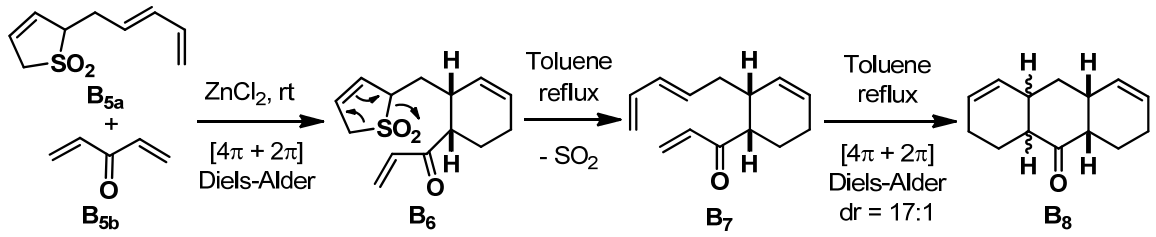
Tietze has defined a cascade (domino) reaction in which two or more bond-forming events take place based on prior formed functionalities without changing reaction conditions and additional reagents, catalysts, or additives.[6,7] Furthermore, Denmark defined that most cascade (domino) reactions fall under the broader category of tandem processes: (a) cascade or domino reactions; (b) consecutive reactions; (c) sequential reactions.[8]

A tandem cascade reaction, as suggested by Denmark, follows the same criteria as defined by Tietze, i.e., the reaction should occur without the change of reaction conditions and addition of extra reagents or additives or even catalysts. In addition, the intermediates are non-isolatable and bring forth required structural change for the following steps (Scheme 1).[9]



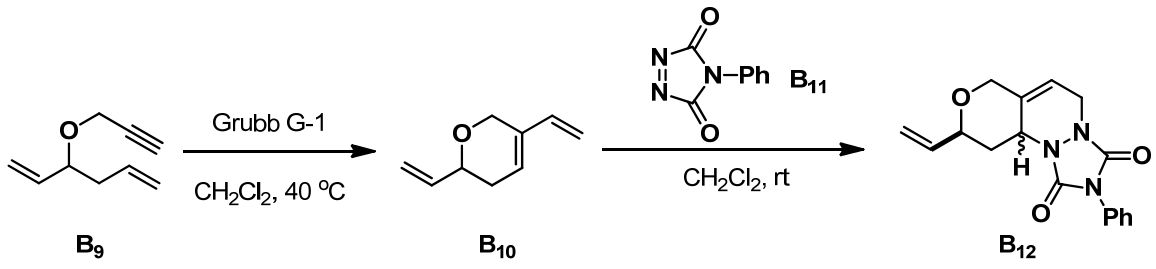
Scheme 1. Example of a tandem cascade reaction.

In contrary to tandem cascade reaction, intermediates are isolatable in a tandem consecutive reaction and they contain the requisite functionality for the next desired step. However, the next step usually has higher activation energy and additional energy in the form of light or heat or catalyst is required. As shown in Scheme 2, additional activation energy in the form of heat is required to drive the reaction to the final product **B$_8$** from the isolatable intermediates **B$_6$** and **B$_7$**.[10]



Scheme 2. Example of a tandem consecutive reaction.

A tandem sequential reaction requires the addition of extraneous reagents and potential changes in conditions. The intermediates contain requisite functionalities for the next step and may be isolated. However, isolation of the intermediate it is not necessarily a requirement. As shown in Scheme 3, the intermediate **B$_{10}$** is isolatable and requires addition of **B$_{11}$** and a change in reaction conditions to provide **B$_{12}$**.[11]



Scheme 3. Example of a tandem sequential reaction.

According to the classification of tandem reactions suggested by Tietze and Denmark, multicomponent coupling reactions (MCCRs) are a special class of tandem sequential reactions in which at least three starting materials or coupling partners/components react together to form a product in such a way that the maximum number of atoms of the reacting components can be found in the target molecule.[12] In a typical MCCR, the coupling partners do not react concurrently in a single step; instead in sequential elementary steps. Many of the MCCRs often involve an irreversible step that drives the overall reaction in favor of the final product.

MCCRs can be further classified into three categories depending upon different types of equilibrium involved. Type-I MCCRs are those in which the equilibrium between reacting components, intermediates and products are changeable. In general, type-I MCCRs are incomplete and vulnerable to side product formation that lead to extraneous isolation protocols. The Strecker reaction is an example of type-I MCCR.

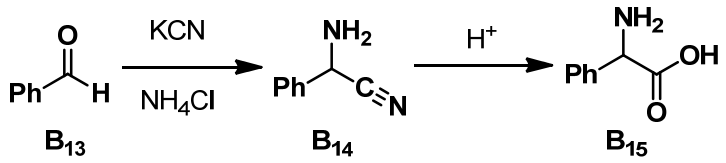
On the other hand, in type-II MCCRs, the reacting components and intermediates are in equilibrium and lead to partial reactivity. However, the last highly exothermic and irreversible step drives the overall reaction to the product side. The exothermic step usually involves a change in oxidation state of carbon ($C^{II} \rightarrow C^{IV}$),[13] ring closure, or an aromatization event. The Biginelli, Passerini and Ugi reactions are the most widely studied and successful type II MCCRs.

Reactions in which each elementary step is irreversible are known as type-III MCCRs. Most biomimetic reactions fall into this highly selective category. An example of type-III MCCR is the ATP coupling during phosporylation.

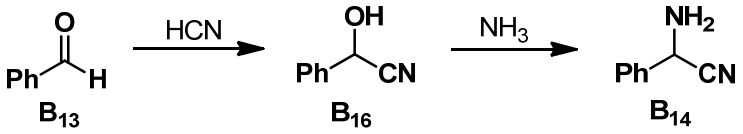
Depending upon the functional groups present in the coupling partners, MCCRs can be further categorized as imine-based MCCRs (IMCCRs), isocyanide-based MCCRs (ICMCCRs) and carbene-based MCCRs (CMCCRs). For example, the Passerini three component coupling reaction (P-3CCR) is an ICMCCR, whereas the Ugi four component coupling reaction (U-4CCR) belongs to both IMCCRs and ICMCCRs.

By employing a few multifunctional starting materials, alternative source of energy and altering the sequence of addition of coupling partners; a single synthetic transformation can provide diverse array of products. Moreover, "off-the-shelf" starting materials can be used in many known MCCRs and many other common starting materials are easily accessible. Thus, many known MCCRs have emerged as an effective tool for environmentally benign and atom economic syntheses of diverse small, complex architectures in a single operation by virtue of their convergent nature, high yield, facile execution and generation of less waste materials.[14] Consequently, in comparison to multistep total synthesis, rationally, the MCCRs are a close fit to the concept of an "ideal synthesis" as suggested by Wender.

160 years ago, Strecker had reported that condensation of the benzaldehyde, potassium cyanide and ammonium chloride generates the α-amino cyanide (**B_{14}**) which upon subsequent hydrolysis provides the desired α-amino acid **B_{15}** (Scheme 4).[15] The reaction is generally accepted to be the first MCCR and commonly described as S-3CCR after Strecker. However, in 1838, Laurent and Gerhardt had isolated a product called hydrocyanic acid-containing benzaldehyde (**B_{16}**) that reacted with ammonia, giving aminobenzyl cyanide (**B_{14}**) via a S-3CCR (Scheme 5).[16]



Scheme 4. Strecker α-amino acid synthesis: the 1st MCCR



Scheme 5. The purported 1st MCCR.

Over the past century, many new MCCRs were discovered and employed in the synthesis of many heterocycles. Among those MCCRs the Asinger reaction (A-4CCR)[17], Radziszewski reaction (R-3CCR)[18], Hanztsch dihydropyridine (H-4CCR) synthesis[19], Hantzsch pyrrole synthesis,[20] Bignelli reaction (B-3CCR)[21], Mannich reaction (M-3CCR)[22], Passerini (P-3CCR) reaction[23], Ugi (U-4CCR) reaction[24], Bucherer-Bergs (BB-4CCR) reaction[25], Kabachnik-Field (KF-3CCR) reaction[26], Petasis (Pt-3CCR) reaction[27], Gewald reaction (G-3CCR)[28], Groebke-Blackburn-Bienyeme reaction (GBB-3CCR)[29], Passerini-Smiles reaction (PS-3CCR)[30], Ugi-Smiles reaction (US-4CCR)[31] have become very useful in combinatorial chemistry as well as in diversity-oriented synthesis for diversification of libraries and have helped to increase chemical space. It is noteworthy that isocyanides have been found to be a versatile coupling partner in many of the aforementioned MCCRs.[12]

1.2. History of Isonitriles/Isocyanides

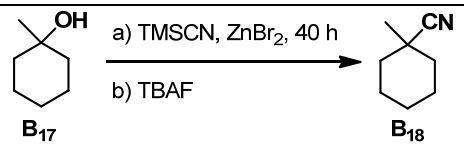
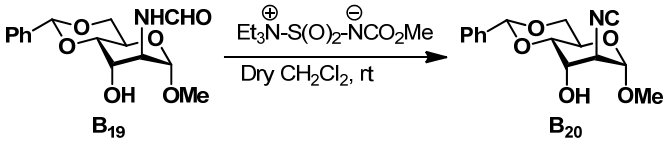
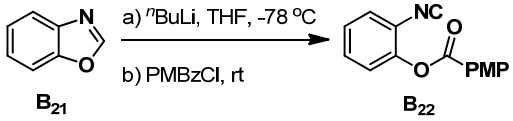
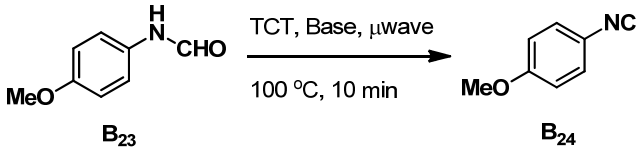
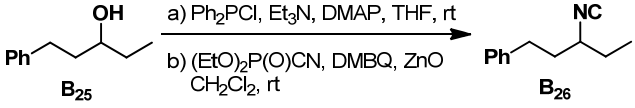
In 1859, Leike had synthesized the first isonitrile (allyl isonitrile) while he was studying the conversion of nitriles into corresponding carboxylic acids.[32] Isonitriles are also known as isocyanides and often times the scientific community will intermix their terminology. Other than few stable carbenes e.g. the *N*-heterocyclic carbenes (NHCs), the ICs are the only known organic compounds having divalent (C^{II}) carbon and quite stable. Due to their very unusual valence shell electron configuration they exhibit extraordinary reactivity and thus, fundamentally differ from other functional groups.[33] Their versatile reactivity made them very useful functional handles not only in MCCRs but also in a variety of organic reactions including free radical addition[34a], Ferrier rearrangement,[34b] organometallic transformation like the Pauson-Khand reaction[35] and polymerizations.[36]

It has been widely described that most commercially available isocyanides are volatile and carry repulsive odor "which is reminiscent of artichokes and phosphorous at the same time."[37] Ugi admits "The development of the chemistry of isonitriles has probably suffered through the characteristic odor of volatile isonitriles, which has been described by Hofmann and Gautier as 'highly specific, almost overpowering', 'horrible', and 'extremely distressing'". Demhardter *et al.* further noted that very long-term inhalation of volatile isocyanides e.g., the allyl, benzyl, methyl, or *tert*-butyl isocyanides can lead to sensory disorder and intense dreams.[3a]

A few liquid ICs e.g., the isomeric picolyl isocyanides do not smell and the L-phenylglycine methyl ester has the smell of rhubarb plant. Notably, most solid isocyanides have been found to be very less repulsive or odorless.

Over 3000 isocyanides are known and several methods for their synthesis have been developed in the past few decades.[38] Due to their very offensive odor and preparative difficulty, only few isocyanides are commercially available. This limits the scope of routine experimentations and thereby rapid generation of molecular diversity. Thus, over the past decade, the scientific community has continued to devise preparatively easy routes for the synthesis of isonitriles/isocyanides (Table 1).[39-43]

Table 1. Recently developed methods for isocyanides/isonitriles synthesis.

Kitano (1998)[39]	
McCarthy (1998)[40]	
Pirrung (2003)[41]	
Porcheddu (2005)[42]	
Mukaiyama (2005)[43]	

Furthermore, scientific community showed interest in developing fragrant smelling isocyanides to avoid their repulsive odor during experimentation. In addition, the U-4CCR products derived from most 'off-the-shelf' isocyanides, typically can not be modified at the *N*-terminal of the dipeptide without using harsh reaction conditions which

are not usually compatible with many commonly used functional groups. Despite profound advancement of the art of organic synthesis, selective hydrolysis of secondary amide functional groups is a nontrivial task in highly functionalized organic compounds. This further limits the scope of generating molecular diversity by post-Ugi modification. Thus, in recent years, there has been a growing interest among the scientific community to develop fragrant-like 'convertible isocyanides' (CICs). These new CICs (Figure 2) by virtue of their selective cleavage ability, have been found to be useful for the synthesis of diverse small molecules as well as complex natural products having biological activities related to human health.[44]

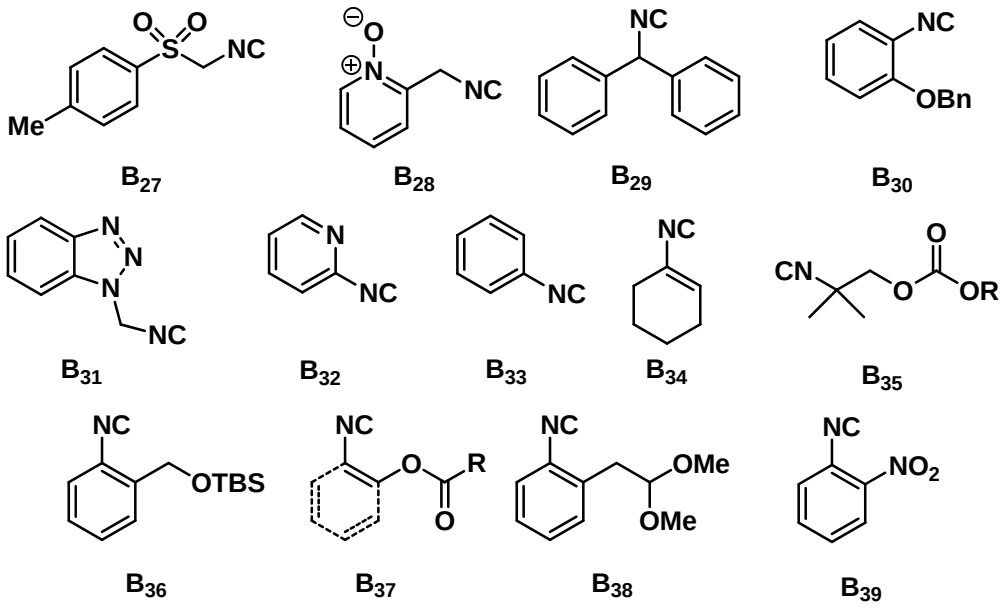
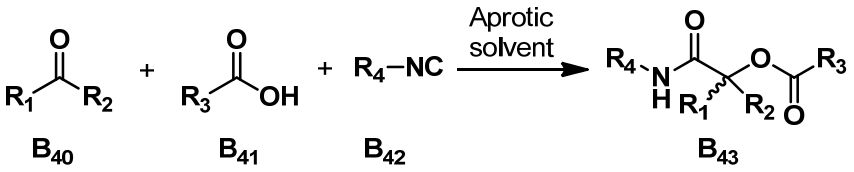


Figure 2. Convertible isocyanides employed in MCCRs.

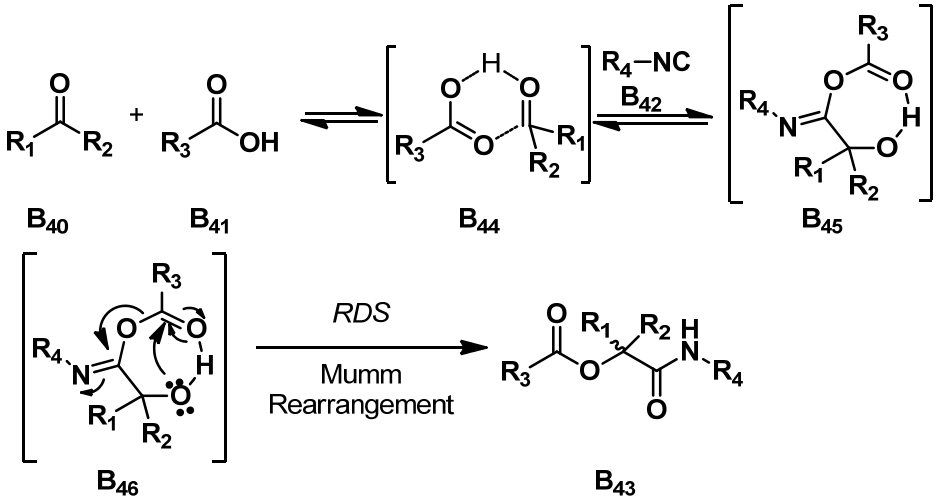
1.3. Multicomponent Name Reactions

Among many MCCRs, the isocyanide/isonitrile-based P-3CCR and U-4CCR have been most widely used in combinatorial synthesis. In recent years, there is a revival of interest in devising new variations of these MCCRs as exemplified in this section.

(a) **Passerini Reaction**: In 1921, Italian scientist Mario Passerini had discovered that an aldehyde (or ketone), isocyanide and carboxylic acid can condense together to provide α-acyloxycarboxamides in one step (Scheme 6).[23] Typically, the reaction has been reported to accelerate in aprotic solvents and thus possibly non-ionic intermediates are involved.[45] Many pharmaceutically active compounds contain the α-acyloxycarboxamide moiety (**B_{43}**). The reaction has been named after Passerini and generally described as P-3CCR.



Scheme 6. The P-3CCR for synthesis of α-acyloxycarboxamides.

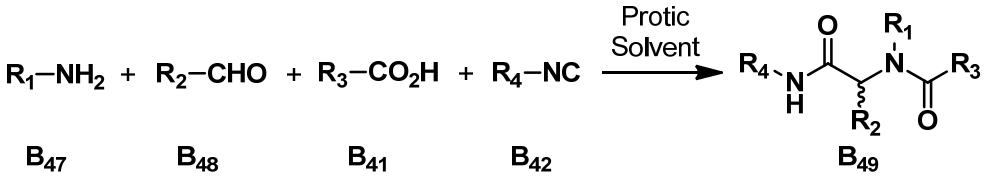


Scheme 7. Mechanism of the P-3CCR.

The most widely accepted mechanism of the P-3CCR is depicted in Scheme 7. Initially, the carbonyl compound **B_{40}** and a carboxylic acid **B_{41}** forms an adduct **B_{44}** via hydrogen-bonding. The isocyanide attacks the electrophilic carbonyl carbon, following which the carboxylate attacks the terminal electrophilic carbon of the isocyanide to

provide the α-addition intermediate **B_{46}** via a cyclic transition state. The non-isolatable α-addition intermediate **B_{46}** then provides more stable α-acyloxy carboxamide **B_{43}** via an intramolecular transacylation.

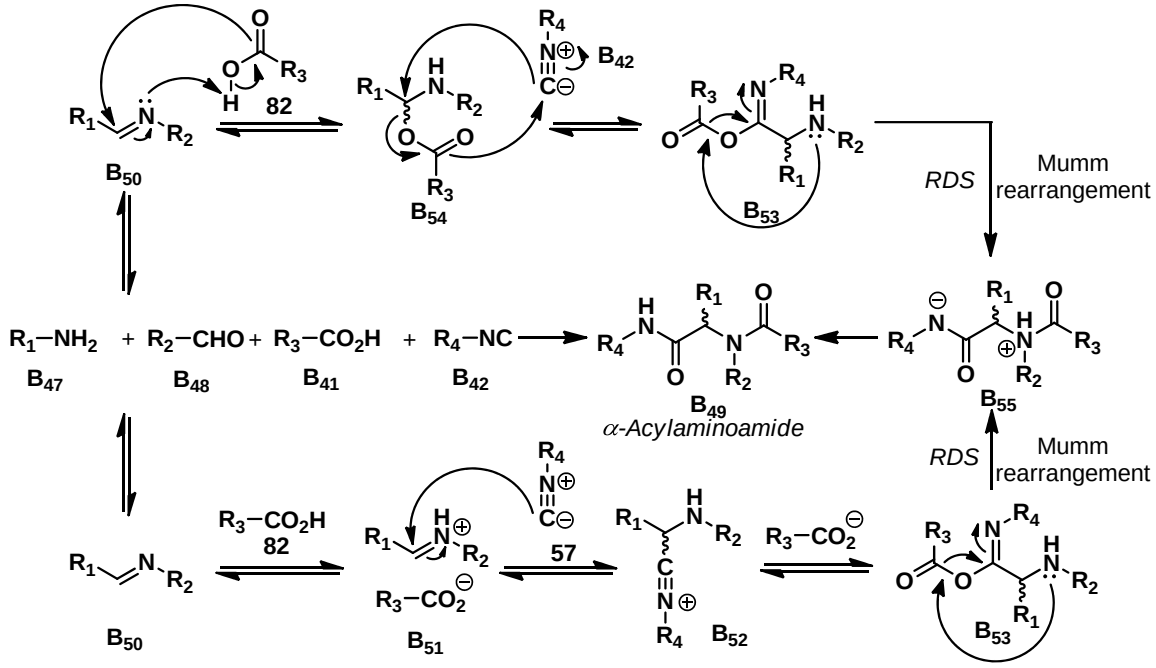
(b) **Ugi Reaction:** In 1959, German chemist Ivar Karl Ugi discovered that an amine, aldehyde, carboxylic acid and isocyanide condense together to provide α-acylaminoamide (Scheme 8).[24] Typically, the Ugi reaction requires protic polar solvents e.g. methanol. In general, the reaction works well with high concentration of starting materials. McFarland noted that the reactivity of the isocyanides is primarily influenced by electronic effects and reactant concentration plays more of an important role than the properties of the solvent.[46] The reaction has been named after Ugi and commonly described as U-4CCR. The U-4CCR generates one new C-C bond and several carbon-hetero atom bonds are concommitantly formed.



Scheme 8. The U-4CCR.

In Scheme 9, two postulated mechanisms of the U-4CCR are shown.[47] Condensation of the amine **B_{47}** and the oxo compound **B_{48}** (aldehyde or ketone) forms imine **B_{50}** in the first step of two pathways. The nitrogen of the imine, thus increases the electrophilicity of the C=N bond. The next step involves the protonation of imine that leads to formation of iminium-carboxylate ion-pair **B_{51}** (depending upon solvent) followed by nucleophilic attack of isocyanide carbon atom onto the electrophilic iminium carbon atom and nucleophilic attack of the carboxylate anion onto the electrophilic

isocyanide carbon atom to form **B$_{53}$**. Alternatively, the formation of ester **B$_{54}$** can take place via nucleophilic attack of the carboxylate anion, followed by S_N2 attack of **B$_{42}$** onto the α-carbon to form **B$_{53}$**. However, because of competing reactions and other equilibria involved, detail experimentations to support the formation of intermediate **B$_{52}$** versus **B$_{54}$** have not been reported.[47] Although, the debate still rages over possible intermediates, formation of intermediate **B$_{52}$** has been widely accepted by the scientific community.



Scheme 9. Mechanism of the U-4CCR.

Intramolecular acylation of nitrogen derived from the amine component provides the intermediate **B$_{55}$**. This type of intramolecular acylation is known as the Mumm rearrangement.[48] The Mumm rearrangement has been widely accepted as the rate determining step of the U-4CCR. After the intramolecular acylation, the hydroxylamine converts to stable amide to provide the final U-4CCR α-acylaminoamide **B$_{49}$** (Scheme 9).

Although, the P-3CCR and U-4CCR are closely related, stereochemical control of the U-4CCR has proven to be difficult despite the development of chiral Lewis acid

catalysts for the P-3CCR.[49] Use of Lewis acid catalysts, chiral starting materials, low temperature or low concentration of the isocyanides in the U-4CCR provided low enantioselectivity (<11:1).[50]

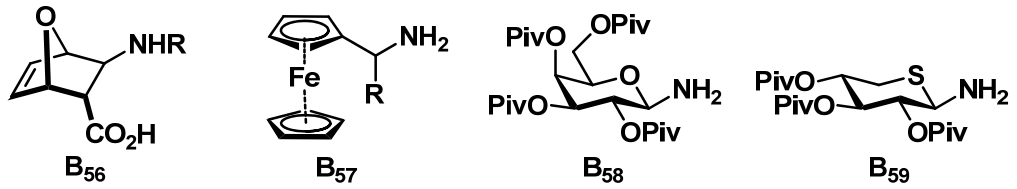
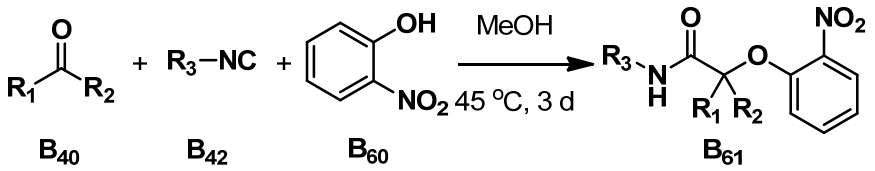


Figure 3. Bifunctional substrate and chiral auxiliaries employed in the U-4CCR.

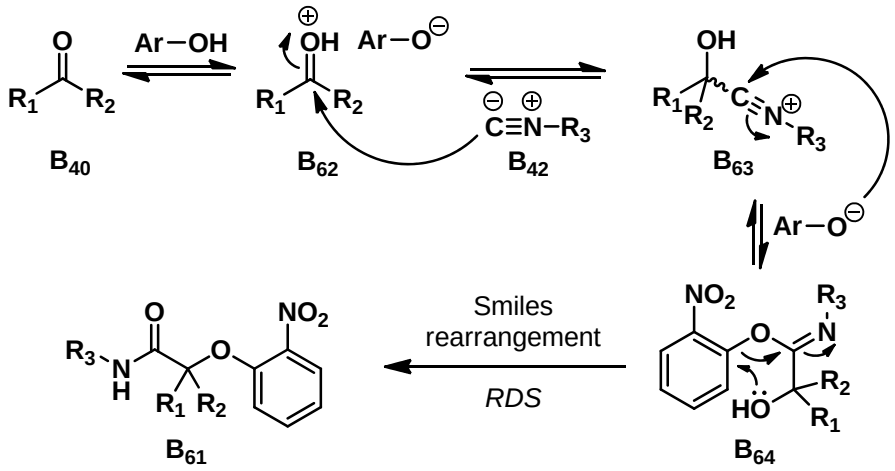
Several chiral auxiliaries e.g. chiral amine auxiliaries and bifunctional substrates have been developed to control the stereoselectivity of the U-4CCR and many of them provided good-to-excellent enantioselectivity (<99:1) and yield (43-91%) respectively (Figure 3).[51] Kunz and co-workers have reported that when pivaloyl galactopyranosylamine **B_{58}** and zinc chloride etherate were employed in stoichiometric amounts, the U-4CCR provided *R*-configured products; on the other hand arabinosylamine (not shown) provided the corresponding *S*-configured products. Both the chiral amines provided excellent enantioselectivity (>99:1), good-to-excellent yields and can be cleaved in two additional steps.[52] Most recently, Kunz and co-workers have developed, chiral thio-xylopyranosyl amine auxiliary **B_{59}** which provided both *R*- or *S*-configured products in good diatereoselectivity (96:4) and yield (92%) and can be cleaved under mild conditions.[53]

(d) **Passerini-Smiles Reaction:** Recently, Grimaud and coworkers[30] discovered that phenolic compounds having strong electron-withdrawing groups are sufficiently acidic to replace carboxylic acid in the P-3CCR and can provide similar type of products (Scheme

10). Various substituted *o*-nitrophenol as well as *o*-nitro substituted hydroxyquinolines, pyridines and 4-hydroxypyrimidines provides desired products in moderate yield.



Scheme 10. The Passerini-Smile three component reaction (PS-3CCR).

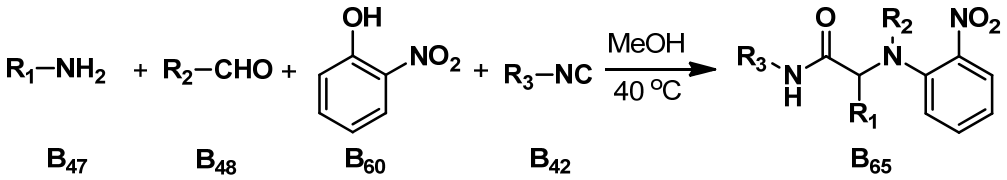


Scheme 11. Postulated mechanism of the PS-3CCR.

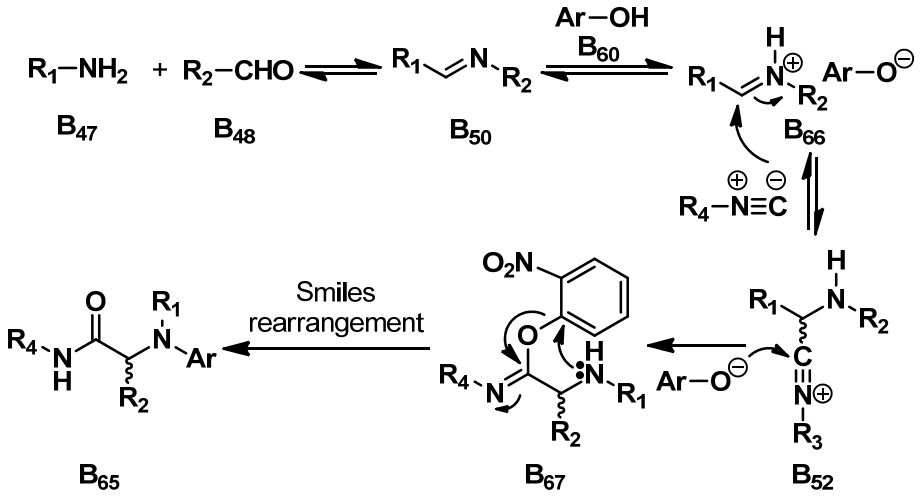
A postulated mechanism of the PS-3CCR is shown in Scheme 11. Protonation of the carbonyl forms the activated intermediate **B$_{62}$** and nucleophilic attack by isocyanide **B$_{42}$** onto the electrophilic α-carbon of **B$_{62}$** generates the intermediate **B$_{63}$**. The nucleophilic phenolate ion then attacks the electrophilic carbon of the isocyanide and traps the nitrilium intermediate to form imidate **B$_{64}$** which then undergoes Smiles rearrangement[54] to provide the desired product **B$_{61}$**.

(e) **Ugi-Smiles reaction**: Laurent El Kaim's group from France has modified the Ugi reaction by replacing the carboxylic acid component with phenolic derivatives having strong electron-withdrawing groups to couple with the Smiles rearrangement. Thus, an

amine, aldehyde, phenolic compound and isocyanide condense to provide the Ugi-Smiles product **79** (Scheme 12).[30b,31] Phenolic compounds act as proton donor-like carboxylic acids and generally require the presence of a strong electron withdrawing group at the *para* or *ortho* position to the hydroxyl group of the phenol. The reaction works well in polar protic solvents like methanol at elevated temperature.



Scheme 12. The Ugi-Smiles four component reaction (US-4CCR).

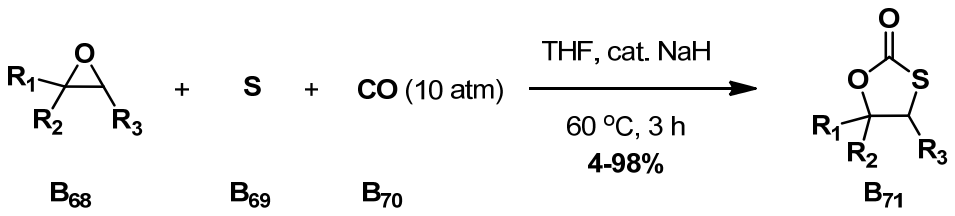


Scheme 13. Mechanism of the US-4CCR.

The mechanism of the Ugi-Smiles reaction (Scheme 13) is quite similar to that of the Ugi reaction (Scheme 9). The amine and aldehyde condense to form the imine $\mathbf{B_{50}}$. The phenolic compound protonates the imine $\mathbf{B_{50}}$ and activates the carbon atom of the C=N bond. The isocyanide attacks the electrophilic carbon of the activated imine-phenolate ion-pair $\mathbf{B_{66}}$ and the phenolate ion attacks the electrophilic carbon of the

isocyanide in the intermediate $\mathbf{B_{52}}$. Smiles rearrangement[54] of the α-adduct $\mathbf{B_{67}}$ provides the final product $\mathbf{B_{65}}$ (Scheme 13).

The versatility of MCCRs is often referred to its exploratory power (E_N). All multicomponent reactions do not have the same E_N. For example, if the number of starting materials in a MCCR is N for each of the four components (e.g. U-4CCR or Povarov 4CCR), the exploratory power $E_N = N^4 = 1000^4 = 1\times10^{12}$; which means that 1000 trillion products could be potentially accessible from only 4000 starting materials.[55] Thus, a 7-CCR would have more exploratory power than a 3-CCR; would provide more potentially accessible products when 7 starting materials are variable. For example, the synthesis of 1,3-oxathiolan *via* three component reaction of epoxides, sulfur and carbon dioxide developed by Sonoda, is an example of MCCR having low E_N since two components (sulfur and carbon monoxide) are not variable (Scheme 14).[55e]



Scheme 14. 1,3-oxathiolan synthesis via Sonoda's 3-CCR.

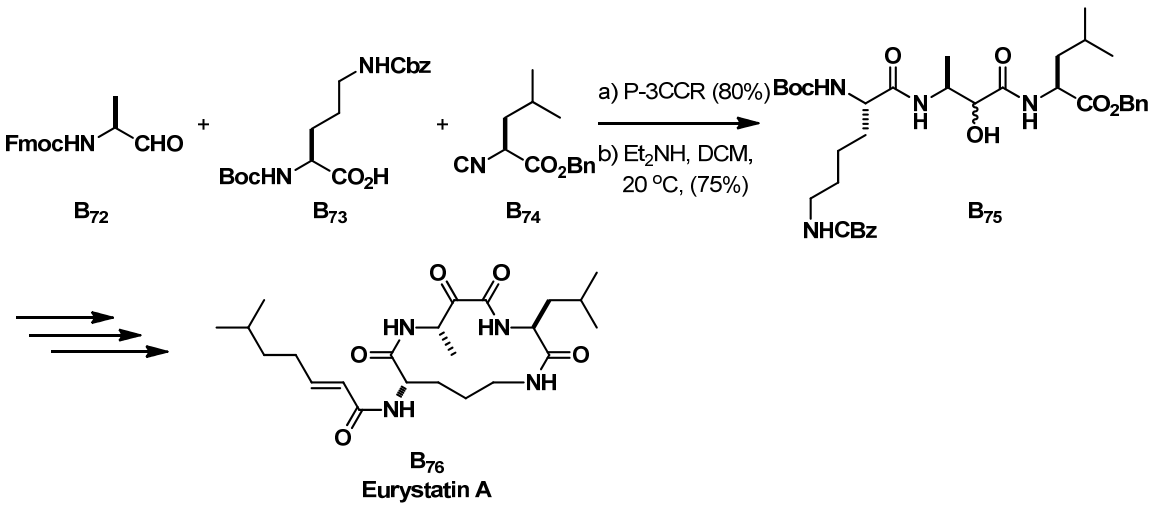
In recent years, there is a growing tendency among the scientific community to combine two or more MCCRs to increase dimensionality and access diverse and complex products. Thus, the Asinger-Ugi (Ugi-Dömling) reaction (U-8C-7CCR),[56] U-5CCR,[57] Interrupted Ugi reaction,[58] Ugi-Ugi reaction (U-8CCR),[59] Tandem Ugi-Passerini reaction (U-7C-6CCR),[60] Petasis-Ugi reaction (U-7C-6CCR).[61] have been developed over the

years to increase E_N. In addition, MCCRs have been used in conjunction other reaction such as Diels-Alder, Heck reaction, RCM and others.[62]

1.4. Application of Multicomponent Reactions in Natural Product Total Synthesis

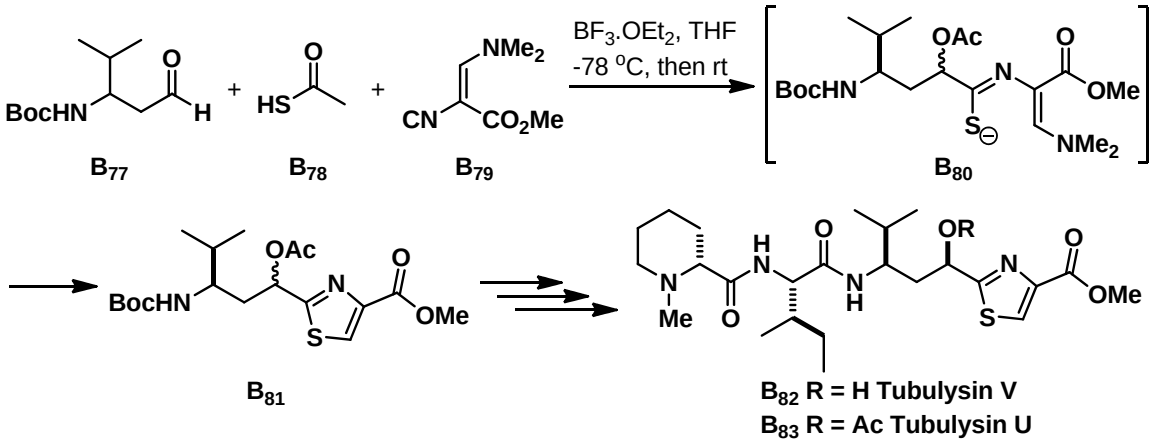
In recent years there have been a number of applications of MCCRs in total synthesis. Interestingly, in several cases other traditional methods failed to provide the desired product in appreciable yield, but selective MCCRs provided the desired product in good yield. Moreover, MCCRs have been employed as key step in many total syntheses.

The Eurystatins A and B are isolated from *Streptomyces eurythermus* R353-21. These 13-membered macrocyclic compounds have shown to strongly inhibit the serine protease prolyl endopeptidase (PEP). Semple and co-workers have reported a short total synthesis of Eurystatin A (**B_{76}**) employing the P-3CCR/amine deprotection/acyl migration (PADAM) strategy (Scheme 15).[63]

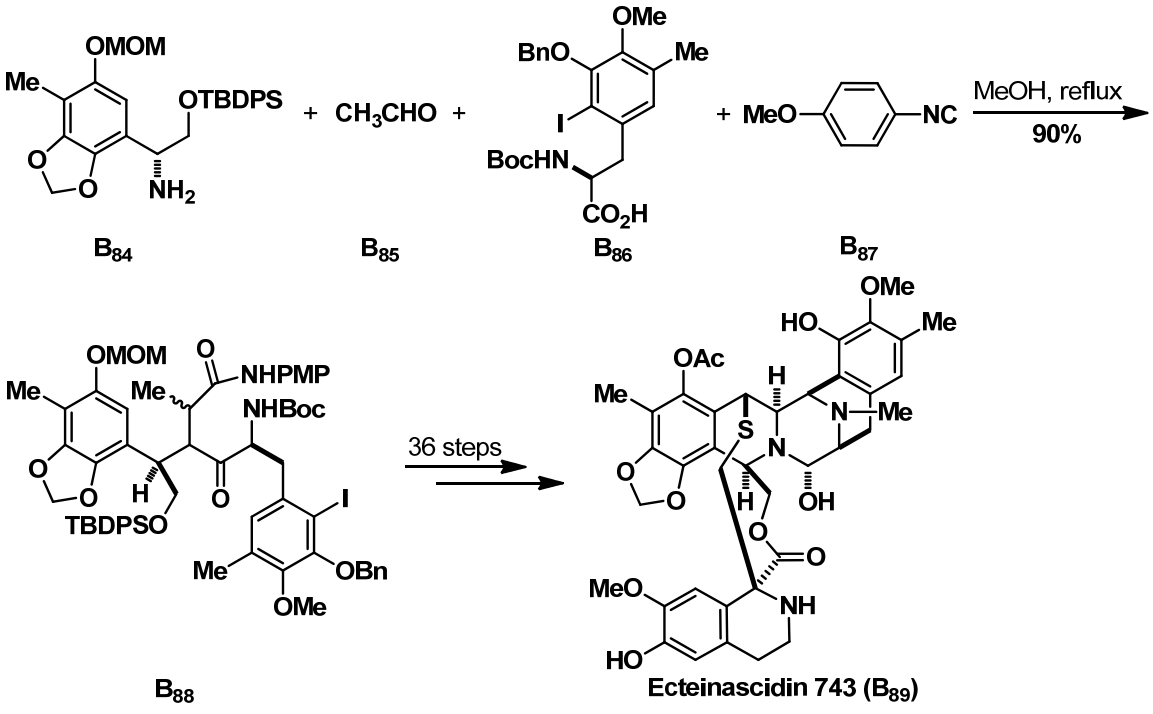


Scheme 15. Total synthesis of Eurystatin A using the P-3CCR.

Dömling and co-workers have developed a *de novo* strategy for the first total synthesis of tubulysin V (**B_{82}**) and U (**B_{83}**) employing Lewis acid catalyzed Passerini-type 3CCR using Schöllkopf's isocyanide **(B_{79})** (Scheme 16). The first step works best when the reaction is carried out at -78 ^{o}C under inert atmosphere.[64]



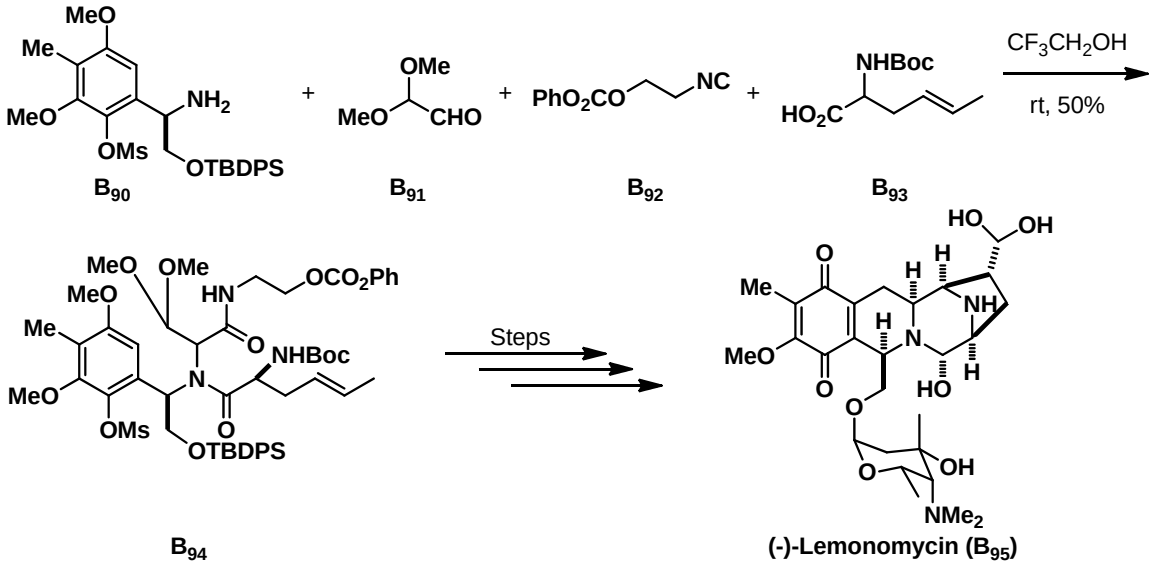
Scheme 16. Total synthesis of tubulysin V and U employing P-3CCR type reaction.



Scheme 17. Application of the U-4CCR in the total synthesis of Ecteinascidin 743.

The antitumor antibiotic Ecteinascidine 743 (**B_{89}**) of the marine tunucate, *Ecteinascidia turbinate*, is currently undergoing advanced clinical trials and has been approved for the treatment of soft tissue sarcomas in Europe.[65] The total synthesis of **B_{89}** was achieved by the Fukuyama group in 37 steps utilizing a planned U-4CCR as a key reaction that generated the important precursor **B_{88}** containing significant architecture as part of the final target molecule (Scheme 17).[66]

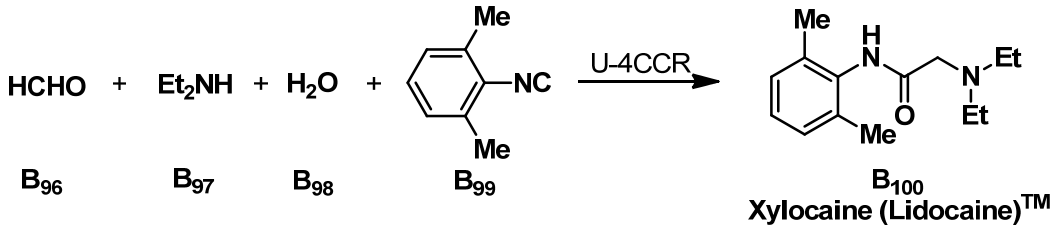
Similarly, Fukuyama et al.[67] have employed the U-4CCR in the stereocontrolled synthetic approach (Scheme 18) for the total synthesis of antitumor antibiotic tetrahydroisoquinoline alkaloid (-)-Lemonomycin (**B_{95}**) which was isolated from the fermentation broth of *Streptomyces candidus* (LL-AP191).[68] Zhu and coworkers are also studying the synthesis of **B_{95}** using U-4CCR as a key step in the their strategy (Scheme 18) as well.[69] Several other biologically relevant natural products have been synthesized using MCCR as a key step in their synthetic strategy.[70]



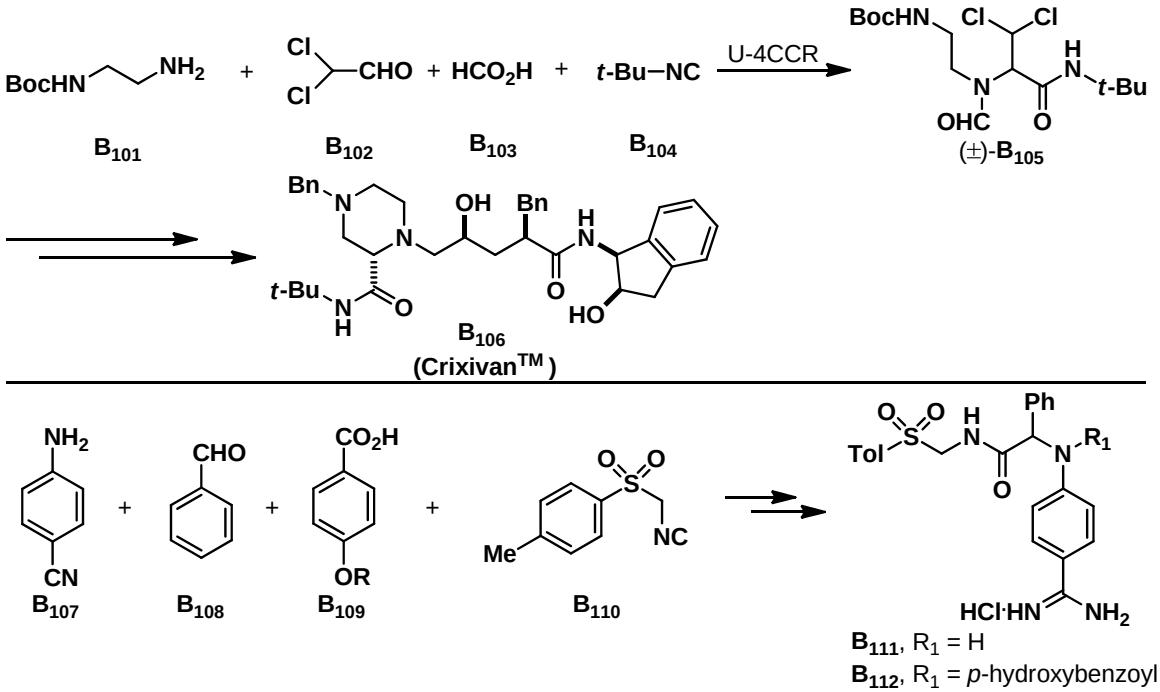
Scheme 18. Utilization of U-4CCR in the synthesis of (-)-Lemonomycin.

1.5. Application of MCCRs in Drug Discovery

Although, in the last decade MCCRs have not been utilized much in drug discovery process, recent advancement of high-throughput-screening (HTS) have led the scientific community in pharmaceutical companies as well as in academia to apply MCCRs in particular IMCCRs for rapid identification of drug-like molecules. Among several known MCCRs, the U-4CCR was first applied for the synthesis of local anesthetic Xylocaine™ (**114**) by the pharmaceutical company AB Astra (Scheme 19).[71]



Scheme 19. Synthesis of Xylocaine using U-4CCR.



Scheme 20. Application of U-4CCR in the synthesis of Crixivan™ and thrombin inhibitor.

Merck research has utilized the U-4CCR as a key step for the large scale synthesis of Crixivan^{TM} (**B_{106}**) which is currently marketed as an HIV-1 aspartyl protease inhibitor.[72] Researchers in the Hofmann and LaRoche company recently found two desirable thrombin inhibitors **B_{111}**, **B_{112}** using the U-4CCR (Scheme 20).[73]

In recent years, MCCRs have become a rapid platform in the drug discovery process and many MCCR-derived small molecules showed promising results in clinical trials. For example, tubulin inhibitor **B_{113}**, kinase inhibitor **B_{114}**, aspartyl-protease inhibitor **B_{115}**, serine-protease inhibitor **B_{116}**, phosphatase inhibitor **B_{117}**, metallo-protease inhibitor **B_{118}**, CCR5 antagonist **B_{119}**, antituberculosis **B_{120}**, antiproliferative **B_{121}**, protein-protein interaction inhibitor **B_{122}** and cystine protease inhibitor **B_{123}** to name a few (Figure 4).[70b, 74]

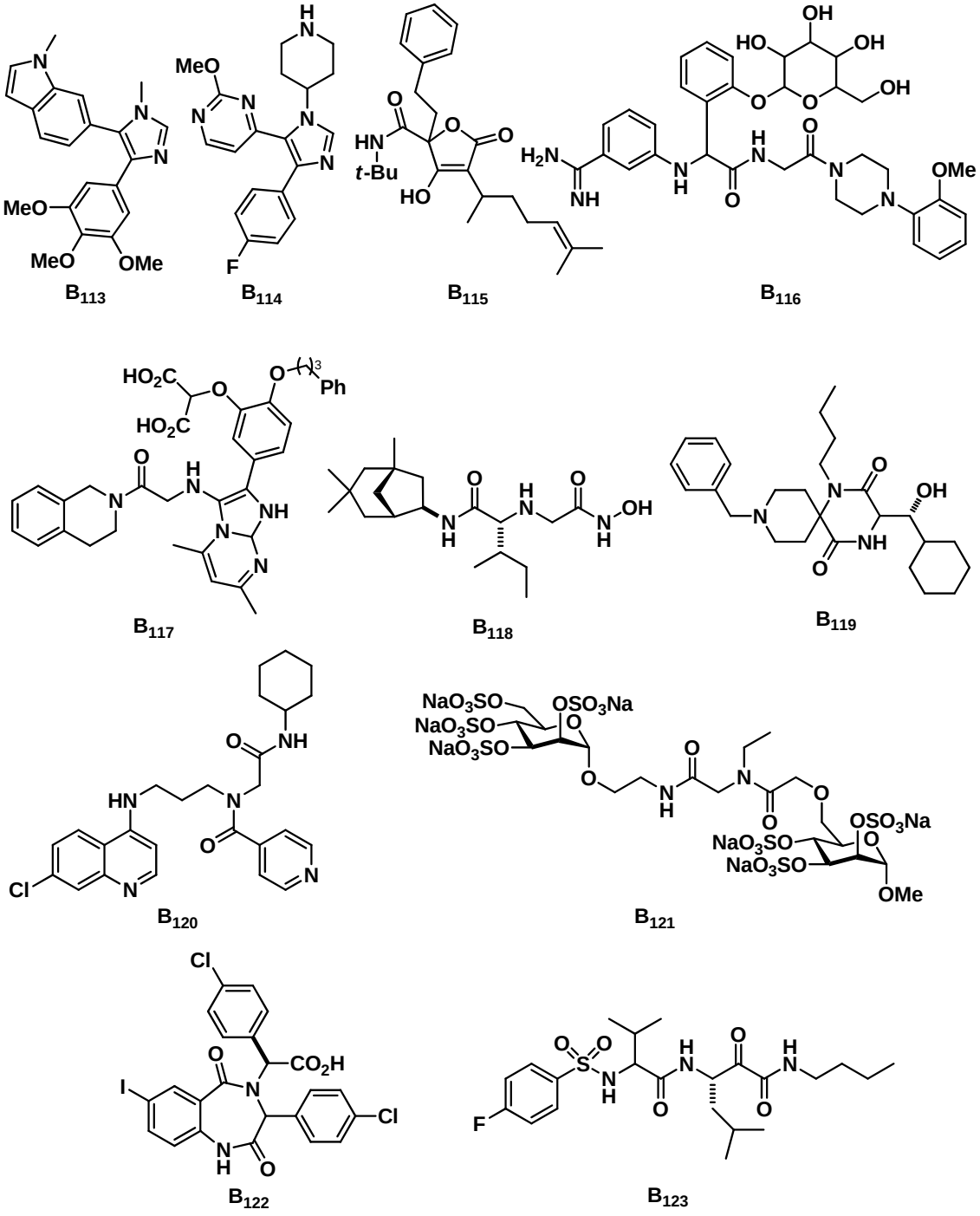


Figure 4. MCCRs are used in synthesizing pharmaceuticals.

1.6. Diversity-Oriented Synthesis of Small Molecules

Small molecules are known to interact with the active site of proteins, enzymes and disrupt biological events. Thus they have been used frequently by chemists to study various complicated biological systems in order to develop new therapeutic agents.[75] However, many naturally occurring small molecules do not induce the desired biological response and thus further structural modifications are required.

In target-oriented synthesis (TOS), a specific target molecule in chemical space is usually deconstructed in a backward direction *via* a retrosynthetic analysis pioneered by Woodward and Corey;[76] then reconstructed in the forward direction. Whereas, in diversity-oriented synthesis (DOS), wide arrays of structurally and skeletally diverse, complex molecules can be synthesized in the forward direction from simple, readily available starting materials via "split-pool" concept of combinatorial synthesis (Scheme 5).[77] Since, DOS has the ability to generate structurally as well skeletally rigid and complex molecules (spirocycles, fused-polycycles, macrocycles etc.), it has emerged as a very powerful tool to provide a diverse library of compounds that can be screened against an entire collection of enzymes or proteins.[78]

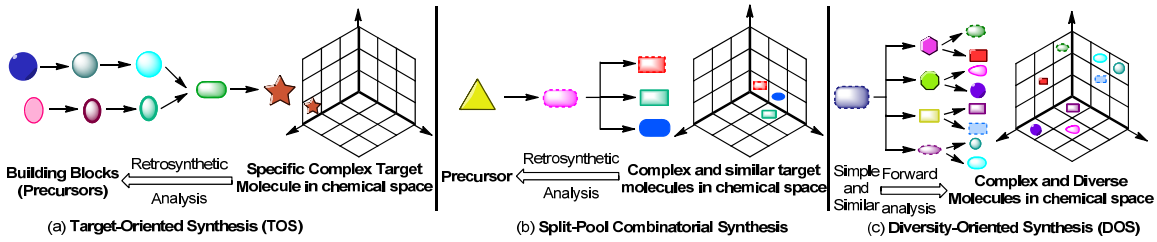


Figure 5. Schematic representation of TOS, traditional combinatorial synthesis and DOS (adapted from Spring *et al.* with permission from Prof. Spring).[79]

Since the mantra of DOS strategy does not provide identical compounds and incorporates structural diversity, any racemic synthesis of diverse compounds can also be classified as DOS. The DOS strategy is designed in such way that it incorporates both diversity and complexity. Since the number of all possible "drug-like" molecules is calculated to be astronomical, it is quite impossible to synthesize the entire chemical space.[80] Hence, ideal goal of DOS is to cover maximum possible chemical space that will not only include "drug-like" but also skeletally diverse molecules.[80]

There are four key types of diversity strategies those must be incorporated in designing a DOS: (a) appendage diversity (employing various suitably functionalized precursors); (b) stereochemical diversity (employing chiral reagents); (c) functional group diversity; (iv) skeletal diversity.[81] Among these, the skeletal diversity is the most important strategy in DOS.[81b] Skeletal diversity can be achieved via branching pathways or folding pathways (Figure 6). In a branching pathway, different reagents are used to convert a specific starting material into various scaffolds using various reagents. Thus, branching pathway is often referred to as "reagent-based approach". On the other hand, in the folding pathway, similar reagents are used to obtain varying scaffolds from pre-encoded starting materials from MCCRs or others (σ-elements) and are often referred to as a "substrate-based approach".

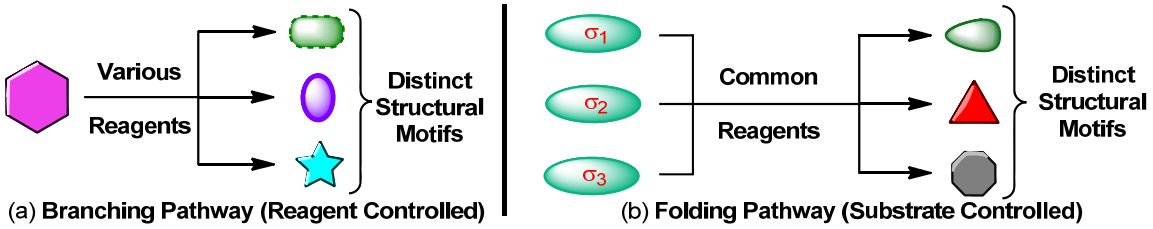
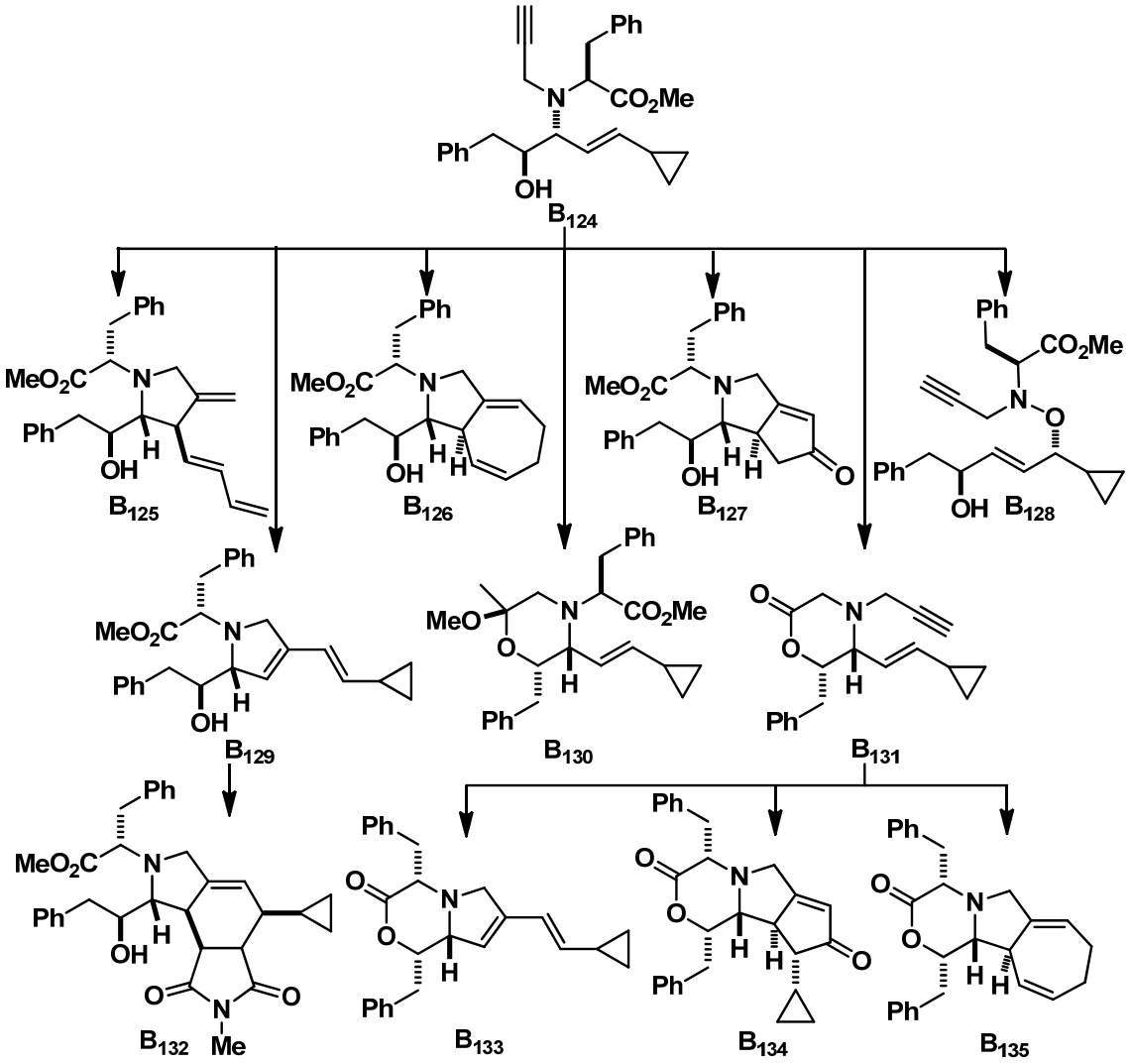


Figure 6. Pathways of skeletal diversity (adapted from Spring *et al.* with permission from Prof. Spring).[79]

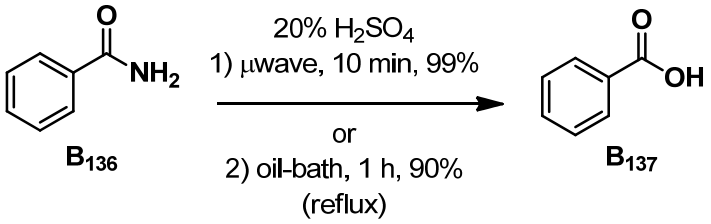
Branching pathways can be achieved *via* either pluripotent functionality strategy or multiple group pair strategy. Recently, Schreiber and co-workers have described a build/couple/pair strategy which combines many essentials from the above described approaches.[82] The required chiral starting units are "built" from chiral pool reagents and they are then transformed into densely functionalized molecules through coupling condensation reactions (e.g. MCCRs). Specific transformations of the densely functionalized molecules generate various structural motifs (Scheme 21).[83]



Scheme 21. An example of build/couple/pair strategy in DOS.[122]

1.7. Microwave-Assisted Organic Synthesis for Diversity in MCCRs

During the World War II, Percy LeBaron Spencer accidentally discovered that microwave (μwave) energy could cook food while experimenting with radar waves during his tenure at the Raytheon company.[84] Further exploration showed that microwaves could increase the internal temperature of foods much quicker than a conventional oven and the first commercial microwave oven for home was introduced in 1954. However, the effects of microwave irradiation in organic synthesis were not explored until Giguere and coworkers as well as Gedye, Westway reported on the use of microwave-assisted organic synthesis (MAOS) in 1986 (Scheme 22).[85] Following this report, industrial and academic multi-mode as well as single-mode microwaves have been developed. They are featured with corrosion-resistant stainless steel cavities, reinforced doors, real-time temperature and pressure monitoring, and automatic safety controls.



Scheme 22. Example of the first MAOS.[85b]

Understanding the basic theory behind microwaves might help the scientific community to apply this powerful and reliable energy source to any synthetic route and thereby discover novel reaction pathways. A μwave is a form of electromagnetic energy (Figure 7) that falls between the infrared and radio frequency regions (300-300,000 MHz) of the electromagnetic spectrum (Figure 8). Although the microwave energy consists of an electric and a magnetic field component, only the electric component of the electromagnetic field interacts with matters to heat the substance in chemical synthesis.[86]

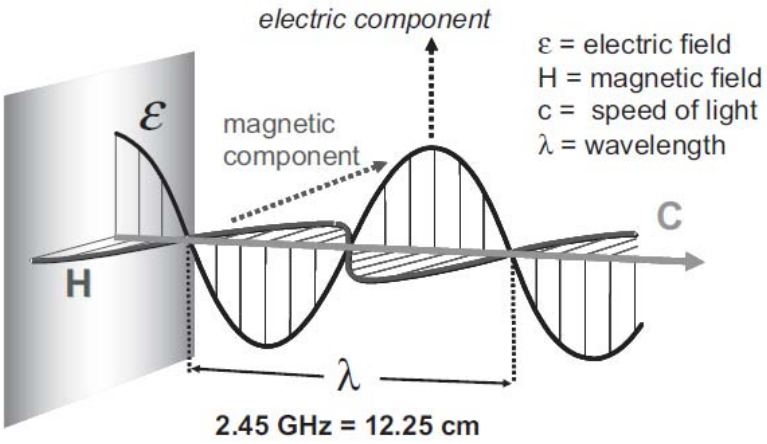


Figure 7. Electric and magnetic components of microwave (Reproduced after permission from Prof. Kappe, Copyright: Wiley-Blackwell Publishing Group).[88]

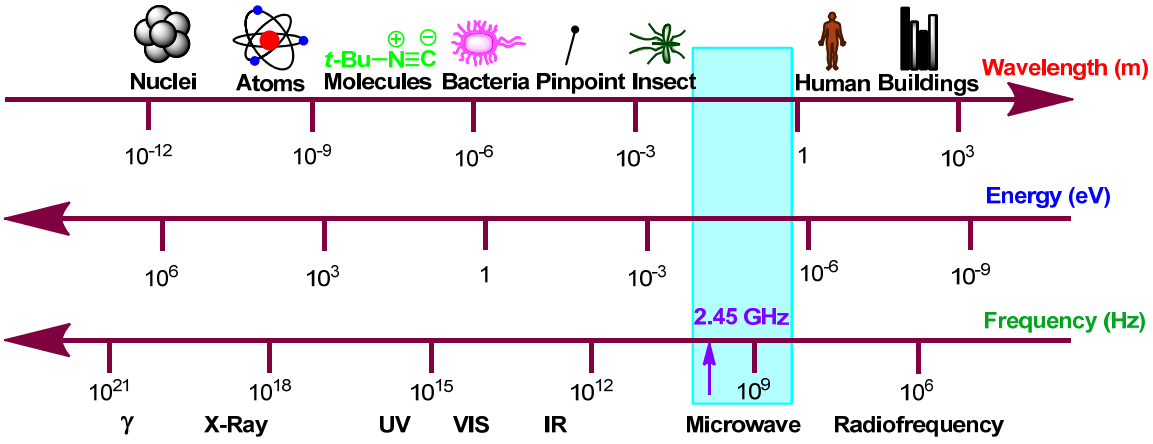


Figure 8. Microwave region in the electromagnetic spectrum.

To avoid interference between different applications, all domestic microwave ovens and dedicated microwave reactors available today for heating purposes, operate at a frequency of 2.45 GHz corresponding to a wavelength 12.2 cm. The energy of microwave at frequency of 2.45 GHz is 1.6×10^{-3} eV or the energy of microwave photons is 0.037 kcal per mole. On the other hand, typical energy required to cleave molecular bonds lies between 80-120 kcal/mole. Consequently, it is quite understandable from the data in Table 2 that the microwave energy is too low to cleave molecular bonds and thus can not affect molecular structure of organic compounds; however it can affect molecular

rotation.[84a, 87] Hence, microwaves can not induce chemical transformation by direct absorption of electromagnetic radiation, similar to ultraviolet and visible radiation. Microwave absorption is completely kinetic during molecular excitation.

Table 2. Comparison of radiation type and bond energy[88]

Radiation Type	**Frequency (MHz)**	**Quantum Energy (eV)**	**Bond Type**	**Bond Energy (eV)**
Gamma rays	3.0×10^{14}	1.24×10^{6}	C-C	3.61
X-rays	3.0×10^{13}	1.24×10^{5}	C=C	6.35
Ultraviolet	1.0×10^{9}	4.1	C-O	3.74
Visible light	6.0×10^{8}	2.5	C=O	7.71
Infrared light	3.0×10^{6}	0.012	C-H	4.28
Microwaves	2450	0.0016	O-H	4.80
Radiofrequencies	1	4.0×10^{-9}	Hydrogen bond	0.04-0.44

Traditional organic synthesis has been carried out through conductive heating process, typically by heating glass vessels emerged in a silicone-based oil-bath with an external heat source e.g. hot-plate or heating mantle. The oil-bath heating process is inherently slow because the heat passes first through the walls of the vessel and then reaches the solvent and reacting components. Moreover, the transfer of energy through the walls of the vessels depends on the thermal conductivity of the various materials. Consequently, a temperature difference between the inner and outer walls of the vessel occurs (Figure 9). This introduces another temperature differences between the inner walls of the vessel and the reaction mixture. These events make the measurement of actual temperature of reaction mixture inaccurate unless otherwise the temperature is being monitored by emerging a thermometer into the reaction mixture. Thus, conductive

heating is relatively insufficient method of transferring energy in the form of heat. In addition, the oil-bath heating process can take hours to reach a specific temperature.

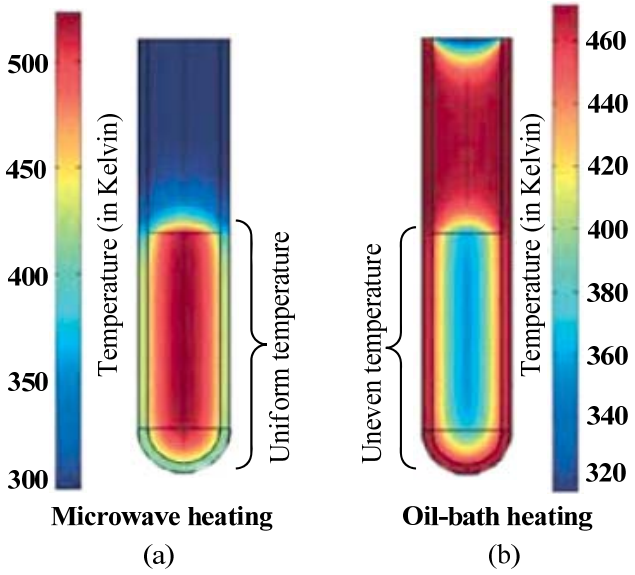


Figure 9. A comparison of temperature (Kelvin) gradients between microwave and oil-bath heating processes: (a) in microwave heating, the temperature of the entire reaction mixture volume increases simultaneously, (b) in the oil bath heating, only the reaction mixture volume in contract with the vessel wall is increased first.(adapted from Kappe *et al.* after permission from Prof. Kappe).[88]

In MAOS, on the other hand, microwaves interact directly with the solvent and reacting components present in the reaction vessel. Thus, microwave heating leads to rapid increase in temperature because the heating process is independent of the thermal conductivity of vessel materials which is nearly microwave-transparent (Figure 10). As a result, microwave heating can provide instantaneous localized superheating of reaction mixture. There are two fundamental mechanisms by which the electric component of an electromagnetic field transfers energy from microwaves to reaction mixture being heated: dipolar polarization and ionic conduction.[88, 89]

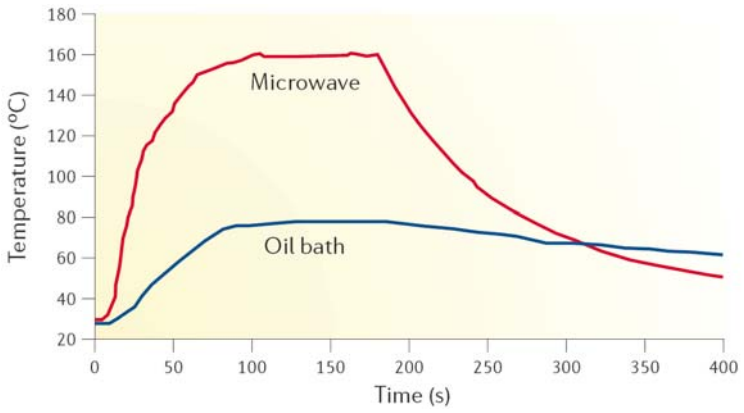


Figure 10. Temperature profile of microwave and oil-bath heating of ethanol (Reproduced with permission from Prof. Kappe, Copyright: Nature Publishing Group)[88]

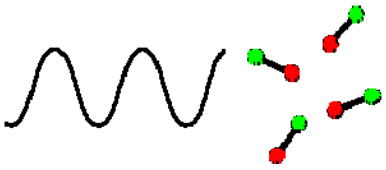


Figure 11. Dipolar polarization (reproduced with permission from Dr. Ioannidis, Biotage, Sweden AB) [Copyright: Biotage, Sweden).[90]

The dipolar polarization mechanism is a phenomenon in which the electric field component interacts with the matrix or components of reaction mixture (Figure 11). Thus, in order to generate heat upon microwave irradiation, a substance must possess dipole moment. When a sample is exposed to microwaves, the dipoles try to align in the direction of the applied electric field. As the applied electromagnetic field oscillates, the dipole of the sample tries to realign with the alternating electric field. Due to this rotational motion of the molecules of the sample some energy is lost through molecular friction and dielectric loss and results in the transfer of energy in the form of heat. Thus, the amount of heat that will be generated by this process is directly proportional to the ability of the molecules to align themselves with the frequency of applied field. The efficiency of this dipolar coupling depends on a number of factors; however, polar

solvents will also encounter this mechanism of energy transfer. The extent of interaction between microwave irradiation and a particular solvent depends upon the average rotational frequency or its inverse, the average relaxation time (τ). Debye postulated that τ is dependent on the nature of various intermolecular forces present in solution as well as molecular size. Thus, the average relaxation time of a molecule is dependent on the average time of the molecules to attain a random orientation when microwave irradiation is turned off. Thus τ is defined as $\tau = 4\pi r^3\eta/kT$, where r^3 represents the size of the molecules and η is the viscosity which represents the intermolecular forces. Viscosity clearly depends upon the strength of intermolecular forces in a complex way because the dipole-dipole, induced dipole-dipole and hydrogen bonding may contribute to intermolecular forces. The relaxation time is also dependent on temperature because molecules can rotate faster at higher temperature. The ability of any solvent to absorb microwave energy and convert into thermal energy (heat) at the applied frequency is called the loss tangent or energy dissipation factor. The loss tangent is defined as: $\tan\delta = \varepsilon''/\varepsilon'$, where ε" is the loss factor that reflects the conductance of the material and ε' is the dielectric constant of the solvent. Since the interaction of electromagnetic field from microwave irradiation with matter is dependent upon absorption, transmission and reflection, polar solvents with high dielectric constant e.g. H_2O, EtOH, MeOH etc will absorb microwave energy readily and ensue rapid heating of the medium. On the other hand, since non-polar solvents have low dielectric constant, they are not capable of absorbing microwave energy readily (Table 3).

Table 3. Physical properties of selected common solvents.[89b]

Solvent	**Bp** (^{o}C)	**Dielectric constant** (ε')	**Loss factor** (ε")	**tan δ**	**Viscosity** (η)
Water	100	80.4	9.889	0.123	10.1
Formic acid	100	58.5	42.237	0.722	15.7
DMSO	189	45	37.125	0.825	2.45
DMF	153	37.7	6.070	0.161	0.85
Acetonitrile	82	37.5	2.325	0.062	3.8
Nitromethane	101	36	2.304	0.064	0.61
Nitrobenzene	202	34.8	20.497	0.589	
Methanol	65	32.6	21.483	0.659	5.5
NMP	215	32.2	8.855	0.275	16.7
Ethanol	78	24.3	22.866	0.941	10.8
Isobutanol	108	15.8	8.248	0.522	3.95
1,2-Dichloroethanne	83	10.4	1.321	0.127	0.84
Dichloromethane	40	9.1	0.382	0.042	0.44
THF	66	7.4	0.348	0.047	0.55
Ethyl acetate	77	6.0	0.354	0.059	0.45
Chlorobenzene	132	2.6	0.263	0.101	0.80
Toluene	111	2.4	0.096	0.040	0.59

The second way to transfer microwave energy is through ionic conduction which occurs if there are free ions or ionic species present in the substance being heated (Figure 12). When the sample is heated, the ions oscillate back and forth and in the event they collide with their neighboring ions, molecules or atoms; this results agitations or motions that generate heat. Furthermore, at higher temperature, the rate of collision increases which leads to efficient transfer of energy in the form heat.

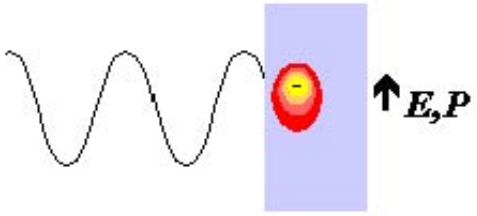


Figure 12. Ionic conduction mechanism (reproduced with permission from Dr. Ioannidis, Biotage, Sweden AB) [Copyright: Biotage, Sweden][90]

Since the microwave reaction vessels are usually made of microwave transparent materials quartz or Teflon, uniform increase in temperature is more likely to occur. It is quite evident from recent literature reports that microwaves definitely accelerate the rate of organic reactions. However, it is not fully understood how microwaves accelerate reaction rates in general. Among the scientific community, some believe that this rate acceleration is due to the distinct wave-material interaction that leads to a decrease in the required activation energy. Others believe that the rate acceleration is due to the rapid heating which enables to reach high temperature very quickly or due to a "specific microwave effect".

According to the Arrhenious equation, the rate constant of a particular reaction, $\kappa = Ae^{-Ea/RT}$. Thus, for a particular reaction the rate constant is dependent on the frequency of collisions between molecules having correct spatial orientation (A) and the fraction of those molecules having minimum energy needed to overcome the activation energy barrier ($e^{-Ea/RT}$). Although, some speculates that microwave affects the orientation of the molecular collisions as well as the activation energy, there is currently a lack of concrete evidence in support of these arguments.[91] Thus, an increase in temperature causes molecules to move around rapidly which leads to increased number of energetic collisions. This phenomenon occurs at a much faster rate under microwave irradiation

than traditional oil bath heating. Although the debate currently looms, microwave technology has become a powerful and efficient tool in organic synthesis, medicinal chemistry as well as drug discovery.

1.8. Principle of Green Chemistry

In the last decade, there has been a growing interest among scientists as well governments around the world in 'sustainable chemistry or green chemistry'. The United States Environmental Protection Agency (US EPA) had started the green chemistry movement in 1990s to encourage scientists in chemical industry and academia to use chemistry in order to prevent pollution of environment. Thereafter, the American Chemical Society (ACS) and the US EPA have jointly developed a set of 12 guiding principles of green chemistry.[92] In summary, these principles are:

(a) Minimization of waste materials

(b) Synthetic strategy should be devised in such a way that most starting materials can be incorporated into the target product.

(c) Synthetic methods should be devised to minimize the use of hazardous chemicals

(d) Synthetic method should be devised to avoid unnecessary use of solvents or auxiliaries.

(e) Synthetic methods should generate chemicals those have less toxicity.

(f) All chemical synthetic strategy should be designed to increase energy efficiency.

(g) Whenever possible renewable materials should be used in chemical processes.

(h) Whenever possible, derivatization of chemicals should be minimized.

(i) Use of catalyst is better than stoichiometric reagents.

(j) Synthetic strategy should be designed to generate degradable products.

(k) All chemical processes should be monitored in real-time to prevent hazardous materials formation.

(l) Safer chemical methods should be designed to prevent accidents

Thus, employing MCCRs in chemical synthesis fulfils many criteria of green chemistry. Organic solvents have been used for routine experimentation and scale-up process in chemical industry as well academia due to critical 'enabling' role in solubilization, chelation etc. However, many of them are carcinogenic and are significant sources of air and water pollution. In order to solve these problems, recently reactions have been carried out without any solvent or in solvents those are environmentally benign such as water. In terms of a synthetic application, water, to date, has been a much under-utilized solvent despite being cheap and safe for various reaction processes. Unlike other solvents, water exhibits higher ionic product at elevated temperature. Consequently, water exhibits stronger acid-base character at elevated temperature and thus behaves more likely to that of an organic solvent. Moreover, water is abundant and causes no pollution. Hence, water is a worthy candidate to consider as a solvent in designing synthetic strategy especially those reactions requiring high temperature.[93] In various monographs, it has been established that microwave irradiation can reduce reaction time courses as well. Thus, utilization of microwave irradiation in the synthetic design can subsequently reduce energy consumption. Therefore, according to the principles of green chemistry set up by the EPA and ACS, dedicated microwave irradiated reactions in water can be considered as valuable contributions for their stated missions.[93b, 94]

CHAPTER 2

Microwave-Influenced Diversity-Oriented Synthesis of Biologically Relevant Small Molecules via Multicomponent Coupling Reactions and Development of New Methodology

2. Introduction

MCCRs have been frequently used by synthetic chemists as a facile means to generate molecular diversity from multifunctional substrates that can sequentially react in intramolecular processes.[95] Devising new strategies employing MCCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern-day organic synthesis.[96] Perhaps the most promising, efficient and powerful method for covering maximum chemical space by generating skeletal diversity are the MCCRs.[97]. In particular, the MCCRs should be versatile so that any combinations of functional groups can be incorporated in starting materials and those functional groups would be compatible for subsequent derivatization. By virtue of their simple execution in one-pot, they are well suited for automated synthesis which allows for maximum exploration of novel chemical space.

In order to facilitate the high throughput screening (HTS)[98] of small molecules against proteins, enzymes, and macromolecules, rapid generation of libraries is essential. In recent years microwave irradiation has emerged as an alternative and powerful tool over traditional heating processes and is becoming widely accepted by the scientific community for discovery in microwave-assisted organic synthesis (MAOS) which offers

(a) reduced reaction time, (b) cleaner products, (c) avoids purifications and handling, (d) less waste material.[99]

Designing a synthetic strategy that will not only retain the mantra of DOS, but also employ sustainable/green chemistry is a significant challenging problem amongst the scientific community.

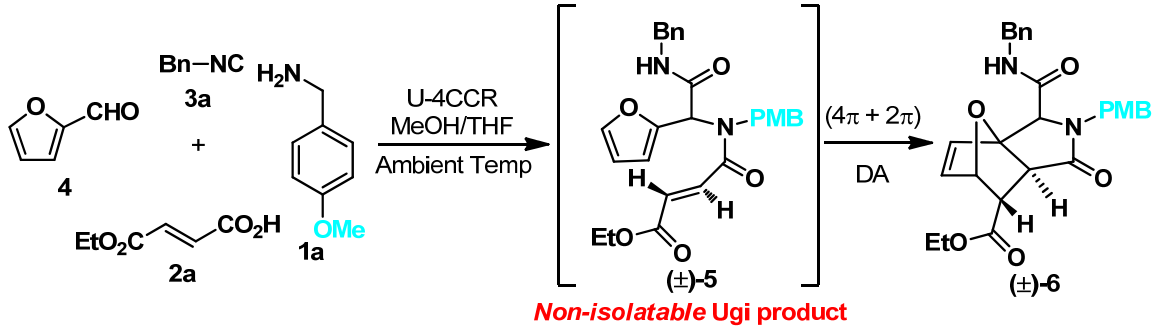
2.1. Goal of the Research

The *short-term goal* of the project was to develop very efficient and environmentally benign methodology that would provide access to a wide variety of biologically relevant small and highly complex molecules via multicomponent coupling reactions in conjunction with microwave irradiation from cheap and readily available starting materials. The *long-term goal* was to apply the novel methodologies to achieve structural and skeletal diversity; extend into other areas of chemistry to develop further new chemistry, establish a discovery platform and conduct structure-activity relationships (SARs) studies to find potential hits.

In order to achieve these goals, we questioned (i) if the novel method(s) could provide structural and skeletal diversity by tuning reacting components?, (ii) the possibility to establish a new paradigm of diversity-activity relationships (DARs)?, (iii) the conventional use of microwave irradiation as rate-accelerating tool (could it be used as a *reagent* in synthesis?), (iv) the influence of microwave irradiation on molecular properties/reactivities?, (v) if it was possible to find a common platform that would enable us to achieve both the *short-term* and *long-term* goals?.

2.2. Results and Discussion

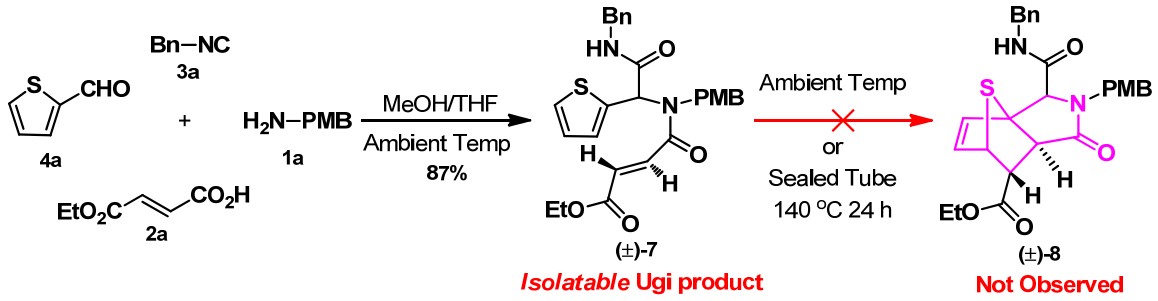
While we were planning to execute an efficient synthetic strategy for small molecule synthesis, we came across a literature which reported that the U-4CCR between *p*-methoxy benzylamine (**1**), fumaric acid monoethyl ester (**2**), bezyl isocyanide (**3**) and furan-2-aldehyde (**4**) provided a (4π +2π) Diels-Alder (DA) cycloaddition adduct **6** at ambient temperature (Scheme 23).[100] It is noteworthy that the Ugi product (±)-**5** was not isolable because of rapid intramolecular bond construction from the diene and dienophile.[100] We envisioned that the proposed olefinic acyclic intermediate could, however, be engineered to gain access to various other structural motifs. After a thorough literature survey it became evident that thiophene usually does not undergo (4π + 2π) DA cycloaddition reactions under normal conditions; it prefers to undergo (2π +2π) cycloaddition reaction.[101] In some cases where the sulfur atom of thiophene was converted to a sulfoxide or if the reaction was performed under extremely high pressure, then thiophene did provide the (4π +2π) DA cycloaddition product.[102]



Scheme 23. Furan-2-aldehyde provides Diels-Alder product at ambient temperature.

Hence, we speculated that we could isolate a thiophene-derived U-4CCR product using similar reaction substrates and conditions. To our expectation, acyclic (±)-**7** was isolated in excellent yield (**87%**) yet did not spontaneously undergo a [4π + 2π] DA

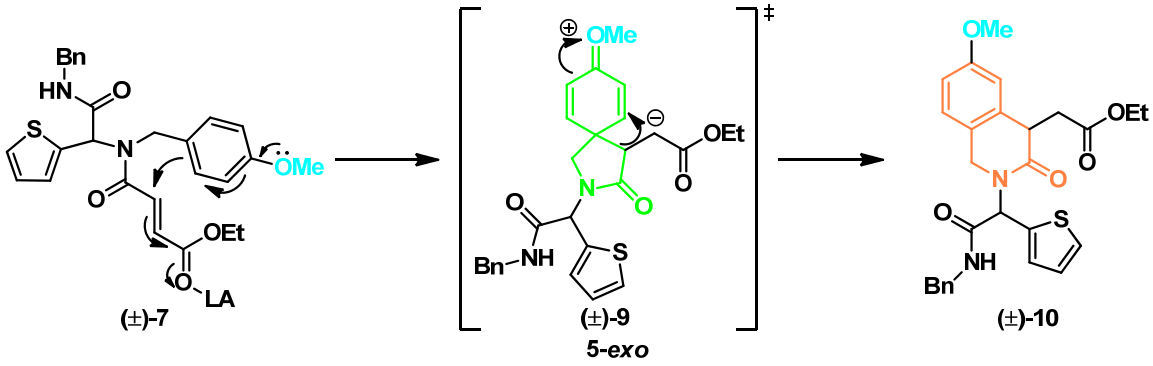
cycloaddition at ambient temperature (Scheme 24). To explain this, one must understand that although furan and thiophene obey Hückel's rule for aromaticity, in terms of reactivity in a [4π + 2π] DA cycloaddition, thiophene will undergo this type of reaction only when forced to do so with extreme heat and an immense amount of pressure. In fact, it requires, in some instances, over 120,000 psi to do so. A likely explanation for this could be that thiophene is more aromatic that furan due to large differences in LUMO energy. Furthermore, longer C-S vs C-O bond (1.73 cm vs 1.43 cm) might increase the TS energy. Even in a sealed tube, run at 140 °C, thiophene does not undergo DA cycloadditions.



Scheme 24. The U-4CCR using thiophene-2-aldehyde results in an isolatable acyclic Ugi product (**7**) at ambient temperature.

We then decided to explore the use of microwaves as a tool and observe how it would affect the reaction for new bond formation. We speculated that in presence of a suitable Lewis acid, the isolated Ugi product **7** might undergo Fridel-Craft alkylation to provide 1,4-dihydroisoquinolinone **10** via an *5-exo-trig* intermediate **9** (Scheme 25). However, when $AlCl_3$ and $FeCl_3$ were used as Lewis acid, either degradation of **7** occurred or unreacted **7** was isolated. Literature precedent revealed that a number of rate accelerated Fridel-Crafts alkylation reactions had been accomplished using microwave irradiation and an appropriate additive.[103] Unfortunately, when these literature protocols

were employed in our system, the aforementioned problems were not negated. Thus, we switched our focus to alternative possibilities.

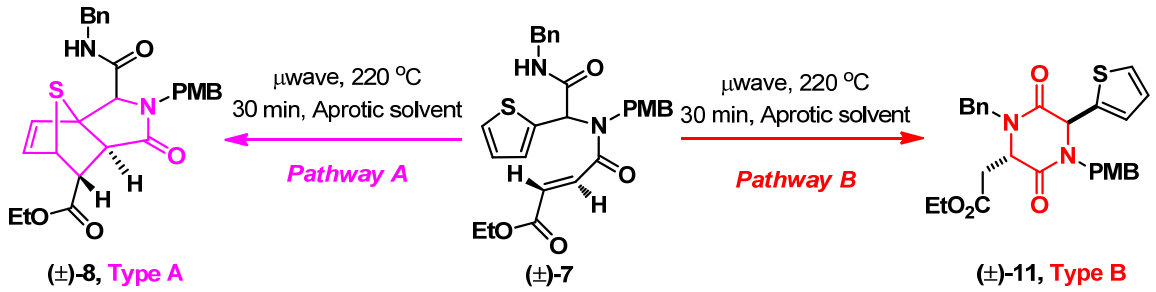


Scheme 25. Proposed synthesis of isoquinolinones under Lewis acid conditions.

2.2.1. Effect of Solvents under Microwave Irradiation

When the acyclic Ugi product (±)-**7** was dissolved in DMF without any Lewis acid additives and irradiated under microwave (CEM Discover, 300 W, 220°C, and 17 bar) for 30 min, to our delight, it provided a 9:1 diastereomeric mixture of [4π + 2π] Diels-Alder cycloaddition product (±)-**8** in 15% yield. On the other hand, when the reaction was carried out in CH_3OH under similar conditions, an intramolecular *6-exo-trig* aza-Michael reaction ensued to reveal a 1.5:1 diastereomeric mixture of a biologically validated scaffold[104] 2,5-diketopiperazine (±)-**11** in 70% yield (Scheme 26). Diastereomeric ratios were determined using ^{1}H NMR from the crude reaction mixture in $CDCl_3$. In the case of pathway B, the major diastereoisomer had a *trans* relationship between the aldehyde and acid component and the stereochemistry was confirmed by nOe studies. With these initial promising results in hand, we then decided to explore the effect(s) of different solvents that might shed more indepth insight into the reaction. As shown in Table 4, it was observed that aprotic (polar/non-polar) solvents like DMF, dichloromethane, dichloroethane favor the [4π + 2π] DA cycloaddition (pathway A) and

protic polar solvents like methanol and water favor the *6-exo-trig* aza-Michael reaction (pathway B). It is well worth noting that the two pathways ***do not*** overlap and the outcome of the reaction is completely solvent controlled. This dependency could be explained by the fact that *6-exo-trig* aza-Michael reactions are stabilized through ionic intermediates and use of protic polar solvents assist in this regard. On other hand, [4π + 2π] DA cycloaddition proceeds through non-ionic intermediates and aprotic non-polar solvents assist in the stabilization. This result is totally contrary to Breslow's report on the enhancement of the DA reaction in water.[101]



Scheme 26. Pathway selectivity of the microwave-influenced reaction.

Table 4. Effect of solvents on microwave-influenced reaction of **7**[a].

Entry	Solvent	Yield (%)[b]	
		Type A	Type B
1	DMF	15	0
2	CH_2Cl_2	20	0
3	DCE	30	0
4	MeOH	0	30
5	MeOH/H_2O	0	65
6	H_2O	0	85

[a]Microwave was equilibrated to 300 W, 220 °C, 17 bar for 30 min; [b]Isolated yield

2.2.2. Effect of Temperature, Pressure and Power

With our noted solvents for the two pathways, we then elected to screen various microwave-based temperature, pressure and power ranges to further explore the optimum condition for our observed pathways (A and B). From our data, it was observed that microwave power (W), temperature (^{o}C) and pressure (bar) have correlating relationships. For a given power setting, the temperature and pressure adjust accordingly. At lower power settings, desired temperature and pressure can not be achieved. On the other hand, at high power settings, desired temperature and pressure are achievable. In our examples, the reactions were found to be completely controlled by temperature and pressure. When the microwave power was set to 50 W, the temperature and pressure reached 110 ^{o}C and 1.5 bar respectively yet there was no conversion. Whereas at a microwave power of 100 W, the temperature and pressure were 138 ^{o}C and 4.1 bar respectively and corresponding yield was 10%. At a higher microwave power 200 W, the temperature and pressure were 160 ^{o}C and 6 bar respectively and the corresponding yield was 20%. When we had set a microwave power 250 W, the temperature and pressure were 200 ^{o}C and 15 bar respectively and corresponding yield was 70%. Finally after tuning the power, temperature and bar, a microwave setting at 300 W, 200 ^{o}C and 18 bar provided the best yield (85%) (Table 5). It must be noted that the reaction does not provide the desired product when it was thermally refluxed under similar conditions. Primarily, microwaves work on the Arrhenious equation concept and according to ideal gas law ($pV = nRT$), temperature (T) is directly proportional to pressure (P). On the other hand, according to Stefan-Boltzman Law (eq. 1) and Wein's Displacement Law of emission (eq. 2), power (W) is directly proportional to temperature with a factor of 4.

Thus, if power (W) goes down by a factor 16, temperature (^{o}C) and pressure (bar) will go down by a factor of 2.

$J = kT^4$ (J = power in Watt, k = constant) eq. 1

$J = \lambda T^4$ eq. 2

$J \propto T^4 \propto P$ eq. 3

Table 5. Optimization of μwave-influenced *6-exo-trig* aza-Michael reaction leading to **11**.

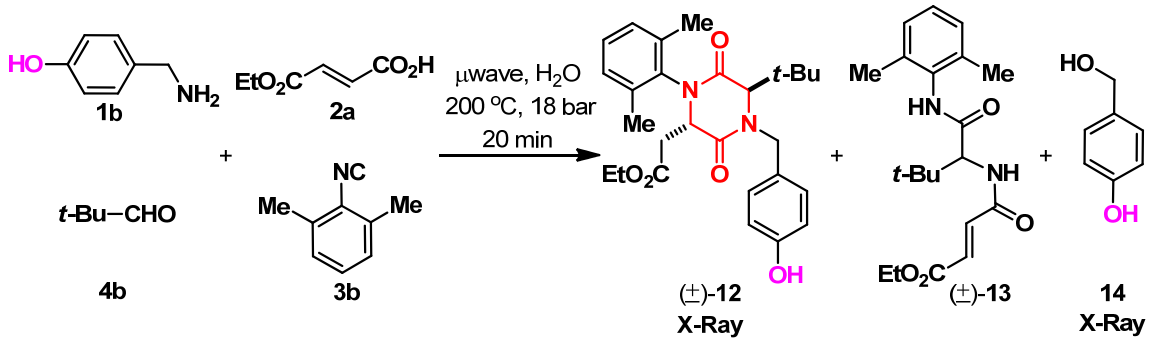
Entry	Solvent	Time (min)	Power (W)	Temp (^{o}C)	Pressure (bar)	Yield (%)
1	H_2O	30	300	100[a]	1.5	0
2	H_2O	30	300	140[a]	4	11
3	H_2O	30	300	150[a]	5	15
4	H_2O	30	300	170	9	45
5	H_2O	30	300	175[a]	9	50
6	H_2O	30	300	200[a]	18.5	85
7	H_2O	30	250	200[a]	15	70
8	H_2O	30	200	160[b]	6	20
9	H_2O	30	150	151[b]	5.1	15
10	H_2O	30	100	138[b]	4.1	10
11	H_2O	30	50	110[b]	1.5	0
12	H_2O	25	300	200[a]	18	85
13	H_2O	20	300	200[a]	18	85

[a]Observed temperature (set at 100 ^{o}C), [b]Observed temperature (set at 200 ^{o}C).

2.3.3. Scope: Effect of Substituents on Amine and Isocyanide Components

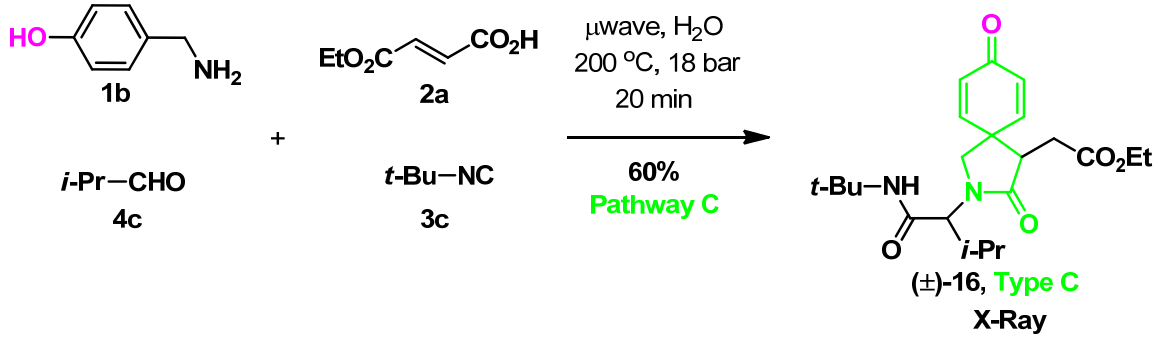
Various isocyanides and amines were also screened. We were interested in how the electronic nature of substituents on benzyl groups pertaining to the amine component affected the reaction outcome. It was observed that weak or moderately strong electron-donating groups (e.g. OMe, CH_3) or electron-withdrawing groups (e.g. Cl, CF_3) at *para*, *meta* or *ortho* position on the amine component do not have any effect on the reaction

outcome and yield (Table 10). However, when we changed the methoxy group (-OMe) with a stronger electron-donating hydroxyl group (-OH) (**1b**) on the benzyl group of the amine component and used 2,6-dimethylphenyl isocyanide (**3b**), the Ugi reaction provided 2, 5-diketopiperazine (±)-**12** as the major product and *p*-hydroxyl benzyl (PHB) alcohol as the minor product under the optimized microwave reaction conditions (Scheme 27). The stereochemistry of the 2,5-diketopiperazine (±)-**12** was determined by nOe experiment. Identity of (±)-**12** and **14**[104h] were unequivocally confirmed by X-ray structure analysis (Figure 14 and 15 respectively).



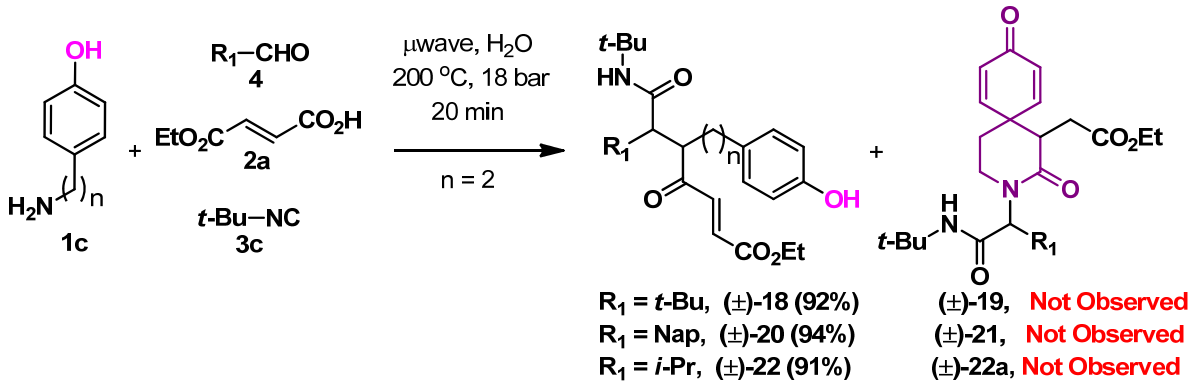
Scheme 27. Formation of *p*-hydroxy benzyl alcohol from acyclic Ugi product.

Formation of the minor product **14** was quite unexpected and we envisioned that the pathway could be further tuned by taking advantage of this side reaction. Thus, when we used *p*-hydroxy benzylamine (**1b**), isopropyl aldehyde (**4c**), *tert*-butyl isocyanide (**3c**) and monoethyl ester of fumaric acid (**2a**); the one-pot microwave reaction afforded biologically validated scaffold 2-azaspiro[4.5]deca-6,9-diene-3,8-diones[105] exclusively under the optimized conditions (Scheme 28). The structure and identification of **16** was determined by ^{1}H, ^{13}C, GDQFCOSY, GHMQC spectral analysis and unequivocally confirmed by X-ray crystal structure analysis (Figure 16).[106]



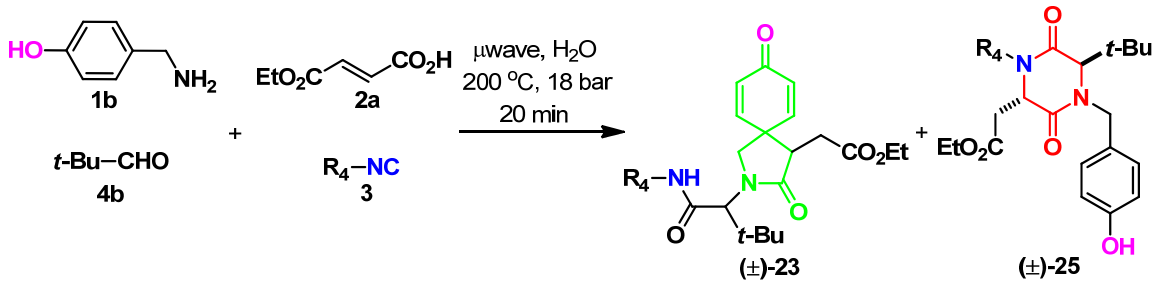
Scheme 28. Formation of 2-azaspiro[4.5]deca-6,9-diene-3,8-dione scaffold from single-pot U-4CCR using μwave irradiation.

In order to examine the effect of a spacer on the amine component in the microwave-influenced reaction, we elected to use 2-(4-hydroxyl phenyl)ethylamine (**1c**), trimethylacetaldehyde (**4b**), monoethyl ester of fumaric acid (**2a**) and *tert*-butyl isocyanide (**3c**). However, the expected product 3-azaspiro[5.5]deca-7,10-diene-2,9-dione (±)-**19** was not observed and the reaction provided only acyclic Ugi product (±)-**18** (Scheme 29). Replacement of the aldehyde coupling partner (e.g. isopropyl and 2-napthyl) did not have an effect on the reaction. Although, Baldwin's rule[107] favors a 6-*exo-trig* ring closure, however 6-*exo-trig* Michael pathway is not favored under the reaction conditions mentioned. A plausible explanation could be that the Michael-acceptor is not in close proximity.



Scheme 29. Effect of spacer on the intramolecular Michael reaction.

Table 6. Effect of substituents on isocyanide on reaction outcome.



Entry	R_4	Yield/dr[a]	
		23a-f	25a-f
1	*t*-butyl (**3c**)	60/3:1	-
2	cyclohexyl (**3d**)	82/1:1	5/20:1
3	cyclopentyl (**3e**)	81/2:1	7/18:1
4	isopropyl (**3f**)	80/2:1	10/15:1
5	benzyl (**3a**)	5/2:1	91/10:1
6	*n*-butyl (**3g**)	-	92/15:1

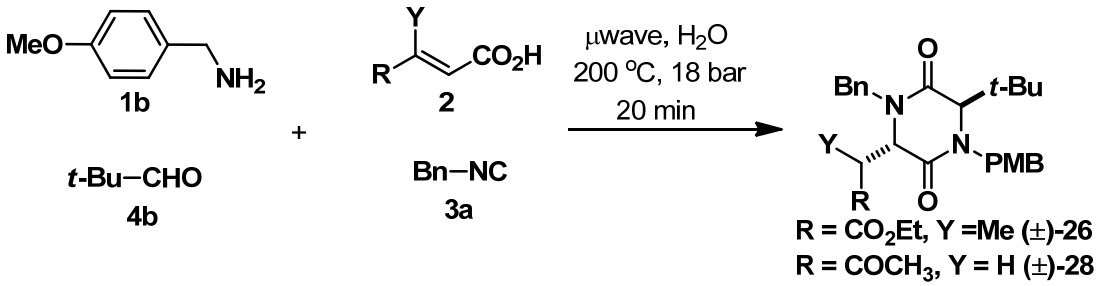
[a]Determined from ^{1}H NMR of unpurified reactions.

Next we examined the effect of substituents on isocyanides on the reaction. We chose *p*-hydroxy benzylamine (**1b**), trimethylacetaldehyde (**4b**), monoethyl ester of fumaric acid (**2a**) and different isocyanides to examine their on the reaction outcome (Table 6). Thus, when we used *tert*-butyl isocyanide (**3c**), the reaction afforded 2-azaspiro[4.5]deca-6,9-diene-3,8-dione (±)-**16** exclusively. Replacement of *t*-butyl isocyanide (**3c**) with cyclohexyl isocyanide (**3d**) in the reaction provided 82% of **23c** and 5% of **25c**. On the other hand, *n*-butyl isocyanide (**3g**) provided 92% of **25f**. The bulkyness of substituents on the isocyanides increases in the order *n*-butyl<isopropyl<cyclopentyl<cyclohexyl<*tert*-butyl and the yield of **25** decreases in the same order. In general, it has been observed that bulky isocyanides provide 2-

azaspiro[4.5]deca-6,9-diene-3,8-dione **23** as the major product and less bulky isocyanides provide 2, 5-diketopiperazine **25** as the major product.[106]

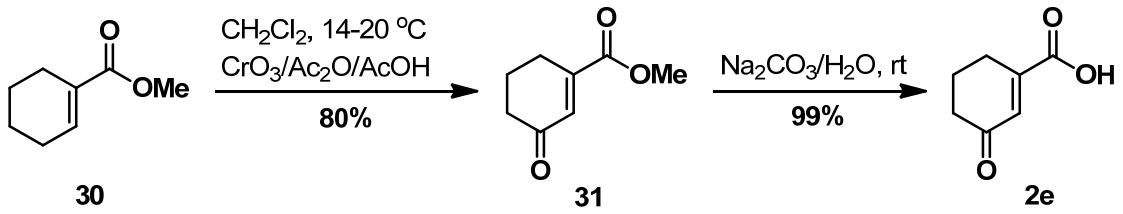
2.2.4. Scope: Effect of Substituents on Carboxylic Acid Component

Different carboxylic acid components were also screened in the coupling reaction (Scheme 30). Electron withdrawing groups (R = CO_2Et, $COCH_3$; Y = Me) provided 2, 5-diketopiperazines (Type B) in good to excellent yield. When, R = CO_2Et and Y = Me (**2c**), the expected product **26** was not observed in the ^1H NMR of the unpurified reaction mixture. A probable explanation could be that 6-*exo-trig* cyclization is not favored under this condition probably due to steric effects. However, when R = $COCH_3$ and Y = H (**2d**), the reaction provided **28** good yield (**80%**).



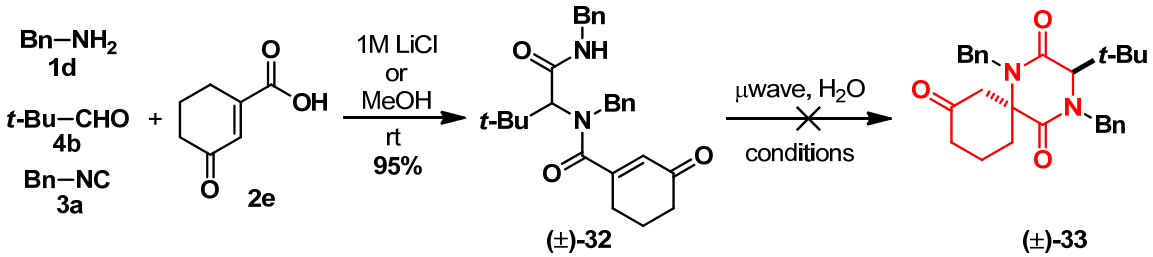
Scheme 30. Effect of substituents on carboxylic acid component of the U-4CCR.

To further examine the carboxylic acid substrate scope, 3-oxo-cyclohexene-1-carboxylic acid (**2e**) was synthesized from methyl ester of cyclohexene carboxylic acid. Allylic oxidation of **30** in the presence of CrO_3 and AcOH[108] provided methyl 3-oxo-1-cyclohexene-1-carboxylate **31** in 80% yield. Saponification of **31** with aqueous Na_2CO_3 afforded the desired 3-oxo-cyclohexene-1-carboxylic acid **2e** in quantitative yield (Scheme 31).



Scheme 31. Synthesis of 3-oxo-cyclohexene-1-carboxylic acid (**2e**).

With **2e** in hand, we examined the possibility of forming spiro-2, 5-diketopiperazine[109] and dispirocyclohexadienone. Thus, the U-4CCR of benzylamine (**1d**), trimethylacetaldehyde (**1d**), 3-oxo-cyclohexene-1-carboxylic acid (**2e**) benzyl isocyanide (**4a**) provided acyclic product (±)-**32**. Varying temperature, pressure and time were screened to find the right reaction conditions (Table 7). However, none of the conditions provided the desired spiro-2,5-diketopiperazine (±)-**33** (Scheme 32).



Scheme 32. Efforts toward the synthesis spiro-2,5-diketopiperazines (spiro-DKP).

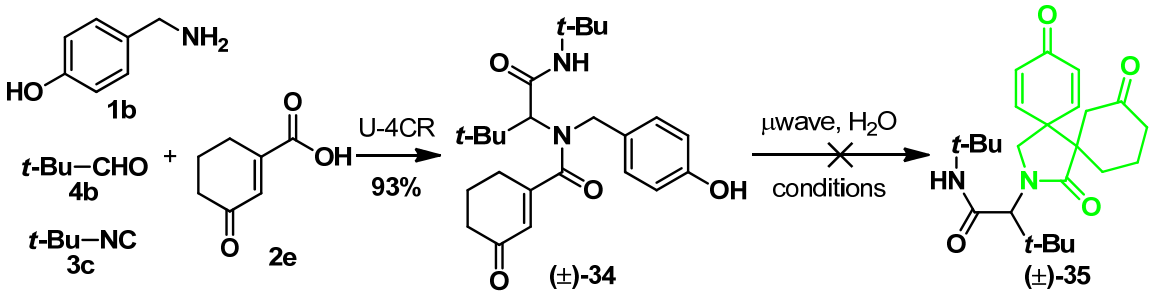
Table 7. Microwave conditions toward the synthesis of spiro-DKP.

Entry	Power (W)	Temp (°C)	Pressure (bar)	Time (min)	Yield (%) of **33**
1	300[a]	200	18	30	0
2	800[b]	200	27	35	0
3	1600[b]	215	41	65	0

[a]CEM Discover Microwave; [b]MARS Microwave

Next, we synthesized acyclic Ugi product **34** from the reaction between *p*-hydroxy benzylamine (**1b**), trimethylacetaldehyde (**4b**), 3-oxo-cyclohexene-1-carboxylic acid (**2e**) and *tert*-butyl isocyanide (**3c**) (Scheme 33). However, when the acyclic product

34 was subjected to microwave reaction conditions, the desired product **35** was not obtained using various conditions (Table 8).



Scheme 33. Efforts toward the synthesis of aza-dispirocyclohexadienone.

Table 8. Microwave conditions for the synthesis of aza-dispirocyclohexadienone (±)-**35**[a].

Entry	Power (W)	Temp (^{o}C)	Pressure (bar)	Time (min)	Yield (%) of 35
1	300	192	18	30	0
2	300	192	18	60	0
3	300	198	18	75	0
4	300	210	18.5	90	0
5	300	220	19	120	0

[a]CEM Discover Microwave

To invoke a S_N2' or S_N2 type pathway that will provide 2, 5-diketopiperazines and the method can be applied for the synthesis of billion (>10) dollar drug Cialis and its derivatives for ED treatment (Figure 13, **36**)[110], few carboxylic acid components were also screened initially. Thus, U-4CCR of *p*-methoxy benzylamine (**1a**), trimethylacetaldehyde (**4b**), (*E*)-4-bromo-2-butenoic acid (**2f**) and benzyl isocyanide (**3a**) provided (±)-**37a** and that of *p*-methoxy benzylamine (**1a**), trimethylacetaldehyde (**4b**), 2-iodoacetic acid (**2g**) and benzyl isocyanide (**3b**) provided (±)-**37b**. However, none of the microwave conditions (Table 9) provided the desired products (±)-**38** and (±)-**39**; instead displacement acyclic products (±)-**40** (R = 3-hydroxy propene), (±)-**41** (R = 3-

methoxypropene), (±)-**42** (R = hydroxyl) and (±)-**43** (R = methoxy) were obtained in protic solvents (e.g. H_2O, MeOH) whereas in aprotic solvent (e.g. CH_2Cl_2) only acyclic products were recovered (Scheme 34).

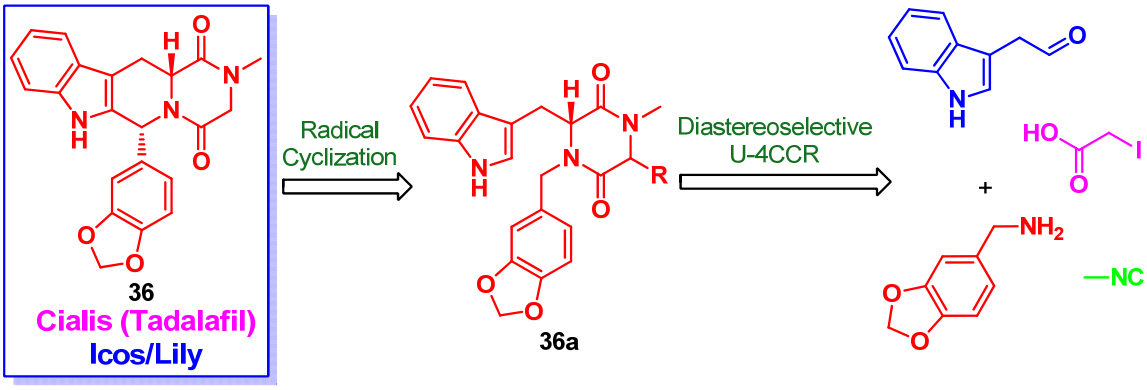
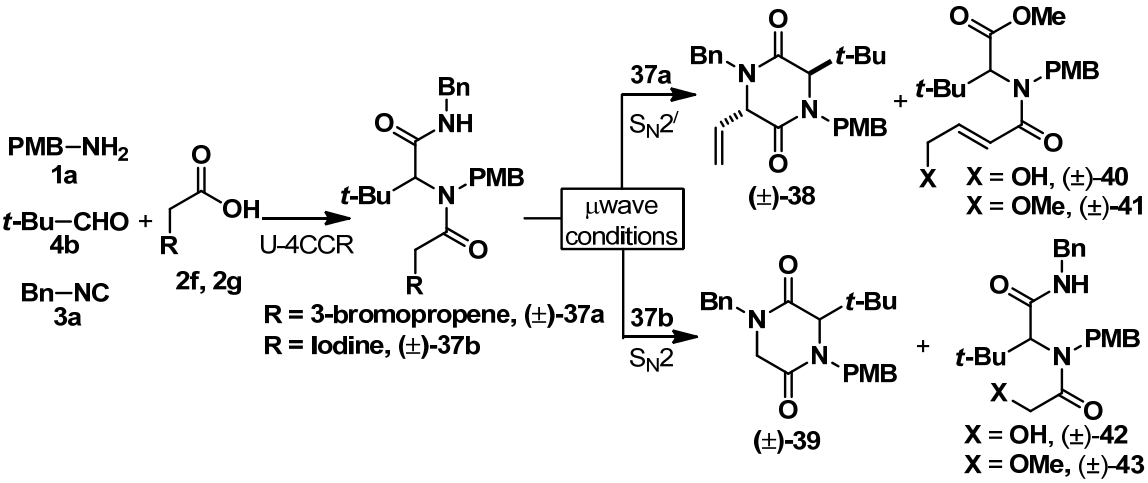


Figure 13. Retrosynthetic analysis for the ED treatment drug Cialis.



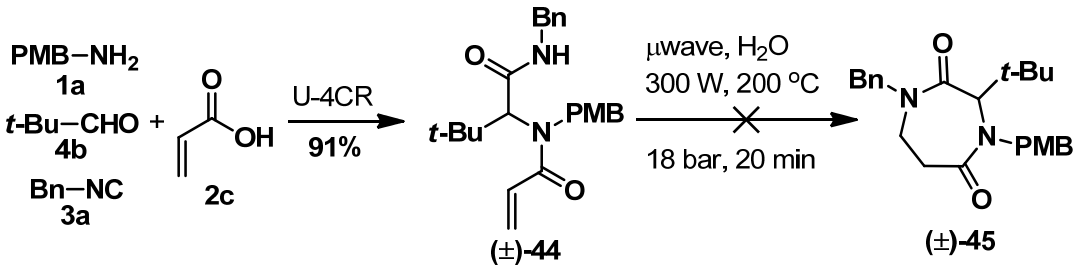
Scheme 34. S_N2 and S_N2' pathways for the synthesis of 2, 5-diketopiperazines.

Table 9. Microwave reaction conditions for S_N2 and S_N2' pathway.[a]

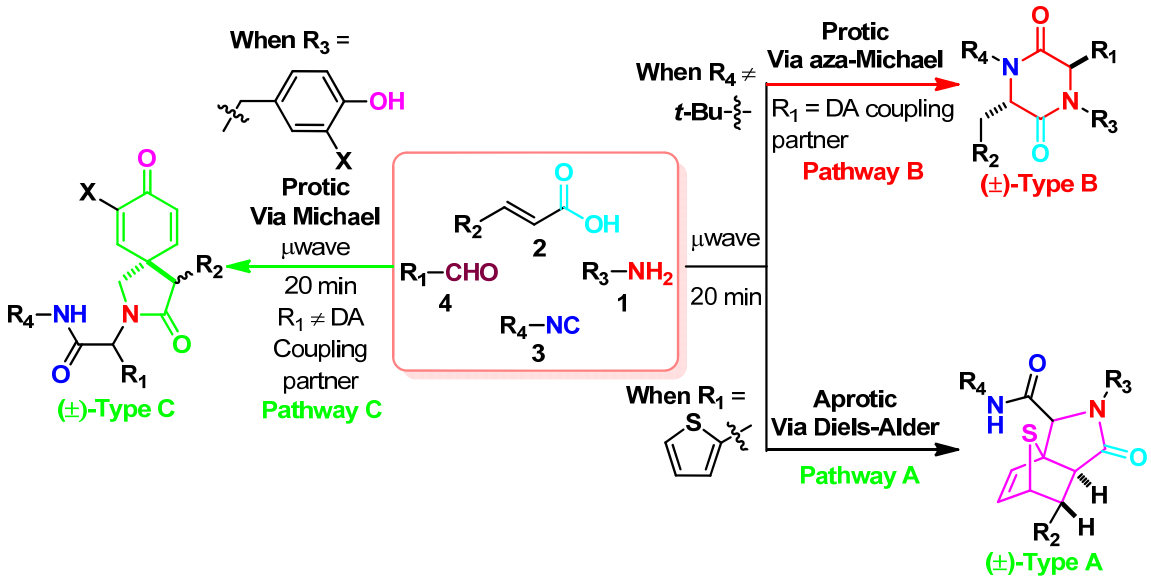
Entry	Solvent	Power (W)	Temp (°C)	Pressure (bar)	Time (min)	Yield (%)					
						38	39	40	41	42	43
1	H_2O	300	200	18	25	0	0	95	0	96	0
2	MeOH	300	210	18	30	0	0	0	94	0	95
3	CH_2Cl_2	300	170	15	30	0	0	0	0	0	0

[a]CEM Discover Microwave.

In order to examine the possibility of a 7-*endo-trig* aza-Michael pathway, acyclic Ugi product **44** was synthesized from the U-4CCR between *p*-methoxy benzylamine (**1a**), trimethyl acetaldehyde (**4d**), acrylic acid (**2c**) and benzyl isocyanide (**3a**). However, the desired diazepine product **45** was not obtained using various conditions (Scheme 35). A probable explanation could be that the Michael acceptor is either not in close proximity or it is deactivated due to lone pair delocalization from nitrogen onto the amide carbonyl group.



Scheme 35. Approach toward 7-*endo-trig* aza-Michael pathway.



Scheme 36. General molecular diversity from a single-pot microwave reaction.

Table 10. Substrate scope of microwave-influenced syntheses of small molecules.

Entry	R_1	R_2	R_3	R_4	Compd type/%yield[a]/dr[b]		
					H_2O	CH_2Cl_2	dr
1	2-thienyl (**4a**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	See entry 2	A (**8**)/25	10:1
2	2-thieny l(**4a**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	**B** (**11**)/**83**	See entry 1	7:1
3	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	2,6-dimethylphenyl (**3b**)	**B** (**12**)/85	acyclic (**15**/91	9:1
4	isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	*tert*-butyl (**3c**)	**C** (**16**)/60	acyclic (**17**)/92	3:1
5	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	2-(4-hydroxyphenyl)ethyl (**1c**)	*tert*-butyl (**3c**)	Acyclic (**18**)/90		
6	piperonyl (**4d**)	Ethoxycarbonyl (**2a**)	2-(4-hydroxyphenyl)ethyl (**1c**)	*tert*-butyl (**3c**)	Acyclic (**20**)/91		
7	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	2-(4-hydroxyphenyl)ethyl (**1c**)	*tert*-butyl (**3c**)	Acyclic (**22**)/91		
8	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	*tert*-butyl (**3c**)	**C** (**23a**)/60	acyclic (**24a**)/85	1:1
9	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	Cyclohexyl (**3d**)	**C (23b)/82**	acyclic (**24b**)/89	1:1
10	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	Cyclopentyl (**3e**)	**C (23c)/81**	acyclic (**24c**)/90	2:1
11	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	Isopropyl (**3f**)	**C (23d)/80**	Acyclic (**24d**)/90	2:1
12	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	Benzyl (**3a**)	**C (23e)/5**	acyclic (**24e**)/93	2:1
13	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	*n*-butyl (**3g**)	**B** (**25f**)/**92**	acyclic (**24f**)/91	15:1
14	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	B (**27**/94)	acyclic (**27b**/92)	10:1
15	*tert*-butyl (**4b**)	Methylcarbonyl (2b)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	**B (28)/85**	acyclic (29)/92	1:1
16	*tert*-butyl (**4b**)	3-oxocyclohexene (**2c**)	Benzyl (**1d**)	Benzyl (**3a**)	Acyclic (**32**)/89		
17	*tert*-butyl (**4b**)	3-oxocyclohexene (**2c**)	4-hydroxybenzyl (**1b**)	*tert*-butyl (**3c**)	Acyclic (**34**)/87		
18	*tert*-butyl (**4b**)	3-bromopropene (**2d**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	Acyclic (**37a**, **40**, **41**)/93, 95		
19	*tert*-butyl (**4b**)	Iodine (**2e**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	Acyclic (**37b**, **42**, **43**)/91, 96		
20	*tert*-butyl (**4b**)	Hydrogen (**2f**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	Acyclic (**44**)/90		
21	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	Benzyl (**1d**)	Benzyl (**3a**)	**B** (**46**)/96	acyclic (**47**)/97	11:1
22	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	Cyclohexylmethyl (**1e**)	Benzyl (**3a**)	**B** (**48**)/88	Acyclic (**49**)/92	20:1
23	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	Benzyl (**1d**)	4-methoxyphenyl (**3h**)	**B** (**50**)/85	Acyclic (**51**)/90	6:1
24	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	4-methoxyphenyl (**3h**)	**B** (**52**)/81	Acyclic (**53**)/82	7:1
25	*tert*-butyl (**4b**)	Benzoyl (**2g**)	Benzyl (**1d**)	Benzyl (**3a**)	**B** (**54**)/98	Acyclic (**55**)/98	2:1
26	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	*n*-butyl (**3g**)	**B** (**56**)/92	Acyclic (**57**)/90	15:1
27	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	Benzyl (**3a**)	**B** (**25e**)/83	See entry 12	12:1
28	2-thienyl (**4a**)	Ethoxycarbonyl (**2a**)	3.5-dimethoxybenzyl (**1e**)	Benzyl (**3a**)	**B** (**58**)/87	See entry 32	7:1
29	2-thienyl (**4a**)	Benzoyl (**2g**)	4-bromophenyl (**1f**)	*n*-butyl (**3g**)	**B** (**59**)/83	See entry 33	7:1
30	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxy-3-methoxybenzyl (**1g**)	*tert*-butyl (**3c**)	**C** (**60**)/60	Acyclic (**61**)/80	3:1
31	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzylmethyl (**1h**)	*tert*-butyl (**3c**)	**C** (**62**)/95	Acyclic (**63**)/96	3:1
32	2-thienyl (**4a**)	Ethoxycarbonyl (**2a**)	3.5-dimethoxybenzyl (**1e**)	Benzyl (**3a**)	See entry 28	**A** (**64**)/23	8:1
33	2-thienyl (**4a**)	Ethoxycarbonyl (**2a**)	4-Bromophenyl (**1f**)	Benzyl (**3a**)	See entry 29	**A** (**65**)/25	10:1
34	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	*tert*-butyl (**3c**)	Acyclic (**66**)/92		
35	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	3,4-dimethoxybenzyl (**1h**)	*tert*-butyl (**3c**)	B (**67**)/93	Acyclic (**67a**)/95	12:1
36	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	Benzyl (**1d**)	*tert*-butyl (**3c**)	Acyclic (68)/90		
37	Cyclopropyl (**4e**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	**B** (**69**)/88	Acyclic (**70**)/90	4:1
38	Phenyl (**4f**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	**B** (**71**)/90	Acyclic (**72**)/93	6:1
39	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Cyclohexyl (**3d**)	Acyclic (**73**)/88		
40	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-chlorobenzyl (**1i**)	*tert*-butyl (**3c**)	Acyclic (**74**)/90		
41	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-trifluoromethylbenzyl (**1j**)	*tert*-butyl (**3c**)	Acyclic (**75**)/93		
42	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	3,5-dimethoxybenzyl (**1e**)	*tert*-butyl (**3c**)	Acyclic (**76**)/92		
43	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	3,4-methylenedioxybenzyl (**1k**)	*tert*-butyl (**3c**)	Acyclic (**77**)/91		
44	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-methylthiobenzyl (**1l**)	*tert*-butyl (**3c**)	Acyclic (**78**)/90		
45	2-thienyl (**4a**)	Hydrogen (**2e**f	4-methoxybenzyl (**1a**)	*tert*-butyl (**3c**)	Acyclic (**79**)/91		
46	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-methoxyphenylethyl (**1m**)	*tert*-butyl (**3c**)	Acyclic (**80**)/92		
47	2-thienyl (**4a**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	*tert*-butyl (**3c**)	C (**81**)/89	–	
48	Isopropyl (**4c**)	Hydrogen (**2f**)	4-methoxybenzyl (**1a**)	*tert*-butyl (**3c**)	Acyclic (**82**)/90		
49	2-thienyl (**4a**)	Ethoxycarbonyl (**2a**)	3-methoxybenzyl (**1o**)	Benzyl (**3c**)	B (**83**)/93	–	5:1
50	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	1-(4-methoxyphenyl)ethyl (**1p**)	*tert*-butyl (**3c**)	Acyclic (**84**)/89		
51	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	3-hydroxybenzyl (**1q**)	*tert*-butyl (**3c**)	Acyclic (**85**)/93		
52	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-hydroxybenzyl (**1b**)	Benzyl (**3a**)	**B** (**86**)/89	Acyclic (**87**)/92	11:1
53	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Cyclohexyl (**3d**)	Acyclic (**88**)/91		
54	Cyclopentyl (**4g**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	**B** (**89**)/85	Acyclic (**90**)/91	10:1
55	Cyclohexyl (**4h**)	Ethoxycarbonyl (**2a**)	4-methoxybenzyl (**1a**)	Benzyl (**3a**)	**B** (**91**)/83	Acyclic (**92**)/90	7:1
56	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	1-(4-methoxyphenyl)ethyl (**1p**)	Benzyl (**3a**)	**B** (**93**)/93	Acyclic (**94**)/93	10:1
57	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	3,4-methylenedioxybenzyl (**1k**)	Benzyl (**3a**)	**B** (**95**)/91	Acyclic (**96**)/92	9:1
58	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	4-methylthiobenzyl (**1l**)	Benzyl (**3a**)	**B** (**97**)/90	Acyclic (**98**)/92	11:1
59	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	3-hydroxybenzyl (**1q**)	Benzyl (**3a**)	**B** (**99**)/92	Acyclic (**100**)/93	13:1
60	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	6-methoxynapthylmethyl (**1r**)	Benzyl (**3a**)	**B** (**101**)/93	Acyclic (**102**)/95	8:1
61	2-napthyl (**4d**)	Ethoxycarbonyl (**2a**)	4-methoxyoxylbenzyl (**1a**)	Benzyl (**3a**)	B (**103**)/91	Acyclic (**103a**)/90	35:1
62	*tert*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	2-(4-hydroxyl phenyl)ethyl (**1s**)	*tert*-butyl (**3c**)	Acyclic (**104**)/92		
63	Isopropyl (**4c**)	Ethoxycarbonyl (**2a**)	2-(4-hydroxyl phenyl)ethyl (**1s**)	*tert*-butyl (**3c**)	Acyclic (**105**)/90		

[a]Isolated. [b]Determined from the ^{1}H NMR of unpurified reaction mixture.

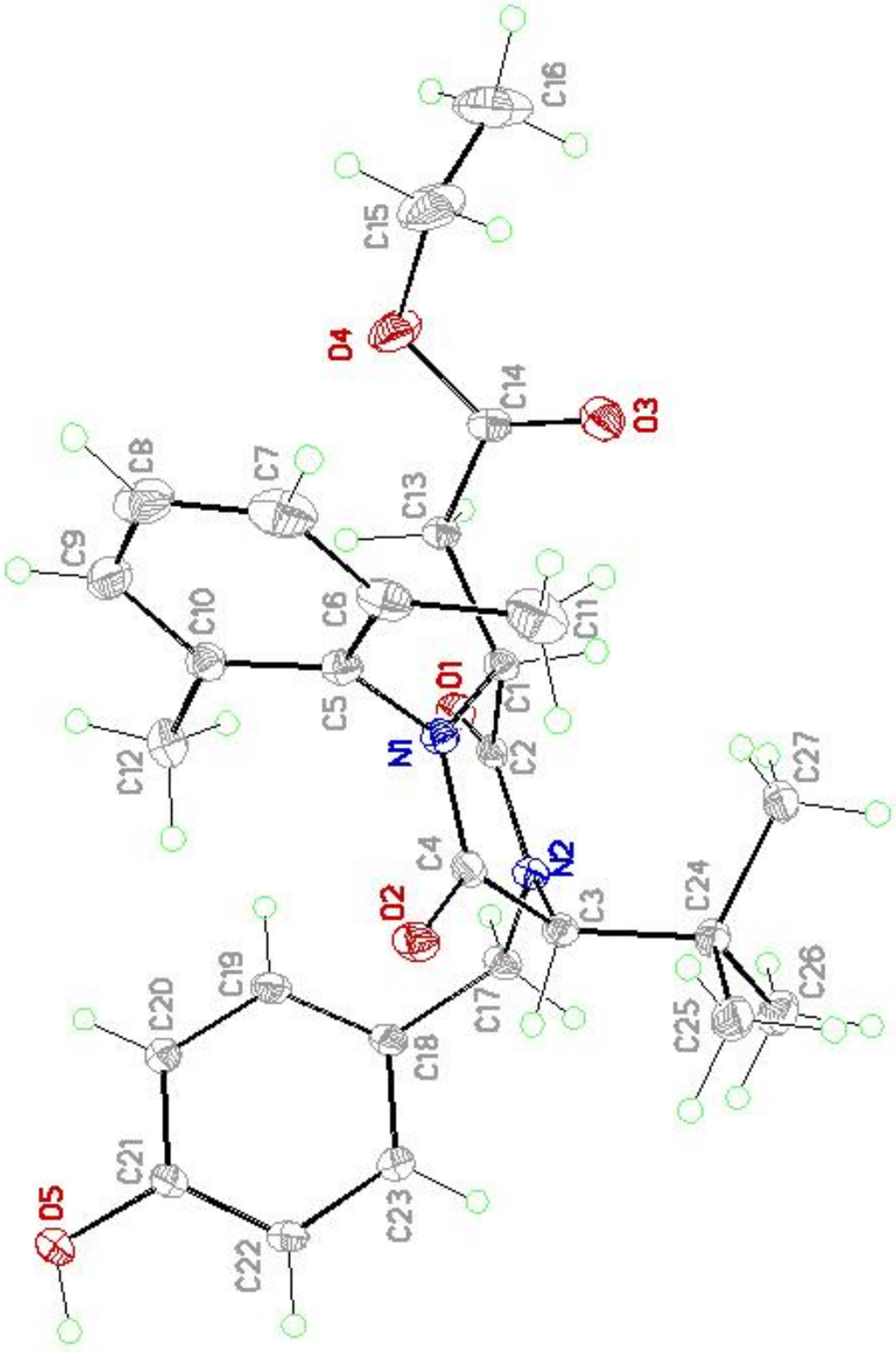


Figure 14. X-ray crystal structure of major diastereomer of diketopiperazine (±)-**12**.

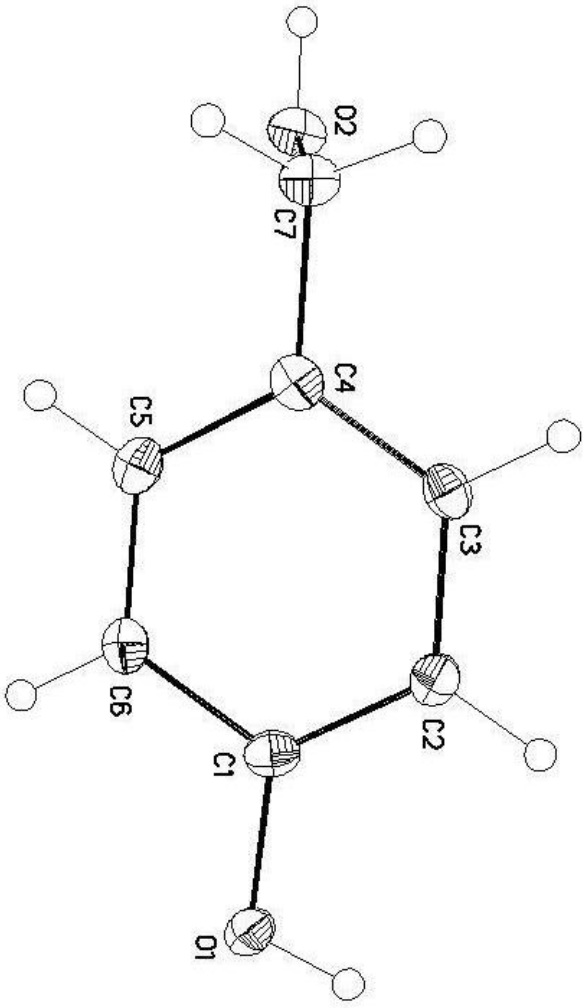


Figure 15. X-ray crystal structure of 4-hydroxybenzyl alcohol (**14**) from μwave reaction.

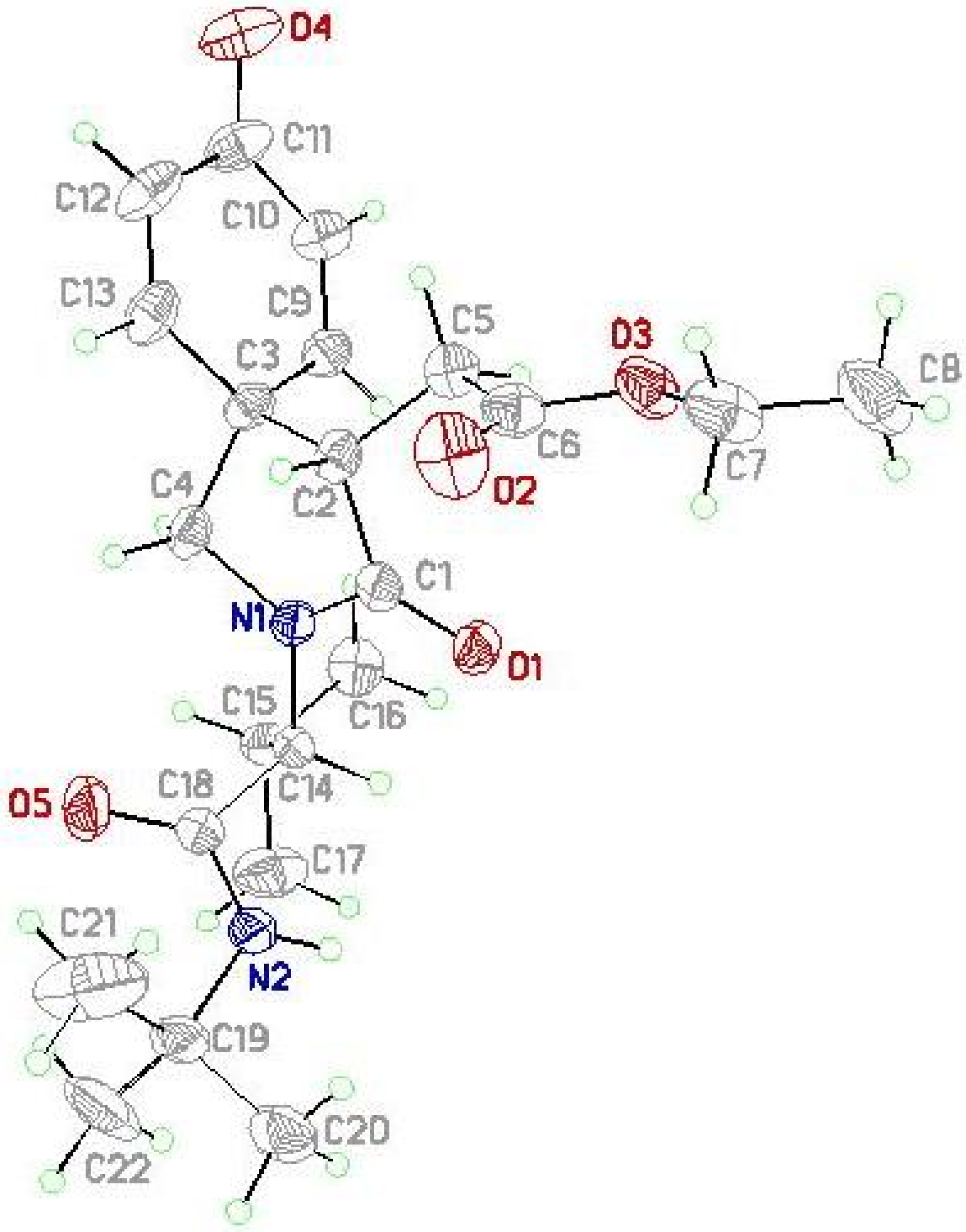
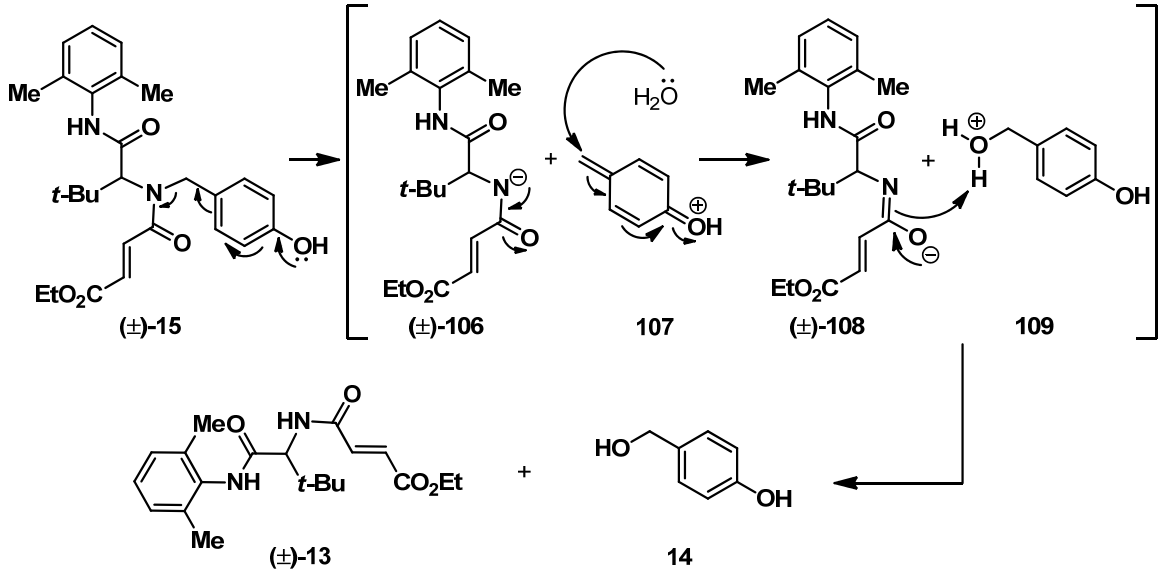


Figure 16. X-ray crystal structure of 2-azaspiro[4.5]deca-6,9-diene-3,8-dione (±)-**16**.

2.2.5. Mechanism of the Microwave-Influenced One-Pot Reaction

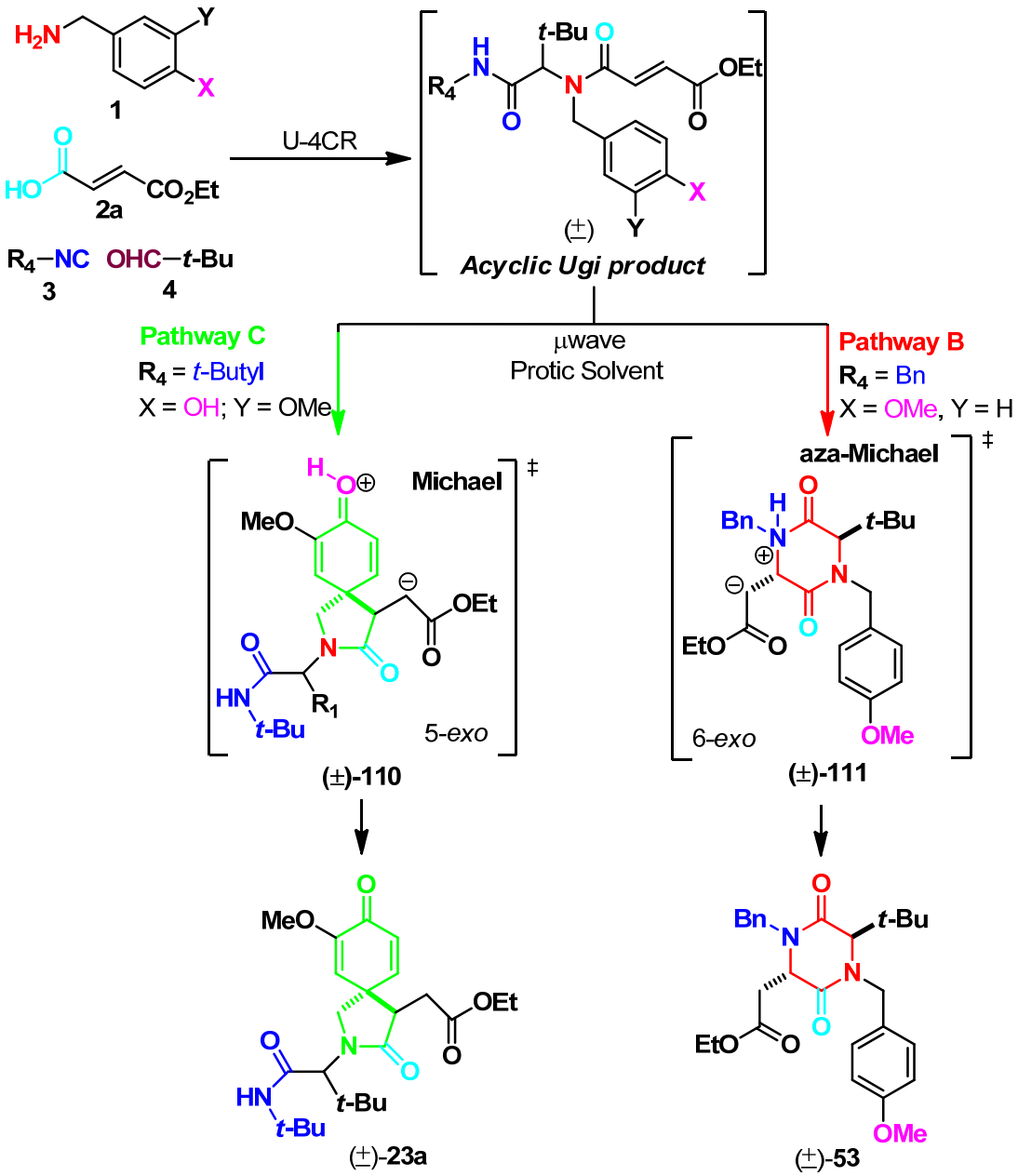
The substrate scope of the microwave-influenced one-pot reaction provided insight into the mechanism of different pathways. At very high temperatures (180-220 ^{o}C), lone pairs on the hydroxyl group of *p*-hyrdoxy benzylamine become activated and formed the acyclic intermediate **106** along with the quinonemethide intermediate **107**. Nucleophilic attack by water on the quinonemethide intermediate (**107**) formed the phenolic intermediate **109** which finally provided **14** (Scheme 37).



Scheme 37. Mechanism of formation of **14** from acyclic U-4CCR product **15** under μwave irradiation.

When $R_4 \neq$ *t*-Bu (e.g. Bn), 2, 5-diketopiperazines arose from a 6-*exo*-*trig* aza-Michael reaction forming a zwitterionic intermediate (±)-**111** (Scheme 38) which is believed to be stabilized by hydrogen bonding in water and provided 2, 5-diketopiperazine (±)-**53**. When R_4 = *tert*-butyl (**3c**), the reaction does not provide 2, 5-diketopiperazines, instead it undergoes a 5-*exo*-*trig* Michael reaction to form zwitterionic

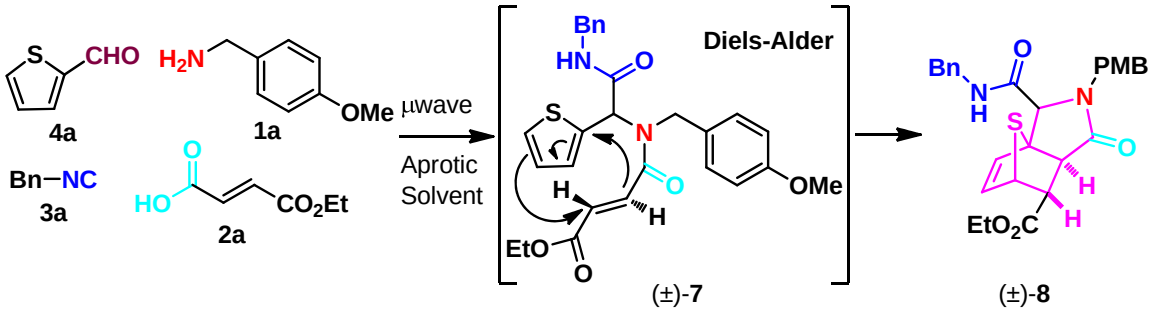
intermediate (±)-**110** which is believed to be stabilized by hydrogen bonding in water to provide 2-azaspiro[4.5]deca-6,9-diene-3,8-dione (±)-**57**.



Scheme 38. Mechanism of Microwave-influenced Michael and aza-Michael reaction.

We argued that steric effects of the substituents (R_4), in the transition state of the reaction, leads to pathway C and this is evident from the trend of yields referring to Type-B products (Table 6). When R_4 = Bn (**3a**) and R_3 = PHB (**1b**), the reaction provides 2, 5-

diketopiperazine; whereas when R_4 = *tert*-butyl (**3c**) and R_3 = PHB (**1b**), the reaction provides 2-azaspiro[4.5]deca-6,9-diene-3,8-dione. This result indicates that the 6-*exo-trig* aza-Michael reaction process is faster and preferred over the 5-*exo-trig* Michael process; likely due to the fact that during a 5-*exo-trig* Michael process there is loss of aromaticity which requires a higher energy of activation.



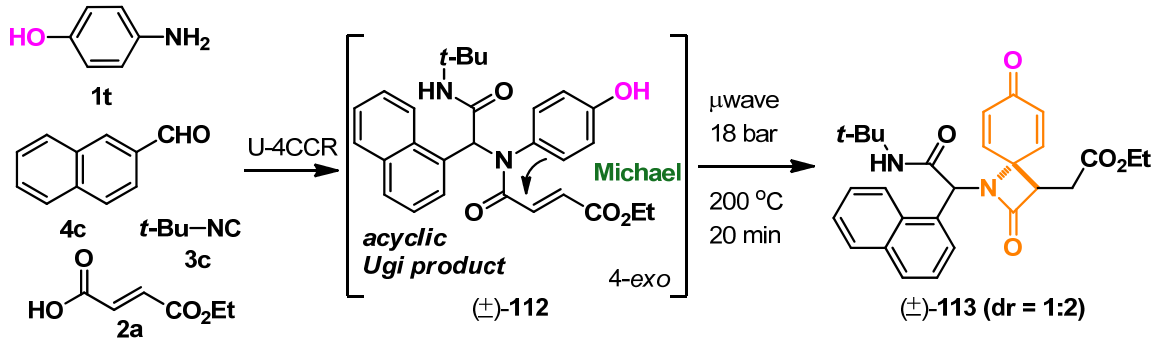
Scheme 39. Mechanism of Diels-Alder reaction leading tricyclic lactam (±)-**8**.

2.3.6. Extension Toward the Synthesis of Spiro-β-Lactams

Apart from being antibacterial agents[111], β-lactams have been found to be very useful synthons for the preparation of a variety of molecules of biological and medicinal interest.[112] In particular, the spiro β-lactams have become the center of attention among the scientific community as they can behave as β-turn mimetics[113] and are precursor of α,α-disubstituted β-amino acids.[114] In addition, the spirocyclic β-lactam motif is also present in the chartellin family of marine natural products[115] that are known to have a wide variety of biological activity.[116]

Although, to date, there is no precedence of spiro-β-lactam formation under microwave irradiation, we anticipated that *p*-hydroxy aniline (**1t**) might have similar reactivity like *p*-hydroxyl benzylamine (**1b**) that would undergo a 4-*exo-trig* Michael process. Thus *p*-hydroxyl aniline, 2-napthaldehyde (**4c**), monoethyl fumarate (**2a**) and *tert*-butyl isocyanide (**3b**) under the microwave irradiation (300 W, 200 ^{o}C,18 bar, 20

min) provided spiro-β-lactam (±)-**113** in about **20%** yield (Scheme 40) which was proved to be inseparable from the acyclic U-4CCR **112**. Further optimization of reaction conditions might provide higher yields. By employing substituted *p*-hydroxy aniline, different aldehydes, acids and other bulky isocyanides, a library of similar types of spiro-β-lactam can be generated to screen against various biological events.



Scheme 40. Synthesis of spiro β-lactam *via* microwave irradiation.

2.2.7. Extension Toward the Synthesis of 1,4-Benzodiazepine-3-Ones For Anti-Cancer Therapy and Anti-Depressants

Benzodiazepines (BDZs) are psychoactive drugs whose chemical structure is the fusion of a benzene ring and a diazepine ring. The first BDZ was discovered by Leo Sternbach of the Hoffmann La Roche Company and was marketed as Librium (chlordiazepoxide, **114**, Figure 17).[117] Over the past decade, BDZ have attracted a considerable interest among the scientific community as well as pharmaceutical companies due to their wide spread biological activities e.g. hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, muscle relaxant, amnesic, sedative, fibrinogen receptor antagonist, anticancer.[118, 119, 120, 121, 122] As a result a number of BDZ drugs have been marketed by many pharmaceutical companies (Figure 17). In recent years, several synthetic approaches toward 1,4-benzodiazepin-3-ones have been reported including a

CuI-catalyzed Ullmann aryl amination,[123] addition/elimination nucleophilic substitution of primary or secondary amines,[124] and retro-Michael/amidation,[125] and an intramolecular 1,3-dipolar cycloaddition.[126] However, a majority of these synthesis are lengthy and require costly reagents. Although, these reported methods can provide substrate diversity, they do not provide regiochemical substitution on the diazepine ring.

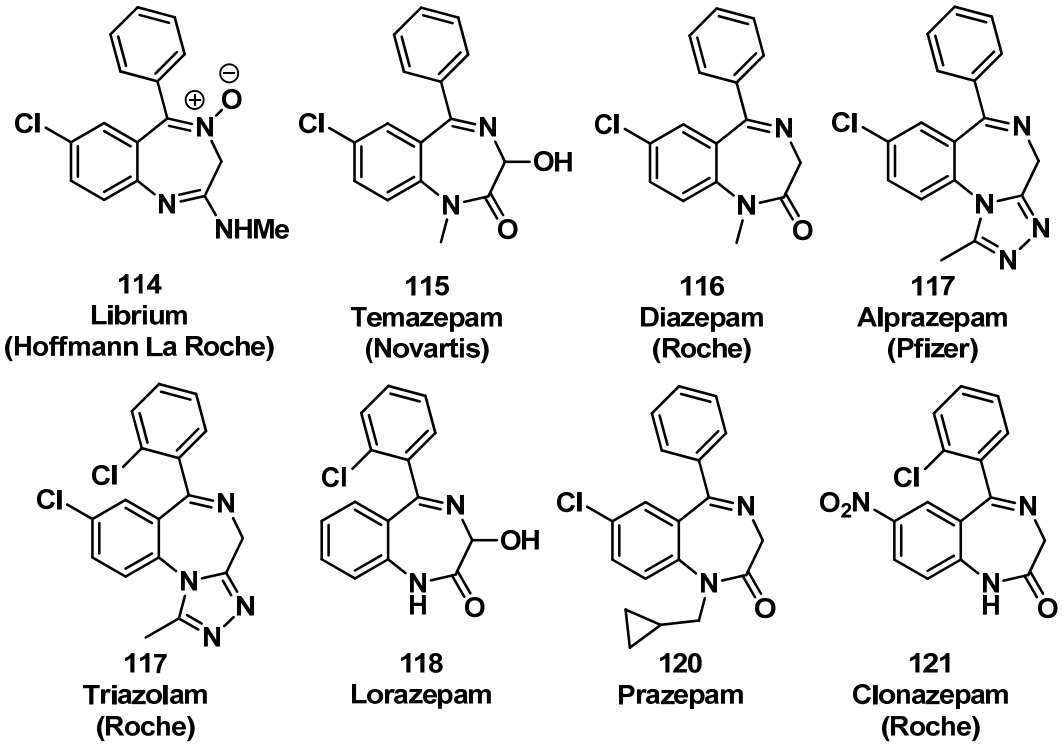


Figure 17. Commercialized BDZ drugs.

It has been well established that BDZs increase the efficiency of gamma amino butyric acid (GABA) – a natural brain neurotransmitter. The excitability of neurons thus decreases. Consequently, this phenomenon reduces the ability of neurons to communicate with each other and renders a calming effect on normal brain functions. The excitation of neurons is controlled by the binding of GABA to the protein complex $GABA_A$ receptor which is located in the synapses of neurons.[127] The heteromeric

$GABA_A$ receptor is composed of five subunits, most commonly two α units, two β units and one γ ($\alpha_2\beta_2\gamma$) unit. All $GABA_A$ receptors contain two binding sites for GABA located at the interface of α and β subunits; one binding site for BDZs located at the interface of α and γ subunits; and a center chloride ion channel that allows transportation of chlorides ions across the neuronal cell membranes (Figure 18). The binding of BDZs at the interface of α and γ subunits requires the presence of histidine amino acid residue in α subunits. Thus, BDZs do not have affinity toward arginine containing α_4 and α_6 subunits. Binding of BDZs to the BDZ-binding site promotes binding of GABA. This results in an increased conduction of chloride ions across the neuronal cell membranes and raises the membrane potential of the neuron itself. Consequently, the process inhibits neuronal firing. Hence, activation of GABA binding to the $GABA_A$ receptor by BDZs may provide distinct pharmacological events that might allow to develop new BDZs as therapeutic drug.[128, 129]

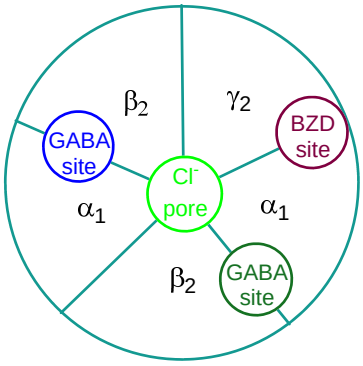
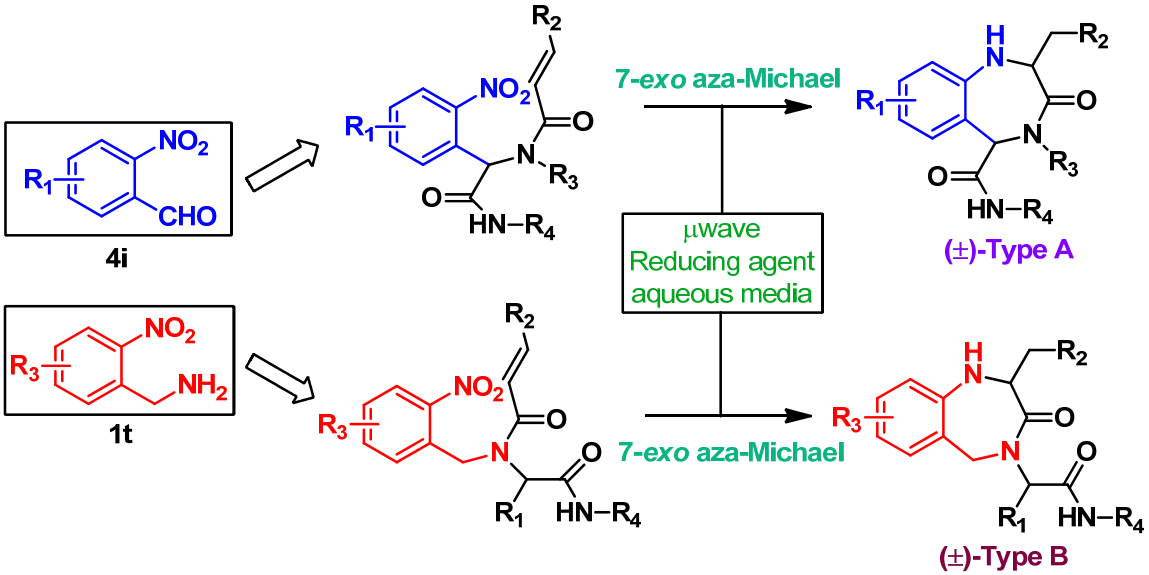


Figure 18. A schematic representation of the $(\alpha1)_2(\beta2)_2(\gamma2)_2$ $GABA_A$ receptor complex.

We became interested in 1,4-BDZ-3-ones primarily because in recent years they have found to be useful adjuncts to cancer chemotherapy[122b] and many commercialized BDZ drugs have severe side-effect. Moreover, recently 1,4-BDZ-3-ones have been

reported to be fibrinogen receptor antagonist.[118] Thus, we envisioned that 1, 4-benzodiazepin-3-ones could be synthesized utilizing the U-4CCR in conjunction with μwave irradiation to rapidly access differentially substituted motifs in a one-pot[130] protocol utilizing environmentally benign reagents. We speculated that use of *o*-nitrobenzylamine and *o*-nitrobenzaldehyde in the U-4CCR could provide acyclic products that could undergo tandem reduction and 7-*exo* aza-Michael cyclization in presence of a suitable catalyst to provide differentially substituted 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones (Scheme 41).

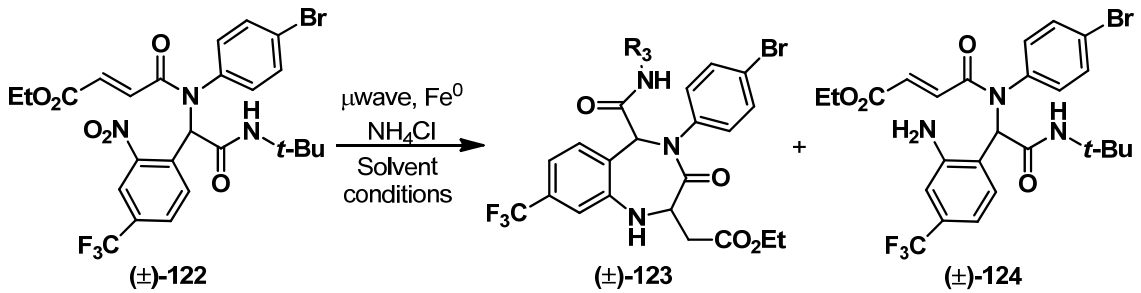


Scheme 41. Proposed synthetic route for 1,4-benzodiazepin-3-ones.

Thus, we chose 2-nitro-4-(trifluromethyl)phenyl (**4i**), *p*-bromoaniline (**1f**), fumaric acid monotheyl ester (**2a**) and *tert*-butyl isocyanide (**3c**) to synthesize the acyclic Ugi product (±)-**122** and isolated the compounds according to Pirrung's method.[131] The acyclic product was subjected to reduction conditions and it was observed that benzyl-based substrates did not fair well under hydrogenolysis conditions with palladium or platinum. Although tin (II) chloride worked reasonably well for the aryl nitro reduction,

we elected to use the two electron reducing conditions of Fe (0)[132] and NH_4Cl in an aqueous media due to its mild nature and the fact that iron has a high functional group tolerance.[133]

Table 11. 7-*exo-trig* aza-Michael cyclization yielding C2, N4, C5 substitution of 1,4-BDZ-3-ones.



(±)-122 (±)-123 (±)-124

Entry	Conditions	% Yield	
		123	**124**
1	rt, Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 48 h	0	0
2	140 $^oC^a$, Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 5 h	$<1^c$	$>98^c$
3	140 $^oC^a$, Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 24 h	$<1^c$	$>98^c$
4	Sealed tube, 140 $^oC^a$, Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 4 h	$<1^{c,d}$	$>98^c$
5	μwave, 140 $^oC^b$, Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 1h	70^e	30^e
6	μwave, 140 $^oC^b$, Fe/NH_4Cl (15:1), EtOH/H_2O (4:1), 1h	70^e	30^e
7	μwave, 140 $^oC^b$, Fe/NH_4Cl (10:1), EtOH/H_2O (3:1), 1h	70^e	30^e
8	μwave, 150 $^oC^b$, Fe/NH_4Cl (10:1), EtOH/H_2O (3:1), 45 min	75^e	25^e

[a] Denotes oil bath temperature. [b]Microwave equilibrated to 300 W, 10 bar. [c] Determined by ^1H NMR. [d] At temperature exceeding 200 ^oC, <10% product observed. [e] Isolated.

Different temperatures and solvent conditions were screened to find the optimum reaction yield. Stirring the acyclic product (±)-**122** in a 5:1 mixture of ethanol and water in the presence of Fe/NH_4Cl (20:1 mol ratio) did not provide any product. The reaction mixture was heated at 140 ^oC in an silicone-based oil bath for 5-24 h and only ~1%

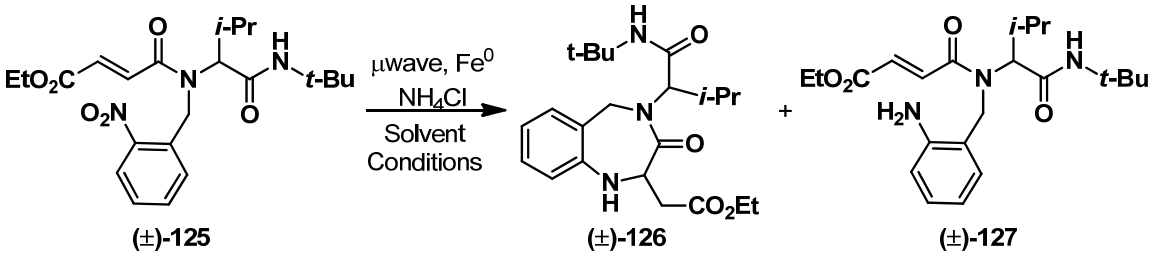
conversion was observed by GC-MS and ^{1}H NMR. Heating the same reaction mixture in a sealed tube under similar conditions did not provide a better result. However, when a solution of **122** in a 5:1 mixture of ethanol and water in presence of Fe/NH_4Cl (20:1 mol ratio) was irradiated at a microwave setting of 300 W, 180 ^oC, 18 bar, 60 min, the desired product (±)-**123** was obtained in about 60% yield. Further optimization of solvent (3:1), catalyst loading (10:1 mol ratio) temperature (150 ^oC), pressure (10 bar) and time (45 min) provided good yield (75%) of (±)-**123**.[134]

It must be noted that when the reaction was run in a sealed tube or microwave vial, when temperatures exceeding 200 ^oC, extensive decomposition of starting material was observed. However, at the optimized microwave condition, both the cyclized (**123**) and reduced acyclic anilne (**124**) products were isolated in quantitative yield, indicating that product degradation did not occur. It is important to note that compound **122** or **124** would not undergo an aza-Michael cyclization unless microwave irradiation was applied.

A similar study was conducted to optimize a 7-*exo*-*trig* aza-Michael cyclization for C2, N4 substituted 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones. A purified Ugi product **125** arising from isobutyraldehyde (**4d**), *o*-nitrobenzylamine (**1t**), fumaric acid monoethyl ester (**2a**) and *tert*-butyl isocyanide (**3b**), was used as the starting material. Stirring the acyclic product **125** in a 51 mixture of ethanol and water in the presence of Fe/NH_4Cl (20:1 mol ratio) did not provide any product. The reaction mixture was heated at 140 ^oC in oil bath for 5-24 h and a moderate yield (55-73%) was observed by GC-MS and ^{1}H NMR. Heating the same reaction mixture in a sealed tube under similar conditions provided a better result but not satisfactory. However, when a solution of **125** in a 5:1 mixture of ethanol and water in presence of Fe/NH_4Cl (20:1 mol ratio) was

irradiated at a microwave setting of 300 W, 180 °C, 18 bar, 60 min, the desired product **126** was obtained in about 85% yield. Further optimization of solvent ratio (3:1), catalyst loading (10:1 mol ratio) temperature (150 °C), pressure (10 bar) and time (45 min) provided excellent yield (90%) of **126** along with 7% of reduced acyclic aniline product **127**.[134]

Table 12. Optimization of 7-*exo-trig* aza-Michael cyclization yielding C2, N4 substitution of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-one.



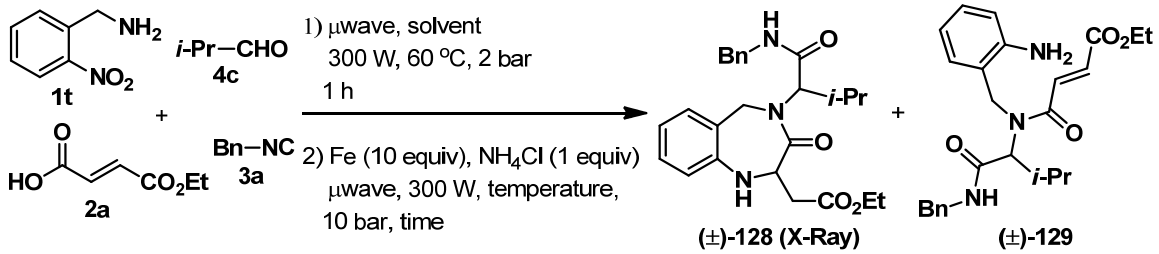
Entry	Conditions	% Yield	
		126	**127**
1	rt, Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 48 h	0	0
2	140 °C[a], Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 5 h	55[c]	40[c]
3	140 °C[a], Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 24 h	73[c]	22[c]
4	Sealed tube, 140 °C[a], Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 4 h	80[c,d]	17[c]
5	μwave, 140 °C[b], Fe/NH_4Cl (20:1), EtOH/H_2O (5:1), 1h	85[e]	12[e]
6	μwave, 140 °C[b], Fe/NH_4Cl (15:1), EtOH/H_2O (4:1), 1h	85[e]	12[e]
7	μwave, 140 °C[b], Fe/NH_4Cl (10:1), EtOH/H_2O (3:1), 1h	85[e]	12[e]
8	μwave, 150 °C[b], Fe/NH_4Cl (10:1), EtOH/H_2O (3:1), 45 min	90[e]	7[e]

[a] Denotes oil bath temperature. [b] Microwave equilibrated to 300 W, 10 bar. [c] Determined by ^1H NMR. [d] At temperature exceeding 200 °C, <10% product observed. [e] Isolated.

We were then encouraged to develop a one-pot protocol for the synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones based on our results with the 7-*exo* Michael cyclization described in Tables 11 and 12. We selected to use isobutyraldehyde (**4c**), 2-

nitrobenzylamine (**1t**), fumaric acid monoethyl ester (**2a**) and benzyl isocyanide (**3a**) as our intitial set of starting substrates leading to BDZ of type **B** (Table 13). Protic solvents such as aqueous methanol or ethanol gave the desired Ugi product in high yield (>98%) after being subjected to microwave irradiation for 1 h at 60 °C. Fe(0) and NH_4Cl were then added to the reaction flask, and the mixture was further subjected to microwave irradiation until all starting materials were converted to **128** and **129**. The structure of compound **128** was unequivocally confirmed by X-ray analysis (Figure 19).[134]

Table 13. Optimization of conditions for one-pot synthesis of BDZ.



Entry	Solvent	Time (min)	T (°C)	% yield of **128**[a]	% yield of **129**[b]
1	EtOH	30	150	77	10
2	H_2O	30	150	73	5
3	EtOH/H_2O, 3:1	30	150	85	3
4	EtOH/H_2O, 3:1	15	180	71	7
5	EtOH/H_2O, 3:1	75	140	82	3
6	EtOH/H_2O, 3:1	100	120	80	3
7	EtOH/H_2O, 3:1	180	110	81	3

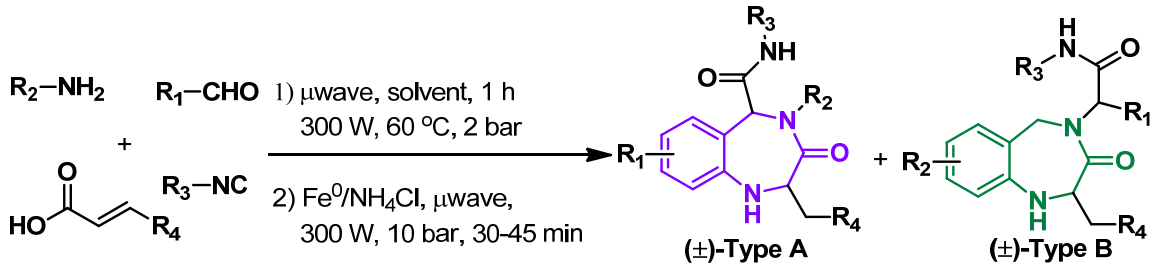
[a] Isolated. [b] Determined by ^{1}H NMR

The reduction worked best in the microwave at 150 °C for 30 min in a 3:1 ratio of EtOH/H_2O. It is important to note that in the absence of microwave irradiation or other heat sources in the one-pot protocol, only the acyclic Ugi product could be isolated

(approximately 80% yield in 18 h, refer to Table 12 for cyclization conditions) suggesting that a high energy of activation for nitro group reduction with Fe (0).[134]

We next turned our attention to examining the scope of the one-pot protocol. As noted in Table 14, entries 1-5, BDZs of the type A were formed in 70-80% yield with high diastereomeric ratios. In fact, compounds **135** and **137** (Table 14, entries 4 and 5) were obtained as single diastereomers, as determined by ^{1}H NMR. NOe data assisted in elucidating a 2,5-*cis* relationship between the acid and aldehyde components of the coupling products.[134]

These data correspond nicely with literature precedent in which similar types of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones were synthesized.[124b] Diastereomers are rationalized to arise from the *E* olefin geometry of the fumaric acid component. Using 2-nitrobenzylamine (**1t**) as a substrate in the U-4CCR gave benzodiazepines of the type B following the one-pot protocol (Table 14, entries 6-7). Although we observed higher yields of C2, N4 substituted 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones, diastereomeric raios were determined to be, at best, 1.5:1 (^{1}H NMR). The diastereomeric mixture proved difficult to separate and required a silica gel column of considerable length. In a similar fashion (Table 14, entry 8), when acrylic acid (**2f**) was used as coupling component and subjected to the one-pot cyclization conditions, a 8-*endo*-*trig* aza-Michael cyclization leading to an eight-membered ring was not observed and only the acyclic aniline U-4CCR product **139** was isolated. The structure of **139** was unequivocally confirmed by X-ray analysis (Figure 20).



Scheme 42. General route toward the synthesis of regiochemically substituted BDZs.

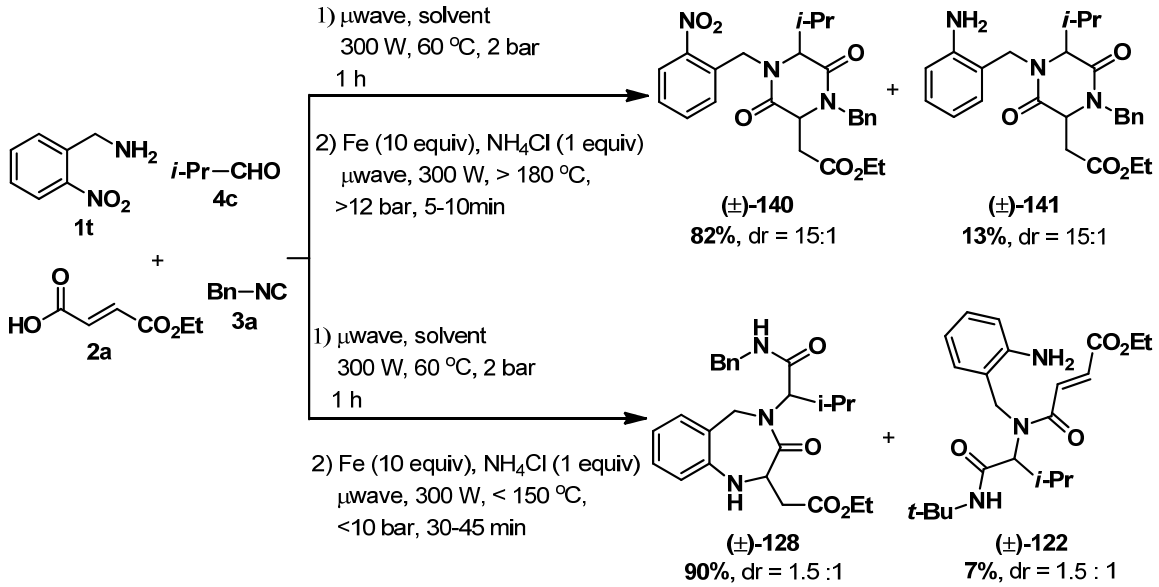
Table 14. Scope of the one-pot microwave-assisted synthesis of regiochemically differentiated 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-one.

Entry	R_1	R_2	R_3	R_4	Compd type[a]/ % yield[b]/dr[c]
1	2-Nitro-4-(trifluorometthyl)-phenyl (**4i**)	4-Bromophenyl (**1f**)	*tert*-butyl (**3c**)	Ethoxycarbonyl (**2a**)	**A** (**123**)/75/5:1
2	2-Nirophenyl (**4j**)	Benzyl (**1d**)	*tert*-butyl (**3c**)	Ethoxycarbonyl (**2a**)	**A** (**131**)/75/20:1
3	4,5-dimethoxy-2-nitrophenyl (**4k**)	Allyl (**1u**)	Cyclohexyl (**3d**)	Benzoyl (**2g**)	**A** (**133**)/70/20:1
4	2-Nitrophenyl (**4j**)	Piperonyl (**1v**)	*tert*-butyl (**3c**)	Ethoxycarbonyl (**2a**)	**A** (**135**)/73/ single
5	2-Nitrophenyl (**4j**)	4-aminoacetophenone (**1w**)	cyclopentyl (**3e**)	4-methylbenzoyl (**2h**)	**A** (**137**)/78/ single
6	Isopropyl (**4c**)l	2-Nitrobenzyl (**1t**)	*tert*-butyl (**3c**)	Ethoxycarbonyl (**2a**)	**B** (**126**)/90/1.5:1
7	Isopropyl (**4c**)	2-Nitrobenzyl (**1t**)	Benzyl (**3a**)	Ethoxycarbonyl (**2a**)	**B** (**128**[d,e])/85/1.5:1
8	Isopropyl (**4c**)	2-Nitrobenzyl (**1t**)	*tert*-butyl (**3c**)	H (**2f**)	Acyclic (**139**[d,f])/100

[a]Compound number denoted in parentheses. [b] Isolated. [c] Determined by using an unpurified sample with ^{1}H NMR. [d] X-ray structure. [e] At temperature >180 °C the major product was 2,5-diketopiperazine. [f] Isolated the acyclic aniline U-4CCR product.

At high μwave intensity, a one-pot 6-*exo* aza-Michael cyclization occurred to from 2,5-diketopiperazines **140** and **141** as illustrated in Scheme 43.[106] This potentially competing reaction pathway could readily be suppressed by reduction of μwave intensity to exclusively form BDZ **128**. This transformation indicates that a 6-*exo* aza-Michael

cyclization, from an amide occurs faster than the zero valent iron metal reduction. Our results suggest that compound **141** resulted from the direct reduction of **140** and not from prior $–NO_2 \rightarrow –NH_2$ reduction.



Scheme 43. Microwave intensity controls pathway selectivity.

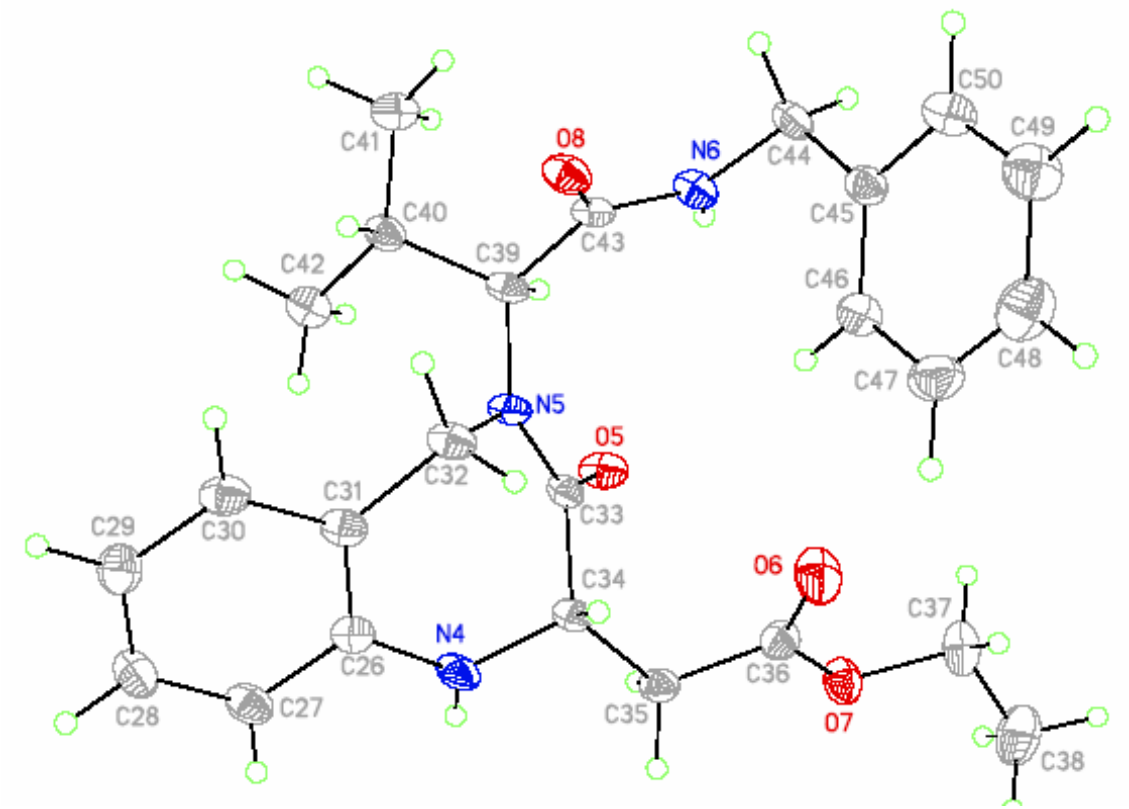


Figure 19. X-ray structure of (±)-**128**.

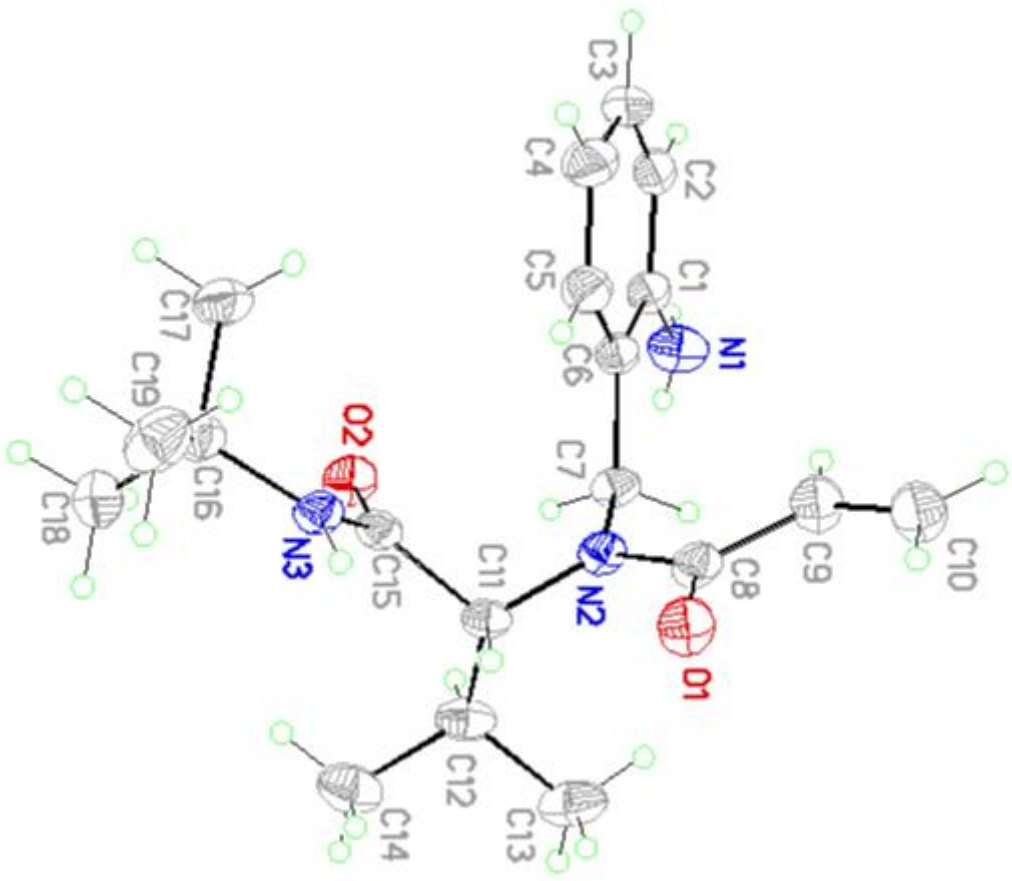
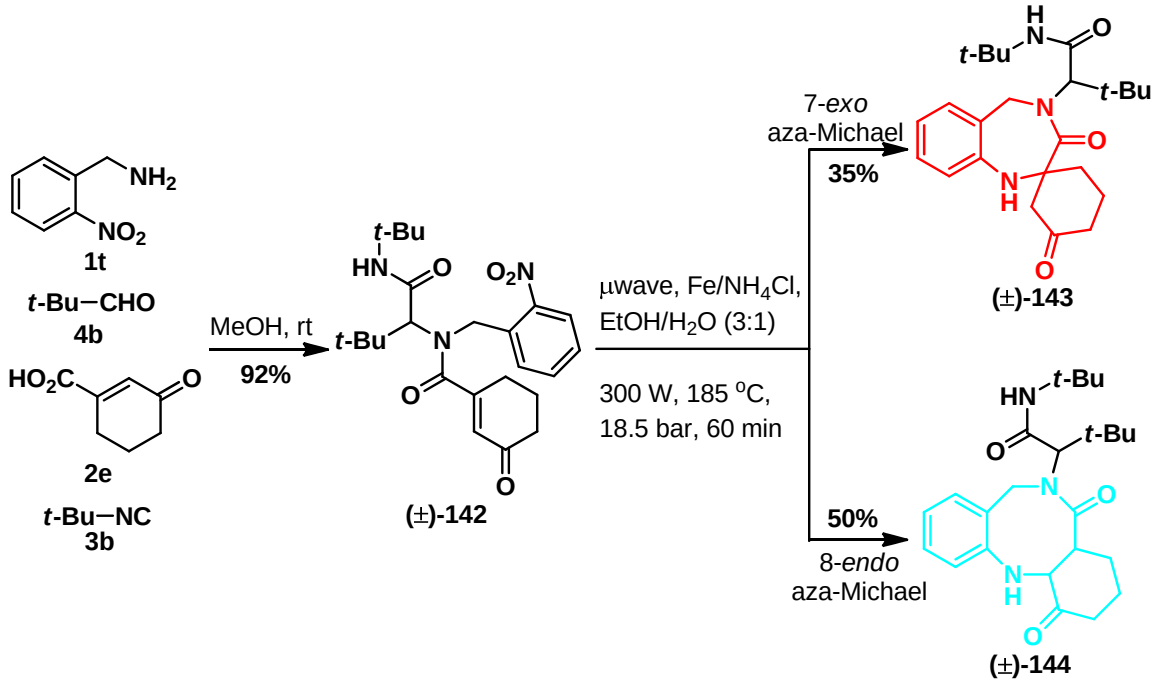


Figure 20. X-ray structure of compound (±)-**139**.

As a part of our interest in spiro-cyclic motifs, we next embarked on devising synthetic route for spiro-benzodiazepines as they have become attractive synthetic target due to their biological activity.[135] A thorough literature survey revealed that aza-Michael reactions had not been utilized to construct spiro-BDZ motifs and there were few reports that described the synthesis of these motifs. However, we envisioned that use of previously synthesized (Scheme 31) 3-oxo-cyclohexene-1-carboxylic acid (**2e**) in the U-4CCR might provide spirocyclic 1,4-benzodiazepine-3-ones. Thus, Ugi acyclic product **142** was synthesized from a coupling reaction of 2-nitrobenzylamine (**1t**), trimethylacetaldehyde (**4b**), 3-oxo-cyclohexene-1-carboxylic acid (**2e**) and *tert*-butyl

isocyanide (**3c**). When **142** was subjected to microwave irradiation under previously established reaction conditions (Table 12), spirocyclic 1,4-benzodiazepin-3-one **143** and octahydrodibenzodiazocine-1,5-dione **144** were obtained in **35%** and **50%** respectively. The identity of **143** and **144** was confirmed by ^{1}H NMR as well as nOe studies. It is noteworthy that **144** was less polar than **143** (Scheme 44).



Scheme 44. Synthesis of spiro-1,4-benzodiazepine and octahydrodibenzodiazocine-1,5-dione.

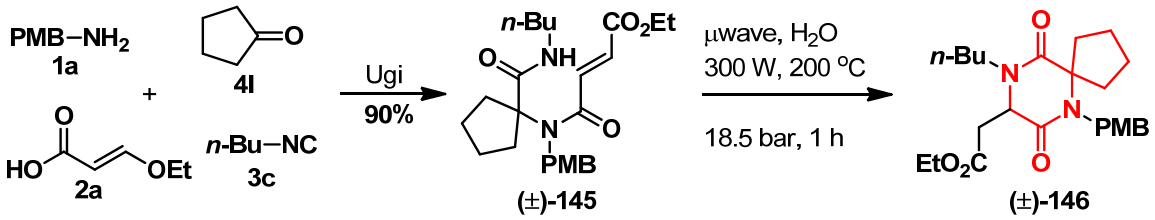
2.2.8. Extension Toward the Synthesis of Spiro-2,5-Diketopiperazines to Develop CCR5 Antagonist

2,5-Diketopiperazines are the simplest member of cyclic dipeptides. In other words, cyclic peptides are surrogates of simple amino acids. Consequently, spirocyclic amino acids might have the ability to restrict conformational flexibility when they are incorporated into bioactive peptide frameworks. Potentially, they can provide critical

information on the spatial requirement of peptide receptors.[136] More importantly, such pseudopeptides often display several advantages over natural peptides including improved bio-stability and selectivity toward specific biological target.

Spiro-2,5-diketopiperazines (Spiro-DKP) are the cyclic dipeptides containing α, α-disubstituted amino acid moieties with wide range of pharmacological activities which includes neuroprotection, anti-proliferative, anti-inflammatory, anti-allergic and also prevent immune diseases.[137] These bioactivities make the spiro-DKP motif an attractive core in medicinal chemistry. Recently, spiro-DKPs have gained wide spread attention among scientific community since it has emerged as potential antagonist of HIV (human immunodeficiency virus) receptor CCR5. Chemokines are chemotactic cytokines that play a key role in leukocyte migration, adhesion, and activation involved in inflammation and immune cell differentiation.[138] The chemokines receptors, belong to the family of seven transmembrane (7TM) G-protein-coupled receptors (GPCRs), are broadly classified into two families based on their cytocine residue structure: CC and CXC. Similarly, their corresponding receptors are also classified into two groups: CCR and CXCR respectively. In the HIV (human immunodeficiency virus) infection process of target cells requires viral binding to the chemokine receptors CCR5 and CXCR4.[139] In particular, the entry of R5 tropic strains of HIV-1, HIV-2 and simian immunodeficiency virus (SIV) requires the CCR5 co-receptor. Consequently, preventing or disrupting the HIV-chemokine receptor binding could lead to potential route for the development of inflammatory drugs, antiallergic drugs, immunosuppressants, and/or antiviral drugs for HIV infection. Moreover, they are monoamine oxidase inhibitors and calcium channel blockers.

To date, only few literatures are available which reported the synthesis of spiro-DKPs. However, many of these syntheses require either multiple steps or external additives which are not environmentally benign.[140] We envisioned that use of cyclic ketones in the U-4CCR in conjunction with microwave irradiation might provide an environmentally benign route for the synthesis of spiro-DKPs. Thus, acyclic U-4CCR product **145** was obtained from four component coupling reaction of *p*-methoxy benzylamine (**1a**), cyclopentanone (**4l**), fumaric acid monoethyl ester (**2a**) and *n*-butyl isocyanide (**3g**). When **145** was subjected to microwave irradiation under previously established conditions (Table 2, entry 13), a 6-*exo*-*trig* aza-Michael reaction provided compound **146** in about 50% yield (scheme 46). Further optimization of reaction conditions provided **146** in about 85% yield. We then examined the substrate scope of this spiro-DKP synthesis using various cyclic ketones, amines and isocyanides (scheme 47). Majority of the substrates provided good to excellent yields. In general it has been observed that spiro-DKPs formation requires longer reaction time compared to DKPs probably due to ring strain of the resulting products



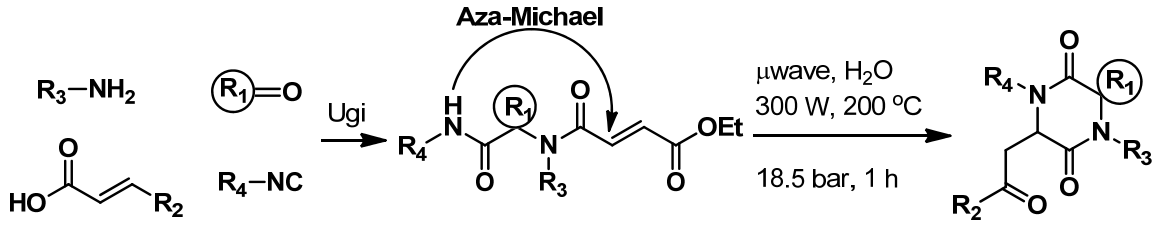
Scheme 45. Synthesis of spiro-DKP under microwave irradiation.

Table 15. Optimization of microwave[a] reaction conditions leading to spiro-DKP.

Entry	Solvent	Time (min)	Power (W)	Temp (^{o}C)	Pressure (bar)	Yield (%)[b]
1	H_2O	20	300	200	18	50
2	H_2O	30	300	200	18	60
3	H_2O	30	300	200	18.5	65
4	H_2O	40	300	200	18.5	70
5	H_2O	50	300	200	18.5	80
6	H_2O	60	300	200	18.5	85

[a] CEM Discover Microwave. [b] Isolated

While we were working on the project, astonishingly, a thorough literature survey revealed that cyclopropanone and cyclobutanone have been used in the IMCCRs in very few cases.[141] Therefore, we decided to use commercially available cyclobutanone **4l** as coupling partner in the U-4CCR. Gratifyingly, the U-4CCR reaction between benzyl amine **1d**, cyclobutanone **4l**, fumaric acid monoethyl ester **2a** and benzyl isocyanide **3a** provided the desired spiro-DKP **154** in excellent yield. During the progress of the project, Pirrung and coworkers reported that cyclobutanones work well in Ugi and Passerini reactions and reasoned that the lack of past reports was due to the unusual reaction course of cyclobutanones.[142] It is quite noteworthy that in our hand, the cyclobutane ring opening does not occur in the presence of microwave irradiation under high temperature and pressure, although there was speculation that due to ring strain, it might undergo ring opening.[143]



Scheme 46. General scheme for microwave-influenced spiro-DKP synthesis.

Table 16. Substrate scope of microwave-influenced synthesis of spiro-DKPs.

Entry	R_1	R_2	R_3	R_4	Compd/% yield[a]
1	Cyclopentyl (**4l**)	Ethoxycarbonyl (**2a**)	4-Methoxybenzyl (**1a**)	*n*-butyl (**3g**)	**146**/85
2	Cyclohexyl (**4m**)	Ethoxycarbonyl (**2a**)	4-Methoxybenzyl (**1a**)	*n*-butyl (**3g**)	**148**/80
3	4-Thio-pyran (**4n**)	Ethoxycarbonyl (**2a**)	3,4-Dimethoxybenzyl (**1f**)	Benzyl (**3a**)	**150**/82
4	4-pyran (**4o**)	Ethoxycarbonyl (**2a**)	3,4-methylenedioxybenzyl (**1j**)	Benzyl (**3a**)	**152**/83
5	Cyclobutane (**4p**)	Ethoxycarbonyl (**2a**)	Benzyl (**1d**)	Benzyl (**3a**)	**154**/98
6	3-methyl-Cyclopentane (**4q**)	Tolylcarbonyl (**2h**)	4-bromophenyl (**1f**)	*n*-butyl (**3g**)	**156/n.d**[b]
7	1-phenethyl-Piperidine (**4r**)	Ethoxycarbonyl (**2a**)	Propargyl (**1x**)	*n*-butyl (**3g**)	**158/n.d**[b]

[a]Isolated. [b]Not determined

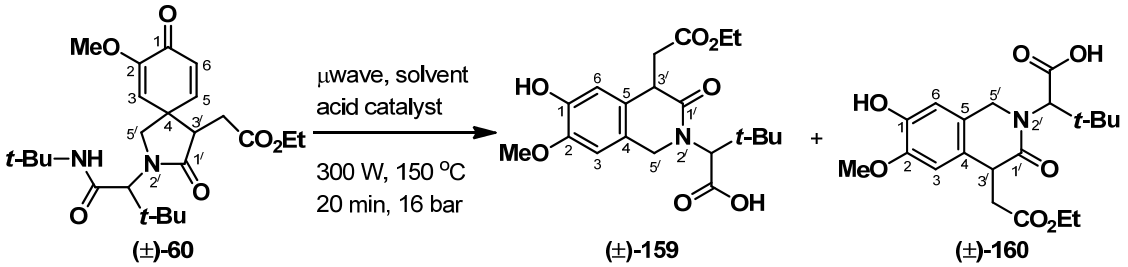
2.2.9. Extension Toward the Synthesis of Tetrahydro-Isoquinolinones

Isoquinolinone is a very important heterocyclic privileged scaffold and present in wide range of natural products that possesses a broad spectrum of biological activities e.g., anticancer, antileukemic, antitumor, antiulcer, antidepressant, anti-inflammatory,

analgesic, hypolipidemic, antihypertensive as well as inhibits PARP-1 and topoisomerase-1. A large number of syntheses of isoquonolinone (IQ) motifs have been reported. Because of the therapeutic value of such motifs in various bioactive molecules, there has been an increasing interest among the scientific community to construct these motifs. Since it was discovered over 75 year ago,[144] scientific community have extensively studied the acid catalyzed dienone-phenol rearrangement (DPR)[145] and widely reviewed.[146] However, there is lack of study on the rearrangement of corresponding 4,4-disubstituted 2-alkoxycyclohexa-2,5-dien-1-ones.[147] Primarily, the C-4 substituents have been observed to migrate almost exclusively to C-5.[148] When the C-5 is substituted in these α-keto enol ethers, migration to C-3 is observed only.

We envisioned that previously synthesized 2-azaspiro-[4.5]deca-6,9-diene-3,8-dienone **61** can undergo DPR in presence of a suitable acid catalyst to provide isoquinolinones.[105d] Thus, we screened various Lewis acid and Bronsted acid catalysts and nitromethane was used as solvent as there are literature precedents.[105d] In view of some recent reports that lanthanide-based catalyst are water stable and can catalyze many reactions; we also screened lanthanide-based catalyst in water. Moreover, there is minuscule literature precedence of using microwave irradiation to perform DPR. Thus, we were interested to study microwave irradiation on DPR. It has been found that 1.5 equiv. of $BF_3.OEt_2$ and TMSOTf were the best catalyst and provided 90% yield of **159** where as $TiCl_4$, $FeCl_3$ and Bronsted acids lead to decomposition of starting material (when the microwave was equilibrated to 300 W, 150 ^oC, 20 min, 16 bar). However, the reaction gave no recognizable amount (or at best a trace amount) of compound **160**

(Scheme 47). The identity of **159** was confirmed by ^{1}H, GQFCOSY, nOe study and mass spectrometry (HRMS).



Scheme 47. Synthesis of tetrahydroisoquinolinone under microwave irradiation.

Table 17. Screening of Lewis/Bronsted Acids for DPR under microwave irradiation[a]

Entry	Lewis/Bronsted Acid	Solvent	% yield of **159**[b]	% yield of **160**
1	$BF_3.OEt_2$	CH_3NO_2	100	0
2	$Yb(Otf)_3$	CH_3NO_2	NR	0
3	$Yb(OTf)_3$	H_2O	NR	0
4	$Sc(OTf)_3$	CH_3NO_2	NR	0
5	$Sc(OTf)_3$	H_2O	NR	0
6	$AlCl_3$	CH_3NO_2	NR	0
7	$InCl_3$	CH_3NO_2	NR	0
8	CuI	CH_3NO_2	NR	0
9	$FeCl_3$	CH_3NO_2	Decomposition	0
10	$TiCl_4$	CH_3NO_2	Decomposition	0
11	$Ti(i\text{-}PrO)_4$	CH_3NO_2	NR	0
12	$ZnCl_2$	CH_3NO_2	NR	0
13	AgI	CH_3NO_2	NR	0
14	TMSOTf	CH_3NO_2	100	0
15	PTSA	CH_3NO_2	Decomposition	0
16	CSA	CH_3NO_2	Decomposition	0
17	HCl	CH_3NO_2	Decompostion	0

[a] Microwave was equilibrated to 300 W, 150 °C, 16 bar for 20min. [b] Based on TLC

Next we screened various solvents for DPR in presence of $BF_3.OEt_2$ and TMSOTf. It has been observed that polar aprotic solvents (e.g., CH_3NO_2 and CH_3CN) except DMF and DMSO highly favored the DPR, whereas polar protic solvents e.g.,

MeOH gave no recognizable (or at best a trace amount) of DPR product **159**. A plausible explanation could be that the DPR involves a carbocationic intermediate and polar protic solvents might act as proton source leading to protonation of the intermediate which prevents the final irreversible rearrangement step.

Table 18. Solvent effects on DPR under microwave irradiation.[a]

Entry	Lewis Acid	Solvent	% yield of **159**[b]
1	$BF_3.OEt_2$	CH_3CN	89
2		CH_3NO_2	90
3		CH_2Cl_2	15
4		DMF	NR
5		DMSO	NR
6		MeOH	NR
7		THF	NR
8	TMSOTf	CH_3CN	90
9		CH_3NO_2	90
10		CH_2Cl_2	10
11		DMF	NR
12		DMSO	NR
13		MeOH	NR
14		THF	NR

[a] Microwave was equilibrated to 300 W, 150 ^oC, 16 bar for 20 min. [b] Isolated

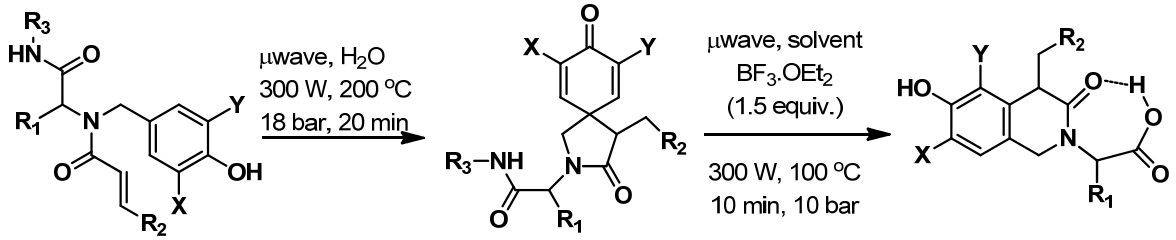
Having best solvents and catalysts in hand, we elected to use CH_3NO_2 as solvent and $BF_3.OEt_2$ as the Lewis acid catalyst for the optimization of microwave reaction conditions. When microwave was equilibrated to 300 W, 100 ^oC, 10 bar for 10 min, the reaction provided the best result (96% yield of **159**). A series of acyclic Ugi products (Table 21) have been synthesized and currently, we are performing the spiro cyclization (Table 2) and resulting spiro compounds will be subjected to DPR (Table 21) conditions to study substrate scope of this novel method.

Table 19. Optimization of microwave reaction conditions for the DPR.[a]

Entry	Power (W)	Temperature (^oC)	Pressure (bar)	Time (min)	% yield of **159**[b]
1	300	150	16	20	90
2	300	140	14	20	91
3	300	130	13	20	92
4	300	110	10	10	94
5	300	100	10	10	96

[a] CH_3NO_2 was used as solvent and $BF_3.OEt_2$ (1.5 equiv.) was used as Lewis acid catalyst. [b] Isolated

Table 20. Substrate scope of the microwave-assisted synthesis isoquinolinones *via* DPR.



Entry	R_1	R_2	R_3	X	Y	Compd/% yield/dr		
						Acyclic	Spiro	IQ
1	*t*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	*t*-butyl (**3b**)	OMe (**1c**)	H	**61**/80	**60**/60/1:2	**159**/96[a]/1:1.5
2	*t*-butyl (**4b**)	Tolylcarbonyl (**2h**)	*t*-butyl (**3b**)	OMe	H	–/82	**161**/70	**162**/65[b]/1:2
3	*t*-butyl (**4b**)	benzoyl (**2f**)	*t*-butyl (**3b**)	OMe	H	–/85	**163**/75	**164**/68[b]/n.d
4	4-fluorophenyl (**4s**)	Ethoxycarbonyl (**2a**)	*t*-butyl (**3b**)	OMe (**1y**)	OMe	**165**/81	**166**/73	**167**/67[c]/n.d
5	Piperonyl (**4t**)	Ethoxycarbonyl (**2a**)	Cyclohexyl (**3b**)	OMe (**1c**)	H	–	**168**/87	**169**/n.d[c]/n.d
6	4-fluorophenyl (**4s**)	Ethoxycarbonyl (**2a**)	Cyclohexyl (**3c**)	OMe (**1c**)	H	**170**/84	**171**/nd[c]	**172**/nd[c]
7	*t*-butyl (**4b**)	Ethoxycarbonyl (**2a**)	Cyclopentyl (**3g**)	H (**1b**)	H	**24c**/90	**23c**/81	**173**/85

[a] Isolated yield. [b] based on crude ^1H NMR, not isolated yield. [c] reaction will be performed

As shown in table 20 (entry 2, 3, 5), the U-4CCR provided the 2-azaspiro-[4.5]deca-6,9-diene-3,8-dienone when the reaction was carried out at room temperature and warmed upto 70 ^oC. The probable explanation could be that the π-cloud of aromatic

groups of the U-4CCR products stack together and the π-stacking effect[149] (Figure 21) might help to bring the reacting centers closer; lowers the activation barrier for 5-*exo* Michael pathway leading to **161**, **163** and **168**.

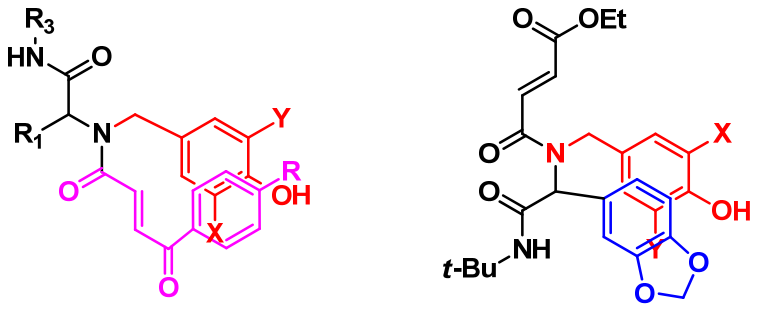
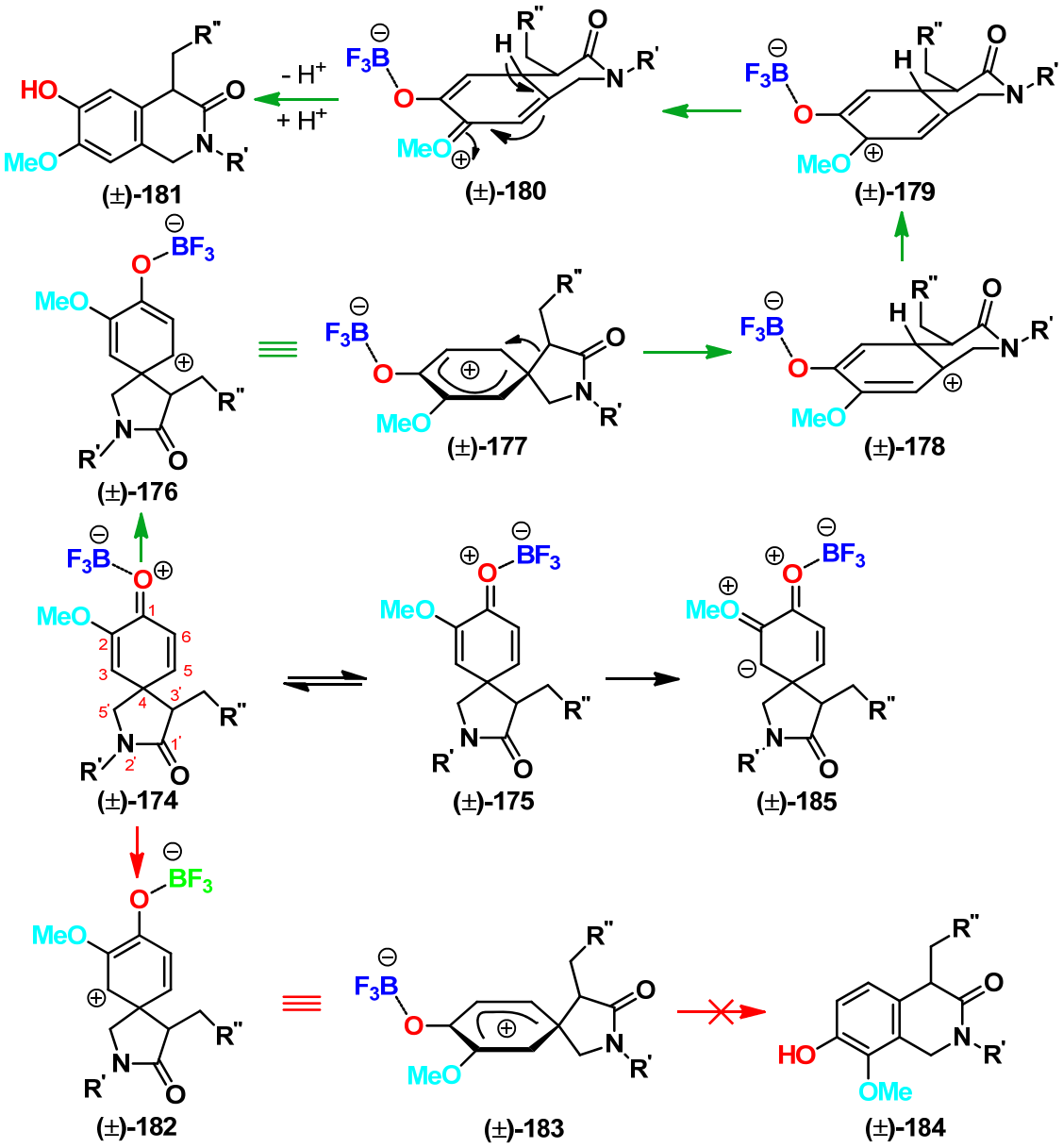


Figure 21. Possible π-stacking effect led to the spiro-cyclization via 5-*exo*-*trig* Michael pathway.

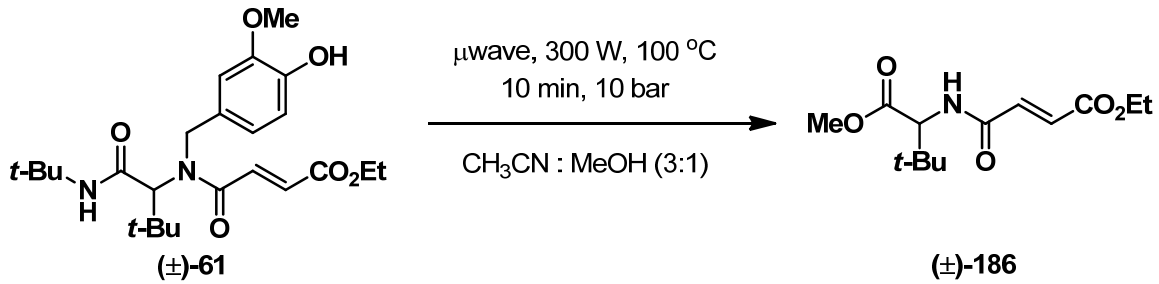
The C-5 regioselectivity in methoxy/hydroxy dienones (e.g., **60**) in DPR can be simply rationalized by considering the electron density at C-3 vs C-5. in the coordinated form of **60** with Lewis acid.[147l] It should be clear that while the coordinated carbonyl induces a partial positive charge at both carbons, represented by resonance structures **176** (**177**) and **182** (**183**), the overall charge at C-3 is neutralized to a large extent by the electron donation of the enol ether moiety, as shown in structure **185** (Scheme 48). Since it is the positive charge character of C-3 or C-5 that induces this rearrangement, it is their relative sizes that control the overall regioselectivity.[149] The potential migrating groups (C-3′ and C-5′) are in the same steric environment, held conformationally rigid on either side of the planner dienone ring, so their setric effects in the rearrangement are minimized. The C-3′ is a 1° carbon and C-5′ is a 2° carbon, thus C-5′ has higher migratory aptitude and will migrate (1,2-shift) preferentially. Furthermore, resulting carobocation intermediate after 1,2-shift is resonance stabilized by the methoxy group at the C-2 position. The large driving force for the rearrangement is the aromatization of



Scheme 48. Proposed mechanism of the microwave-assisted DPR.

Understanding the mechanism of the DPR can provide some shed on the solvent effect on the reaction. As shown in Table 19, polar nucleophilic protic solvents did not provide any product. The probable explanation is that the rearrangement involves carbocation intermediates that might capture a good nucleophile e.g. MeOH. On the other hand, polar aprotic solvents with no nucleophlic character (e.g. CH_3NO_2) or very low nucleophilic character (e.g. CH_3CN) favors the DPR because the carbocationic intermediate can avoid any short of nucleophilic attack.

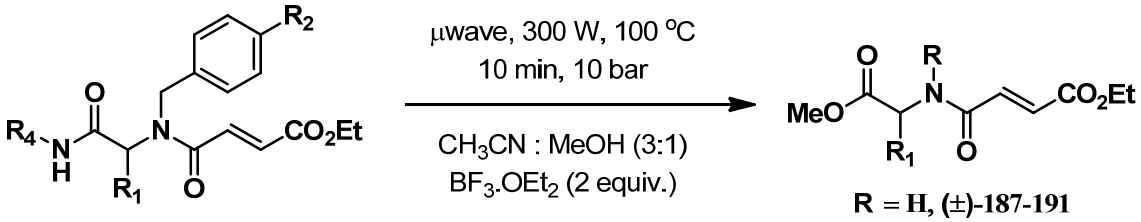
It is quite noteworthy that under the reaction conditions, the *t*-Bu-NH group from **61** (derived from *tert*-Butyl isocyanide) spontaneously cleaved to provide corresponding acid **159**. We speculated that, in presence of a nucleophilic solvent, we might be able tune the reaction. Thus we decided to revisit our single-step synthesis effort (Scheme 25) and chose to subject the acyclic precursor of **61** under the same microwave irradiation conditions in 3:1 mixture o CH_3CN and MeOH using $BF_3.OEt_2$ (Scheme 49). To our surprise, compound **186** was obtained with concurrent loss of the *tert*-butyl-NH (derived from *tert*-butyl isocyanide) and 3-methoxy-4-hydroxy benzyl groups. Identity of compound **186** was confirmed by ^1H NMR, ^{13}C and HRMS.



Scheme 49. Conversion of an amide into an ester under microwave irradiation.

Thus, *tert*-butyl isocyanide can act as convertible isocyanide (CIC)[44] in presence of $BF_3.OEt_2$ under microwave irradiation. During the progress of the project, Kravasin and coworkers also reported that *tert*-butyl isocyanide acts as a CIC in presence of TFA under microwave irradiation.[150] Next, we decided to explore the outcome of this reaction and study whether other commercial 'off-the-shelf' isocyanides can be cleaved and can act as CICs. A series of acyclic Ugi products were synthesized employing commercial 'off-the-shelf' isocyanides. Purified acyclic Ugi products **24b** was subjected to the microwave irradiation using $BF_3.OEt_2$ (1 .5 equiv., 2 equiv. and 2.5 equiv.). Gratifyingly, the removal of cyclohexyl amine was observed and the reaction provided best yield of **187** when 2 equiv. of $BF_3.OEt_2$ was used.[151] Thus, we decided to use 2 equiv. of $BF_3.OEt_3$ for other precursors. In general, it has been observed that all of the commercial 'off-the-shelf' isocyanides can act as CICs under our reaction conditions.[152]

Table 21. Scope of 'off-the-shelf' isocyanides as CICs.

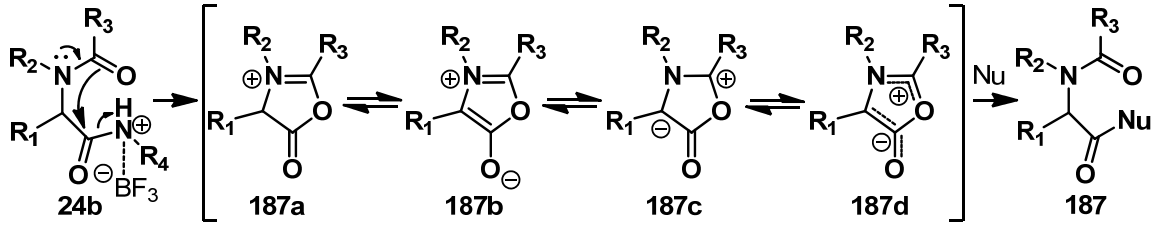


(±)-24b-f, (±)-51

R = H, (±)-187-191
R = Bn, 192

Entry	R_1	R_2	R_4	% Yield[a]/ (U-4CCR pdt)	% Yield/ (Deprotected pdt)
1	*t*-butyl	hydroxyl	cyclohexyl	**89**/(**24b**)	**90**[a]/(**187**)
2	*t*-butyl	hydroxyl	cyclopentyl	**90**/(**24c**)	**70**[b]/(**188**)
3	*t*-butyl	hydroxyl	isopropyl	**90**/(**24d**)	**75**[b]/(**189**)
4	*t*-butyl	hydroxyl	benzyl	**93**/(**24e**)	**69**[b]/(**190**)
5	*t*-butyl	hydroxyl	*n*-butyl	**91**/(**24f**)	**72**[b]/(**191**)
6	isopropyl	hydrogen	4-methoxyphenyl	**90**/(**51**)	**65**[b]/(**192**)

[a] Isolated. [b] Based on crude ^{1}H NMR

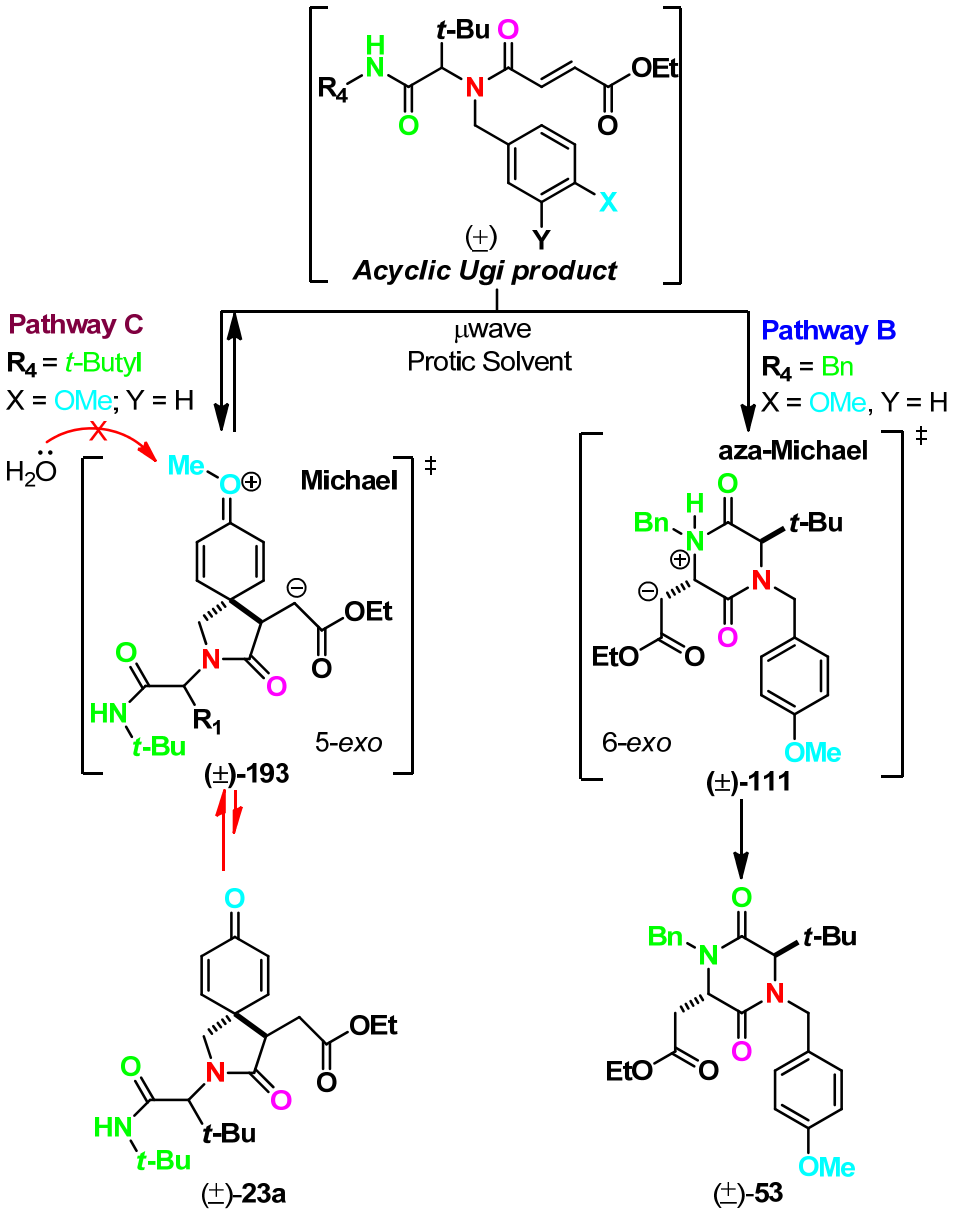


R_1 = *t*-Bu, R_2 = PHB, R_3 = Ethyl acrylate, R_4 = *t*-Bu, Nu = MeOH

Scheme 50. Possible mechanism for the formation of compound **187**.

A possible mechanism for the formation of compound **187** is shown in Scheme 50. Nucleophilic attack of the carbonyl group (from the carboxylic acid component) onto the carbonyl group (derived from isocyanide component) forms the müchanone. The müchanone is further stabilized resonance structure (**187b**-**187d**) and finally nucleophilic attack onto the ester carbonyl of **187a** provides the observed product **187**.

From Table 11, it is quite clear that microwave irradiation can influence electronic property of molecules and can be used as a reagent to construct new bonds. It must be noted that a hydroxyl group is a stronger electron-donating group than a methoxy group. Although, a *p*-methoxy group does undergo spiro-cyclization under other conditions,[153] we think that it might form a spiro-intermediate like **193**, but under the neutral reaction conditions the methyl group of the OMe does not fall off spontaneously. Consequently, the intermediate collapse and follow an alternative 6-*exo*-*trig* aza-Michael pathway to form DKP (Scheme 51).

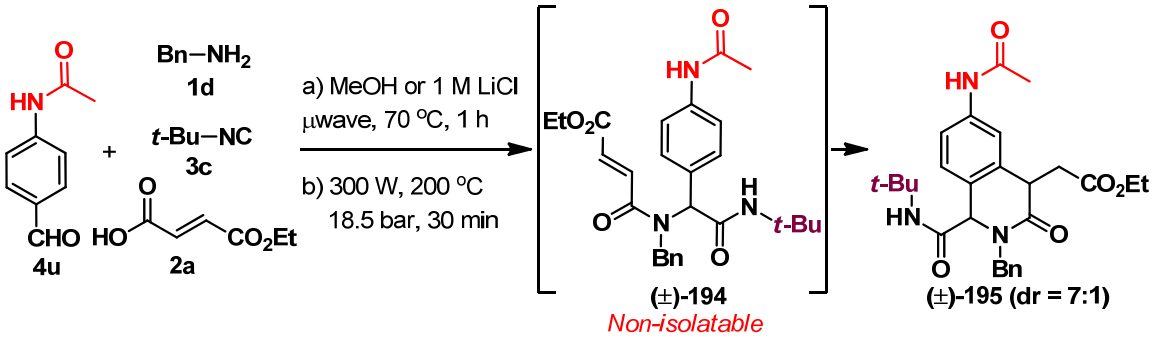


Scheme 51. Methyl group does not fall off spontaneously under neutral conditions.

We decided that it would be interesting to study how microwave irradiation can influence other functional groups e.g. *N*-acetyl group at the para positon of phenyl ring and alter the reaction course. Thus, we elected to use 4-acetamidobenzaldehyde in the one-pot U-4CCR. Gratifyingly, when benzylamine **1d**, 4-acetamidobenzaldehyde **4u**, furmaic acid monoethyl ester **2a** and t-butyl isocyanide **3c** was subject to U-4CCR under microwave conditions as shown in scheme 69, IQ **195** was obtained in about 60% yield

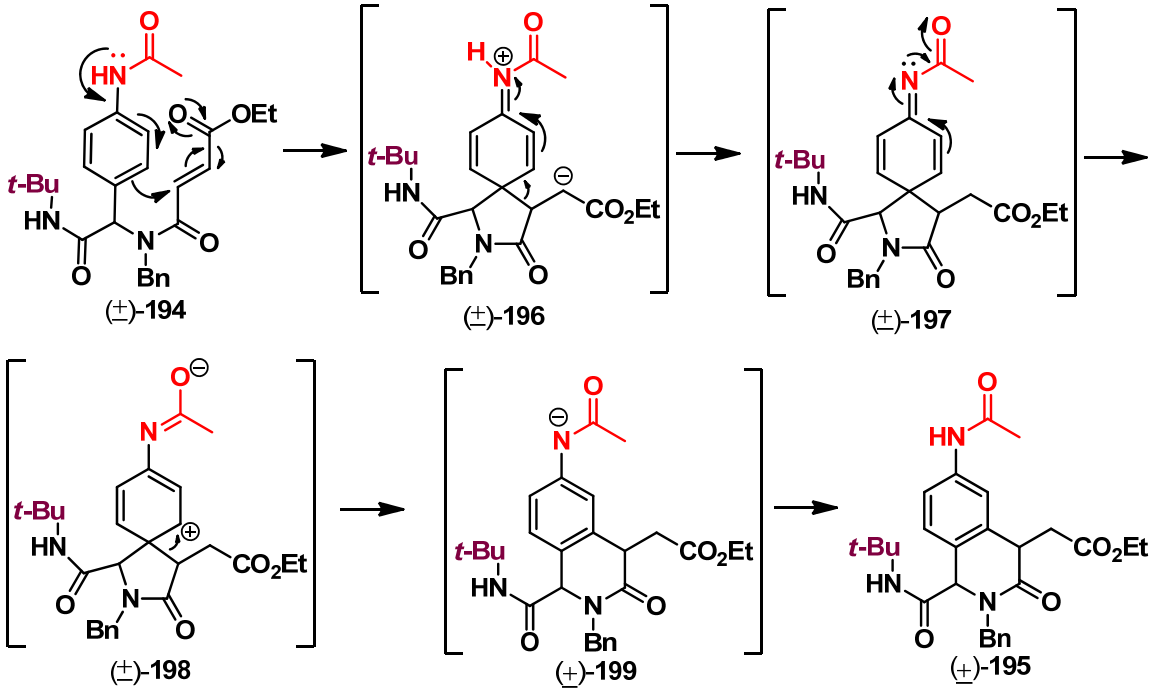
via non-isolatable U-4CCR product **194**. For spectroscopic comparison, the acyclic Ugi product **194** was separately synthesized at room temperature.

Employing other 4-amidobenzaldehydes, amines, acids and bulky isocyanides a library of these 1,4-dihydroisoquinolinones can be envisioned in one-pot.



Scheme 52. Microwave-influenced one-pot synthesis of IQ *via* cascade Ugi/Michael/DPR-type rearrangement.

A probable mechanism for the formation of IQ **195** via cascade Ugi/Michael/DPR-type pathway is shown in scheme 53. Initial 5-*exo*-*trig* Michael addition form the spiro acyliminium intermediate **196** which upon proton loss form intermediate **197**. Delocalization of double bond forms the carbocationic spiro intermediate **198** which then undergoes a 1,2-shift to form **199**. Protonation provides the final IQ product **195**. By employing various substituted 4-acetamidobenzaldehydes, other acids amines and bulky isocyanides a library of these amino IQs can generated for conducting SAR study.



Scheme 53. Proposed mechanism for the formation of IQ *via* Cascade Ugi/Michael/DPR-type rearrangement.

2.3. Materials and Methods

All Reagents were purchased from Aldrich unless otherwise mentioned. 4-Hydroxybezylamine was purchased from Matrix Scientific. 4-Hydroxy-3-methoxybenzylamine hydrochloride was purchased from Alfa Aesar. 6-Nitroveratraldehyde and 4-aminoacetophenone were purchased from Alfa Aesar. Allyl amine was purchased from Acros. 2-Nitrobenzylamine was obtained from 2-nitrobenzylamine hydrochloride. Except as otherwise indicated, reactions were carried out under argon. Microwave reactions were carried out in a capped vial on CEM Discover System. All reactions were monitored by thin layer chromatography using 0.25 mm Dynamic Adsorbents, L.L.C. precoated silica gel (particle size 0.03-0.07 mm, catalog no. 84111. Column chromatography was perfomed using Whatman Purasil 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and

spectroscopically pure compounds, except as noted. Diasteremeric ratio was determined from ^{1}H NMR spectra of crude reactions. Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Unity 500 and Varian 500 Direct Drive System spectrometers. The residual $CDCl_3$ singlet at δ 7.26 ppm and δ 77 ppm were used as the standard for ^{1}H NMR and ^{13}C NMR spectra respectively. Mass spectra were recorded on Micromass GCT at 70 eV. IR spectra were recorded on Varian/Digilab Excalibur 3100 High Resolution FT-IR. Automatic LC-MS was performed on a WATERS LCT PREMIER XE ELECTROSPRAY TOF with waters BEH C_{18} column (2.1 mmx 50 mm, 1.7 μm). The eluent was mixture of acetonitrile and water containing 0.05% HCOOH with linear gradient from 10:90 (v:v) acetonitrile-water to 90:10 acetonitrile-water within 10 minutes at 0.7 mL/min. UV absorption detection was conducted at 254 nm.

2.3.1. General Procedure 1 for 2,5-diketopiperazines or 2-azaspirocyclohexadienones synthesis (Starting with four separate substrates)

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, 15 mg (0.14 mmol) of Benzyl amine, 12 mg (0.14 mmol) of Trimethyl acetaldehyde, 25 mg (0.14 mmol) of *trans*-3-Benzoylacrylic acid and 17 μL (0.14 mmol) of Benzyl isocyanide were taken in a mixture of 1.5 mL LiCl and 1 mL MeOH. The vial was capped properly and placed in the microwave. Then the microwave was run at two stages: (a) 1 hr at 50 ^{o}C, 10 Bar and 300 W (b) 20-25 min, 210 ^{o}C, 18 Bar and 300 W. After cooling the vial at room temperature, ethyl acetate was added and shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate twice (2 mL each). The organic layers were combined and washed with $NaHCO_3$ (3 mL each), 1 N HCl (3 mL each), Brine (3 mL each). The organic layer was separated. All aqueous layers were

combined and extracted with 3 mL ethyl acetate. The organic layers were combined and dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified by silica gel column chromatography using 1:2 mixture of ethyl acetate and hexane as eluent.

2.3.1.1. General Procedure 2 for 2,5-diketopiperazines or 2-azaspirocyclohexadienones synthesis (Starting from the acyclic Ugi product)

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, 50 mg of acyclic Ugi starting material was taken and 2.5 mL of distilled water was added to it. The vial was capped properly and placed in the microwave. Then microwave was run for 20-25 min at 210 ^oC, 18 Bar and 300 W. After cooling the vial at room temperature, ethyl acetate was added and shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate twice (2 mL each). The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified by silica gel column chromatography using 1:2 mixture of ethyl acetate and hexane as eluent.

2.3.1.2. Modified General Procedure 2 for the synthesis of tricyclic lactam (Starting from the acyclic Ugi product).

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar under argon, 50 mg of acyclic Ugi starting material was taken and 2.5 mL of dry CH_2Cl_2 was added to it. The vial was capped properly and placed in the microwave. Then microwave was run for 20-25 min at 210 ^oC, 18 Bar and 300 W. After cooling the vial at room temperature, ethyl acetate was added and shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate twice (2 mL each).

The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified by silica gel column chromatography using 1:2 mixture of ethyl acetate and hexane as eluent.

2.3.1.3. General Procedure 3 (for acyclic intermediates):

To a 10 mL RB flask 0.3 g (2.19 mmol) of 4-Methoxybenzylamine was dissolved in 3 mL LiCl (or 3 mL MeOH) and 0.24 mL (2.19 mmol) of Trimethyl acetaldehyde was added. The mixture was stirred for 10 min. Then 0.32 g (2.19 mmol) of Fumaric acid monoethyl ester and 0.27 mL (2.19 mmol) were added respectively. The resulting solution was allowed to stir overnight at room temperature and quenched with 1mL of 1N HCl. To the mixture CH_2Cl_2 was added and stirred well. The organic layer was separated and aqueous layer was extracted twice with CH_2Cl_2 (2 mL each). The organic layers were collected and dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified by silica gel column chromatography using a 1:2 mixture of ethyl acetate and hexane as eluent.

2.3.1.4. General Procedure for the synthesis of carboxylic acid 2e:

To a 50 mL dry RB flask containing 3.02 mL of acetic anhydride (Ac_2O), 3.85 g (38 mmol) of chromium trioxide (CrO_3) was added slowly. When all CrO_3 was dissolved completely, 6.05 mL of glacial acetic acid (AcOH) was added slowly. The resulting oxidizing solution was added dropwise to a stirred, cooled (11-14 ^oC) solution of 2 g (14.3 mmol) methyl-1-cyclohexene-1-carboxylate in 28 mL of dry dichloromethane over 45 min. The resulting solution was allowed to stir for additional 15 min and slowly added to ice-cold 19.8 mL KOH (12.5 M). The organic layer was separated and the aqueous layer was then extracted twice with diethyl ether (20 mL). The organic layers

were combined and washed with saturated $NaHCO_3$, brine respectively and separated again. The organic layer was then dried over Na_2SO_4 and concentrated on rotary evaporator. The crude ^1H NMR was >97% clean and the product was used in next step without further purification.

Next, 1.75 g (11.4 mmol) of the enone carboxylate was stirred with 1.48 g (14 mmol) in 14 mL water for 7 h at room temperature. The reaction mixture was then acidified with 10% HCl to maintain pH 2 and immediately extracted with dichloromethane (15 mL × 3). After evaporation on rotary evaporator, the residue was dissolved in 2.8 mL of dichloromethane and precipitated by addition of 14 mL of pentane. The ^1H NMR of the acid **2e** was in excellent agreement with reported values and also it's identity was confirmed by HRMS. The acid was used directly in the next step without further purification

2.3.2. General Procedure 1 (One-pot, two-steps synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones)

In a 10 mL vial (CEM Discover System) equipped with a magnetic stir bar, 2-nitrobenzylamine (15 mg, 0.099 mmol), 2,2-dimethylpropanal (7 mg, 0.099 mmol), fumaric acid monoethyl ester (14 mg, 0.099 mmol) and *tert*-butyl isocyanide (8 mg, 0.099 mmol) were added to a mixture of 1.8 mL of ethanol and 0.6 mL of distilled water (3:1 ratio). The vial was capped and placed in the microwave. The microwave was then run at 300 W, 60 ^oC, for 60 min. After cooling the vial to room temperature, 10 equivalent of Fe(0) powder (40 mess, 55 mg, 0.99 mmol) followed by 0.5-1.0 equivalent of NH_4Cl (5 mg, 0.099 mmol) were added to the same vial (assume the multicomponent acyclic Ugi reaction went to completion). The microwave was then run at 300 W, 150

^{o}C, 10 bar for 30-45 min. Then the vial was cooled to room temperature, filtered through a pad of celite and washed with ethyl acetate (3 x 5 mL) followed by saturated $NaHCO_3$ (5 mL). The filtrate was then transferred to a separatory funnel and the mixture was shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 2.5 mL). The organic layers were combined, dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

2.3.2.1. General Procedure 2 for the synthesis of 1,4-BDZ-3-ones(Two-step reaction): Step 1 (Four component acyclic Ugi reaction):

In a 10 mL round-bottomed flask, 2-nitrobenzylamine (0.5g, 3.3 mmol) was dissolved in 5 mL of MeOH and 2,2-dimethylpropanal (0.237 mg, 3.3 mmol) was added. The mixture was stirred for 10 min. Then fumaric acid monoethyl ester (0.473 g, 3.3 mmol) and *tert*-butyl isocyanide (0.273 mg, 3.3 mmol) were added consecutively. The resulting solution was allowed to stir overnight at room temperature and then quenched with 1 mL of 1N HCl. To the mixture, 5 mL of CH_2Cl_2 was added and the reaction was vigorously stirred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were collected, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

2.3.2.2. Step 2 (Synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones):

To a 10 mL vial (CEM Discover System) equipped with a magnetic stir bar, 50 mg of the acyclic Ugi product from step 1 was added along with 1.8 mL of ethanol and 0.6 mL of distilled water. Then 10 equivalent of Fe(0) powder (40 mess) followed by 0.5-1.0 equivalent of NH_4Cl were added to the same vial. The vial was capped and placed in the microwave. The microwave was then run for 30-45 min at 150 ^oC, 10 bar and 300 W. Then the vial was cooled to room temperature and filtered through a pad of celite and washed with ethyl acetate (3 x 5 mL) followed by saturated $NaHCO_3$ (5 mL). The filtrate was then transferred to a separatory funnel and the mixture was shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 2.5 mL). The organic layers were combined, dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

2.3.2.3. Sealed Tube Reaction Condition for the Synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones):

To a 20 mL sealed tube equipped with a magnetic stir bar, 50 mg of the acyclic Ugi product (**5**) from step 1 was added along with 1.8 mL of ethanol and 0.6 mL of distilled water. Then 10 equivalent of Fe(0) powder (40 mess) followed by 0.5-1.0 equivalent of NH_4Cl were added to the same sealed tube. The sealed tube was placed in the silicone oil bath and heated at 200-205 ^oC for one hour. Then the sealed tube was cooled to room temperature and filtered through a pad of celite and washed with ethyl acetate (3 x 5 mL) followed by saturated $NaHCO_3$ (5 mL). The filtrate was then transferred to a separatory funnel and the mixture was shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 2.5 mL).

The organic layers were combined, dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography using a 1:3 mixture of ethyl acetate to hexane as the eluent.

2.3.3. General procedure for the synthesis of 1,2,3,4-tetrahydroisoquinolinones from 2-azaspirocyclohexadienones:

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, 50 mg of acyclic Ugi starting material was taken and 2.5 mL of dry nitromethane (CH_3NO_2) or acetonitrile (CH_3CN) was added to it under Argon. The vial was capped properly and 14 μL of dry $BF_3.OEt_2$ or TMSOTf was added carefully. The vial was capped with a new cap very quickly and placed in the microwave cavity. Then microwave was run for 10-15 min at 100 ^oC, 16 Bar and 300 W. After cooling the vial at room temperature, the reaction mixture was transferred to a 25 mL RB flask and concentrated on rotary evaporator. The residue was purified by gradient silica gel column chromatography using mixture of ethyl acetate and hexane (1:4 to 1:1) as the eluent.

2.3.3.1. General Procedure for the 'off-the-shelf' convertible isocyanides:

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, 50 mg of acyclic Ugi starting material was taken and 2.5 mL of dry nitromethane (CH_3NO_2) or acetonitrile (CH_3CN) was added to it under Argon. The vial was capped properly and 14 μL of dry $BF_3.OEt_2$ was added carefully. The vial was capped with a new cap very quickly and placed in the microwave cavity. Then microwave was run for 10-15 min at 100 ^oC, 16 Bar and 300 W. After cooling the vial at room temperature, the

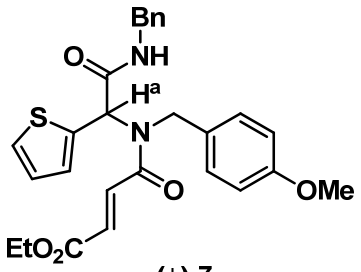
reaction mixture was transferred to a 25 mL RB flask and concentrated on rotary evaporator. The residue was purified by gradient silica gel column chromatography using mixture of ethyl acetate and hexane (1:4 to 1:1) as the eluent.

2.3.3.2. General procedure for the one-pot synthesis of 1,2,3,4-tetrahydroisoquinolinones (starting from four separate substrates):

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, 15 mg (0.14 mmol) of Benzyl amine, 12 mg (0.14 mmol) of 4-acetamidobenzaldehyde, 25 mg (0.14 mmol) of *trans*-3-Benzoylacrylic acid and 17 μL (0.14 mmol) of Benzyl isocyanide were taken in a mixture of 1.5 mL LiCl and 1 mL MeOH. The vial was capped properly and placed in the microwave. Then the microwave was run at two stages: (a) 1 hr at 50 ^{o}C, 10 Bar and 300 W (b) 20-25 min, 210 ^{o}C, 18 Bar and 300 W. After cooling the vial at room temperature, ethyl acetate was added and shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate twice (2 mL each). The organic layers were combined and washed with $NaHCO_3$ (3 mL each), 1 N HCl (3 mL each), Brine (3 mL each). The organic layer was separated. All aqueous layers were combined and extracted with 3 mL ethyl acetate. The organic layers were combined and dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified by silica gel column chromatography using 1:2 mixture of ethyl acetate and hexane as eluent.

2.4. Experimental Data

1. **(*E*)-Ethyl 4-((2-(benzylamino)-2-oxo-1-(thiophen-2-yl)ethyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



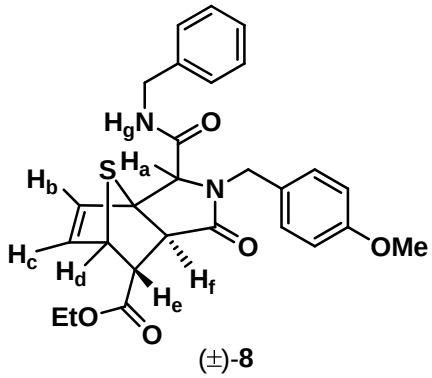
(±)-7

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.36 (m, 7 H, Ph , thienyl and –C<u>H</u>=CH- overlap)), 7.08 (d, 1 H, *J* = 3.2 Hz, thienyl), 7.01 (d, 2 H, *J* = 8.8 Hz, Aryl), 6.91 (dd, 1 H, *J* = 5.2, 4 Hz, thienyl), 6.87 (d, 1 H, *J* = 15.2 Hz, -CH=C<u>H</u>-), 6.77 (d, 2 H, *J* = 8.4 Hz, Aryl), 6.33 (t, 1 H, *J* = 5.6 Hz, -N<u>H</u>), 5.95 (s, 1 H, H^a), 4.69 (dd, 2 H, *J* = 24.4, 17.2 Hz, -NC<u>H</u>$_2$Ar), 4.44 (ddd, 2 H, *J* = 48.0, 14.8, 5.6 Hz, -NC<u>H</u>$_2$Ar), 4.19 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$$CH_3$), 3.76 (s, 3 H, O<u>Me</u>), 1.26 (t, 3 H, *J* = 7.3 Hz, -OCH_2C<u>H</u>$_3$)

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 166.2, 165.5, 159.2, 137.9, 136.1, 133.8, 132.9, 130.2, 128.9, 128.6, 128.3, 128.2, 127.8, 127.7, 126.8, 125.1, 114.3, 61.3, 59.2, 55.5, 50.4, 44.0, 14.3.

HRMS (EIMS, M^+): calcd for $C_{28}H_{29}NO_5S$ 491.1766, found 491.1769.

2. **Thiophene-derived tricyclic lactam**



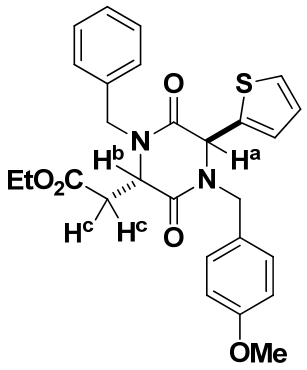
(±)-**8**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.38 (m, 3H, aryl), 7.19-7.24 (m, 2H, aryl), 7.10 (d, 2H, *J* = 8.6 Hz, aryl), 6.81 (d, 2H, *J* = 8.6 Hz, aryl), 6.48 (d, 1H, *J* = 6.1 Hz, H_b), 6.32 (dd, 1H, *J* = 3.6, 6.1 Hz, H_c), 6.30 (br t, 1H, H_g), 4.93 (d, 1H, *J* = 14.7 Hz, bn), 4.41-4.46 (m, 3H, bn and H_d overlap), 4.14 (q, 2H, *J* = 7.1 Hz, –OC<u>H</u>$_2$CH$_3$), 3.98 (s, 1H, H_a), 3.94 (d, 1H, *J* = 14.7 Hz, bn and H_e overlap), 3.92 (t, 1H, *J* = Hz, H_e and bn overlap), 3.78 (s, 3H, OCH_3), 3.42 (d, 1H, *J* = 3.6 Hz, H_f), 1.25 (t, 3H, *J* = 7.1 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 170.5, 166.9, 159.5, 136.9, 136.6, 129.9, 128.9, 127.9, 127.8, 126.8, 114.3, 71.3, 62.3, 61.4, 55.3, 54.9, 54.3, 51.7, 45.9, 43.9, 29.7, 14.2.

HRMS: EIMS (M^+) calcd for $C_{27}H_{28}N_2O_5S$ 492.1719, found 492.1713.

2. **Ethyl 2-((2S,5S)-1-benzyl-4-(4-methoxybenzyl)-3,6-dioxo-5-(thiophen-2-yl)piperazin-2-yl)acetate**



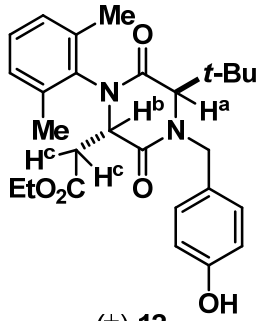
(±)-**11**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (m, 1H), 7.3-7.36 (m, 3H), 7.14-7.2 (m, 4H), 7.06-7.12 (m, 2H), 6.86-6.9 (m, 2H), 5.52 (d, 1H, *J*=14.4 Hz), 5.37 (d, 1H, *J*=15.6 Hz), 4.26 (m, 1H), 4.12-4.18 (m,1H), 4.02-4.08 (m, 1H), 3.99 (d, 1H, *J*=15.6 Hz), 3.85 (s, 3H), 3.64 (d, 1H, *J*=14.4 Hz), 3.32 (dd, 1H, *J*=3, 17.4 Hz), 2.96 (dd, 1H, *J*=4.8, 17.4 Hz), 1.21 (t, 3H, *J*=7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 165.1, 165.0, 159.3, 139.9, 134.9, 130.2, 128.9, 127.9, 127.8, 127.1, 126.4, 113.9, 61.0, 58.4, 55.2, 54.5, 46.7, 46.6, 34.5, 14.0.

HRMS (EIMS, M^+): calcd for $C_{27}H_{28}N_2O_8S$ 492.1719, found 492.1721.

3. **Ethyl 2-((2S,5R)-5-(*tert*-butyl)-1-(2,6-dimethylphenyl)-4-(4-hydroxybenzyl)-3,6-dioxopiperazin-2-yl)acetate**



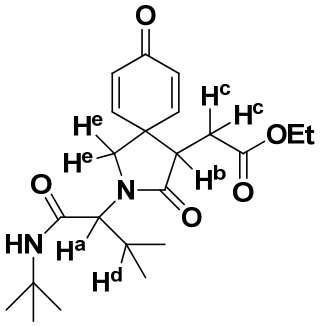
(±)-**12**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (br s, 1 H, -O<u>H</u>), 7.12-7.18 (t, 1 H, *J* = 7.6 Hz, Ar), 7.02-7.10 (m, 4 H, Ar), 6.58 (d, 2 H, *J* = 8.5 Hz, Ar), 5.56 (d, 1 H, *J* = 14.3 Hz, -C<u>H</u>$_2$Ar), 5.30 (dd, 1 H, J = 7.9, 5.5 Hz, H^b), 4.03 (s, 1 H, H^a), 3.90-4.06 (m, 2 H, -OC<u>H</u>$_2$CH$_3$), 3.83 (d, 1 H, J = 14.3 Hz, -C<u>H</u>$_2$Ar), 2.80 (dd, 1 H, *J* = 16.2, 7.9 Hz, H^c), 2.24 (s, 3 H, -C<u>H</u>$_3$), 2.25 (dd, 1 H, *J* = 16.2, 5.5 Hz, H^c), 1.80 (s, 3 H, -C<u>H</u>$_3$), 1.30 (s, 9 H, *t*-Bu), 1.13 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 167.9, 167.5, 156.7, 136.7, 136.1, 135.4, 129.8, 129.0, 128.9, 128.8, 126.9, 115.6, 69.6, 61.0, 55.9, 51.4, 39.5, 34.0, 28.9, 19.1, 18.1, 13.9

HRMS: EIMS (M^+) calcd for $C_{27}H_{34}N_2O_5$ 466.2468, found 466.2466.

4. **Ethyl 2-(2-(1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



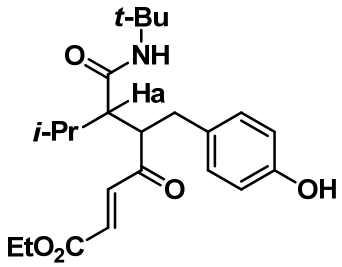
(±)-**16**

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (m, 2H), 6.32 (m, 2H), 5.79 (br s, 1H, NH), 4.07 (m, 2H, –OC$\underline{H}_2$CH$_3$), 3.95 (d, 1H, *J* = 11 Hz, H_a), 3.78 (d, 1H, *J* = 10.4 Hz, H_e), 3.53 (d, 1H, *J* = 10.4 Hz, H_e), 3.39 (dd, 1H, *J* = 6.1, 7.6 Hz, H_b), 2.65 (dd, 1H, *J* = 6.1, 16.6 Hz, H_c), 2.09 (dd, 1H, *J* = 7.6, 16.8 Hz, H_c), 1.20 (t, 3H, *J* = 7.3 Hz, CH_3), 0.95 (d, 3H, *J* = 6.1 Hz, CHC$\underline{H}_3$), 0.90 (d, 3H, *J* = 4.9 Hz, CHC$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 172.6, 171.3, 168.2, 149.2, 145.9, 131.4, 130.9, 62.8, 61.1, 50.8, 50.1, 48.1, 47.4, 30.3, 28.6, 27.3, 19.3, 19.3, 14.

HRMS: EIMS (M^+) calcd for $C_{22}H_{32}N_2O_5$ 404.2311, found 404.2317.

5. **(*E*)-ethyl 6-(*tert*-butylcarbamoyl)-5-(4-hydroxybenzyl)-7-methyl-4-oxooct-2-enoate**



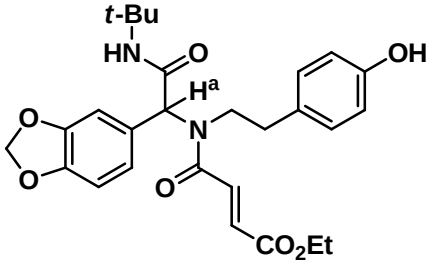
(±)-**17**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 8.12 (bs, 1H), 7.3 (d, 1H, *J*=15.2 Hz), 6.89 (d, 2H, *J*=8.6 Hz), 6.81 (d, 1H, *J*=15.2 Hz), 6.6 (d, 2H, *J*=8.6 Hz), 4.74 (d, 1H, *J*=16.7 Hz), 4.5 (d, 1H, *J*=16.7 Hz), 4.19 (q, 2H, *J*=7.1 Hz), 2.5 (bs, 1H), 1.26 (t, 3H, *J*=7.1 Hz), 0.94 (d, 3H, *J*=6.6 Hz), 0.81 (d, 3H, *J*=6.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 169.5, 166.9, 165.4, 156.3, 134.1, 132.1, 127.8, 127.1, 115.7, 61.2, 51.4, 28.7, 28.5, 27.3, 19.5, 18.9, 14.0.

HRMS: EIMS (M^+) calcd for $C_{23}H_{33}NO_5$ 403.2359, found 403.2357.

6. **(*E*)-Ethyl 4-((2-(*tert*-butylamino)-1-(naphthalen-2-yl)-2-oxoethyl)(4-hydroxyphenethyl)amino)-4-oxobut-2-enoate**



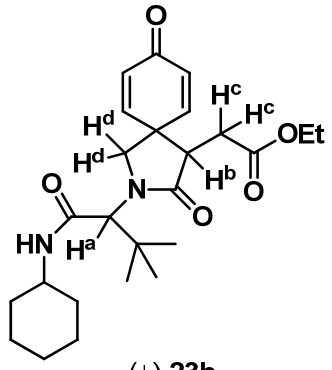
(±)-**20**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.99 (m, 4 H, Aryl), 7.48-7.59 (m, 3 H, Aryl), 7.36 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.85 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.59 (s, 2 H, -OC<u>H</u>$_2$O-), 6.19 (s, 1 H, H^a), 5.89 (s, 1 H, -N<u>H</u>), 5.77 (s, 1 H, -O<u>H</u>), 4.26 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.55-3.71 (m, 2 H, -NC<u>H</u>$_2$CH$_2$Ar), 2.42-2.57 (m, 1 H, -NCH$_2$C<u>H</u>$_2$Ar), 2.0-2.12 (m, 1 H, -NCH$_2$C<u>H</u>$_2$Ar), 1.36 (s, 9 H, *t*-Bu), 1.32 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 166.5, 163.0, 155.7, 149.3, 147.7, 135.7, 132.0, 130.2, 130.2, 127.5, 126.7, 115.8, 114.7, 112.9, 101.2, 71.0, 61.4, 60.0, 47.3, 33.7, 29.2, 14.2.

HRMS: EIMS (M^+) calcd for $C_{30}H_{34}N_2O_5$ 502.2468, found 502.2468.

7. **Ethyl 2-(2-(1-(cyclohexylamino)-3,3-dimethyl-1-oxobutan-2-yl)-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



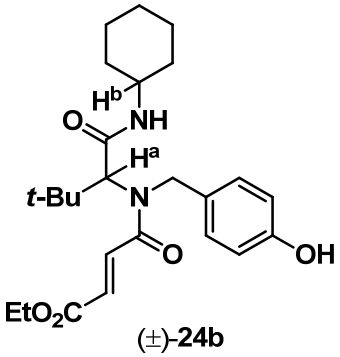
(±)-**23b**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81-6.93 (m, 2H), 6.33-6.47 (m, 2H), 5.62 (d, 1H, *J* = 7.6 Hz, –N<u>H</u>), 4.25 (s, 1H, H_a), 4.08 (dq, 2H, *J* = 1.4, 7.2 Hz, –OC<u>H</u>$_2$CH$_3$), 3.69-3.78 (m, 3H, H_e and H_d overlap), 3.29 (dd, 1H, *J* = 6.1, 7.6 Hz, H_b), 2.90 (dd, 1H, *J* = 5.9, 16.6 Hz, H_c), 2.13 (dd, 1H, *J* = 7.6, 16.8 Hz, H_c), 1.83-1.97 (m, 3H, Cy), 1.66-1.77 (m, 3H, Cy), 1.57-1.65 (m, 2H, Cy), 1.30-1.41 (m, 2H, Cy), 1.20 (t, 3H, *J* = 7.3 Hz, –OCH$_2$CH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 185.1, 173.8, 171.3, 166.6, 149.7, 146.1, 131.4, 131.3, 64.1, 61.1, 53.9, 48.5, 47.5, 46.6, 36.1, 33.1, 32.9, 30.7, 27.6, 25.4, 24.8, 24.7, 14.1.

HRMS (EIMS, M^+): calcd for $C_{25}H_{36}N_2O_5$ 444.2624, found 444.2632.

8. **(*E*)-Ethyl 4-((1-(cyclohexylamino)-3,3-dimethyl-1-oxobutan-2-yl)(4-hydroxybenzyl)amino)-4-oxobut-2-enoate**



(±)-**24b**

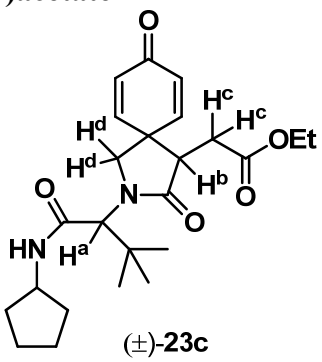
^{1}H NMR (300 MHz, CD_3OD): δ 7.20 (d, 1 H, *J* = 15.8 Hz, -C<u>H</u>=CH-), 6.86 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.62 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.44 (d, 1 H, *J* = 15.3 Hz, -CH=C<u>H</u>-), 5.43

(d, 1 H, *J* = 17.7 Hz, -NC<u>H</u>$_2$Ar), 5.07 (s, 1 H, H^{a}0, 4.68 (d, 1 H, *J* = 17.7 Hz, -NC<u>H</u>$_2$Ar), 4.07 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.32-3.50 (m, 1 H, H^b), 1.45-1.86 (m, 8 H, Cy), 1.09-1.32 (m, 5 H, Cy and –OCH$_2$CH$_3$ overlap), 1.01 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, CD$_3$OD): δ 169.7, 169.0, 166.7, 157.6, 136.4, 131.5, 131.3, 128.2, 116.3, 64.2, 62.1, 50.3, 49.7, 38.1, 33.7, 33.4, 28.0, 26.6, 26.1, 14.4.

HRMS (EIMS, M$^+$): calcd for $C_{25}H_{36}N_2O_5$ 444.2624, found 444.2619.

9. **Ethyl 2-(2-(1-(cyclopentylamino)-3,3-dimethyl-1-oxobutan-2-yl)-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



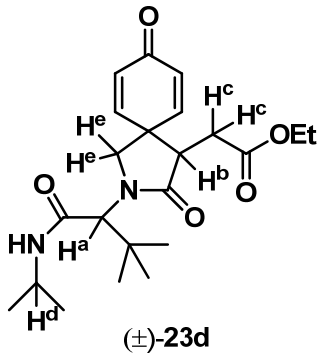
(±)-**23c**

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.89 (m, 2H), 6.36 (m, 2H), 5.94 (d, 1H, *J* = 7.3 Hz, –N<u>H</u>), 4.28 (s, 1H, H$_a$), 4.12-4.18 (m, 1H, H$_d$), 4.07 (q, 2H, *J* = 7.3 Hz, –OC<u>H</u>$_2$CH$_3$).. 3.70 (dd, 2H, *J* = 11.4, 14.6 Hz, H$_e$), 3.30 (dd, 1H, *J* = 6.5, 8.1 Hz, H$_b$), 2.67 (dd, 1H, *J* = 6.1, 16.7 Hz, H$_c$), 2.12 (dd, 1H, *J* = 7.3, 16.2 Hz, H$_c$), 1.88-2.23 (m, 2H, Cp), 1.51-1.72 (m, 4H, Cp), 1.29-1.44 (m, 2H, Cp), 1.20 (t, 3H, *J* = 7.3 Hz, –OCH$_2$C<u>H</u>$_3$), 1.05 (s, 9H, *t*-Bu).

^{13}C NMR (100 MHz, CDCl$_3$): δ 185.1, 173.3, 171.4, 168.2, 149.3, 145.9, 131.5, 130.9, 63.1, 61.1, 52.6, 51.2, 47.6, 47.0, 35.1, 33.0, 32.9, 30.4, 27.8, 27.6, 23.7, 14.0.

HRMS: EIMS (M$^+$) calcd for $C_{24}H_{34}N_2O_5$ 430.2488, found 430.2487.

10. **Ethyl 2-(2-(1-(isopropylamino)-3,3-dimethyl-1-oxobutan-2-yl)-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



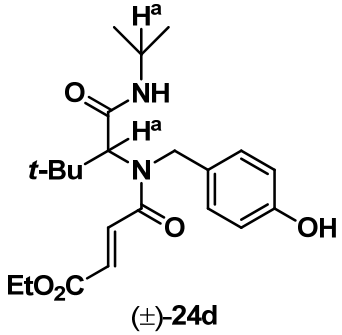
(±)-**23d**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (m, 1H), 6.63 (m, 1H), 6.36 (m, 2H), 5.65 (d, 1H, *J* = 7.3 Hz, –N<u>H</u>), 4.33 (s, 1H, H_a), 4.17 (d, 1H, *J* = 10.4 Hz, H_e), 4.00-4.12 (m, 3H, H_d and – OC<u>H</u>2CH3 overlap), 3.74 (d, 1H, *J* = 10.4 Hz, H_e), 3.38 (dd, 1H. *J* = 6.4, 7.6 Hz, H_b), 2.64 (dd, 1H, *J* = 5.8, 16.7 Hz, H_c), 2.07 (dd, 1H, *J* = 7.6, 16.7 Hz, H_e), 1.20 (t, 3H, *J* = 7.3 Hz, –OCH_2C<u>H</u>$_3$), 1.16 (d, 3H, *J* = 6.1 Hz, *i*-Pr), 1.15 (d, 3H, *J* = 6.1 Hz, *i*-Pr), 1.07 (s, 9H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 185.1, 173.3, 171.4, 167.7, 149.3, 145.9, 131.5, 131.0, 63.2, 61.1, 52.6, 47.6, 47.0, 41.5, 35.1, 30.4, 27.8, 22.6, 14.0.

HRMS: EIMS (M^+) calcd for $C_{22}H_{32}N_2O_5$ 404.2311, found 404.2308.

11. **(*E*)-Ethyl 4-((4-hydroxybenzyl)(1-(isopropylamino)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



(±)-**24d**

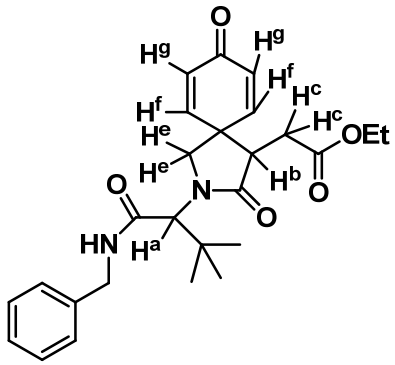
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, 1 H, *J* = 15.3 Hz, -C<u>H</u>=CH-), 6.83 (d, 2 H, *J* = 8.5 Hz, Aryl), 6.76 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.55 (d, 2 H, *J* = 8.5 Hz, Aryl), 5.36

(d, 1 H, J = 17.1 Hz, -NC<u>H</u>$_2$Ar), 4.96 (s, 1 H, H^a), 4.66 (d, 1 H, J = 17.1 Hz, -NC<u>H</u>$_2$Ar), 4.17 (dq, 2 H, J = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.84 (sept, 1 H, J = 6.7 Hz, H^b), 1.26 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.11 (d, 3 H, J = 6.7 Hz, *i*-Pr), 1.08 (s, 9 H, *t*-Bu), 0.91 (d, 3 H, J = 6.7 Hz, *i*-Pr).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 165.4, 155.3, 135.1, 134.0, 132.8, 131.9, 127.1, 114.6, 61.2, 41.4, 37.1, 27.5, 22.5, 22.1, 14.1.

HRMS (EIMS, M$^+$): calcd for $C_{22}H_{32}N_2O_5$ 404.2311, found 404.2321.

12. **Ethyl 2-(2-(1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**

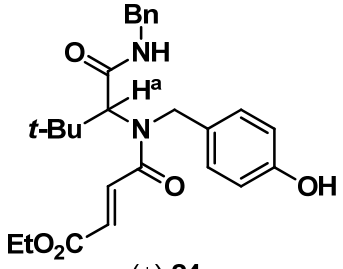


(±)-**23e**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22-7.37 (m, 5 H, Ph), 6.86 (dd, 1 H, J = 10.1, 3.1 Hz, H^g), 6.34 (dd, 1 H, J = 10.1, 1.8 Hz, H^g), 6.30 (dd, 1 H, J = 3.1 Hz, 3.1 Hz, H^f), 6.22 (dd, 1 H, J = 10.4, 1.8 Hz, H^f), 6.15 (t, 1 H, J = 6.1 Hz, -N<u>H</u>), 4.61 (s, 1 H, H^a), 4.44 (dd, 1 H, J = 14.7, 6.1 Hz), H^e), 4.35 (dd,1 H, J = 5.8, 14.7 Hz, H^e), 4.05-4.12 (m, 2 H, -OC<u>H</u>$_2$CH$_3$), 4.04 (d, 1 H, J = 10.1 Hz, -NHC<u>H</u>$_2$Ph), 3.75 (d, 1 H, J = 10.4 Hz, -NHC<u>H</u>$_2$Ph), 3.36 (dd, 1 H, J = 7.3, 6.1 Hz, H^b), 2.59 (dd, 1 H, J = 16.8, 6.1 Hz, H^c), 2.01 (dd, 1 H, J = 16.8, 7.6 Hz, H^c), 1.25 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.09 (s, 9 H, *t*-Bu).

HRMS (EIMS, M$^+$): calcd $C_{26}H_{32}N_2O_5$ 452.2311, found 452.2317.

13. **(*E*)-Ethyl 4-((1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)(4-hydroxybenzyl)amino)-4-oxobut-2-enoate**



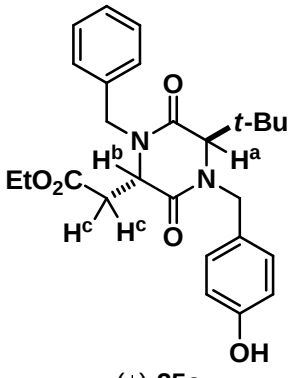
(±)-**24e**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.5-7.7 (bs, 1H), 7.1-7.38 (m, 6H), 6.78 (d, 2H, J = 8.1 Hz), 6.66 (d, 1H, J = 15.2 Hz), 6.49 (d, 2H, J = 8.1 Hz), 5.34 (d, 1H, J = 15.2 Hz), 5.05-5.26 (bs, 1H), 4.68 (d, 1H, J = 15.2 Hz), 4.38 (dd, 1H, J = 6.1, 14.7 Hz), 4.15 (m, 2H), 4.02 (d, 1H, J = 12.7 Hz), 1.24 (t, 3H, J = 7.1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 168.8, 167.6, 165.4, 155.4, 137.3, 134.1, 131.7, 128.6, 127.8, 127.5, 126.9, 115.6, 61.2, 43.5, 36.9, 27.6, 13.9.

HRMS (EIMS, M^+) calcd for $C_{26}H_{32}N_2O_5$ 452.2311, found 452.2314.

14. **(3R,6S)-1-benzyl-3-(*tert*-butyl)-4-(4-hydroxybenzyl)-6-(2-oxopropyl)piperazine-2,5-dione**



(±)-**25e**

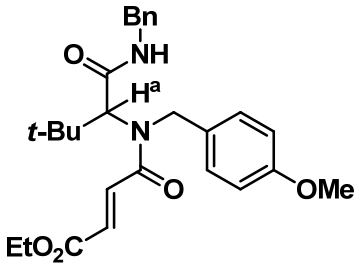
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (bs, 1H, –O<u>H</u>), 7.24-7.37 (m, 3H, aryl), 7.20 (m, 2H, aryl), 7.08 (d, 2H, *J* = 8.1 Hz, aryl), 6.63 (d, 2H, *J* = 8.6 Hz), 5.56 (d, 1H, *J* = 15.2 Hz,

Bn), 5.16 (d, 1H, *J* = 15.2 Hz, Bn), 4.53 (dd, 1H, *J* = 4.1, 5.6 Hz, H_b), 4.32 (d, 1H, *J* = 15.7 Hz, Bn), 3.98-4.16 (m, 2H, –OC<u>H</u>$_2$CH$_3$), 3.88 (d, 1H, *J* = 15.2 Hz, Bn), 3.17 (dd, 1H, *J* = 3.6, 17.2 Hz, H_c), 2.97 (dd, 1H, *J* = 6.1, 17.2 Hz, H_c), 1.18 (t, 3H, *J* = 7.3 Hz, –OCH$_2$C<u>H</u>$_3$), 1.12 (s, 9H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 170.1, 167.7, 167.5, 156.4, 136.1, 129.5, 128.9, 127.8, 127.6, 126.3, 115.7, 67.7, 61.0, 55.8, 51.3, 47.0, 40.1, 34.6, 28.3, 14.0.

HRMS (EIMS, M^+): calcd for $C_{26}H_{32}N_2O_5$ 452.2311, found 452.2314.

15. **(*E*)-Ethyl 4-((1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



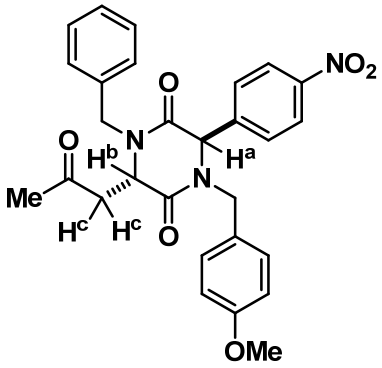
(±)-**27a**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.1-7.35 (m, 6H, aryl), 6.96 (d, 2H, *J* = 8.1 Hz, aryl), 6.75 (d, 2H, *J* = 8.6 Hz, aryl), 6.62 (d, 1H, *J* = 15.2 Hz, HC=CH), 5.27 (d, 1H, *J* = 17.2 Hz, bn), 4.96-5.18 (br, 1H,), 4.72 (d, 1H, *J* = 17.2 Hz, bn), 4.35 (dd, 1H, *J* = 5.6, 14.2 Hz), 4.03-4.22 (m, 3H), 3.8 (s, 3H, OCH_3), 1.24 (t, 3H, *J* = 7.1 Hz, CH_3), 1.1 (s, 9H, *t*-butyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 167.2, 165.3, 158.6, 137.6, 134.2, 131.4, 128.7, 127.9, 127.5, 127.2, 114.1, 60.9, 55.2, 43.4, 36.7, 27.6, 14.0.

HRMS: EIMS (M^+) calcd for $C_{27}H_{34}N_2O_5$ 466.2468, found 466.2481.

16. **(3R,6S)-1-benzyl-4-(4-methoxybenzyl)-3-(4-nitrophenyl)-6-(2-oxopropyl)piperazine-2,5-dione**



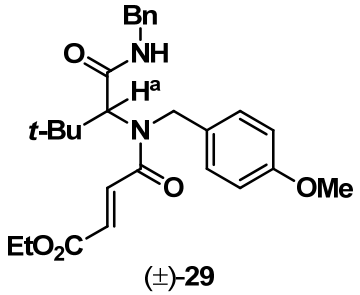
(±)-**28**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, 1 H, *J* = 8.9 Hz, Aryl), 7.72 (d, 1 H, *J* = 8.9 Hz, Aryl), 7.44 (d, 1 H, *J* = 8.9 Hz, Aryl), 7.22-7.34 (m, 5 H, Ph), 7.02 (d, 2 H, *J* = 8.1 Hz, Aryl), 6.81 (d, 2 H, *J* = 8.1 Hz, Aryl), 5.47 (d, 1 H, *J* = 14.6 Hz, -NC$\underline{H}_2$Ar), 5.43 (d, 1 H, *J* = 14.6 Hz, -NC$\underline{H}_2$Ar), 5.23 (s, 1 H, H^a), 4.67 (d, 1 H, *J* = 15.4 Hz, -NC$\underline{H}_2$Ar), 4.65 (dd, 1 H, *J* = 5.7, 4.1 Hz, H^b), 4.50 (d, 1 H, *J* = 14.6 Hz, -NC$\underline{H}_2$Ar), 3.81 (s, 3 H, O$\underline{Me}$), 3.27 (dd, 1 H, *J* = 15.4, 3.2 Hz, H^c), 3.10 (dd, 1 H, *J* = 18.7, 4.9 Hz, H^c), 2.10 (s, 3 H, -CO$\underline{Me}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 170.2, 166.3, 158.4, 146.9, 143.2, 136.7, 132.1, 129.1, 128.9, 128.6, 128.2, 127.9, 127.2, 114.4, 70.3, 61.3, 55.9, 50.9, 49.1, 43.1, 29.4.

HRMS (EIMS, M^+): calcd for $C_{28}H_{27}N_3O_6$ 501.1900, found 501, 1910.

17. **(*E*)-Ethyl 4-((1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



(±)-**29**

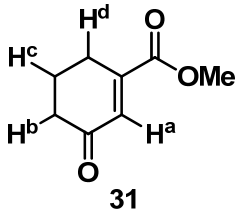
^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.1-7.35 (m, 6H), 6.96 (d, 2H, J = 8.1 Hz), 6.75 (d, 2H, J = 8.6 Hz), 6.62 (d, 1H, J = 15.2 Hz), 5.27 (d, 1H, J = 17.2 Hz), 4.96-5.18 (bs, 1H), 4.72

(d, 1H, J = 17.2 Hz), 4.35 (dd, 1H, J = 5.6, 14.2 Hz), 4.03-4.22 (m, 3H), 3.8 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 1.1 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 168.7, 167.2, 165.3, 158.6, 137.6, 134.2, 131.4, 128.7, 127.9, 127.5, 127.2, 114.1, 60.9, 55.2, 43.4, 36.7, 27.6, 14.0.

HRMS (EIMS, M^+): calcd for $C_{27}H_{34}N_2O_5$ 466.2468, found 466.2471.

18. **Methyl 3-oxocyclohex-1-enecarboxylate**



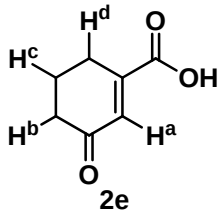
31

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (s, 1 H, H^a), 3.82 (s, 3 H, O<u>Me</u>), 2.58 (dt, 2 H, *J* = 5.8, 1.5 Hz, H^b), 2.44 (t, 2 H, *J* = 7.0 Hz, H^d), 2.05 (quintet, 2 H, *J* = 6.7 Hz, H^c).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.0, 166.9, 148.7, 133.1, 52.6, 37.7, 24.8, 22.1.

HRMS (EIMS, M^+): calcd for $C_8H_{10}O_3$ 154.0630, found 154.0641.

19. **3-Oxocyclohex-1-enecarboxylic acid**



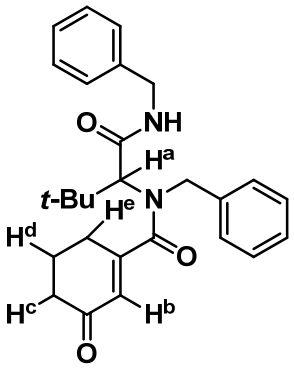
2e

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.3 (br s, 1 H, -CO_2<u>H</u>), 6.80-6.84 (m, 1 H, H^a), 2.55-2.61 (m, 1 H, H^b), 2.44-2.50 (m, 2 H, H^d), 2.03-2.10 (m, 2 H, H^c).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 171.2, 148.5, 134.1, 37.5, 24.4, 21.9.

HRMS (EIMS, M^+): calcd for $C_7H_8O_3$ 140.0473, found 140.0482.

20. ***N*-Benzyl-*N*-(1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)-3-oxocyclohex-1-enecarboxamide**



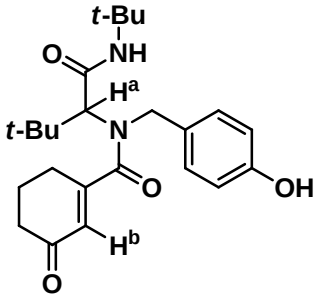
(±)-**32**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.38 (m, 10 H, 2 × Ph), 6.83 (t, 1 H, *J* = 5.6 Hz, -N<u>H</u>), 5.99 (s, 1 H, H^b), 5.44 (d, 1 H, *J* = 16.2 Hz, -NC<u>H</u>$_2$Ph), 5.02 (s, 1 H, H^a), 4.53 (d, 1 H, *J* = 16.2 Hz, -NC<u>H</u>$_2$Ph), 4.46 (dd,1 H, *J* = 14.6, 5.7 Hz, -NC<u>H</u>$_2$Ph), 4.34 (dd, 1 H, *J* = 14.6, 5.7 Hz, -NC<u>H</u>$_2$Ph), 2.01-2.28 (m, 4 H, H^c and H^e overlap), 1.59-1.74 (m, 1 H, H^d), 1.32-1.44 (m, 1 H, H^d), 1.15 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 172.5, 168.8, 156.4, 138.8, 137.6, 128.8, 128.1, 127.6, 127.5, 127.2, 125.5, 63.1, 51.4, 43.5, 37.0, 36.9, 27.6, 25.8, 21.9.

HRMS (EIMS, M^+): calcd for $C_{27}H_{32}N_2O_3$ 432.2413, found 432.2422.

21. ***N*-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-N-(4-hydroxybenzyl)-3-oxocyclohex-1-enecarboxamide**



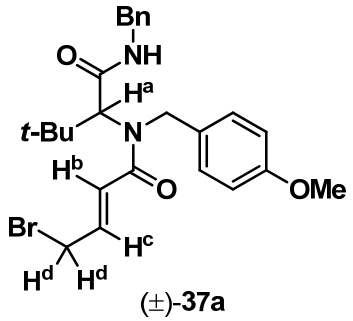
(±)-**34**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (d, 2 H, *J* = 8.2 Hz, Aryl), 6.66 (d, 2 H, *J* = 8.2 Hz, Aryl), 5.99 (s, 1 H, H^b), 5.42 (s, 1 H, -NC$\underline{H}_2$Ar), 4.78 (br s, 1 H, -O$\underline{H}$), 4.40 (d,1 H, *J* = 15.6 Hz, -NC$\underline{H}_2$Ar), 2.10-2.40 (m, 3 H, cyclohexenone), 1.57-1.85 (m,1 H, cyclohexenone), 1.20-1.42 (m, 11 H, *t*-Bu and cyclohexenone overlap), 1.12 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 172.8, 168.5, 156.8, 155.7, 128.7, 125.2, 115.7, 51.8, 37.1, 37.0, 28.5, 27.6, 26.1, 22.1.

HRMS (EIMS, M^+): calcd for $C_{24}H_{34}N_2O_4$ 414.2519, found 414.2527.

22. **(*E*)-*N*-(1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)-4-bromo-N-(4-methoxybenzyl)but-2-enamide**



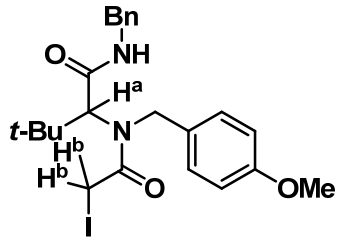
(±)-**37a**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18-7.32 (m, 5 H, Ph), 6.97 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.77 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.71 (dt, 1 H, *J* = 14.7, 7.3 Hz, H^c), 6.24 (d, 1 H, *J* = 14.7 Hz, H^b), 5.10-5.31 (m, 2 H, -NC$\underline{H}_2$Ph and H^a overlap), 4.72 (d, 1 H, *J* = 17.1 Hz, -NC$\underline{H}_2$Ph), 4.45 (ddd, 1 H, *J* = 27.8, 14.9, 5.8 Hz, H^d), 4.39 (dd, 1 H, *J* = 14.9, 6.1 Hz, -NC$\underline{H}_2$Ar), 4.15 (dd, 1 H, *J* = 14.7, 5.2 Hz, -NC$\underline{H}_2$Ar), 3.99 (dd, 1 H, *J* = 7.0, 1.1 Hz, H^d), 3.59 (s , 3 H. O$\underline{Me}$), 1.15 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 167.7, 158.4, 139.7, 137.9, 128.5, 127.9, 127.2, 126.9, 124.7, 113.9, 55.2, 48.9, 43.2, 36.5, 29.9, 27.6.

HRMS (EIMS, M^+): calcd for $C_{25}H_{31}BrN_2O_3$ 486.1518, found 486.1527.

23. ***N*-benzyl-2-(2-iodo-N-(4-methoxybenzyl)acetamido)-3,3-dimethylbutanamide**



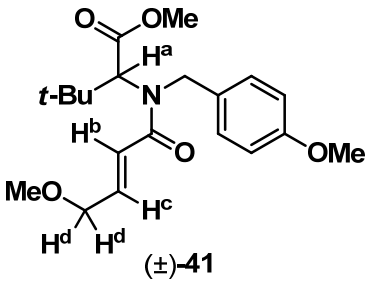
(±)-**37b**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21-7.38 (m, 5 H, Ph), 6.96 (d, 2 H, *J* = 8.5 Hz, Aryl), 6.77 (d, 2 H, *J* = 8.5 Hz, Aryl), 5.41 (d, 1 H, *J* = 17.4 Hz, -NC$\underline{H}_2$Ar), 5.11 (br s, 1 H, H^a), 4.60 (d, 1 H, *J* = 17.4 Hz, -NC$\underline{H}_2$Ar), 4.32 (dd, 1 H, *J* = 14.7, 5.8 Hz, -NC$\underline{H}_2$Ar), 4.22 (dd, 1 H, *J* = 14.7, 5.5 Hz, -NC$\underline{H}_2$Ar), 3.78 (s, 3 H, -O$\underline{Me}$), 3.53 (d, 1 H, *J* = 9.8 Hz, H^b), 3.33 (d, 1 H, J = 9.5 Hz, H^b), 1.12 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.6, 158.6, 137.9, 128.7, 128.6, 128.1, 127.9, 127.3, 126.2, 114.3, 82.2, 55.2, 43.3, 37.5, 27.6, 26.2, -2.0.

HRMS: EIMS (M^+) calcd for $C_{23}H_{29}IN_2O_3$ 508.1223, found 508.1221.

24. **(*E*)-methyl 2-(4-methoxy-N-(4-methoxybenzyl)but-2-enamido)-3,3-dimethylbutanoate**



(±)-**41**

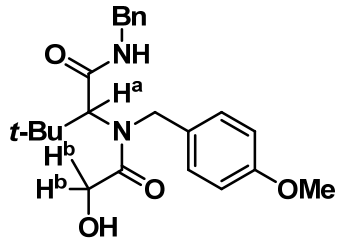
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, 2 H, *J* = 8.1 Hz, Aryl), 6.91 (dt, 1 H, *J* = 15.4, 4.1 Hz, H^c), 6.83 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.33 (d, 1 H, *J* = 14.6 Hz, H^b), 5.24 (s, 1 H, H^a),

4.93 (d, 1 H, *J* = 17.8 Hz, -NC<u>H</u>$_2$Ar), 4.70 (d, 1 H, *J* = 17.8 Hz, -NC<u>H</u>$_2$Ar), 3.89-4.04 (m, 2 H, H^d), 3.77 (s, 3 H, O<u>Me</u>), 3.42 (s, 3 H, O<u>Me</u>), 3.17 (s, 3 H, O<u>Me</u>), 1.08 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 167.9, 158.6, 142.7, 129.9, 127.2, 120.7, 113.9, 71.4, 62.9, 58.3, 55.2, 51.3, 49.7, 36.5, 27.5.

HRMS (EIMS, M^+): calcd for $C_{20}H_{29}NO_5$ 363.2046, found 363.2053.

25. ***N*-benzyl-2-(2-hydroxy-N-(4-methoxybenzyl)acetamido)-3,3-dimethylbutanamide**



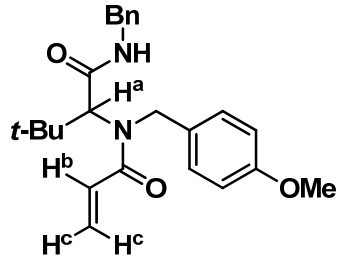
(±)-**42**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23-7.38 (m, 5 H, Ph), 7.11 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.86 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.58 (t, 1 H, *J* = 1.8 Hz, -N<u>H</u>), 5.59 (d, 1 H, *J* = 14.9 Hz, -NC<u>H</u>$_2$Ar), 4.94 (d, 1 H, *J* = 16.8 Hz, Aryl), 4.73 (d, 1 H, *J* = 16.8 Hz, -NC<u>H</u>$_2$Ar), 4.46 (ddd, 1 H, *J* = 25.0, 14.6, 6.1 Hz, -NC<u>H</u>$_2$Ar), 3.75-3.83 (m, 6 H, O<u>Me</u>, H^a and H^b overlap), 1.15 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 164.7, 159.6, 137.9, 129.4, 128.7, 127.9, 127.6, 114.6, 79.6, 67.9, 66.4, 55.3, 50.3, 39.5, 27.9.

HRMS (EIMS, M^+): calcd for $C_{23}H_{30}N_2O_4$ 398.2206, found 398. 2213.

26. ***N*-Benzyl-2-(*N*-(4-methoxybenzyl)acrylamido)-3,3-dimethylbutanamide**



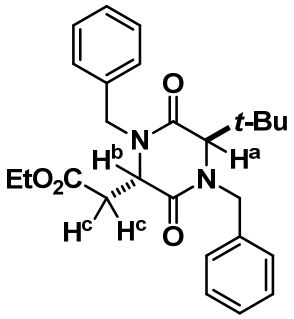
(±)-**44**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (t, 1 H, *J* = 1.8 Hz, -N<u>H</u>), 7.15-7.29 (m, 5 H, Ph), 6.98 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.75 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.36 (dd, 1 H, *J* = 17.0, 10.5 Hz, H^b), 6.14 (dd, 1 H, *J* = 17.0, 2.0 Hz, H^c), 5.48 (dd,1 H, *J* = 10.4, 2.0 Hz, H^c), 5.31 (br s, 1 H, H^a), 5.27 (d, 1 H, *J* = 17.0 Hz, -NC<u>H</u>$_2$Ph), 4.75 (d, 1 H, *J* = 17.8 Hz, -NC<u>H</u>$_2$Ph), 4.32 (dd,1 H, *J* = 14.6, 5.7 Hz, -NC<u>H</u>$_2$Ar), 4.16 (dd,1 H, *J* = 15.4, 5.7 Hz, -NC<u>H</u>$_2$Ar), 3.75 (s, 3 H, O<u>Me</u>), 1.10 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 168.4, 158.2, 138.1, 130.7, 128.3, 128.3, 127.8, 127.0, 126.8, 62.3, 55.1, 48.8, 43.1, 36.5, 27.6.

HRMS (EIMS, M^+): calcd for $C_{24}H_{30}N_2O_3$ 394.2256, found 394.2263.

27. **Ethyl 2-((2S,5R)-1,4-dibenzyl-5-(*tert*-butyl)-3,6-dioxopiperazin-2-yl)acetate**



(±)-**46**

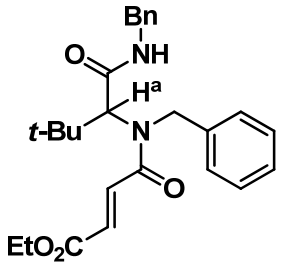
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.37 (m, 10H, aryl), 5.64 (d, 1H, *J* = 15.4 Hz, bn), 5.11 (d,1H, *J* = 15.4 Hz, bn), 4.49 (dd, 1H, *J* = 4.1, 5.7 Hz, H_b), 4.29 (d, 1H, *J* = 15.4 Hz, bn), 4.0-4.15 (m, 2H, –OC<u>H</u>$_2$CH$_3$), 3.29 (d, 1H, *J* = 15.4 Hz, bn), 3.78 (s, 1H, H_a), 3.16

(dd, 1H, J = 4.1, 17 Hz, H_c), 2.96 (dd, 1H, J = 5.7, 17.4 Hz, H_c), 1.20 (t, 3H, J = 7.3 Hz, CH_3), 1.11 (s, 9H, *t*-butyl)

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 167.7, 166.6, 136.5, 135.6, 128.8, 128.7, 127.9, 127.8, 127.7, 127.6, 68.1, 60.8, 55.6, 51.4, 46.9, 40.0, 34.8, 28.3, 14

HRMS (EIMS, M^+): calcd for $C_{26}H_{32}N_2O_4$ 436.2362, found 436.2372.

28. **(*E*)-Ethyl 4-(benzyl(1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



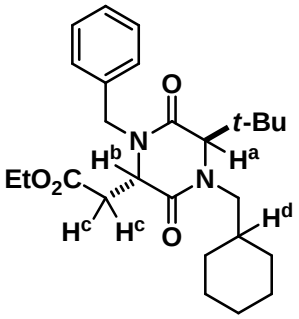
(±)-**47**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.39 (m, 8 H, Ph), 7.17 (d, 1 H, J = 15.4 Hz, -C<u>H</u>=CH-), 6.89-7.16 (m, 2 H, Ph), 6.60 (d, 1 H, J = 15.4 Hz, -CH=C<u>H</u>-), 5.39 (d, 1 H, J = 17.1 Hz, -NC<u>H</u>$_2$Ph), 5.10 (s, 1 H, H^a), 4.77 (d,1 H, J = 17.7 Hz, -NC<u>H</u>$_2$Ph), 4.63 (t, 1 H, J = 1.8 Hz, -N<u>H</u>), 4.31 (dd, 1 H, J = 14.7, 6.1 Hz, -NCH$_2$Ph), 4.04-4.16 (m, 3 H, -OC<u>H</u>$_2$CH$_3$ and –NC<u>H</u>$_2$Ph overlap), 1.20 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.08 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 167.3, 165.3, 138.3, 137.6, 133.9, 131.6, 128.7, 128.6, 127.9, 127.4, 127.1, 125.8, 60.9, 50.6, 43.4, 36.7, 27.5, 13.9.

HRMS (EIMS, M^+): calcd for $C_{26}H_{32}N_2O_4$ 436.2362, found 436.2375.

29. **2-((2S,5R)-1-benzyl-5-(*tert*-butyl)-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl)acetate**



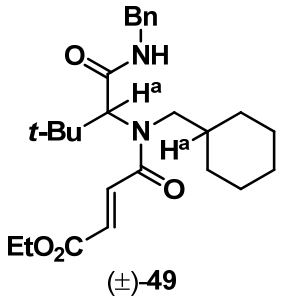
(±)-**48**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.35 (m, 5H, aryl), 5.14 (d, 1H, *J* = 15.4 Hz, bn), 4.32 (dd, 1H, *J* = 3.3, 5.7 Hz, H_b), 4.23-4.30 (m, 2H), 3.99-4.17 (m, 3H), 3.77 (s, 1H, H_a), 3.15 (dd, 1H, *J* = 4.1, 17.4 Hz, H_c), 2.9 (dd, 1H, *J* = 6.5, 17.0 Hz, H_c), 2.50 (dd, 1H, *J* = 9.7, 13.8 Hz), 1.45-1.85 (m, 8H, cyclohexyl), 1.21 (t, 3H, *J* = 7.3 Hz, CH_3), 1.05 (s, 9H, *t*-butyl), 0.75-0.93 (m, 2H, cyclohexyl)

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 167.1, 166.8, 136.5, 128.8, 127.8, 127.7, 71.5, 60.8, 56.9, 55.9, 46.9, 40.2, 35.6, 35.1, 31.2, 30.6, 28.0, 26.4, 25.7, 14.1

HRMS (EIMS, M^+): calcd for $C_{26}H_{38}N_2O_4$ 442.2832, found 442.2841.

30. **(*E*)-Ethyl 4-((1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)(cyclohexylmethyl)amino)-4-oxobut-2-enoate**



(±)-**49**

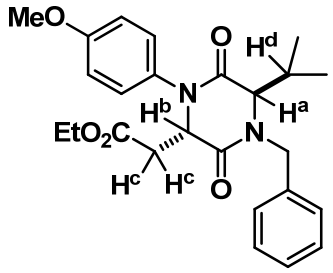
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d,1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 7.18-7.31 (m, 5 H, Ph), 6.69 (d,1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 4.63 (t, 1 H, *J* = 1.9 Hz, -N<u>H</u>), 4.48 (dd, 1 H, *J* = 14.6 Hz, 6.5 Hz, -NC<u>H</u>$_2$Ph), 4.18-4.31 (m, 4 H, -OC<u>H</u>$_2$$CH_3$, H^a and –NC<u>H</u>$_2$Ph overlap),

3.70 (br s, 1 H, -NC$\underline{H}_2$Cy), 3.25 (br s, 1 H, -NC$\underline{H}_2$Cy), 1.38-1.74 (m, 7 H, Cy), 1.30 (t, 3 H, J = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 0.96-1.16 (m, 11 H, *t*-Bu and Cy overlap), 0.70-0.94 (m, 2 H, Cy).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 166.7, 165.5, 137.9, 134.6, 131.1, 128.5, 127.8, 127.2, 43.4, 36.8, 30.8, 29.6, 28.0, 26.0, 25.8, 25.7, 14.1.

HRMS (EIMS, M^+): calcd for $C_{26}H_{38}N_2O_4$ 442.2832, found 442.2839.

31. **Ethyl 2-((2S,5R)-4-benzyl-5-isopropyl-1-(4-methoxyphenyl)-3,6-dioxopiperazin-2-yl)acetate**



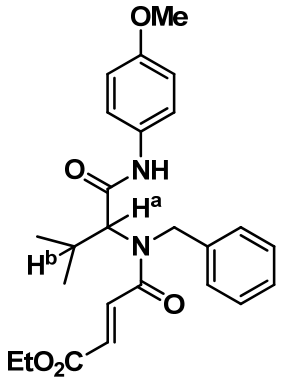
(±)-**50**

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.30-7.45 (m, 5H, aryl), 7.03-7.10 (m, 2H, aryl), 6.92-6.98 (m, 2H, aryl), 5.44 (d, 1H, J = 15.4 Hz, bn), 4.81 (t, 1H, J = 4.1 Hz, H_b), 4.09 (d, 1H, J = 15.4 Hz, bn), 4.03 (q, 2H, J = 7.3 Hz, –OC$\underline{H}_2$CH$_3$), 3.84 (d, 1H, J = 4.9 Hz, H_a), 3.82 (s, 3H, OCH$_3$), 2.98 (dd, 1H, J = 4.1, 17 Hz, H_c), 2.64 (dd, 1H, J = 5.3, 17.4 Hz, H_c), 2.32-2.46 (m, 1H, H_d), 1.16 (t, 3H, J = 7.3 Hz, CH$_3$), 1.12 (d, 3H, J = 6.5 Hz, CHC$\underline{H}_3$), 1.1 (d, 3H, J = 6.5 Hz, CHC$\underline{H}_3$)

^{13}C NMR (100 MHz, CD_2Cl_2): δ 170.3, 166.1, 165.9, 136.4, 131.1, 129.5, 129.1, 128.4, 128.0, 114.8, 65.1, 60.9, 57.7, 55.8, 48.5, 35.9, 32.5, 20.2, 17.7, 14.2

HRMS: EIMS (M^+) calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2162.

32. **(*E*)-ethyl 4-(benzyl(1-((4-methoxyphenyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



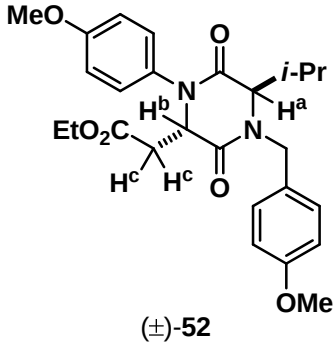
(±)-**51**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (br s, 1 H, -N<u>H</u>), 7.10-7.32 (m, 8 H, Aryl, -C<u>H</u>=CH- overlap), 6.82 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.79 (d, 2 H, *J* = 8.9 Hz, Aryl), 4.77 (t from dd, 2 H, *J* = 17.0 Hz, -NC<u>H</u>$_2$Ph), 4.55 (br s, 1 H, H^a), 4.16 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.76 (s, 3 H, -O<u>Me</u>), 2.50-2.66 (m, 1 H, H^b), 1.24 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.10 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.85 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 166.9, 164.9, 156.2, 136.6, 133.7, 132.3, 130.6, 128.6, 127.4, 126.4, 121.7, 66.3, 60.9, 55.3, 49.1, 26.9, 19.6, 18.7, 13.9.

HRMS (EIMS, M^+): calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2169.

33. **Ethyl 2-((2S,5R)-5-isopropyl-4-(4-methoxybenzyl)-1-(4-methoxyphenyl)-3,6-dioxopiperazin-2-yl)acetate**



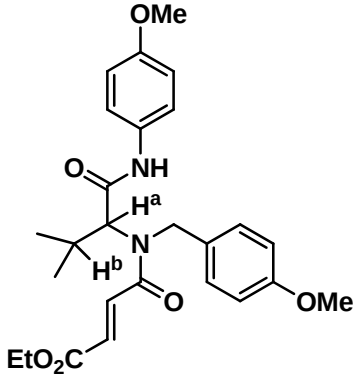
(±)-**52**

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.24-7.30 (m, 2H), 7.0-7.06 (m, 2H), 6.85-6.95 (m, 4H), 5.48 (d, 1H, *J*=14.6 Hz), 4.78 (t, 1H, *J*=4.5 Hz), 4.04 (q, 2H, *J*=7.3 Hz), 3.97 (d, 1H, *J*=15.4 Hz), 3.89 (d, 1H, *J*=4.1 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.02 (dd, 1H, *J*=3.5, 17.4 Hz), 2.63 (dd, 1H, *J*=4.9, 17 Hz), 2.35-2.42 (m, 1H), 1.16 (t, 1H, *J*=7.3 Hz), 1.11 (d, 3H, *J*=6.5 Hz), 1.08 (d, 3H, *J*=6.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.3, 166.0, 165.9, 159.7, 159.5, 131.2, 130.0, 129.4, 128.1, 114.8, 114.4, 64.7, 60.8, 57.7, 55.8, 55.5, 47.9, 35.9, 32.5, 20.2, 17.6, 14.2.

HRMS (M^+) calcd for $C_{26}H_{32}N_2O_6$ 468.2260, found 468.2273.

34. **(*E*)-Ethyl 4-((4-methoxybenzyl)(1-((4-methoxyphenyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



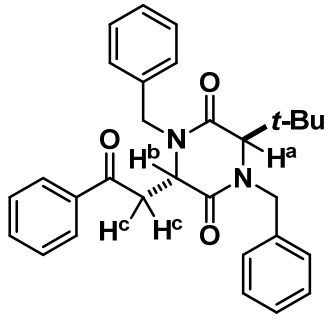
(±)-**53**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (br s, 1 H, -N<u>H</u>Ar), 7.32 (d, 1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 7.27 (d, 2 H, J = 8.9 Hz, Ar), 7.05 (d, 2 H, *J* = 8.1 Hz, Ar), 6.81 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.78 (d, 2 H, *J* = 8.9 Hz, Ar), 6.72 (d, 2 H, *J* = 8.1 Hz, Ar), 4.68 (s, 2 H, -NC<u>H</u>$_2$Ar), 4.16 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.72 (s, 3 H, O<u>Me</u>), 3.69 (s, 3 H, O<u>Me</u>), 2.48-2.70 (m, 1 H, H^b), 1.24 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.99 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.82 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 166.9, 165.1, 158.9, 156.2, 133.8, 132.4, 130.8, 128.3, 128.1, 121.6, 114.1, 113.9, 67.8, 61.1, 55.3, 55.1, 48.7, 26.8, 19.8, 18.9, 14.0.

HRMS (EIMS, M^+): calcd for $C_{26}H_{32}N_2O_6$ 468.2260, found 468.2273.

35. **(3R,6S)-1,4-dibenzyl-3-(*tert*-butyl)-6-(2-oxo-2-phenylethyl)piperazine-2,5-dione**



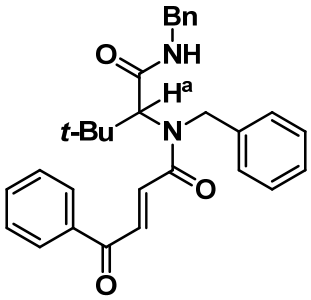
(±)-**54**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.8-7.89 (m, 2H, aryl), 7.52-7.61 (m, 1H, aryl), 7.05-7.49 (m, 12H, aryl), 5.65 (d, 1H, *J* = 14.6 Hz, bn), 4.89 (d, 1H, *J* = 15.4 Hz, bn), 4.87 (dd, 1H, *J* = 4.1, 5.7 Hz, H_b), 4.41 (d, 1H, *J*=15.4 Hz, bn), 4.03 (d, 1H, *J* = 14.6 Hz), 3.86 (s, 1H, H_a), 3.79 (dd, 1H, *J* = 4.9, 17.8 Hz, H_c), 3.61 (dd, 1H, *J* = 4.9, 17.8 Hz, H_c), 1.18 (s, 9H, CH_3)

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 168.2, 166.8, 137.1, 136.3, 133.4, 128.9, 128.7, 128.6, 128.0, 127.9, 127.3,68.5, 55.5, 51.6, 47.2, 39,9, 38,6, 28.5.

HRMS: EIMS (M^+) calcd for $C_{30}H_{32}N_2O_3$ 468.2413, found 468.2408.

36. **(*E*)-N-benzyl-N-(1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)-4-oxo-4-phenylbut-2-enamide**



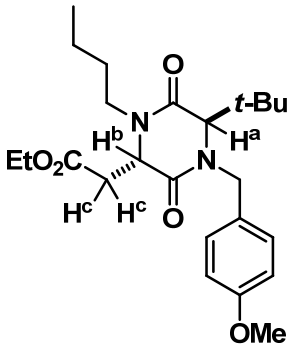
(±)-**55**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.82 (m, 3H), 7.52-7.59 (m, 1H), 7.37-7.45 (m, 2H), 7.14-7.34 (m, 9H), 7.07-7.12 (m, 2H), 5.40 (d, 1H, *J* = 17.8 Hz), 5.15 (bs, 1H), 4.85 (d, 1H, *J* = 17.8 Hz), 4.37 (dd, 1H, *J* = 5.7, 14.6 Hz), 4.15 (dd, 1H, *J* = 5.7, 14.6 Hz), 1.14 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 168.6, 167.7, 138.3, 137.6, 136.7, 134.9, 133.5, 132.9, 128.7, 128.6, 128.0, 127.6, 127.2, 125.6, 43.5, 36.7, 27.6.

HRMS: EIMS (M^+) calcd for $C_{30}H_{32}N_2O_3$ 468.2413, found 468.2411.

37. **Ethyl 2-((2S,5R)-5-(*tert*-butyl)-1-butyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl)acetate**



(±)-**56**

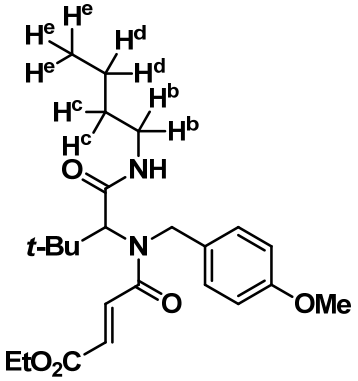
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, 2H, *J* = 8.9 Hz, aryl), 6.83 (d, 2H, *J* = 8.6 Hz, aryl), 5.57 (d, 1H, *J* = 14.9 Hz, Bn), 4.54 (dd, 1H, *J* = 4.3, 5.8 Hz, H_b), 4.08-4.21 (m, 2H, –OC$\underline{H}_2$CH$_3$), 3.93-4.03 (m, 1H, *n*-Bu), 3.88 (d, 1H, *J* = 14.9 Hz, Bn), 3.77 (s, 3H, OC$\underline{H}_3$), 3.65 (s, 1H, H_a), 3.17 (dd, 1H, *J* = 4.1, 16.9 Hz, H_c), 3.01 (dd, 1H, *J* = 6.1, 16.9 Hz, H_c),

2.78-2.87 (m, 1H, *n*-Bu), 1.26-1.56 (m, 4H, *n*-Bu), 1.23 (t. 3H, *J* = 7.3 Hz, –$OCH_2C\underline{H}_3$), 1.09 (s, 9H, *t*-Bu), 0.92 (t, 3H, *J* = 7.3 Hz, –$CH_2CH_2CH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 170.1, 167.5, 165.9, 159.2, 129.4, 127.6, 114.2, 67.6, 60.9, 55.2, 55.1, 50.9, 42.9, 39.9, 35.1, 29.4, 20.3, 14.1, 13.7.

HRMS: EIMS (M^+) calcd for $C_{24}H_{36}N_2O_5$ 432.2624, found 432.2625

38. **(*E*)-Ethyl 4-((1-(butylamino)-3,3-dimethyl-1-oxobutan-2-yl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



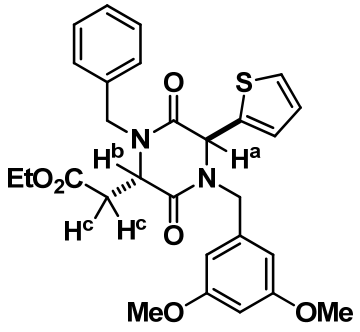
(±)-**57**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 1 H, *J* = 15.2 Hz, -C$\underline{H}$=CH-), 6.98 (d, 2 H, *J* = 8.5 Hz, Aryl), 6.93 (br s, 1 H, -N$\underline{H}$), 6.76 (d, 2 H, *J* = 8.5 Hz, Aryl), 6.62 (d, 1 H, *J* = 15.2 Hz, -C$\underline{H}$=CH-), 5.34 (d, 1 H, *J* = 17.1 Hz, -NC$\underline{H}_2$Ar), 5.11 (br s, 1 H, H^a), 4.70 (d, 1 H, *J* = 17.1 Hz, -NC$\underline{H}_2$Ar), 4.12 (dq, 2 H, *J* = 7.3, 1.8 Hz, -OC$\underline{H}_2CH_3$), 3.72 (s, 3 H, O$\underline{Me}$), 2.90-3.18 (m, 2 H, H^b), 1.24-1.41 (m, 4 H, H^c and H^d overlap). 1.20 (t, 3 H, *J* = 7.3 Hz, -$OCH_2C\underline{H}_3$), 1.06 (s, 9 H, *t*-Bu), 0.83 (t, 3 H, *J* = 7.3 Hz, H^e).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 167.1, 165.2, 158.5, 134.5, 131.1, 130.5, 127.0, 113.9, 60.9, 55.1, 38.9, 36.6, 31.1, 27.5, 20.0, 13.9, 13.6.

HRMS (EIMS, M^+): calcd for $C_{24}H_{36}N_2O_5$ 432.2624, found 432.2633.

39. **Ethyl 2-((2S,5S)-1-benzyl-4-(3,5-dimethoxybenzyl)-3,6-dioxo-5-(thiophen-2-yl)piperazin-2-yl)acetate**



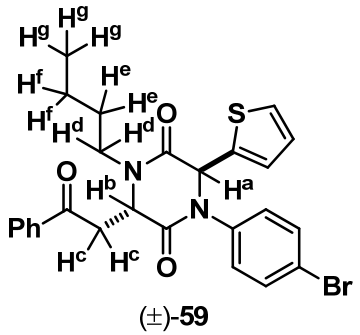
(±)-**58**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.0-7.35 (m, 8H, aryl), 6.36-6.45 (m, 3H, aryl), 6.29 (s, 1H, H_a), 5.55 (d, 1H, *J* = 14.9 Hz, bn), 5.32 (d, 1H, *J* = 15.6 Hz, bn), 4.22 (dd, 1H, *J* = 2.8, 4.6 Hz, H_b), 4.02-4.15 (m, 2H, –OC<u>H</u>$_2$CH$_3$), 3.98 (d, 1H, *J* = 15.6 Hz, bn), 3.77 (s, 6H), 3.56 (d, 1H, *J* = 14.9 Hz, bn), 3.32 (dd, 1H, *J* = 2.8, 17.5 Hz, H_c), 2.95 (dd, 1H, *J* = 4.9, 17.5 Hz, H_c), 1.17 (t, 3H, *J* = 7.3 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 165.1, 164.9, 160.9, 139.8, 137.1, 134.9, 128.9, 127.9, 127.1, 126.4, 106.2, 100.2, 60.9, 58.5, 55.2, 54.5, 47.1, 46.7, 34.4, 13.9.

HRMS: EIMS (M^+) calcd for $C_{28}H_{30}N_2O_6S$ 522.1825, found 522.1829.

40. **Ethyl 2-((2S,5S)-4-(4-bromophenyl)-1-butyl-3,6-dioxo-5-(thiophen-2-yl)piperazin-2-yl)acetate**



(±)-**59**

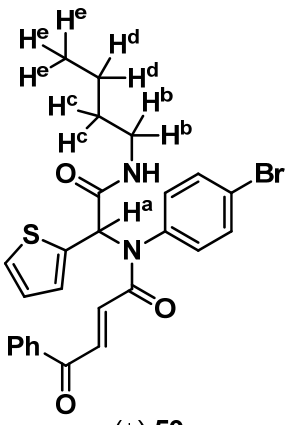
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 2 H, *J* = 7.3 Hz, Aryl), 7.59 (t, 1 H, *J* = 7.3 Hz, Aryl), 7.51 (d, 2 H, *J* = 8.9 Hz, Aryl), 7.38-7.49 (m, 4 H, Aryl), 7.28 (d, 1 H, *J* = 8.9 Hz,

thienyl), 7.11-7.14 (m, 1 H, thienyl), 7.05-7.08 (m, 1 H, thienyl), 5.72 (s, 1 H, H^a), 5.08 (dd, 1 H, J = 7.3, 3.4 Hz, H^b), 3.73-3.81 (m, 1 H, H^d), 3.47 (dd, 1 H, J = 17.4, 3.7 Hz, H^c), 3.18 (dd, 1 H, J = 17.4, 7.3 Hz, H^c), 2.97-3.06 (m, 1 H, H^d), 1.64-1.75 (m, 1 H, H^e), 1.42-1.54 (m, 1 H, H^e), 1.32 (sextet, 2 H, J = 7.3 Hz, H^f), 0.90 (t, 3 H, J = 7.3 Hz, H^g).

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 167.3, 164.2, 139.5, 138.3, 135.9, 133.8, 132.4, 128.8, 128.1, 127.4, 127.1, 126.6, 121.1, 63.8, 56.2, 45.6, 43.6, 29.0, 19.9, 13.7.

HRMS (EIMS, M^+): calcd for $C_{26}H_{25}BrN_2O_3S$ 524.0769, found 524.0762.

41. **(*E*)-N-(4-bromophenyl)-*N*-(2-(butylamino)-2-oxo-1-(thiophen-2-yl)ethyl)-4-oxo-4-phenylbut-2-enamide**



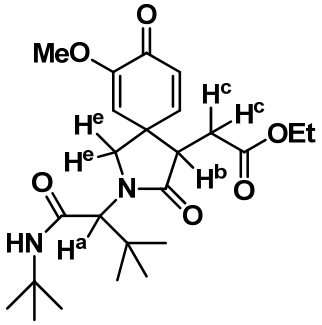
(±)-**59a**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89-8.02 (m, 3 H, Aryl), 7.58 (t, 1 H, J = 7.3 Hz, Aryl), 7.36-7.49 (m, 5 H, Aryl), 7.29 (d, 1 H, J = 4.9 Hz, thienyl), 7.27 (d, 1 H, J = 15.7 Hz, -C<u>H</u>=CH-), 6.86-6.98 (m, 2 H, thienyl), 6.74 (d,1 H, J = 14.9 Hz, -CH=C<u>H</u>-), 6.24 (s, 1 H, H^a), 6.08 (t, 1 H, J = 5.2 Hz, -N<u>H</u>), 3.24-3.38 (m, 2 H, H^b), 1.49 (quintet, 2 H, J = 7.3 Hz, H^c), 1.31 (sextet, 2 H, J = 7.3 Hz, H^d), 0.90 (t, 3 H, J = 7.3 Hz, H^e).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.4, 167.9, 164.7, 138.0, 136.7, 135.3, 134.9, 133.7, 132.6, 132.5, 131.4, 130.2, 128.8, 128.7, 128.3, 126.6, 123.1, 61.2, 39.8, 31.4, 20.0, 13.7.

HRMS (EIMS, M^+): calcd for $C_{26}H_{25}BrN_2O_3S$ 524.0769, found 524.0775.

42. **Ethyl 2-(2-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-7-methoxy-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



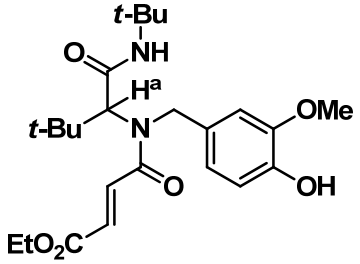
(±)-**60**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (dd, 1H, *J* = 2.7, 10.1 Hz), 6.38 (d, 1H, *J* = 10.1 Hz), 5.57 (d, 1H, *J* = 2.7 Hz), 5.51 (br s, 1H, NH), 4.31 (d, 1H, *J* = 10.1 Hz, H_d),, 4.28 (s, 1H, H_a), 4.08 (m, 2H, –OC$\underline{H_2}$CH$_3$), 3.78 (d, 1H, *J* = 10.1 Hz, H_d), 3.61 (s, 3H, OCH_3), 3.39 (dd, 1H, *J* = 5.8, 7.4 Hz, H_b), 2.66 (dd, 1H, *J* = 6.1, 16.6 Hz, H_c), 2.09 (dd, 1H, *J* = 7.3, 16.8 Hz, H_c), 1.34 (s, 9H, *t*-butyl), 1.21 (t, 3H, *J* = 7.3 Hz, CH_3), 1.08 (s, 9H, *t*-butyl). (Major Isomer)

^{13}C NMR (125 MHz, $CDCl_3$): δ 180.4, 173.9, 171.6, 167.1, 152.7, 146.4, 130.7, 116.5, 64.2, 61.2, 55.1, 54.8, 51.9, 48.3, 47.3, 36.2, 30.4, 28.6, 27.6, 14.0. (Minor Isomer)

HRMS: EIMS (M^+) calcd for $C_{24}H_{36}N_2O_6$ 448.2573, found 448.2582.

43. **(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)(4-hydroxy-3-methoxybenzyl)amino)-4-oxobut-2-enoate**



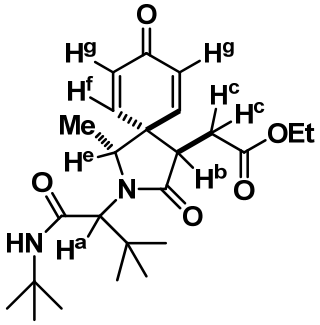
(±)-**61**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, 1H, *J* = 14.6 Hz), 6.4-6.74 (m, 4H), 5.38 (d, 1H, *J* = 17 Hz), 4.98 (bs, 1H), 4.65 (d, 1H, *J* = 17 Hz), 4.06 (q, 2H, *J* = 7.3 Hz), 3.73 (s, 3H), 1.18 (t, 3H, *J* = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ167.9, 167.2, 165.3, 146.8, 144.6, 134.1, 134.0, 131.3, 118.4, 114.5, 108.8, 60.9, 60.2, 55.7, 51.2, 36.9, 28.1, 27.4, 13.8.

HRMS: EIMS (M^+) calcd for $C_{24}H_{36}N_2O_6$ 448.2573, found 448.2578.

44. **Ethyl 2-(2-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-7-methoxy-1-methyl-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



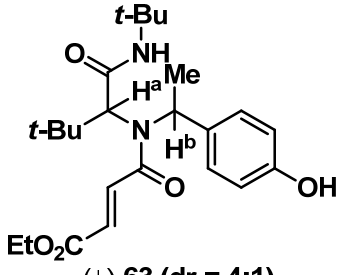
(±)-**62**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, 1 H, *J* = 8.1 Hz, H^g), 7.07 (d, 1 H, *J* = 8.1 Hz, H^g), 6.71-6.79 (m, 1 H, H^f), 6.58-6.67 (m, 1 H, H^f), 4.02-4.15 (m, 2 H, -OC<u>H$_2$</u>CH$_3$), 3.93 (q, 1 H, *J* = 6.5 Hz, H^e), 3.49 (s, 1 H, H^a), 3.48 (dd, 1 H, *J* = 12.3, 6.5 Hz, H^b), 3.18 (dd, 1 H, *J* = 8.1, 4.9 Hz, H^c), 2.65 (dd, 1 H, *J* = 7.3, 4.9 Hz, H^c), 1.34 (d, 3 H, *J* = 6.5 Hz, -<u>Me</u>), 1.29 (s, 9 H, *t*-Bu), 0.90 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.9, 172.6, 171.3, 169.5, 165.5, 145.9, 131.4, 130.9, 62.8, 61.1, 50.8, 50.1, 48.1, 47.4, 30.3, 28.6, 27.3, 19.3, 19.3, 14.1.

HRMS (EIMS, M^+): calcd for $C_{24}H_{36}N_2O_5$ 432.2624, found 432.2621.

45. **(*E*)-ethyl 4-((1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)(1-(4-hydroxyphenyl)ethyl)amino)-4-oxobut-2-enoate**



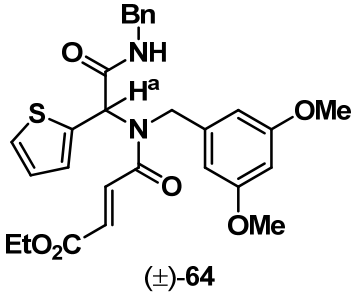
(±)-**63 (dr = 4:1)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1 H, -NH), 7.62 (d, 1 H, *J* = 15.4 Hz, -CH=CH-), 7.01 (d, 2 H, *J* = 8.1 Hz, Aryl), 6.82 (d, 1 H, *J* = 15.4 Hz, -CH=CH-), 6.63 (d, 2 H, *J* = 8.2 Hz, Aryl), 5.41 (q, 1 H, *J* = 6.5 Hz, H^b), 4.28 (q, 2 H, *J* = 7.3 Hz, -OCH_2CH_3), 3.29 (s, 1 H, H^a), 1.60 (d, 3 H, *J* = 6.5 Hz, -Me), 1.32 (t, 3 H, *J* = 7.3 Hz, -OCH_2CH_3), 1.22 (s, 9 H, *t*-Bu), 1.13 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 167.8, 165.3, 157.6, 136.2, 131.5, 129.9, 128.8, 126.8, 116.0, 72.4, 61.4, 58.1, 35.1, 29.7, 28.6, 17.2, 14.1.

HRMS (EIMS, M^+): calcd for $C_{24}H_{36}N_2O_5$ 432.2624, found 432.2631.

46. **(*E*)-Ethyl 4-((2-(benzylamino)-2-oxo-1-(thiophen-2-yl)ethyl)(3,5-dimethoxybenzyl)amino)-4-oxobut-2-enoate**



(±)-**64**

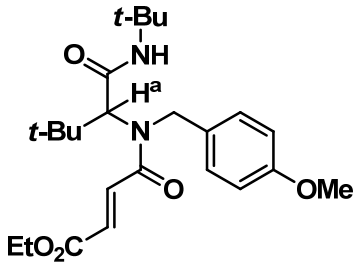
^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.17-7.34 (m, 6H, aryl), 7.12 (m, 1H, aryl), 6.90-6.95 (m, 1H, aryl), 6.87 (d, 1H, *J* = 14.7 Hz, HC=CH), 6.23-6.33 (m, 4H), 5.96 (s, 1H), 4.71 (s,

2H), 4.52 (dd, 1H, *J* = 5.5, 14.9 Hz, bn), 4.40 (dd, 1H, *J* = 5.6, 15.2 Hz, bn), 4.19 (q, 2H, *J* = 7.1 Hz, –OC<u>H</u>$_2$CH$_3$), 3.7 (s, 6H, OCH$_3$), 1.26 (t, 3H, *J* = 7.1 Hz, CH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$) : δ 167.9, 166.1, 165.2, 161.0, 138.9, 137.7, 135.9, 133.4, 132.8, 130.1, 128.7, 128.2, 127.6, 127.5, 126.7, 104.3, 99.8, 61.1, 59.1, 55.3, 50.8, 43.8, 14.

HRMS: EIMS (M$^+$) calcd for $C_{28}H_{30}N_2O_6S$ 522.1825, found 522.1816.

47. **(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



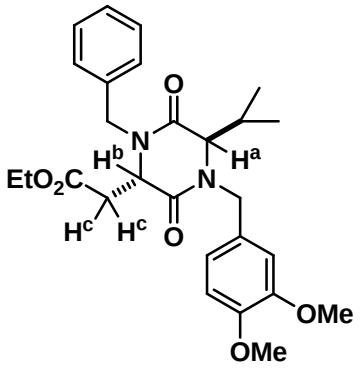
(±)-**66**

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.18 (d, 1H, *J*=15.2 Hz, –C<u>H</u>=CH–), 7.01 (d, 2H, *J*=8.6 Hz, aryl), 6.78 (d, 2H, *J*=8.6 Hz, aryl), 6.70 (d, 1H, *J*=15.2 Hz, –CH=C<u>H</u>–), 5.77 (bs, 1H, –N<u>H</u>), 5.36 (d, 1H, *J*=16.7 Hz, Bn), 4.91 (bs, 1H, H$_a$), 4.68 (d, 1H, *J*=17.2 Hz, Bn), 4.09-4.21 (m, 2H, –OC<u>H</u>$_2$CH$_3$), 1.24 (t, 3H, *J*=7.1 Hz, –OCH$_2$C<u>H</u>$_3$), 1.22 (s, 9H, N-*t*-Bu), 1.09 (s, 9H, C-*t*-Bu).

^{13}C NMR (125 MHz, CDCl$_3$) : δ 168.1, 167.2, 165.4, 158.6, 134.3, 131.4, 127.2, 113.9, 60.9, 55.2, 51.6, 37.0, 28.6, 28.4, 27.5, 26.2, 14.1.

HRMS (M$^+$) calcd for $C_{24}H_{36}N_2O_5$ 432.2624, found 432.2632.

48. **Ethyl 2-((2S,5R)-1-benzyl-4-(3,4-dimethoxybenzyl)-5-isopropyl-3,6-dioxopiperazin-2-yl)acetate**



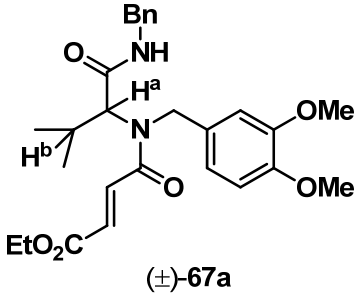
(±)-**67**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20-7.34 (m, 5 H, Ph), 6.99 (s, 1 H, Aryl), 6.79 (s, 2 H, Aryl), 5,54 (d, 1 H, *J* = 15.2 Hz, -NC$\underline{H}_2$Ar), 5.11 (d, 1 H, *J* = 15.2 Hz, -NC$\underline{H}_2$Ar), 4.14-4.24 (m, 2 H, H^a and -NC$\underline{H}_2$Ar overlap), 3.65-4.03 (m, 9 H; H^b, -OC$\underline{H}_2$CH$_3$, O$\underline{Me}$, O$\underline{Me}$ overlap), 3.29 (dd, 1 H, *J* = 17.2, 2.5 Hz, H^c), 2.90 (dd,1 H, *J* = 17.2, 5.1 Hz, H^c), 2.26-2.40 (m, 1 H, *i*-Pr), 1.13 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 1.11 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.94 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (125 MHz, $CDCl_3$): 168.9, 166.6, 165.3, 148.9, 148.4, 134.1, 131.9, 129.5, 119.1, 111.0, 110.2, 78.3, 61.9, 61.1, 55.9, 51.2, 50.9, 35.9, 27.5, 27.4, 19.0, 14.2.

HRMS (M^+) calcd for $C_{27}H_{34}N_2O_6$ 482.2417, found 482.2427.

49. **(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)(3,4-dimethoxybenzyl)amino)-4-oxobut-2-enoate**



(±)-**67a**

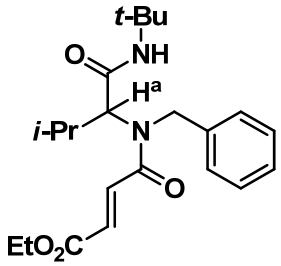
^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.24-7.32 (d, 1H, –C$\underline{H}$=CH–), 6.66-6.82 (m, 4H, aryl overlap with –CH=C$\underline{H}$–), 4,73 (d, 1H, *J*=16.7 Hz, Bn), 4.61 (d, 1H, *J*=17.2 Hz, Bn), 4.27 (br s, 1H, –N$\underline{H}$), 4.23 (bs, 1H, H^a), 4.12-4.21 (m, 2H, –OC$\underline{H}_2$CH$_3$), 3.81 (s, 6H, –OC$\underline{H}_3$),

2.32-2.45 (m, 1H, H^b), 1.21-1.27 (m, 12H, *t*-Bu and $-OCH_2C\underline{H}_3$ overlap), 0.93 (d, 3H, *J*=6.6 Hz, *i*-Pr), 0.78 (d, 3H, *J*=6.6 Hz, *i*-Pr).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 168.9, 166.6, 165.3, 148.9, 148.4, 134.1, 131.9, 129.5, 119.1, 111.0, 110.2, 61.1, 55.8, 51.2, 28.5, 27.4, 19.5, 19.0, 14.0.

HRMS (M^+) calcd for $C_{27}H_{34}N_2O_6$ 482.2417, found 482.2424.

50. **(*E*)-Ethyl 4-(benzyl(1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



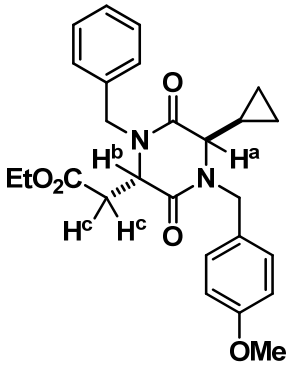
(±)-**68**

^1H NMR (500 MHz, $CDCl_3$) : δ 7.09-7.26 (m, 6H, aryl overlap with $-C\underline{H}$=CH–), 6.74 (d, 1H, *J*=15.7 Hz, –CH=C<u>H</u>–), 6.37 (bs, 1H, –N<u>H</u>), 4.84 (d, 1H, *J*=17.8 Hz, Bn), 4.64 (d, 1H, *J*=17.2 Hz, Bn), 4.4 (d, 1H, *J*=8.6 Hz, H_a), 4.08-4.16 (m, 2H, $-OC\underline{H}_2CH_3$), 2.31-2.42 (m, 1H, H_b), 1.21 (s, 9H, *t*-Bu), 1.19 (t, 3H, *J*=7.1 Hz, $-OCH_2C\underline{H}_3$), 0.92 (d, 3H, *J*=6.6 Hz, *i*-Pr), 0.78 (d, 3H, *J*=6.6 Hz, *i*-Pr).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 168.5, 166.5, 165.1, 137.2, 133.9, 131.9, 128.5, 127.3, 126.5, 60.9, 51.2, 28.3, 27.4, 19.4, 18.7, 13.9.

HRMS (M^+) calcd for $C_{22}H_{32}N_2O_4$ 388.2362, found 388.2359

51. **Ethyl 2-((2S,5R)-1-benzyl-5-cyclopropyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl)acetate**



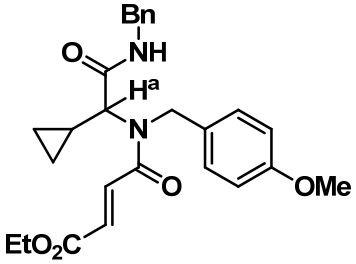
(±)-**69**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.16-7.37 (m, 7H), 6.8-6.89 (m, 2H), 5.4 (d, 1H, J = 15.4 Hz), 5.35 (d, 1H, J = 15.4 Hz), 4.26 (dd, 1H, J = 3.2, 5.7 Hz), 4.21 (d, 1H, J = 14.6 Hz), 4.0-4.17 (m, 2H), 3.8 (s, 3H), 4.05 (d, 1H, J = 14.6 Hz), 3.36 (d, 1H, J = 8.9 Hz), 3.21 (dd, 1H, J = 3.2, 17 Hz), 2.93 (dd, 1H, J = 5.7, 17 Hz), 1.19 (t, 3H, J = 7.3 Hz), 1.05 (m, 1H), 0.75 (m, 3H), 0.48 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 169.7, 167.0, 165.7, 159.1, 135.7, 129.2, 128.9, 128.7, 127.9, 127.8, 127.6, 127.5, 114.1, 62.1, 60.9, 55.3, 54.5, 46.6, 46.4, 34.4, 14.6, 14.1, 6.1, 1.9.

HRMS (M^+) calcd for $C_{26}H_{30}N_2O_5$ 450.2155, found 450.2154

52. **(*E*)-Ethyl 4-((2-(benzylamino)-1-cyclopropyl-2-oxoethyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



(±)-**70**

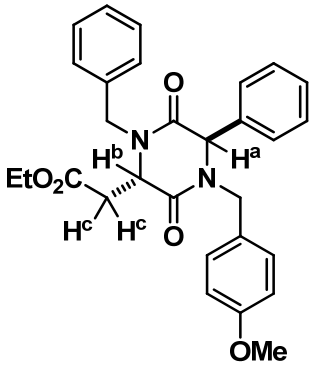
^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.19-7.35 (m, 5H), 7.10-7.19 (m, 2H), 6.75-6.89 (m, 3H), 4.76 (dd, 2H, J = 17.5, 40 Hz), 4.42 (ddd, 2H, J = 5.6, 14.7, 30.4 Hz), 4.19 (q, 2H, J = 7.1

Hz), 3.96 (d, 1H, J = 10.1 Hz), 1.38 (m, 1H), 1.26 (t, 3H, J = 7.1 Hz), 0.69 (m, 1H), 0.34 (m, 2H), 0.15 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 169.8, 166.3, 165.3, 158.9, 138.0, 133.7, 132.6, 128.9, 128.6, 127.8, 127.5, 127.3, 114.0, 64.5, 61.1, 55.2, 49.3, 43.4, 14.1, 10.5, 5.6, 4.7.

HRMS (EIMS, M^+): calcd for $C_{26}H_{30}N_2O_5$ 450.2155, found 450.2157.

53. **Ethyl 2-((2S,5R)-1-benzyl-4-(4-methoxybenzyl)-3,6-dioxo-5-phenylpiperazin-2-yl)acetate**



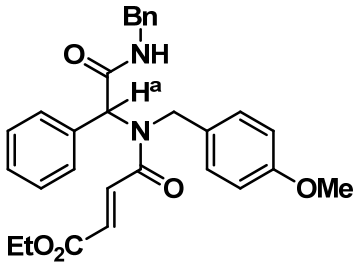
(±)-**71**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.37-7.45 (m, 3H), 7.23-7.31 (m, 5H), 7.03-7.11 (m, 4H), 6.78-6.85 (m, 2H), 5.44 (d, 1H, J = 14.6 Hz), 5.26 (d, 1H, J = 15.4 Hz), 4.24 (dd, 1H, J = 3.2, 4.9 Hz), 4.06-4.16 (m, 1H), 3.95-4.04 (m, 1H), 3.95 (d, 1H, J = 15.4 Hz), 3.39 (d, 1H, J = 14.6 Hz), 3.27 (dd, 1H, J = 2.4, 17.0 Hz), 2.93 (dd, 1H, J = 4.9, 17.0 Hz), 1.16 (t, 3H, J = 7.3 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 169.8, 166.7, 165.9, 156.2, 135.6, 129.7, 128.9, 127.9, 127.8, 126.2, 115.7, 63.7, 54.9, 47.9, 46.8, 34.7, 31.7, 19.9, 17.5, 13.9.

HRMS (M^+) calcd for $C_{29}H_{30}N_2O_5$ 486.2155, found 486.2153.

54. **(*E*)-Ethyl 4-((2-(benzylamino)-2-oxo-1-phenylethyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



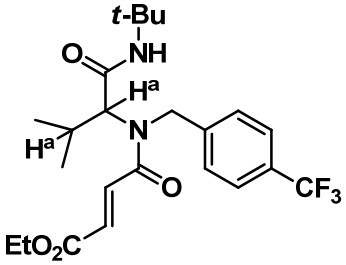
(±)-**72**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.16-7.4 (m, 11H), 6.92 (d, 2H, J = 8.6 Hz), 6.85 (d, 1H, J = 15.2 Hz) 6.71 (d, 2H, J = 8.1 Hz), 4,76 (d, 1H, J = 17.2 Hz), 4.54 (d, 1H, J = 17.2 Hz), 4.46 (ddd, 2H, J = 5.6, 14.7, 30.4 Hz), 4.19 (q, 2H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 169.0, 166.3, 165.4, 158.8, 137.8, 134.2, 133.9, 132.4, 129.8, 128.9, 128.6, 127.7, 127.6, 127.4, 113.9, 63.6, 61.0, 55.2, 49.81, 43.7, 14.1.

HRMS (EIMS, M^+): calcd for $C_{29}H_{30}N_2O_5$ 486.2155, found 486.2157.

55. **(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)(4-(trifluoromethyl)benzyl)amino)-4-oxobut-2-enoate**



(±)-**75**

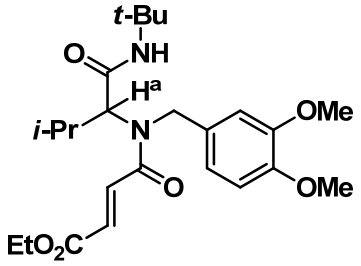
^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.54 (d, 2 H, *J* = 8.2 Hz, Aryl), 7.27 (d, 2 H, *J* = 8.2 Hz, Aryl), 7.12 (d, 1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 6.80 (d,1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.18 (br s, 1 H, -N<u>H</u>), 4.97 (d, 1 H, *J* = 17.7 Hz, -NC<u>H</u>$_2$Ar), 4.74 (d, 1 H, *J* = 17.7 Hz, -NC<u>H</u>$_2$Ar), 4.51 (d, 1 H, *J* = 10.1, H^a), 4.17 (dq, 2 H, *J* = 7.3, 1.8 Hz, -OC<u>H</u>$_2$CH$_3$), 2.30-2.43 (m, 1 H, H^b), 1.25 (s, 9 H, *t*-Bu), 1.27 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.97 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.85 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 168.5, 166.5, 165.2, 141.6, 133.3, 132.7, 126.7, 125.6, 125.6, 123.6 (J_{C-F} = 272.2 Hz), 61.2, 51.5, 28.4, 27.5, 19.4, 18.7, 13.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ - 63.55.

HRMS (EIMS, M^+): calcd for $C_{29}H_{30}N_2O_5$ 486.2155, found 486.2157.

56. **(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)(3,4-dimethoxybenzyl)amino)-4-oxobut-2-enoate**



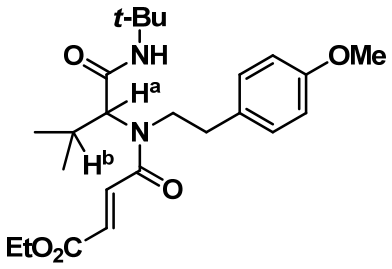
(±)-**77**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.24-7.32 (m, 1H, -C<u>H</u>=CH-), 6.66-6.82 (m, 4H, Aryl and –CH=C<u>H</u>- overlap), 4,73 (d, 1H, *J* = 16.7 Hz, -NC<u>H</u>$_2$Ar), 4.61 (d, 1H, *J* = 17.2 Hz, -NC<u>H</u>$_2$Ar), 4.27 (br s, 1H, H^a), 4.12-4.21 (m, 2H), 2.26-2.34 (m, 1 H, *i*-Pr)1.21-1.27 (m, 12H, *t*-Bu and –OCH$_2$C<u>H</u>$_3$ overlap), 0.93 (d, 3H, *J*=6.6 Hz), 0.78 (d, 3H, *J*=6.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 168.9, 166.6, 165.3, 148.9, 148.4, 134.1, 131.9, 129.5, 119.1, 111.0, 110.2, 61.1, 55.8, 51.2, 28.5, 27.4, 19.5, 19.0, 14.0.

HRMS (EIMS, M^+): calcd for $C_{24}H_{36}N_2O_6$ 448.2573, found 448.2581.

57. **(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)(4-methoxyphenethyl)amino)-4-oxobut-2-enoate**



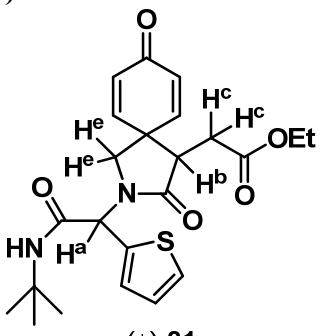
(±)-**80**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, 1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 7.10 (d, 2 H, *J* = 8.9 Hz, Ar), 6.78 (d, 2 H, *J* = 8.9 Hz, Ar), 7.20 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.36 (br s, 1 H, -N<u>H</u>), 4.22 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.66-3.77 (m, 4 H, OMe and H^b overlap), 2.76-2.88 (m, 2 H, -NC<u>H</u>$_2$CH$_2$Ar), 2.59-2.71 (m, 2 H, -NCH$_2$C<u>H</u>$_2$Ar), 1.32 (s, 9 H, *t*-Bu), 1.30 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.95 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.75 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C (125 MHz, $CDCl_3$): δ 169.1, 165.7, 165.3, 158.4, 133.0, 131.4, 129.8, 129.7, 113.9, 65.8, 60.9, 55.0, 51.2, 47.8, 35.8, 28.4, 26.5, 19.4, 18.3, 14.0.

HRMS (EIMS, M^+): calcd for $C_{24}H_{36}N_2O_5$ 432.2624, found 432.2631.

58. **Ethyl 2-(2-(2-(tert-butylamino)-2-oxo-1-(thiophen-2-yl)ethyl)-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



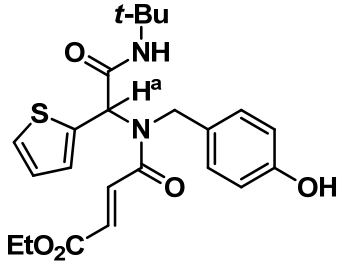
(±)-**81**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (t, 1 H, *J* = 4.1 Hz, -N<u>H</u>), 7.14-7.18 (m, 2 H), 6.99-7.04 (m, 1 H), 6.91-6.96 (m, 1 H), 6.81-6.86 (m, 1 H), 6.67-6.73 (m, 2 H), 5.67 (s, 1 H, H^a), 5.0 (d, 1 H, *J* = 14.6 Hz, H^e), 4.30 (d, 1 H, *J* = 14.6 Hz, H^e), 4.14 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.93 (dd, 1 H, *J* = 12.2, 3.2 Hz, H^b), 2.72 (dd, 1 H, *J* = 15.4, 3.2 Hz, H^c), 2.34 (dd, 1 H, *J* = 18.7, 12.2, Hz, H^c), 1.09-1.15 (m, 12 H, *t*-Bu and –OCH$_2$C<u>H</u>$_3$ overlap).

^{13}C NMR (100 MHz, $CDCl_3$): δ 185.1, 172.8, 171.6, 168.3, 149.8, 145.9, 131.4, 130.9, 127.1, 126.9, 125.6, 71.2, 62.8, 61.1, 50.8, 50.1, 48.1, 47.4, 30.3, 28.6, 27.3, 19.3, 19.3, 14.

HRMS (EIMS, M^+): calcd for $C_{23}H_{28}N_2O_5S$ 444.1719, found 444.1729.

59. **(*E*)-Ethyl 4-((2-(*tert*-butylamino)-2-oxo-1-(thiophen-2-yl)ethyl)(4-hydroxybenzyl)amino)-4-oxobut-2-enoate**



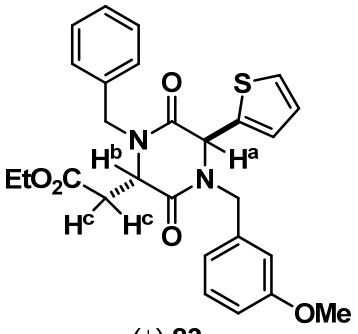
(±)-**81a**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, 1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 7.24 (d, 1 H, *J* = 5.7 Hz, thienyl), 7.25 (d, 1 H, *J* = 2.4 Hz, thienyl), 6.90 (t, 1 H, *J* = 5.7 Hz, thienyl), 6.87 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.82 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.66 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.05 (s, 1 H, H^a), 5.80 (s, 1 H, -O<u>H</u>), 4.60 (dd, 2 H, *J* = 50.3, 17.0 Hz, -NC<u>H</u>$_2$Ar), 4.16 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 1.28 (s, 9 H, *t*-Bu), 1.24 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): 167.5, 166.0, 165.4, 156.0, 136.1, 133.9, 132.3, 129.6, 127.9, 127.7, 127.5, 126.5, 115.6, 65.8, 61.1, 59.2, 51.8, 49.9, 28.4, 15.1, 14.0.

HRMS (EIMS, M^+): calcd for $C_{23}H_{28}N_2O_5S$ 444.1719, found 444.1727.

60. **Ethyl 2-((2S,5S)-1-benzyl-4-(3-methoxybenzyl)-3,6-dioxo-5-(thiophen-2-yl)piperazin-2-yl)acetate**



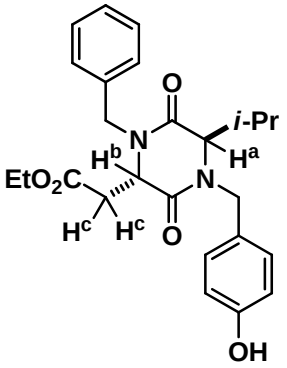
(±)-**83**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.3-7.36 (m, 3 H, Aryl), 7.14-7.2 (m, 4 H, Aryl), 7.06-7.12 (m, 2 H, Aryl), 6.86-6.9 (m, 2H, Aryl), 5.52 (d, 1 H, *J* = 14.4 Hz, -NC$\underline{H}_2$Ar), 5.37 (d, 1 H, *J* = 15.6 Hz, -NC$\underline{H}_2$Ar)), 4.26 (m, 1 H), 4.12-4.18 (m,1 H), 4.02-4.08 (m, 1 H), 3.99 (d, 1 H, *J* = 15.6 Hz, -NC$\underline{H}_2$Ar)), 3.85 (s, 3 H), 3.64 (d, 1 H, *J* = 14.4 Hz, -NC$\underline{H}_2$Ar)), 3.32 (dd, 1 H, *J* = 17.4, 3.0 Hz, H^c), 2.96 (dd, 1 H, *J* = 17.4, 4.8 Hz, H^c), 1.21 (t, 3 H, *J* = 7.2 Hz, -$OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 165.2, 165.1, 159.9, 139.9, 136.4, 134.9, 128.9, 127.9, 127.8, 127.1, 126.4, 113.9, 61.0, 58.4, 55.2, 54.5, 46.7, 46.6, 34.5, 14.0.

HRMS (EIMS, M^+): calcd for $C_{27}H_{28}N_2O_8S$ 492.1719, found 492.1721.

61. **Ethyl 2-((2S,5R)-1-benzyl-4-(4-hydroxybenzyl)-5-isopropyl-3,6-dioxopiperazin-2-yl)acetate**



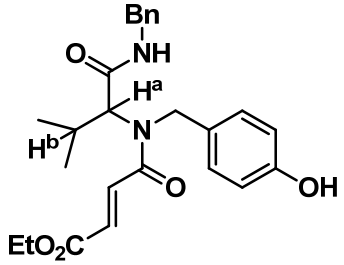
(±)-**86**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.18-7.4 (m, 5H), 7.1 (d, 2H, J = 8.1 Hz), 6.69 (d, 2H, J = 8.1 Hz), 5.36 (d, 1H, J = 15.2 Hz), 5.21 (d, 1H, J = 15.2 Hz), 4.29 (dd, 1H, J = 3.5, 5.1 Hz), 4.18 (d, 1H, J = 15.2 Hz), 4.04-4.14 (m, 1H), 3.94-4.03 (m, 1H), 3.9 (d, 1H, J = 15.2 Hz), 3.89 (d, 1H, J = 5.1 Hz), 3.22 (dd, 1H, J = 3.6, 17.2 Hz), 2.94 (dd, 1H, J = 5.6, 17.2 Hz), 1.15 (t, 3H, J = 7.6 Hz), 1.12 (d, 3H, J = 6.6 Hz), 0.96 (d, 3H, J = 6.6 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 169.8, 166.7, 165.9, 156.2, 135.6, 129.7, 128.9, 127.9, 127.8, 126.2, 115.7, 63.7, 61.0, 54.9, 47.9, 46.8, 34.7, 31.7, 19.9, 17.5, 13.9.

HRMS (M^+) calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2161.

62. **(*E*)-Ethyl 4-((1-(benzylamino)-3-methyl-1-oxobutan-2-yl)(4-hydroxybenzyl)amino)-4-oxobut-2-enoate**



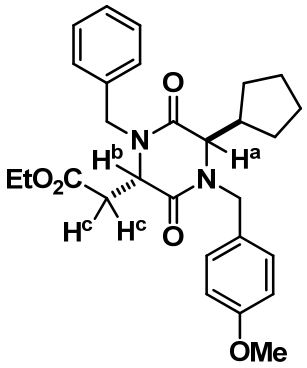
(±)-**87**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.99 (br s, 1 H, -N<u>H</u>), 7.33 (d, 1 H, *J* = 15.2 Hz, -C<u>H</u>=CH-), 7.21-7.32 (m, 3 H, Aryl), 7.18 (d, 2 H, *J* = 7.1 Hz, Aryl), 6.86 (d, 2 H, *J* = 8.1 Hz, Aryl), 6.78 (d, 1 H, *J* = 15.2 Hz, -CH=C<u>H</u>-), 6.55 (d, 2 H, *J* = 8.1 Hz, Aryl), 4.68 (d, 1 H, *J* = 16.7, -NC<u>H</u>$_2$Ar), 4.56 (d, 1 H, *J* = 16.7 Hz, -NC<u>H</u>$_2$Ar), 4.41 (dd, 1 H, *J* = 14.7, 6.1 Hz, -NC<u>H</u>$_2$Ar), 4.31 (br s, 1 H, H^a), 4.15-4.24 (m, 3 H, -NC<u>H</u>$_2$Ar and –OC<u>H</u>$_2$CH$_3$ overlap), 2.51-2.64 (m, 1 H, H^b), 1.27 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.98 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.84 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 170.3, 166.9, 165.4, 156.2, 137.5, 133.9, 132.3, 128.6, 127.9, 127.6, 127.4, 115.7, 61.3, 43.5, 27.0, 19.7, 18.9, 14.0.

HRMS (M^+) calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2166.

63. **Ethyl 2-((2S,5R)-1-benzyl-5-cyclopentyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl)acetate**



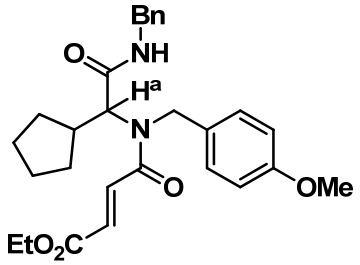
(±)-**89**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14-7.36 (m, 7 H, Ph and Aryl overlap), 6.86 (d, 2 H, *J* = 8.9 Hz, Aryl), 5.45 (d, 1 H, *J* = 15.2 Hz, -NC$\underline{H}_2$Ar), 5.21 (d, 1 H, *J* = 15.7 Hz, -NC$\underline{H}_2$Ar), 4.35 (d, 1 H, *J* = 5.6, 3.6 Hz, H^b), 4.12 (q, 2 H, *J* = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 4.05 (d, 1 H, *J* = 3.4 Hz, H^a), 3.80 (s, 3 H, OMe), 3.16 (dd, 1 H, *J* = 17.2, 3.6 Hz, H^c), 2.93 (dd, 1 H, *J* = 17.3, 6.1 Hz, H^c), 1.25 (t, 3 H, *J* = 7.3 Hz-OC$\underline{H}_2$CH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): 171.3, 165.4, 165.3, 158.9, 136.7, 131.7, 128.9, 128.5, 127.9, 127.2, 114.2, 72.1, 61.7, 61.2, 56.1, 50.9, 50.5, 40.1, 35.9, 29.5, 24.7, 14.2.

HRMS (EIMS, M^+): calcd for $C_{28}H_{34}N_2O_5$ 478.2468, found 478.2473.

64. **(*E*)-Ethyl 4-((2-(benzylamino)-1-cyclopentyl-2-oxoethyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



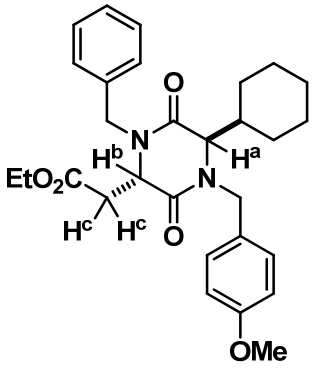
(±)-**90**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.39 (m, 6 H, Ph and –C<u>H</u>=CH- overlap), 7.05 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.78 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.77 (d, 2 H, *J* = 8.6 Hz, Aryl), 4.66 (s, 2 H, -NC<u>H</u>$_2$Ar), 4.64 (d, 1 H, *J* =3.6 Hz, H^a), 4.41 (dd, 1 H, *J* = 15.2, 6.1 Hz, -NC<u>H</u>$_2$Ar), 4.28 (dd, 1 H, *J* = 15.2, 6.3 Hz, -NCH_2Ar), 4.21 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 1.28 (t, 3 H, *J* = 7.3 Hz, -OCH_2C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 166.7, 165.2, 158.8, 138.0, 133.9, 132.0, 128.7, 128.5, 127.9, 127.5, 127.2, 113.9, 61.0, 55.1, 43.1, 37.9, 30.3, 29.4, 25.5, 25.2, 13.9.

HRMS (EIMS, M^+): calcd for $C_{28}H_{34}N_2O_5$ 478.2468, found 478.2475.

65. **Ethyl 2-((2S,5R)-1-benzyl-5-cyclohexyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl)acetate**



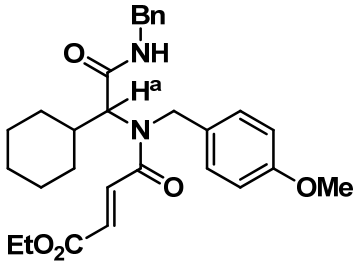
(±)-**91**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18-7.38 (m, 5 H, Ph), 7.03 (d, 2 H, *J* = 8.1 Hz, Aryl), 6.76 (d, 2 H, *J* = 8.5 Hz, Aryl), 5.37 (d, 1 H, *J* = 14.7 Hz, -NC<u>H</u>$_2$Ar), 5.14 (d, 1 H, *J* = 15.7 Hz, -NC<u>H</u>$_2$Ar), 4.46 (dd, 1 H, *J* = 12.7, 6.1 Hz, H^b), 4.15-4.31 (m, 4 H, -OC<u>H</u>$_2$CH$_3$, Cy, -NC<u>H</u>$_2$Ar overlap), 3.95 (d,1 H, *J* = 14.7 Hz, -NC<u>H</u>$_2$Ar), 3.20 (dd,1 H, *J* = 7.2, 3.6 Hz, H^c), 2.92 (dd, 1 H, J = 7.2, 5.6 Hz, H^c), 2.16-2.26 (m, 1 H, Cy), 1.43-1.93 (m, 6 H, Cy), 1.17 (t, 3 H, *J* = 7.3 Hz, -OCH_2C<u>H</u>$_3$), 0.69-1.15 (m, 4 H, Cy).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 166.1, 165.7, 159.1, 137.1, 132.2, 128.9, 128.7, 127.9, 127.3, 114.2, 72.1, 60.9, 60.3, 55.6, 50.9, 50.4, 35.9, 30.1, 27.9, 27.1, 25.4, 14.2.

HRMS (EIMS, M^+): calcd for $C_{29}H_{36}N_2O_5$ 492.2624, found 492.2633.

66. **(*E*)-Ethyl 4-((2-(benzylamino)-1-cyclohexyl-2-oxoethyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



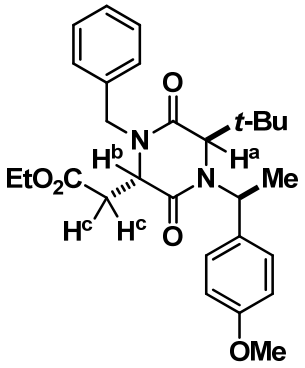
(±)-**92**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.35 (m, 6 H, Ph and –C<u>H</u>=CH- overlap), 7.03 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.76 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.73 (d, 1 H, *J* = 15.2 Hz, -CH=C<u>H</u>-), 4.67 (dd, 2 H, *J* = 47.1, 16.7 Hz, NC<u>H</u>$_2$Ar), 4.41 (dd, 1 H, *J* = 14.7, 6.1 Hz, -NC<u>H</u>$_2$Ar), 4.24 (dd,1 H, *J* = 14.7, 5.6 Hz, -NC<u>H</u>$_2$Ar), 4.17 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 1.27 (t, 3 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 166.6, 165.2, 158.8, 137.9, 134.0, 131.8, 128.9, 128.5, 127.9, 127.6, 127.2, 113.9, 62.5, 60.9, 55.1, 48.3, 43.2, 36.1, 29.9, 29.2, 26.1, 25.5, 13.9.

HRMS (EIMS, M^+): cacld for $C_{29}H_{36}N_2O_5$ 492.2624, found 492.2632.

67. **Ethyl 2-((2S,5R)-1-benzyl-5-(*tert*-butyl)-4-((S)-1-(4-methoxyphenyl)ethyl)-3,6-dioxopiperazin-2-yl)acetate**



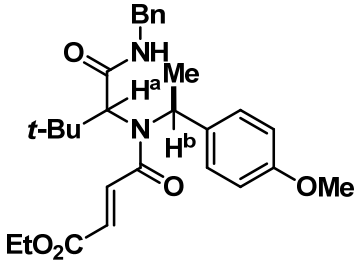
(±)-**93**

^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.24-7.36 (m, 5H), 7.17-7.22 (m, 2H), 6.85-6.90 (m, 2H), 5.07 (q, 1H, J = 7.3 Hz), 5.01 (d,1H, J = 16.2 Hz), 4.48 (dd, 1H, J = 4.1, 6.1 Hz), 4.31 (d, 1H, J = 15.4 Hz), 4.10 (m, 2H), 3.06 (dd, 1H, J = 4.1, 17.03 Hz), 2.92 (dd, 1H, J = 5.7, 17.03 Hz) 1.72 (d, 3H, J = 6.5 Hz), 1.25 (t, 3H, J = 7.3 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 170.2, 168.4, 167.6, 158.7, 136.8, 131.9, 128.8, 128.6, 127.6, 127.5, 113.8, 69.6, 60.9, 59.9, 55.9, 55.2, 46.8, 37.8, 34.4, 28.8, 18.7, 14.1.

HRMS (M^+) calcd for $C_{28}H_{36}N_2O_5$ 480.2624, found 480.2630.

68. **(*E*)-Ethyl 4-((1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl)((S)-1-(4-methoxyphenyl)ethyl)amino)-4-oxobut-2-enoate**



(±)-**94**

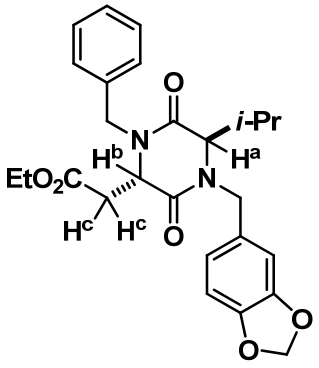
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.24-7.36 (m, 5H), 7.10-7.22 (m, 6H,), 7.03 (br s, 2H, Aryl), 6.79 (d, 1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 6.70 (d, 2 H, *J* = 8.2 Hz, Aryl), 5.76 (t, 1 H, *J* = 4.8 Hz, -N<u>H</u>), 4.54 (dd, 1 H, *J* = 14.6, 4.5 Hz, -NCH_2Ph), 4.10-4.44 (m, 5H; H^a, H^b, -

OCH_2CH_3 and -NCH_2Ph overlap), 3.76 (s, 3 H, O<u>Me</u>), 1.49 (d, 3 H, *J* = 6.5 Hz, -<u>Me</u>), 1.31 (t, 3 H, *J* = 7.3 Hz, -$OCH_2C\underline{H}_3$), 1.15 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): 171.2, 167.4, 165.1, 136.7, 136.1, 128.3, 128.3, 127.7, 127.6, 126.9, 126.3, 113.7, 63.5, 60.1, 54.9, 43.2, 29.6, 27.3, 20.8, 13.9.

HRMS (M^+) calcd for $C_{28}H_{36}N_2O_5$ 480.2624, found 480.2633.

69. **Ethyl 2-((2S,5R)-4-(benzo[d][1,3]dioxol-5-ylmethyl)-1-benzyl-5-isopropyl-3,6-dioxopiperazin-2-yl)acetate**



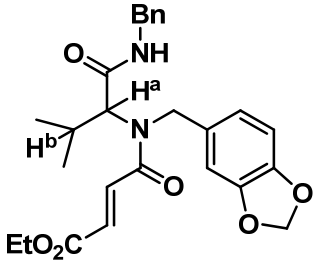
(±)-**95**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20-7.36 (m, 5 H, Ph), 6.72-6.85 (m, 3 H, Aryl), 5.92 (s, 2 H, -OC<u>H</u>$_2$O-), 5.39 (d, 1 H, *J* = 15.4 Hz, -NC<u>H</u>$_2$Ar), 5.19 (d,1 H, *J* = 15.4 Hz, -NC<u>H</u>$_2$Ar), 4.23 (dd,1 H, *J* = 6.2, 3.2 Hz, H^b), 4.14 (d,1 H, *J* = 15.4 Hz, -NC<u>H</u>$_2$Ar), 3.99-4.15 (m, 2 H, -OC<u>H</u>$_2$$CH_3$), 3.88 (d,1 H, *J* = 15.4 Hz, -NC<u>H</u>$_2$Ar), 3.86 (d,1 H, *J* = 2.1 Hz, H^a), 3.22 (dd, 1 H, *J* = 7.2, 3.6 Hz, H^c), 2.92 (dd, 1 H, J = 7.2, 5.6 Hz, H^c), 2.21-2.36 (m, 1 H, *i*-Pr), 1.17 (t, 3 H, *J* = 7.3 Hz, -$OCH_2C\underline{H}_3$), 1.12 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.94 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 166.7, 165.9, 147.2, 145.3, 135.9, 129.7, 128.9, 127.9, 127.8, 126.2, 110.5, 107.9, 101.6, 78.8, 62.7, 61.0, 52.9, 50.6, 35.9, 28.1, 19.2, 14.2.

HRMS (M^+) calcd for $C_{25}H_{30}N_2O_5$ 466.2104, found 466.2111

70. **(*E*)-Ethyl 4-((benzo[d][1,3]dioxol-5-ylmethyl)(1-(benzylamino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



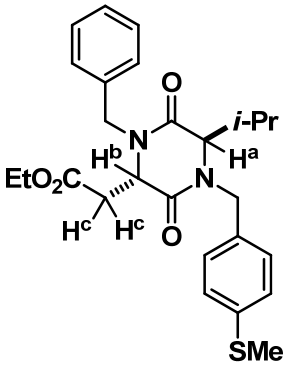
(±)-**96**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.35 (m, 6 H, Ph and –C<u>H</u>=CH- overlap), 6.89 (t, 1 H, *J* = 1.8 Hz, -N<u>H</u>), 6.76 (d, 1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.55-6.70 (m, 3 H, Aryl), 5.99 (s, 2 H, -OC<u>H$_2$</u>O-), 4.64 (dd, 2 H, *J* = 35.2, 8.8 hz, -NC<u>H$_2$</u>Ar), 4.46 (dd, 1 H, *J* = 12.4, 8.3 Hz, -NC<u>H$_2$</u>Ar), 4.42 (dd, 1 H, dd, *J* = 12.4, 6.5 Hz, -NC<u>H$_2$</u>Ar), 4.20 (q, 2 H, *J* = 7.3 Hz, -OC<u>H$_2$</u>CH$_3$), 2.43-2.57 (m, 1 H, H^b), 1.27 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H$_3$</u>), 0.97 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.82 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 165.9, 163.2, 145.2, 145.1, 136.5, 136.2, 129.6, 128.7, 127.8, 127.1, 126.9, 124.1, 110.6, 108.1, 101.4, 67.9, 61.8, 49.2, 42.9, 27.5, 19.1, 14.2.

HRMS (EIMS, M^+): calcd for $C_{26}H_{30}N_2O_6$ 466.2104, found 466.2112.

71. **Ethyl 2-((2S,5R)-1-benzyl-5-isopropyl-4-(4-(methylthio)benzyl)-3,6-dioxopiperazin-2-yl)acetate**



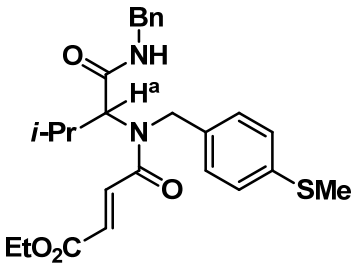
(±)-**97**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.34 (m, 5 H, Ph), 7.08 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.99 (d, 2 H, *J* = 8.3 Hz, Aryl), 5.39 (d, 1 H, *J* = 15.4 Hz, -NC$\underline{H}_2$Ar), 5.18 (d, 1 H, *J* = 15.4 Hz, -NC$\underline{H}_2$Ar), 4.24 (dd, 1 H, J = 6.2, 3.2 Hz, H^b), 4.15 (d, 1 H, *J* =15.4 Hz, -NC$\underline{H}_2$Ar), 4.01-4.11 (m, 2 H, -OC$\underline{H}_2$$CH_3$), 3.84 (d, 1 H, *J* = 4.1 Hz, H^a), 3.24 (dd,1 H, *J* = 17.0, 3.2 Hz, H^c), 2.92 (dd,1 H, *J* = 17.0, 5.7 Hz, H^c), 2.47 (s, 3 H, S$\underline{Me}$), 2.22-2.39 (m, 1 H, *i*-Pr), 1.16 (t, 3 H, *J* = 7.3 Hz, -OC$\underline{H}_2$$CH_3$), 1.12 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.93 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 165.8, 165.1, 138.7, 137.9, 134.2, 128.7, 128.3, 127.9, 127.2, 75.1, 61.1, 61.4, 50.6, 50.2, 35.9, 27.5, 18.9, 14.9, 14.2.

HRMS (EIMS, M^+) cacld for $C_{26}H_{32}N_2O_4S$ 468.2083, found 468.2093.

72. **(*E*)-Ethyl 4-((1-(benzylamino)-3-methyl-1-oxobutan-2-yl)(4-(methylthio)benzyl)amino)-4-oxobut-2-enoate**



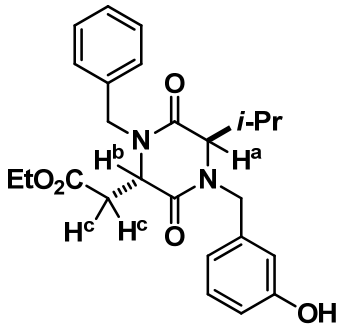
(±)-**98**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (br s, 1 H, -NH), 7.10-7.29 (m, 6 H, Ph and –CH=CH- overlap), 7.05 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.98 (d, 2 H, *J* = 8.3 Hz, Aryl), 6.62 (d, 1 H, *J* = 15.4 Hz, -CH=CH-), 4.72 (dd, 2 H, *J* = 71.4, 17.0 Hz, -NCH_2Ar), 4.64 (d, 1 H, *J* = 3.4 Hz, *i*-Pr), 4.34 (dd, 1 H, *J* = 15.4, 6.5 Hz, -NCH_2Ar), 4.18 (dd, 1 H, *J* = 14.6, 5.7 Hz, -NCH_2Ar), 4.12 (q, 2 H, *J* = 7.3 Hz, -OCH_2CH_3), 2.23-2.45 (m, 4 H, *i*-Pr and SMe overlap), 1.21 (t, 3 H, *J* = 7.3 Hz, -OCH_2CH_3), 0.94 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.79 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 166.5, 165.7, 138.9, 138.7, 134.2, 134.1, 132.4, 128.8, 127.9, 127.5, 127.3, 126.9, 65.1, 61.5, 48.5, 43.3, 27.6, 19.8, 19.1, 15.9, 14.2.

HRMS (EIMS, M^+) cacld for $C_{26}H_{32}N_2O_4S$ 468.2083, found 468.2091.

73. **Ethyl 2-((2S,5R)-1-benzyl-4-(3-hydroxybenzyl)-5-isopropyl-3,6-dioxopiperazin-2-yl)acetate**



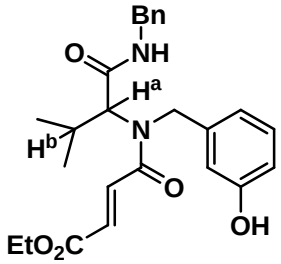
(±)-**99**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.36 (m, 5 H, Ph), 6.70-6.87 (m, 3 H, Aryl), 5.38 (d, 1 H, *J* = 15.4 Hz, -NC$\underline{H}_2$Ar), 5.24 (d, 1 H, *J* = 15.4 Hz, -NC$\underline{H}_2$Ar), 4.26 (dd, 1 H, J = 3.3 Hz, H^b), 4.15 (d, 1 H, *J* = 15.4 Hz, -NC$\underline{H}_2$Ar), 4.05-4.15 (m, 2 H, -OC$\underline{H}_2$CH$_3$), 3.98 (d, 1 H, *J* = 15.4 Hz, -NC$\underline{H}_2$Ar), 3.88 (d, 1 H, *J* = 4.1 Hz, H^a), 3.25 (dd, 1 H, *J* = 17.0, 3.2 Hz, H^c), 2.93 (dd, 1 H, *J* = 17.0, 4.7 Hz, H^c), 2.26-2.37 (m, 1 H, *i*-Pr), 1.16 (t, 3 H, *J* = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 1.13 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.96 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (125 MHz, $CDCl_3$) : δ 170.1, 167.7, 167.5, 156.4, 136.1, 129.5, 128.9, 127.8, 127.6, 126.3, 115.7, 67.7, 61.0, 55.8, 51.3, 47.0, 40.1, 34.6, 28.3, 14.0.

HRMS (EIMS, M^+): calcd for $C_{26}H_{32}N_2O_5$ 452.2311, found 452.2314.

74. **(*E*)-Ethyl 4-((1-(benzylamino)-3-methyl-1-oxobutan-2-yl)(3-hydroxybenzyl)amino)-4-oxobut-2-enoate**



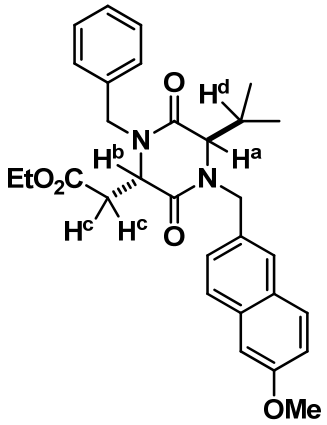
(±)-**100**

^{1}H NMR (400 MHz,): δ 7.17-7.32 (m, 6 H, Ph and –C$\underline{H}$=CH- overlap), 6.99-7.06 (m, 1 H, Aryl), 6.75 (d, 1H, *J* = 15.4 Hz, -CH=C$\underline{H}$-), 6.52-6.66 (m, 3 H, -N$\underline{H}$ and Aryl overlap), 4.63 (dd, 2 H, *J* = 51.9, 17.8 Hz, -NC$\underline{H}_2$Ar), 4.42 (dd, 2 H, *J* = 14.6, 5.7 Hz, -NC$\underline{H}_2$Ar), 4.24 (d, 1 H, *J* = 4.3 Hz, H^a), 4.16 (q, 2 H, *J* = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 2.45-2.59 (m 1 H, H^b), 1.25 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 0.96 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.83 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 166.5, 163.0, 156.8, 137.9, 137.8, 129.9, 128.5, 126.9, 126.7, 120.5, 114.2, 113.6, 67.7, 61.4, 49.7, 43.6, 27.3, 18.8, 14.2.

HRMS (EIMS, M^+): calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2162.

73. **Ethyl 2-((2S,5R)-1-benzyl-5-isopropyl-4-((6-methoxynaphthalen-2-yl)methyl)-3,6-dioxopiperazin-2-yl)acetate**

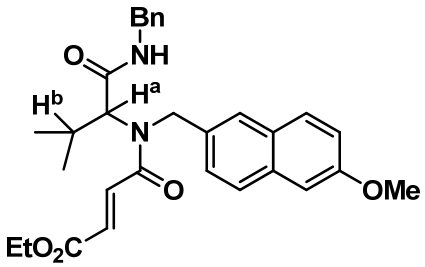


(±)-**101**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.74 (m, 3 H, Ar), 7.20-7.40 (m, 6 H, Ar), 7.08-7.16 (m, 2 H, Ar), 5.56 (d, 1 H, *J* = 15.4 Hz, -NC<u>H</u>$_2$Ar), 5.18 (d, 1 H, *J* = 14.6 Hz, -NC<u>H</u>$_2$Ar), 4.27 (dd, 1 H, *J* = 4.9, 3.2 Hz, H^b), 4.05-4.17 (m, 5 H, -NC<u>H</u>$_2$Ar, -OCH_2CH_3 and H^a overlap), 3.90 (s, 3 H, O<u>Me</u>), 3.25 (dd, 1 H, *J* = 17.8, 3.3 Hz, H^c), 2.93 (dd, 1 H, *J* = 17.8, 5.7 Hz, H^c), 2.30-2.43 (m, 1 H, H^d), 1.24 (t, 3 H, *J* = 7.3 Hz, -OCH_2C<u>H</u>$_3$), 1.11 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.94 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

HRMS (EIMS, M^+): cacld for $C_{30}H_{34}N_2O_5$ 502.2468, found 502.2479.

74. **(*E*)-Ethyl 4-((1-(benzylamino)-3-methyl-1-oxobutan-2-yl)((6-methoxynaphthalen-2-yl)methyl)amino)-4-oxobut-2-enoate**



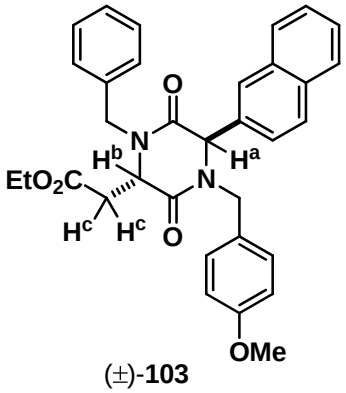
(±)-**102**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.68 (m, 3 H, Aryl), 7.08-7.36 (m, 9 H, Aryl and –C<u>H</u>=CH- overlap), 6.96 (br s, 1 H, -N<u>H</u>), 6.77 (d,1 H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 4.86 (dd, 2 H, *J* = 47.2, 17.2 Hz, -NC<u>H</u>$_2$Ar), 4.51 (d, 1 H, *J* = 3.4 Hz, H^b), 4.44 (dd, 1 H, *J* = 14.7, 10.4 Hz, -NC<u>H</u>$_2$Ar), 4.19 (dd, 1 H, *J* = 14.7, 10.4 Hz, -NC<u>H</u>$_2$Ar), 4.14 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.91 (s, 3 H, O<u>Me</u>), 2.48-2.63 (m, 1 H, H^b), 1.22 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.98 (d, 3 H, *J* = 6.5 Hz, *i*-Pr), 0.83 (d, 3 H, *J* = 6.5 Hz, *i*-Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 166.6, 163.2, 156.3, 137.9, 135.8, 132.9, 133.1, 129.4, 129.1, 128.7, 128.6, 127.6, 126.5, 126.1, 117.8, 108.5, 67.9, 61.3, 49.7, 43.7, 27.3, 18.7, 14.1.

HRMS (EIMS, M$^+$): cacld for $C_{30}H_{34}N_2O_5$ 502.2468, found 502.2476.

75. **Ethyl 2-((2S,5R)-1-benzyl-4-(4-methoxybenzyl)-5-(naphthalen-2-yl)-3,6-dioxopiperazin-2-yl)acetate**



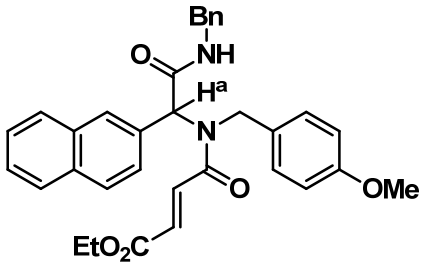
(±)-**103**

^{1}H NMR (400 MHz, CD_2Cl_2) : δ 7.86-7.98 (m, 3H), 7.76 (s, 1H), 7.53-7.61 (m, 2H), 7.38-7.45 (m, 1H), 7.24-7.35 (m, 3H), 7.05-7.19 (m, 4H), 6.80-6.89 (m, 2H), 5.43 (d, 1H, *J*=14.6 Hz), 5.11-5.21 (m, 2H), 4.33-4.38 (m, 1H), 3.98-4.17 (m, 3H), 3.8 (s, 3H), 3.42 (d, 1H, *J*=14.6 Hz), 3.28 (dd, 1H, *J*=17.4 Hz), 2.98 (dd, 1H, *J*=5.3, 17.4 Hz), 1.20 (t, 3H, *J*=7.3 Hz).

^{13}C NMR (100 MHz, CD_2Cl_2) : δ 170.1, 166.1, 165.7, 159.7, 136.1, 135.1, 133.7, 133.6, 130.5, 129.4, 129.2, 128.4, 128.3, 128.2, 128.0, 127.8, 127.6, 126.9, 125.1, 63.2, 61.4, 55.6, 55.5, 47.2, 46.8, 35.3, 14.2.

HRMS (M^+) calcd for $C_{38}H_{32}N_2O_5$ 536.2311, found 536.2317.

76. **(*E*)-Ethyl 4-((2-(benzylamino)-1-(naphthalen-2-yl)-2-oxoethyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



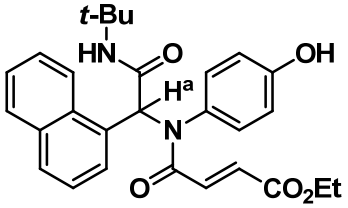
(±)-**103a**

^{1}H NMR (500 MHz, $CDCl_3$) : δ 7.68-7.83 (m, 4H), 7.45-7.53 (m, 3H), 7.36-7.43 (m, 1H), 7.19-7.35 (m, 6H), 6.84-6.94 (m, 3H), 6.6-6.67 (m, 2H), 6.19 (t, 1H, *J*=5.7 Hz), 6.15 (s, 1H), 4.79 (d, 1H, *J*=17.8 Hz), 4.58 (d, 1H, *J*=17.8 Hz), 4.49 (ddd, 1H, *J*=5.7, 15.2, 38.8 Hz), 4.19 (q, 2H, *J*=7.3 Hz), 3.68 (s, 3H), 1.26 (t, 3H, *J*=7.3 Hz).

^{13}C NMR (100 MHz, CD_2Cl_2) : δ 170.1, 166.1, 165.7, 159.7, 136.1, 135.1, 133.7, 133.6, 130.5, 129.4, 129.2, 128.4, 128.3, 128.2, 128.0, 127.8, 127.6, 126.9, 125.1, 63.2, 61.4, 55.6, 55.5, 47.2, 46.8, 35.3, 14.2.

HRMS (M^+) calcd for $C_{38}H_{32}N_2O_5$ 536.2311, found 536.2318.

77. **(*E*)-Ethyl 4-((2-(*tert*-butylamino)-1-(naphthalen-1-yl)-2-oxoethyl)(4-hydroxyphenyl)amino)-4-oxobut-2-enoate**



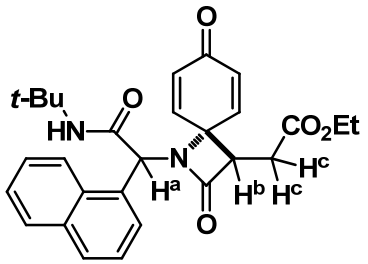
(±)-**112**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.81 (m, 5 H, Aryl), 7.65 (d, 2 H, *J* = 8.9 Hz, Aryl), 7.42-7.52 (m, 3 H, Aryl), 7.16 (dd, 1 H, *J* = 8.9, 1.6 Hz, Aryl), 6.84 (dd, 2 H, *J* = 32.4, 15.4 Hz, -C<u>H</u>=C<u>H</u>-), 6.58 (br s, 1 H, -N<u>H</u>), 6.10 (s, 1 H, H^a), 5.78 (br s, 1 H, -O<u>H</u>), 4.15 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 1.33 (s, 9 H, *t*-Bu), 1.23 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 165.9, 165.1, 156.4, 134.6, 132.9, 131.7, 131.4, 131.3, 130.8, 129.8, 128.2, 128.1, 127.6, 127.1, 126.7, 126.4, 66.5, 61.2, 51.9, 28.6, 14.0.

HRMS (EIMS, M^+): calcd for $C_{28}H_{30}N_2O_5$ 474.2155, found 474.2167.

78. **Ethyl 2-((3R)-1-(2-(*tert*-butylamino)-1-(naphthalen-1-yl)-2-oxoethyl)-2,7-dioxo-1-azaspiro[3.5]nona-5,8-dien-3-yl)acetate**



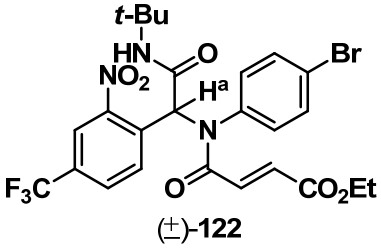
(±)-**113 (dr = 1:2)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.81 (m, 4 H, Aryl), 7.42-7.52 (m, 2 H, Aryl), 7.16 (m, 2 H, Aryl and cyclohexadienone overlap), 6.60-6.90 (m, 3 H, cyclohexadienone), 6.58 (br s, 1 H, -NH), 5.82 (s, 1 H, H^a), 4.15 (q, 2 H, J = 7.3 Hz, -OCH_2CH_3), 4.03 (dd, 1 H, J = 9.2, 4.9 Hz, H^b), 2.76 (dd, 1 H, J = 18.3, 3.7 Hz, H^c), 2.28 (dd, 1 H, J = 18.3, 12.2, Hz, H^c), 1.33 (s, 9 H, *t*-Bu), 1.23 (t, 3 H, J = 7.3 Hz, -OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 186.1, 171.2, 169.1, 168.9, 154.3, 134.6, 132.9, 131.7, 131.4, 131.3, 130.8, 129.8, 128.2, 128.1, 127.6, 127.1, 126.7, 126.4, 68.1, 62.3, 61.8, 59.6, 45.2, 35.2, 28.9, 14.0.

HRMS (EIMS, M^+): calcd for $C_{28}H_{30}N_2O_5$ 474.2155, found 474.2152.

79. **(*E*)-Ethyl 4-((4-bromophenyl)(2-(*tert*-butylamino)-1-(2-nitro-4-(trifluoromethyl)phenyl)-2-oxoethyl)-4-oxobut-2-enoate**



(±)-**122**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, aryl), 7.64 (d, 2H, J = 8.9 Hz, aryl), 7.58 (d, 1H, J = 8.1 Hz, aryl), 7.34 (d, 2H, J = 8.1 Hz, aryl), 7.10 (br s, 1H, -NH), 6.80 (d, 1H, J =

14.6 Hz, -C<u>H</u>=CH-), 6.70 (d, 1H, *J* = 14.6 Hz, -CH=C<u>H</u>-), 6.54 (s, 1H, aryl), 6.00 (s, 1H, H_a), 4.16 (q, 2H, *J* = 8.0 Hz, -OC<u>H_2</u>CH_3), 1.27 (s, 9H, *t*-butyl), 1.25 (t, 3H, *J* = 7.3 Hz, -OCH_2C<u>H_3</u>).

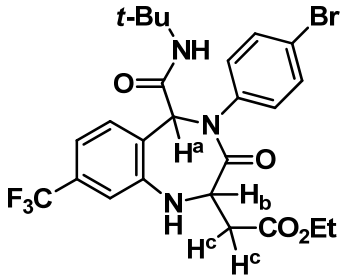
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 165.3, 164.7, 149.9, 137.2, 133.3, 133.2, 133.1, 133.0, 132.9, 132.7, 132.6, 131.6, 129.5, 129.4, 123.6 (J_{C-F} = 272.2 Hz), 122.4, 122.3, 61.5, 61.1, 52.5, 28.6, 14.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ - 63.51.

HRMS: EIMS (M^+) calcd for $C_{25}H_{25}BrF_3N_3O_6$ 599.0879 found 599.0889.

IR (neat): 3322, 3070, 2968, 2933, 1714, 1690, 1664, 1542, 1486, 1362, 1324, 1298, 1221, 1154, 1136, 1089, 1033, 975, 654.

80. **Ethyl 2-(4-(4-bromophenyl)-5-(*tert*-butylcaramoyl)-3-oxo-8-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl)acetate**



(±)-**123**

^{1}H NMR (400 MHz, $CDCl_3$): **(major)** δ 8.43 (s, 1 H, aryl), 7.79 (d, 1 H, *J* = 8.1 Hz, aryl), 7.46 – 7.38 (m, 3H, aryl), 7.30 – 7.24 (m, 2H, aryl), 5.92 (s, 1H, H^a), 4.58 (m, 1H, H_b), 4.11 – 3.99 (m, 2H, -OC<u>H_2</u>CH_3), 2.43 (dd, 1H, J_1 = 5.7 Hz, J_2 = 16.2 Hz, H^c), 2.28 (dd, 1H, , J_1 = 8.1 Hz, J_2 = 16.2 Hz, H^c), 1.23 (s, 9H, *t*-butyl), 1,17 (t, 3H, *J* = 7.3 Hz, -OCH_2C<u>H_3</u>).

^{1}H NMR (400 MHz, $CDCl_3$): **(minor)** δ 8.32 (s, 1H, aryl), 7.43 (d, 1H, J = 8.1 Hz, aryl), 7.46 – 7.38 (m, 3H, aryl), 7.30 – 7.24 (m, 2H, aryl), 6.88 (s, 1H, H^a), 4.58 (m, 1H, H_b), 4.28 – 4.20 (m, 2H, -OC$\underline{H}_2$CH_3), 3.29 (dd, 1H, J_1 = 4.8 Hz, J_2 = 17.2 Hz, H^c), 2.28 (dd, 1H, , J_1 = 7.3 Hz, J_2 = 18.1 Hz, H^c), 1.31 (t, 3H, J = 7.3 Hz, -OCH_2C$\underline{H}_3$), 1.21 (s, 9H, *t*-butyl).

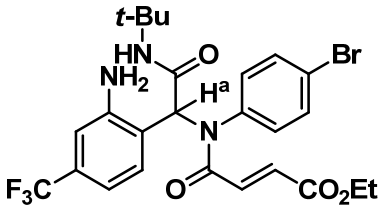
^{13}C NMR (100 MHz, $CDCl_3$): **(major and minor)** δ 172.3, 169.7, 165.8, 165.6, 165.4, 163.3, 150.0, 135.9, 135.7, 132.9, 132.8, 132.7, 130.6, 129.9, 129.8, 129.6, 128.4, 124.0 (q, $J_{C\text{-}F}$ = 270.7 Hz), 123.0, 122.9,122.8, 119.1, 119.0, 118.4, 76.9, 71.5, 62.2, 61.6, 61.0, 58.5, 53.4, 53.1, 31.9, 31.2, 29.9, 28.6, 28.5, 14.3, 14.2. ($J_{C\text{-}F}$ for other diastereomer could not be detected clearly).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 63.50 (major), - 63.52 (minor).

HRMS: EIMS (M^+) calcd for $C_{25}H_{27}BrF_3N_3O_4$ 569.1137 found 569.1130.

IR (neat): 3362, 3019, 2924, 1738, 1738, 1715, 1604, 1456, 1364, 1219, 1046, 968, 747, 676.

81. **(*E*)-Ethyl 4-((1-(2-amino-4-(trifluoromethyl)phenyl)-2-(*tert*-butylamino)-2-oxoethyl)(4-bromophenyl) amin o)-4-oxobut-2-enoate**



(±)-**124**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>=CH-), 6.84 (m, 2H, aryl), 6.74 (m, 3H, aryl), 6.65 (d, 1H, *J* = 14.6 Hz, -CH=C<u>H</u>-), 6.56 (s, 1H, aryl), 6.24 (s, 1H, aryl), 5.40 (s, 1H, H_a), 4.24 (s, 2H, -N<u>H</u>$_2$), 4.16 (q, 2H, *J* = 8.0 Hz, -OC<u>H</u>$_2$CH$_3$), 1.27 (s, 9H, *t*-butyl), 1.21 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

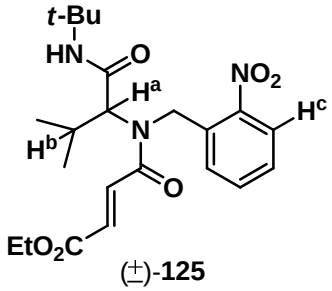
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 167.0, 166.0, 137.6, 133.4, 133.3, 133.2, 133.1, 133.0, 132.9, 132.8, 132.7, 132.2, 131.7, 131.6, 123.6, 119.4 ($J_{C\text{-}F}$ = 270.6 Hz), 118.7, 61.5, 59.7, 47.9, 28.6, 19.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ – 63.51.

HRMS: EIMS (M^+) calcd for $C_{25}H_{27}BrF_3N_3O_4$ 569.1137 found 569.1139.

IR (neat): 3402, 3270, 3068, 2963, 1716, 1681, 1367, 1244, 1159, 1064, 784, 751

82. **(*E*)-Ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)(2-nitrobenzyl)amino)-4-oxobut-2-enoate**



(±)-**125**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d,1H, *J* = 8.9 Hz, H^c), 7.51 (dd, 1H, J_1 = 7.1 Hz, J_2 = 6.48 Hz, aryl), 7.41 (dd, 1H, J_1 = 10.5, J_2 = 7.3, aryl), 7.20 (d, 1H, *J* = 8.1 Hz, aryl), 6.98 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>=CH-), 6.82 (d, 1H, *J* = 14.6 Hz, -CH=C<u>H</u>-), 6.12 (br s, 1H, -N<u>H</u>), 5.30 (d, 1H, *J* = 18.7 Hz, Bn), 5.10 (d, 1H, *J* = 19.7 Hz, Bn), 4.55 (d, 1H, *J* = 10.5 Hz, H^a), 4.13 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 2.38 (m, 1H, C<u>H</u>(CH$_3$)$_2$, H^b), 1.20 (m, 12H, -

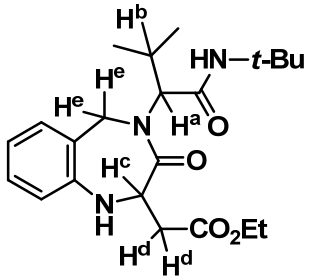
$OCH_2C\underline{H}_3$ and *t*-butyl overlap), 0.95 (d, 3H, *J* = 6.5 Hz, -CH($C\underline{H}_3$)$_2$), 0.90 (d, 3H, *J* = 7.3 Hz. -CH($C\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 166.7, 165.0, 133.8, 133.6, 133.2, 132.6, 128.2, 128.0, 127.9, 125.6, 61.2, 51.5, 46.0, 28.5, 28.4, 27.9, 19.2, 18.6, 14.0.

HRMS: EIMS (M^+) calcd for $C_{22}H_{31}N_3O_6$ 433.2213, found 433.2210.

IR (neat): 3322, 3071, 2968, 2934, 1720, 1678, 1655, 11528, 1449, 1365, 1296, 1218, 1178, 971, 731.

83. **Ethyl 2-(4-(1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)-3-oxo-2,3,4,5-tetrahydro-1H-benzo[*e*][1,4]diazepin-2-yl)acetate**



(±)-**126**

^{1}H NMR (400 MHz, $CDCl_3$): (**major**) δ 6.70 (t, 1H, *J* = 7.3 Hz, aryl), 6.65 (t, 1H, *J* = 7.3 Hz, aryl), 6.53 (d, 1H, *J* = 7.2 Hz, aryl), 6.50 (d, 1H, *J* = 8.1 Hz, aryl), 5.64 (s, 1H, -N$\underline{H}$), 5.08 (d, 1H, *J* = 17.0 Hz, H^e), 5.00 (d, 1H, *J* = 7.3 Hz, H^a), 4.54 (d, 1H, *J* = 17.0 Hz, H^e), 4.42 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.1 Hz, H^c), 4.16 (m, 2H, -O$C\underline{H}_2$CH$_3$), 2.70 (dd, 1H, J_1 = 10.1 Hz, J_2 = 5.7 Hz, H^d), 2.60 (dd, 1H, J_1 = 11.0 Hz, J_2 = 4.9 Hz, H^d), 2.20 (m, 1H, H^b), 1.27 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 0.94 (s, 9H, *t*-butyl), 0.80 (d, 3H, *J* = 6.8 Hz, -CH($C\underline{H}_3$)$_2$), 0.50 (d, 3H, *J* = 6.8 Hz, -CH($C\underline{H}_3$)$_2$).

^{1}H NMR (400 MHz, $CDCl_3$): (**minor**) δ 7.10 (t, 1H, *J* = 7.3 Hz, aryl), 7.00 (t, 2H, *J* = 7.3 Hz, aryl), 6.90 (d, 1H, *J* = 8.1 Hz, aryl), 5.70 (s, 1H, -N$\underline{H}$), 5.20 (d, 1H, *J* = 17.0 Hz, H^e),

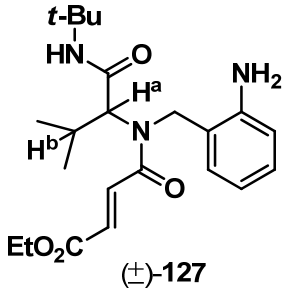
5.10 (d, 1H, J = 17.0 Hz, H^e), 5.00 (d, 1H, J = 7.0 Hz, H^a), 4.42 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.1 Hz, H^c), 4.16 (m, 2H, -OC$\underline{H}_2$CH$_3$), 2.90 (dd, 2H, J_1 = 15.8 Hz, J_2 = 6.5 Hz, H^d), 2.40 (m, 1H, H^b), 1.32 (s, 9H, *t*-butyl), 1.28 (t, 3H, J = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 0.97 (d, 3H, J = 6.5 Hz, -CH(C$\underline{H}_3$)$_2$), 0.90 (d, 3H, J = 6.5 Hz, -CH(C$\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): (**major and minor**) δ 171.6, 171.3, 171.1, 170.5, 169.4, 168.2, 144.9, 144.6, 131.2, 129.6, 128.8, 120.9, 119.8, 119.3, 119.1, 118.7, 117.3, 116.8, 63.7, 62.8, 60.9, 60.8, 59.7, 52.3, 51.5, 51.4, 50.9, 46.6, 46.2, 36.17, 36.1, 29.6, 28.5, 28.3, 28.0, 27.3, 25.9, 19.5, 18.6, 18.4, 14.2, 14.1.

HRMS: EIMS (M^+) calcd for $C_{22}H_{33}N_3O_4$ 403.2471 found 403.2472.

IR (neat): 3339, 3066, 2967, 2873, 1714, 1635, 1612, 1537, 1426, 1362, 1204, 1043, 752.

84. **(*E*)-ethyl-4((2-aminobenzyl)(1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



(±)-**127**

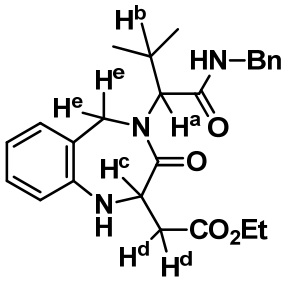
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.20 (M, 4H, aryl), 7.41 (dd, 1H, J_1 = 10.5, J_2 = 7.3, aryl), 6.98 (d, 1H, J = 14.6 Hz, -C$\underline{H}$=CH-), 6.83 (d, 1H, J = 14.6 Hz, -CH=C$\underline{H}$-), 5.25 (d, 1H, J = 18.7 Hz, Bn), 5.00 (d, 1H, J = 19.5 Hz, Bn), 4.40 (d, 1H, J = 10.6 Hz, H_a), 4.13 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.20 (br s, 2H, -N$\underline{H}_2$), 2.42 (m, 1H, H^b), 1.20 (m, 12H, -OCH$_2$C$\underline{H}_3$ and *t*-butyl overlap), 0.95 (d, 3H, J = 6.5 Hz, -CH(C$\underline{H}_3$)$_2$), 0.90 (d, 3H, J = 7.3 Hz, -CH(C$\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 166.8, 165.0, 131.8, 131.0, 130.9, 130.6, 130.3, 129.5, 129.0, 128.6, 61.2, 61.1, 51.8, 46.0, 28.9, 28.2, 27.8, 19.2, 18.6, 14.2.

HRMS: EIMS (M^+) calcd for $C_{22}H_{33}N_3O_4$ 403.2471 found 403.2480.

IR (neat): 3452, 3400, 3021, 2814, 1690, 1600, 1537, 1290 1060.

85. **Ethyl 2-(4-(1-(benzylamino)-3-methyl-1-oxobutan-2-yl)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo [*e*][1,4] diazepin-2yl)acetate**



(±)-**128**

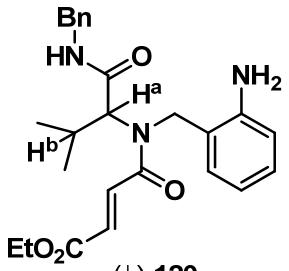
^{1}HNMR (400 MHz, $CDCl_3$): **(major and minor)** δ 7.35 - 6.98 (m, 12H, aryl), 6.80 (bd, 2H, *J* = 5.0 Hz, aryl), 6.70 (t, 2H, *J* = 7.3 Hz, aryl), 6.54 (dd, 2H, J_1 = 8.1 Hz, J_2 = 3.2 Hz, aryl), 6.28 (br t, 1H, *J* = 5.7 Hz, -N<u>H</u>), 6.00 (br s, 1H, -N<u>H</u>), 5.20 (d, 1H, *J* = 16.2 Hz, H^e), 5.10 – 4.95 (m, 3H, 2 x H^e , *J* = 16.2 Hz , *J* = 16.0 Hz and -N<u>H</u> overlap), 4.60 – 4.45 (m, 3H, 2 x H^d and H^e overlap), 4.31 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 4.23 (d, 1H, *J* = 16.2 Hz, Bn), 4.20 – 4.10 (m, 5H, H^a, -N<u>H</u>, -OC<u>H</u>$_2$CH$_3$ and Bn overlap), 4.01 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 3.98 (br d, 1H, *J* = 5.7 Hz, H^a), 2.96 – 2.90 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 2.63 (dd, 2H, J_1 = 16.2 Hz, J_2 = 6.5 Hz, H^d), 2.49 (m, 2H, H^d), 2.27 (m, 2H, 2x H^b), 1.28 – 1.23 (m, 6H, -OCH$_2$C<u>H</u>$_3$), 0.99 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H</u>$_3$)$_2$), 0.92 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H</u>$_3$)$_2$) , 0.87 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H</u>$_3$)$_2$, 0.51 (d, 3H, *J* = 6.5 Hz, -CH(C<u>H</u>$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): **(major and minor)** δ 172.2, 171.6, 171.4, 170.7, 170.1, 169.4, 145.3, 145.0, 138.2, 137.9, 131.0, 130.0, 129.3, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.0, 127.8, 127.7, 127.4, 121.0, 120.1, 119.3, 119.1, 117.7, 117.3, 63.6, 61.2, 61.2, 60.6, 52.6, 52.0, 47.2, 46.8, 43.4, 36.5, 36.4, 29.93, 27.4, 26.5, 21.3, 19.9, 19.8, 18.9, 14.4, 14.3.

HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2328.

IR (neat): 3331, 3030, 2965, 2933, 2873, 1715, 1644, 1494, 1452, 1365, 1221, 1174, 1029, 969, 748, 700.

86. **(*E*)-Ethyl 4-((2-aminobenzyl)(1-(benzylamino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



(±)-**129**

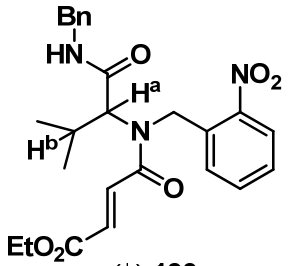
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 - 6.95 (m, 9H, aryl, and -C<u>H</u>=CH-, *J* = 15.4 Hz,), 6.80 (1H, *J* = 8.0 Hz, aryl), 6.70 (d, 1H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 5.18 (d, 1H, *J* = 19.4 Hz, Bn), 5.00 (d, 1H, *J* = 19.4 Hz, Bn), 4.72 (br d, 1H, *J* = 10.5 Hz, H_a), 4.33 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 4.12 (m, 3H, Bn and -OC<u>H</u>$_2$CH$_3$ overlap), 3.40 (br s, 2H, NH_2), 2.44 (m, 1H, H_b), 1.23 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.95 (d, 3H, *J* = 6.5 Hz, -CH$_2$(C<u>H</u>$_3$)$_2$), 0.90 (d, 3H, *J* = 6.5 Hz, -CH$_2$(C<u>H</u>$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169, 167.2, 165.3, 137.4, 133.3, 132.6, 131.6, 128.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.6, 127.3, 126.0, 64.8, 61.6, 46.2, 43.8, 27.8, 19.1, 18.1, 14.1.

HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2321.

IR (neat): 3552, 3395, 3000, 2965, 2933, 2873, 1781, 1644, 1367, 1360, 1215, 1166, 1023, 900.

87. **(*E*)-Ethyl 4-((1-(benzylamino)-3-methyl-1-oxobutan-2-yl)(2-nitrobenzyl)amino)-4-oxobut-2-enoate**



(±)-**130**

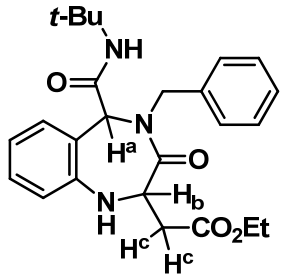
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1H, *J* = 8.1 Hz, H_c), 7.37 (t, 1H, *J* = 8.1 Hz, aryl), 7.28 (m, 4H, aryl), 7.1 (br s, 1H, aryl), 7.00 (br s, 1H, aryl), 6.99 (br s, 1H, aryl), 6.95 (d, 1H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 6.70 (d, 1H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 5.20 (d, 1H, *J* = 19.4 Hz, Bn), 5.00 (d, 1H, *J* = 19.4 Hz, Bn), 4.60 (br d, 1H, *J* = 10.5 Hz, H_a), 4.30 (dd, 1H, J_1 = 14.6 Hz, J_2 = 5.7 Hz, Bn), 4.14 (m, 3H, Bn and -OC<u>H</u>$_2$CH$_3$ overlap), 2.45 (m, 1H, H_b), 1.22 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.97 (d, 3H, *J* = 6.5 Hz, -CH$_2$(C<u>H</u>$_3$)$_2$), 0.91 (d, 3H, *J* = 6.5 Hz, -CH$_2$(C<u>H</u>$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 167.1, 165.1, 147.5, 137.9, 133.9, 133.6, 133.4, 133.3, 132.8, 128.9, 128.5, 128.1, 128.0, 127.9, 127.6, 125.9, 65.0, 61.6, 46.5, 43.5, 27.7, 19.1, 18.9, 14.2.

HRMS: EIMS (M^+) calcd for $C_{25}H_{29}N_3O_6$ 467.2056 found 467.2050.

IR (neat): 3323, 3066, 3032, 2966, 2873, 1717, 1655, 1525, 1498, 1442, 1342, 1298, 1174, 1164, 1031, 970, 727, 700.

88. **Ethyl 2-(4-benzyl-5-(*tert*-butylcarbamoyl)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-2-yl) acetate**



(±)-**131**

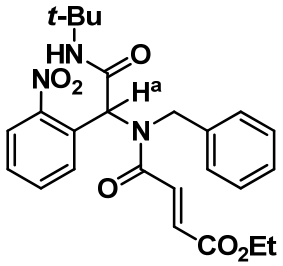
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.23 (m, 5H, aryl), 7.11 (t, 1H, J = 7.3 Hz, aryl), 6.82 (d, 1H, J = 7.3 Hz, aryl), 6.68 (t, 1H, J = 7.3 Hz, aryl), 6.64 (d, 1H, J = 8.1 Hz, aryl), 5.52 (s, 1H, H^a), 4.85 (d, 1H, J = 15.4 Hz, Bn), 4.66 (d, 1H, J = 15.4 Hz, Bn), 4.45 – 4.41 (m, 1H, H_b), 4.16 (m, 2H, -OC$\underline{H}_2$CH$_3$), 3.04 (dd, 1H, J_1 = 16.2 Hz, J_2 = 6.5 Hz, H^c), 2.64 (dd, 1H, J_1 = 16.2 Hz, J_2 = 6.5 Hz, H^c), 1.27 (t, 3H, J = 7.2 Hz, -OCH$_2$C$\underline{H}_3$), 1.17 (s, 9H, *t*-butyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 170.37, 169.1, 144.2, 137.0, 132.7, 129.8, 129.3, 129.2, 129.0, 128.9, 128.8, 128.2, 119.2, 118.7, 66.9, 61.1, 52.8, 52.6, 51.9, 36.1, 28.5, 28.4, 28.2, 14.4.

HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2323.

IR (neat): 3318, 2928, 2856, 1714, 1682, 1515, 1451, 1240, 1096, 1047, 847, 750.

89. **(*E*)-Ethyl 4-(benzyl(2-*tert*-butylamino)-1-(2-nitrophenyl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



(±)-**132**

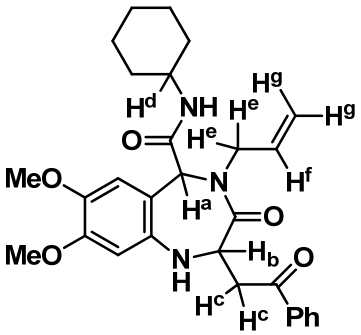
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, 1H, *J* = 7.3 Hz, aryl), 7.57 – 7.49 (m, 2H, aryl), 7.41 – 7.19 (m, 5H, aryl and -C<u>H</u>=CH- overlap), 7.02 (br d, 2H, *J* = 7.3 Hz, aryl), 6.92 (d, 1H, *J* = 15.0 Hz -CH=C<u>H</u>-), 5.70 (s, 1H, H_a), 5.19 (s, 1H, -N<u>H</u>), 4.88 (d, 1H, *J* = 17.8 Hz, Bn), 4.74 (d, 1H, *J* = 17.8 Hz, Bn), 4.19 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 1.30 (m, 3H, -OCH$_2$C<u>H</u>$_3$), 1.20 (s, 9H, *t*-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 166.4, 165.5, 149.6, 136.5, 133.8, 133.4, 133.2, 130.5, 129.9, 129.7, 129.4, 128.9, 128.7, 128.5, 127.8, 126.5, 125.4, 62.9, 61.4, 60.2, 52.2, 50.6, 28.4, 14.3.

HRMS: EIMS (M^+) calcd for $C_{25}H_{29}N_3O_6$ 467.2056 found 467.2048.

IR (neat): 3325, 2969, 2930, 1720, 1678, 1644, 1620, 1525, 1453, 1418, 1363, 1348, 1222, 1031, 976, 853, 790, 718.

90. **4-allyl-*N*-cyclohexyl-7,8-dimethoxy-3-oxo-2-(2-oxo-2-phenylethyl)-2,3,4,5-tetrahydro-1H-benzo[*e*] [1,4] diazepine-5-carboxamide**



(±)-133

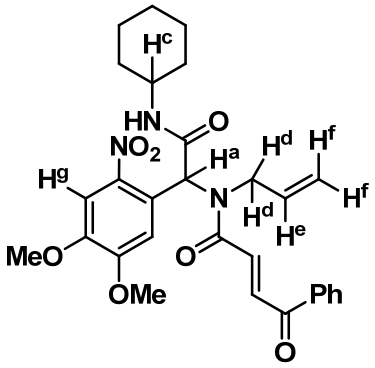
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.92 (m, 2H, aryl), 7.51-7.41 (m, 4H, aryl), 6.61 (s, 1H, aryl), 6.18 (s, 1H, H^a), 5.87 – 5.77 (m, 1H, H^f), 5.31 – 5.18 (m, 2H, H^g), 4.64 – 4.50 (m, 2H, H^e), 4.20 (dd, 1H, J_1 = 6.5 Hz, J_2 = 7.3 Hz, H^b), 4.10 (br d, 1H, J = 4.8 Hz, -N<u>H</u>), 3.90 (s, 3H, -OC<u>H</u>$_3$), 3.70 (s, 3H, -OC<u>H</u>$_3$), 3.66 – 3.58 (m, 2H, H^d and H^c overlap), 3.18 (dd, 1H, J_1 = 5.0 Hz, J_2 = 16.4 Hz, H^c), 1.80 – 1.00 (m, 10H, Cy).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 166.8, 155.6, 146.6, 143.4, 133.2, 133.8, 132.0, 129.2, 128.9, 128.8, 128.7, 127.6, 112.6, 112.7, 105.9, 104.0, 96.0, 65.9, 63.2, 56.7, 56.5, 52.4, 49.2, 32.7, 32.6, 24.98, 24.9, 24.7.

HRMS: EIMS (M^+) calcd for $C_{29}H_{35}N_3O_5$ 505.2577 found 505.2589.

IR (neat): 3320, 2927, 2854, 1740, 1608, 1454, 1373, 1240, 1047, 969, 751.

91. **(*E*)-*N*-allyl-*N*-(2-(cyclohexylamino)-1-(4,5-dimethoxy-2-nitrophenyl)-2-oxoethyl)-4-oxo-4-phenylbut-2-enamide**



(±)-**134**

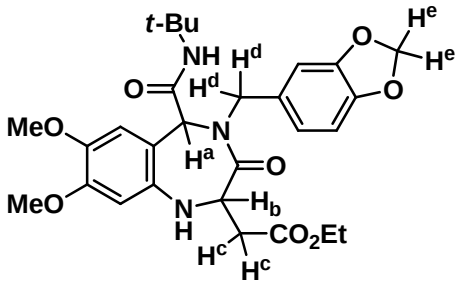
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.90 (m, 3H, aryl), 7.60 – 7.57 (m, 2H, aryl), 7.51 – 7.46 (m, 2H, aryl and C<u>H</u>=CH-), 7.36 (d, 1H, *J* = 15.0 Hz, -CH=C<u>H</u>-), 7.14 (s, 1H, H^g), 6.55 (s, 1H, H^a), 5.91 (br d, 1H, *J* = 6.4 Hz, -N<u>H</u>), 5.66 – 5.59 (m, 1H, H^e), 5.12 (d, 1H, *J* = 17.0 Hz, H^f), 5.08 (d, 1H, *J* = 17.0 Hz, H^f), 4.15 (br s, 2H, H^d), 3.94 (s, 3H, -OC<u>H</u>$_3$), 3.91 (s, 3H, -OC<u>H</u>$_3$), 3.70 (m, 1H, H^c), 1.91 – 1.10 (m, 10H, Cy).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 167.4, 166.4, 152.9, 148.8, 142.3, 136.7, 135.2, 133.7, 133.4, 132.4, 128.8, 128.7, 124.3, 117.6, 112.1, 108.5, 58.9, 56.5, 56.4, 49.0, 48.9, 32.5, 25.4, 24.7, 24.6.

HRMS: EIMS (M^+) calcd for $C_{29}H_{33}N_3O_7$ 535.2319 found 535.2311.

IR (neat): 3321, 3068, 2932, 2854, 1711, 1675, 1643, 1521, 1449, 1410, 1358, 1332, 1275, 1217, 1063, 924.

92. **Ethyl 2-(4-(benzo[*d*][1,3]dioxol-5-ylmethyl)-5-(*tert*-butylcarbamoyl)-3-oxo-2,3,4,5-tetrahydro-1*H*-benzo [*e*][1,4]diazepin-2-yl)acetate**



(±)-**135**

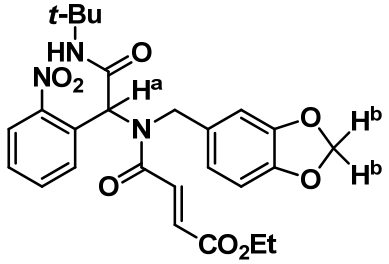
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (m, 1H, aryl), 6.85 – 6.61 (m, 6H, aryl), 5.91 (s, 2H, H^e), 5.57 (s, 1H, H^a), 4.77 (d, 1H, J = 14.6 Hz, H^d), 4.52 (d, 1H, J = 14.6 Hz, H^d), 4.42 (dd, 1H, J_1 = 5.6 Hz, J_2 = 6.5 Hz, H^b), 4.19 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 3.02 (dd, 1H, J_1 = 7.3 Hz, J_2 = 16.2 Hz, H^c), 2.62 (dd, 1H, J_1 = 7.3 Hz, J_2 = 16.2 Hz, H^c), 1.27 (t, 3H, J = 6.5 Hz, -OCH$_2$C<u>H</u>$_3$), 1.20 (s, 9H, *t*-butyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 170.3, 169.1, 148.4, 147.6, 144.4, 132.7, 129.9, 129.8, 126.6, 122.4, 119.1, 118.7, 109.2, 108.6, 101.3, 66.7, 61.1, 52.8, 52.2, 51.8, 36.1, 28.5, 14.4.

HRMS: EIMS (M^+) calcd for $C_{26}H_{31}N_3O_6$ 481.2213 found 481.2218.

IR (neat): 3348, 2976, 2934, 1734, 1662, 1608, 1503, 1444, 1368, 1245, 1183, 1100, 1039, 930, 808, 674.

93. **(*E*)-Ethyl 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)(2-(*tert*-butylamino)-1-(2-oxoethyl)amino-4-oxobut-2-enoate**



(±)-**136**

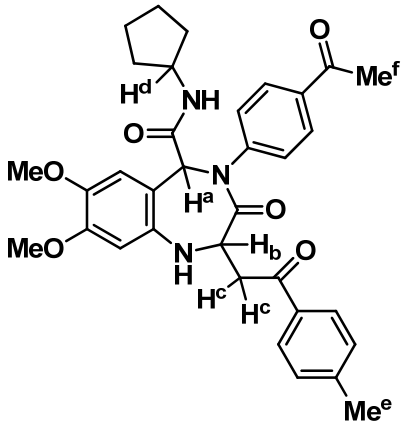
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, 1H, *J* = 8.1 Hz, aryl), 7.63 – 7.24 (m, 3H, aryl and -C<u>H</u>=CH-), 7.02 – 6.85 (m, 2H, aryl and -CH=C<u>H</u>- overlap), 6.75 – 6.63 (m, 2H, aryl), 6.43 (s, 1H, aryl), 5.91 (s, 2H, H^b), 5.70 (s, 1H, H^a), 4.76 (d, 1H, *J* = 17.0 Hz, Bn), 4.58 (d, 1H, *J* = 17.0 Hz, Bn), 4.21 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 1.28 (t, 3H, *J* = 6.5 Hz, -OCH$_2$C<u>H</u>$_3$), 1.22 (s, 9H, *t*-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 166.3, 165.5, 149.7, 148.3, 147.8, 147.3, 133.7, 133.4, 133.3, 133.2, 130.3, 130.1, 129.5, 125.4, 122.4, 120.0, 108.6, 107.1, 101.4, 61.5, 60.3, 52.3, 50.7, 28.5, 14.3.

HRMS: EIMS (M^+) calcd for $C_{26}H_{29}N_3O_8$ 511.1955 found 511.1947.

IR (neat): 3339, 3074, 2970, 1829, 1715, 1685, 1657, 1629, 1490, 1420, 1393, 1364, 1296, 1243, 1223, 1173, 1095, 1037, 973, 926, 808, 657.

94. **4-(4-acetylphenyl)-*N*-cyclopentyl-3-oxo-2-(2-oxo-2-*p*-tolylethyl)-2,3,4,5-tetrahydro-1-*H*-benzo [*e*][1,4] diazepine-5-carboxamide**



(±)-137

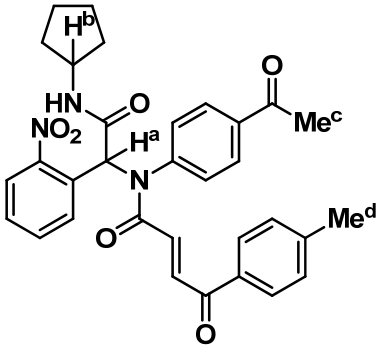
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 2H, *J* = 8.1 Hz, aryl), 7.86 (d, 2H, *J* = 8.9 Hz, aryl), 7.46 (d, 2H, *J* = 8.1 Hz, aryl), 7.25 (m, 2H, aryl), 7.19 (m, 1H, aryl), 7.02 (d, 1H, *J* = 7.3 Hz, aryl), 6.80 (t, 1H, *J* = 7.3 Hz, aryl), 6.70 (d, 1H, *J* = 8.0 Hz, aryl), 5.90 (d, 1H, *J* = 8.1 Hz, -N<u>H</u>), 5.06 (s, 1H, H^a), 4.76 (m, 1H, H^b), 4.19 (m, 1H, H^d), 3.76 (dd, 1H, J_1 = 17.0 Hz, J_2 = 5.0 Hz, H^c), 3.20 (dd, 1H, J_1 = 17.0 Hz, J_2 = 7.0 Hz, H^c), 2.57 (s, 3H, -Me^f), 2.40 (s, 3H, -Me^e), 1.96 – 1.87 (m, 2H, Cp), 1.60 – 1.49 (m, 4H, Cp), 1.36 – 1.24 (m, 2H, Cp).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 197.4, 170.1, 169.6, 148.5, 145.1, 144.7, 135.8, 134.0, 132.0, 130.5, 129.8, 129.6, 128.6, 127.1, 119.6, 119.2, 119.0, 118.9, 118.8, 70.3, 53.3, 52.4, 39.7, 33.1, 32.8, 26.8, 23.8, 21.9.

HRMS: EIMS (M^+) calcd for $C_{32}H_{33}N_3O_4$ 523.2471 found 523.2466.

IR (neat): 3348, 2957, 2870, 1735, 1679, 1601, 1508, 1494, 1426, 1406, 1224, 1203, 1181, 824, 754.

95. **(*E*)-*N*-(4-acetylphenyl)-*N*-(2-(cyclopentylamino)-1-(2-nitrophenyl)-2-oxoethyl)-4-oxo-4-*p*-tolylbut-2-enamide**



(±)-**138**

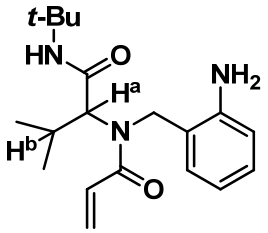
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, 1H, *J* = 14.9 Hz, C<u>H</u>=CH-), 7.88 – 7.84 (m, 3H, aryl), 7.76 (d, 2H, *J* = 7.3 Hz, aryl), 7.39 – 7.33 (m, 5H, aryl), 7.24 (d, 2H, *J* = 7.0 Hz, aryl), 6.71 (d, 1H, *J* = 15.0 Hz, -CH=C<u>H</u>-), 6.67 (s, 1H, H^a), 5.94 (s, 1H, -N<u>H</u>), 4.24 (m, 1H, H^b), 2.53 (s, 3H, -Me^c), 2.40 (s, 3H, -Me^d), 2.03 – 1.91 (m, 2H, Cp), 1.68 – 1.53 (m, 4H, Cp), 1.47 – 1.41 (m, 1H, Cp), 1.32 – 1.25 (m, 1H, Cp).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.2, 188.9, 168.1, 164.9, 145.1, 142.7, 137.1, 135.4, 135.3, 134.6, 134.5, 133.3, 133.2, 132.2, 132.1, 130.6, 130.2, 129.7, 129.4, 129.2, 129.1, 129.0, 128.9, 128.5, 125.1, 60.7, 52.2, 33.0, 26.9, 24.0, 23.9, 22.0.

HRMS: EIMS (M^+) calcd for $C_{32}H_{31}N_3O_6$ 553.2213 found 553.2218.

IR (neat): 3309, 3067, 2916, 2869, 1712, 1684, 1647, 1599, 1526, 1443, 1407, 1350, 1292, 1262, 1194, 1181, 1027, 1013, 969, 858, 789, 741, 704.

96. **2-(*N*-(2-aminobenzyl)acrylamido)-*N*-*tert*-butyl-3-methylbutanamide**



(±)-**139**

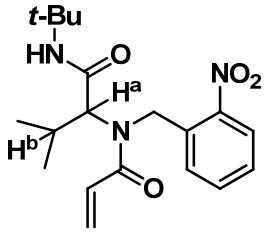
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 1H, aryl), 7.10 (d, 1H, *J* = 7.5 Hz, aryl), 6.70 (m, 1H, aryl), 6.65 (m, 3H, aryl and NH_2 overlap), 5.80 (d, 1H, *J* = 19.0 Hz, Bn), 5.70 (m, 1H, -CH=C$\underline{H}_2$), 5.60 (m, 1H, -C$\underline{H}$=CH_2), 5.50 (br s, 1H, -CH=C$\underline{H}_2$), 3.60 (d, 1H, *J* = 19.0 Hz, Bn), 3.36 (d, 1H, *J* = 10.5 Hz, H_a), 2.55 – 2.60 (m, 1H, H_b), 1.10 (s, 9H, *t*-butyl), 0.96 (m, 6H, 2x –CH(C$\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 168.0, 131.2, 133.4, 130.6, 129.6, 128.2, 128.1, 127.4, 119.4, 118.2, 60.6, 51.4, 44.8, 28.5, 23.8, 19.2.

HRMS: EIMS (M^+) calcd for $C_{19}H_{29}N_3O_2$ 331.2260 found 331.2267.

IR (neat): 3423.03, 3326.61, 2966.95, 2873.42, 1735.62, 1671.02, 1641.13, 1456.96, 1221.68.

97. ***N-tert*-butyl-3-methyl-2-(*N*-(2-nitrobenzyl)acrylamido)butanamide**



(±)-**139a**

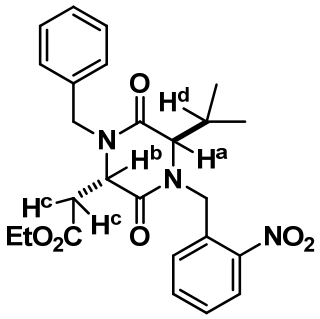
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1H, *J* = 7.4 Hz, aryl), 7.50 (t, 1H, *J* = 7.3 Hz, aryl), 7.40 (t, 1H, *J* = 7.3 Hz, aryl), 7.25 (m, 1H, aryl), 6.40 (d, 1H, *J* = 16.2 Hz, -CH=C$\underline{H}_2$), 6.16 (m, 1H, -C$\underline{H}$=CH_2), 5.62 (d, 1H, *J* = 16.0 Hz, -CH=C$\underline{H}_2$), 5.24 (d, 1H, *J* = 19.5 Hz, Bn), 5.60 (d, 1H, *J* = 19.5 Hz, Bn), 4.60 (d, 1H, *J* = 10.5 Hz, H_a), 2.43 – 2.34 (m, 1H, H_b), 1.22 (s, 9H, *t*-butyl), 0.96 (d, 3H, *J* = 6.5 Hz, -CH(C$\underline{H}_3$)$_2$) , 0.91 (d, 3H, *J* = 6.5 Hz, -CH(C$\underline{H}_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 169.0, 148.6, 133.4, 130.1, 128.2, 128.1, 127.9, 127.1, 125.4, 59.6, 51.4, 45.8, 28.6, 28.4, 27.8, 19.3, 18.6.

HRMS: EIMS (M^+) calcd for $C_{19}H_{27}N_3O_4$ 361.2002 found 361.2005.

IR (neat): 3328, 3077, 2965, 2874, 1714, 1675, 1644, 1525, 1448, 1344, 1301, 1222, 1194, 1060, 971, 861, 728,676.

98. **Ethyl 2-(1-benzyl-5-isopropyl-4-(2-nitrobenzyl)-3,6-dioxopiperazin-2-yl)acetate**



(±)-**140**

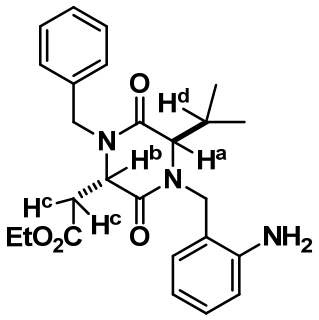
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H, *J* = 7.9 Hz, aryl), 7. 69 – 7.59 (m, 2H, aryl), 7.45 – 7.25 (m, 6H, aryl), 5.54 (d, 1H, *J* = 17.0 Hz, Bn), 5.28 (d, 1H, *J* = 15.2 Hz, Bn), 4.62 (d, 1H, *J* = 17.0 Hz, Bn), 4.26 – 3.93 (m, 5H, Bn, H^b, H^a and –OC<u>H</u>$_2$CH$_3$ overlap), 3.60 (dd, 1H, J_1 = 3.0 Hz, J_2 = 17.7 Hz, H^c), 2.94 (dd, 1H, , J_1 = 5.0 Hz, J_2 = 17.7 Hz, H^c), 2.34 (m, 1H, H^d), 1.19 (m, 6H, -OCH$_2$C<u>H</u>$_3$ and -CH(C<u>H</u>$_3$)$_2$ overlap), 0.98 (d, 3H, *J* = 6.7 Hz, -CH(C<u>H</u>$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 166.8, 165.9, 148.5, 136.0, 134.2, 134.1, 131.6, 129.3, 129.1, 128.5, 128.2, 125.3, 125.2, 65.9, 61.2, 55.1, 47.1, 45.8, 34.6, 32.5, 20.2, 17.6, 14.2.

HRMS: EIMS (M^+) calcd for $C_{25}H_{29}N_3O_6$ 467.2056 found 467.2053.

IR (neat): 3309, 3065, 2965, 2934, 2876, 1733, 1660, 1526, 1446, 1294, 1222, 1192, 1030, 727, 701.

99. **Ethyl 2-(4-(2-aminobenzyl)-1-benzyl-5-isopropyl-3,6-dioxopiperazin-2-yl)acetate**



(±)-**141**

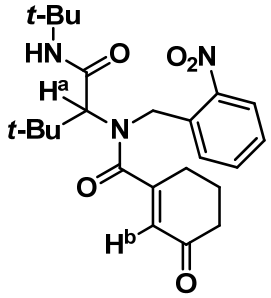
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 -7.20 (m, 5H, aryl), 7.10 (t, 1H, *J* = 6.5 Hz, aryl), 7.00 (d, 1H, *J* = 7.3 Hz, aryl), 6.70 (m, 2H, aryl), 5.38 (d, 1H, *J* = 14.6 Hz, Bn), 5.10 (d, 1H, *J* = 15.4 Hz, Bn), 4.24 – 3.85 (m, 6H, Bn, H^b, H^a, and –OC<u>H</u>$_2$CH$_3$ overlap), 3.26 (dd, 1H, J_1= 17.0 Hz, J_2 = 2.6 Hz, H^c), 2.90 (dd, 1H, J_1= 17.0 Hz, J_2 = 4.8 Hz, H^c), 2.37 – 2.30 (m, 1H, H^d), 1.10 (m, 6H, –OCH$_2$C<u>H</u>$_3$ and -CH(C<u>H</u>$_3$)$_2$ overlap), 0.80 (d, 3H, *J* = 6.4 Hz, -CH(C<u>H</u>$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.4, 165.9, 146.5, 136.0, 132.0, 130.0, 129.0, 128.3, 128.0, 117.8, 117.5, 116.1, 62.4, 61.2, 55.5, 47.1, 45.8, 35.4, 31.6, 20.1, 17.0, 14.1.

HRMS: EIMS (M^+) calcd for $C_{25}H_{31}N_3O_4$ 437.2315 found 437.2312.

IR (neat): 3447, 3367, 3251, 2965, 2935, 2876, 1732, 1652, 1584, 1496, 1445, 1374, 1294, 1250, 1194, 1164, 1031, 919, 750, 736, 709.

100. ***N*-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-N-(2-nitrobenzyl)-3-oxocyclohex-1-enecarboxamide**



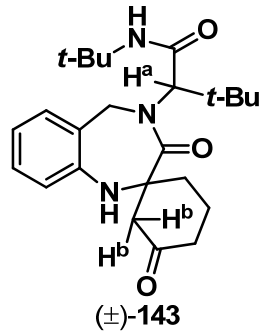
(±)-**142**

^{1}H NMR (500 MHz, CDC_3): δ 7.90-7.99 (m, 1 H, aryl), 7.49-7.58 (m, 1 H, aryl), 7.35-7.42 (m, 1 H, aryl), 7.21-7.28 (m, 1 H, aryl), 6.25 (br s, 1 H, -NH), 5.78 (d, 1 H, *J* = 18.6 Hz, -CH_2Ar), 5.74 (s, 1 H, H^b), 5.0 (d, 1 H, *J* = 18.3 Hz, -CH_2Ar), 4.92 (br s, 1 H, H^a), 2.34-2.49 (m, 1 H, 3-oxocyclohex-1-ene), 2.20-2.30 (m, 2 H, 3-oxocyclohex-1-ene), 1.81-1.90 (m, 1 H, 3-oxocyclohex-1-ene), 1.61-1.80 (m, 2 H, 3-oxocyclohex-1-ene), 1.20 (s, 9 H, *t*-Bu), 1.11 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 172.4, 167.5, 155.0, 147.9, 133.1, 128.1, 127.9, 126.2, 125.0, 51.7, 37.6, 36.9, 28.3, 27.5, 26.6, 22.3.

HRMS (EIMS, M^+ + Na): calcd for $C_{24}H_{33}N_3O_5Na$ 466.2318, found 466.2318.

101. ***N*-(*tert*-butyl)-2-(3,3'-dioxospiro[benzo[e][1,4]diazepine-2,1'-cyclohexan]-4(1H,3H,5H)-yl)-3,3-dimethylbutanamide**

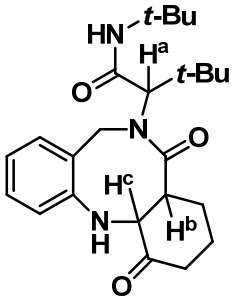


(±)-**143**

^{1}H NMR (500 MHz, CDC_3): δ 7.28 (d, 1 H, *J* = 7.3 Hz, aryl), 7.15-7.20 (m, 1 H, aryl), 6.93 (t, 1 H, *J* = 7.6 Hz, aryl), 6.83 (d, 1 H, *J* = 7.6 Hz, aryl), 5.52 (br s, 1 H, -NH), 4.92 (d, 1 H, *J* = 13.7 Hz, -CH_2Ar), 4.79 (s, 1 H, H^a), 4.78 (d, 1 H, *J* = 13.7 Hz, -CH_2Ar), 3.10 (d, 1 H, *J* = 14.3 Hz, H^b), 2.37-2.53 (m, 2 H, cyclohexanone), 2.22-2.32 (m, 1 H, cyclohexanone), 2.17 (d, 1 H, *J* = 14.3 Hz, H^b), 1.90-2.02 (m, 3 H, cyclohexanone), 1.24 (s, 9 H, *t*-Bu), 1.11 (s, 9 H, *t*-Bu).

HRMS (EIMS, M^+ + H): calcd for 414.2757, found 414.2747.

102. ***N*-(*tert*-butyl)-2-(7,11-dioxo-7,7a,8,9,10,11,11a,12-octahydrodibenzo[b,g][1,5]diazocin-6(5H)-yl)-3,3-dimethylbutanamide**



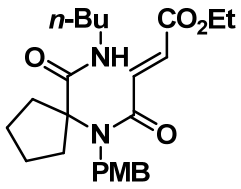
(±)-**144**

^{1}H NMR (500 MHz, CDC_3): δ 7.27-7.37 (m, 3 H, aryl), 7.07-7.16 (m 1 H, aryl), 5.38 (br s, 1 H, -NH), 5.10 (d, 1 H, *J* = 14.7 Hz, -CH_2Ar), 4.50 (s, 1 H, H^a), 4.01 (d, 1 H, *J* = 14.4 Hz, -CH_2Ar), 2.90-2.99 (m, 1 H, H^b), 2.80-2.89 (m, 1 H, H^c), 2.61 (t, 2 H, *J* = 7.3 Hz), 2.05 (sx, 2 H, *J* = 7.3 Hz, cyclohexanone), 1.21-1.34 (m, 2 H, cyclohexanone), 1.15 9s, 9 H, *t*-Bu), 1.11 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.3, 167.4, 166.6, 164.0, 146.8, 129.1, 128.9, 128.7, 126.2, 125.6, 62.3, 51.6, 45.5, 43.0, 37.3, 36.6, 29.9, 28.5, 27.2, 20.5.

HRMS (EIMS, $M^+ + H$): calcd for $C_{24}H_{35}N_3O_3$ 414.2757, found 414.2744.

103. **(*E*)-ethyl 4-((1-(butylcarbamoyl)cyclopentyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



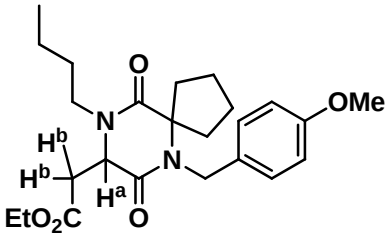
(-)-**145**

^{1}H NMR (500 MHz, CDC_3): δ 7.17 (d, 1 H, *J* = 15.0 Hz, -C<u>H</u>=CH-), 7.14 (br d, 2 H, aryl), 6.88 (d, 2 H, *J* = 8.5 Hz, aryl), 6.81 (d, 1 H, *J* = 15.0 Hz, -CH=C<u>H</u>-), 4.66 (br s, 1 H, -N<u>H</u>), 4.17 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.78 (s, 3 H, OMe), 3.09-3.27 (m, 2 H, *n*-Bu), 2.50-2.69 (m, 2 H, cyclopentyl), 1.78-1.94 (m, 2 H, cyclopentyl), 1.56-1.68 (m, 4 H, *n*-Bu and cyclopentyl overlap), 1.35-1.48 (m, 2 H, *n*-Bu), 1.25-1.33 (m, 2 H, *n*-Bu), 1.23 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.88 (t, 3 H, *J* = 7.3 Hz, -NHCH$_2$CH$_2$CH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 167.4, 165.3, 158.9, 135.3, 132.3, 129.9, 127.0, 114.4, 73.8, 61.0, 55.2, 50.3, 39.4, 35.8, 31.4, 23.1, 19.9, 14.0, 13.7.

HRMS (EIMS): calcd for $C_{24}H_{34}N_2O_5$ 430.2468, found 430.2474.

104. **Ethyl 2-(9-butyl-6-(4-methoxybenzyl)-7,10-dioxo-6,9-diazaspiro[4.5]decan-8-yl)acetate**



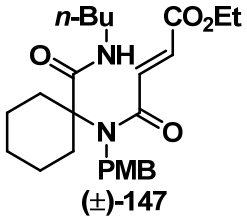
(±)-**146**

^{1}H NMR (500 MHz, CDC_3): δ 7.15 (d, 2 H, *J* = 8.6 Hz, aryl), 6.83 (d, 2 H, *J* = 8.6 Hz, aryl), 4.80 (d, 1 H, J = 15.0 Hz, -C$\underline{H}_2$Ar), 4.45 (t, 1 H, *J* = 5.5 Hz, H^a, dd overlap), 4.30 (d, 1 H, *J* = 15.0 Hz, -C$\underline{H}_2$Ar), 4.10-4.21 (m, 2 H, -OC$\underline{H}_2$$CH_3$), 3.74-3.82 (m, 4 H, OMe and *n*-Bu overlap), 3.02 (dd, 1 H, J = 16.5, 4.6 Hz, H^b), 2.96-3.04 (m, 1 H, *n*-Bu), 2.89 (dd, 1 H, J = 16.5, 5.5 Hz, H^b), 2.26-2.40 (m, 2 H, cyclopentyl), 1.71-2.02 (m, 7 H, *n*-Bu and cyclopentyl overlap), 1.59-1.69 (m, 2 H, *n*-Bu), 1.44-1.55 (m, 1 H, *n*-Bu), 1.33 (sx, 3H, *n*-Bu), 1.26 (t, 3 H, *J* = 7.3 Hz, -$OCH_2C\underline{H}_3$), 0.94 (t, 3 H, J = 7.3 Hz, -$NHCH_2CH_2CH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 169.8, 166.4, 158.6, 130.1, 127.7, 113.9, 70.7, 61.2, 56.3, 55.3, 46.5, 44.6, 39.9, 37.7, 37.6, 29.0, 27.2, 27.0, 20.1, 14.2, 13.8.

HRMS (EIMS): calcd for $C_{24}H_{34}N_2O_5$ 430.2468, found 430.2473.

105. **(*E*)-ethyl 4-((1-(butylcarbamoyl)cyclohexyl)(4-methoxybenzyl)amino)-4-oxobut-2-enoate**



(±)-147

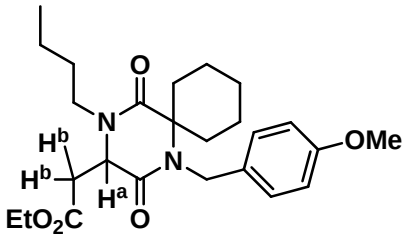
^{1}H NMR (500 MHz, CDC_3): δ 7.23 (d, 1 H, *J* = 15.2 Hz, -C$\underline{H}$=CH-), 7.16 (d, 2 H, *J* = 8.2 Hz, aryl), 6.86 (d, 2 H, *J* = 8.2 Hz, aryl), 6.75 (d, 1 H, *J* = 15.0 Hz, -CH=C$\underline{H}$-), 6.50 (br s, 1 H, -N$\underline{H}$), 4.63 (s, 2 H, -C$\underline{H}_2$Ar), 4.16 (q, 2 H, *J* = 7.3 Hz, -OC$\underline{H}_2$$CH_3$), 3.77 (s, 3 H,

OMe), 3.18 (q, 2 H, J = 6.7 Hz, *n*-Bu), 2.40 (d, 2 H, *J* = 13.4 Hz), 1.66-1.77 (m, 2 H), 1.37-1.48 (m, 2 H), 1.18-1.33 (m, 9 H), 0.79-0.95 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 171.0, 167.4, 165.4, 158.9, 136.3, 131.8, 129.9, 127.5, 114.3, 66.6, 60.9, 60.3, 55.2, 47.9, 39.3, 32.8, 31.5, 31.3, 25.2, 22.8, 22.6, 20.1, 14.1, 14.0, 13.7.

HRMS (EIMS): calcd for $C_{25}H_{36}N_2O_5$ 444.2624, found 444.2629.

106. **Ethyl 2-(4-butyl-1-(4-methoxybenzyl)-2,5-dioxo-1,4-diazaspiro[5.5]undecan-3-yl)acetate**



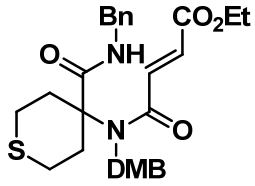
(±)-**148**

^{1}H NMR (500 MHz, CDC_3): δ 7.15 (d, 2 H, *J* = 8.6 Hz, aryl), 6.82 (d, 2 H, *J* = 8.6 Hz, aryl), 4.80 (d, 1 H, *J* = 15.6 Hz, -C$\underline{H}_2$Ar), 4.48-4.60 (m, 2 H, -CH_2Ar and H^a overlap), 4.19 (q, 2 H, J = 7.3 Hz, -OC$\underline{H}_2CH_3$), 3.77 (s, 3 H, OMe), 3.70-3.77 (m, 1 H), 2.97-3.05 (m, 2 H), 2.94 (dd, 1 H, J = 10.7, 5.8 Hz, H^b), 2.10-2.24 (m, 1 H), 1.42-1.94 (m, 11 H), 1.30-1.37 (m, 2 H), 1.27 (t, 3 H, *J* = 7.3 Hz, -$OCH_2C\underline{H}_3$), 1.02-1.14 (m, 1 H), 0.94 (t, 3 H, J = 7.3 Hz, -$NHCH_2CH_2CH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.9, 167.8, 158.5, 130.3, 127.8, 113.9, 62.6, 61.2, 56.1, 55.2, 45.2, 44.5, 38.3, 34.9, 33.6, 29.1, 24.4, 22.9, 22.5, 20.1, 14.1, 13.8.

HRMS (EIMS): calcd for $C_{25}H_{36}N_2O_5$ 444.2624, found 444.2627.

107. **(*E*)-ethyl 4-((4-(benzylcarbamoyl)tetrahydro-2H-thiopyran-4-yl)(3,4-dimethoxybenzyl)amino)-4-oxobut-2-enoate**



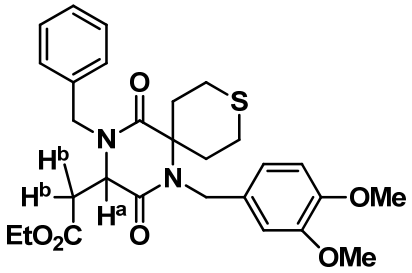
(±)-149

^{1}H NMR (500 MHz, CDC_3): δ 7.23-7.34 (m, 6 H, aryl and –C<u>H</u>=CH- overlap), 6.84 (d, 1 H, *J* = 15.3 Hz, -C<u>H</u>=CH-), 6.67-6.76 (m 3 H, aryl), 6.21 (t, 1 H, *J* = 5.2 Hz, -N<u>H</u>), 4.66 (s, 2 H, -C<u>H</u>$_2$Ar), 4.42 (d, 2 H, *J* = 5.5 Hz, -C<u>H</u>$_2$Ar), 4.24 (q, 2 H, J = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.85 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 3.12 (m, 1 H, thiopyran), 2.58-2.67 (m, 2 H, thiopyran), 2.0-2.10 (m, 2 H, thiopyran), 1.25 (t, 3 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 166.8, 165.3, 149.6, 148.7, 138.1, 135.1, 133.1, 129.9, 128.8, 127.9, 127.6, 118.2, 111.6, 109.1, 65.6, 61.3, 55.9, 55.8, 47.7, 44.0, 34.2, 24.9, 14.1.

HRMS (EIMS): calcd for $C_{28}H_{34}N_2O_6S$ 526.2138, found 526.2142.

108. **Ethyl 2-(4-benzyl-1-(3,4-dimethoxybenzyl)-2,5-dioxo-9-thia-1,4-diazaspiro[5.5]undecan-3-yl)acetate**



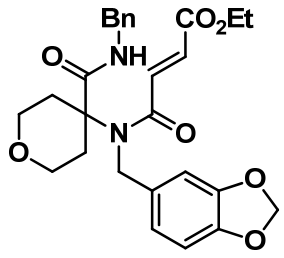
(±)-**150**

^{1}H NMR (500 MHz, CDC_3): δ 7.29-7.37 (m, 3 H, Bn), 7.21-7.25 (m, 1 H, Bn), 6.76-6.85 (m, 3 H, aryl), 5.19 (d, 1 H, *J* = 15.0 Hz, -C<u>H</u>$_2$Ph), 4.74 (s, 2 H, -C<u>H</u>$_2$Ar), 4.28 (t, 1 H, *J* = 4.4 Hz, H^a, dd overlap), 4.16 (d, 1 H, J = 15.0 Hz, -C<u>H</u>$_2$Ph), 4.07 (q, 2 H, J = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.84 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.49-3.64 (m, 2 H, thiopyran), 3.09 (dd, 1 H, *J* = 17.1, 3.7 Hz, H^b), 2.89 (dd, 1 H, J = 17.1, 5.5 Hz, H^b), 2.39-2.56 (m, 3 H, thiopyran), 2.01-2.27 (m, 3 H, thiopyran), 1.21 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 168.9, 166.7, 149.1, 147.9, 135.8, 130.5, 128.9, 127.9, 127.8, 118.3, 111.1, 109.8, 61.7, 61.1, 55.9, 55.8, 55.1, 47.2, 45.8, 36.4, 35.3, 34.6, 25.3, 14.1.

HRMS (EIMS): calcd for $C_{28}H_{34}N_2O_6S$ 526.2138, found 526.2136.

109. **(*E*)-ethyl 4-((benzo[d][1,3]dioxol-5-ylmethyl)(4-(benzylcarbamoyl)tetrahydro-2H-pyran-4-yl)amino)-4-oxobut-2-enoate**



(±)-**151**

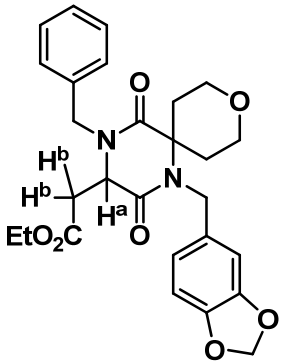
^{1}H NMR (500 MHz, CDC_3): δ 7.22-7.34 (m 5 H, Bn), 7.15 (d, 1 H, *J* = 15.3 Hz, -C<u>H</u>=CH-), 6.77 (d, 1 H, *J* = 15.3 Hz, -C<u>H</u>=CH-), 6.75 (m 1 H, aryl), 6.61-6.68 (m, 2 H, aryl), 5.97 (s, 2 H, -OC<u>H</u>$_2$O-), 4.56 (s, 2 H, -C<u>H</u>$_2$Bn), 4.45 (d, 2 H, *J* = 5.8 Hz, -C<u>H</u>$_2$Ar), 4.21 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.76-3.84 (m, 2 H, pyran), 3.55-3.67 (m, 2 H,

pyran), 2.68 (d, 2 H, *J* = 13.1 Hz, pyran), 1.9 (m, 2 H, pyran), 1.27 (t, 3 H, *J* = 7.3 Hz, -$OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 167.8, 165.3, 148.5, 147.3, 138.2, 135.6, 132.9, 131.3, 128.7, 127.7, 127.5, 119.0, 108.8, 106.3, 101.3, 64.8, 64.4, 61.2, 48.4, 43.8, 33.6, 14.1.

HRMS (EIMS): calcd for $C_{27}H_{30}N_2O_7$ 494.2053, found 494.2059.

110. **Ethyl 2-(1-(benzo[d][1,3]dioxol-5-ylmethyl)-4-benzyl-2,5-dioxo-9-oxa-1,4-diazaspiro[5.5]undecan-3-yl)acetate**



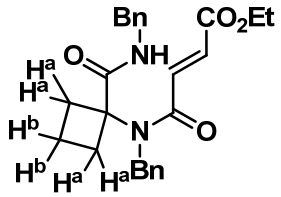
(±)-**152**

^1H NMR (500 MHz, CDC_3): δ 7.29-7.37 (m, 3 H, Bn), 7.21-7.25 (m, 2 H, Bn), 6.71-6.74 (m, 2 H, aryl), 6.65-6.69 (m, 1 H, aryl), 5.92 (s, 2 H, -$OC\underline{H}_2O$-), 5.12 (d, 1 H, *J* = 15.3 Hz, -$C\underline{H}_2Ph$), 4.78 (d, 1 H, *J* = 15.3 Hz, -$C\underline{H}_2Ar$), 4.58 (d, 1 H, *J* = 15.3 Hz, -$C\underline{H}_2Ar$), 4.36 (t, 1 H, *J* = 4.9 Hz, H^a, dd overlap), 4.28 (d, 1 H, J = 15.3 Hz, -$C\underline{H}_2Ph$), 4.20-4.28 (m, 1 H), 4.08-4.15 (m, 3 H, -$OC\underline{H}_2CH_3$ and pyran overlap), 3.85-3.97 (m, 2 H, pyran), 3.02 (dd, 1 H, *J* = 16.8, 3.9 Hz, H^b), 2.89 (dd, 1 H, *J* = 16.8, 5.2 Hz, H^b), 2.0-2.25 (m, 3 H, pyran), 1.76 (d, 1 H, *J* = 14.0 Hz, pyran), 1.21 (t, 3 H, *J* = 7.3 Hz, -$OC\underline{H}_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.4, 166.9, 147.9, 146.5, 135.8, 131.7, 128.9, 127.9, 127.7, 119.4, 108.3, 107.1, 101.0, 64.9, 64.5, 61.2, 60.1, 55.5, 47.5, 45.6, 36.6, 33.8, 33.6, 14.1.

HRMS (EIMS): calcd for $C_{27}H_{30}N_2O_7$ 494.2053, found 494.2049.

111. **(*E*)-ethyl 4-(benzyl(1-(benzylcarbamoyl)cyclobutyl)amino)-4-oxobut-2-enoate**



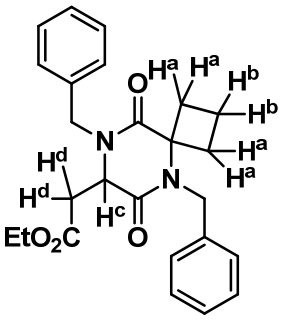
(±)-153

^{1}H NMR (500 MHz, CDC_3): δ 7.78 (b t, 1 H, *J* = 5.2 Hz, -N<u>H</u>), 7.16-7.40 (m, 10 H, Ph), 7.09 (d, 1 H, *J* = 15.3 Hz, -C<u>H</u>=CH-), 6.79 (d, 1 H, *J* = 15.3 Hz, -CH=C<u>H</u>-), 4.56 (s, 2 H, -C<u>H</u>$_2$Ph), 4.40 (d, 2 H, -C<u>H</u>$_2$Ph), 4.17 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 2.70-2.84 (m, 2 H, H^a), 2.27-2.40 (m, 2 H, H^a), 1.67-.184 (m, 2 H, H^b), 1.24 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$)

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 166.1, 165.1, 138.3, 137.1, 133.9, 132.6, 128.9, 128.5, 127.6, 127.2, 127.1, 125.8, 66.0, 61.0, 49.2, 43.4, 31.2, 14.6, 13.9.

HRMS (EIMS): calcd for $C_{25}H_{28}N_2O_4$ 420.2049, found 420.2043

112. **Ethyl 2-(5,8-dibenzyl-6,9-dioxo-5,8-diazaspiro[3.5]nonan-7-yl)acetate**



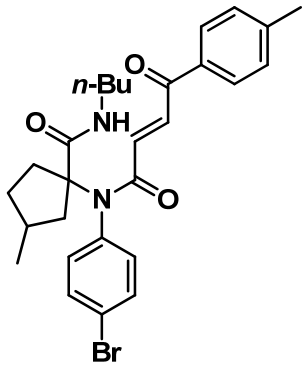
(±)-**154**

^{1}H NMR (500 MHz, CDC_3): δ 7.21-7.37 (m, 8 H, Ph), 7.16-7.21 (m, 2 H, Ph), 5.17 (d, 1 H, *J* = 15.3 Hz, -C$\underline{H}_2$Ph), 5.10 (d, 1 H, *J* = 15.9 Hz, -C$\underline{H}_2$Ph), 4.70 (d, 1 H, *J* = 15.9 Hz, -C$\underline{H}_2$Ph), 4.38 (t from dd overlap, 1 H, *J* = 5.5 Hz, H^c), 4.29 (d, 1 H, *J* = 15.3 Hz, -C$\underline{H}_2$Ph), 4.10 (q, 2 H, *J* = 7.3 Hz, -OC$\underline{H}_2$$CH_3$), 2.85 (dd, 1 H, *J* = 16.2, 5.5 Hz, H^d), 2.80-2.84 (m, 1 H, cyclobutane), 2.78 (dd, 1 H, *J* = 16.2, 5.5 Hz, H^d), 2.46-2.69 (m, 3 H, cyclobutane), 2.07-2.19 (m, 1 H, cyclobutane), 1.78-1.89 (m, 1 H, cyclobutane), 1.23 (t, 3 H, *J* = 7.3 Hz, -$OCH_2C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 169.6, 166.5, 137.8, 136.1, 128.9, 128.7, 127.9, 127.2, 126.4, 63.1, 61.2, 56.2, 53.4, 48.0, 46.4, 37.1, 34.4, 31.2, 14.5, 14.1.

HRMS (EIMS): calcd for $C_{25}H_{28}N_2O_4$ 420.2049, found 420.2051

113. **(*E*)-1-(N-(4-bromophenyl)-4-oxo-4-(p-tolyl)but-2-enamido)-N-butyl-3-methylcyclopentanecarboxamide**



(±)-155

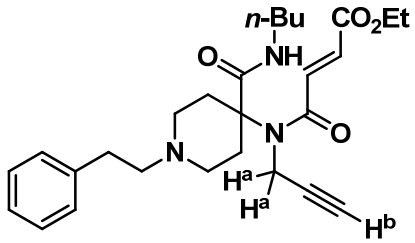
^{1}H NMR (500 MHz, CDC_3): δ 7.80 (d, 4 H, *J* = 8.2 Hz, Ar), 7.73 (d, 1 H, *J* = 15.3 Hz, -C$\underline{H}$=CH-)7.70 (d, 4 H, *J* = 8.5 Hz, Ar), 6.64 (d, 1 H, J = 15.3 Hz, -CH=C$\underline{H}$-), 6.18 (br t, *J* = 5.5 Hz, -N$\underline{H}$), 3.29-3.39 (m, 2 H, *n*-Bu), 2.39 (s, 3 H, Ar-C$\underline{H}_3$), 1.34-1.73 (m, 9 H, *n*-Bu

and cyclopentyl overlap), 1.10-1.23 (m, 2 H, *n*-Bu), 0.94 (t, 3 H, *J* = 7.3 Hz, -NHCH$_2$CH$_2$CH$_2$C<u>H</u>$_3$), 0.85 (d, 3 H, *J* = 6.4 Hz, -C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 175.0, 166.0, 144.6, 138.4, 134.2, 133.9, 132.9, 132.6, 132.3, 129.4, 128.9, 122.9, 67.7, 42.3, 39.7, 34.1, 33.9, 31.5, 29.4, 21.6, 20.1, 13.8.

HRMS (EIMS): calcd for $C_{28}H_{33}BrN_2O_3$ 524.1675, found 524.1671.

114. **(*E*)-ethyl 4-((4-(butylcarbamoyl)-1-phenethylpiperidin-4-yl)(prop-2-yn-1-yl)amino)-4-oxobut-2-enoate**



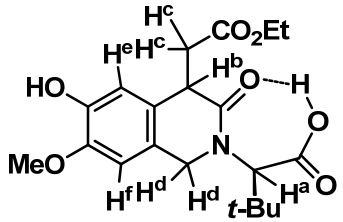
(±)-157

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, 1 H, *J* = 15.3 Hz, -C<u>H</u>=CH-), 7.24-7.32 (m, 3 H, Ph), 7.16-7.23 (m, 2 H, Ph), 6.78 (d, 1 H, *J* = 15.3 Hz, -CH=C<u>H</u>-), 6.54 (br t, 1 H, *J* = 5.5 Hz, -N<u>H</u>), 4.27 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 4.17 (br s, 2 H, H^a), 3.23 (dd, 2 H, *J* = 16.8, 7.0 Hz, -NHC<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 2.76-2.88 (m, 5 H), 2.53-2.68 (m, 7 H), 2.46 (t, 1 H, *J* = 1.5 Hz, H^b), 2.21-2.32 (m, 2 H), 1.41-1.48 (m, 2 H, *n*-Bu), 1.32 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.25-1.35 (m, 3 H), 0.89 (t, 3 H, J = 7.3 Hz, -NHCH$_2$CH$_2$CH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 167.1, 165.3, 135.1, 132.5, 128.7, 128.4, 126.2, 79.6, 74.3, 64.6, 61.3, 59.9, 53.4, 52.3, 50.1, 39.4, 35.1, 33.5, 32.4, 31.4, 20.1, 14.1, 13.7.

HRMS (EIMS): calcd for $C_{27}H_{37}N_3O_4$ 467.2784, found 467.2779.

115. **2-(4-(2-ethoxy-2-oxoethyl)-6-hydroxy-7-methoxy-3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-3,3-dimethylbutanoic acid**



(±)-**159**

^{1}H NMR (500 MHz, $CDCl_3$): (**Major diastereomer**) δ 6.77 (s, 1 H, H^e), 6.69 (s, 1 H, H^f), 5.66 (br s, 1 H, -O<u>H</u>), 5.10 (s, 1 H, H^a), 4.64 (d, 1 H, J = 14.9 Hz, H^d), 4.44 (d, 1 H, J = 15.3 Hz, H^d), 4.17 (m, 2 H, -OC<u>H</u>$_2$CH$_3$), 3.95 (dd, 1 H, J = 13.4, 6.7 Hz, H^b), 3.87 (s, 3 H, O<u>Me</u>), 3.09 (dd, 1 H, J_1 = 16.0 Hz, J_2 = 6.4 Hz, H^c), 2.88 (dd, 1 H, J_1 = 16.0 Hz, J_2 = 3.1 Hz, H^c), 1.25 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.07 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): (**Major diastereomer**) δ 173.1, 172.3, 171.8, 146.2, 144.5, 126.5, 126.1, 111.7, 108.0, 60.9, 56.1, 43.4, 43.1, 35.8, 34.2, 27.9, 14.2.

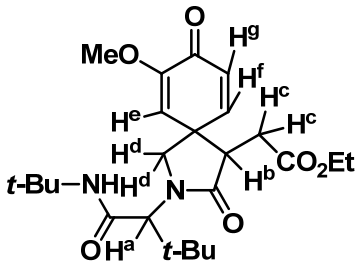
HRMS (EIMS, M^+-H): calcd for $C_{20}H_{27}NO_7$ 393.1788, found 392.1799.

^{1}H NMR (500 MHz, $CDCl_3$): (**Minor diastereomer**) δ 6.77 (s, 1 H, H^e), 6.72 (s, 1 H, H^f), 5.66 (br s, 1 H, -O<u>H</u>), 5.10 (s, 1 H, H^a), 4.54 (dd, 2 H, J = 28.9, 15.3 Hz, H^d), 4.17 (m, 2 H, -OC<u>H</u>$_2$CH$_3$), 3.95 (dd, 1 H, J = 13.4, 6.7 Hz, H^b), 3.87 (s, 3 H, O<u>Me</u>), 3.04 (dd, 1 H, J_1 = 15.9 Hz, J_2 = 6.4 Hz, H^c), 2.85 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 3.1 Hz, H^c), 1.25 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.12 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): (**Minor diastereomer**) δ 173.2, 173.2, 171.9, 146.2, 144.5, 126.6, 126.1, 111.8, 108.2, 60.9, 56.1, 43.4, 43.1, 35.7, 34.5, 27.9, 14.2.

HRMS (EIMS, M^+-H): calcd for $C_{20}H_{27}NO_7$ 393.1788, found 392.1799.

116. **Ethyl 2-(2-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-7-methoxy-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



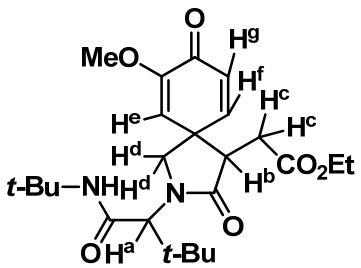
60a (Major Diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (dd, 1 H, J_1 = 10.1 Hz, J_2 = 2.7 Hz, H^g), 6.38 (d, 1 H, J = 10.1 Hz, H^f), 5.57 (d, 1 H, J = 2.7 Hz, H^e), 5.52 (br s, 1 H, -N<u>H</u>), 4.32 (d, 1 H, J = 10.1 Hz, H^d), 4.28 (s, 1 H, H^a), 4.04-4.13 (m, 2 H, -OC<u>H</u>$_2$CH$_3$), 3.77 (d, 1 H, J = 9.8 Hz, H^d), 3.66 (s, 3 H, O<u>Me</u>), 3.39 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 6.1 Hz, H^b), 2.65 (dd, 1 H, J_1 = 16.6 Hz, J_2 = 6.1 Hz, H^c), 2.08 (dd, 1 H, J_1 = 16.8 Hz, J_2 = 7.3 Hz, H^c). 1.39 (s, 9 H, *t*-Bu), 1.21 (s, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.06 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 180.4, 173.3, 171.5, 168.4, 152.5, 149.9, 130.8, 112.6, 63.2, 61.1, 55.0, 54.7, 53.6, 48.7, 47.8, 30.3, 28.5, 27.8, 13.9.

HRMS (EIMS, M^+): calcd for $C_{24}H_{36}N_2O_6$ 448.2573, found 448.2584.

117. **Ethyl 2-(2-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)-7-methoxy-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



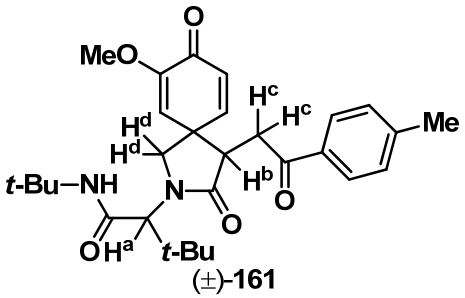
60b (Minor Diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): (**Minor Diastereomer**) δ 6.89 (dd, 1 H, J_1 = 10.1 Hz, J_2 = 2.8 Hz, H^g), 6.45 (d, 1 H, J = 10.1 Hz, H^f), 5.55 (d, 1 H, J = 2.5 Hz, H^e), 5.52 (br s, 1 H, -NH), 4.32 (d, 1 H, J = 10.1 Hz, H^d), 4.28 (s, 1 H, H^a), 4.04-4.13 (m, 3 H, -OCH_2CH$_3$ and H^d overlap), 3.67 (s, 3 H, OMe),3.61 (d, 1 H, J = 9.8 Hz, H^d), 3.31 (dd, 1 H, J_1 = 7.3 Hz, J_2 = 6.4 Hz, H^b), 2.64 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 6.1 Hz, H^c), 2.08 (dd, 1 H, J_1 = 16.5 Hz, J_2 = 7.6 Hz, H^c). 1.40 (s, 9 H, *t*-Bu), 1.21 (s, 3 H, J = 7.3 Hz, -OCH$_2$CH$_3$), 1.05 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): (**Minor Diastereomer**) δ 180.3, 173.9, 171.6, 167.1, 152.7, 146.4, 130.6, 116.5, 64.2, 61.2, 55.1, 54.8, 48.3, 47.3, 36.2, 30.4, 28.6, 27.6.

HRMS (EIMS, M^+): calcd for $C_{24}H_{36}N_2O_6$ 448.2573, found 448.2586.

118. ***N*-(*tert*-butyl)-2-(7-methoxy-3,8-dioxo-4-(2-oxo-2-(*p*-tolyl)ethyl)-2-azaspiro[4.5]deca-6,9-dien-2-yl)-3,3-dimethylbutanamide**



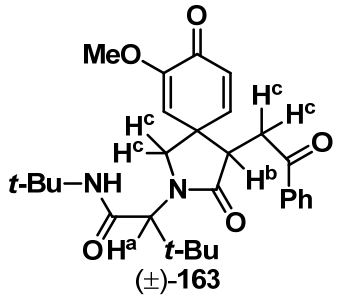
(±)-161

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, 2H, J = 6.0, 8.2 Hz, aryl), 7.22 (d, 2H, J = 7.6 Hz, aryl), 6.98 (m, 1H, vinyl), 6.34 (m, 1H, vinyl), 5.82 (m, 1H, vinyl), 5.55 (d, 1H, J = 8.8 Hz, NH), 4.32 (s, 1H, H^a), 3.79 (m, 2H, H^d), 3.70 (m, 1H, H^b) 3.69 (s, 3H,-OMe), 3.36 (m, 1H, H^c), 2.70 (m, 1H, H^c), 2.39 (s, 3H, -Me), 1.35 (s, 9H, t-butyl), 1.09 (s, 9H, t-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 180.4, 174.7, 168.5, 152.6, 150.4, 146.8, 144.2, 133.8, 130.5, 129.2, 128.0, 117.1, 116.6, 113.0, 63.9, 55.2, 53.7, 51.6, 49.0, 48.0, 46.8, 43.9, 36.2, 34.9, 28.4, 27.8, 21.5.

HRMS: EIMS (M^+) calculated for $C_{29}H_{38}N_2O_5Na$ 517.2678, found 517.2677.

119. ***N*-(*tert*-butyl)-2-(7-methoxy-3,8-dioxo-4-(2-oxo-2-phenylethyl)-2-azaspiro[4.5]deca-6,9-dien-2-yl)-3,3-dimethylbutanamide**



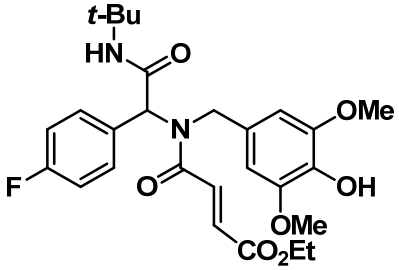
(±)-**163**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, 2H, *J* = 7.2 Hz, aryl), 7.55 (t, 1H, *J* = 8.0 Hz, aryl), 7.43 (t, 2H, *J* = 8.0 Hz, aryl), 6.99 (m, 1H, vinyl), 6.36 (m, 1H, vinyl), 5.83 (m, 1H, vinyl), 5.56 (d, 1H, *J* = 9.6 Hz, NH), 4.23 (s, 1H, H_d), 3.80 (m, 2H, H_c), 3.71 (m, 1H, H_b) 3.70 (s, 3H, -0Me), 3.39 (m, 1H, H_a), 2.70 (m, 1H, H_a), 1.35 (s, 9H, t-butyl), 1.09 (s, 9H, t-butyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 180.3, 174.4, 168.4, 152.6, 150.3, 146.7, 136.1, 133.3, 130.5, 128.5, 117.0, 113.0, 63.8, 55.2, 53.6, 51.5, 49.0, 46.7, 36.2, 34.9, 33.8, 28.4, 27.7.

HRMS: EIMS (M^+) calculated for $C_{28}H_{37}N_2O_5$ 481.2702, found 481.2699

120. **(*E*)-Ethyl 4-((2-(*tert*-butylamino)-1-(4-fluorophenyl)-2-oxoethyl)(4-hydroxy-3,5-dimethoxybenzyl)amino)-4-oxobut-2-enoate**

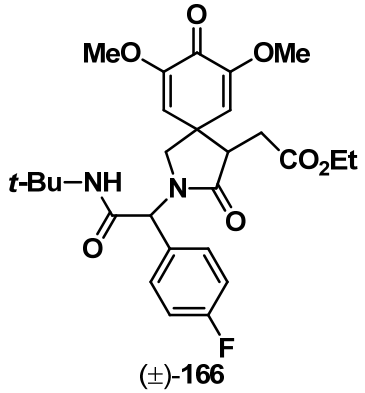


(±)-**165**

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (dd, 2H, *J* = 3.1, 5.5 Hz, aryl), 7.38 (d, 1H, *J* = 15.9 Hz, vinyl), 7.09 (t, 2H, *J* = 8.6 Hz, aryl), 6.92 (d, 1H, *J* = 15.3, vinyl), 6.27 (s, 2H, aryl), 6.06 (s, 1H, NH), 5.85 (s, 1H, H_a), 5.72 (bs, 1H, -OH), 4.77 (dd, 2H, *J* = 17.7, 28.2, benzyl), 4.29 (q, 2H, *J* = 7.2 Hz, -OC$\underline{H}_2$CH$_3$), 3.84 (s, 6H, 2(-OCH$_3$)), 1.44 (s, 9H, t-butyl), 1.37 (t, 3H, *J* = 6.8 Hz, -OCH$_2$CH$_3$).

HRMS: EIMS (M^+) calculated for $C_{27}H_{33}N_2O_7FNa$ 539.2169, found 539.2166.

121. **Ethyl 2-(2-(2-(*tert*-butylamino)-1-(4-fluorophenyl)-2-oxoethyl)-7,9-dimethoxy-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



(±)-**166**

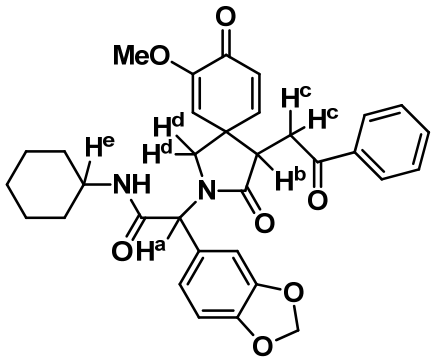
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 2H, aryl), 7.08 (m, 2H, aryl), 6.30 (d, 1H, *J* = 2.0, vinyl), 5.80 (d, 1H, *J* = 2.4, vinyl), 4.04 (m, 2H, -0C$\underline{H}_2$CH$_3$), 4.0 (s, 1H, H_d), 3.61 (s, 6H, 2(-OMe)), 3.33 (t, 1H, *J* = 2.8 Hz, H_b), 3.11 (d, 1H, *J* = 9.6 Hz, H_c), 2.91 (d, 1H, *J* =

10.8 Hz, H_c), 2.62 (m, 1H, H_a), 2.04 (m, 1H, H_a), 1.24 (s, 9H, t-butyl), 1.18 (m, 3H, -0$CH_2C\underline{H}_3$).

^{13}C (100 MHz, $CDCl_3$): δ 190.7, 176.1, 172.8, 167.7, 164.0, 161.6, 152.2, 130.9, 116.6, 114.7, 112.5, 107.0, 61.1, 58.1, 56.4, 55.4, 52.9, 48.7, 30.2, 14.1.

HRMS: EIMS (M^+) calculated for $C_{27}H_{33}N_2O_7FNa$ 539.2169, found 539.2166.

122. **2-(benzo[d][1,3]dioxol-5-yl)-N-cyclohexyl-2-(7-methoxy-3,8-dioxo-4-(2-oxo-2-phenylethyl)-2-azaspiro[4.5]deca-6,9-dien-2-yl)acetamide**



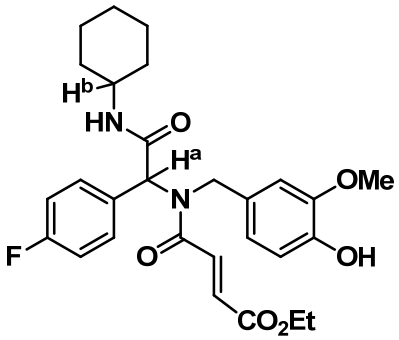
(±)-**168**

^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J* = 8.4 Hz, aryl), 7.54 (t, 1H, *J* = 7.6 Hz, aryl), 7.42 (t, 2H, *J* = 8.0 Hz, aryl), 7.02 (dd, 1H, *J* = 3.2, 10 Hz, vinyl), 6.85 (m, 3H, aryl), 6.28 (d, 1H, *J* = 9.6 Hz, vinyl), 5.98 (s, 2H, -OCH_2O-), 5.82 (s, 1H, H_d), 5.56 (d, 1H, *J* = 8.0 Hz, NH), 5.32 (d, 1H, *J* = 2.4 Hz, vinyl), 4.14 (m, 2H, H_c), 3.66 (s, 3H, -OMe), 3.40 (m, 1H, H_e), 3.01 (dd, 1H, *J* = 2.4, 10.4 Hz, H_c), 2.69 (m, 2H, H_a), 1.91 (m, 2H, cy), 1.66 (m, 3H, Cy), 1.36 (m, 2H, Cy), 1.15 (m, 3H, Cy)

^{13}C NMR (100 MHz, $CDCl_3$ in CD_3OD (3 drops)): δ 196.8, 180.5, 173.5, 167.5, 150.8, 148.1, 136.1, 133.4, 129.9, 128.6, 122.2, 117.4, 113.1, 108.6, 101.4, 58.3, 54.6, 52.2, 47.7, 46.7, 34.2, 32.5, 25.3, 24.6.

HRMS: EIMS (M^+) calculated for $C_{33}H_{34}N_2O_7Na$ 593.2264, found 593.2254.

123. **(*E*)-Ethyl 4-((2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)(4-hydroxy-3-methoxybenzyl)amino)-4-oxobut-2-enoate**



(±)-**170**

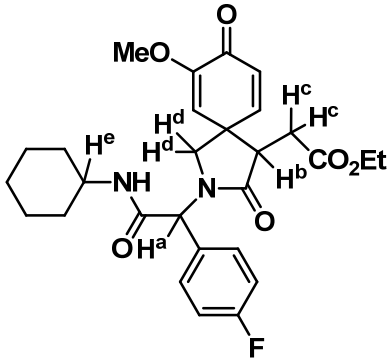
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36(t, 2H, *J* = 7.2 Hz, aryl), 7.27 (d, 1H, *J* = 14.4 Hz, vinyl), 6.97 (t, 2H, *J* = 9.2 Hz, aryl), 6.85 (d, 1H, *J* = 14.8 Hz, vinyl), 6.76 (d, 1H, *J* = 8.4 Hz, aryl), 6.51 (m, 2H, aryl), 5.77 (s, 1H, H_a), 5.57 (d, 1H, *J* = 8.0 Hz, NH), 5.51 (s, 1H, -OH), 4.62 (dd, 2H, *J* = 18.0, 81.4 Hz, benzyl), 4.19 (q, 2H, *J* = 7.2 Hz, -OC$\underline{H}_2$CH$_3$), 3.79 (m, 1H, cy, overlapping with -OMe) 3.76 (s, 3H, -OMe), 1.88 (m, 2H, cy), 1.64 (m, 3H, Cy), 1.32 (m. 2H, Cy) 1.26 (t, 3H, *J* = 7.2 Hz, -OCH$_2$C$\underline{H}_3$), 1.09 (m, 3H, Cy).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 166.3, 165.3, 164.0, 161.5, 146.7, 144.9, 133.9, 132.4, 131.7, 131.6, 130.7, 128.7, 119.4, 115.9, 115.7, 114.4, 109.1, 62.6, 61.1, 55.9, 50.0, 48.6, 32.7, 25.4, 24.7, 24.6, 14.0

^{19}F NMR (376 MHz $CDCl_3$) δ −112.8

HRMS: EIMS (M^+) calculated for $C_{28}H_{33}N_2O_6FNa$ 535.2220, found 535.2211

124. **Ethyl 2-(2-(2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)-7-methoxy-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



(±)-**171**

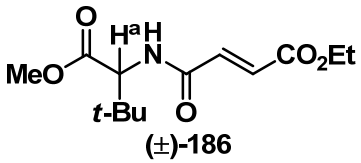
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 1H, aryl), 7.31 (m, 1H, aryl), 7.10 (m, 2H, aryl), 6.91 (dd, 1H, *J* = 2.4, 10.0 Hz, vinyl), 6.33 (dd, 1H, *J* = 1.6, 9.6 Hz, vinyl), 5.86 (s, 1H, H_d), 5.44 (d, 1H, *J* = 8.4 Hz, NH), 5.16 (d, 1H, *J* = 2.4 Hz, vinyl), 4.08 (m, 2H, -OC$\underline{H_2}$CH$_3$), 3.80 (m, 1H, H_e), 3.39 (s, 3H, -OMe), 3.33 (t, 1H, *J* = 2.4 Hz, H_b),3.11 (dd, 1H, *J* = 10.0, 42.9 Hz, H_c), 2.95 (d, 1H, *J* = 10.4 Hz, H_c), 2.66 (m, 1H, H_a), 2.10 (m, 1H, H_a)

^{13}C NMR (100 MHZ $CDCl_3$): δ 180.2, 172.7, 171.1, 167.2, 164.1, 161.6, 152.1, 149.8, 147.7, 146.2, 116.4, 114.2, 112.2, 61.0, 58.0, 54.6, 52.0, 48.9, 47.6, 32.7, 30.4, 25.3, 14.0

^{19}F NMR (376 MHz $CDCl_3$) δ -112.0

HRMS: EIMS (M^+) calculated for $C_{28}H_{33}N_2O_6FNa$ 535.2220, found 535.2209

125. **(*E*)-Ethyl 4-((1-methoxy-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



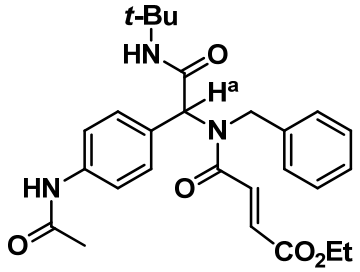
(±)-**186**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (d, 1 H, *J* = 15.6 Hz, -C<u>H</u>=CH-), 6.82 (d, 1 H, *J* = 15.3 Hz, -CH=C<u>H</u>-), 6.32 (d, 1 H, *J* = 9.2 Hz, -N<u>H</u>), 4.59 (d, 1 H, *J* = 9.8 Hz, H^a), 4.26 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.75 (s, 3 H, O<u>Me</u>), 1.32 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.99 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 165.4, 163.3, 135.7, 131.2, 61.2, 60.2, 52.0, 35.1, 29.7, 26.5, 14.1.

HRMS (EIMS, M^+): calcd for $C_{13}H_{21}NO_5$ 271.1420, found 271.1432.

126. **(*E*)-Ethyl 4-((1-(4-acetamidophenyl)-2-(tert-butylamino)-2-oxoethyl)(benzyl)amino)-4-oxobut-2-enoate**



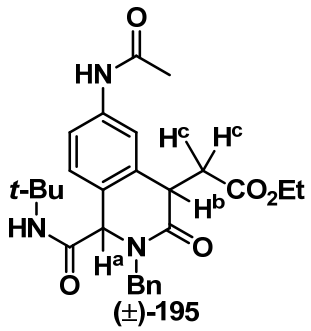
(±)-**194**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1 H, -N<u>H</u>), 7.36 (d, 2 H, *J* = 8.2 Hz, Aryl), 7.06-7.25 (m, 6 H, Ph and –C<u>H</u>=CH- overlap), 6.92 (d, 2 H, *J* = 7.0 Hz, Aryl), 6.81 (d, 1 H, *J* = 15.3 Hz, -CH=C<u>H</u>-), 5.87 (s, 1 H, H^a), 5.72 (s, 1 H, -N<u>H</u>), 4.78 (d, 1 H, *J* = 17.4, -NC<u>H</u>$_2$Ph), 4.57 (d, 1 H, *J* = 17.7 Hz, -NC<u>H</u>$_2$Ph), 4.16 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 2.10 (s, 3 H, -CO<u>Me</u>), 1.30 (s, 9 H, *t*-Bu), 1.22 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 168.4, 166.3, 165.3, 138.5, 137.2, 133.9, 132.3, 130.4, 129.9, 128.4, 127.2, 126.2, 119.8, 62.9, 61.0, 51.8, 49.8, 28.5, 24.4, 14.1.

HRMS (EIMS, M^+): calcd for $C_{27}H_{33}N_3O_5$ 479.2420, 479.2414.

127. **Ethyl 2-(6-acetamido-2-benzyl-1-(tert-butylcarbamoyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)acetate**



(±)-195

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, 1 H, Aryl), 7.16-7.42 (m, 7 H, Aryl), 5.49 (s, 1 H, H^a), 4.56 (d, 1 H, J = 15.9 Hz, -NC$\underline{H}_2$Ar), 4.17 (dd, 1 H, J_1 = 6.7 Hz, J_2 = 3.1 Hz, H^b), 4.15 (q, 2 H, J = 7.3 Hz, -OC$\underline{H}_2$CH$_3$) 4.04 (d, 1 H, J = 15.3 Hz, -NC$\underline{H}_2$Ar), 2.91 (dd,1 H, J_1 = 18.0 Hz, J_2 = 4.6 Hz, H^c), 2.79 (dd,1 H, J_1 = 17.7 Hz, J_2 = 9.8 Hz, H^c), 2.17 (s, 3 H, --CO$\underline{Me}$), 1.24 (t, 3 H, J = 7.3 Hz, -OCH$_2$C$\underline{H}_3$), 0.99 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 169.5, 168.4, 168.2, 138.4, 136.6, 131.9, 131.5, 129.0, 128.9, 128.5, 128.3, 127.9, 127.7, 119.9, 70.9, 61.1, 56.1, 51.7, 45.3, 31.0, 28.2, 24.6, 14.1.

HRMS (EIMS, M^+): calcd for $C_{27}H_{33}N_3O_5$ 479.2420, 479.2432.

CHAPTER 3

A Microwave-Influenced, Diastereoselective Cascade Ugi/Michael/aza-Michael Reaction In Water: Proximity Effect Leads To Natural-Product-Like Diverse Aza-Spiro Tri- And Tetracycles

3. Introduction

Rapid construction of diverse complex molecular architectures especially spirocyclic frameworks, having all carbon quaternary centers[154] in a regio- and stereospecific manner from simple substrates, continues to be a significant challenge in organic synthesis.[4,155] To this extent, MCCRs involving cascade processes have been utilized in TOS as well DOS and have emerged as powerful tools for the construction of complex architectures as these reactions often provide excellent chemoselectivities.[7, 156]

As a component of our on-going research in developing new cascade approaches using MCCRs to generate biologically relevant diverse small and complex molecules, we were particularly interested in spirocyclic scaffolds especially that of aza and/or oxa spiro [4.5]decanes[157] which are typically synthesized using toxic hyper-valent iodine (e.g. PIFA, DIB), ICl, or expensive metal reagents.[153, 158]

Over the past century, nearly 500 alkaloids have been isolated from the herbaceous Amaryllidaceae plant family. Among these alkaloids (+)-Plicamine (**200**), (+)-Plicane (**201**), (-)-Obliquine (**202**), 3-*epi*-Plicane (**203**), 3-*epi*-Obliquine (**204**), (+)-Pretazettine (**205**), (+)-Tazettine (**206**); Marine alkaloid (+)-Discorhabdin A (**207**); Lycopodium alkaloids Magellanine (**208**), Magellaninone (**209**) and Paniculatine (**210**); Simomenine (**211**), Erythratinone (**212**) have unique nitrogen-containing spiro-fused cyclic structures.[159] We were particularly interested in the family of amaryllidaceae

alkaloids because of their extensive structural diversity and broad biological activities e.g. antitumor, antibacterial, antifungal, antimalarial, antiviral, analgesic and acetylcholinesterase (AChE) inhibitory activities. In addition, they inhibit various cell cycles (e.g. G_o/G_1 phase in tumor progression, G_2/M phase in HIV-1) and have found application in the therapeutic treatment of Schizophernia, Alzheimer's diseases.[160] The most notable structural feature common to all of these alkaloids is the presence of the sterically congested quaternary carbon center at the arylhydroindolone bridgehead, which represents one major challenge to their synthetic make-up.

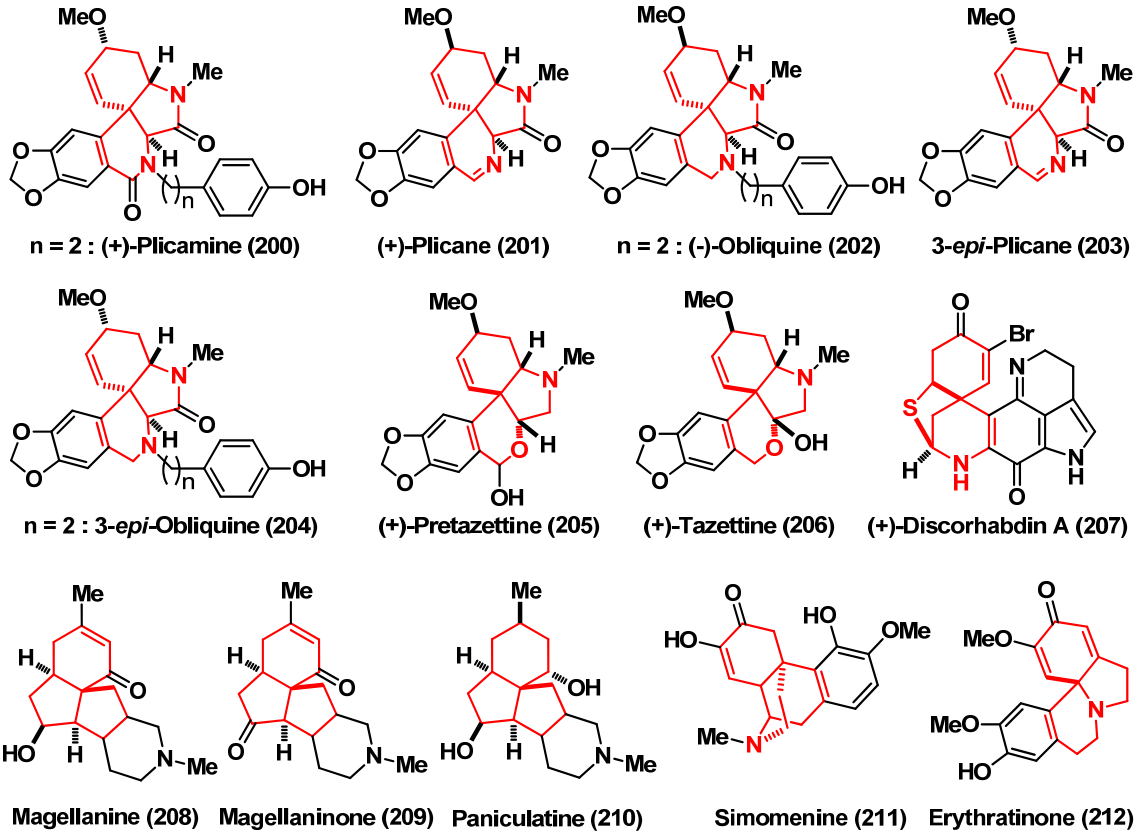


Figure 22. Biologically relevant amaryllidaceae, marine and lycopodium alkaloids.

(+)-Plicamine (**200**), the first bis-nitrogen (two N atoms in the skeleton) containing alkaloid of the amaryllidaceae family, was isolated from extracts of the

Turkish *Galanthus plicastus* (subsp. Byzantinus).[161] The most interesting feature of the tetracyclic structure of plicamine is the presence of a 6,6-spirocyclic core having three stereogenic centers. Recently, Ley and coworkers[162] have reported the first total synthesis of (+)-plicamine and structurally related compounds in over 30 steps employing polymer supported phenyliodine (III) bis(trifluoroacetate) (PIFA) to construct the key 6,6-spiro cyclic intermediate. Although its biological property has not been entirely evaluated, in view of a recent literature report,[163] structural modifications will alter biological and toxicological activities such that improved efficacy be realized. Thus, the synthesis of structural motifs which are similar to (+)-Plicamine and its family are necessary to conduct SAR studies.

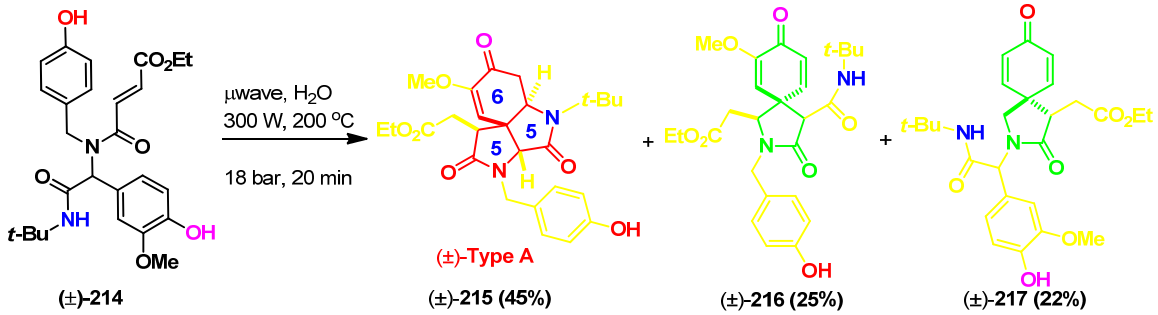
3.1. Results and Discussions

3.1.1. A Cascade Ugi/Michael/aza-Michael Pathway Leads To Diazaspiro-fused Tricycles and Tetracycles

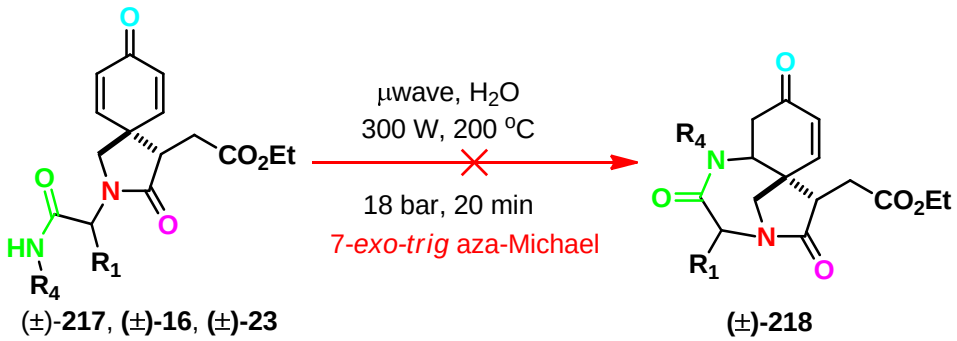
We envisioned that a multicomponent coupling reaction, mainly the Ugi four component coupling reaction (U-4CCR), would provide an acyclic trifunctional precursor that would undergo a 5-*exo* Michael addition to form 2-azaspirocyclohexadienone[106] which could then undergo a 5-*exo*-*trig*/6-*exo*-*trig* aza-Michael reaction under microwave irradiation and bring forth structurally similar azasprio-fused polycyclic skeletons as those affiliated to the amaryllidaceae alkaloids.

The requisite substrates to test this hypothesis were *p*-hydroxy benzylamine (PHB, **1b**), *p*-hydroxy benzaldehyde (**213a**), fumaric acid monethyl ester (**2a**) and *tert*-butyl isocyanide (**3c**) (Scheme 54). The U-4CCR afforded acyclic tetrafunctional precursor **214** in excellent yield (92%); it was then subjected to μwave irradiation in

water (300 W, 200 °C, 18 bar, 20 min). To our delight, the desired diazaspiro-5,5,6-fused-tricycle **215** was obtained via a 5-*exo* Michael addition followed by a 5-*exo-trig* aza-Michael in about 45% along with 2-azaspirocyclohexadienones **216** and **217**. Although the reaction gave a moderate diastereoselectivity (1:3) for **215**, we were quite satisfied with the result. It must be noted that compound **217** (or structurally similar **16, 23**) did not undergo a 7-*exo-trig* aza-Michael addition to give any recognizable amount (or at best a trace amount) of diazaspiro-7,5,6-fused tricycle under microwave irradiation (Scheme 55).



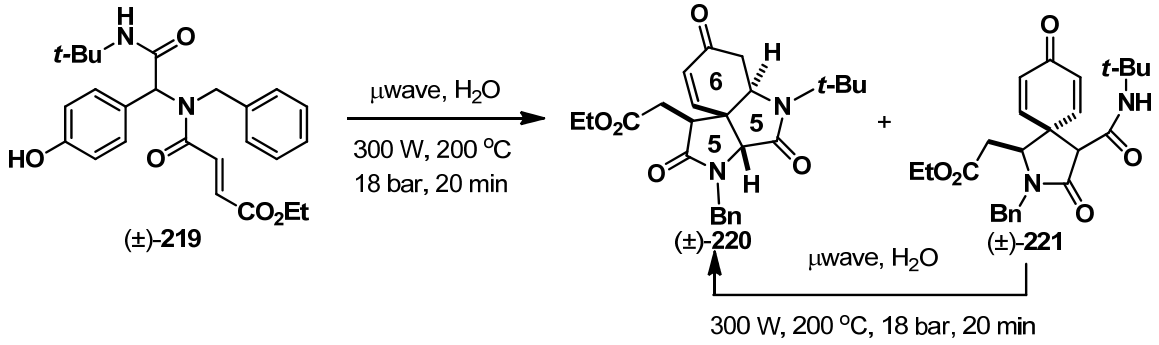
Scheme 54. Synthesis of azaspiro-5,5,6-fused tricycle via Ugi/Michael/aza-Michael (UMAM) reaction under μwave irradiation.



Scheme 55. 7-*exo-trig* aza-Michael reaction does not occur.

Next, we focused on improving the reaction yield and replaced *p*-hydroxy benzylamine (**1b**) with benzyl amine (**1d**) in the U-4CCR. The trifunctional acyclic precursor **219** was obtained in excellent yield (93%). When **219** was subjected to

microwave irradiation under the previous conditions, an improved yield of diazaspiro-5,5,6-fused tricycle **220** (65%) was obtained along with 2-azaspirocyclohexadienone **221**. It is noteworthy that, isolated **221** can be converted to **220** upon further microwave irradiation (Scheme 56).



Scheme 56. Modified Ugi acyclic product provides excellent yield of (±)-**220.**

Table 22. Optimization of conditions for the synthesis of diazaspiro-5,5,6-fused tricycle.

Entry	Time (min)	Power (W)	Temp (°C)	Pressure (bar)	% yield[a]/dr[b]	
					220	221
1	20	300	200	18	65/1:3	30/1:2
2	20	300	220	18	60/1:3	23/1:2
3	20	250	200	15	45/1:3	50/1:2
4	20	200	160	6	25/1:3	25/1:2
5	20	150	151	5.1	10/1:3	15/1:2
6	20	100	138	4.1	0	7/1:2
7	20	50	100	1.5	0	0
8	25	300	200	18	70/1:3	25/1:2
9	30	300	200	18	73/1:3	22/1:2
10	30	300	200	18.5	77/1:3	15/1:2
11	30	300	200	19	80/1:3	10/1:2

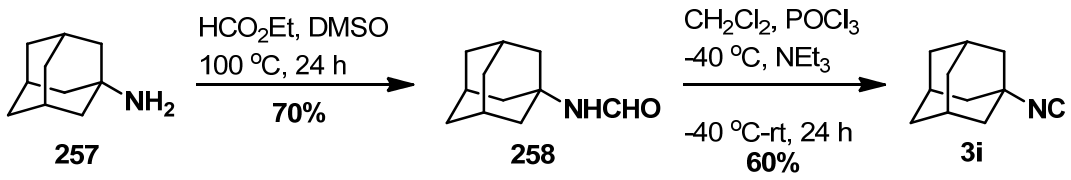
[a] Isolated. [b] Determined from ^{1}H NMR of crude reaction mixture.

Next we examined different temperatures pressures, power and times to optimize the yield of **220**. After several trials (Table 22), when the microwave was equilibrated to

300 W, 200 ^{o}C, 18 bar for 30 min, the reaction gave a diastereomeric mixture of **220** in 89% yield. Diastereoselectivity was determined from the ^{1}H NMR of the unpurified reaction mixture.

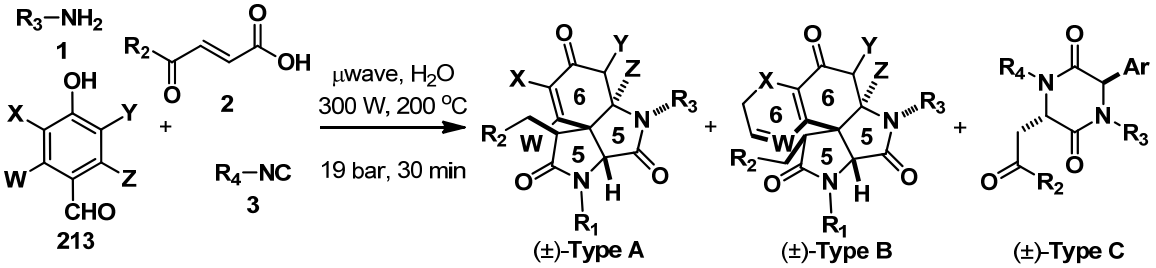
With the optimized conditions in hand, we examined the substrate scope of this novel cascade UMAM reaction as a means to understand the process. The majority of the substrates used, provided good to excellent yield (up to 99%) with moderate to excellent diastereoselectivities (up to 99:1). It was observed that the reaction is highly sensitive to electronic nature of substituents on the phenyl ring of the aldehyde coupling partner (*p*-hydroxy benzaldehyde). Electron donating groups (e.g., OMe, Table 23) on *p*-hydroxy benzaldehyde highly favor the reaction. However, 3,4-dimethyl benzaldehyde (Table 23, entry 18) did not provide expected diazaspiro-fused tricycle, only 2-azaspirocyclohexadienone product was obtained most likely due to steric effect of the methyl groups which prevented the 5-*exo*-*trig* aza-Michael attack. On the other hand, electron withdrawing groups (e.g., Br, NO_2) disfavored the reaction and gave no recognizable amount (or at best a trace amount) of the desired product. However, it is quite surprising that the use of 3-fluro-4-hydroxy benzaldehyde in the UMAM reaction provided a good yield (70%) of the desired product. When 4-hydroxyl-1-napthaldehyde (**213k**) was used as a coupling partner, the reaction provided a quantitative yield and excellent diastereoselectivity (99:1). It is noteworthy that **213k** also provided 2-azaspirocyclohexadienone **252** spontaneously at room temperature. This unusual result could arise from the high reactivity of 4-hydroxy-1-napthaldehyde. Moreover, refluxing **213k** along with other reacting partners in a sealed tube for 6 h provided **252** exclusively, and only a trace amount of **251** was observed on TLC. It must be noted that, except

213k, other aldehydes afforded the acyclic U-4CCR product which did not undergo a UMAM convention upon refluxing in water in a oil-bath or in a sealed tube. Use of the very bulky adamantyl isocyanide[39, 164] (**3i**) provided only a single UMAM product, whereas the less bulky isocyanide e.g., cyclohexyl isocyanide (**3d**) provided a trace amount of 2,5-diketopiperazine **229** via 6-*exo*-*trig* aza-Michael pathway.[144]



Scheme 57. Synthesis of adamantyl (ada) isocyanide **3i**.

Table 23. Substrates scope of the microwave-influenced synthesis of azaspiro-fused tricycles.

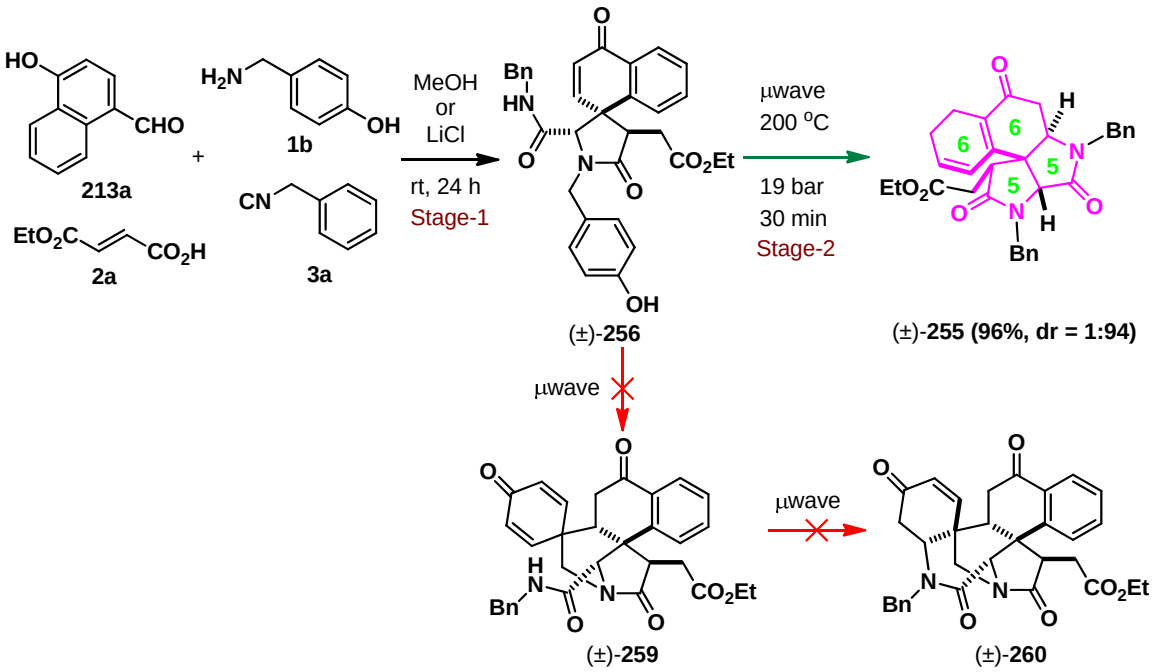


Entry	R_1				R_2	R_3	R_4	Compd type/ %yield[a]/dr[b]
	X	Y	W	Z				
1	OMe	H	H	H (**213a**)	OEt (**2a**)	*p*-hydroxylbenzyl (1b)	*t*-Bu (3b)	A(**215**)/35/1:2
2	H	H	H	H (**213**[a])	OEt (**2a**)	Benzyl (1d)	*t*-Bu (3b)	A(**220**)/80/1:3
3	OMe	H	H	H (**213b**)	OEt (**2a**)	Benzyl (1d)	*t*-Bu (3b)	A(**222**)/85/1:3
4	OMe	OMe	H	H (**213c**)	OEt (**2a**)	Benzyl (1d)	*t*-Bu (3b)	A(**225**)/89/1:3
5	H	H	H	H (**213a**)	OEt (2a)	Propargyl (1x)	Cy (3c)	A(**228**)/90/1:3 C(**229**)/6/1:5
6	OMe	H	H	H (**213b**)	OEt (2a)	Benzyl (1d)	Ada (3h)	A(**230**)/65/single
7	H	H	OMe	H (**213d**)	OEt (2a)	Benzyl (1d)	*t*-Bu (3b)	A(**233**)85/1:3
8	H	H	OMe	OMe (**213e**)	OEt (2a)	Benzyl (1d)	*t*-Bu (3b)	A(**236**)/80/1:6
9	Br	H	H	H (**213f**)	OEt (2a)	Propargyl (1x)	*t*-Bu (3b)	–
10	Br	H	H	H (**213f**)	OEt (2a)	Propargyl (1x)	Cy (3c)	–
11	NO_2	H	H	H (**213g**)	OEt (2a)	Benzyl (1d)	*t*-Bu (3b)	–
12	OMe	NO_2	H	H (**213b**)	OEt (2a)	Benzyl (1d)	*t*-Bu (3b)	–
13	F	H	H	H (**213h**)	OEt (2a)	Benzyl (1d)	*t*-Bu (3b)	A(**238**)/70/1:3
14	OMe	H	H	H (**213b**)	Ph (2f)	Benzyl (1d)	*t*-Bu (3b)	A(**240**)/84/1:4
15	OMe	H	H	H (**213b**)	Tol (2h)	Benzyl (1d)	*t*-Bu (3b)	A(**243**)/83/1:4
16	OMe	H	H	H (**213b**)	Tol (2h)	3,5-dimethoxybenzyl (1e)	*t*-Bu (3b)	A(**246**)/82/1:3
17	H	H	H	H (**213a**)	OEt (2a)	Benzyl (1d)	Cy (3c)	A (**249**)/85/1:4 C (**250**)/5/1;3
18	Me	Me	H	H (**213j**)	OEt (2a)	Benzyl (1d)	*t*-Bu (3b)	–
19	4-hydroxyl-1-napthaldehyde (**213k**)				OEt (2a)	Benzyl (1d)	*t*-Bu (3b)	B(**251**)/99/1:99
20	4-hydroxyl-1-napthaldehyde (**213k**)				OEt (2a)	*p*-hydroxylbenzyl (1b)	*t*-Bu (3b)	B(**253**)/99/1:98
21	4-hydroxyl-1-napthaldehyde (**213k**)				OEt (2a)	*p*-hydroxylbenzyl (1b)	Bn (3a)	B(**255**)/96/1:94

[a] Isolated. [b] Determined from ^{1}H NMR from the unpurified reaction mixture.

In an attempt to examine whether less bulky or linear isocyanides could be used in the UMAM pathway, we took advantage of the spontaneous reactivity of 4-hydroxy-1-

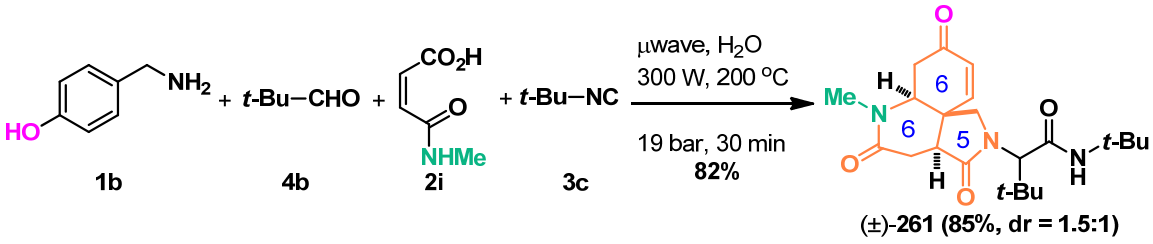
napthaldehyde and employed benzyl isocyanide (Table 23, entry 21) in the UMAM reaction at room temperature. Gratifyingly, the reaction gave 2-aza-spirocyclohexadienone **256** as a 94:1 disatereomeric mixture. Having **256** in hand, we rationalized, based on previous results, that it could undergo a cascade Michael/aza-Michael process to provide the highly complex diazaspiro-fused polycycles **259** and **260**. However, upon microwave irradiation, **256** provided quantitative yield of **255** (Scheme 58).



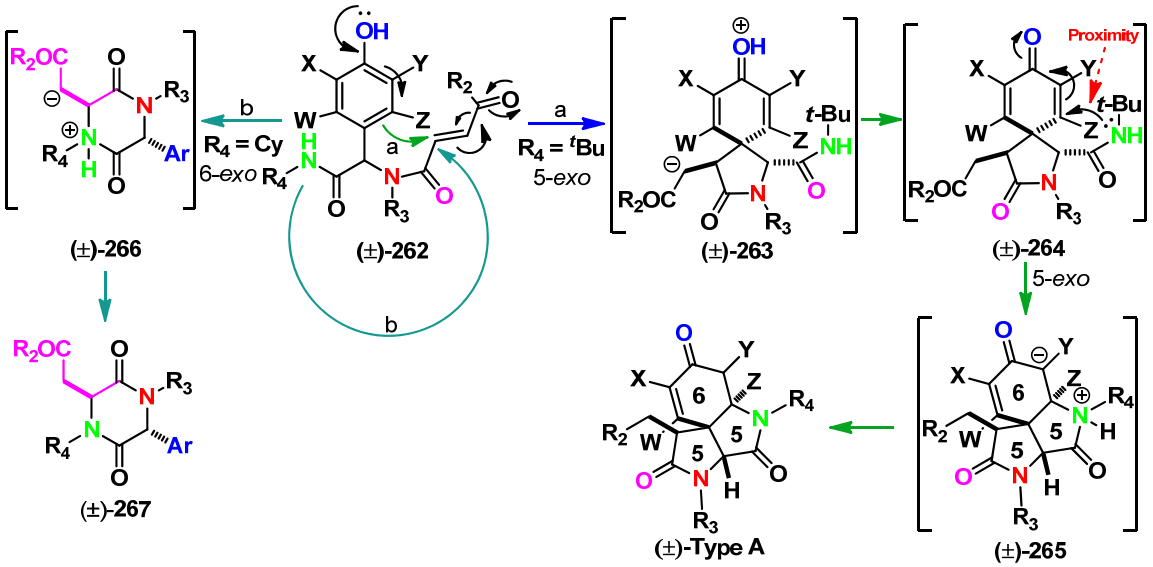
Scheme 58. Benzyl isocyanide in U-4CCR provided diazaspiro-fused tetracycle.

Further substrate scope was also examined as a means to diversify the convention(s). Thus, we chose to use *p*-hydroxy benzylamine (**1b**), trimethylacetaldehyde (**4b**), *N*-methylmaleic acid (**2i**) and *tert*-butyl isocyanide (**3b**) in the cascade process and to our delight the reaction afforded diazaspiro-6,5,6-fused

tricycle **261** in excellent yield (Scheme 59). It is noteworthy that compound **261** have very similar structural core to that of (+)-plicamine.



Scheme 59. Synthesis of diazaspiro-6,5,6-fused tricycle *via* UMAM reaction.



Scheme 60. Proposed mechanism for the formation of diazaspiro-fused polycycles via UMAM pathway.

A proposed mechanism that accounts for the formation of diazaspiro-fused polycycles is depicted in Scheme 60. We rationalized that the electron donating *p*-hydroxy group on the benzaldehyde, under the influence of μwaves, led to the formation of zwitterionic intermediate **263** which is believed to be stabilized by hydrogen bonding with water. Furthermore, zwitterionic character of the intermediate **263** probably helps to absorb μwave energy and thus might lower the activation energy barrier. Upon

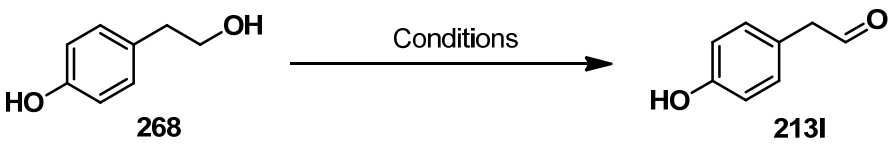
protonation and deprotonation, compound **263** formed 2-aza-spiro[4.5]deca-6,9-diene-3,8-dione product **264** which under the influence of μwaves undergoes a 5-*exo-trig* aza-Michael addition to form the zwitterionic intermediate **265**. Proton transfer finally provides the final products (Type **A**). The mechanism of formation of Type **B** a is very similar to that of Type **A**.

The major isomer of 2-aza-spiro[4.5]deca-6,9-diene-3,8-diones has a trans relationship between the isocyanide and acid coupling partners as determined by nOe study, H-H COSY, HMQC, HMBC experiments and unequivocally confirmed by X-ray crystal structure analysis (Figure 23). The stereochemistry of the major diastereomer of diazaspiro-fused polycycles was determined by nOe, ^{1}H-^{1}H GDQFCOSY, HMQC, HMBC experiments and unequivocally confirmed by X-ray crystal structure analysis (Figure 24).

In our previous study, bulky substituents at R_4 (e.g. *tert*-butyl) and *p*-hydroxy benzylamine at R_3 led to the formation of 2-aza-spiro[4.5]deca-6,9-diene-3,8-diones probably due to the steric effect in the transition state and less bulky substituents at R_4 (e.g., benzyl) led to 2,5-diketopiperazine formation exclusively.[144] Given this fact, one might not expect that in the presence of a bulky substituent at R_4 (e.g., *tert*-butyl), 2-aza-spiro[4.5]deca-6,9-diene-3,8-diones **264** would undergo a 5-*exo-trig* aza-Michael addition to afford the desired diazaspiro polycycles. The possible explanation could be that the amide group with bulky substituent at R_4 is in close proximity to the dienone Michael acceptor. In fact, entry 5 (Table 23) shows that when R_4 is cyclohexyl (**3d**), 2-aza-spiro[4.5]deca-6,9-diene-3,8-diones **264** is the major product and only small amount

of 2,5-diketopiperazine **267** was obtained. It must be kept in mind that 2-aza-spiro[4.5]deca-6,9-diene-3,8-diones **217** does not undergo 7-*exo* aza-Michael addition.

To confirm that spirocycle formation is driven by proximity effect,[165] we decided to use 4-hydroxylbenzyl acetaldehyde (**213l**) instead of *p*-hydroxyl benzaldehyde (**213a**) (Scheme 61). Initial attempt to synthesize **213l** via pyridinium chloro chromate (PCC) or pyridinium dichromate (PDC) or 2-iodoxybenzoic acid (IBX) oxidation of 4-(2-hydroxylethyl)phenol (**268**) only gave trace amount of product probably due to a oxa-Pictet-Spengler side reaction leading to **275** as depicted in Scheme 62.[166] However, Doering-Parikh oxidation[167] of **268** (Table 24, entry 4) provided 65% yield of desired aldehyde **213l** which was used without further purification.



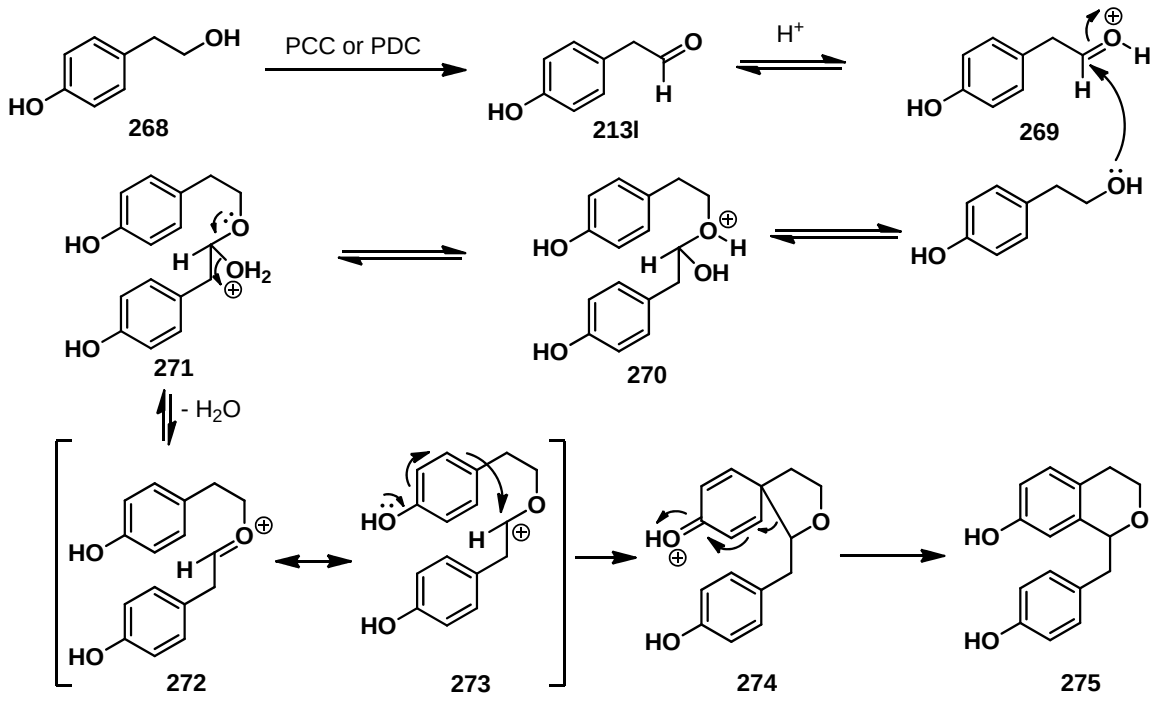
268 **213l**

Scheme 61. Synthesis of 4-hydroxylbenzyl acetaldehyde.

Table 24. Optimization of reaction conditions for the synthesis of **213l**.

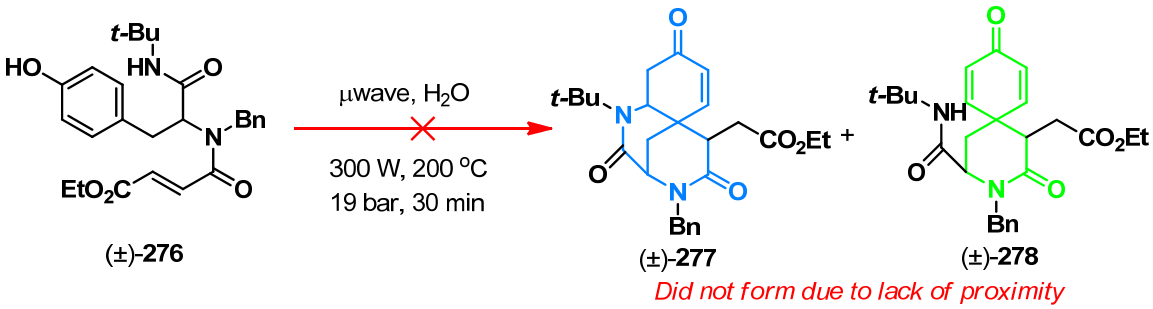
Entry	Conditions	% yield of **213l**[a]
1	PCC, CH_2Cl_2/EtOAc, 0 $^oC \rightarrow$rt, 6 h	10
2	PDC, CH_2Cl_2/EtOAc, 0 $^oC \rightarrow$rt, 6 h	11
3	IBX, DMSO, 0 $^oC \rightarrow$ rt, 5 h	15
4	SO_3.Py, DMSO, Et_3N, 0 $^oC \rightarrow$ rt, 7 h	65

[a] Isolated.



Scheme 62. Mechanism of side product formation via oxa-Pictet-Spengler reaction.

Due to the sensitivity of the aldehyde **213l**, the Ugi reaction between benzylamine (**1d**), 4-hydroxylphenyl acetaldehyde (**213l**, fumaric acid monoethyl ester (**2a**) and *tert*-butyl isocyanide (**3d**) was carried out at room temperature and acyclic product **276** was obtained in **75%** yield. When **276** was subjected to microwave irradiation, neither a 6-*exo-trig* Michael/6-*exo-trig* aza-Michael nor a 6-*exo-trig* Michael reaction occurred to give any recognizable (or at best a trace) amount of **277** or **278** respectively. A probable explanation could be that the 6-*exo-trig* Michael addition did not occur because the Michael acceptor (ethyl acrylate) was not in close proximity of the *p*-hydroxy phenyl group. Furthermore, six-membered ring formation is slower than five-membered rings. This further confirmed that azaspirocyclohexadienone and diazaspiro-fused polycycle formation is driven by proximity effect.



Scheme 63. Further proof of proximity effect.

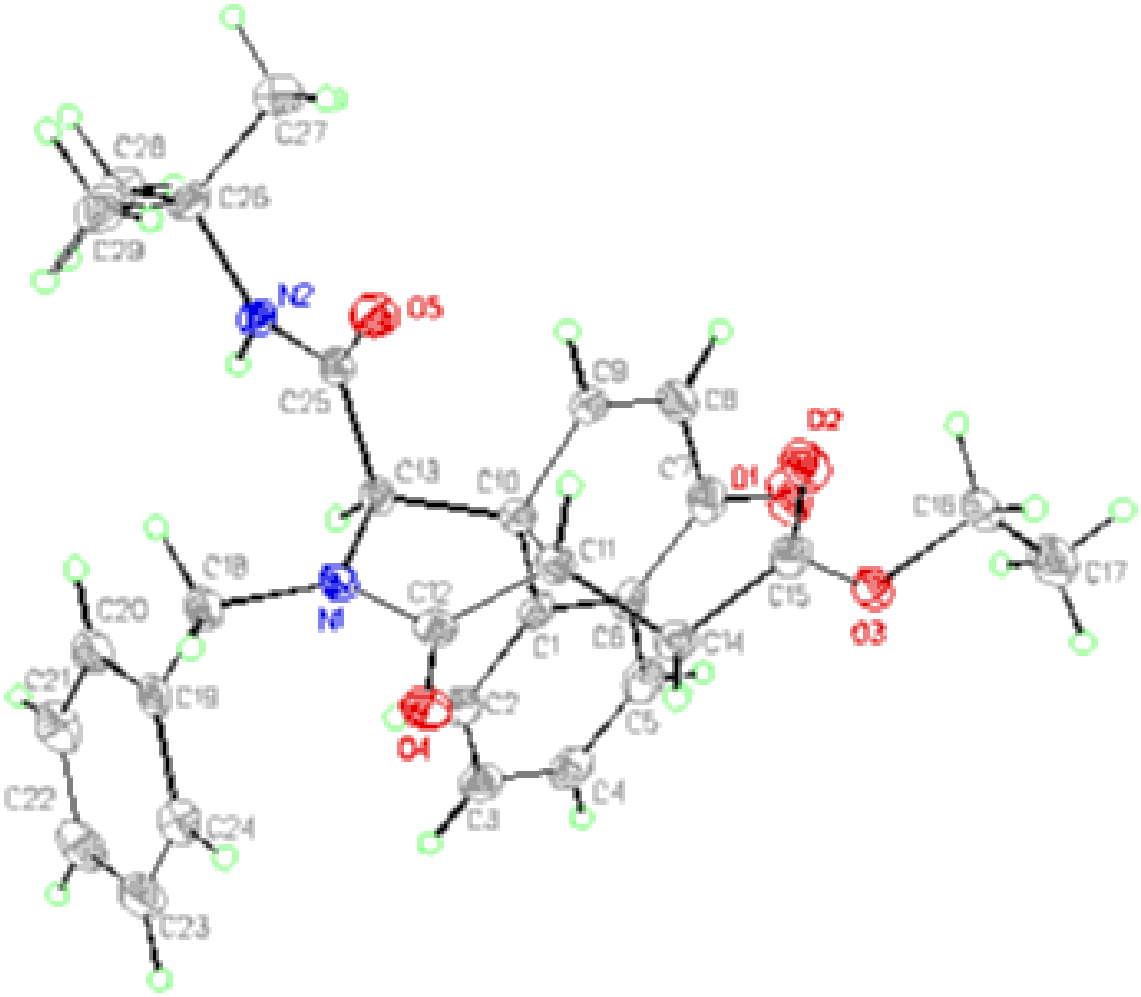


Figure 23. X-ray crystal structure of 2-aza-spiro[4.5]deca-6,9-diene-3,8-dione (±)-**252**.

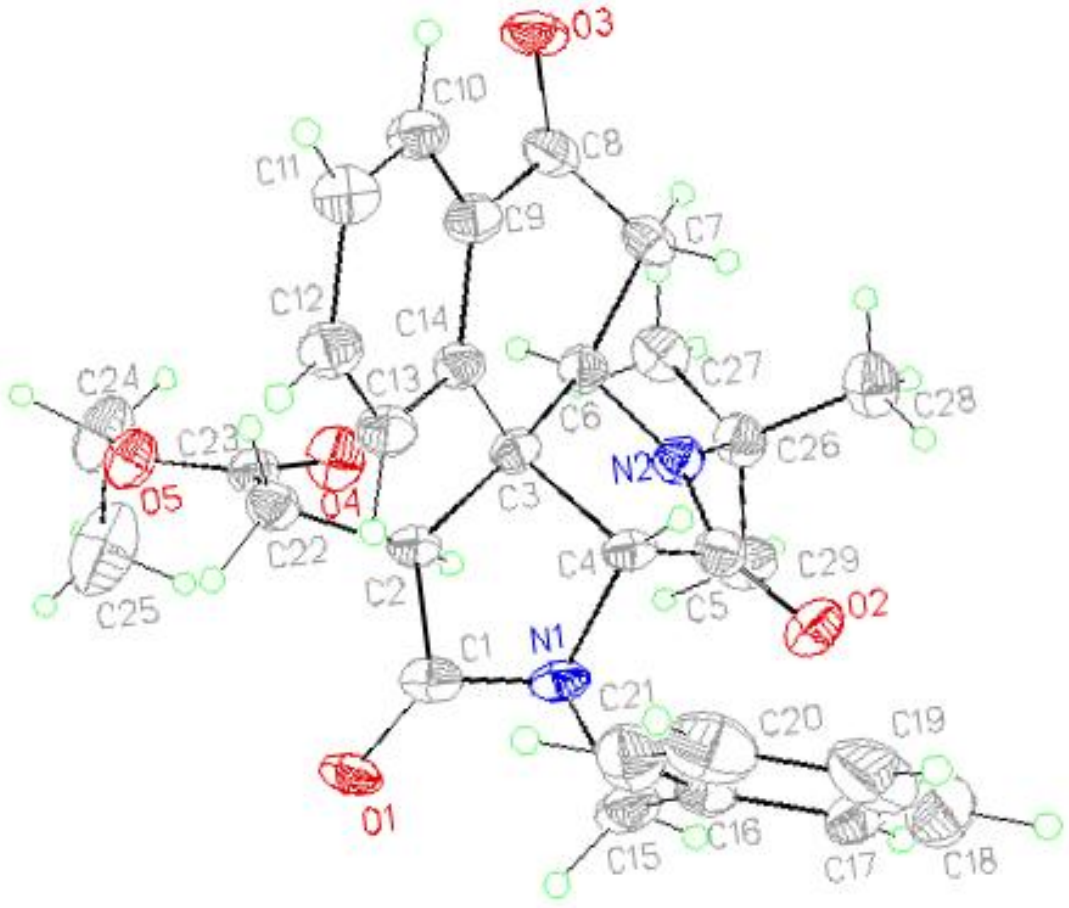
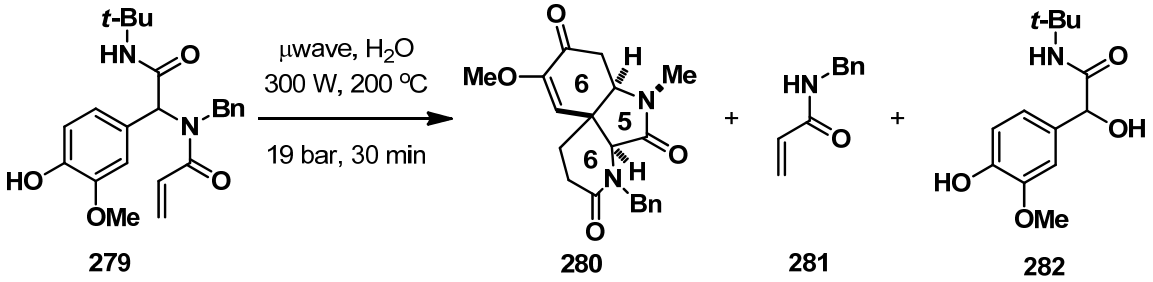


Figure 24. X-ray crystal structure of diazaspiro-fused polycycle (±)-**251**.

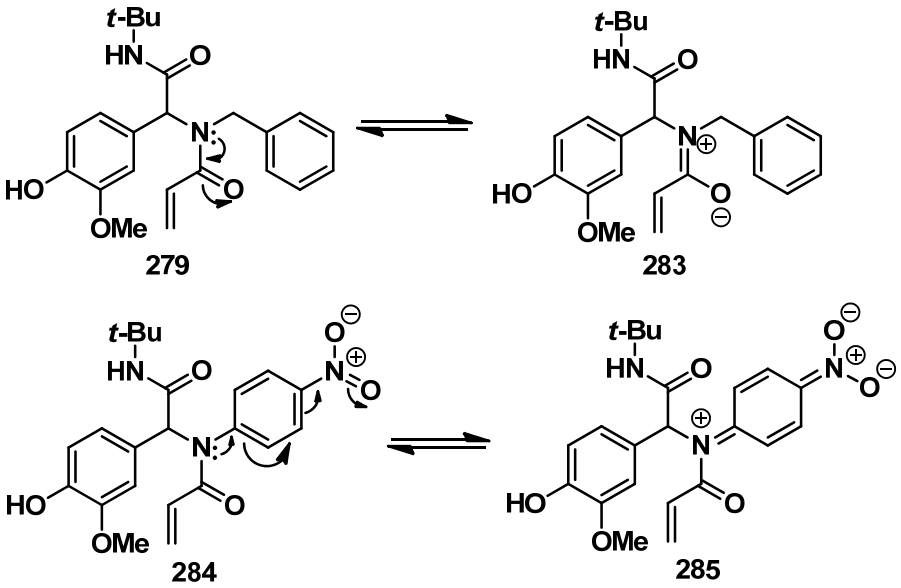
3.1.2. Synthetic Studies Toward The Synthesis of (+)-Plicamine Core

With a better understanding of our system, we next embarked on devising a strategy toward the synthesis of (+)-plicamine core. Although as previously noted, acrylic acid did not provide any 7-membered diazepine rings via 7-*exo*-*trig* aza-Michael pathway (chapter 2, scheme 36), we speculated that it might exhibit different reactivity in the presence of a different set of substituents. Thus, benzylamine **1d**, 4-hydroxy-3-methoxy-benzaldehyde **213b**, acrylic acid **2f** and *t*-butyl isocyanide **3c** provided the acyclic Ugi product **279** in good yield. However, when microwave irradiation was

employed, the desired product **280** was not obtained; rather formation the deprotected compound **281** was observed.

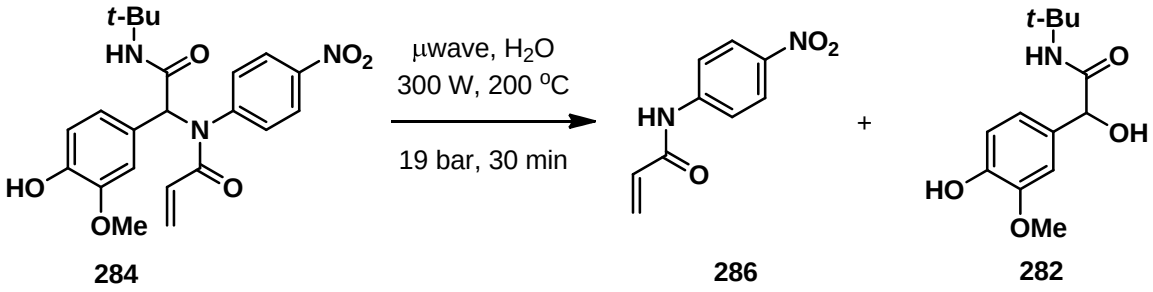


Scheme 64. Attempt to synthesize (+)-Plicamine core.



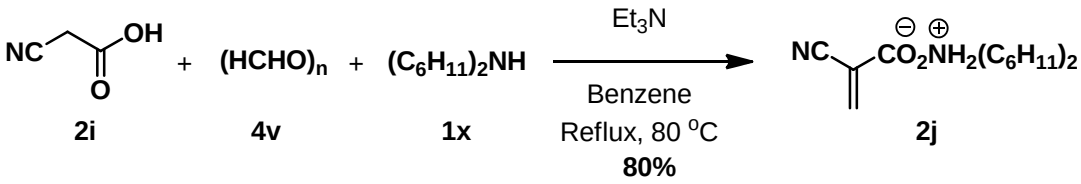
Scheme 65. Effect of electron withdrawing group on the amine component.

We reasoned that due to the lone pair donation from nitrogen to the amide carbonyl, the Michael acceptor itself was weak and it was not in close proximity. Hence, we decided to replace benzylamine **1d** with *p*-nitro aniline in the U-4CCR. To our disappointment, only the deprotected products **286a** and **286b** were obtained.

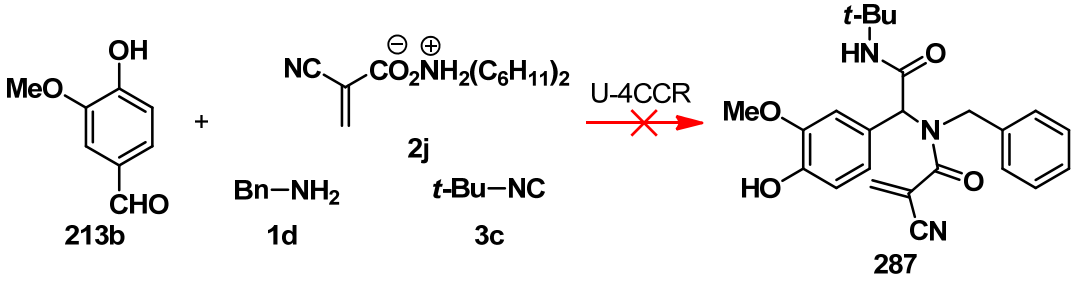


Scheme 66. Synthetic study toward (+)-Plicamine core.

Next, we decided to employ carboxylic acid salt **2j** (Scheme 67) in the U-4CCR. Thus, **2j** was synthesized from refluxing 2-cyano acetic acid **2i** in benzene in presence of para-formaldehyde **4v**, dicyclohexyl amine **1x** and triethyl amine.[168] The identity of compound **2j** was confirmed by ^{1}H NMR and HRMS. However, when the acid **2j** was employed in the U-4CCR, the desired Ugi product **287** was not obtained (Scheme 68).

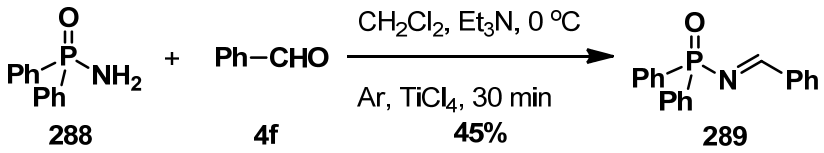


Scheme 67. Synthesis of acid **2j**.

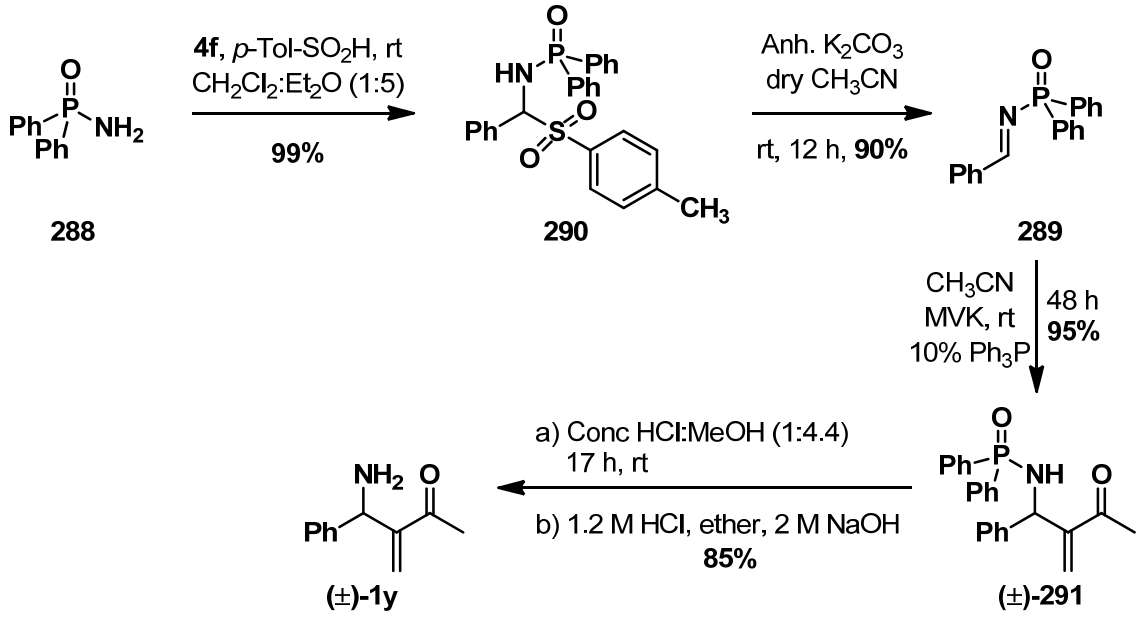


Scheme 68. Attempt to synthesize acyclic U-4CR product **287**.

Next, we speculated that amine **1y** might be a better fit for the required proximity of the reacting centers to form 2-aza-spiro[5.5]deca-6,9-diene-8-ones. Compound **1y** was synthesized in 5 steps from *P*,*P*-dipenylphosphinic amide **288**. Initial attempt to convert **288** into (*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide **289** using $TiCl_4$ as a catalyst provided moderate yields of **289** (Scheme 69).[169]



Scheme 69. Synthesis of amide **289**.

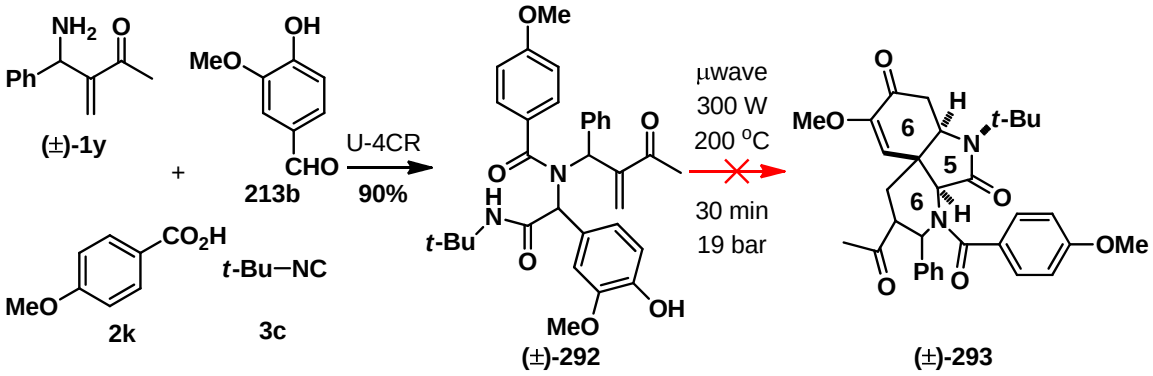


Scheme 70. Synthesis of amine **1y**.

Thus, we chose an alternative route for the synthesis of **1y** (Scheme 70). Commercially available sodium salt of toluenesulfinic acid was converted to corresponding free acid by treating with conc HCl in a mixture of water and methyl *tert*-butyl ether (MTBE) at room temperature. Treatment of **288** with benzaldehyde **4f** in the presence of *p*-toluenesulfinic acid in a 1:5 mixture of dichloromethane and ether afforded

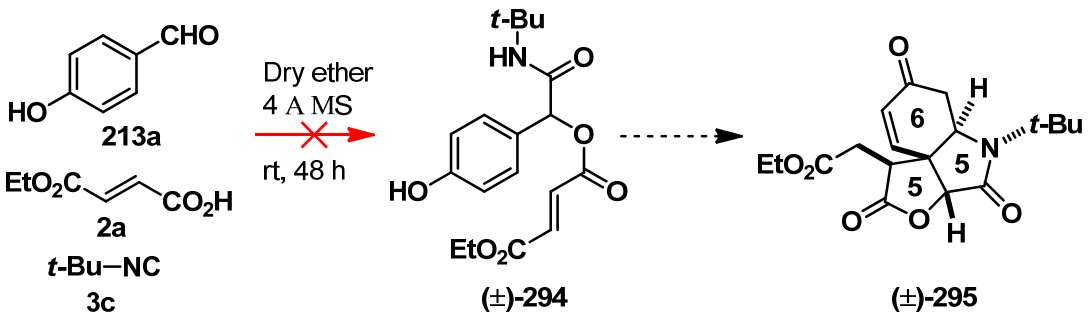
a quantitative yield of **290**. Anhydrous K_2CO_3 mediated elimination of *p*-toluenesulfinate in dry CH_3CN provided the amide **289** in excellent yield.[170] The aza-Baylis-Hillman reaction of methyl vinyl ketone (MVK) with **289** in the presence of 10 mol% PPh_3 catalyst in anhydrous CH_3CN afforded an excellent yield of the desired product **291**. Hydrolysis of the phosphonamide **291** in the presence of conc HCl in methanol, followed by basification provided the amine **1y** in good yield (Scheme 70).[170, 171]

With **1y** in hand, we synthesized acyclic Ugi product **292** employing 4-hydroxy-3-methoxy-benzaldehyde **213b**, *p*-methoxy benzoic acid **2k** and *tert*-butyl isocyanide **3c**. However, when **292** was subjected to previously established microwave irradiation conditions, the desired product was not obtained (Scheme 71).



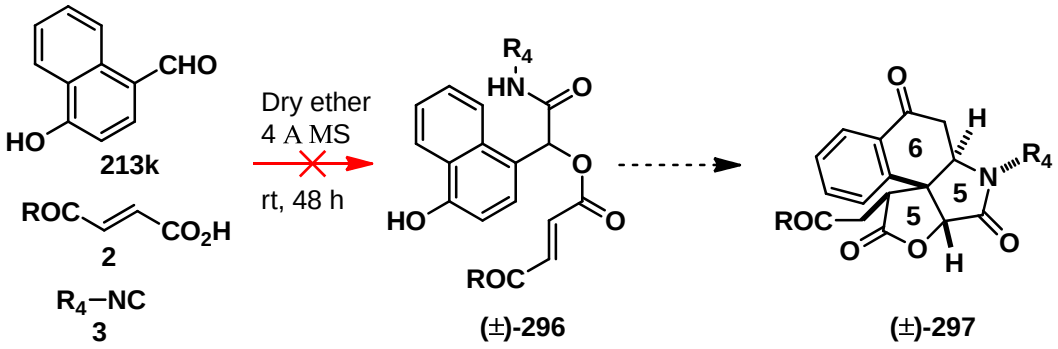
Scheme 71. Alternative route for the synthesis of (+)-Plicamine core.

Next, we focused on applying the Passerini reaction to synthesize acyclic precursors that might lead to the formation of scaffolds similar to Pretazettine and Tazettine. Thus, *p*-hydroxy benzaldehyde **213a**, fumaric acid monoethyl ester **2a** and *tert*-butyl isocyanide **3c** was employed in the P-3CR, however, the desired product **294** was not obtained. Use of other solvents e.g. CH_2Cl_2, THF, PEG-400, H_2O or other isocyanides did not provide a trace of the desired product **294** (Scheme 72).



Scheme 72. Effort toward the synthesis of (±)-**295**

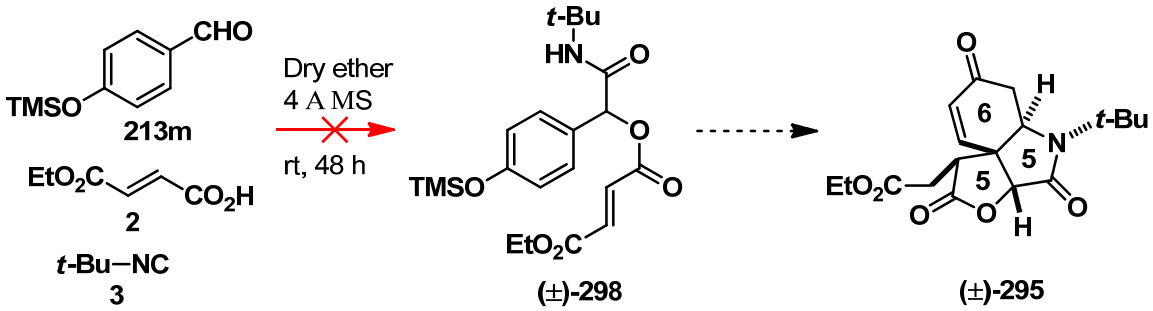
We speculated that the spontaneous reactivity of 4-hydroxy-1-napthadehyde (entry 15-17, Table 23) might help to obtain similar type of P-3CCR product. However, to our disappointment, the desired product **296** was not obtained under any conditions explored (Scheme 73).



Scheme 73. Effort toward the application of P-3CCR for complex molecule synthesis.

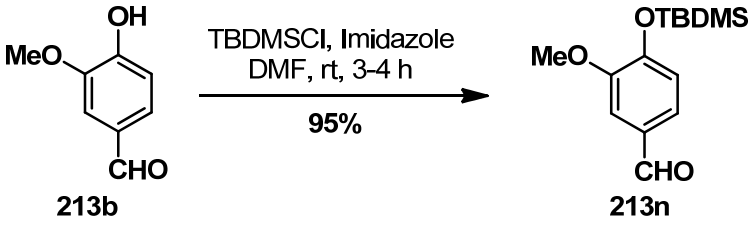
We speculated that the aldehydes (**213a**, **213k**) used in the P-3CCR, were behaving like *para*-substituted nitro-phenols and undergoing a Passerini-Smile (PS-3CCR) type of reaction. Hence, we decided to employ silyl-protected *p*-hydroxy benzaldehyde in the P-3CCR (Scheme 74). Unfortunately, trimethylsilyl (TMS) protected aldehyde **213m** was too unstable under our reaction conditions probably due

the presence of the acid **2a**. Even when we used PEG-400, it did not provide any trace of the desired product **298**.



Scheme 74. TMS-protected aldehyde in the P-3CCR.

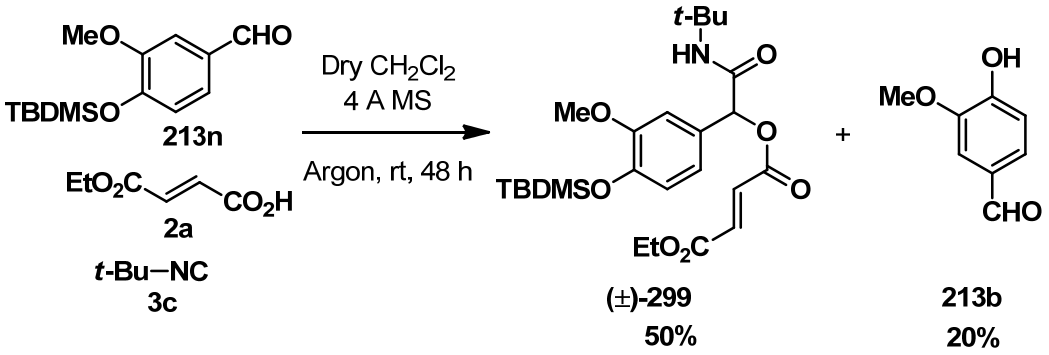
Next, we decided to use a more acid stable silyl protecting group to protect the *p*-hydroxyl group that would be removed under the same reaction conditions in one-pot. Thus, 4-tert-butyldimethylsilyloxy-3-methoxy benzaldehyde **213n** was synthesized from aldehyde **213b** using *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF at room temperature (Scheme 75).[172]



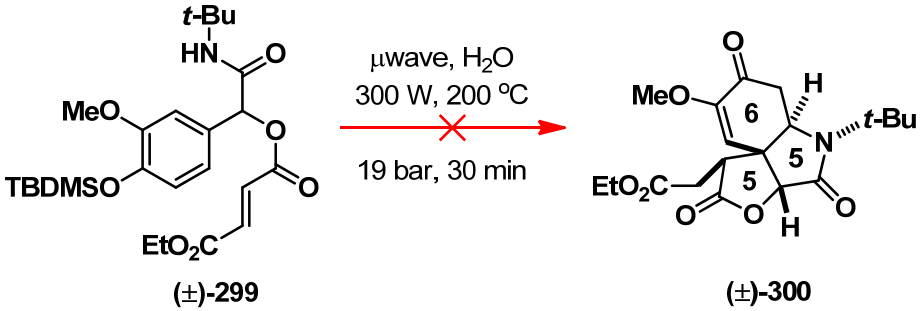
Scheme 75. Synthesis of TBDMS protected aldehyde **213n**.

When the TBDMS protected aldehyde **213n** was employed in the P-3CCR, the expected product **299** was obtained in 50% yield along with 20% of the TBDMS deprotected aldehyde **213b** (Scheme 76). The P-3CCR product **299** was purified via gradient silica gel column chromatography and about 20% of unreacted TBDMS

protected aldehyde **213n** was recovered. Having **299** in hand, we speculated that the TBDMS group would fall off under the microwave reaction conditions and the resulting *p*-hydroxy product would undergo a cascade 5-*exo*-*trig* Michael/5-*exo*-*trig* aza-Michael reaction. However, when prior microwave irradiation conditions were employed the desired product **300** was not obtained and only decomposition was observed (Scheme 77).



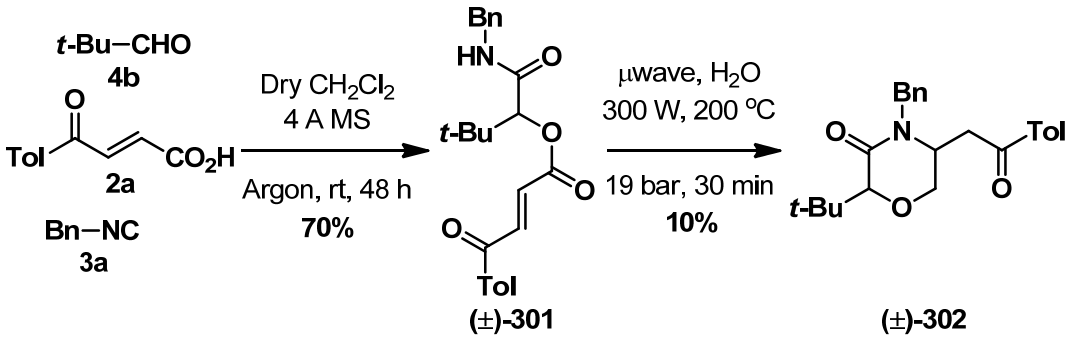
Scheme 76. Synthesis of TBDMS-protected P-3CCR product (±)-**299**.



Scheme 77. Attempted synthesis of compound (±)-**300**.

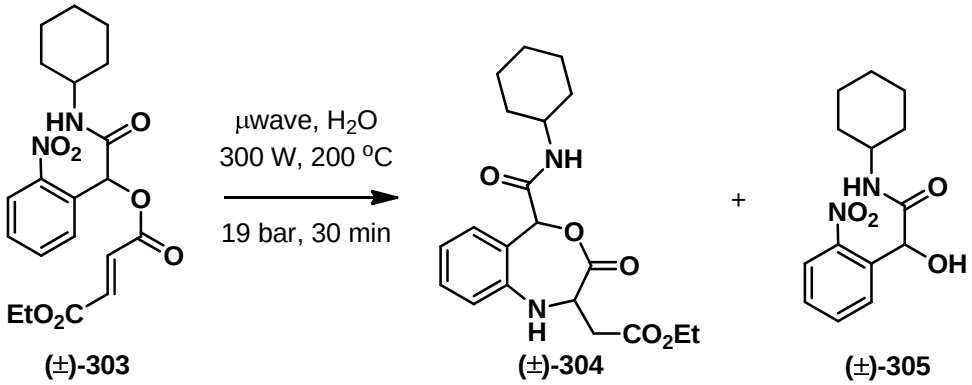
Before trying other conditions and strategies, we decided to examine whether other P-3CCR products were suitable for microwave irradiation and can undergo Michael or aza-Micalel additions. Thus, compound **301** was synthesized via the P-3CCR of isobutyraldehyde **4b**, fumaric acid monoethyl ester **2a** and benzyl isocyanide **3a**. Gratifyingly, when **301** was subjected to microwave irradiation, biologically relevant

morpholin-3-one[173] **302** was obtained in 10% yield (Scheme 78). The low yield could be attributed to the flexible ester bond bearing the Michael acceptor that might not easily come to proximity in the transition state.



Scheme 78. Synthesis of morpholin-3-one via P-3CR and 6-exo aza-Michael reaction.

Furthermore, we examined the utilization of P-3CCR products under our previously established tandem reduction/aza-Michael addition conditions (Table 13, Chapter 2). Thus, we focused on synthesizing benzoxapines[174] via P-3CCR and a 6-*exo*-*trig* aza-Michael reaction. The acyclic P-3CCR product **303** was synthesized from *o*-nitro benzaldehyde **4j**, fumaric acid monoethyl ester **2a** and cyclohexyl isocyanide **3d** in PEG-400 in about 70% yield. However, when our previously established tandem reduction-cyclization conditions were employed, expected product **304** was not obtained, instead deprotected product **305** was isolated (Scheme 79).



Scheme 79. Effort toward the synthesis of benzoxapines.

Hence, it can be concluded that the P-3CCR products are not suitable candidates for microwave irradiation chemistry in water. However, they might be suitable candidates for exploration in other solvents in the presence of additives.

3.1.3. Extension Toward the Synthesis β-Spiro-Indoles and Azaspiro-Fused Polycyclic Indoles

The pharmacophore indole nucleus has been found in many natural products and many of them exhibit wide range of biological activities.[175] Thus, the chemistry of substituted indoles has received wide attention[176] and there is a continuing search for synthetic methods to prepare new types of indoles for screening in medicinal and pharmaceutical programs among scientific community. Due to their role in many cell cycle mechanisms, spiro-indoles and spiro-oxindoles represent very important "privileged" scaffolds among various indole derivatives. Spirotyrptostatins **A 306** which was isolated from *Aspergillus fungigatus*, is known to block cell growth via M-phase specific inhibition and microtubule disassembly.[177] Horsfiline **307** and Elacomine **308** are the simplest oxindole alkaloids that exhibit cell cycle inhibition.[178] Chartellines (**309**, **310**, **311**), isolated from marine bryozoan *Chartella papyracea*[179]; Phalarine (**312**), isolated from *Phalaris coerulescens* (blue canary grass)[180]; Kopsine (**313**), isolated from Malyan *Kopsia fructicosa*[181] also contain embedded spirocyclic indole motifs. Other β-spiroindolenine moieties containing natural products are the Strychnos, Curare, Aspidosperma:[182] (a) Strychnine (**314**), a potent central nervous system stimulant that inhibits inhibitory reflexes;[183] (b) Aspidospermine (**315**), Aspidospermidine (**316**), are respiratory stimulants and exhibit atropine-like activity on smooth muscle;[184] (c) Aspidospermidine (**317**); (d) Toxiferine-I (**318**), has the best potency among curare

alkaloids and causes selective paralysis of motor neuron endplates in skeletal muscle as well as autonomic ganglionic cells.[185] Rhyncophylline (**315**) has been found to cause motor paralysis and inhibition of respiration in mice. In addition, it causes miosis in frogs and hypertension in rabbits (Figure 25).[186]

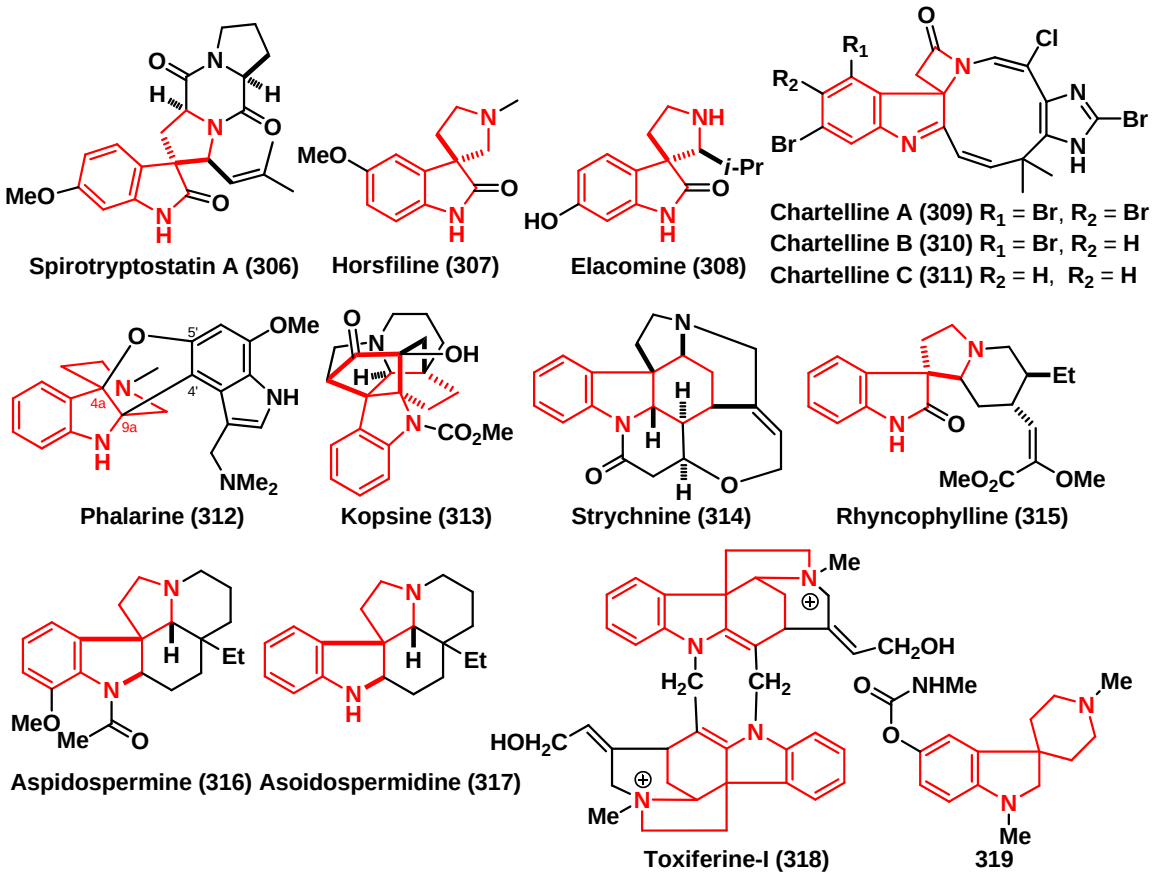
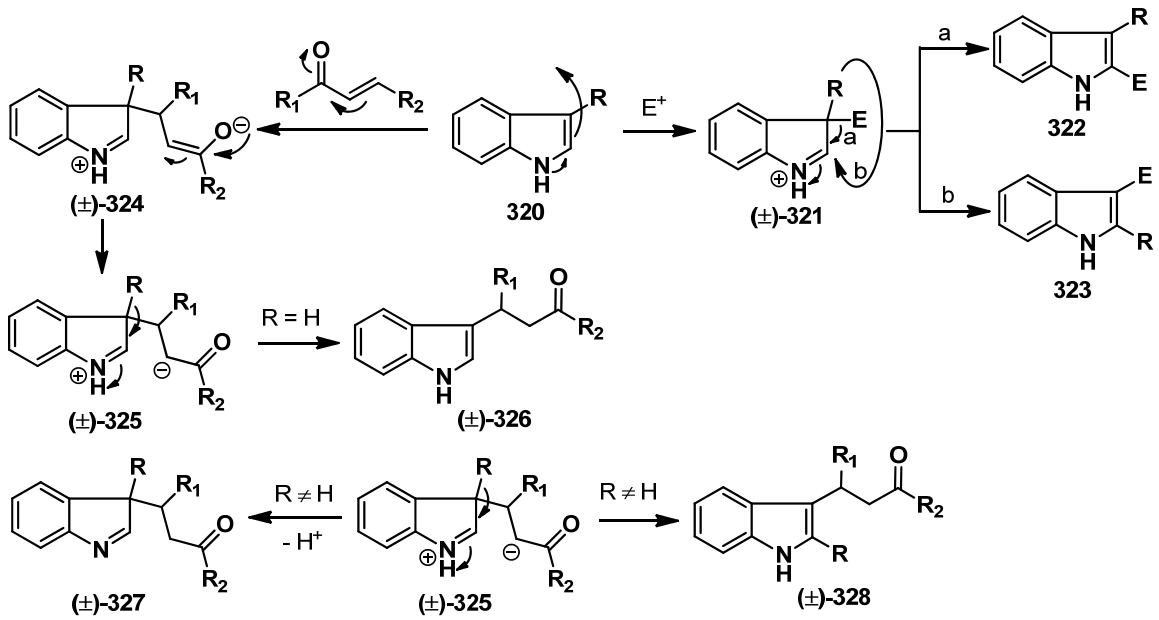


Figure 25. Azaspiro-indole containing natural products.

As a part of our interest in spirocylic motifs, the starting point would be to consider Horsfiline (**307**), Elacomine (**308**) and rhyncophylline (**315**) as they are the structurally simplest members of the β-spiro-indolenine family containing a second basic nitrogen incorporated in the five-membered exocyclic spiro ring. A closely related compound **319** was synthesized[187] as an analog of the reversible cholinesterase inhibitor

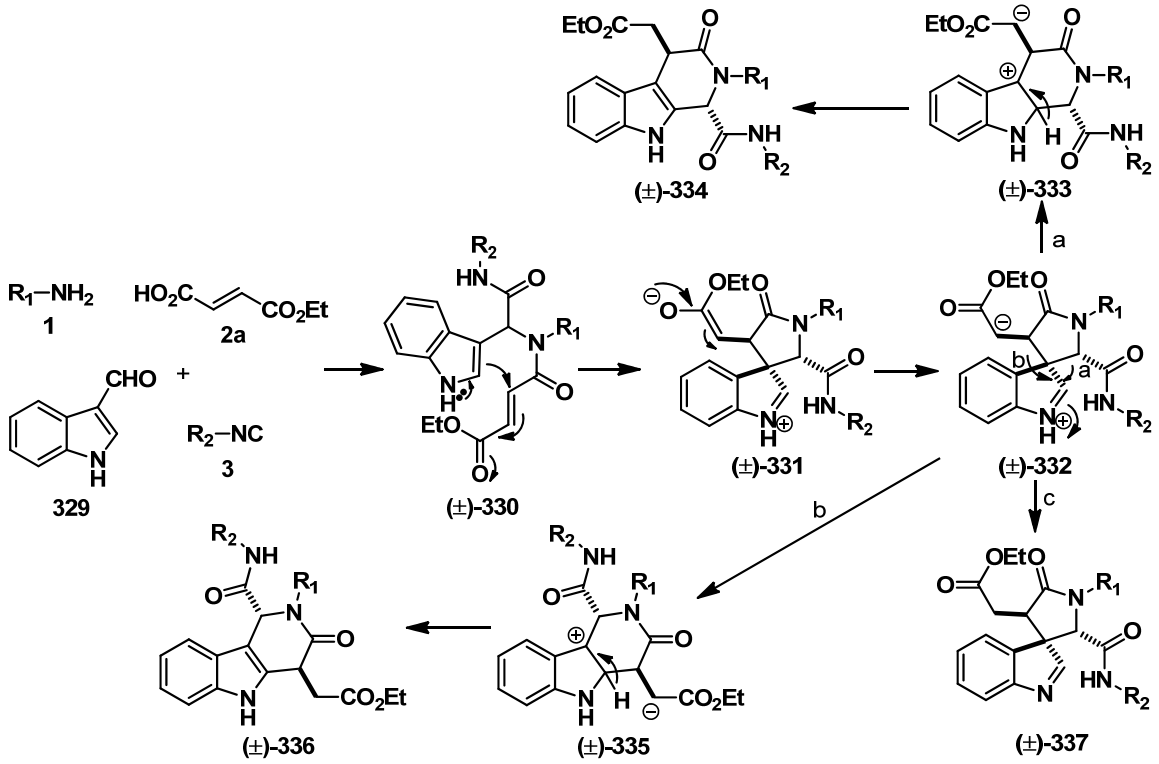
drug physostigmine.[188] Surprisingly, **319** also exhibited cholinesterase-inhibiting properties. However, the observed activity was diminished to some extent (Figure 25).



Scheme 80. Electrophilic substitution and Michael addition reactions of 3-substituted indoles.

It has been reported that indoles can behave like enamines and undergo electrophilic substitution. Furthermore, they are known to undergo Michael addition to electron-deficient alkenes.[189] Typically, electrophilic substitution of 3-substituted indoles involves prior attack at the 3-position to give an indolenine **321** which undergoes rearrangement to the corresponding 2,3-disubstitued indole (Scheme 80). Depending upon the relative migratory aptitude of the substituents (R vs E) at 3-position of **321**, two possible products (**322** or **333**) might form. Michael addition of indole to electron deficient alkene works in a similar way and thus when R = H, it undergoes rearomatization to provide **326**. However, it is not so well known about the fate of the intermediate **325** of the Michael addition of indole to electron deficient alkene when there

is a substituent (R ≠ H) present at the 3-position. Taking consideration of the corresponding electrophilic substitution, two possibilities are : (a) either the R group will migrate to 2-position and rearomatize to provide 2,3-disubstituted indole **327** or (b) it might undergo a deprotonation-protonation process to provide 3,3-disubstituted indolenine **328** (Scheme 80).

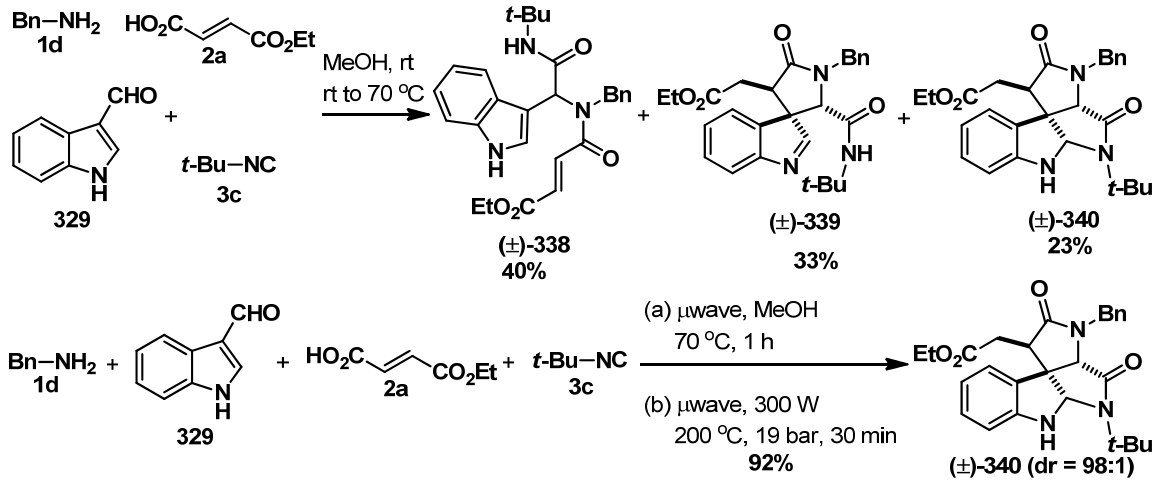


Scheme 81. Speculated pathway of Michael addition of the Ugi product (±)-**330**.

A number of synthetic efforts have been reported[190] for the synthesis of spiro-indoles, many of them involve lengthy processes and use costly reagents. We envisioned that a multicomponent reaction, namely the Ugi four component coupling reaction, involving indole-2-aldehyde **329**, an amine **1**, fumaric acid monoethyl ester **2a** and an isocyanide **3** could provide acyclic Ugi product **330** (Scheme 81) that might undergo 5-*exo-trig* Michael addition either at room temperature or upon heating or under microwave irradiation to provide intermediate **331**. We speculated that **331** might provide β-

carboline-type products (**334** or **336**) via a 1,2-shift[190i, 190k] or β-spiro-indolenine **337** via a deprotonation-protonation process as shown in Scheme 81.

Thus, we elected to use benzylamine (**1d**), indole-2-aldehyde (**329**), furmaric acid monoethyl ester (**2a**) and *tert*-butyl isocyanide (**3c**) in the Ugi reaction. The reaction was allowed to stir at room temperature for 24 h with occasional warming up to 60-70 ^{o}C. TLC and ^{1}H NMR of the crude reaction mixture showed that three distinct compounds are present in the product and separated by gradient column chromatography using silica gel. Further spectroscopic analysis (^{1}H, H-H GDQFCOSY, HMQC, nOe) of the isolated fractions revealed the identity of azaspiro-indolenine **339**[190i, 190n, 190o] and diazaspiro-fused tetracyclic indole **340** as shown in Scheme 82. It is quite noteworthy that **340** resembles the ABCE tetracyclic framework of Strychnos alkaloids.[190p]

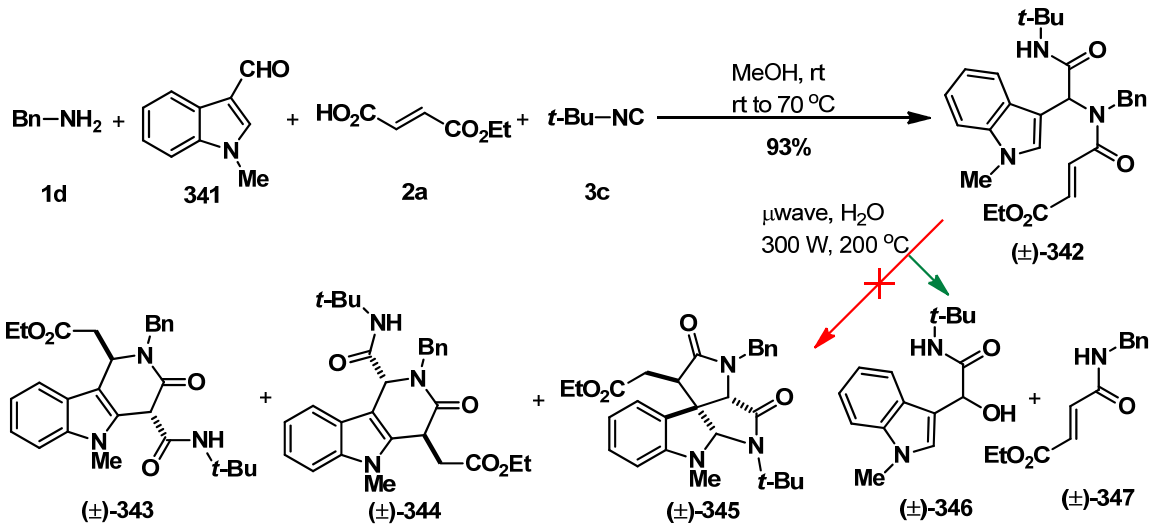


Scheme 82. Synthesis of azaspiroindolenine and diazaspiro-fused poycyclic indoles.

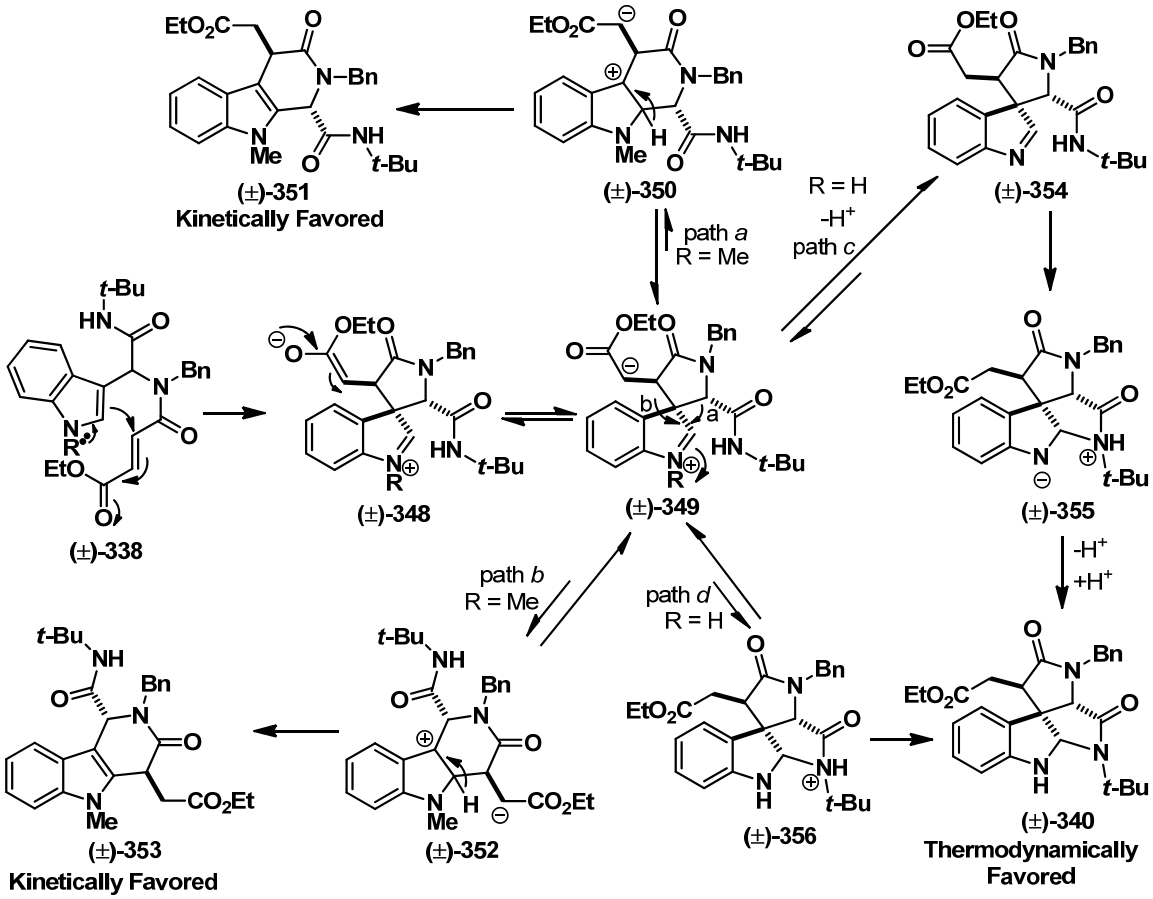
When the crude reaction mixture (containing **338**, **339** and **340**) was irradiated under microwave (300 W, 200 ^{o}C, 19 bar, 30 min), 92% of **340** was obtained as the major product. Moreover, isolated azaspiroindolenine **339** under microwave irradiation gave quantitative yield of **340**. With these results in hand, we decided to run the Ugi reaction

in the presence of microwave irradiation in two stages: (a) stage 1 was run at 70 °C (b) stage 2 was run at 200 °C. To our expectation, the reaction gave an excellent yield (92%) of **340** as a 98:1 mixture of diastereomers (Scheme 82).

Next, we replaced indole-3-aldehyde (**329**) with 1-methyl-indole-3-aldehyde (**341**) in the U-4CCR. We anticipated that the presence of an electron donating methyl group on nitrogen (indole motif) might help to stabilize intermediate **332** that would allow the 1,2-shift to occur. In order to understand this new reaction and compare with the previous reaction conditions, we decided to run the Ugi reaction at room temperature and occasionally warm to 70 °C. To our surprise, the reaction gave only acyclic Ugi product **342** which under microwave irradiation gave no significant amount (or a trace amount) of 1H-pyrido[4,3-b]indole-3-ones (**343** and **344)** and diazaspiro-fused tetracyclic indole **345**. Instead, the reaction gave fragmented products **346** and **347** (Scheme 83) as determined by ^{1}H NMR.



Scheme 83. 1-Methyl-indole-3-aldehyde (**341**) gave Ugi product **342** and did not undergo a μwave-asisted 5-*exo*-*trig* Michael addition.



Scheme 84. Proposed mechanism for the formation of spiro-indolenine and diazaspiro-fused tetracyclic indole.

A probable mechanism which accounts for the formation of azaspiroindolenine **339** and diazaspiro-fused tetracyclic indole **340** is depicted in Scheme 84. 5-*exo*-*trig* Michael addition of 3-substituted indole led to the formation of intermediate **348** which is equilibrium with intermediate **349**. Intermediate **349** might also be in partial equilibrium with **350** and **352** (*pathway a* and *pathway b* respectively). However, 1H-pyrido[4,3-b]indole-3-ones (**351** and **353**) are kinetically controlled products[191] derived from intermediates **350** and **352** respectively. Consequently, at higher temperature (70 ^{o}C to 200 ^{o}C), the equilibrium between **348**, **350** and **352** lies largely in favor of **349**. The presence of electron donating methyl group on indole nitrogen does not help to stabilize

349 and thus the 1,2-shift can not take place. Thus, **349** can undergo a deprotonation-protonation process (pathway C) to form **354** or a competitive intramolecular 5-*exo*-*trig* aza-Michael reaction (pathway D) to form intermediate **356** that leads to the final product **340**.

3.3. Material and Methods

All reagents were purchased from Aldrich unless otherwise noted. 4-Hydroxybezaldehyde, 4-hydroxy-3-methoxybenzaldehyde, 4-hydroxy-3,5-dimethoxybenzaldehyde, 4-hydroxy-3-bromobenzaldehyde, 4-hydroxy-3-methoxy-5-nitrobenzaldehyde and 4-hydroxy-1-napthaldehyde were purchased from Alfa Aesar. 4-Hydroxy-2-methoxybenzaldehyde was purchased from ASDI Product List, and 4-hydroxy-2,6-dimethoxybenzaldehyde was purchased from Frinton Labs. 4-Hydroxy-2-nitrobenzaldehyde was purchased from TCI America. 4-Hydroxy-2-fluorobenzaldehyde was purchased from Matrix Scientific. *tert*-Butyl isocyanide was purchased from TCI America. 1-Adamantyl isocyanide was synthesized following a precedented literature procedure (*Org. Lett.* **2003**, *5*, 901-904). Sodium *p*-toluenesulfinate and methyl vinyl ketone (MVK) were purchased from Alfa Aesar. Except as otherwise indicated, reactions were carried out under argon. Microwave reactions were conducted using a capped vial on CEM Discover System. All reactions were monitored by thin layer chromatography using 0.25 mm Dynamic Adsorbents, L.L.C. precoated silica gel (particle size 0.03-0.07 mm, catalog no. 84111). Column chromatography was performed using Whatman Purasil 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise noted. Diastereomeric ratios were determined from ^{1}H NMR spectra of non-purified reaction mixtures. Proton and

carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Unity 500 and Varian 500 Direct Drive System spectrometers. The residual $CDCl_3$ singlet at δ 7.26 ppm and δ 77 ppm were used as the standard for ^{1}H NMR and ^{13}C NMR spectra respectively. Mass spectra were recorded on Micromass GCT at 70 eV.

3.3.1. General Procedure 1 – Commencing with four distinct Ugi substrates

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, benzylamine (15 mg, 0.14 mmol), 4-hydroxybenzaldehyde(12 mg, 0.14 mmol), fumaric acid monoethyl ester (25 mg, 0.14 mmol)and *tert*-butyl isocyanide (17 μL, 0.14 mmol) were added sequentially to a mixture of 1.5 mL LiCl (1 M) and 1 mL MeOH or 2.5 mL distilled water with a pH of 7.0. The vial was capped according to manufacturer instructions and placed in the single-mode microwave cavity. Then the microwave was run at two stages: (a) 1 hr at 50 ^{o}C, 10 Bar and 300 W (b) 25-30 min, 190 ^{o}C, 18.5 Bar and 300 W. After allowing the vial to cool to room temperature, ethyl acetate (3 mL) was added and the 10 mL vial was shaken vigorously. The organic layer was separated using a separatory funnel and the aqueous layer was extracted with ethyl acetate (2 x 2 mL). The organic layers were combined and washed with $NaHCO_3$ (2 x 3 mL), 1N HCl (2 x 3 mL) and brine (2 x 3 mL). The organic layer was separated. All aqueous layers were combined and extracted one final time with ethyl acetate (3 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified by gradient silica gel column chromatography using a mixture of ethyl acetate and hexane (1:5 to 1:1) as the eluent.

3.3.2. General Procedure 2 – Commencing from pre-formed acyclic Ugi product

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, 50 mg of acyclic Ugi product was taken-up in 2.5 mL of distilled water with a pH of 7.0. The vial was capped according to manufacturer's instructions and placed in the single-mode microwave cavity. The microwave was run for 25-30 min at 190 ^{o}C, 18.5 Bar and 300 W. After allowing the vial to cool to room temperature, ethyl acetate (3 mL) was added and the 10 mL vial was shaken vigorously. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 2 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified using gradient silica gel column chromatography employing a mixture of ethyl acetate and hexane (1:5 to 1:2) as the eluent.

3.3.3. General procedure for sealed tube reaction:

To a 20 mL sealed tube equipped with a magnetic stir bar, benzylamine (15 mg, 0.14 mmol), 4-hydroxybenzaldehyde (12 mg, 0.14 mmol), fumaric acid monoethyl ester (25 mg, 0.14 mmol) and 17 μL (0.14 mmol) of *tert*-butyl isocyanide (17 μL, 0.14 mmol) were added sequentially to a mixture of 1.5 mL LiCl (1 M) and 1 mL MeOH or 2.5 mL distilled water with a pH of 7.0.. The sealed tube was placed in a silicone-based oil bath and heated at 70 ^{o}C for one hour and then at 190 ^{o}C for 2-12 h. The sealed tube was then cooled to room temperature and filtered through a pad of celite (Aldrich) and washed with ethyl acetate (3 x 5 mL) followed by saturated $NaHCO_3$ (5 mL). The filtrate was then transferred to a separatory funnel and the mixture was shaken vigorously. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x

2.5 mL). The organic layers were combined, dried with Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and the residue was purified using gradient silica gel column chromatography employing a mixture of ethyl acetate and hexane (1:5 to 1:1) as the eluent.

3.3.4. Synthesis of Isocyanide 3i:

To a 100 mL oven dried round bottom (RB) flask conataining magnetic stirrer under Argon, 5 g (33.04 mmol) of 1-adamantamine was taken. 66 mL of Ethyl formate followed by 22 mL of DMSO were added to the flask and a condenser was attached to the flask. The mixture was then refluxed at 100 ^oC for 24 h and excess ethyl formate was removed on a rotary evaporator. Ice-cold water was added to the residue and resulting solid was filtered. Next, the solid was dissolved in dichloromethane and anhydrous sodium sulfate was added to remove traces of water. The dichloromethane solution was concentrated over rotavap to obtain the crude formamide (4.7 g, 79%). The crude formamide was pure enough (confimed from ^1H NMR) and used directly for the next step without further purification.

The crude *N*-1-adamantyl formamide (4.7 g, 26.3 mmol) was dried under high vacuum for overnight and kept under Argon. Magnetic stir bar was added to the flask and the solid was dissolved in dichloromethane. After the solution was cooled to -40 ^oC, phosphoroyl chloride ($POCl_3$, 9.16 g, 78.7 mmol) was added slowly. To the resulting mixture, triethylamine (Et_3N, 32.9 mL, 236.2 mmol) was added very slowly (caution: generates heat!!!). The solution was then allowed to reach room temperature and stirred for 24 h. The mixture was then poured slowly into ice-cold water (300 mL) and the entire mixture was transferred to a separatory funnel. The organic layer was separated and aqueous layer was washed with dichloromethane (25 mL × 2). The organic layers

were combined, washed with saturated $NaHCO_3$, dried over sodium sulfate and concentrated over rotavap to obtain **3i** as a brownish-yellow solid. The crude **3i** was then purified via column chromatography using silica gel as the stationary phase and dichloromethane to obtain pure isocyanide **3i** (2.7 g, 58%).

3.3.5. Synthesis of amine 1y:

Commercially available sodium *p*-toluenesulfenate (5 g, 20 mmol) was dissolved in water (25.5 mL) and methyl *tert*-butyl ether (MTBE, 25.5 mL) was added to the mixture. Next, concentrated HCl (1.8 mL) was added dropwise to the mixture and stirred for 10 min at room temperature. The mixture was transferred to a separatory funnel and the aqueous layer was separated. The aqueous layer was washed with MTBE (10 mL × 2) and the organic layers were combined. The organic layer was dried over sodium sulfate and concentrated on rotavap to obtain *p*-toluenesulfinic acid as a white solid (4.3 g) which was further dried overnight under high vacuum.

To a 100 mL oven dried RB flask equipped with magnetic stir bar, 0.5 g (2.3 mmol) of *N*,*N*,-diphenyl-phosphinic amide (**288**) was taken under Argon. Then 19 mL of diethyl ether and 4 mL of dichloromethane were added to the flask. To the mixture, 0.35 mL (3.5 mmol) of benzaldehyde was added slowly followed by *p*-Toluenesulfinic acid (0.54 g, 3.5 mmol) in one portion. The resulting solution was stirred at room temperature for 48 h, after which white precipitates were formed. The reaction mixture was filtered over buckner funnel and the solid was washed with diethyl ether. The white solid (**289**, 1.09 g) was further dried overnight under high vacuum.

289 and anhydrous K_2CO_3 were taken in a oven-dried RB flask under Argon. Then anhydrous acetonitrile (CH_3CN) was added to the flask and the resulting mixture was stirred at room temperature for 12-24 h. After TLC showed complete conversion,

the reaction mixture was filtered thourgh a buckner funnel and the residue was washed with CH_3CN (25 mL × 2). The filtrate was concentrated on rotavap to obtain **290** as a while solid (0.67 g, 90%).

Imine **290** (0.42 g, 1.38 mmol) was taken in a oven-dried RB flask and dried further under high vacuum. The flask was capped with a rubber septum and purged with for 5 min. Tripehnyl phosphine (PPh_3, 73 mg, 0.28 mmol) was added to the flask along with a steady stream of Argon was purged again. The flask was capped well, wrapped well parafilm and anhydrous CH_3CN (28 mL) was added at room temperature. Methyl vinyl ketone (MVK, 0.12 g, 1.7 mmol) was added slowly to the solution and the reaction was stirred at room temperature for 48-96 h after which TLC showed complete consumption of imine **290**. The reaction mixture was transferred into a separatory funnel and washed with water (25 mL × 2). The crude product was then extracted with dichloromethane (25 mL × 2), dried over Na_2SO_4 and concentrated on rotavap. Pure product **291** was obtained via gradient column chromatography using silica gel as the stationary phase and a mixture of ethyl acetate-hexane (1:2 to 3:1) as the mobile phase.

Methanol (9.2 mL) was added to 291 (0.41 g, 1.1 mmol, taken in a RB flask. To the solution, conc. HCl (2.1 mL) was dropwise and the resulting mixture stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the crude amine 1y was purified via gradient column chromatography using silica gel as the stationary phase and ethyl acetate-hexane (1:4 to 2:1) followed by dichloromethane-methanol (10:1 to 1:5) mixtures as the mobile phase.

3.3.6. Synthesis of the aldehyde 213n:

3-Methoxy-4-hydroxybenzaldehyde (0.5 g, 3.3 mmol) was taken in dry RB flask and anhydrous DMF (2.5 mL) was added. The mixture was then stirred to dissolve the

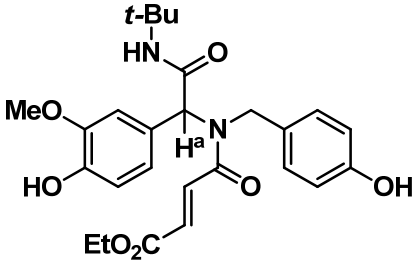
aldehyde and imidazole (0.67 g, 9.9 mmol) was added to the mixture at room tempertaure. After stirring for 5 minutes, *tert*-butyldimethylsilyl chloride (TBDMSCl, 0.79 g, 5.3 mmol) and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was then diluted with diethyl ether (5 mL) and washed with water (50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated on rotavap. The crude product was purified via gradient column chromatography using silica gel as the stationary phase and mixture of ethyl acetate/hexane (1:5 to 1:2) as the mobile phase to afford TBDMS protected aldehyde **213n** in 95% yield.

3.3.7. General procedure for Passerini reaction:

4 Å molecular sieves (MS) was dried in oven for 24 h and then further dried under high vacuum with heating by a heat gun for 1 h. After cooling, the MS (0.1 g) was transferred into a dry RB flask equipped with magnetic stir bar under Argon. 213n (0.15 g, 0.57 mmol) was added to the flask and dissolved in anhydrous CH_2Cl_2 (3 mL). Then fumaric monoethyl ester (**2a**, 0.083 g, 0.57 mmol) was added followed by *tert*-butyl isocyanide (0.05 mL, 0.57 mmol). The resulting mixture was stirred at room temperature for 48 h under Argon and then TLC showed 70% conversion. The reaction was diluted with CH_2Cl_2 (3 mL) and quenched by the addition of 1 N HCl (4 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated on rotavap. Purification of the crude product via gradient column chromatography using silica gel as the stationary phase and mixture of ethyl acetate/hexane (1:5 to 1:1) as the mobile phase provided 50% of **299**.

3.4. Experimental Data

1. **(*E*)-Ethyl 4-((2-(*tert*-butylamino)-1-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl)(4-hydroxybenzyl)amino)-4-oxobut-2-enoate**



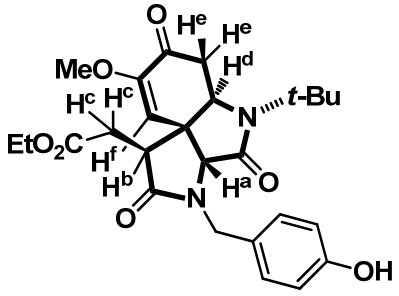
(±)-**214**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, 1 H, *J* = 15.2 Hz, -C<u>H</u>=CH-), 6.72-6.88 (m, 6 H, Aryl and –CH=C<u>H</u>- overlap), 6.62 (d, 2 H, *J* = 8.2 Hz, Aryl), 5.73 (s, 1 H, H^a), 5.64 (br s, 1 H, -O<u>H</u>), 4.70 (d, 1 H, *J* = 17.4 Hz, -NC<u>H</u>$_2$Ar), 4.49 (d, 1 H, *J* = 17.1 Hz, -NC<u>H</u>$_2$Ar), 4.18 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.72 (s, 3 H, O<u>Me</u>), 1.33 (s, 9 H, *t*-Bu), 1.26 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 166.4, 165.4, 156.9, 146.4, 146.1, 137.6, 134.6, 134.1, 132.4, 128.3, 127.1, 126.2, 126.0, 123.2, 115.4, 112.6, 62.9, 61.0, 55.8, 51.7, 49.6, 28.6, 14.1.

HRMS (EIMS): calcd for $C_{26}H_{32}N_2O_7$ 484.2210, found 484.2223.

2. **Ethyl 2-((1S,5aR)-5-(*tert*-butyl)-3-(4-hydroxybenzyl)-8-methoxy-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



(±)-**215**

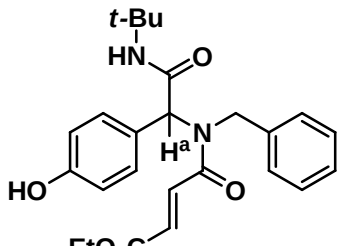
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, 1H, *J* = 8.9 Hz, Aryl), 6.76 (d, 1H, *J* = 8.1 Hz, Aryl), 5.15 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>$_2$Ph), 5.11 (s, 1H, H^f), 4.84 (br s, 1H, -O<u>H</u>), 4.48 (dd,

1H, J = 11.4, 4.9 Hz; H^d), 4.26 (s, 1H, J = 14.6 Hz, -C$\underline{H}_2$Ph), 4.08 (q, 2H, J = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 3.81 (s, 1H, H^a), 3.50 (s, 3H, -OMe), 3.27 (dd, 1H, J = 10.4, 3.2 Hz; H^b), 3.10 (dd, 1H, J = 17.6, 3.2 Hz; H^e), 3.03 (dd, 1H, J = 15.2, 6.0 Hz; H^c), 2.44 (dd, 1H, J = 17.6, 10.4 Hz; H^e), 2.42 (dd, 1H, J = 15.2, 2.8 Hz; H^c), 1.46 (s, 9H, ^{t}Bu), 1.20 (t, 3H, J = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 172.0, 171.9, 169.6, 156.1, 151.3, 130.0, 128.9, 126.8, 119.9, 115.7, 115.4, 114.5, 109.4, 109.3, 74.1, 63.8, 61.3, 56.7, 55.8, 55.5, 55.2, 46.5, 45.6, 45.3, 30.7, 28.6, 27.9, 14.

HRMS (EIMS): calcd for $C_{26}H_{32}N_2O_7$ 484.2210, found 484.2216.

3. **(*E*)-Ethyl 4-(benzyl(2-(*tert*-butylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



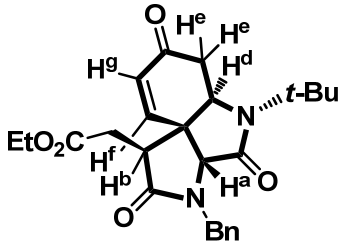
(±)-**219**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, 1H, J = 16.0 Hz, -C$\underline{H}$=CH-), 7.07-7.17 (m, 5H, Ph), 6.9 (d, 2H, J = 6.7 Hz, Aryl), 6.79 (d, 1H, J = 15.3 Hz, -CH=C$\underline{H}$-), 6.58 (d, 2H, J = 8.5 Hz, Aryl), 5.82 (s, 1H, H^a), 5.74 (br s, 1H, -N$\underline{H}$), 4.78 (d, 1H, J = 17.7 Hz, -C$\underline{H}_2$Ph), 4.57 (d, 1H, J = 17.7 Hz, -C$\underline{H}_2$Ph), 4.16 (q, 2H, J = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 1.31 (s, 9H, ^{t}Bu), 1.24 (-OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 166.5, 165.4, 156.7, 137.2, 134.0, 132.3, 131.3, 128.4, 127.2, 126.3, 125.6, 115.8, 63.2, 61.1, 51.9, 49.8, 28.6, 14.1.

HRMS (EIMS): calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2163.

4. **Ethyl 2-((1S,5aR)-3-benzyl-5-(*tert*-butyl)-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



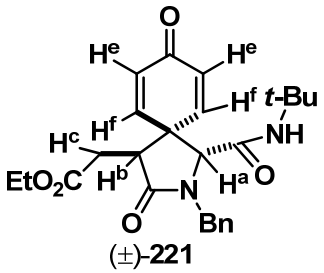
(±)-**220**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-7.38 (m, 5H, Ph), 6.43 (d, 1H, *J* = 10.5 Hz, H^g), 6.09 (d, 1H, *J* = 10.5 Hz, H^f), 5.26 (d, 1H, *J* = 15.4 Hz, -C$\underline{H}_2$Ph), 4.58 (dd, 1H, *J* = 11.0, 5.7 Hz; H^d), 4.41 (d, 1H, *J* = 14.6 Hz, -C$\underline{H}_2$Ph), 4.11 (q, 2H, *J* = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 3.7 (s, 1H, H^a), 3.29 (dd, 1H, *J* = 10.5, 3.2 Hz; H^b), 3.16 (dd, 1H, *J* = 17.8, 3.2 Hz; H^e), 2.97 (dd, 1H, *J* = 15.4, 5.7 Hz; H^c), 2.43 (dd, 1H, *J* = 17.8, 10.5 Hz; H^e), 2.29 (dd, 1H, *J* = 15.4, 11.4 Hz; H^c), 1.48 (s, 9H, ^{t}Bu), 1.22 (t, 3H, *J* = 7.3 Hz, -OCH$_2$CH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 171.8, 171.7, 169.0, 143.4, 135.3, 132.3, 132.3, 130.2, 128.9, 128.5, 128.0, 62.5, 61.3, 57.3, 55.5, 45.9, 45.8, 45.5, 45.1, 30.7, 27.9, 14.1.

HRMS (EIMS): calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2154.

5. **Ethyl 2-((1R,4S)-2-benzyl-1-(*tert*-butylcarbamoyl)-3,8-dioxo-2-azaspiro[4.5]deca-6,9-dien-4-yl)acetate**



(±)-**221**

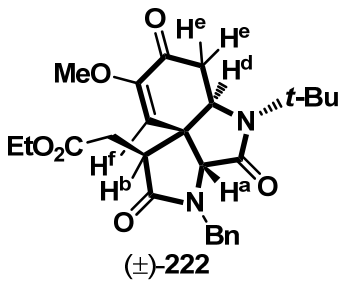
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.36 (m, 4H, Ph), 7.22-7.26 (m, 1H, Ph), 6.84 (dd, 1H, *J* = 10.5, 3.24 Hz, H^e), 6.55 (dd, 1H, *J* = 10.5, 3.24 Hz; H^e), 6.29 (dd, 1H, *J* = 10.5,

1.6 Hz; H^f), 6.23 (dd, 1H, *J* = 9.7, 1.6 Hz, H^f), 5.5 (s, 1H, -N<u>H</u>), 5.05 (d, 1H, *J* = 14.6 Hz; *J* = 14.6Hz, -C<u>H</u>$_2$Ph), 4.02-4.11 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 3.92 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>$_2$Ph), 3.74 (dd, 1H, *J* = 8.9, 5.7 Hz; H^b), 3.30 (s, 1H, H^a), 2.75 (dd, 1H, *J* = 17.0, 5.7 Hz; H^c), 2.12 (dd, 1H, *J* = 16.2, 8.9 Hz; H^c), 1.31 (s, 9H, ^{t}Bu), 1.19 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7, 176.9, 170.9, 165.9, 147.4, 146.4, 135.7, 131.3, 130.5, 129.0, 128.8, 65.5, 60.9, 52.4, 48.0, 46.6, 45.5, 42.4, 30.8, 28.2, 14.0.

HRMS (EIMS): calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2162.

6. **Ethyl 2-((1S,5aR)-3-benzyl-5-(*tert*-butyl)-8-methoxy-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



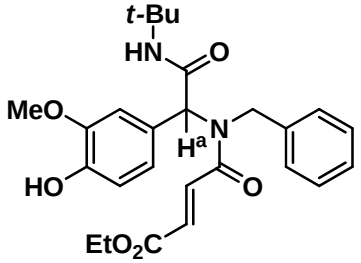
(±)-**222**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22-7.38 (m, 5H, Ph), 5.28 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>$_2$Ph), 5.15 (s, 1H, H^f), 4.50 (dd, 1H, *J* = 12.2, 5.7 Hz, H^d), 4.38 (d, 1H, *J* = 14.6 Hz, -C<u>H</u>$_2$Ph), 4.10 (q, 2H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.53 (s, 1H, H^a), 3.29 (dd, 1H, *J* = 10.5, 3.2 Hz; H^b), 3.14 (dd, 1H, *J* = 17.8, 3.2 Hz; H^e), 3.05 (dd, 1H, *J* = 15.4, 5.7 Hz; H^c), 2.47 (dd, 1H, *J* = 17.8, 10.5 Hz; H^e), 2.41 (dd, 1H, *J* = 15.4, 7.3 Hz; H^c), 1.47 (s, 9H, ^{t}Bu), 1.22 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 171.9, 169.4, 151.3, 135.6, 128.6, 128.5, 128.1, 109.5, 63.8, 61.3, 56.6, 55.4, 55.2, 46.5, 45.8, 45.5, 45.4, 30.8, 28.2, 27.9, 14.1.

HRMS (EIMS): calcd for $C_{26}H_{32}N_2O_6$ 468.2260, found 468.2272.

7. **(*E*)-Ethyl 4-(benzyl(2-(*tert*-butylamino)-1-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



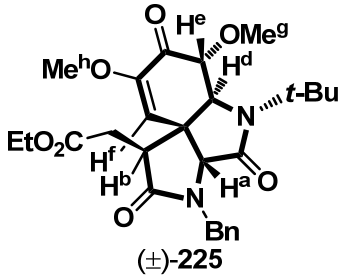
(±)-**224**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, 1H, *J* = 15.3 Hz, -C<u>H</u>=CH-), 7.09-7.17 (m, 3H, Aryl), 6.70-6.94 (m, 6H, -CH=C<u>H</u>- and Aryl overlap), 5.88 (s, 1H, H^a), 5.60 (br s, 1H, -O<u>H</u>), 4.80 (d, 1H, *J* = 17.7 Hz, -C<u>H</u>$_2$Ph), 4.6 (d, 1H, *J* = 17.7 Hz, -C<u>H</u>$_2$Ph), 4.16 (q, 2H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.68 (s, 3H, -OMe), 1.34 (s, 9H, ^{t}Bu), 1.24 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 166.4, 165.4, 146.4, 146.1, 137.6, 134.6, 134.1, 132.4, 128.3, 127.1, 126.2, 126.0, 123.2, 114.4, 112.6, 62.9, 61.0, 55.8, 51.7, 49.6, 28.6, 14.1.

HRMS (EIMS): calcd for $C_{26}H_{32}N_2O_6$ 468.2260, found 468.2256.

8. **Ethyl 2-((1S,5aS,6S)-3-benzyl-5-(*tert*-butyl)-6,8-dimethoxy-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



(±)-**225**

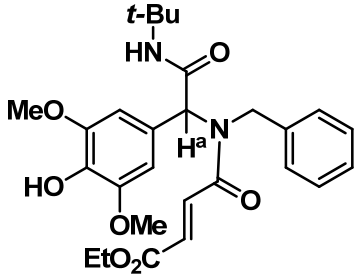
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.38 (m, 5H, Ph), 5.78 (d, 1H, *J* = 2.4 Hz, H^e), 5.52 (s, 1H, H^f), 5.40 (d, 1H, *J* = 1.5 Hz, H^d), 3.97-4.08 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 3.83 (d, 1H, *J* =

14.9 Hz, -C<u>H</u>$_2$Ph), 3.81 (t from dd overlap, 1H, J = 5.7 Hz, H^b), 3.64 (s, 3H, -OMe^h), 3.45 (s, 3H, -OMe^g), 3.27 (s, 1H, H^a), 2.69 (dd, 1H, J = 16.6, 4.9 Hz, H^c), 2.08 (dd, 1H, J = 16.6, 8.9 Hz; H^c), 1.35 (s, 9H, ^{t}Bu), 1.17 (t, 3H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 171.3, 166.6, 152.0, 151.7, 135.5, 129.0, 128.8, 128.4, 114.5, 113.7, 66.8, 60.9, 55.3, 55.2, 52.4, 47.2, 46.4, 30.6, 28.7, 13.9.

HRMS (EIMS): calcd for $C_{27}H_{34}N_2O_7$ 498.2366, found 498.2372.

9. **(*E*)-Ethyl 4-(benzyl(2-(*tert*-butylamino)-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



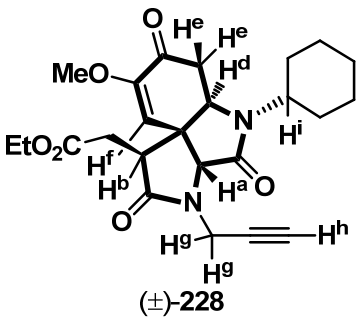
(±)-**227**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 1H, J = 14.6 Hz, -C<u>H</u>=CH-), 7.08-7.19 (m, 3H, Ph), 6.89-6.97 (m, 2H, Ph), 6.86 (d, 1H, CH=C<u>H</u>-), 6.50 (s, 2H, Aryl), 6.32 (br s, 1H, -N<u>H</u>), 5.58 (s, 1H, H^a), 5.52 (br s, 1H, -O<u>H</u>), 4.80 (d, 1H, J = 17.4 Hz, -C<u>H</u>$_2$Ph), 4.61 (d, 1H, J = 17.4 Hz, -C<u>H</u>$_2$Ph), 4.16 (q, 2H, J = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.69 (s, 6H, 2 –OMe), 1.34 (s, 9H, ^{t}Bu), 1.23 (t, 3H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 166.3, 165.3, 146.9, 137.6, 134.9, 133.9, 132.4, 128.3, 127.0, 126.1, 124.9, 106.9, 62.9, 61.0, 56.1, 51.7, 49.5, 28.5, 14.

HRMS (EIMS): calcd for $C_{27}H_{34}N_2O_7$ 498.2366, found 498.2376.

10. **Ethyl 2-((1S,5aR)-5-cyclohexyl-8-methoxy-2,4,7-trioxo-3-(prop-2-yn-1-yl)-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



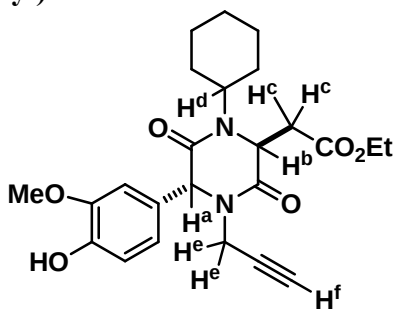
(±)-**228**

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (s, 1H, H^f), 4.77 (dd, 1H, *J* = 17.4, 2.5 Hz; H^g), 4.43 (dd, 1H, *J* = 11.6, 5.8 Hz, H^d), 4.28 (s, 1H, H^a), 4.18 (dd, 1H, *J* = 17.4, 1.5 Hz; H^g), 4.09 (q, 2H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.80-3.90 (m, 1H, H^i), 3.65 (s, 3H, -OMe), 3.12 (dd, 1H, *J* = 10.1, 4.0 Hz; H^b), 3.11 (dd, 1H, *J* = 15.6, 5.8 Hz; H^e), 3.04 (dd, 1H, *J* = 17.8, 4.0 Hz; H^c), 2.58 (dd, 1H, *J* = 15.6, 11.6 Hz; H^e), 2.44 (dd, 1H, *J* = 17.8, 11.0 Hz; H^c), 2.28 (t, 1H, *J* = 2.54 Hz, H^h), 1.54-1.92 (m, 5H, Cy), 1.30-1.42 (m, 4H, Cy), 1.21 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.08-1.19 (m, 1H, Cy).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.9, 171.6, 171.1, 168.7, 151.6, 109.2, 72.9, 63.7, 61.3, 55.9, 55.5, 52.9, 46.8, 46.0, 44.9, 32.0, 30.9, 30.1, 25.7, 25.6, 25.2, 14.1.

HRMS (EIMS): calcd for $C_{32}H_{30}N_2O_6$ 538.2104, found 538.2109.

11. **Ethyl 2-((2S,5R)-1-cyclohexyl-5-(4-hydroxy-3-methoxyphenyl)-3,6-dioxo-4-(prop-2-yn-1-yl)piperazin-2-yl)acetate**



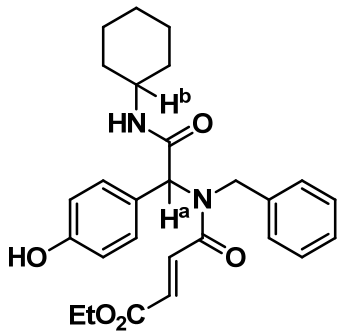
(±)-**229**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (d, 1H, *J* = 7.6 Hz, Aryl), 6.81 (s, 1H, Aryl), 6.80 (d, 1H, *J* = 7.6 Hz, Aryl), 5.71 (s, 1H, -O<u>H</u>), 5.22 (s, 1H, H^a), 4.75 (dd, 1H, *J* = 17.1, 2.5; H^e), 4.37 (dd, 1H, *J* = 8.2, 5.5 Hz; H^b), 4.18 (q, 2H, *J* = 7.3 Hz, -OC<u>H_2</u>CH_3), 3.88 (s, 3H, -OMe), 3.44-3.53 (m, 1H, H^d), 3.29 (dd, 2H, *J* = 17.1, 2.5 Hz; H^e and H^c overlap), 2.95 (dd, 1H, *J* = 17.4, 5.5, H^c), 2.21 (t, 1H, *J* = 2.5 Hz, H^f), 1.91-2.03 (m, 1H, Cy), 1.57-1.87 (m, 8H, Cy), 1.26 (t, 3H, *J* = 7.3 Hz, -OCH_2C<u>H_3</u>), 1.02-1.17 (m, 1H, Cy).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 166.1, 165.7, 146.8, 146.0, 128.7, 120.8, 114.8, 110.7, 76.8, 72.4, 63.4, 61.2, 58.7, 55.9, 55.8, 37.6, 33.5, 30.0, 29.8, 26.1, 26.0, 25.3, 14.2.

HRMS (EIMS): calcd for $C_{32}H_{30}N_2O_6$ 538.2104, found 538.2109.

12. **(*E*)-Ethyl 4-(benzyl(2-(cyclohexylamino)-1-(4-hydroxyphenyl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



(±)-**229a**

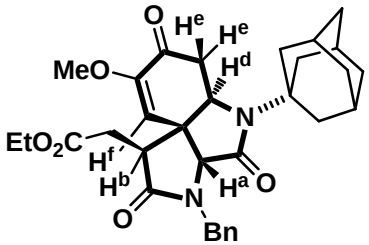
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, 1H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 7.07-7.17 (m, 5H, Ph), 6.96 (d, 2H, *J* = 7.3 Hz, Aryl), 6.78 (d, 1H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.68 (d, 2H, *J* = 8.3 Hz, Aryl), 5.84 (br s, 1H, -O<u>H</u>), 5.80 (s, 1H, H^a), 4.77 (d, 1H, *J* = 17.8 Hz, -C<u>H_2</u>Ph), 4.56 (d, 1H, *J* = 17.8 Hz, -C<u>H_2</u>Ph), 4.16 (q, 2H, *J* = 7.3 Hz, -OC<u>H_2</u>CH_3), 3.69-3.82 (m,

1H, H^h), 1.80-1.92 (m, 2H, Cy), 1.50-1.68 (m, 3H, Cy), 1.25-1.37 (m, 2H, Cy), 1.24 (t, 3H, J = 7.3 Hz, -$OCH_2C\underline{H}_3$), 0.98-1.14 (m , 3H, Cy)

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 166.4, 165.9, 137.0, 134.0, 132.2, 131.2, 128.5, 127.3, 126.3, 125.4, 115.8, 63.1, 61.1, 49.9, 48.8, 32.6, 25.4, 24.7, 24.6, 14.

HRMS (EIMS): calcd for $C_{27}H_{32}N_2O_5$ 464.2325, found 464.2324.

13. **Ethyl 2-((1S,5aR)-3-benzyl-5-adamantyl-8-methoxy-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



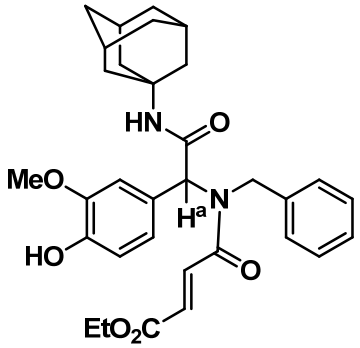
(±)-**230**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.36 (m, 5H, Ph), 5.27 (d, 1H, J = 14.7 Hz, -CH_2Ph), 5.16 (s, 1H, H^f), 4.52 (dd, 1H, J = 12.2, 5.5 Hz, H^d), 4.39 (d, 1H, J = 14.7 Hz, -CH_2Ph), 4.10 (q, 2H, J = 7.3 Hz, -$OC\underline{H}_2CH_3$), 3.67 (s, 1H, H^a), 3.54 (s, 3H, -OMe), 3.30 (dd, 1H, J = 10.9, 3.2 Hz; H^b), 3.13 (dd, 1H, J = 18.0, 3.9 Hz, H^e), 3.07 (dd, 1H, J = 15.6, 5.5 Hz; H^c), 2.47 (dd, 1H, J = 18.0, 10.9 Hz; H^e), 2.43 (dd, 1H, J = 15.6, 12.2 Hz; H^c), 2.09-2.24 (m, 9H, Ada), 1.65-1.75 (m, 6H, Ada), 1.22 (t, 3H, J = 7.3 Hz, -$OCH_2C\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 190.1, 171.9, 171.8, 169.4, 151.3, 135.6, 128.9, 128.1, 109.6, 64.0, 61.2, 56.8, 55.9, 55.2, 46.3, 45.8, 45.6, 41.5, 39.8, 36.1, 30.9, 29.6, 14.1.

HRMS (EIMS): calcd for $C_{32}H_{30}N_2O_6$ 538.2104, found 538.2109.

14. **(*E*)-Ethyl 4-((2-((3s,5s,7s)-adamantan-1-ylamino)-1-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl)(benzyl)amino)-4-oxobut-2-enoate**



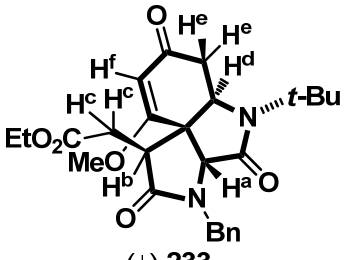
(±)-**232**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, 1H, *J* = 15.6 Hz, -C<u>H</u>=CH-), 7.10-7.19 (m, 3H, Aryl), 6.82-6.97 (m, 4H, Aryl and –CH=C<u>H</u>- overlap), 6.70-6.80 (m, 2H, Aryl), 5.87 (s, 1H, H^a), 5.43 (br s, -O<u>H</u>), 4.80 (d, 1H, *J* = 17.8 Hz, -CH_2Ph), 4.6 (d, 1H, *J* = 17.8 Hz, -CH_2Ph), 4.12-4.22 (q, 2H, *J* = 7.3 Hz, -OC<u>H_2</u>CH_3), 3.69 (s, 3H, -OMe), 1.95-2.12 (m, 9H, Ada), 1.65 (s, 6H, Ada), 1.24 (t, 3H, *J* = 7.3 Hz, -OCH_2C<u>H_3</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 166.3, 165.4, 146.4, 145.9, 134.1, 132.4, 128.3, 127.0, 126.2, 123.2, 114.4, 112.6, 62.9, 61.0, 55.8, 52.5, 49.6, 41.3, 36.2, 29.4, 14.1.

HRMS (EIMS, M^+): calcd for $C_{32}H_{30}N_2O_6$ 538.2104, found 538.2113.

15. **Ethyl 2-((1S,5aR)-3-benzyl-5-(*tert*-butyl)-9-methoxy-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



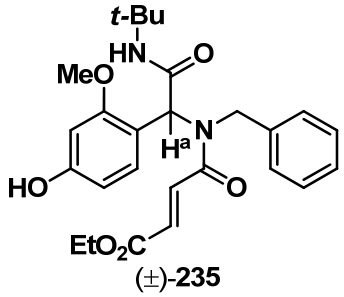
(±)-**233**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.33 (m, 5H, Ph), 5.39 (s, 1H, H^f), 5.26 (d, 1H, *J* = 14.7 Hz, -C<u>H</u>$_2$Ph), 4.53 (dd, 1H, *J* = 11.9, 5.8 Hz; H^d), 4.37 (d, 1H, *J* = 14.7 Hz, -C<u>H</u>$_2$Ph), 4.07-4.17 (m, 2H, -OC<u>H</u>$_2$CH$_3$), 3.54 (s, 1H, H^a), 3.33 (dd, 1H, *J* = 9.5, 3.4 Hz, H^b), 3.18 (dd, 1H, *J* = 18.3, 3.4 Hz, H^e), 2.90 (dd, 1H, *J* = 15.6, 5.8 Hz, H^c), 2.32 (dd, 1H, *J* = 18.3, 9.5 Hz; H^e), 2.22 (dd, 1H, *J* = 15.6, 11.9 Hz; H^c), 1.48 (s, 9H, ^{t}Bu), 1.24 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 172.6, 172.4, 172.2, 168.9, 135.5, 129.0, 128.4, 127.8, 103.8, 61.9, 61.2, 56.4, 56.0, 55.4, 48.5, 45.7, 45.2, 44.8, 30.6, 27.9, 14.2.

HRMS (EIMS): calcd for $C_{26}H_{32}N_2O_6$ 468.2260, found 468.2264.

16. **(*E*)-Ethyl 4-(benzyl(2-(*tert*-butylamino)-1-(4-hydroxy-2-methoxyphenyl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



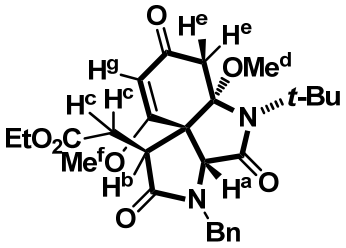
(±)-**235**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 1H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 7.03-7.15 (m, 5H, Ph), 6.78-6.85 (m, 2H, Aryl), 6.75 (d, 1H, *J* = 15.4 Hz, -CH=C<u>H</u>-), 6.29-6.37 (m, 1H, Aryl), 6.12 (s, 1H, H^a), 6.01 (br s, 1H, -N<u>H</u>), 5.81 (br s, 1H, -O<u>H</u>), 4.73 (d, 1H, *J* = 17.8 Hz, -C<u>H</u>$_2$Ph), 4.50 (d, 1H, *J* = 17.8 Hz, -C<u>H</u>$_2$Ph), 4.16 (q, 2H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.46 (s, 3H, -OMe), 1.30 (s, 9H, ^{t}Bu), 1.23 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 166.2, 165.5, 158.9, 158.7, 137.2, 134.1, 131.8, 130.9, 127.9, 127.8, 126.7, 125.9, 113.3, 107.3, 98.6, 61.1, 57.4, 54.7, 51.7, 49.5, 28.5, 14.0.

HRMS (EIMS): calcd for $C_{26}H_{32}N_2O_6$ 468.2260, found 468.2262.

17. **Ethyl 2-((1S,5aS)-3-benzyl-5-(*tert*-butyl)-5a,9-dimethoxy-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



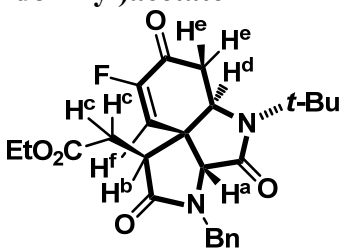
(±)-**236**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.35 (m, 5H, Ph), 5.57 (s, 1H, H^g), 5.36 (s, 1H, H^e), 4.80 (d, 1H, *J* = 14.4 Hz, -C$\underline{H}_2$Ph), 4.15 (d, 1H, *J* = 14.4 Hz, -C$\underline{H}_2$Ph), 4.06 (q, 2H, *J* = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 3.94 (t from dd overlap, 1H, *J* = 6.7 Hz, H^b), 3.77 (s, 1H, H^a), 3.65 (s, 3H, -OMe^f), 3.30 (s, 3H, -OMe^d), 2.73 (dd, 1H, *J* = 17.0, 6.1 Hz; H^c), 2.05 (dd, 1H, *J* = 17.0, 7.6 Hz; H^c), 1.24 (s, 9H, ^{t}Bu), 1.19 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.4, 174.5, 171.2, 170.2, 167.7, 165.6, 135.2, 129.7, 128.8, 128.3, 103.8, 101.7, 66.9, 61.0, 56.2, 55.7, 51.9, 51.7, 47.9, 43.9, 30.5, 28.5, 14.0.

HRMS (EIMS): calcd for $C_{27}H_{34}N_2O_7$ 498.2366, found 498.2368.

18. **Ethyl 2-((1S,5aR)-3-benzyl-5-(*tert*-butyl)-8-fluoro-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-pyrrolo[2,3-c]indol-1-yl)acetate**



(±)-**238**

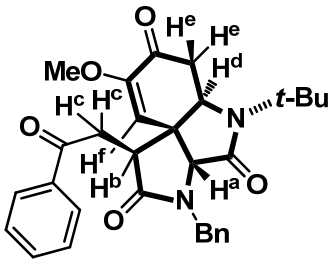
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.39 (m. 5H, Ph), 5.97 (d, 1 H, J = 12.9 Hz, H^f), 5.25 (d, 1 H, J = 14.6 Hz, –CH_2Ph), 4.64 (dd, 1 H, J = 11.4 ,5.7 Hz, H^d), 4.41 (d, 1 H, J = 14.6 Hz, –CH_2Ph), 4.13 (q, 2H, J = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 3.75 (s, 1 H, H^a), 3.24-3.32 (m, 1 H, H^b), 3.19 (dd, 1 H, J = 18.6, 3.2 Hz, H^c), 3.09 (dt, 1H, J = 15.4, 5.3 Hz, H^e), 2.45 (dd, 1 H, J = 10.8, 4.6 Hz, H^e), 2.40 (dd, 1 H, J = 11.3, 8.1 Hz, H^c), 1.47 (s, 9 H, *t*-butyl), 1.23 (t, 3 H, J = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186,7, 171.9, 171.2, 168.9, 154.7, 152.0, 143.1, 135.2 ($J_{C\text{-}F}$ = 48.5 Hz), 128.9, 128.5, 128.1, 119.6 ($J_{C\text{-}F}$ = 72.5 Hz), 62. 7, 62.7, 61.4, 56.6, 55.6, 45.8, 45.4, 45.3, 45.3, 44.8, 30.8, 27.9, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ – 124.9.

HRMS (EIMS): calcd for $C_{25}H_{29}FN_2O_5$ 456.2061, found 456.2065.

19. **(1S,5aR)-3-Benzyl-5-(*tert*-butyl)-8-methoxy-1-(2-oxo-2-phenylethyl)-3,3a,5a,6-tetrahydro-1H-pyrrolo[2,3-c]indole-2,4,7(5H)-trione**



(±)-**240**

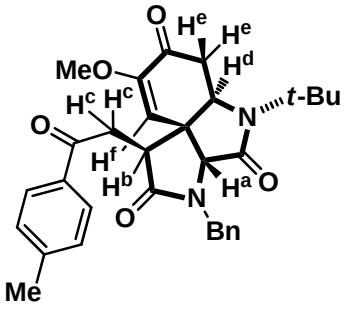
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90-7.99 (m, 2 H, Bz), 7.55-763 (m, 1 H, Bz), 7.42-7.51 (m, 2 H, Bz), 7.31-7.39 (m, 5 H, Ph), 5.32 (d, 1 H, J = 14.6 Hz, -C$\underline{H}_2$Ph), 5.15 (s, 1 H, H^f), 4.70 (dd, 1 H, J = 5.7 Hz, H^d), 4.42 (d, 1 H, J = 14.6 Hz, -C$\underline{H}_2$Ph), 3.89 (dd, 1 H, J = 18.7, 2.4 Hz, H^e), 3.73 (s, 1 H, H^a), 3.59 (m, 1 H, H^b), 3.41 (s, 3 H, OMe), 3.19 (dd, 1 H,

J = 18.7, 10.5 Hz, H^c), 3.06 (dd, 1 H, J = 15.4, 5.7 Hz, H^e), 2.41 (dd, 1 H, J = 15.4, 12.2 Hz, H^c), 1.53 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.5, 189.9, 172.8, 169.6, 151.3, 135.9, 135.7, 133.7, 128.8, 128.7, 128.5, 128.0, 109.8, 64.1, 56.5, 55.5, 55.1, 46.9, 45.9, 45.5, 44.3, 35.5, 27.9.

HRMS (EIMS): calcd for $C_{30}H_{32}N_2O_5$ 500.2311, found 500.2998.

20. **(1S,5aR)-3-Benzyl-5-(*tert*-butyl)-8-methoxy-1-(2-oxo-2-(*p*-tolyl)ethyl)-3,3a,5a,6-tetrahydro-1H-pyrrolo[2,3-c]indole-2,4,7(5H)-trione**



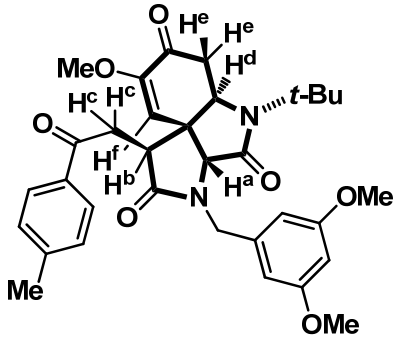
(±)-**243**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, 2 H, J = 8.2 Hz, aryl), 7.29-7.39 (m, 5 H, Ph), 7.27 (d, 2 H, J = 7.9 Hz, aryl), 5.32 (d, 1 H, J = 15.0 Hz, -C$\underline{H}_2$Ph), 5.16 (s, 1 H, H^f), 4.72 (dd, 1 H, J = 12.2, 5.8 Hz, H^d), 4.42 (d, 1 H, J = 14.7 Hz, -C$\underline{H}_2$Ph), 3.86 (dd, 1 H, J = 2.5 Hz, H^c), 3.73 (s, 1H, H^a), 3.58 (m, 1 H, H^b), 3.42 (s, 3 H, OMe), 3.18 (dd, 1 H, J = 18.9, 10.4 Hz, H^c), 3.06 (dd, 1 H, J = 15.6, 5.8 Hz, H^e), 2.41 (m, 4 H, H^e and Me overlap), 1.54 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.1, 189.9, 172.9, 169.6, 151.3, 144.7, 135.8, 133.5, 129.5, 128.8, 128.6, 128.2, 128.0, 109.9, 64.1, 56.5, 55.5, 55.2, 53.4, 46.9, 45.9, 45.5, 44.3, 35.3, 27.9, 21.7.

HRMS (EIMS): calcd for $C_{31}H_{34}N_2O_5$ 514.2468, found 514.2470

21. **(1S,5aR)-5-(*tert*-Butyl)-3-(3,5-dimethoxybenzyl)-8-methoxy-1-(2-oxo-2-(*p*-tolyl)ethyl)-3,3a,5a,6-tetrahydro-1H-pyrrolo[2,3-c]indole-2,4,7(5H)-trione**



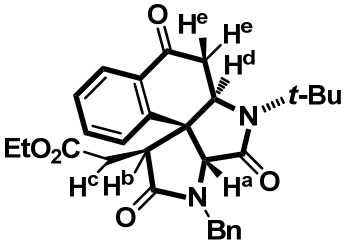
(±)-**246**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, 2 H, J = 8.2 Hz, aryl), 7.25 (d, 2 H, J = 7.9 Hz, aryl), 6.42-6.46 (m, 2 H, aryl), 6.36-6.39 (m, 1 H, aryl), 6.23 (d, 1 H, J = 1.2 Hz, H^f), 5.22 (d, 1 H, J = 15.0 Hz, -CH_2Ph), 4.70 (dd, 1 H, J = 12.2, 5.5 Hz, H^d), 4.40 (d, 1 H, 15.0 Hz, -CH_2Ph), 3.84 (dd, 1 H, J = 18.9, 2.4 Hz, H^c), 3.78 (s, 1 H, H^a), 3.77 (s , 6 H, OMe, OMe), 3.55 (m, 1 H, H^b), 3.13 (dd, 1 H, J = 18.6, 10.1 Hz, H^c), 2.98 (dd, 1 H, J = 15.3, 5.8 Hz, H^e), 2.40 (s, 3 H, Me), 2.29 (dd, 1 H, J = 15.3, 12.2 Hz, H^e), 1.52 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.2, 195.7, 172.9, 169.5, 161.2, 144.6, 138.5, 137.9, 137.1, 133.6, 129.4, 128.2, 106.3, 99.8, 63.0, 57.3, 55.4, 55.3, 46.5, 45.8, 45.4, 44.2, 35.2, 27.9, 21.6, 15.9.

HRMS (EIMS): calcd for $C_{33}H_{30}N_2O_7$ 566.2053, found 566.2057.

22. **Ethyl 2-((5aR)-3-benzyl-5-(*tert*-butyl)-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-benzo[e]pyrrolo[2,3-c]indol-1-yl)acetate**



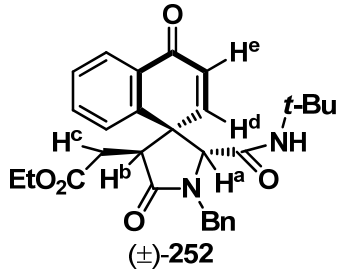
(±)-**251**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.8 (dd, 1H, *J* = 7.6, 1.2 Hz; Aryl), 7.2-7.44 (m, 7h, Aryl), 6.76 (d, 1H, *J* = 7.3 Hz, Aryl), 5.32 (d, 1H, *J* = 14.3 Hz, -C$\underline{H}_2$Ph), 4.70 (dd, 1H, *J* = 12.5, 4.9 Hz; H^d), 4.49 (d, 1H, *J* = 14.3 Hz, -C$\underline{H}_2$Ph), 3.86-3.99 (m , 3H, -OC$\underline{H}_2$CH$_3$ and H^a overlap), 3.49 (dd, 1H, *J* = 10.1, 3.4 Hz, H^b), 3.14 (dd, 1H, *J* = 14.3, 4.9 Hz; H^e), 3.00 (dd, 1H, *J* = 18.0, 3.4 Hz; H^c), 2.48 (dd, 1H, *J* = 13.7, 3.1 Hz, H^e), 2.04 (dd, 1H, *J* = 18.0, 10.1 Hz, H^c), 1.54 (s, 9H, ^{t}Bu), 1.03 (t, 3H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7, 172.7, 171.9, 169.5, 139.0, 135.1, 134.1, 132.1, 129.5, 128.7, 128.2, 128.0, 126.9, 126.7, 64.9, 60.9, 58.4, 55.5, 47.3, 47.2, 46.1, 30.9, 27.9, 13.9.

HRMS (EIMS): calcd for $C_{29}H_{32}N_2O_5$ 488.2311, found 488.2314.

23. **Ethyl 2-((1S,2'R,4'S)-1'-benzyl-2'-(*tert*-butylcarbamoyl)-4,5'-dioxo-4H-spiro[naphthalene-1,3'-pyrrolidin]-4'-yl)acetate (Spiro 11a)**



(±)-**252**

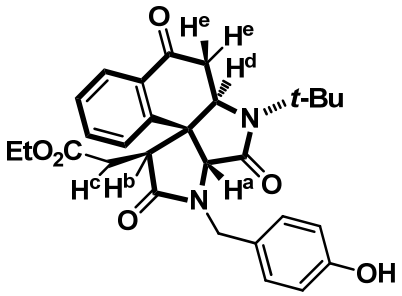
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (dd, 1H, *J* = 7.6, 1.2 Hz, Aryl), 7.27-7.39 (m, 6H, Aryl), 7.21-7.70 (m, 1H, Aryl), 7.08 (dd, 1H, *J* = 7.9, 0.6 Hz, Aryl), 6.99 (d, 1H, *J* = 10.4,

H^e), 6.41 (d, 1H, J = 10.4 Hz, H^d), 5.83 (s, 1H, -N<u>H</u>), 5.14 (d, 1H, J = 14.3 Hz, -C<u>H_2</u>Ph), 3.87-3.97 (m, 3H, -OC<u>H_2</u>CH_3 and –C<u>H_2</u>Ph overlap), 3.73 (dd, 1H, J = 8.6, 5.8 Hz; H^b), 3.64 (s, 1H, H^a), 2.48 (dd, 1H, J = 16.5, 6.1 Hz; H^c), 1.69 (dd, 1H, J = 16.5, 6.1 Hz, H^c), 1.35 (s, 9H, ^{t}Bu), 1.07 (t, 3H, J = 7.3 Hz, -OCH_2C<u>H_3</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.2, 183.7, 173.8, 170.9, 166.4, 150.6, 142.3, 140.2, 134.5, 132.7, 130.2, 129.5, 129.3, 128.2, 128.1, 126.4, 125.1, 68.8, 60.7, 52.2, 47.5, 47.4, 46.7, 30.6, 28.5, 13.8.

HRMS (EIMS): calcd for $C_{29}H_{32}N_2O_5$ 488.2311, found 488.2316.

24. **Ethyl 2-((1S,5aR)-5-(*tert*-butyl)-3-(4-hydroxybenzyl)-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-benzo[e]pyrrolo[2,3-c]indol-1-yl)acetate**



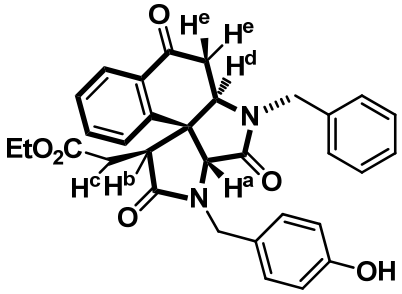
(±)-**253**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78-7.83 (m, 1H, Aryl), 7.29-7.39 (m, 2H, Aryl), 7.25 (d, 2H, J = 8.2 Hz, Aryl), 6.68-6.80 (m, 3H, Aryl), 6.1 (br s, 1H, -O<u>H</u>), 5.22 (d, 1H, J = 14.3 Hz, -C<u>H_2</u>Ph), 4.70 (dd, 1H, J = 12.6, 4.7 Hz; H^d), 4.49 (d, 1H, J = 14.3 Hz, -C<u>H_2</u>Ph), 3.96 (s, 1H, H^a), 3.87-3.95 (m, 2H, -OC<u>H_2</u>CH_3), 4.48 (dd, 1H, J = 10.4, 3.4 Hz; H^b), 3.14 (dd, 1H, J = 14.4, 5.1 Hz; H^e), 2.98 (dd, 1H, J = 18.0, 3.7 Hz; H^c), 2.48 (t from dd overlap, 1H, J = 14.4 Hz, H^e), 2.02 (dd, 1H, 1H, J = 18.0, 10.1 Hz; H^c), 1.53 (s, 9H, ^{t}Bu), 1.05 (t, 3H, J = 7.3 Hz, -OCH_2C<u>H_3</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7, 172.7, 171.9, 169.6, 155.9, 138.9, 134.2, 132.0, 130.9, 128.3, 126.9, 115.6, 64.9, 61.0, 58.5, 55.6, 47.5, 47.3, 46.1, 45.6, 30.8, 27.9, 13.9.

HRMS (EIMS): calcd for $C_{29}H_{32}N_2O_6$ 504.2260, found 504.2272.

25. **Ethyl 2-((1S,11bS)-5-benzyl-3-(4-hydroxybenzyl)-2,4,7-trioxo-2,3,3a,4,5,5a,6,7-octahydro-1H-benzo[e]pyrrolo[2,3-c]indol-1-yl)acetate**



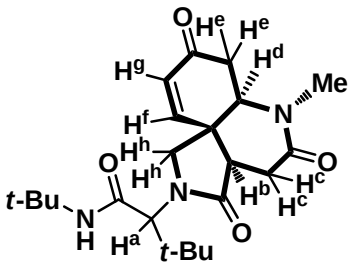
(±)-**255**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.75 (m, 1 H, *J* = 8.2 Hz, Aryl), 7.24-7.38 (m, 9 H, Aryl), 6.82 (d, 2 H, *J* = 7.9 Hz, Aryl), 6.70 (d, 1 H, *J* = 7.6 Hz, Aryl), 5.22 (d, 1 H, *J* = 14.3 Hz, -NC$\underline{H}_2$Ar), 4.92 (d, 1 H, *J* = 14.9 Hz, -NC$\underline{H}_2$Ar), 4.50 (d, 1 H, *J* = 14.3 Hz, -NC$\underline{H}_2$Ar), 4.36 (dd, 1 H, J_1 = 11.3 Hz, J_2 = 5.5 Hz, H^d), 4.18 (d, 1 H, *J* = 14.9 Hz, -NC$\underline{H}_2$Ar), 4.17 (s, 1 H, H^a), 3.74 (q, 2 H, *J* = 7.3 Hz, -OC$\underline{H}_2$CH$_3$), 3.18 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 4.4 Hz, H^b), 3.02 (dd, 1 H, J_1 = 14.3 Hz, J_2 = 5.5 Hz, H^e), 2.78 (dd, 1 H, J_1 = 17.7, J_2 = 4.4 Hz, H^c), 2.39 (dd, 1 H, J_1 = 14.3 Hz, J_2 = 11.3 Hz, H^e), 1.87 (dd, 1 H, J_1 = 17.7 Hz, J_2 = 10.7 Hz, H^c), 0.93 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 172.1, 171.1, 169.3, 156.2, 139.1, 134.9, 134.2, 132.7, 131.3, 129.2, 128.3, 128.2, 126.8, 126.6, 126.4, 115.7, 65.1, 60.9, 59.8, 49.5, 46.2, 45.5, 42.1, 31.6, 13.8.

HRMS (EIMS, M^+): calcd for $C_{32}H_{30}N_2O_6$ 538.2104, found 538.2123.

26. ***N*-(*tert*-butyl)-3,3-dimethyl-2-((3aR,6aR)-6-methyl-3,5,8-trioxo-3,3a,4,5,6,6a,7,8-octahydropyrrolo[3,4-d]quinolin-2(1H)-yl)butanamide**



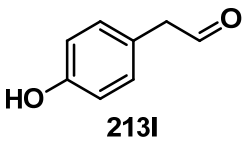
(±)-**261**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (d, 1 H, *J* = 10.1 Hz, H^f), 6.09 (d, *J* = 10.1 Hz, H^g), 5.89 (br s, 1 H, -N<u>H</u>), 4.22 (s, 1 H, H^a), 3.83 (d, 1 H, *J* = 11.0 Hz, H^h), 3.74 (d, 1 H, J = 11.3 Hz, H^h), 3.65-3.68 (m, 1 H, H^d), 2.95 (s, 3 H, -N<u>Me</u>), 2.64-2.95 (m, 4 H, H^c and H^e overlap), 1.31 (s, 9 H, *t*-Bu), 1.07 (s, 9 H, *t*-Bu)

^{13}C NMR (125 MHz, $CDCl_3$): δ 195.6, 174.4, 168.2, 167.3, 151.8, 128.1, 63.5, 60.0, 55.1, 51.8, 44.0, 40.4, 39.9, 35.1, 33.8, 31.2, 28.4, 27.5.

HRMS (EIMS): calcd for $C_{22}H_{33}N_3O_4$ 403.2471, found 403.2475.

27. **2-(4-hydroxyphenyl)acetaldehyde**



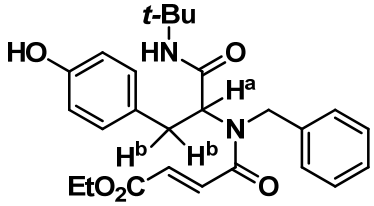
213l

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (t, 1 H, *J* = 2.5 Hz, -C<u>H</u>O), 7.06 (d, 2 H, *J* = 8.5 Hz, Aryl), 6.83 (d, 2 H, *J* = 8.5 Hz, Aryl), 5.83 (br s, 1 H, -O<u>H</u>), 3.63 (d, 2 H, *J* = 2.1 Hz, -C<u>H_2</u>CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 155.1, 130.8, 123.4, 115.9, 49.6.

HRMS (EIMS, M^+): calcd for $C_8H_8O_2$ 136.0524, found 136.0533.

28. **(*E*)-Ethyl 4-(benzyl(1-(*tert*-butylamino)-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)amino)-4-oxobut-2-enoate**



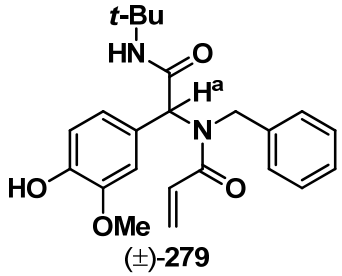
(±)-**276**

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10-7.36 (m, 6 H, Ph and –C<u>H</u>=CH- overlap), 6.95 (d, 2 H, *J* = 8.5 Hz, Aryl), 6.84 (d, 1 H, *J* = 15.3 Hz, -CH=C<u>H</u>-), 6.69 (d, 2 H, *J* = 8.2 Hz, Aryl), 5.01 (br s, 1 H, -O<u>H</u>), 4.91 (t, 1 H, *J* = 7.6 Hz, H^a), 4.78 (d, 1 H, *J* = 17.7 Hz, -NC<u>H</u>$_2$Ph), 4.65 (d, 1 H, *J* = 17.7 Hz, -NC<u>H</u>$_2$Ph), 4.18 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.15 (dd, 1 H, J_1 = 13.4 Hz, J_2 = 9.2 Hz, H^b), 2.87 (dd, 1 H, J_1 = 13.7 Hz, J_2 = 6.4 Hz, H^b), 1.25 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.16 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 166.6, 165.3, 155.1, 136.7, 133.6, 132.8, 130.2, 129.8, 128.9, 128.7, 128.1, 127.7, 126.4, 115.5, 61.4, 61.2, 60.5, 51.4, 34.4, 28.4, 14.1.

HRMS (EIMS, M^+): calcd for $C_{26}H_{32}N_2O_5$ 452.2311, found 452, 2324.

29. ***N*-benzyl-*N*-(2-(*tert*-butylamino)-1-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl)acrylamide**



(±)-**279**

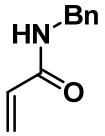
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69-7.24 (m, 9 H; Ph, Aryl and vinyl overlap), 6.39-6.48 (m, 2 H, vinyl and –N<u>H</u> overlap), 5.95 (s, 1 H, H^a), 5.83 (br s , 1 H, -O<u>H</u>), 5.60-5.68 (m, 2

H, vinyl), 4.78 (d, 1 H, *J* = 18.0 Hz, -NC<u>H</u>$_2$Ph), 4.61 (d, 1 H, *J* = 18.0 Hz, -NC<u>H</u>$_2$Ph), 3.68 (s, 3 H, O<u>Me</u>), 1.33 (s, 9 H, *t*-Bu)

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 167.9, 146.4, 145.9, 138.1, 129.3, 128.2, 128.1, 126.7, 126.4, 125.9, 123.0, 114.4, 112.6, 62.5, 55.8, 51.6, 49.2, 28.6.

HRMS (EIMS, M^+): calcd for $C_{23}H_{28}N_2O_4$ 396.2049, found 396.2057.

30. ***N*-benzylacrylamide**



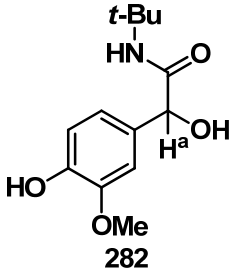
281

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.38 (m, 5 H, Ph), 6.34 (d, 1 H, *J* = 17.1 Hz, vinyl), 6.13 (d, 1 H, *J* = 10.4 Hz, vinyl), 6.09 (d, 1 H, *J* = 10.4 Hz, vinyl), 5.82 (br s, 1 H, -N<u>H</u>), 5.68 (d, 1 H, *J* = 10.4 Hz, vinyl), 4.53 (d, 2 H, *J* = 5.8 hz, -NC<u>H</u>Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 138.0, 130.6, 128.8, 127.9, 127.6, 126.9.

HRMS (EIMS, M^+): calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0853.

31. ***N*-(*tert*-butyl)-2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)acetamide**



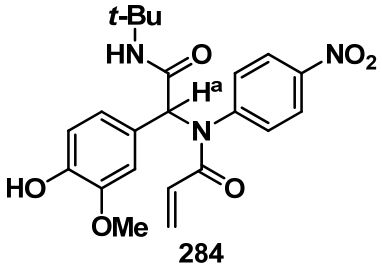
282

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82-6.92 (m, 3 H, Aryl), 5.70 (br s, 1 H, -OH), 4.83 (d, 1 H, *J* = 3.1 Hz, H^a), 3.88 (s, 3 H, OMe), 3.73 (d, 1 H, *J* = 3.4 Hz, -OH), 1.32 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): 178.3, 138.7, 136.1, 132.8, 126.9, 121.2, 115.7, 80.7, 62.7, 35.4.

HRMS (EIMS, M^+): calcd for $C_{13}H_{19}NO_4$ 253.1314, found 253.1329.

32. ***N*-(2-(*tert*-butylamino)-1-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl)-N-(4-nitrophenyl)acrylamide**



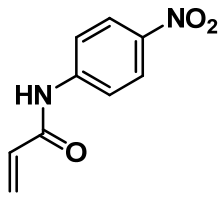
284

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, 2 H, *J* = 8.3 Hz, Aryl), 7.10-7.60 (m, 2 H, Aryl and vinyl overlap), 6.30-6.81 (m, 4 H, Aryl and vinyl overlap), 6.08 (s, 1 H, H^a), 5.70-5.90 (m 1 H, vinyl), 5.56 (s, 2 H, vinyl), 4.01 (br s, 1 H, -OH), 3.64 (s, 3 H, OMe), 1.12 (s, 9H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 165.2, 146.9, 146.5, 146.1, 145.4, 132.1, 129.3, 128.2, 125.5, 123.7, 114.5, 112.3, 64.6, 55.9, 51.8, 28.6.

HRMS (EIMS, M^+):

33. **N-(4-nitrophenyl)acrylamide**



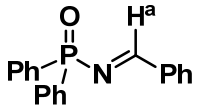
286

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, 2 H, J = 9.2 Hz, Aryl), 7.73 (d, 2 H, J = 9.2 Hz, Aryl), 6.37 (dd, 1 H, J_1 = 16.8 Hz, J_2 = 1.2 Hz, vinyl), 6.28 (dd, 1 H, J_1 = 17.1 Hz, J_2 = 10.1 Hz, vinyl), 5.70 (dd, 1 H, J_1 = 10.1 Hz, J_2 = 1.2 Hz, vinyl), 4.70 (s, 1 H, -N<u>H</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 146.9, 145.7, 131.6, 130.4, 124.7, 119.6.

HRMS (EIMS, M^+): calcd for $C_9H_8N_2O_3$ 192.0535, found 192.0546.

34. **(*E*)-*N*-benzylidene-*P*,*P*-diphenylphosphinic amide**



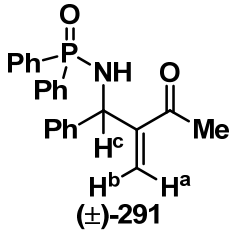
289

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.32 (d, 1 H, J = 32.0 Hz, H^a), 7.91-8.41 (m, 5 H, Ph), 7.41-7.58 (m, 10 H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 135.8, 135.6, 133.6, 132.4, 131.7, 131.5, 130.1, 128.8, 128.5, 128.4.

HRMS (EIMS, M^+): calcd for $C_{19}H_{16}NOP$ 305.0970, found 305.0983.

35. ***N*-(2-methylene-3-oxo-1-phenylbutyl)-*P*,*P*-diphenylphosphinic amide**



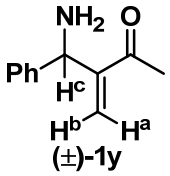
(±)-291

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80-7.92 (m, 4 H, Ph), 7.14-7.49 (m, 12 H, Ph and –N<u>H</u> overlap), 6.16 (s, 1 H, H^a), 6.09 (s, 1 H, H^b), 5.05 (t, 1 H, J = 10.7 Hz, H^c), 4.42 (dd, 1 H, J_1 = 11.0 Hz, J_2 = 8.6, -N<u>H</u>), 2.22 (s, 3 H, -<u>Me</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.3, 148.7, 141.4, 133.2, 132.2, 132.1, 131.9, 128.3, 128.2, 126.9, 126.3, 57.0, 26.6.

HRMS (EIMS, M^+): calcd for $C_{23}H_{22}NO_2P$ 375.1388, found 375.1394.

36. **3-(amino(phenyl)methyl)but-3-en-2-one**



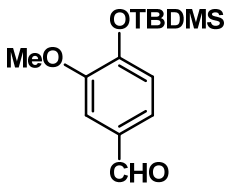
(±)-1y

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.38 (m, 5 H, Ph), 6.40 (s, 1 H, H^a), 6.27 (s, 1 H, H^b), 5.40 (br d, 1 H, J = 4.3 Hz, H^c), 3.73 (d, 2 H, J = 11.3 Hz, -N<u>H</u>$_2$), 2.26 (s, 3 H, -<u>Me</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.8, 143.9, 134.8, 128.8, 127.3, 126.7, 125.9 54.3, 25.9.

HRMS (EIMS, M^+): calcd for $C_{11}H_{13}NO$ 175.0997, found 175.1015.

37. **4-((tert-butyldimethylsilyl)oxy)-3-methoxybenzaldehyde**



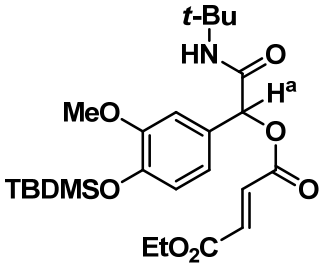
213n

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.84 (s, 1 H, -C<u>H</u>O), 7.33-7.42 (m, 2 H, aryl), 6.93-6.99 (m, 2 H, aryl), 3.9 (s, 3 H, OMe), 1.0 (s, 9 H, *t*-Bu), 0.4 (s, 6 H, Me and Me overlap).

^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 151.6, 151.3, 130.9, 126.2, 120.7, 110.1, 55.4, 25.6, -4.6.

HRMS (EIMS, M^+): calcd for $C_{14}H_{23}O_3Si$ 267.1416, found 267.1420.

38. **2-(*tert*-butylamino)-1-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)-2-oxoethyl ethyl fumarate**



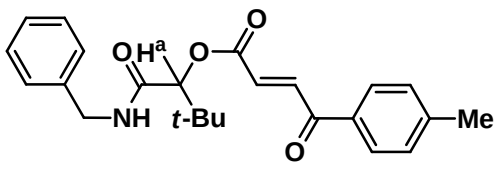
(±)-299

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80-6.98 (m, 5 H, -C<u>H</u>=C<u>H</u>- and aryl overlap), 5.97 (s, 1 H, H^a), 5.68 (bs, 1 H, -N<u>H</u>), 4.26 (q, 2 H, J = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 3.80 (s, 3 H, OMe), 1.34 (s, 9 H, -NH*t*-Bu), 1.31 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 0.97 (s, 9 H, -Si*t*-Bu), 0.15 (s, 6 H, Me and Me overlap).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 164.7, 163.6, 151.2, 146.0, 137.4, 134.9, 132.6, 128.5, 120.9, 120.4, 111.7, 76.2, 61.5, 55.5, 51.7, 29.6, 28.6, 25.7, 18.4, 14.1, -4.6.

HRMS (M^+, EIMS): calcd for $C_{14}H_{23}NaO_3Si$ 516.2394, found 516.2413.

39. **(E)-1-(benzylamino)-3,3-dimethyl-1-oxobutan-2-yl 4-oxo-4-(*p*-tolyl)but-2-enoate**



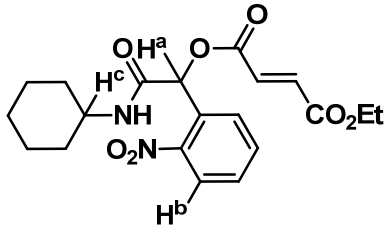
(±)-301

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, 1 H, J = 15.6 Hz, -C<u>H</u>=CH-), 7.79 (d, 1 H, J = 8.3 Hz, Aryl), 7.14-7.27 (m, 7 H, Aryl and Ph overlap), 6.86 (d, 1 H, J = 15.6 Hz, -CH=C<u>H</u>-), 5.20 (s, 1 H, -N<u>H</u>), 4.97 (s, 1 H, H^a), 4.40 (ddd, 2 H, J_1 = 35.1 Hz, J_2 = 15.0 Hz, J_3 = 5.8 Hz, -NC<u>H</u>$_2$Ph), 2.37 (s, 3 H, -<u>Me</u>), 1.05 (s, 9 H, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$): δ 188.4, 167.9, 164.5, 144.9, 137.8, 137.3, 133.6, 130.8, 129.4, 128.8, 128.4, 127.5, 127.2, 81.6, 42.9, 34.1, 26.1, 21.5.

HRMS (EIMS, M^+): $C_{24}H_{27}NO_4$ 393.1940, found 393.1955.

40. **2-(Cyclohexylamino)-1-(2-nitrophenyl)-2-oxoethyl ethyl fumarate**



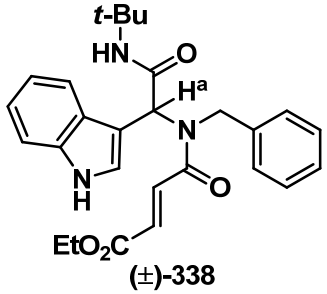
(±)-303

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.0 (dd, 1 H, J_1 = 8.2 Hz, J_2 = 1.2 Hz, H^b), 7.80 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 1.2 Hz, Aryl), 7.67 (dt, 1 H, J_1 = 7.6 Hz, J_2 = 1.2 Hz, Aryl), 7.52 (dt, 1 H, J_1 = 7.6 Hz, J_2 = 1.2 Hz, Aryl), 6.92 (dd, 2 H, J_1 = 17.4 Hz, J_2 = 15.9 Hz, -C<u>H</u>=C<u>H</u>-), 6.67 (s, 1 H, H^a), 6.34 (d, 1 H, J = 7.9 Hz, -N<u>H</u>), 4.22-4.29 (m, 2 H, -OC<u>H</u>$_2$CH$_3$), 3.70-3.79 (m, 1 H, H^c), 1.88-1.98 (m, 1 H, Cy), 1.53-1.83 (m, 4 H, Cy), 1.31 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$), 1.02-1.27 (m, 5 H, Cy).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 164.4, 163.6, 148.0, 135.5, 133.8, 131.8, 130.2, 129.8, 129.7, 124.8, 71.4, 61.5, 48.6, 32.6, 32.5, 25.3, 24.5, 14.0.

HRMS (EIMS, M^+): calcd for $C_{20}H_{24}N_2O_7$ 404.1584, found 404.1597.

41. **(*E*)-Ethyl 4-(benzyl(2-(*tert*-butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



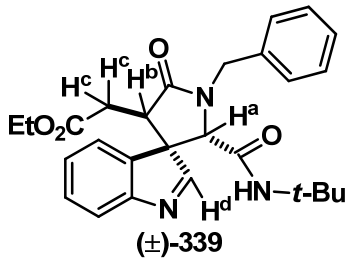
(±)-338

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.36 (m, 2 H, Aryl), 7.18-7.25 (m, 4 H, Aryl and –C<u>H</u>=CH- overlap), 7.08-7.17 (m, 3 H, Aryl), 6.74-6.95 (m, 3 H, Aryl and –CH=C<u>H</u>- overlap), 5.96 (s, 1 H, H^a), 5.56 (br s, 1 H, -N<u>H</u>), 4.84 (d, 1 H, *J* = 17.8 Hz, -NC<u>H</u>$_2$Ph), 4.62 (d, 1 H, *J* = 17.8 Hz, -NC<u>H</u>$_2$Ph), 4.16 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 1.33 (s, 9 H, *t*-Bu), 1.24 (t, 3 H, *J* = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 167.2, 164.9, 136.9, 136.3, 129.2, 128.8, 127.9, 127.7, 127.1, 122.9, 121.8, 120.1, 118.9, 112.8, 111.6, 71.9, 61.8, 60.7, 28.7, 14.1.

HRMS (EIMS, M^+): calcd for $C_{27}H_{31}N_3O_4$ 461.2315, found 461.2327.

42. **Ethyl 2-((2'S,3S,4'R)-1'-benzyl-2'-(*tert*-butylcarbamoyl)-5'-oxospiro[indole-3,3'-pyrrolidin]-4'-yl)acetate**



(±)-339

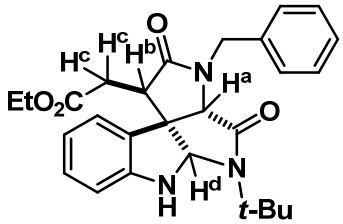
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1 H, H^d), 7.49 (d, 1 H, *J* = 7.9 Hz, Aryl), 7.26-7.36 (m, 6 H, Aryl), 7.14 (t, 1 H, *J* = 7.6 Hz, Aryl), 7.02 (d, 1 H, *J* = 7.3 Hz, Aryl), 5.27 (br s, 1 H, -N<u>H</u>), 5.09 (d, 1 H, *J* = 14.3 Hz, -NC<u>H</u>$_2$Ph), 4.09 (dd, 1 H, J_1 = 9.5 Hz, J_2 = 4.9

Hz, H^b), 4.06 (d, 1 H, J = 14.7 Hz, -NC$\underline{H}_2$Ph), 3.93 (dq, 2 H, J_1 = 7.3 Hz, J_2 = 1.2 Hz, -OC$\underline{H}_2$CH$_3$), 3.90 (s, 1 H, H^a), 2.64 (dd, 1 H, J_1 = 16.8 Hz, J_2 = 4.9 Hz, H^c), 1.74 (dd, 1 H, J_1 = 17.1 Hz, J_2 = 9.5 Hz, H^c), 1.31 (s, 9 H, *t*-Bu), 1.08 (t, 3 H, J = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 172.6, 170.7, 166.8, 155.0, 137.6, 135.2, 129.4, 129.1, 128.9, 128.6, 128.3, 126.8, 121.9, 64.3, 62.8, 60.7, 52.3, 46.8, 41.2, 30.9, 28.5, 13.9.

HRMS (EIMS, M^+): calcd for $C_{27}H_{31}N_3O_4$ 461.2315, found 461.2329.

43. **Ethyl 2-((1R,3aS,5aS,10bS)-3-benzyl-5-(*tert*-butyl)-2,4-dioxo-1,2,3,3a,4,5,5a,6-octahydropyrrolo[3',2':3,4]pyrrolo[2,3-b]indol-1-yl)acetate**



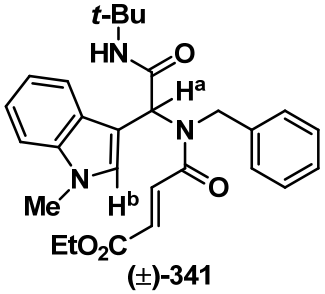
(±)-340

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20-7.38 (m, 5 H, Ph), 6.98-7.09 (m, 1 H, Aryl), 6.63-6.74 (m, 2 H, Aryl), 6.58 (d, 1 H, J = 7.9 Hz, Aryl), 5.81 (s, 1 H, H^d), 5.24 (d, 1 H, J = 14.1 Hz, -NC$\underline{H}_2$Ph), 4.48 (d, 1 H, J = 14.1 Hz, -NC$\underline{H}_2$Ph), 3.76-3.96 (m, 2 H, -OC$\underline{H}_2$CH$_3$), 3.74 (s, 1 H, H^a), 3.24 (dd, 1 H, J_1 = 11.6 Hz, J_2 = 3.7 Hz, H^b), 3.11 (dd, 1 H, J_1 = 18.3 Hz, J_2 = 4.3 Hz, H^c), 2.70 (dd, 1 H, J_1 = 18.3 Hz, J_2 = 11.6 Hz, H^c), 1.50 (s, 9 H, *t*-Bu), 0.98 (t, 3 H, J = 7.3 Hz, -OCH$_2$C$\underline{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 172.1, 171.0, 149.4, 135.8, 129.3, 128.9, 128.6, 127.7, 126.7, 124.2, 119.9, 110.9, 83.2, 66.0, 60.7, 55.1, 52.6, 47.1, 45.2, 31.8, 28.1, 13.9.

HRMS (EIMS, M^+): calcd for $C_{27}H_{31}N_3O_4$ 461.2315, found 461.2321.

44. **(*E*)-Ethyl 4-(benzyl(2-(*tert*-butylamino)-1-(1-methyl-1H-indol-3-yl)-2-oxoethyl)amino)-4-oxobut-2-enoate**



(±)-341

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80-7.48 (m, 10 H, Aryl and –C<u>H</u>=CH- overlap), 6.64 (d, 1 H, J = 15.6 Hz, -CH=C<u>H</u>-), 6.46 (s, 1 H, H^b), 6.10 (s, 1 H, H^a), 5.72 (t, 1 H, J = 4.8 Hz, -N<u>H</u>), 4.72 (dd, 2 H, J_1 = 44.9 Hz, J_2 = 17.4 Hz, -NC<u>H</u>$_2$Ph), 4.10-4.19 (m, 2 H, -OC<u>H</u>$_2$CH$_3$), 3.85 (s, 3 H, -<u>Me</u>), 1.34 (s, 9 H, *t*-Bu), 1.23 (t, 3 H, J = 7.3 Hz, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 167.2, 164.9, 136.9, 136.3, 129.2, 128.8, 127.9, 127.7, 127.1, 122.9, 121.8, 120.1, 118.9, 112.8, 111.6, 71.9, 61.8, 60.7, 34.9, 28.7, 14.1.

HRMS (EIMS, M^+): calcd for $C_{28}H_{33}N_3O_4$ 475.2471, found 475.2483.

CHAPTER 4

Rapid Entry into Anomeric Substituted D-Galactofuranosides: Effect of Lewis Acids under Microwave Irradiation using Modified Fischer/Lubineau Conditions

4. Introduction

The cyclic hemiacetal forms of monosaccharides having five-membered ring or the tetrahydrofuran skeleton are commonly known as furanoses. Glycosides are molecules in which a sugar group or monosaccharide is linked to a non-sugar group either by nitrogen, oxygen, sulfur or halogen (Figure 26). Glycosides having furanose form are called furanosides. The furanosides were known to adopt a puckered conformation for many years. However, Beevers and Cochran in 1947 had utilized X-ray study to show that the D-fructofuranose residue in sucrose sodium bromide dehydrate adopts an envelope conformation.[192]

X = OR, NR, SR, F, Cl, Br

357

Figure 26. Furanosides.

Furanosides have been found in many natural products, especially in nucleic acids. However, there is remarkable contrast in biodistribution among various furanose-containing glycoconjugates. For example, D-galactofuranosides (D-Gal*f*, **358a**, hexafuranoside, Figure 27), have been found in many microorganisms such as pathogenic bacteria, fungi, and protozoan parasites, and are highly immunogenic.[193] D-Gal*f* is essential for the survival of various pathogenic bacteria e.g. anaerobic bacteria

Bacteoride fragilis,[193c, 194] however it is absent in higher eukaryotes e.g. in mammalian cells.[193a] Consequently, in recent years, the scientific community has realized that D-Gal*f* can be utilized to study various biological systems to develop potential new therapeutics.[195] On the other hand, structurally analogous pentafuranoside L-arabinofuranose (L-Ara*f*, **358b**, Figure 27) is present in soil fungi, bacteria, and plants.[196] The D-Gal*f* and L-Ara*f* have been found to be very essential components of the glycocalix of these pathogens for their cell survival and morphology. For example, internal D-Gal*f* units are present in the cell wall of arabinogalactan. The *Mycobacterium tuberculosis* and *Mycobacterium leprae* contain internal D-Gal*f* units in their cell wall composed of L-Ara*f*. The lipopolysaccharide of *Klebsiella pneumoniae*, and lipophospoglycan of *Leishmania* also contain internal D-Gal*f* units. In addition, the lipopeptidophosphoglycan (LPPG) and *O*-linked oligosaccharides of *Trypanosoma cruzi* have been found to contain terminal nonreducing residues of D-Gal*f* units.

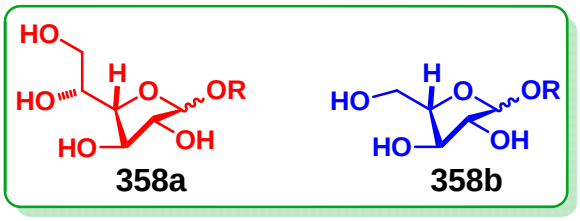


Figure 27. D-Galactofuranoside and L-Arabinofuranoside.

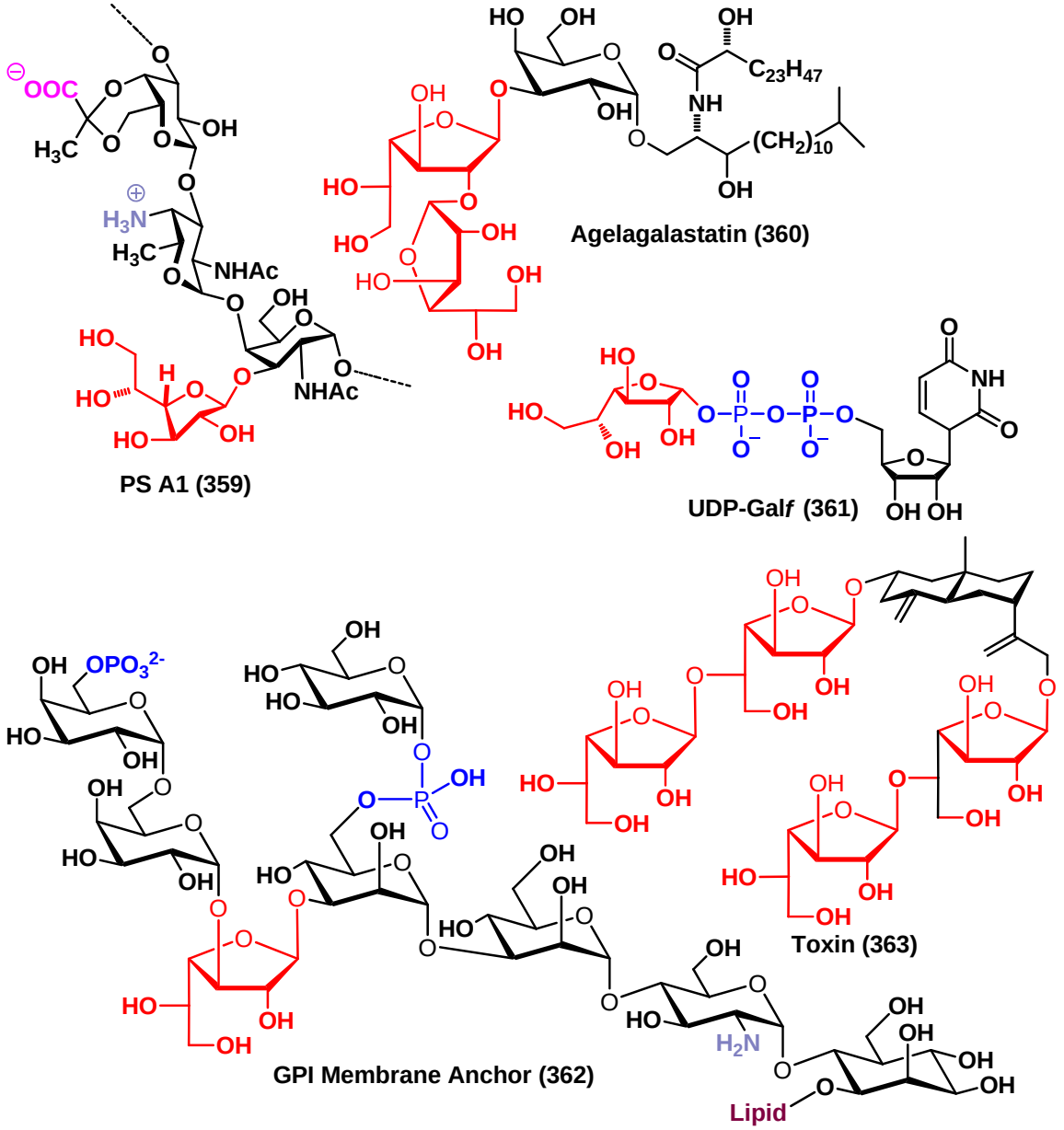


Figure 28. D-Gal*f* containing naturally occurring oligosaccharides.

The mycobacterium species possess a cell wall that is composed of ~30 D-Gal*f* residues and this impermeable cell wall protects them against environment.[197] In recent years, scientist have reported that mycobacterium species causing disease in particular tuberculosis is associated with the increasing occurrence of AIDS in many developing countries. Other examples include the zwitterionic polysaccharide PS A1 (**359**), isolated

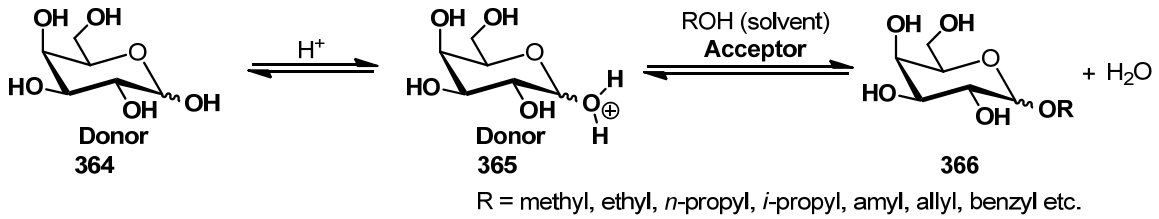
from anaerobic bacteria *Bacteroride fragilis* 9434, is known to modulate immune system by eliciting T-cell response via the MHC II pathway;[198a-d] the glycosphingolipid Agelagalastatin (**360**) which was isolated from Western Pacific marine sponge *Agelas sp.*, have been shown to inhibit human cancer cell growth with very high GI_{50} values in vivo;[198e-f] the UDP-D-Gal*f* (**361**) which is a biosynthetic glycosyl donor, presumably use the enzyme galactofuranosyl tranferase to incorporate it into cell-surface carbohydrates;[198g-h] the GPI membrane anchor (**362**)[198i-l] and the toxin **363** isolated from *Helminthosporium sp.* (Figure 28). Moreover, glycofuranosides are becoming important as surfactants, liquid crystals and building blocks for glycofuranosyl donors in oligosaccharide synthesis.[199] In addition, glycofuranosides have been utilized to synthesize lignin and their monomeric derivatives those are water-soluble as well biodegradable.[200]

4.1. Synthetic Routes and Challenges

Although, most pyranosides are commercially available, corresponding hexofuranosides are typically synthesized from the pyranosides due to their commercial inavailability. Over the past decade, there have been significant advancements in glycosylation methodology using protected carbohydrates. To this extent, there are few literatures that described chemical synthesis of *O*-glycosides from completely unprotected carbohydrates in a single step. Single-step synthesis of *O*-glycosides from completely unprotected carbohydrates is quite challenging due to potential a) self-condensation of unprotected sugars, b) anomerizations and, c) ring-chain tautomerisation of unprotected sugars during reaction time-course.[201] In order to synthesize of hexofuranosides from completely unprotected glycosyl donors directly: (a) the glycosyl

acceptor must be trapped faster to prevent any undesired coupling with glycosyl donors having unprotected hydroxyl groups, (b) the over equilibrium between starting materials, intermediates and products must be controlled effectively and should be toward product side, (c) the α/β-anomeric ratio of products must be good to excellent.

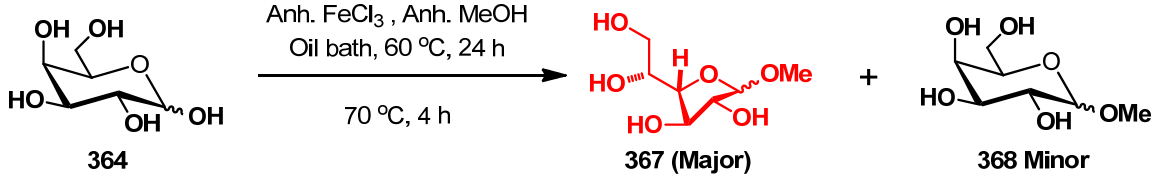
In 1893, Fischer developed the method of glycosylation of lower alcohols with unprotected carbohydrates e.g. **364** using protic acids (Scheme 85).[202] Because the reaction is carried out under thermodynamic control, generally it is conducted with a large excess of glycosyl acceptor alcohol (ROH) to drive the equilibrium to glycoside **366**. Consequently, this method is useful for the synthesis of glycosides of lower alcohols such as methyl, benzyl or allylic alcohol. Typically, the reaction requires high temperature, long reaction time and leads to a mixture of the anomeric mixture of furanosides and pyranosides. Thus the reaction is practically useful since it provides the thermodynamically stable axial glycoside of pyranosides as the major product.



Scheme 85. The Fischer glycosylation of unprotected sugars.

In an advancement, Fischer and Lubineau established that when pyranosides are subjected to glycosylation using $FeCl_3$ as a Lewis acid and methanol as an acceptor under refluxing conditions, the reaction provided the kinetically favored methyl furanoside **367** as major product as a mixtures α and β anomers (Scheme 86).[203] The reaction provides minor amount of the thermodynamically favored methyl pyranoside **368**, also as a mixtures of α and β anomers. However, the reaction takes about 28 h to complete which

is inconvenient for practical purposes. In addition, it is cumbersome to separate the α/β anomers of furaosides from the α/β anomers of pyranosides if the crystallization method does not work.



Scheme 86. The Fischer-Lubineau glycosylation using $FeCl_3$ as catalyst.

In 1986, Gedge,[204a] Westaway[204a] and Majetich[204b] reported the use of microwave (μwave) in chemical reactions for the first time and since then, interest within the scientific community in this extraordinary synthetic tool has increased exponentially. To date, microwave irradiation has been successfully applied in enzymatic reaction, despite the fact that enzymes are sensitive to heat.[205]

In recent years, although μwave technology has become a powerful and alternative tool over the traditional heating process in organic synthesis, this technology has not been employed widely in carbohydrate synthesis probably due to the fact that carbohydrates have been known to be very sensitive to heat. According to Abramovitch[206] and Loupy[243a], if in a reaction the '*polarity is increased from the ground state toward the transition state*', μwave irradiation can influence them. Furthermore, Westway and co-workers validated that '*microwave heating is less destructive than thermal heating'*.[207] These hypothesis have encouraged scientific community toward the use of μwave in carbohydrate synthesis. Microwave irradiation has been successfully employed to perform protection/deprotection,[208] S_N2 reaction,[209] and enzyme-catalyzed glycosylation.[210a] Most recently, it has also been utilized to perform glycosylation of

oxazolidine donors.[210b] Current μwave technology offers precise control of temperature and pressure in capped vial; even temperature range up to -78 ^{o}C can reached. With the recent advancement, scale-up of products can be easily performed via dedicated continuous flow microwave. Whatsmore is the fact that reports have emerged describing '*microwave effects*' on reaction outcomes are far different and unexpected than what was originally designed.[106]

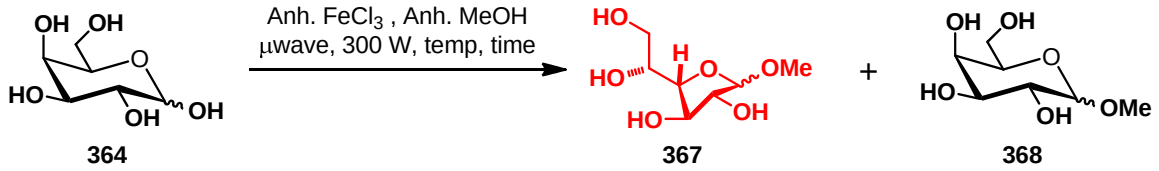
To this extent, the chemical synthesis of glycofuranosides remains important yet challenging as α/β mixtures of both furanosides and pyranosides are not easily isolatable, the lengthy reaction time course. Furthermore, most reaction protocol suffers from an inability to achieve conditions necessary to obtain the kinetically favored furanoside in good yields and high anomeric excess. Although, a few literature reports are available on the use of microwave in glycosylation of the hexopyranoses to synthesize hexopyranosides,[211] to date, there is no report on the use of microwave irradiation in synthesis of hexafuranosides synthesis from the hexopyranoses. Thus, we speculated that it would be quite interesting to study the effect of microwave on hexofuranosides synthesis especially that of D-galactofuranosides.

4.2. Results and Discussions

As a part of our research interest in synthesizing zwitterionic polysaccharide PS A1 and our developmental program in sustainable chemistry, we needed to synthesize allyl D-galactofuranoside building blocks. Since the original Fischer/Lubineau method is quite lengthy, we decided to employ μwaves in the Fischer/Lubineau glycosylation method and carry out the reaction in two stages under the same temperature. Since the spectroscopic data of methyl-D-galactofuranosides and methyl-D-galactopyranosides are

ample in literature, methanol was chosen as the acceptor alcohol for the convenience of comparing NMR data and as a measure for our success.

Table 25. Optimization of the microwave-assisted synthesis of D-galactofuranoside.[a]



Entry	Stage 1		Stage 2		% yield[b]/α:β[c]		% yield[b] (overall)
	Temp (°C)	Time (min)	Temp (°C)	Time (min)	D-Gal*f* (**367**)	D-Gal*p* (**368**)	
1	60	5	70	5	25/1:2	5/1.5:1	30
2	60	10	70	5	35/1:3	10/2:1	45
3	60	20	70	15	60/1:5	15/3.1	75
4	60	30	70	25	70/1:7	17/5:1	87
5	60	30	70	35	75/1:8	20/5.5:1	95

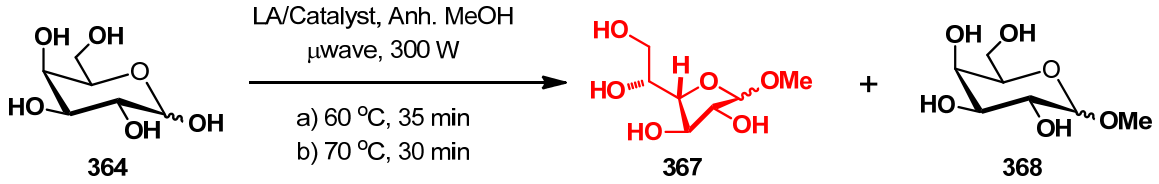
[a] CEM Discover Microwave, microwave power was set to 300 W. [b] Isolated. [c] Determined from ^{1}H NMR sample of unpurified reaction mixture; chemical shift of anomers were compared to literature values.

Thus, when D-galactopyranoside in methanol was subjected to μwave irradiation in the presence of Lewis acid catalyst $FeCl_3$ for 5 min at stage 1 (μwave was equilibrated to 300 W, 60 °C, 4 bar) and 5 min at stage 2 (μwave was equilibrated to 300 W, 70 °C, 5 bar), the overall conversion was 35%. The consumption of starting material was monitored by thin layer chromatography and ^{1}H NMR spectroscopy. Further optimization of time course of the two stages, the reaction after 65 min provided 75% yield of the desired D-Gal*f* with good α/β selectivity (Table 25). It has been observed that continuing the reaction longer than 70 min or increasing the temperatures of the stage 1 and 2, leads to lower yield of D-Gal*f* or decomposition of starting material. D-Gal*f*

anomers were separated from D-Gal*p* anomers by column chromatography on a silica gel column using a 20:1 CH_2Cl_2-MeOH mixture and their structural assignments were based on the ^1H and ^{13}C NMR spectroscopy and on previously reported data.[203] It is quite significant that we have been able to reduce the reaction time from 28 h to 65 min and also improved the yield of D-galactofuranosides over the original method.

Next, we were interested to study the effect of other Lewis acids and catalysts on D-Gal*f*/D-Gal*p* ratio (Table 26). A thorough literature search revealed that carbohydrate and their derivatives are well known to form complexes with metal ions.[212] Furthermore, experimental studies showed that the Fischer glycosylation of methanol in presence of strong acids may be affected by the presence of metal cations, in particular those from second row of the periodic table and thus can influence the α/β selectivity as well as the D-Gal*f*/D-Gal*p* ratio.[213] Table 26 shows the effect of different Lewis acids and catalyst on yield of D-Gal*f*/D-Gal*p* and their α/β selectivity. It has been observed that Lewis acids in which the central atom is in +I, +III or +IV oxidation state provided excellent overall yield. However, Cu(I), Cu(II) and Zn(II) did not provide any product. On the other hand, AgF and $FeCl_3$ gave the best yield of D-Gal*f*, whereas the rest of the Lewis acids employed gave D-Gal*p* as the major product. It can be seen from Table 26 that the oxidation state of central atom of the Lewis acids does not control the ratio of D-Gal*f*/D-Gal*p*, but the nature of the central atom seemed to affect the α/β ratios.

Table 26. Effect of Lewis acids/catalysts on μwave-assisted D-Gal*f* synthesis.[a]



Entry	Catalyst	Central Metal Atom Oxidation State	% yield[b]/α:β[c]		% yield[c] (overall)
			367	**368**	
1	AgF	I	75/1:6	21/5.5:1	96
2	$AlCl_3$	III	15/1:7	80/5:1	95
3	$BF_3.OEt_2$	III	25/1:5	63/5:1	88
4	CuI	I	0/-	0/-	0
5	$CuSO_4$	II	0/-	0/-	0
6	$FeCl_3$	III	75/1:8	20/5:1	95
7	$InCl_3$	III	23/1:7	74/5:1	97
8	$Sc(OTf)_3$	III	25/1:7	70/5:1	95
9	$TiCl_4$	IV	15/1:4	75/4.5:1	90
10	$Ti(O\textit{i}\text{-}Pr)_4$	IV	16/1:4	73/4.5:1	89
11	$Yb(OTf)_3$	III	20/1:7	72/5:1	92
12	$ZnCl_2$	II	0/-	0/-	0
13	TMSOTf	-	0/-	0/-	0
13	Amberlyst 15	-	15/1:5	75/9:1	90

[a] CEM Discover Microwave, microwave power was set to 300 W. [b] Isolated. [c] Determined from ^{1}H NMR of unpurified reaction mixture; chemical shift of anomers were compared to literature values.

In general, metal cations are known to co-ordinate with ligands via their *O*-atoms. A majority of these metal-ligand complexes, however, are formed via co-ordination with negatively charged *O*-atoms of an anion such as carboxylate or enolate. Neutral *O*-atom of the crown compounds and cryptates co-ordinate surrounding the metal cation via six or more *O*-atoms.[214] Angyal and co-workers have studied the complexation of metal cations

in detail using various alkaline-earth metal cations. They have postulated that polyhydroxy cyclohexane/tetrahydropyran rings in which the hydroxyl groups having *axial-equatorial-axial* orientation, are capable to form complexes with alkaline-earth metal ions. On the other hand, polyhydroxy cylcopentane or tetrahydrofuran rings having consecutive *cis* hydroxyl groups, can form complexes (Figure 29).[215] In addition, it was their observation that the radii of metal ions affect the extent of complexion and shifts the equilibrium in favor of α-anomers. Although, there is no literature precedence on the use of Lewis acids in furanoside synthesis under μwave irradiation, our results are in good agreement with Angyal's theory. Thus, we rationalized that the size, coordination number and outer orbital electron configuration of the central atom of the Lewis acids are responsible for the observed α/β ratio and yield of products. However, the mode of complexion might be somewhat different than Angyal's proposal.

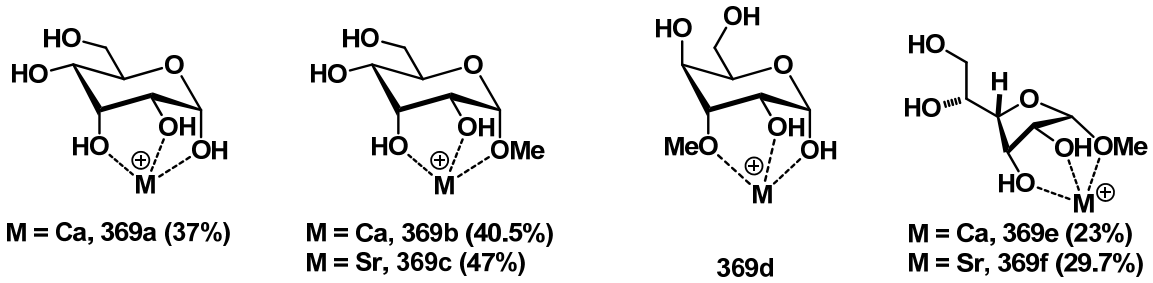
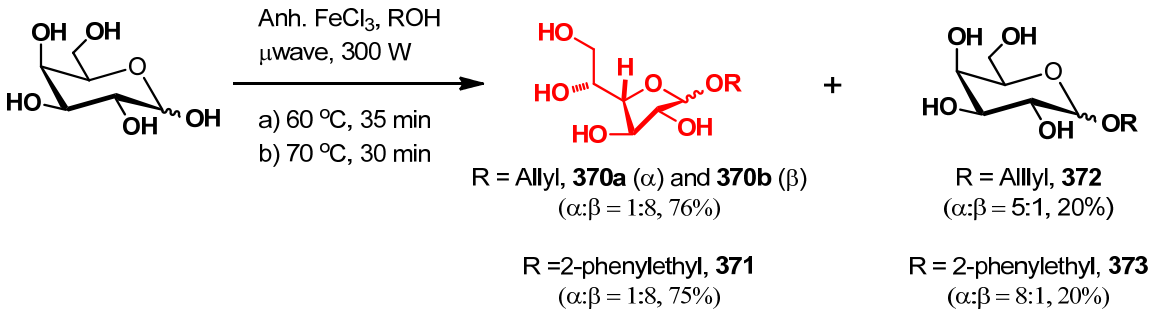


Figure 29. Co-ordination of alkaline-earth metal ions with D-allopyranose, D-allopyranosides, 3-*O*-methyl-D-gulopyranose and D-allofuranosides.

In order to extend this methodology to other alcohols, we decided to use allyl alcohol and 2-phenylethanol in the modified Fischer-Lubineau method of furanoside synthesis. Both 1-allyl-D-galactofuranoside **370** and 2-phenylethyl-D-galactofuranoside **371** were obtained in good yield and α/β selectivities (Scheme 87). Thin layer chromatography showed that the allyl D-galactofuranosides were well separated from

allyl D-galactopyranosides and we have been able separate the anomers of 1-allyl-D-galactofuranosides via column chromatography on a silica gel column using 20:1 mixture of CH_2Cl_2-MeOH as the eluent. The structure of the major product, 1-allyl-α-D-galactofuranoside, was confirmed by ^1H, ^{13}C, GQFCOSY, GHMQC and GNOE spectroscopy, and unequivocally confirmed by X-ray crystal structure analysis (Figure 30).



Scheme 87. Synthesis of 1-allyl- and 2-phenylethyl-D-galactofurnosides.

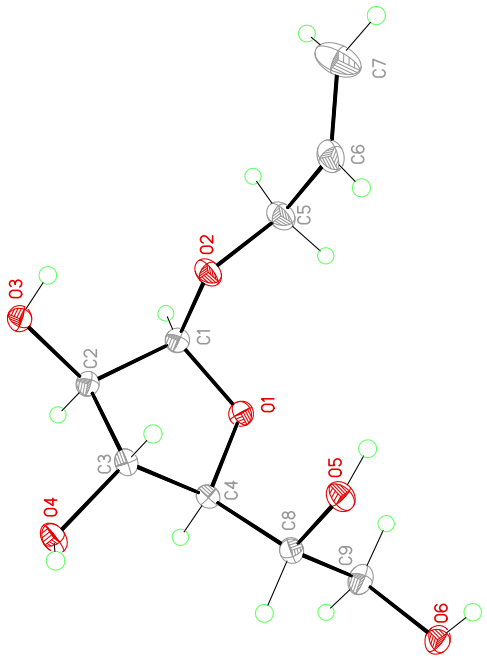
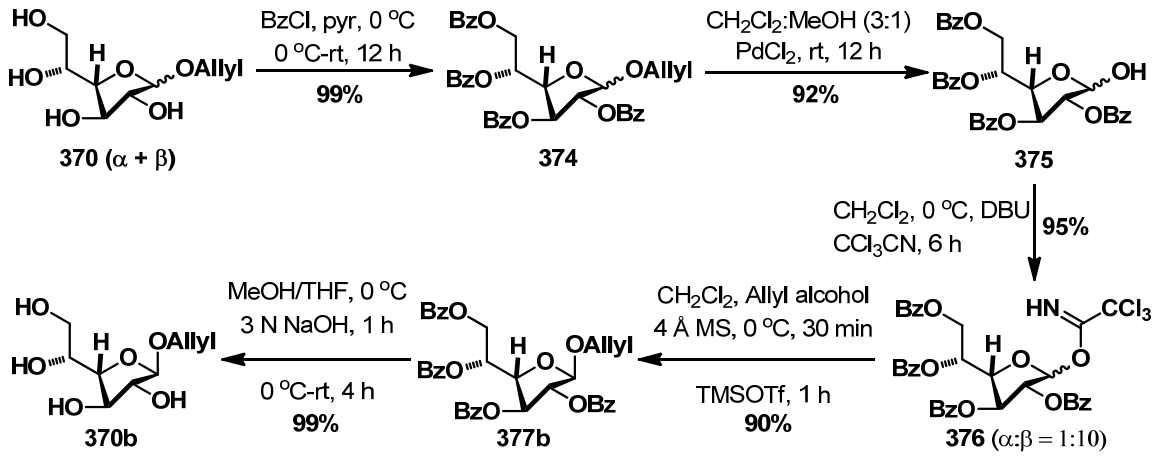


Figure 30. X-ray crystal structure of 1-allyl-α-D-galactofuranoside **370a**.

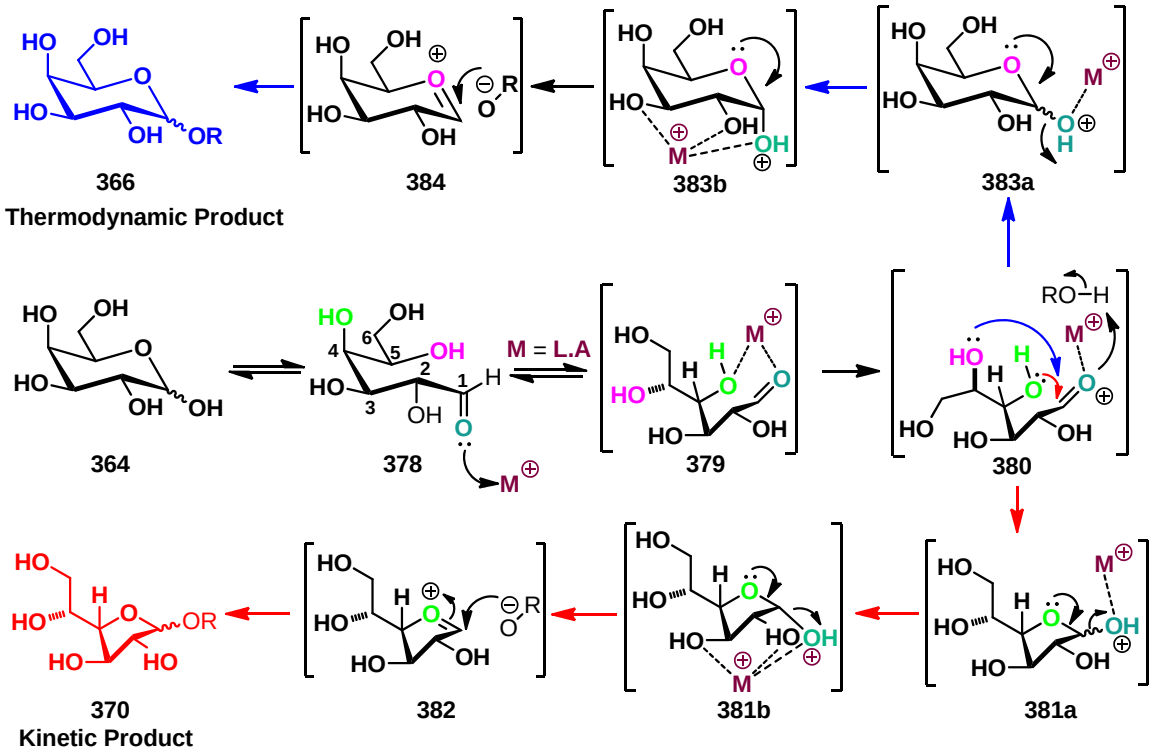
In addition, 1-allyl-β-D-galactofuranoside (**370b**) was synthesized separately (Scheme 88) via Schmidt glycosylation[216] and the chemical shift of the anomeric carbon was used to determinine the α/β ratio from ^{1}H NMR of unpurified reaction mixture after work-up. The chemical shift of anomeric carbons of 1-allyl-D-galactopyranosides was compared with reported values and used to determine the α/β ratio. The α/β ratios were determined from ^{1}H and ^{13}C NMR of crude reaction mixture. Furthermore, 1-allyl-2,3,4,6-tetracetate- α-D-galactofuranoside (**377c**) was also synthesized and compared with literature values. To the best of our knowledge, this is the first X-ray crystal structure of unprotected D-galactofuranoside with an allyl group at the anomeric position.



Scheme 88. Synthesis of 1-allyl β-D-galactofuranoside.

A general mechanism for the formation of 1-alkyl-D-galactofuranoside and -galactopyranoside is shown in Scheme 89. It is well known that the unprotected galactose **364** is in equilibrium with the open chain form **378**. The oxygen of the aldehyde group at C-1 and the hydroxyl group at C-4 coordinate with Lewis form a 7-membered transition state **379** which permits conformation changes that forms intermediate **380**. The hydroxyl group at C-4 then attacks the activated carbonyl carbon

to form the 5-membered ring intermediate **381a** or **381b**. On the other hand, attack of the hydroxyl group at C-5 onto the electrophilic carbonyl carbon form a 6-membered ring intermediate **384**. It is well known that 5-membered ring formation is faster than a 6-membered ring.[217] Thus, the D-galactofuranoside intermediate **381** is the kinetically controlled product and D-galactopyranoside intermediate **384** is the thermodynamically controlled product. The intermediates **381** and **383,** then collapse to form the oxocarbenium intermediate **382** and **384** respectively. Nucleophilic attack by solvent or alcohol onto the anomeric carbon results in the formation of final products having α-anomers as the major isomer probably due to the co-ordination of Lewis acids with the 1,2,3-hydroxyl groups as noted by Angyal.



Scheme 89. Proposed mechanism of D-galactofurnoside synthesis under microwave irradiation.

4.3. Materials and Methods

All Reagents were purchased from Aldrich unless otherwise noted. Anhydrous ferric chloride was purchased from Alfa Aesar. Anhydrous methanol was purchased from EMD chemicals (DriSolv). Palladium chloride was purchased from STREM chemicals. Indium chloride, copper iodide and copper sulfate were purchased from Alfa Aesar. TMSOTf was purchased from Acros organics. Allyl alcohol was distilled prior to use. Except as otherwise indicated, reactions were carried out under argon. Microwave reactions were conducted using a capped vial on CEM Discover System. All reactions were monitored by thin layer chromatography using 0.25 mm Dynamic Adsorbents L.L.C. precoated silica gel (particle size 0.03-0.07 mm, catalog no. 84111). Column chromatography was performed using Whatman Purasil 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise noted. Diastereomeric ratios were determined from ^{1}H NMR spectra of non-purified reaction mixtures. Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Unity 500 and Varian 500 Direct Drive System spectrometers. The residual $CDCl_3$ singlet at δ 7.26 ppm and δ 77 ppm were used as the standard for ^{1}H NMR and ^{13}C NMR spectra respectively. Mass spectra were recorded on Micromass GCT at 70 eV.

4.3.1 General method for silicone oil-bath-mediated D-galactofuranoside synthesis:

A 25 mL RB flask was oven dried, capped and cooled under Argon. To the flask D-galactopyranose (0.2 g, 1.1 mmol) was added followed by $FeCl_3$ (0.18 g, 1.1 mmol). To the mixture, anhydrous methanol (6.2 mL) was added slowly and the mixture

was refluxed at 60 ^{o}C for 24 h followed by 70 ^{o}C for 4 h. The flask was then allowed to reach room temperature, then saturated $NaHCO_3$ (5 mL) was added and stirred for 5 min. The reaction mixture was then filtered through neutral celite and the filtrate was dried on rotavap to afford a yellow slurry. The slurry was then extracted with a mixture of hot ethyl acetate/ethanol mixture (2:1). The extract was then filtered through celite and dried over rotavap. The extraction process was repeated again. The filtrate was concentrated under vacuum and purified by gradient column chromatography using silica gel as the stationary phase and mixture of methanol and dichloromethane (1:15 to 1:5) as the mobile phase.

4.3.2. General method for microwave-assisted D-galactofuranoside synthesis:

A 10 mL CEM Discover microwave vial was oven dried, capped and cooled under Argon. To the vial D-galactopyranose (0.05 g, 0.28 mmol) was added followed by $FeCl_3$ (0.045 g, 0.28 mmol). To the mixture, anhydrous methanol (2.5 mL) was added slowly and then the cap was quickly replaced with a new cap. The vial was capped according to manufacturer's instructions and placed in the single-mode microwave cavity. Then the microwave was run at two stages: (a) 30 min at 60 ^{o}C, 10 Bar and 300 W (b) 35 min, 70 ^{o}C, 10 Bar and 300 W. After allowing the vial to cool to room temperature, saturated $NaHCO_3$ (3 mL) was added and stirred for 5 min. The reaction mixture was then filtered through neutral celite and the filtrate was dried on rotavap to afford a yellow slurry. The slurry was then extracted with a mixture of hot ethyl acetate/ethanol mixture (2:1). The extract was then filtered through celite and dried over rotavap. The extraction process was repeated again. The filtrate was concentrated under vacuum and purified by gradient column chromatography using silica gel as the

stationary phase and mixture of methanol and dichloromethane (1:15 to 1:5) as the mobile phase.

4.3.3 Synthesis of 1-allyl-β-D-galactofuranoside from anomeric mixture of 1-allyl-D-galactofuranoside:

Anomeric mixture of 1-allyl-D-galactofuranoside (**369**) (0.39 g, 1.77 mmol) was taken in a dry RB flask equipped with magnetic stir bar. To the flask pyridine (5.34 mL, 68.75 mmol) was added at 0 ^{o}C under Argon and the solution was stirred for 5 min. Next, benzoyl chloride (2.65 mL, 15.55 mmol) was added dropwise to the stirring solution. The resulting mixture was allowed to reach room temperature slowly and monitored by thin layer chromatography (TLC). After 5 h, TLC showed complete consumption of **369** and the reaction was solidified. Dichloromethane (5 mL) was added to the flask to dissolve the solid. Next, toluene (50 mL) was added to the flask and the mixture was concentrated on rotavap. The crude product was purified via gradient column chromatography using silica gel as the stationary phase and mixture of ethyl acetate/hexane (1:20 to 1:3) as the mobile phase to afford 1-allyl-2,3,5,6-tetrabenzoyl-D-galactofuranoside (**374**)(1.11 g, 99%) as a white solid.

1.11 g (1.75 mmol) of **374** was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, anhydrous methanol (8.8 mL) was added followed by anhydrous dichloromethane (14 mL). To the stirred solution under Argon, palladium chloride (39 mg, 0.22 mmol) was added at room temperature. The resulting solution was stirred at room temperature for 12 h, after which TLC showed complete consumption of starting material. The solvent was removed on rotavap and the crude product was purified via gradient column chromatography using silica gel as the

stationary phase and a mixture of ethyl acetate/hexane (1:5 to 1:1) as the mobile phase to obtain 0.96 g (92%) of the hemiacetal **375** as a white solid.

Hemiacetal 375 (0.29 g, 0.48 mmol) was taken in an oven dried RB flask under Argon and dissolved in anhydrous dichloromethane (1.5 mL). After cooling the solution to 0 ^{o}C, DBU (37 μL, 0.25 mmol) was via syringe. To mixture, CCl_3CN (0.48 mL, 4.8 mmol) was added dropwise at 0 ^{o}C and the resulting solution was stirred for 1-2 h at 0 ^{o}C. After TLC showed completion of reaction, the solvent was removed under reduced pressure on rotavap. The crude product was purified via silica gel column chromatography using a 1:6 mixture of ethyl acetate/hexane as the eluent to afford 0.34 g (95%) of the trichloroacetamidate **376** (α:β = 1:10) as colorless oil.

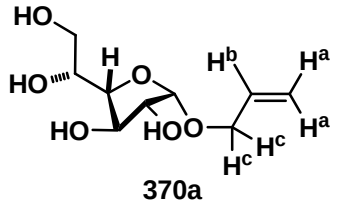
The donor **376** (0.18 g, 0.24 mmol) was taken in an oven dried RB flask and magnetic stir bar was placed inside. To the flask 45 mg 4 Å MS (oven dried 24 h followed by heat gun dried under high vacuum) was added followed by the acceptor allyl alcohol (14 μL, 0.25 mmol) and the solution was stirred at room temperature for 30 min. After cooling to -20 ^{o}C (ice-NaCl mixture), TMSOTf (0.5 μL) was added and the resulting mixture was stirred at -20 ^{o}C for 1 h. Next, the reaction was allowed to reach 0 ^{o}C slowly and quenched with Et_3N (10 μL). The solution was filtered and concentrated on rotavap. The crude product was purified via silica gel column chromatography using a 1: 4 mixture of ethyl acetate/hexane to afford 0.14 g (90%) of 1-allyl-2,3,5,6-tetrabenzoyl-β-D-galactofuranoside (**377**) as a white solid.

To a RB flask containing 0.11 g (0.18 mmol) of **377**, a 5:1 mixture of methanol/THF (11.3 mL) was added and the solution was cooled to 0 ^{o}C. Next, 3 N NaOH (0.74 mL) was added to the flask and reaction was allowed to reach room

temperature slowly over 1 h and stirred for additional 4 h. The reaction mixture was then concentrated on rotavap and the crude product was purified via gradient silica gel column chromatography using a mixture of dichloromethane/methanol (20:1 to 6:1) as the eluent to afford 38 mg (99%) of the target compound 1-allyl-β-D-galactofuranoside (**370b**).

4.4. Experimental Data

1. **1-Allyl-α-D-galactofuranoside**



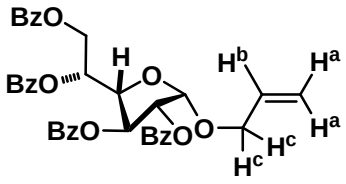
370a

^{1}H NMR (400 MHz, CD_3OD): δ 5.86 (dddd, 1 H, *J* = 17.4, 10.4, 6.2, 5.2 Hz, H^b), 5.19-5.28 (m, 1 H, H^a), 5.04-5.12 (m, 1 H, H^a), 4.81 (d, 1 H, *J* = 4.9 Hz, H-1), 4.15-4.25 (m, 1 H, H-3), 3.95-4.05 (m, 2 H, H-4 and H^c overlap), 3.84-3.90 (m, 1 H, H-2), 3.60-3.66 (m, 1 H, H^c), 3.50-3.58 (m, 2 H, H-6 and H-5 overlap), 3.41-3.50 (m, 1 H, H-6).

^{13}C NMR (100 MHz, CD_3OD): δ 135.7, 117.5, 101.8, 83.5, 78.8, 76.2, 74.5, 69.7, 64.0.

HRMS (EIMS, M^+ + Na): calcd for $C_9H_{16}NaO_6$ 243.0845, observed 243.0847.

2. **1-Allyl-2,3,4,6-tetrabenzoyl-α-D-galactofuranoside**



377a

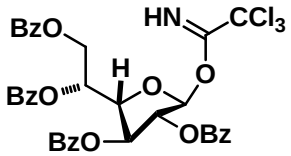
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-8.7 (m, 8 H, Aryl), 7.31-7.59 (m, 12 H, Aryl), 6.25 (t, 1 H, J = 6.5 Hz, H-3), 5.71-5.88 (m, 2 H, H^b and H-2 overlap), 5.47-5.55 (m, 2 H),

5.18-5.25 (m, 1 H, H^a), 5.08-5.15 (m, 1 H, H^a), 4.79 (dd, 1 H, *J* = 12.2, 4.1 Hz, H^c), 4.69 (dd, 1 H, *J* = 11.8, 5.7 Hz, H^c), 4.61 (t, 1 H, *J* = 5.7 Hz, H-4), 4.36 (dd, 1 H, *J* = 13.8, 5.7 Hz, H-6), 4.04 (dd, 1 H, J = 13.0, 5.7 Hz, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 165.7, 165.5, 133.5, 133.4, 133.3, 133.1, 132.9, 130.0, 129.9, 129.8, 129.7, 129.6, 129.0, 128.9, 128.4, 128.3, 128.2, 117.3, 99.5, 78.6, 77.5, 74.6, 71.7, 69.1, 62.9.

HRMS (EIMS, M^+ + Na): calcd for $C_{37}H_{32}NaO_{10}$ 659.1893, observed 659.1895.

3. **1-Trichloroacetamidate-2,3,4,6-tetrabenzoyl-β-D-galactofuranoside**



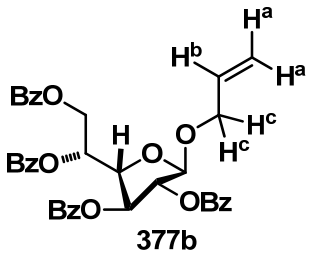
376 (β anomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1 H, =NH), 8.02-8.16 (dd, 4 H, *J* = 18.0, 7.6 Hz, Aryl), 7.86-7.99 (dd, 4 H, *J* = 21.4, 7.6 Hz, Aryl), 7.20-7.65 (m, 12 H, Aryl), 6.71 (s, 1 H, H-1), 6.15-6.21 (m, 1 H, H-2), 5.80 (d, 1 H, *J* = 4.0 Hz), 5.78 (s, 1 H), 4.86-4.91 (m, 1 H), 4.75-4.83 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 165.7, 165.4, 165.1, 160.2, 133.6, 133.5, 133.3, 133.0, 130.0, 129.9, 129.8, 129.6, 129.4, 129.2, 128.7, 128.4, 128.3, 128.2, 102.8, 84.5, 80.7, 76.9, 69.9, 63.3.

HRMS (EIMS, M^+ + Na): calcd for $C_{36}H_{28}Cl_3NNaO_{10}$ 760.0676, observed 760.0679.

4. **1-Allyl-2,3,4,6-tetrabenzoyl-β-D-galactofuranoside**



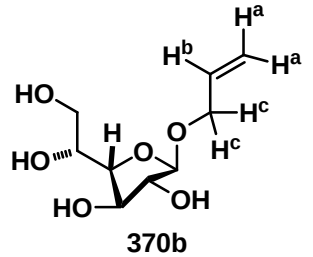
377b

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01-8.11 (m, 4 H, Aryl), 7.96-8.01 (m, 2 H, Aryl), 7.89-7.94 (m, 2 H, aryl), 7.49-8.0 (m, 4 H, Aryl), 7.22-7.45 (m, 8 H, Aryl), 6.05-6.11 (m, 1 H, H-4), 5.95 (dddd, 1 H, *J* = 17.4, 10.4, 6.2, 5.2 Hz, H^b), 5.65 (d, 1 H, *J* = 5.2 Hz, H-2), 5.52 (d, 1 H, *J* = 0.9 Hz, H-3), 5.32-5.39 (m, 2 H, H-1 and H^a overlap), 5.19-5.25 (m, 1 H, H^a), 4.73-4.81 (m, 2 H, H^c), 4.69 (dd, 1 H, *J* = 5.2, 3.4 Hz, H-5), 4.26-4.33 (m, 1 H, H-6), 4.13 (dd, 1 H, *J* = 13.1, 6.1 Hz, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 165.7, 165.6, 165.4, 133.6, 133.5, 133.3, 133.2, 133.1, 129.9, 129.8, 129.7, 129.6, 129.5, 129.0, 128.9, 128.4, 128.3, 117.6, 104.9, 82.2, 81.3, 77.6, 70.3, 68.0, 63.5.

HRMS (EIMS, M^+ + Na): calcd for $C_{37}H_{32}NaO_{10}$ 659.1893, observed 659.1897.

5. **1-Allyl-β-D-galactofuranoside**



370b

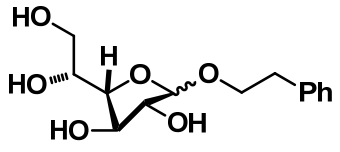
^{1}H NMR (400 MHz, CD_3OD): δ 5.88 (dddd, 1 H, J = 17.4, 10.4, 6.2, 5.2 Hz, H^b), 5.28 (qd, 1 H, *J* = 17.0, 1.6 Hz, H^a), 5.11-5.14 (qd, 1 H, *J* = 10.5, 1.6 Hz, H^a), 4.89 (d, 1 H, *J* =

2.0 Hz, H-1), 4.16-4.23 (m, 1 H, H-3), 3.98-4.03 (m, 1 H, H-6), 3.95-3.98 (m, 3 H, H-2 and H^c overlap), 3.93 (dd, 1 H, *J* = 6.5, 3.2 Hz, H-6), 3.68-3.74 (m, 1 H, H-5), 3.62 (br s, -O<u>H</u>), 3.60 (d, 1 H, *J* = 1.3 Hz, H-4).

^{13}C NMR (100 MHz, CD_3OD): δ 135.9 (C^b), 117.1 (C^a), 108.7 (H-1), 84.3 (C-6), 83.4 (C-2), 78.8 (C^c), 72.4 (C-5), 69.4 (C-3), 64.5 (C-4).

HRMS (EIMS, M^+ + Na): calcd for $C_9H_{16}NaO_6$ 243.0845, observed 243.0848.

6. **1-Phenylethyl-α-D-galactofuranoside**



371

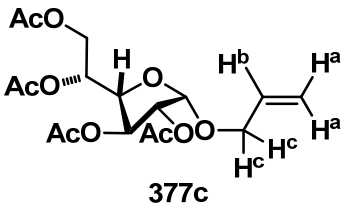
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23-7.29 (m, 2 H, Ph), 7.15-7.21 (m, 3 H, Ph), 4.90 (d, 1 H, *J* = 3.4 Hz, H-1), 3.66-4.6 (m, 7 H, H-2, H-3, H-4, H-5, H-6 and -OC<u>H</u>$_2$CH$_2$Ph overlap), 3.40-3.46 (m, 1 H, -OC<u>H</u>$_2$CH$_2$Ph), 2.88 (t, 2 H, *J* = 6.7 Hz, -OCH$_2$C<u>H</u>$_2$Ph).

^{13}C NMR (125 MHz, acetone-d6): δ 140.1, 129.8, 129.0, 126.9, 99.9, 85.6, 83.8, 78.9, 76.1, 71.4, 62.5. 36.7.

^{13}C NMR (125 MHz, CD_3OD): δ 140.3, 130.1, 129.3, 127.2, 100.2, 84.2, 83.3, 78.7, 76.6, 72.2, 71.5, 62.8. 36.9.

HRMS (EIMS, M^+ + Na): calcd for $C_{14}H_{20}NaO_6$ 307.1158, observed 307.1163.

7. **Allyl-2,3,4,6-tetraacetate-α-D-galactofuranoside**



377c

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86 (dddd, 1 H, *J* = 17.4, 10.4, 6.2, 5.2 Hz, H^b), 5.58 (t, 1 H, *J* = 7.3 Hz, H-2), 5.11-5.30 (m, 4 H), 5.02 (dd, 1 H, *J* = 8.1, 4.9 Hz), 4.30 (dd, 1 H, *J* = 12.2, 4.9 Hz), 4.18-4.25 (m, 1 H), 4.05-4.16 (m, 2 H), 3.86-3.96 (m, 2 H), 2.09 (s, 3 H, -$OCOCH_3$), 2.08 (s, 3 H, -$OCOCH_3$), 2.05 (s, 3 H, -$OCOCH_3$), 2.02 (s, 3 H, -$OCOCH_3$).

^{13}C NMR (100 MHz, CD_3OD): δ 170.3, 169.9, 169.7, 133.6, 117.1, 98.6, 77.7, 76.3, 73.5, 70.5, 68.5, 62.2, 20.8, 20.7, 20.6, 20.5.

HRMS (EIMS, M^+ + Na): calcd for $C_{17}H_{24}NaO_{10}$ 411.1267, observed 411.1265.

CHAPTER 5

p-*N*,*N*-Dimethylamino Benzyl (PDMAB) Group as an Ammonia Equivalent and Novel Functional Handle in Organic Synthesis

5. Introduction

The art of organic synthesis relies on novel strategies for protection and deprotection of functional groups.[218] Protecting groups (PGs) have been found to be very crucial handles for the synthesis of wide range of oligosaccharides[219], peptides[220], polyketides[221] and complex natural products[222] possessing significant biological activities. Although, there are some recent reports on protection group free complex molecule synthesis[223], the protection-deprotection strategy still remains a significant mainstay of organic synthesis. There are several criteria for a PG to be employed in a synthetic strategy: (a) facile access of the PG; (b) the PG can be installed easily in good-to-high yield; (c) the PG should not have another potential reactive functionality that might participate in other reaction during installation/removal; (d) the PG should not be affected by other synthetic transformations i.e. should be compatible with other functionalities; (e) removal of the PG should form a by-product that can easily be separated; and (f) the PG can be deprotected easily under mild conditions at a desired stage of synthetic strategy. Furthermore, incorporating PGs, having orthogonal reactivity with other common PGs, are valuable synthetic blocks that can offer flexibility to design strategies for the synthesis of complex architectures.

Among many protecting groups in organic synthesis, the benzyl as well as modified benzyl ethers have been frequently used.[224] They are most commonly

employed to protect hydroxyl groups in carbohydrate or polyhydroxy compounds. The robust nature along with their unique cleavage mechanism makes them compatible with many other common PGs. Benzyl ethers are commonly cleaved by oxidation in presence of DDQ,[225] CAN,[226] DDQ-$Mn(OAc)_3$,[227] or by hydrogenolysis, Lewis acids[228] and others.[229] However, tuning of electronic property of the phenyl group of the benzyl ether has generated a range of arylmethyl PGs having alter reactivity e.g. *para*-methoxybenzyl (PMB, **388**). dimethoxybenzyl (DMB, **389**), napthylmethyl (NAP, **390**),[230] *para*-bromobenzyl (PBB, **391**)[231], and many others (Figure 31).

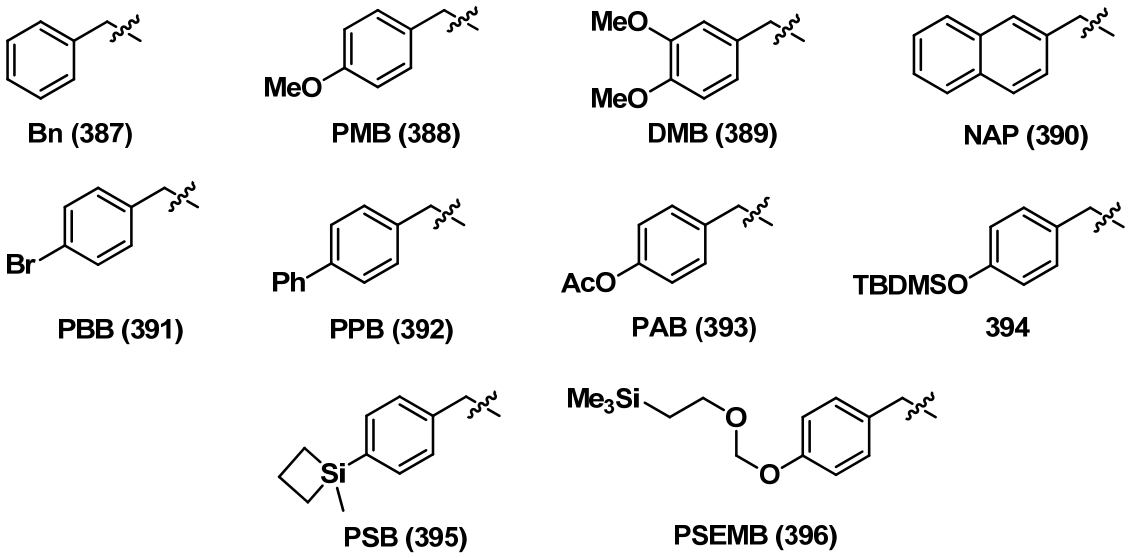


Figure 31. Benzyl protecting groups employed in carbohydrate synthesis.

Although the use of *para*-hydroxy benzyl (PHB) group has not seen much success due to its relatively unstable nature under very mild conditions,[232] recently, Jobron and Hindsgaul have reported that protected-PHB ethers *para*-acetoxybenzyl (PAB, **393**) and *para*-(*tert*-butyldimethylsilyl)-oxybenzyl (**394**) are promising in the art of carbohydrate synthesis. They have shown that these groups (**393**, **394**) can be cleaved under mild conditions.[224b] Unlike the electron withdrawing acetate esters and silyl ethers, the

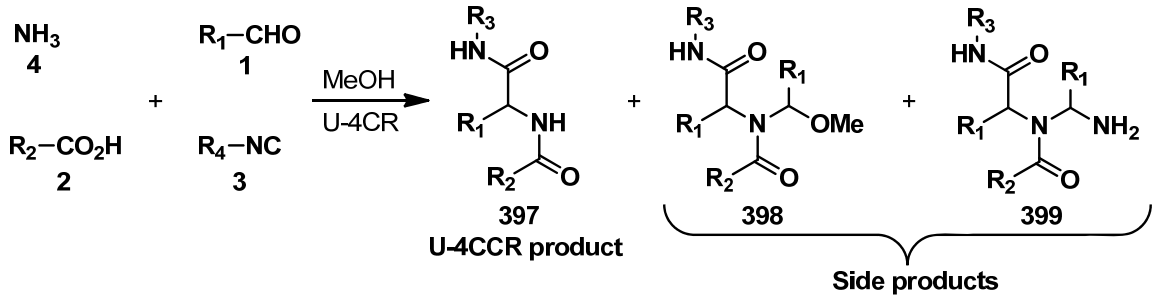
protected-PHB ethers exert less electronic influence on glycosyl donors.[233] More recently, Dudley *et al* reported the use of *para*-siletanylbenzyl (PSB, **395**) in carbohydrate synthesis.[234]

Every protection-deprotection strategy has its own limitations. For example, DDQ is commonly used for the removal of PMB and DMB groups under nearly neutral conditions. However, DDQ is an expensive reagent and chromatographic removal of the by-product, HDDQ can be a cumbersome process. Although, several catalytic systems have been developed[235] to recycle HDDQ into DDQ, they are not typically compatible with other functionalities present in carbohydrates or other molecules. Moreover, Lewis acids (e.g. $BF_3.OEt_2$, Me_2BBr) and DDQ mediated unmasking of PMB group suffers from the drawback of using stoichiometirc amounts. Despite recent advancements, there is no single PG in a particular series that can be regarded as the best. As a result there are continuous efforts among the scientific community to develop new protecting groups that will not only be cleavable under mild/neutral conditions and orthogonal to other commonly used protecting groups but also a close fit to the hypothetical best PG.

From the preceding discussion, it can be seen that over the last decade, several new PGs have been developed primarily for their application in carbohydrate synthesis. Ironically, most of these new PGs have not found any application in other areas of synthetic chemistry.

Peptides are an important class of compounds and there are reports that polypeptides which contain unnatural peptides can have increased bioavailability, resistance to degradation and improved bioactivity. Among many reactions, the U-4CCR has the capability to generate unnatural peptides from simple starting materials.

However, to mimic any natural peptide, the U-4CCR must incorporate ammonia as the amine component. There are only few literature precedents where ammonia has been used in the U-4CCR.[236] The potential problem of using ammonia in U-4CCR is the formation of undesired side products (Scheme 90).[237a]



Scheme 90. Ammonia in U-4CCR generates side products **398** and **399**.

In order to solve this problem, less nucleophilic solvents e.g. trifluoroethanol have been employed or the side products are selectively hydrolyzed using mild acids e.g. pyridinium *p*-toluenesulfonate (PPTS).[237b] Furthermore, chiral primary amines bearing auxiliaries have also been utilized as the amine component, since the auxilaries can be cleaved after post-Ugi condensation.[238] To date, 1-amino glycopyranoses, ferrocenylmethylamine have been used successfully for this purpose and employed in the synthesis of chiral amino acids. However, the synthesis of these chiral auxiliaries requires multistep syntheses, rendering it costly and time consuming.[239]

Thus, in recent years, there is a continuous effort among the scientific community to develop new types of ammonia equivalents for enantioselective synthesis of unsaturated amino acids,[240] Ugi reaction,[241] reductive amination,[242] palladium-catalyzed amination,[243] intramolecular hydroamination,[244] amino carbonylation,[245] synthesis of primary amine,[246] and aza-Michael addition (Figure 32).[247]

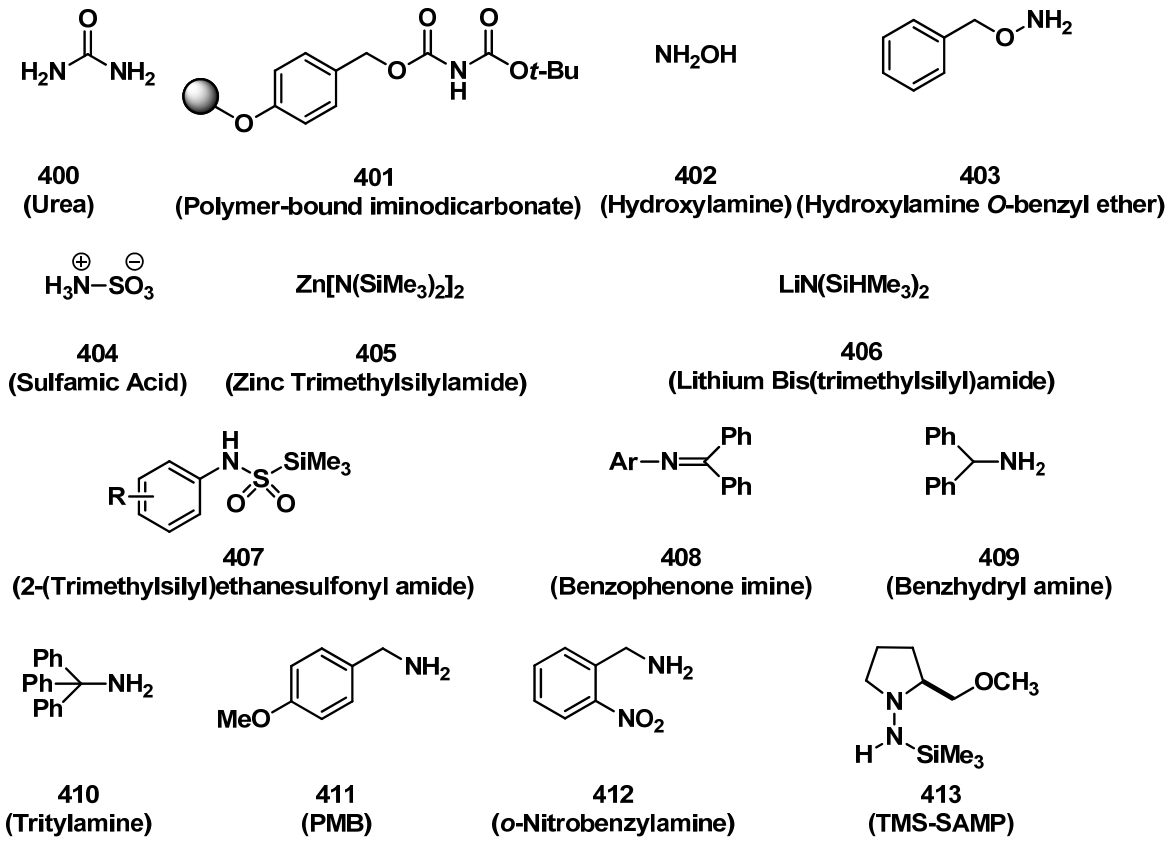


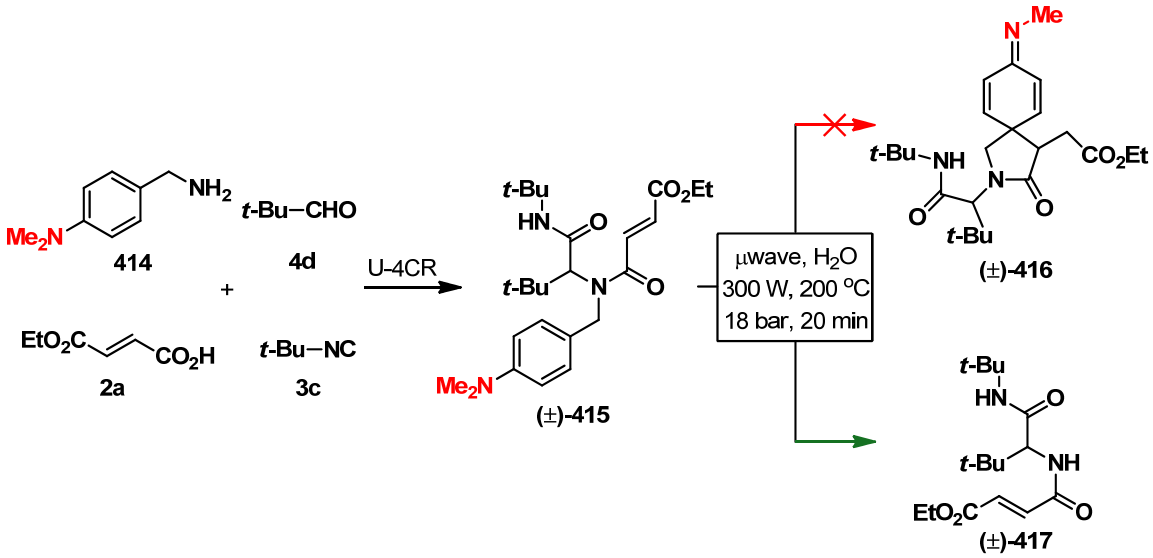
Figure 32. Examples of ammonia equivalents employed in organic synthesis.

As a part our ongoing research program in developing new methods and strategies for sustainable chemistry, we were interested to develop a new reaction that would be useful in synthetic chemistry especially in MCCR and carbohydrate chemistry. From our established methodology, we envisioned that microwaves could possibly alter reactivity of *para*-substituted benzyl groups.

5.1. *p*-*N*,*N*-Dimethylamino Benzyl (PDMAB) Group as an Ammonia (NH_3) Equivalent in MCCR

During our small molecule synthesis, we observed that when *para*-hydroxy benzylamine was used in the U-4CCR and the resulting acyclic product was irradiated under microwave, the reaction provided an appreciable amount of *para*-hydroxy benzyl

alcohol (**14**, Chapter 2, Scheme 38) along with the desired DKP product (chapter 2, Scheme 28). We anticipated that the use of a stronger electron donating group on the phenyl ring of the benzyl group might provide this product (**14**) in increased yield and would help us to study the effect on electron donating groups on benzyl group under μwave irradiation. Thus we decided to use *p*-*N*,*N*-dimethyl benzylamine (PDMAB-NH_2, **414**), trimethylacetaldehyde **4d**, fumaric acid monoethyl ester **2a** and *tert*-butyl isocyanide **3c** in the Ugi 4CCR and isolated the acyclic product **415** in excellent yield. When **415** was irradiated under microwave at 300 W, 200 ^{o}C, 18 bar for 20 min in water, the reaction did not provide the expected 2-azaspiro[4.5]decane-3,8-dienone **416**. Instead, compound **417** was obtained which lacks the *p*-*N*,*N*-dimethylbenzyl (PDMAB) group (Scheme 91).

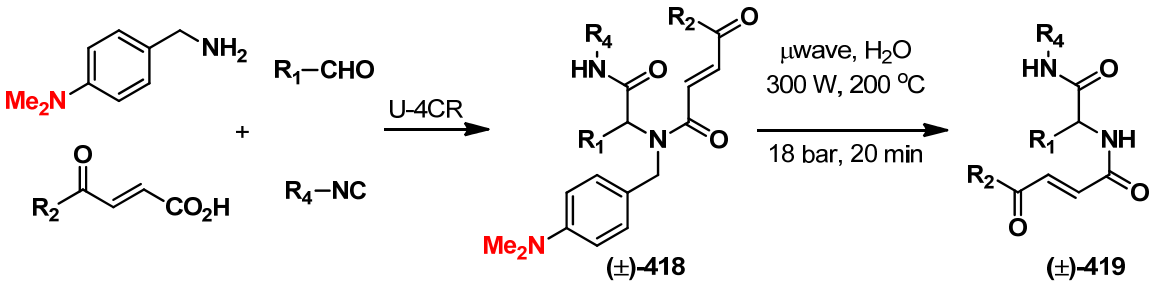


Scheme 91. PDMAB group is labile under microwave irradiation.

The identity of the deprotected product **417** was established by ^{1}H, ^{13}C, DEPT, mass spectroscopy and unequivocally confirmed by X-ray structure analysis (Figure 33). From Scheme 91, it is quite clear that *p*-*N*,*N*-dimethylbenzyl (PDMAB) amine can act as

ammonia equivalent in the U-4CCR and can be removed under microwave irradiation in water without any additives. It must be noted that the acyclic compound **415** is stable on bench-top for several months. Next, we decided to study the substrate scope of this reaction and a series of acyclic Ugi product has been synthesized using various aldehydes, acids and isocyanides and will be subjected to μwave irradiation(Table 27).

Table 27. Scope of PDMAB group as ammonia (NH_3) equivalent in U-4CCR.[a]

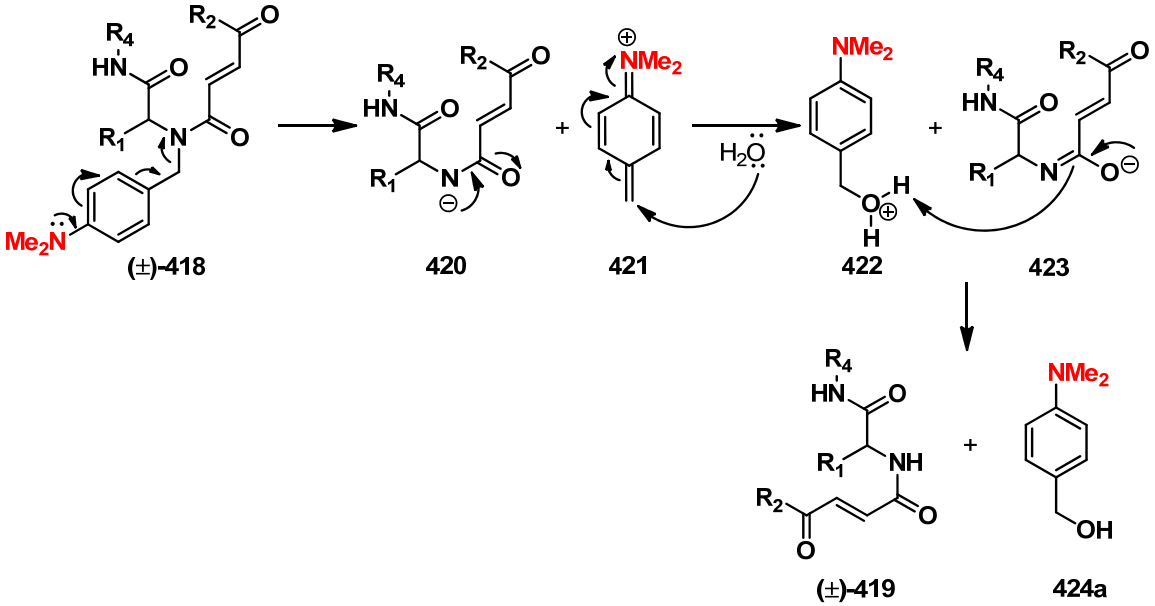


Entry	R_1	R_2	R_4	Compd/ % yield
1	*t*-butyl (1c)	Ethylacrolein (2a)	*t*-butyl (3c)	**415 (98)/417(98)**
2	*p*-methoxyphenyl (1)	Ethelnene (2f)	Cyclohexyl (3d)	**418a(96)/419a(n.d[b])**
3	Piperonyl (1)	Cyclopropyl (2)	2,6-dimethylphenyl (3b)	**418b(95)/419b(n.d)**
4	*o*-nitophenyl (1)	Cyclopropyl (2)	Isopropyl (3f)	**418c(93)/419c(n.d)**
5	Piperonyl (1)	*p*-methoxyphenyl (2)	2,6-dimethylphenyl (3b)	**418d(94)/419d(n.d)**
6	Isopropyl (1)	*p*-bromophenyl (2)	2,6-dimethylphenyl (3b)	**418e(92)/419e(n.d)**
7	Naphthalene (1)	*m*-bromophenyl (2)	Cyclohexyl (3d)	**418f(95)/419f(n.d)**

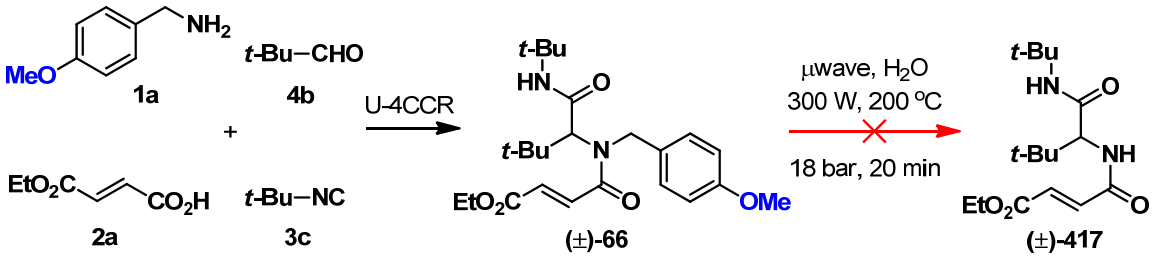
[a] CEM Discover Microwave. [b] Reaction will be performed.

A proposed mechanism for the formation of PDMAB deprotected product **419** is shown in Scheme 92. Microwave irradiation influences the lone pair on the nitrogen of the *N*,*N*-dimethyl group, allowing to fall down, break the benzylic carbon-nitrogen bond that results in the formation of the deprotected intermediate **420** and aza-quinone methide intermediate **421**. Nucelophilic attack by water onto the electrophilic methide carbon

forms the intermediate **422**. Protonation-deprotonation provides the final products **419** and the PDMAB alcohol **424**.



Scheme 92. Proposed mechanism for the formation of PDMAB deprotected product **419**.



Scheme 93. PMB group is not labile under microwave irradiation.

To determine the applicability of the PDMAB group in carbohydrate chemistry, we decided to revisit our earlier finding and elected to use *para*-methoxy benzyl (PMB) amine as a coupling partner in the Ugi reaction having same coupling partners (Scheme 93). Thus, when the acyclic Ugi product **66** was irarradiated under microwave using previous conditions, thin layer chromatography showed that there was no reaction. This

further confirmed that the PMB group was stable and not labile in the presence of microwave irradiation.

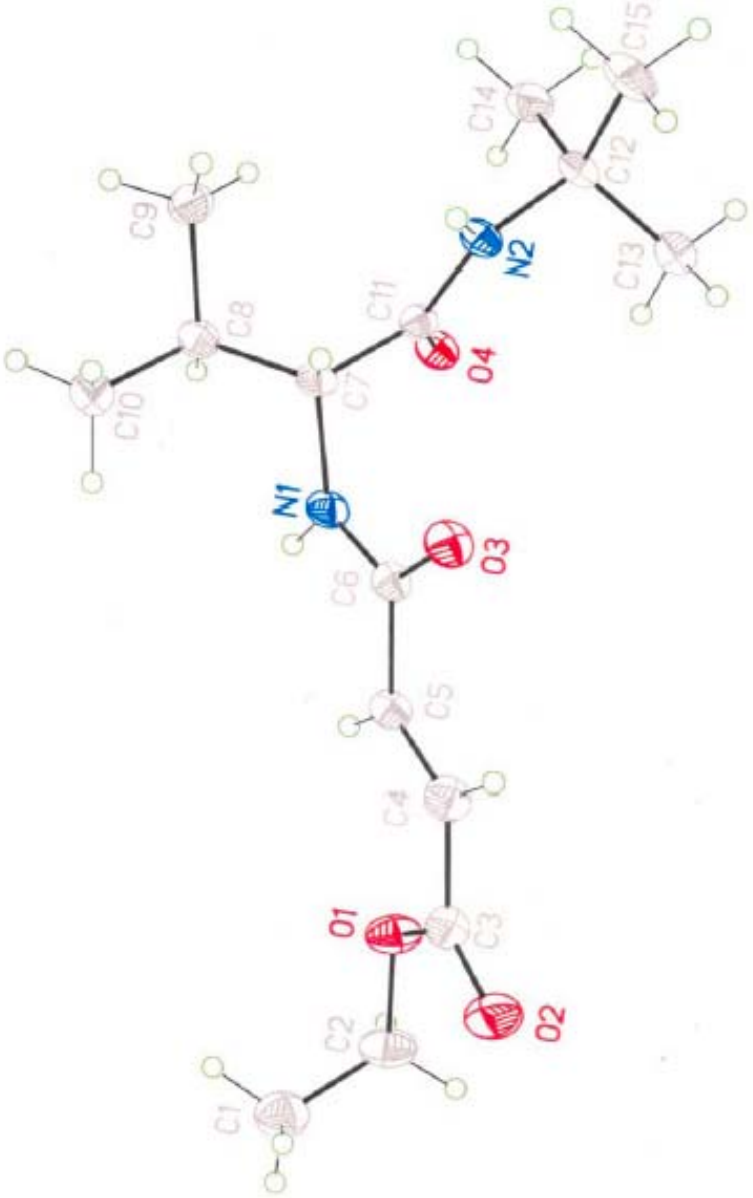
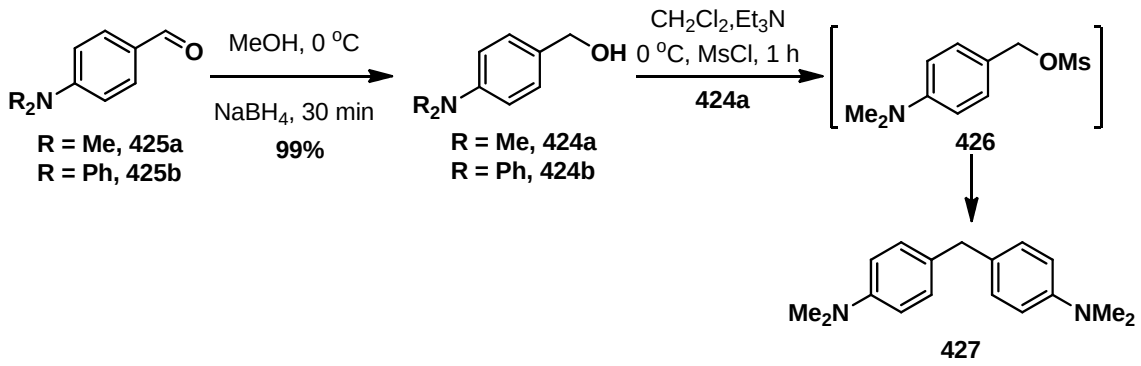


Figure 33. X-ray crystal structure of PDMAB deproteced product (±)-**417**.

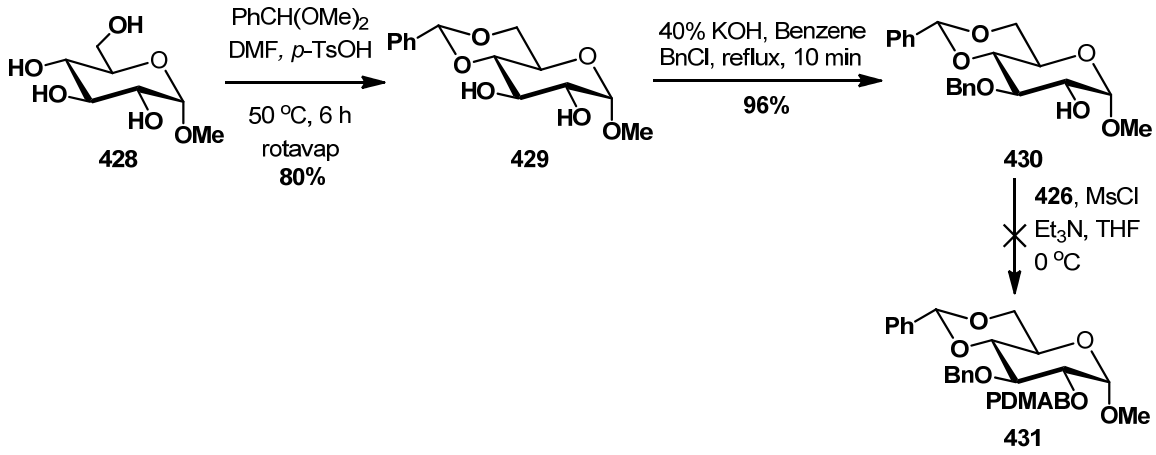
5.2. PDMAB as a Novel, Alternative Protecting Group in Carbohydrate Synthesis

With this result in hand (Scheme 92), we then decided to synthesize *p*-*N*,*N*-dimethylaminobenzyl (PDMAB) alcohol **424a** from *p*-*N*,*N*-dimethylamino benzaldehyde **425a**. PDMAB alchol was then converted to the corresponding methanesulfonate **426**. However, compound **426** is quite unstable and converts into a dimeric species **427** (Scheme 94). Hence, we decided to prepare **426** as the semi-stable compound.



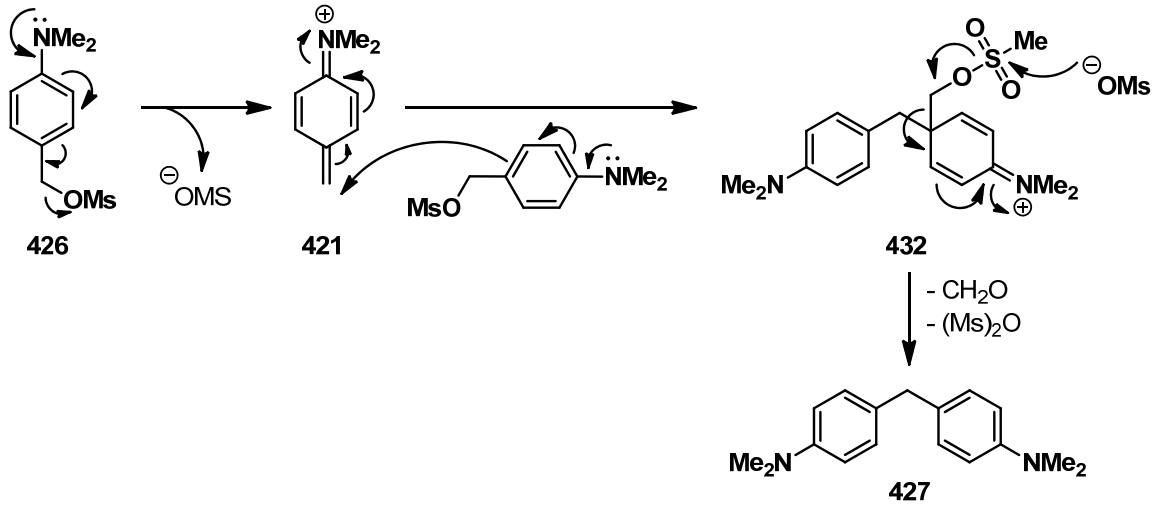
Scheme 94. Synthesis of PDMAB methanesulfonate.

In order to install the PDMAB group on carbohydrate alcohols, compound **430** was synthesized from commercially available **428** *via* benzylidene acetal formation followed by chemoselective benzyl protection of the 3-hydroxyl group.[248] Treatment of **430** with NaH in anhydrous THF at 0 °C followed by addition of freshly prepared **426** in THF, did not provide the desired product **431**, probably due to dimerization of **426** (Scheme 95).



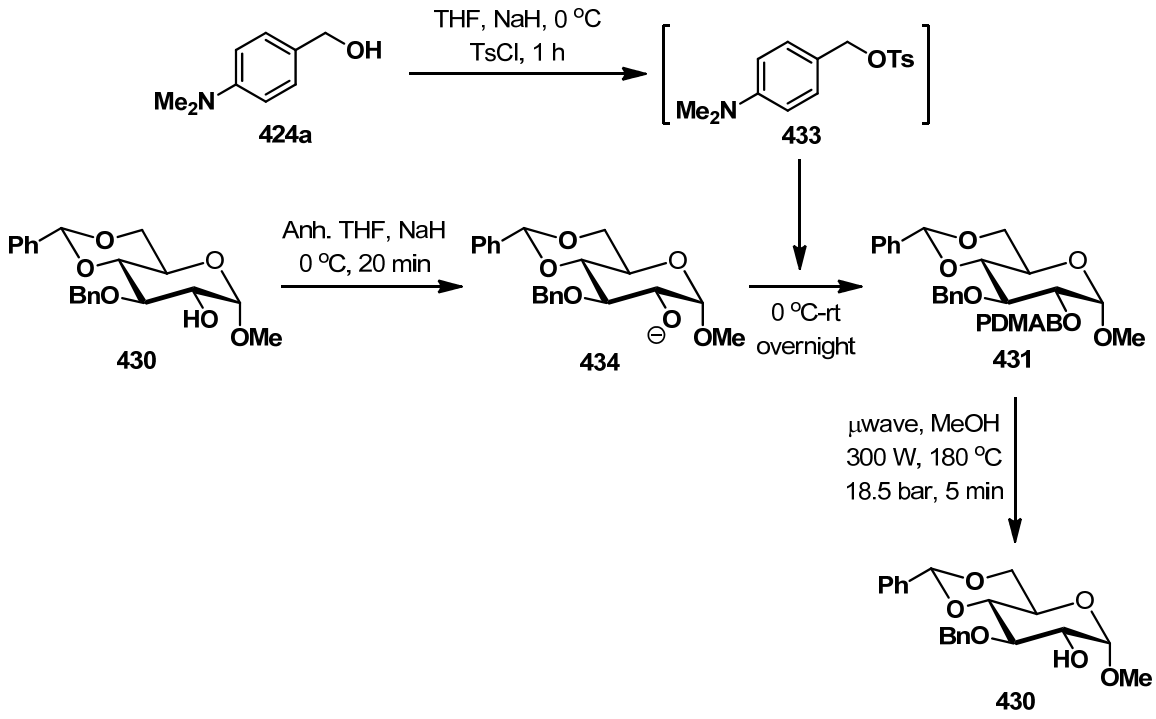
Scheme 95. Initial attempt to install PDMAB group at C-2.

A probable mechanism for the formation of dimmer **427** is shown in Scheme 96. Since OMs is a very good leaving group and **426** is a nucleophilic moiety, electron-donation from them *p*-*N*,*N*-dimethyl group promotes the formation of aza-quinone methide intermediate **421**. Nucleophilic attack onto the methide carbon by **426** forms the intermediate **432**. The mesylate ion then attacks the sulfur atom of the intermediate **432** forming mesyl anhydride, formaldehyde as by product and provides the dimmer **427**.[249]



Scheme 96. Proposed mechanism for the formation dimer **427**.

Thus, we speculated that the corresponding tosylate derivative might be more stable and easy to handle. Accordingly, the tosylate derivative **433** was synthesized from PDMAB alcohol **424a** using tosyl chloride (TsCl) and NaH in THF at 0 ^{o}C and immediately transferred into the flask containing **434**. Gratifyingly, the reaction provided 60% yield of the desired product. With **431** in hand, we then subjected it to previously established microwave irradiation conditions in a 10:1 mixture of methanol and dichloromethane and the reaction afforded **430** in albeit low yield (Scheme 97). Further adjustment of microwave irradiation conditions and use of methanol as solvent provided the desired product in good yield.



Scheme 97. Installation and removal of PDMAB group under microwave irradiation.

With this result in hand, we next decided to examine the installation of PDMAB group at different positions of D-glucose. We have been successful at illustrating that the

PDMAB group can be easily installed on carbohydrates and selectively removed in the presence of benzyl as well as the PMB group (Figure 34).[250]

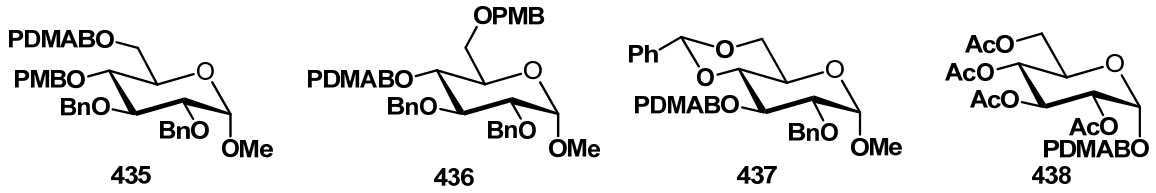


Figure 34. PDMAB is removable in presence of PMB under microwave irradiation.

5.3. *p*-(*N*,*N*-Dimethylamino)-Benzyl Thiol (PDMAB-SH) as a Novel Functional Handle to Install Thiol Group in Carbohydrate Synthesis

Glycobiology[251] has been rapidly developing in the combined areas of carbohydrate chemistry and biochemistry as a means to study the synthesis and biological properties of natural polysaccharides.[252] In recent years, glycobiology has utilized well-defined carbohydrates and derivatives to study various biological systems. These studies have shown that carbohydrates interact with proteins in a specific manner and they play crucial roles in cell proliferation, communication, death, and adhesion. Furthermore, carbohydrates have been implicated to be involved in many infectious diseases as well as cancer.[253]

However, for a detail understanding of these specific interactions, well-defined carbohydrate ligands are essential for the development of new therapeutic drugs. Toward this extent, thioglycosides in which sulfur replaces oxygen of normal glycosidic bond, have become the typical glycosyl donors in the synthesis of thio-oligoaccharides. In addition, protein-thio-oligoaccharide binding studies indicate that *S*-linked oligosaccharides are more flexible and have more conformational isomers than their

counterpart natural *O*-linked.[254] Furthermore, the *S*-atom of the *S*-linked oligosaccharides can form hydrogen bonds with ligands and thus provide additional advantages over *C*-linked oligosaccharides.[255]

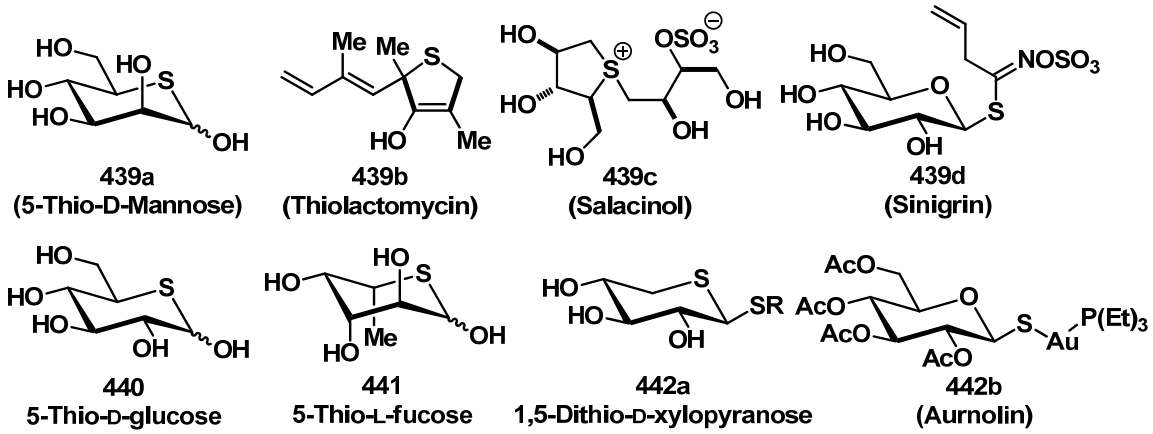
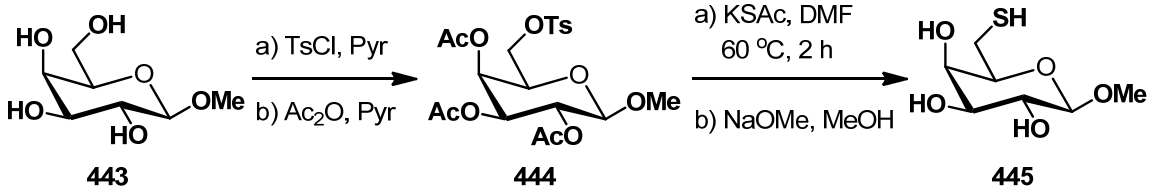


Figure 35. Examples of bioactive thioglycosides.

To date, 5-thio-D-mannose (**439a**, isolated from the marine sponge *Clathia pyramida*), thiolactomycin (**439b**, isolated from *Norcardia sp.*), salacinol (**439c**, isolated from Indian anti-diabetes herb *Salacia reticulata*) and the plant metabolite sinigrin (**439d**) are the only known natural thioglycosides (Figure 35).[256] Although, natural thio-glycosides are rare, thioaldoses are known to inhibit glycosidases.[257] D-glucose transportation across membranes and release of insulin are known to be affected by 5-thio-D-glucose.[258] 5-Thio-L-fucose has shown strong inhibition of bovine α-L-fucosidase.[259] The 1,5-dithio-D-xylopyranoses have been found to be essential components of orally active antithrombotic glycoside theraputics.[260a] Auranolin was marketed as Ridaura for the treatment of Rheumatoid arthritis (Figure 35).[260b] Several other synthetic thiophycosides have shown promising biological activities.[260c] Moreover, recent study showed that *S*-linked glycosides are not being easily degraded by chemical

and enzymatic hydrolysis compared to their *O*-linked counter parts.[255b, 261] Experimental evidence suggests that thio-glycosides have potential as therapeutics to treat cancer and other infectious diseases.[262] In addition, thio-glycosides have also been employed to introduce fatty alkyl chains on sugars for the preparation of non-ionic surfactant and liquid crystals. Conversion of glyconolactones into *S*-alkyl-1-thiopentitols, has provided important molecular properties e.g. amphiphilic and mesophasic.[263]

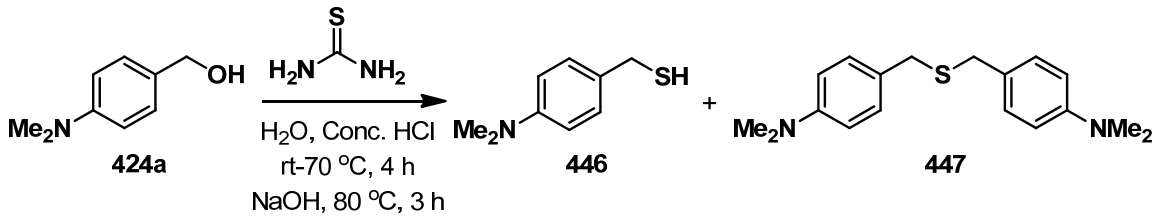
Thus, efficient synthetic methods for synthesizing thio-glycosides are necessary since these structures can serve as acceptors in the synthesis of bioactive thio-oligosaccharides. In 1961, Schwartz *et al.* and Adley *et al.* independently synthesized thioglycosides for the first time.[264] Thereafter, the chemistry of thioglycosides was advanced by many groups e.g. Whistler *et al.*[265], Al-Masoudi-Hughes,[266] Hashimoto-Yusua,[267] and others.[268]



Scheme 98. Representative synthetic method to install thiol group on carbohydrates.

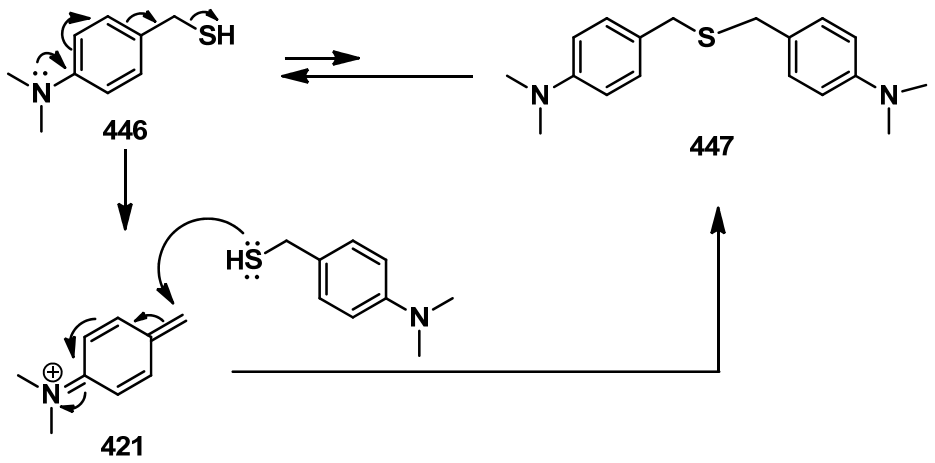
There are few synthetic methods available to install a thiol (-SH) group on carbohydrates.[269] Existing methods require external additives to install a sulfur-bearing group followed by a chemical deprotection. In addition, these reaction suffers from low yields and removal of the by-products remains problematic.[270] For example, to install a thiol group at the 6-position, the most common method is the nucleophilic displacement of 6-iodo/6-tosyl group by a thioacetate group, followed by base-catalyzed removal of the

acetate group (Scheme 98) which is not compatible if benzoyl or chloroacetyl groups are present in the same carbohydrate. With the success of PDMAB group as new functional handle and protecting group under neutral conditions, we envisioned that the PDMAB alcohol **424a** can be converted into the corresponding thiol **446** and used as a masked thiol (Scheme 99). Moreover, we speculated that the PDMAB thiol can also be removed under microwave irradiation employing previously established conditions.

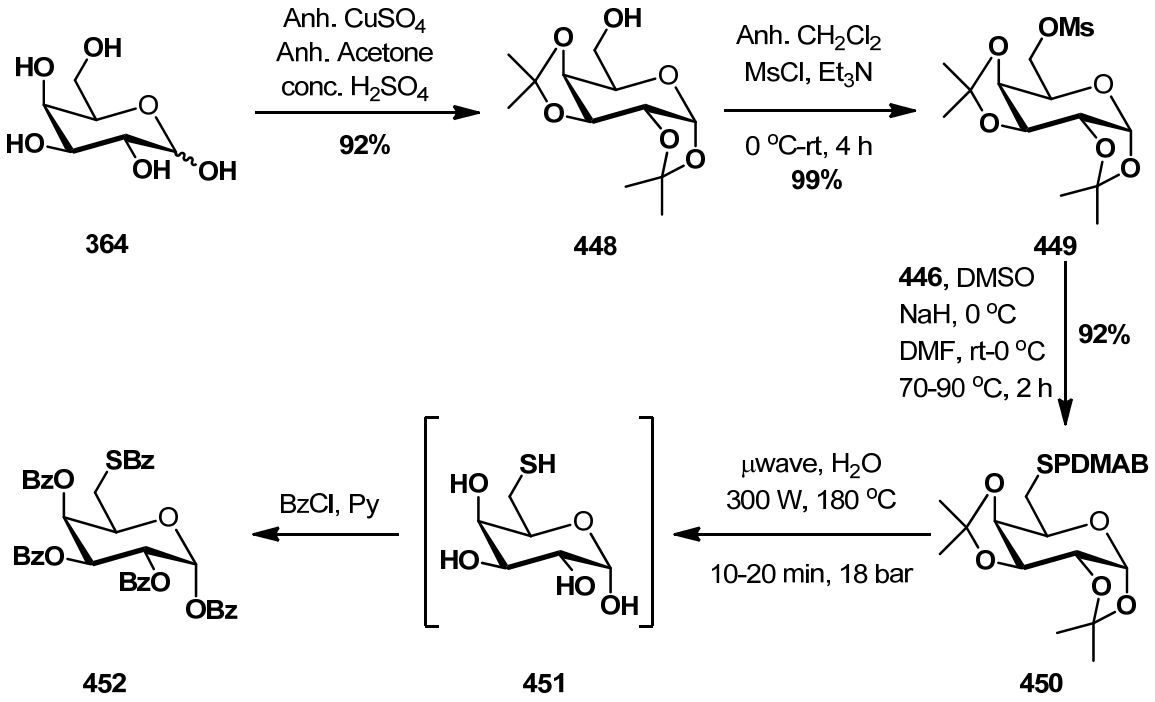


Scheme 99. Synthesis of PDMAB-SH.

PDMAB thiol **446** was synthesized following a literature procedure on similar substrate.[271] Treatment of **424** with a aqueous HCl solution of thiourea, refluxing the solution at 70 °C, followed by basification and refluxing provides 70% of the desired product **446** along with the 20% of the dimerized side-product **447** (Scheme 99). It has been observed that storage of compound **446** as a concentrated solution, in particular nonpolar solvents, leads to reversible formation of the dimeric species **447**. It is quite noteworthy that **446** forms a different dimer compared to **424** (Scheme 94 and Scheme 99) This may be due to the fact that –SH is bad leaving group compared to –OH and sulfur is more nucleophilic than oxygen. Hence, the thiol group of remaining **446** can attack the methide carbon of the aza-quinone methide intermediate and deprotonation provides dimeric coumpound **447** (Scheme 100).



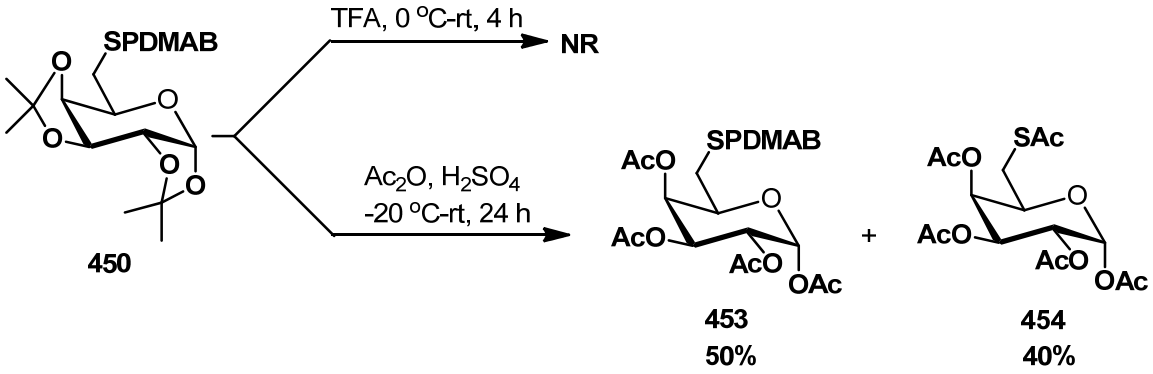
Scheme 100. Proposed mechanism for the formation of dimer **447**.



Scheme 101. Installation of PDMAB-SH on C-6 of galactoside.

We speculated that the dimer **447** might not interfere with the installation of PDMAB-S group on carbohydrates and decided to use the crude reaction immediately without purification. D-Galactose **364** was converted to the corresponding1,2,3,4-diisopropylidine derivative **448** in presence of anhydrous $CuSO_4$ in dry acetone and

concentrated sulfuric acid.[309] Mesylation of **448** using MsCl in presence of Et_3N afforded quantitative yield of **449**. Initial attempts to perform a S_N2 displacement on **449** using NaH, DMF and **446** at room temperature did not provide any of the desired product. After a thorough literature search, we decided to use DMSO a primary solvent and DMF as the co-solvent (helps to prevent solidification of solution) in the displacement reaction and the reaction provided excellent yield of the desired product **450** (Scheme 101) Microwave irradiation of **450** in water forms **451** with concurrent loss of PDMAB-S and isopropylidine groups. Since it is known that compound of the type **451** are susceptible to undergo dimerization, we decided not to isolate **451** and treat with benzoyl chloride to afford the corresponding benzoyl derivative **452**.

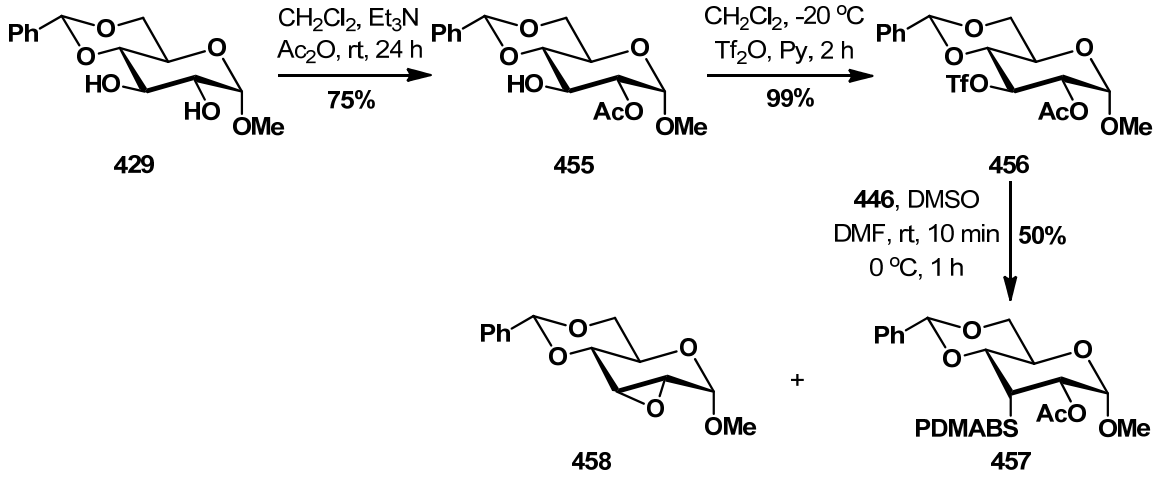


Scheme 102. Stability of PDMAB-S group under acidic conditions.

Next, we examined the stability of the PDMAB-S group under acidic conditions. It has been observed that the PDMAB-S group is quite stable under acidic conditions. Treatment of **450** with trifluoroacetic acid (TFA) for 4 h did not provide the expected product; only starting material was recovered (Scheme 102). In order to remove the isopropylidine groups and simultaneously protect by acetate group, **450** was treated with acetic anhydride and concentrated sulfuric acid at -20 °C. Even, under this condition, the

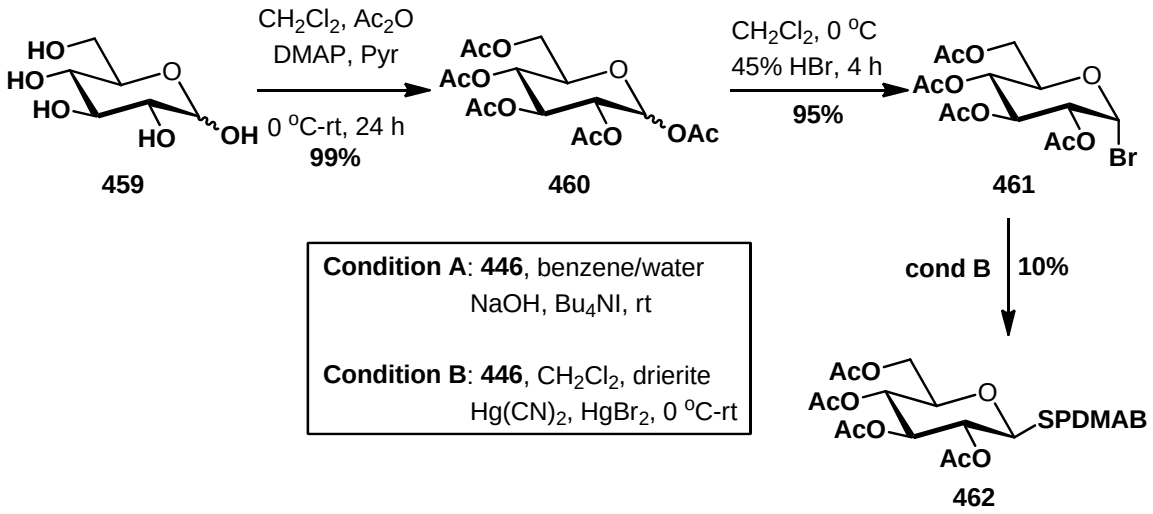
PDMAB-S was quite stable the expected product **453** was obtained in about 50% yield (Scheme 102).

Then, we examined the installation of PDMAB-S group on the C-3 position of galactoside. Thus, compound **455** was synthesized from **429** by treating with acetic anhydride in presence of Et_3N at room temperature. Compound **455** was converted to the triflate **456** by treating with triflic anhydride and pyridine at -20 ^oC. The triflate 456 was used directly after work for the S_N2 displacement in presence of **426** and NaH in DMSO/DMF. Gratifyingly, the reaction provided expected product **457** was obtained in 60% yield along with 30% of the unexpected product **458** (Scheme 103) Identity of compound **457** and **458** was confirmed by ^1H, ^{13}C NMR as well as HRMS. It is known that neighbouring group participation of ester functionalities in the triflate-activated carbohydrates, where 5- or 6-membered acyloxonium intermediates may form during thiolation and also solvent plays important roles.[310] We think that compound **458** is forming *via* a 5-membered ring intermediate, however, the detailed mechanism is not known at this point in time.



Scheme 103. Installation of PDMAB-S group at C-3 of D-glucoside.

Next, we focused on installing PDMAB-S group at the anomeric carbon. Thus, the glycosyl bromide **461** was synthesized from D-glucose **459** via peracetylation followed by bromination using 45% HBr in AcOH. Initial attempt to install **446** under phase transfer conditions did not provide the desired product **462**. However, when $HgBr_2$-$Hg(CN)_2$ catalyst was employed, **462** was obtained in low yield (Scheme 104).

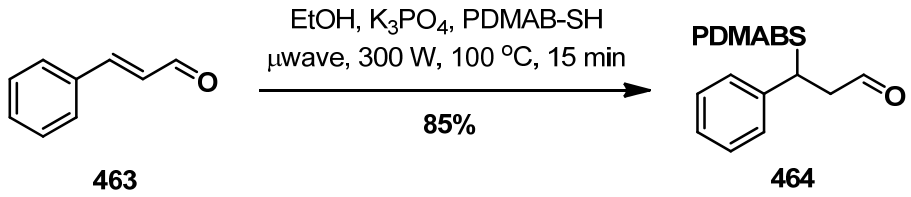


Scheme 104. Installation of PDMAB-S group at the C-1 of glucoside.

5.4. Application of *p*-(*N*,*N*-Dimethylamino)-Benzyl Thiol (PDMAB-SH) Toward the Synthesis of β-Thio Carbonyl Building Blocks

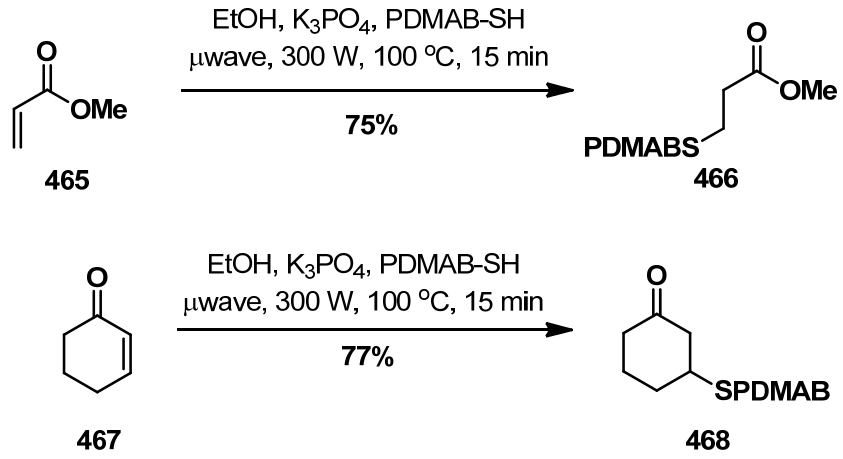
β-Thio aldehydes are very important synthetic building blocks because the sulfur functionality can be readily removed by oxidative or reductive means, or converted into other useful functional groups e.g. sulfoxides or disulfides. Thus, they are the part of active research interest of many chemists.[274] We examined the possibility of of using PDMAB-SH to synthesize β-thio aldehydes in conjunction of microwave irradiation.

Thus, we elected to use cinnamaldehyde **463**, the thio-Michael reaction and the reaction provided good of the desired sulfa-Michael addition (SMA) product **464** (Scheme 105).



Scheme 105. Sulfa-Michael addition toward β-thio aldehyde synthesis.

Following these studies, we have synthesized a few other sulfa-Michael products as shown in Scheme 106. These thio-Michael/sulfa-Michael products can be irradiated under microwave in future to obtain β-thio/β-sulfa carbonyl building blocks. In addition, employing a chiral catalyst in the sulfa-Michael addition can lead to an asymmetric synthesis of these β-thio/ β-sulfa ketones.



Scheme 106. Examples of additional SMA products.

5.5. Studies Toward the Synthesis of *p*-(*N*,*N*-Dimethylamino)-Benzyl Selenol (PDMAB-SeH) as Novel Functional Handle to Install Selenol on Carbohydrates.

In contrary to recent developments in glycobiology and of interest in thio-oligosaccharide, there are very few literature reports available on seleno-glycosides or seleno-oligosaccharides. This could be due to the rare occurrence of seleno-containing natural carbohydrates. However, in 1977, Zingaro and coworkers[275] strongly suggested the presence of naturally-containing seleno-glycosides in *Astragalus racemosus*. Although, nearly 20 years earlier, scientists had suggested that selenium is essential for mammalian organisms.[276] In 1974, Zingaro and co-workers discovered the presence of selenium in the enzyme glutathione peroxidase.[277a] Recent studies indicate that selenium plays essential roles to prevent inflammatory, cardiovascular, neurological, cancer, infectious diseases as well as in aging.[277] Furthermore, seleno-sugars metabolites have been found in rats (Figure 36).[277]

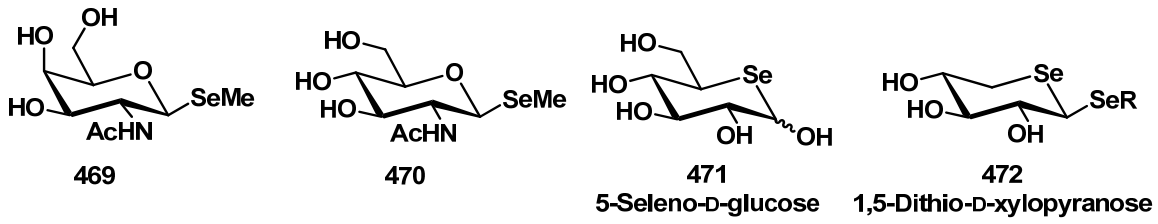
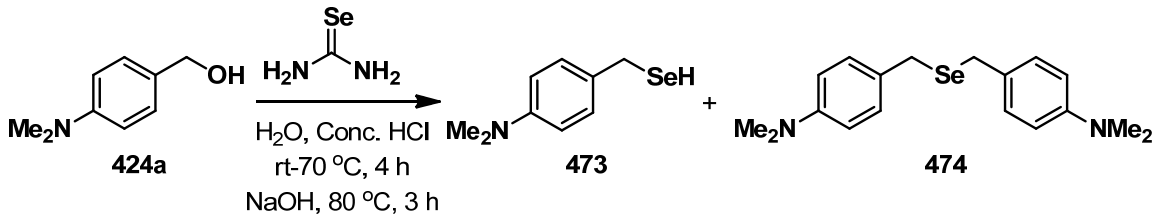


Figure 36. Metabolites and bioactive seleno-glycosides.

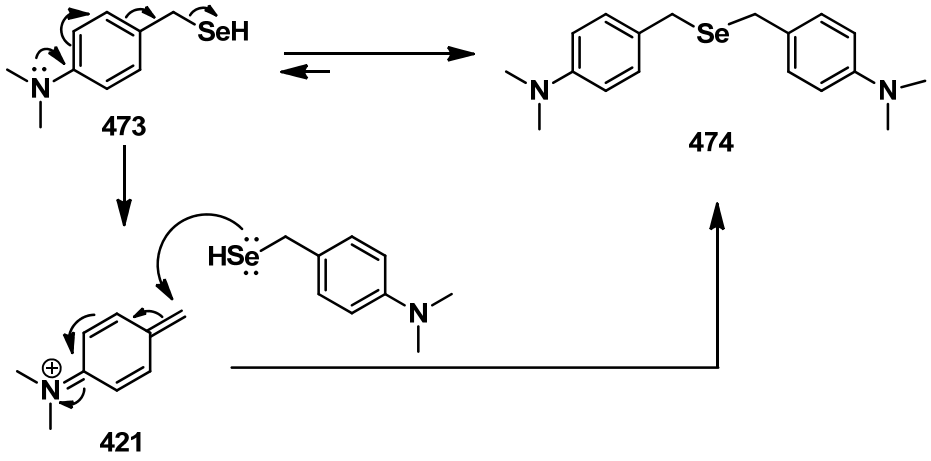
We speculated that *p*-(*N*,*N*-dimethylamino)benzyl selenol **473** (PDMAB-SeH) can synthesized using selenourea under similar conditions to that of PDMAB-SH (Scheme 107). However, when we attempted the reaction, only the dimeric species **474** was obtained as the major product as confirmed by ^{1}H, ^{13}C NMR and HRMS. Although, we

had isolated a fraction from the crude reaction mixture and ^{1}H NMR was quite satisfactory to that of **473**, the HRMS did not match with our expected exact mass. It could be due to the very unstable nature of compound **473** under the HRMS measurement conditions. Formation of **474** takes place via similar mechanism as shown earlier except the equilibrium lies completely toward the dimer.



Scheme 107. Effort toward the synthesis of **473**.

The mechanism of formation for the dimer **474** is presumed to follow the same pathway as that for PDMAB-SH (Scheme 108). It must be noted that PDMAB-SeH and PDMAB-SH forms dimeric species containing their hetero atoms incorporated within the benzylic carbons; whereas PDMAB-OH forms dimeric compound without incorporating *O*-atom within the benzylic carbons (Scheme 94).



Scheme 108. Proposed mechanism for the formation of **474**.

5.6. Materials and Methods

All Reagents were purchased from Aldrich unless otherwise noted. *p*-*N*,*N*-dimethylamino benzaldehyde was purchased from Alfa Aesar. Anhydrous methanol, tetrahydrofuran, acetone and dichloromethane were purchased from Alfa Aesar. Anhydrous methanol was purchased from EMD chemicals (DriSolv). *p*-Toluene sulfonic acid was purchased from Acros organics. Thiourea and selenourea were purchased from Alfa Aesar. Except as otherwise indicated, reactions were carried out under Argon. Microwave reactions were conducted using a capped vial on CEM Discover System. All reactions were monitored by thin layer chromatography using 0.25 mm Dynamic Adsorbents, L.L.C. precoated silica gel (particle size 0.03-0.07 mm, catalog no. 84111). Column chromatography was performed using Whatman Purasil 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise noted. Diastereomeric ratios were determined from ^{1}H NMR spectra of non-purified reaction mixtures. Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Unity 500 and Varian 500 Direct Drive System spectrometers. The residual $CDCl_3$ singlet at δ 7.26 ppm and δ 77 ppm were used as the standard for ^{1}H NMR and ^{13}C NMR spectra respectively. Mass spectra were recorded on Micromass GCT at 70 eV.

5.6.1. General method for PDMAB deprotection from acyclic Ugi product:

To a 10 mL vial (CEM Discover System) equipped with magnetic stirring bar, 50 mg of acyclic Ugi starting material was taken and 2.5 mL of distilled water was added to it. The vial was capped properly and placed in the microwave. Then microwave was run for 20-25 min at 200 ^{o}C, 18 Bar and 300 W. After cooling the vial at

room temperature, ethyl acetate was added and shaken thoroughly. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 2 mL). The organic layers were combined, dried over Na_2SO_4 and filtered. The filtrate was dried under vacuum and purified by gradient silica gel column chromatography using a mixture of ethyl acetate and hexane (1:5 to 1:2) as the eluent.

5.6.2. General method for the installation of PDMAB group starting from PDMAB alcohol:

To a oven dried RB flask equipped with magnetic stir bar, *p*-*N*,*N*-dimethylamino benzaldehyde (2 g, 13.4 mmol), was taken. Anhydrous methanol (52 mL) was added to the flask and stirred at 0 ^oC for 15 min. To the stirring solution, $NaBH_4$ (0.83 g, 21.94 mmol) was added slowly in portion. The resulting mixture was stirred for 30 min at 0 ^oC and the reaction was quenched with water (40 mL) slowly. The mixture was then extracted with dichloromethane (2 × 30 mL) and the organic layer was washed with brine (2 × 20 mL). The organic layers were combined and dried over Na_2SO_4 and concentrated under vacuum on rotavap. The alcohol **424a** was sufficiently pure (>98%), stored under Argon and used without further purification.

A solution of **424a** (53.6 mg, 0.354 mmol) in anhydrous THF (1.5 mL) was added dropwise to a RB flask containing NaH (60% mineral oil) (14 mg, 0.354 mmol) in 1 anhydrous THF (1 mL) at 0^oC while stirring. After 1 h, TLC showed complete consumption of starting material and formation of **433** (confirmed by ^1H NMR), and the reaction mixture was kept at 0^oC for immediate addition in the next step.

NaH (60% in mineral oil) (28 mg, 0.708 mmol) was taken in a oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, 1 ml anhydrous THF

was added and the solution was cooled to 0°C. The alcohol **430** (100 mg, 0.354 mmol) in 1.5 ml anhydrous THF was added dropwise to the stirring solution at 0 °C. After stirring 20 min, freshly prepared PDMAB (*para*- dimethyl amino benzyl) tosylate (**433**) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was then allowed to warm to room temperature slowly and stirred overnight. The reaction was quenched with water (0.5 mL) and diluted with ethyl acetate (50 mL). The reaction mixture was then washed with brine (2 x 25 mL), water (2 x 25 mL), and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum on rotavap and the residue was purified by gradient silica gel column chromatography using a mixture of ethyl acetate and hexane (1:4 to 1:2) as the eluent.

5.6.3. General method for the installation of PDMAB thio group at C-6 starting from PDMAB thiol:

Thiourea (0.94 g, 12.3 mmol) was dissolved in a mixture of water (1.3 mL) and 12 N HCl (2.5 mL). To stirring mixture, alcohol **424a** (1.85 g. 12.3 mmol) was added and the clear solution was stirred at room temperature for 1 h followed 3 h at 70 °C. The reaction mixture was then cooled to room temperature and solution of NaOH (2.02 g) in water (4.9 mL) was added. A light green precipitate of isothiourea formed which was heated to 80 °C for 30 min. The precipitate was dissolved and an oily organic layer was formed. The reaction mixture was transferred to a separatory funnel and extracted with diethyl ether (2 × 20 mL). The aqueous layer was titrated with 12 N HCl to pH 12 and extracted with diethyl ether (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under vacuum on rotavap. For spectroscopic characterization, the small amount of the crude product (40 mg) was purified via preparative TLC using a

1:10 mixture of ethyl acetate and hexane as the eluent to obtain the pure thiol **446**. The crude product contains ~20% of the dimeric compound **447** and used without further purification for subsequent experimentations.

D-Galactose (4 g, 22 mmol) and anhydrous $CuSO_4$ (8 g, 50 mmol) were taken in a oven dried RB flask equipped with magnetic stir bar under Argon. Anhydrous acetone (100 mL) was added to the flask and stirred for 10 min and then concentrated H_2SO_4 (0.5 mL) was added to the mixture. The resulting solution was stirred at room temperature for 40 h. The reaction was then filtered and the residue was washed with acetone (2 × 10 mL). The filtrate was then treated $NaHCO_3$ (25 mL) and concentrated under reduced pressure on rotavap. The residue was extracted with $CHCl_3$ (4× 40 mL) and the combined $CHCl_3$ extracts were dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The crude product was purified via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent to afford **448**.

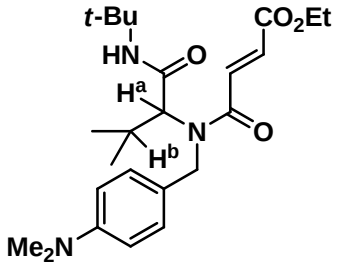
To an oven dried RB flask **448** (2.23 g, 0.86 mmol) was taken and dissolved in dichloroemethane (3.5 mL). Triethylamine (0.14 mL, 1.03 mmol) was added dropwise to the stirring solution at -5 ^oC. To the resulting mixture, methanesulfonyl chloride (0.09 mL, 1.12 mmol) was added dropwise. The reaction mixture was then slowly warmed to 25 ^oC and stirred for 4 h until TLC showed complete consumption of starting material. The reaction was then diluted with dichloromethane (3 mL) at 0 ^oC and treated with saturated $NaHCO_3$ (5 mL). The organic layer was separated, washed with brine (2 × 10 mL) and dried over Na_2SO_4. After concentrating the organic layer on rotavap, the syrup

was purified via silica gel column chromatography using a 1:2 mixture of ethyl acetate and hexane as the eluent to afford **449**.

The thiol **446** (0.19 g, 1.15 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. Anhydrous DMSO was added to the flask and the solution was cooled to 0 ^{o}C. NaH (60% in mineral oil, 0.082 g, 1.23 mmol) was added to the solution and the ice-bath was removed. After stirring at room temperature for 30 min, the reaction mixture was cooled to 0 ^{o}C and a solution of the mesylate **449** in anhydrous DMSO was added dropwise. Next, anhydrous DMF (2 mL) was added to the reaction mixture to prevent solidification at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 30 min, then slowly warmed to room temperature and heated to 80-100 ^{o}C until TLC showed complete consumption of the mesylate **449**. The reaction was quenched with slow addition of water (1 mL) at 0 ^{o}C and further diluted with water (50 mL). The solution was extracted with ethyl acetate (2 × 20 mL) and the organic layer was separated. The aqueous layer was washed with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The crude syrup was purified via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent to afford 0.306 g of the pure **450**.

5.7. Experimental Data

1. **(*E*)-ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)(4-(dimethylamino)benzyl)amino)-4-oxobut-2-enoate**



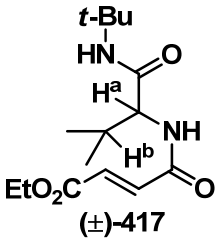
(±)-415

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, 1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 7.03 (d, 2H, *J* = 8.9 Hz, aryl), 6.75 (d, 1 H, *J* = 15.4 Hz, -C<u>H</u>=CH-), 6.44 (bs, 1 H, -N<u>H</u>), 461 (dd, 2 H, *J* = 37.3, 17.3 Hz, -C<u>H</u>$_2$Ar), 4.22 (bs, 1 H, H^a), 4.17 (q, 2 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 2.44 (septet, 1 H, *J* = 6.5 Hz, H^b), 1.27 (s, 9 H, *t*-Bu), 1.25 (t, 3 H, *J* = 7.3 Hz, -OC<u>H</u>$_2$CH$_3$), 0.93 (d, 2 H, *J* = 6.5 Hz, *i*-Pr), 0.75 (d, 3 H, *J* = 6.5 Hz, *i*-Pr)

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 166.6, 165.4, 149.9, 134.4, 131.4, 127.9, 112.5, 60.9, 51.1, 40,5, 28.5, 27.2, 19.6, 19.0, 14.0

HRMS (EIMS, M^+): calcd for $C_{24}H_{37}N_3O_4$ 431.2784, found 431.2787.

2. **(*E*)-ethyl 4-((1-(*tert*-butylamino)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobut-2-enoate**



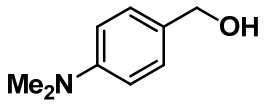
(±)-417

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, 1 H, J = 8.6 Hz, -NH), 7.03 (d, 1 H, J =15.2 Hz, -CH=CH-), 6.81 (d, 1 H, J = 15.2 Hz, -CH=CH-), 4.23 (q, 2 H, J = 7.3 Hz, -OCH_2CH_3), 4.20 (dd, 1 H, J = 9.1, 4.6 Hz, H^a), 2.03 (m, H^b), 1.32 (s, 9 H, *t*-Bu), 1.29 (t, 3 H, J = 7.3 Hz, -OCH_2CH_3), 0.95 (d, 3 H, J = 6.5 Hz, *i*-Pr), 0.93 (d, 3 H, J = 6.5 Hz, *i*-Pr)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 165.4, 163.7, 136.2, 130.6, 61.1, 59.5, 51.7, 31.4, 29.7, 28.6, 19.1, 18.4, 14.1

HRMS (EIMS, M^+): calcd for $C_{15}H_{26}N_2O_4$ 298.1893, found 298.1889.

3. ***p*-*N*,*N*-Dimethylaminobenzyl (PDMAB) alcohol**



424a

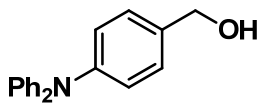
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, 2 H, *J* = 8.3 Hz, aryl), 6.75 (d, 2 H, *J* = 8.9 Hz, aryl), 5.57 (d, 1 H, *J* = 2.7 Hz, -CH_2Ar), 2.98 (s, 6 H, -NMe_2), 1.88 (bs, 1 H, OH)

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 128.9, 128.5, 112.6, 65.2, 40.6

HRMS: EIMS (M^+): calcd for $C_9H_{13}NO$ 151.0997, found 151.0995

4. ***p*-*N*,*N*-Diphenylaminobenzyl (PDPAB) alcohol**

It was synthesized from *p*-*N*,*N*-Diphenylamino benzaldehyde following similar procedure as described for PDMAB alcohol.



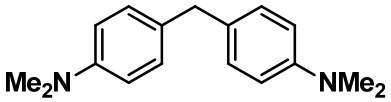
424b

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.32 (m, 6 H, aryl), 7.11-7.17 (m, 6 H, aryl), 7.03-7.09 (m, 2 H, aryl), 4.63 (d, 1 H, *J* = 2.8 Hz, -C<u>H$_2$</u>Ar), 2.85 (bs, 1 H, OH)

^{13}C NMR (125 MHz, $CDCl_3$): δ147.6, 147.2, 134.9, 129.1, 128.2, 124.0, 123.9, 122.6, 64.6,

HRMS (EIMS, M^+): calcd for $C_{19}H_{17}NO$ 275.1310, found 275.1310.

5. **4,4'-methylenebis(*N*,*N*-dimethylaniline)**



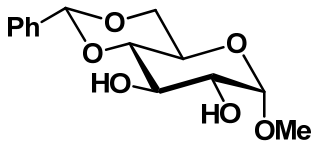
427

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14-7.08 (m, 4H), 6.76-6.71 (m, 4H), 3.86 (d, 2H, *J* = 4.4 Hz), 2.95 (s, 6H), 2.94 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.3, 130.6, 129.7, 113.3, 41.2, 40.2.

HRMS (EIMS, M^+): calcd for $C_{17}H_{22}N_2$ 254.1783, found 254.1786.

6. **Methyl 4-6-O-benzylidine- α-D-glucopyranoside**



429

To a oven dried RB flask equipped with magnetic stir bar under Argon, methyl-α-D-glucopyranoside (1.0 g, 5.15 mmol) was taken and dissolved in anhydrous DMF (20 mL). To the stirring solution, α,α-dimethoxy benzaldehyde (0.95 mL, 6.18 mmol) was

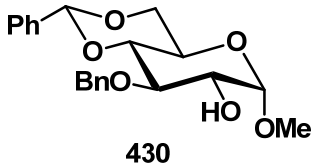
added followed by catalytic amount of *p*-tosyl sulfonic acid at room tempertaure. The resulting solution was stirred at room temperature for 1 h and on rotavap (virtually dried apparatus) for 6 h at 45-50 ^{o}C. Then the reaction mixture was quenched with saturated $NaHCO_3$ (2 mL) and diluted with water (100 mL). The solution was extracted with ethyl acetate (3 × 20 mL) and the organic layers were combined, dried over Na_2SO_4. The organic layer was concentrated under reduced pressure on rotavap and purified via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 2:1) as the eluent to afford 1.16 g of pure methyl 4-6-*O*-benzylidine-α-D-glucopyranoside (**429**).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.50 (m, 2 H, Ph), 7.30-7.36 (m, 3 H), 5.49 (s, 1 H, -CHPh), 4.72 (d, 1 H, *J* = 4.0 Hz, H-1), 4.24 (dd, 1 H, *J* = 9.8, 4.4 Hz, H-4), 3.89 (t, 1 H, *J* = 9.2 Hz, H-2), 3.76 (dt, 1 H, *J* = 15.0, 4.6 Hz, H-6), 3.69 (t, 1 H, *J* = 10.1 Hz, H-3), 3.57 (dd, 1 H, *J* = 9.2, 3.7 Hz, H-6), 3.44 (t, 1 H, *J* = 9.2 Hz, H-5), 3.40 (s, 3 H, OMe), 3.0 (bs, 2 H, 2-OH, 3-OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6, 137.1, 129.1, 128.2, 126.3, 101.8, 99.8, 80.9, 72.7, 71.3, 68.9, 62.3, 55.4, 36.4, 31.4.

HRMS (EIMS, M^+): calcd for $C_{14}H_{18}O_6$ 282.1103, found 282.1101.

7. **Methyl 3-*O*-benzyl-4-6-*O*-benzylidine- α-D-glucopyranoside**



430

Methyl 4-6-*O*-benzylidine-α-D-glucopyranoside (**429**) was dissolved in benzene and 40% KOH was added to the flask. Next, benzyl chloride was added slowly at room

temperature and the resulting mixture was refluxed for 10 min. After TLC showed complete consumption of starting material, the reaction was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent.

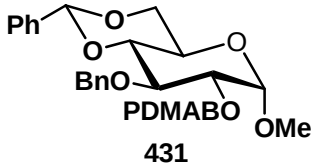
^{1}H NMR (400 MHz, C_6D_6): δ: 7.60 (d, 2H, *J* = 7.3 Hz, aryl), 7.38 (d, 2H, *J* = 7.3 Hz, aryl), 7.17 (dd, 2H, *J* = 7.3, 7.3 Hz, aryl), 7.13-7.08 (m, 3H, aryl), 7.04 (d, 1H, *J* = 7.3 Hz, aryl), 5.27 (s, 1H, benzylidene H), 4.94 (d, 1H, *J* = 11.4 Hz, -Bn), 4.78 (d, 1H, *J* = 11.4 Hz, -Bn), 4.44 (d, 1H, *J* = 4.1 Hz, H_1), 4.06 (dd, 1H, *J* = 10.5, 4.9 Hz, H_6), 3.74 (dd, 1H, *J* = 9.7, 8.9 Hz, H_3), 3.72 (ddd, 1H, *J* = 10.5, 9.7, 4.9 Hz, H_5), 3.66 (dd, 1H, *J* = 9.7, 4.1 Hz, H_2), 3.42 (dd, 1H, *J* = 10.5, 8.9 Hz, H_4), 3.39 (dd, 1H, *J* = 10.5, 9.7 Hz, $H_{6'}$), 2.84 (s, 3H, -OMe).

^{13}C NMR (125 MHz, C_6D_6): δ 139.6, 138.5, 129.0, 128.5, 128.3, 128.1, 127.9, 127.6, 126.6, 101.6, 100.5, 82.2, 79.5, 74.8, 73.2, 69.1, 62.9, 54.9.

IR (neat): 3519, 2954, 2921, 2851, 1737, 1464, 1367, 1330, 1283, 1213, 1174, 1142, 1078, 1032, 993, 968, 749, 736, 695, 672, 657, 621.

HRMS (EIMS, M^+): calcd for $C_{21}H_{24}O_6$ 372.1573, found 372.1574.

8. **Methyl 2-*O*-*p*-*N*,*N*-dimethylaminobenzyl-3-*O*-benzyl-4-6-*O*-benzylidine-α-D-glucopyranoside**



431

^{1}H NMR (400 MHz, C_6D_6): δ: 7.63 (d, 2H, *J* = 6.5 Hz, aryl), 7.45 (d, 2H, *J* = 7.3 Hz, aryl), 7.33 (d, 2H, *J* = 8.9 Hz, aryl), 7.22-7.06 (m, 6H, aryl), 6.58 (d, 2H, *J* = 8.9 Hz, aryl), 5.36 (s, 1H, benzylidene H), 5.02 (d, 1H, *J* = 11.4 Hz, -PDMAB), 4.92 (d, 1H, *J* = 11.4 Hz, -PDMAB), 4.76 (d, 1H, *J* = 11.3 Hz, -Bn), 4.62 (d, 1H, *J* = 11.3 Hz, -Bn), 4.63 (d, 1H, *J* = 3.2 Hz, H_1), 4.27 (dd, 1H, *J* = 9.7, 8.9 Hz, H_3), 4.14 (dd, 1H, *J* = 9.7, 4.9 Hz, H_6), 3.92 (ddd, 1H, *J* = 10.5, 9.7, 4.9 Hz, H_5), 3.67 (dd, 1H, *J* = 8.9, 3.2 Hz, H_2), 3.55 (dd, 1H, *J* = 9.7, 9.7 Hz, H_4), 3.49 (dd, 1H, *J* = 10.5, 9.7 Hz, $H_{6'}$), 3.07 (s, 3H, -OMe), 2.48 (s, 6H, -NMe_2 on PDMAB).

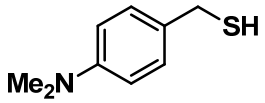
^{13}C NMR (125 MHz, C_6D_6): δ 150.6, 139.9, 138.6, 129.7, 128.9, 128.3, 128.1, 127.9, 127.4, 126.7, 112.7, 101.7, 99.8, 82.9, 79.6, 78.8, 75.2, 73.5, 69.4, 62.8, 55.1, 40.2.

HRMS: ESIMS $(M+H)^+$ calcd for $C_{30}H_{36}NO_6$ 506.2543, found 506.2519.

$[\alpha]^{23}_D$ -51.6^o (c, 0.19, $CHCl_3$)

IR (neat): 3064, 3033, 2923, 2855, 1733, 1708, 1672, 1614, 1523, 1454, 1369, 1352, 1213, 1175, 1086, 1054, 1030, 995, 918, 807, 747, 698, 677, 657, 626, 614.

9. ***p*-*N*,*N*-Dimethylaminobenzyl thiol**



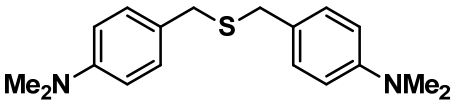
446

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, 2 H, *J* = 8.9 Hz, Aryl), 6.71 (d, 2 H, *J* = 8.6 Hz, Aryl), 3.17 (d, 2 H, *J* = 7.0 Hz, -C<u>H$_2$</u>Ar), 2.95 (s, 6 H, -N<u>Me$_2$</u>).

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 128.9, 128.7, 112.8, 40.7, 28.5.

HRMS: EIMS (M^+) calcd for $C_9H_{13}NS$ 167.0769, found 167.0775.

10. **4,4'-(Thiobis(methylene))bis(*N*,*N*-dimethylaniline)**



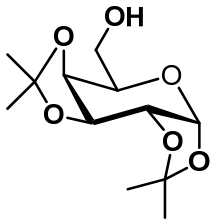
447

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2 H, *J* = 8.6 Hz, Aryl), 7.16 (d, 2 H, J = 8.6 Hz, Aryl), 6.71 (t from d and d overlap, *J* = 8.6 Hz, 4 H, Aryl), 3.63 (s, 2 H, -C$\underline{H}_2$Ar), 3.57 (s, 2 H, -C$\underline{H}_2$Ar), 2.95 (s, 12 H, 2 × –N$\underline{Me}_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.9, 149.5, 130.2, 129.7, 129.4, 126.2, 124.9, 112.7, 112.5, 53.4, 43.1, 40.7, 40.6, 34.9.

HRMS: EIMS (M^+) calcd for $C_{18}H_{24}N_2S$ 300.1660, found 300.1661.

11. **1,2:3,4-Diisopropylidine-α-D-galactopyranoside**



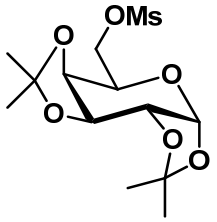
448

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.54 (d, 1 H, J = 5.5 Hz, H-1), 4.59 (dd, 1 H, J = 7.9, 2.4 Hz, H-2), 4.31 (dd, 1 H, J = 5.5, 2.5 Hz, H-3), 4.25 (dd, 1 H, J = 7.9, 1.8 Hz, H-4), 3.66-3.88 (m, 3 H, H-5 and H-6 overlap), 2.34 (bs, 1 H, 6-OH), 1.51 (s, 3H, Me), 1.43 (s, 3 H, Me), 1.31 (s, 6 H, Me and Me overlap).

^{13}C NMR (75 MHz, $CDCl_3$): δ 109.4, 108.6, 96.2, 71.5, 70.7, 70.5, 68.1, 62.2, 25.9, 25.8, 24.9, 24.2

HRMS: EIMS (M^+) calcd for $C_{12}H_{20}O_6$ 260.1260, found 260.1255.

12. **1,2:3,4-Di-*O*-isopropylidine-6-methanesulfonyl-α-D-galactopyranoside**



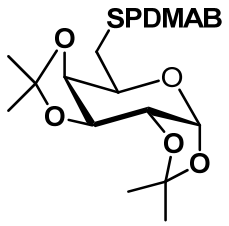
449

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (d, 1 H, J = 4.9 Hz, H-1), 4.58 (dd, 1 H, J = 7.4, 2.4 Hz, H-2), 4.27-4.33 (m, 3 H, H-5 and H-6 overlap), 4.19 (dd, 1 H, J = 8.1, 1.6 Hz, H-3), 4.05 (m, 1 H, H-4), 3.03 (s, 3 H, Me), 1.48 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.28 (s, 6 H, Me and Me overlap).

^{13}C NMR (100 MHz, $CDCl_3$): δ 109.6, 108.8, 96.0, 70.4, 70.1, 68.9, 66.2, 37.7, 25.8, 25.7, 24.7, 24.2.

HRMS: EIMS (M^+) calcd for $C_{13}H_{22}O_8S$ 338.1035, found 338.1029.

13. **1,2:3,4-Di-*O*-isopropylidine-6-*p*-*N*,*N*-dimethylaminobenzyl-thio-α-D-galactopyranoside**



450

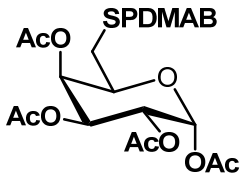
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, 2 H, J = 8.5 Hz, aryl), 6.68 (d, 2 H, J = 8.5 Hz, aryl), 5.54 (d, 1 H, J = 4.9 Hz, H-1), 4.61 (dd, 1 H, J = 7.9, 2.1 Hz, H-2), 4.33 (dd, 1 H, J = 7.9, 1.8 Hz, H-3), 4.30 (dd, 1 H, J = 4.9, 2.4 Hz, H-4), 3.87 (dt, 1 H, J = 7.0, 1.8 Hz, H-

5), 3.71 (s, 2 H, -C<u>H</u>$_2$Ar), 2.92 (s, 6 H, NMe_2), 2,68 (d, 2 H, J = 7.0 Hz, H-6), 1.53 (s, 3 H, Me), 1.45 (s, 3 H, Me), 1.35 (s, 3 H, Me), 1.33 (s, 3 H, Me)

^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 129.8, 129.6, 125.9, 112.7, 109.1, 108.4, 96.6, 71.5, 70.8, 70.5, 67.5, 40.6, 36.1, 30.6, 26.1, 25.9, 24.8, 24.4

HRMS: EIMS (M^+) calcd for $C_{21}H_{31}NO_5S$ 409.1935, found 409.1930

14. **1,2,3,4-tetraacetate-6-*p*-*N*,*N*-dimethylaminobenzyl-thio-α-D-galactopyranoside**



453

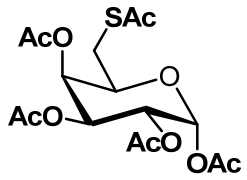
Compound **453** (0.01 g, 0.02 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and Ac_2O (2 mL) was added to the flask at -20 ^oC. To the stirring solution, 2 drops of concentrated H_2SO_4 was added via a syringe. After stirring the solution at -20 ^oC for 2 h, it was allowed to reach room temperature slowly and stirred for 24 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified via preparative TLC using a 1:3 mixture of ethyl acetate/hexane as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, 2 H, J = 8.5 Hz, aryl), 6.69 (d, 2 H, J = 8.3 Hz, aryl), 6.35 (d, 1 H, J = 1.2 Hz, H-1), 5.51-5.54 (m, 1 H, H-2), 5.26-5.29 (m, 1 H, H-3), 4.04 (m, 1 H, H-4), 3.86-3.88 (m, 1 H, H-5), 3.64 (d, 2 H, J = 2.8 Hz, -C<u>H</u>$_2$Ar), 2.94 (s, 6 H, NMe_2), 2.58 (dd, 1 H, J = 13.7, 6.7 Hz, H-6), 2.41 (dd, 1 H, J = 13.7, 7.3 Hz, H-6),

2.15 (s, 3 H, -COC$\underline{H}_3$), 2.09 (s, 3 H, -COC$\underline{H}_3$), 2.01 (s, 3 H, -COC$\underline{H}_3$), 2.00 (s, 3 H, -COC$\underline{H}_3$)

HRMS (M^+, EIMS): calcd for $C_{23}H_{31}NO_9S$ 497.1720, found 497.1710

15. **1,2,3,4-tetraacetate-6-thioacetate-α-D-galactopyranoside**

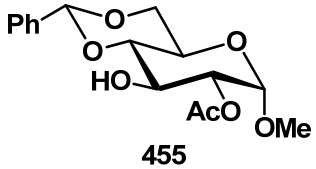


454

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (d, 1 H, J = 4.3 Hz, H-1), 5.47 (t, 1 H, J = 4.3 Hz, H-2), 5.39 (dd, 1 H, J = 6.4, 3.7 Hz, H-3), 4.26 (dd, 1 H, J = 11.6, 6.1 Hz, H-6), 4.15 (dd, 1 H, J = 11.6, 6.1 Hz, H-6), 3.76 (t, 1 H, J = 4.6 Hz, H-4), 2.92-2.95 (m, 1 H, H-5), 2.13 (s, 6 H, -COC$\underline{H}_3$ and -COC$\underline{H}_3$ overlap), 2.10 (s, 3 H, -COC$\underline{H}_3$), 2.09 (s, 3 H, -COC$\underline{H}_3$), 2.08 (s, 3 H, -COC$\underline{H}_3$)

HRMS: EIMS (M^+ + Na) calcd for $C_{16}H_{22}O_{10}NaS$ 429.0831, found 429.0831

16. **Methyl 2-*O*-acetyl-4-6-*O*-benzylidine-α-D-glucopyranoside**



455

To a solution of methyl 4,6-*O*-benzylidine-α-D-glucopyranoside (0.128 g, 0.45 mmol) in anhydrous dichloromethane (1.3 mL) in a oven dried RB flask under under Argon, Ac_2O (0.068 mL, 0.63 mmol) was added slowly. After stirring the solution for 30 min at room temperature, Et_3N (0.41 mL, 4.05 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 24 h and quenched with methanol (5 equiv.)

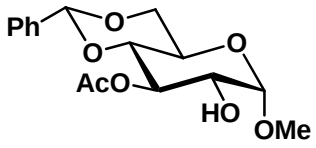
after TLC showed completion of the reaction. The reaction mixture was then concentrated under reduced pressure on rotavap. The residue was dissolved in ethyl acetate (10 mL) and washed with saturated $NaHCO_3$ (2 × 10 mL), brine (2 × 10 mL) respectively. The organic layers were combined and dried over Na_2SO_4. The crude product was purified via gradient column chromatography using silica gel as the stationary phase and a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent to afford the major product as a white solid

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.52 (m, 2 H, Ph), 7.34-7.43 (m, 3 H, Ph), 5.55 (s, 1 H, -C<u>H</u>Ph), 4.95 (d, 1 H, J = 3.7 Hz, H-1), 4.80 (dd, 1 H, J = 9.8, 3.7 Hz, H-4), 4.29 (dd, 1 H, J = 10.1, 4.6 Hz, H-2), 4.17 (t, 1 H, J = 9.5 Hz, H-3), 3.84 (dt, 1 H, J = 10.1, 4.6 Hz, H-6), 3.55 (t, 1 H, J = 9.5 Hz, H-5), 3.44 (s, 3 H, OMe), 2.59 (bs, 1 H, 3-OH), 2.15 (s, 3 H, -COC<u>H</u>$_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 136.9, 129.3, 128.3, 126.3, 102.0, 97.5, 81.3, 73.5, 68.6, 55.4, 20.9.

HRMS: EIMS (M^+) calcd for $C_{16}H_{20}O_7$ 324.1209, found 324.1211

17. **Methyl 3-*O*-acetyl-4-6-*O*-benzylidine-α-D-glucopyranoside**



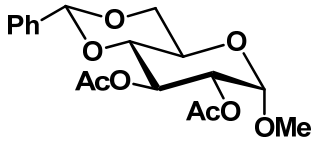
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.47 (m, 2 H, Ph), 7.33-7.38 (m, 3 H, Ph), 5.49 (s, 1 H, -C<u>H</u>Ph), 5.33 (t, 1 H, J = 9.8 Hz, H-3), 4.81 (d, 1 H, J = 3.7 Hz, H-1), 4.31 (dd, 1 H, J = 4.6 Hz, H-4)3.87 (dt, 1 H, J = 10.1, 4.7 Hz, H-6), 3.75 (t, 1 H, J = 10.4 Hz, H-2), 3.66

(dt, 1 H, J = 10.4, 3.8 Hz, H-6), 3.58 (t, 1 H, J = 9.5 Hz, H-5), 3.47 (s, 3 H, OMe), 2.22 (bs. 1 H, 2-OH), 2.12 (s, 3 H, -COC$\underline{H}_3$),

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 136.9, 129.1, 128.2, 126.2, 101.5, 100.1, 78.6, 72.3, 71.9, 68.9, 62.7, 55.6, 21.1

HRMS: EIMS (M^+) calcd for $C_{16}H_{20}O_7$ 324.1209, found 324.1211

18. **Methyl 2,3-di-*O*-acetyl-4-6-*O*-benzylidine-α-D-glucopyranoside**

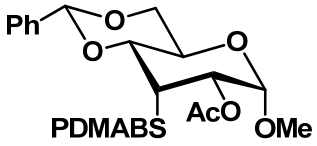


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.47 (m, 2 H, Ph), 7.33-7.38 (m, 3 H, Ph), 5.58 (t, 1 H, J = 9.8 Hz, H-2), 5.55 (s, 1 H, -C$\underline{H}$Ph), 4.89-4.96 (m, 2 H, H-1 and H-3 overlap), 4.33 (dd, 1 H, J = 10.1, 4.9 Hz, H-4), 3.93 (dt, 1 H, J = 9.8, 4.6 Hz, H-6), 3.77 (t, 1 H, J = 10.4 Hz, H-6), 3.67 (t, 1 H, J = 9.8 Hz, H-5), 3.41 (s, 3 H, OMe), 2.09 (s, 3 H, -COC$\underline{H}_3$), 2.05 (s, 3 H, -COC$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.8, 136.9, 129.1, 128.2, 126.1, 101.5, 97.6, 79.2, 71.6, 68.9, 68.8, 62.3, 55.3, 20.8, 20.7.

HRMS: EIMS (M^+) calcd for $C_{18}H_{22}O_8$ 366.1315, found 366.1312

19. **Methyl 2-*O*-acetyl-3-*p*-*N*,*N*-dimethylaminobenzyl-thio-4-6-*O*-benzylidine-α-D-glucopyranoside**



457

Methyl 2-*O*-acetyl-4-6-*O*-benzylidine-α-D-glucopyranoside (**455**) (0.087 g, 0.268 mmol) was dissolved in anhydrous dichloromethane (6.5 mL) and cooled to -40 ^{o}C (dry ice in *m*-xylene). To the stirring solution under Argon, anhydrous pyridine (0.129 mL, 1.6 mmol) was added followed by Tf_2O (0.18 mL, 1.07 mmol) dropwise. The reaction was then monitored via TLC. After 2 h, TLC showed complete consumption of the starting material and the reaction was quenched with 1 N HCl (5 mL). The reaction mixture was then washed with saturated $NaHCO_3$ (10 mL) and water (10 mL) respectively. The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap to obtain the 3-*O*-triflate **456**. Due to the sensitivity toward heat and instability of **456**, it was used directly into the preceding step.

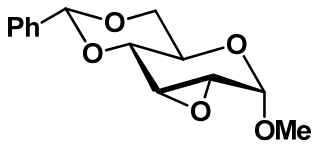
To a oven dried RB flask equipped with magnetic stir bar under Argon, **446** (0.073 g, 0.438 mmol) was dissolved in anhydrous DMSO (1.4 mL). To the flask, NaH (60% in mineral oil, 0.027 g, 0.57 mmol) was added and the mixture was stirred at room temperature for 10 min. The flask was then cooled to -5 ^{o}C and a solution of **456** (0.125 g, 0.274 mmol) in anhydrous DMSO (2 mL) was added slowly. After stirring the solution at 0 ^{o}C for 1 hr, anhydrous DMF (1 mL) was added to prevent further solidification of reaction mixture. The reaction was stirred for additional 1 h at 0 ^{o}C and then slowly warmed to room temperature. After TLC showed complete consumption of starting material, the reaction was quenched with saturated $NaHCO_3$ (5 mL), washed with brine (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.48 (m, 2 H, Ph), 7.32-7.39 (m, 3 H, Ph), 7.22 (d, 2 H, J = 7.7 Hz, aryl), 6.68 (d, 2 H, J = 8.5 Hz, aryl), 5.60 (s, 1 H, -C<u>H</u>Ph), 5.33 (t, 1 H, J = 2.8 Hz, H-2), 4.56 (d, 1 H, J = 1.1 Hz, H-1), 4.24-4.34 (m, 2 H), 4.17 (dd, 1 H, J = 9.2, 3.2 Hz, H-3), 3.85 (dd, 1 H, J = 13.1 Hz, H-6), 3.76 (t, 1 H, J = 11.9 Hz), 3.27 (s, 3 H, OMe), 3.23 (dd, 1 H, J = 2.8, 0.7 Hz, H-4), 2.90-2.96 (m, 7 H, H-5 and NMe_2 overlap), 2.11 (s, 3 H, -COC<u>H</u>$_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 149.9, 137.3, 129.8, 129.1, 128.3, 126.2, 124.8, 112.7, 102.0, 101.6, 74.5, 69.9, 69.3, 58.9, 55.3, 45.8, 40.6, 36.9, 21.3.

HRMS: EIMS (M^+) calcd for $C_{25}H_{31}NO_6S$ 473.1872, found 473.1869

20.



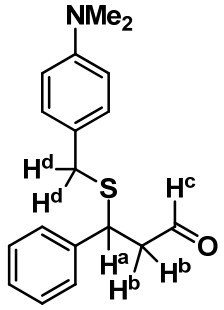
458

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.53 (m, 2 H, Ph), 7.34-7.40 (m, 3 H, Ph), 5.58 (s, 1 H, -C<u>H</u>Ph), 4.89 (d, 1 H, J = 2.7 Hz, H-1), 4.24 (dd, 1 H, J = 10.1, 4.9 Hz), 4.09 (dt, 1 H, J = 9.2, 5.2 Hz), 3.96 (dd, 1 H, J = 9.2, 1.2 Hz), 3.69 (t, 1 H, J = 10.4 Hz), 3.53 (d, 1 H, J = 4.3 Hz), 3.50 (dd, 1 H, J = 4.6, 3.1 Hz), 3.47 (s, 3 H, OMe).

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.1, 129.2, 128.3, 126.3, 102.8, 95.3, 77.9, 68.9, 60.0, 55.9, 53.1, 50.7

HRMS: EIMS (M^+ + Na) calcd for $C_{14}H_{16}NaO_5$ 287.0895, found 287.0895

21. **3-((4-(dimethylamino)benzyl)thio)-3-phenylpropanal**



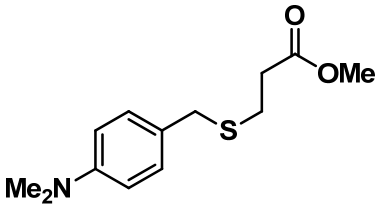
464

To an oven dried 10 mL CEM microwave vial, aldehyde (0.16 g, 1.21 mmol) was dissolved in 2.5 mL EtOH. To the vial, 0.01 g of K_3PO_4 was added followed by the thiol (0.18 g, 1.06 mmol). The vial was capped according to the manufacturer instruction and placed into microwave cavity. Microwave was equilibrated to 100 ^oC for 15 min and TLC showed complete consumption of starting material. The solution was concentrated under reduced pressure on rotavap and the residue was purified via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent. ^1H NMR (500 MHz, $CDCl_3$): δ 9.58 (br t, 1 H, -C<u>H</u>O), 7.32-7.39 (m, 3 H, Ph), 7.24-7.31 (m, 2 H, Ph), 7.09 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.68 (d, 2 H, *J* = 8.6 Hz, Aryl), 4.19 (t, 1 H, *J* = 7.6 Hz, H^a), 3.52 (d, 1 H, *J* = 13.4 Hz, H^d), 3.42 (d, 1 H, *J* = 13.4 Hz, H^d), 2.95 (s, 6 H, -N<u>Me</u>$_2$), 2.86-2.94 (m, 2 H, H^b).

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.7, 149.7, 141.2, 129.7, 128.7, 127.9, 127.5, 124.9, 112.6, 49.5, 42.6, 40.6, 35.1.

HRMS: EIMS (M^+) calcd for $C_{18}H_{21}NOS$ 299.1344, found 299.1342.

22. **Methyl 3-((4-(dimethylamino)benzyl)thio)propanoate**



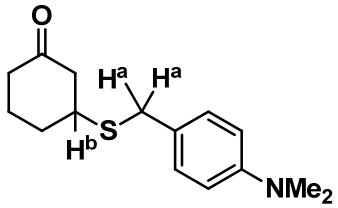
466

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.69 (d, 2 H, *J* = 8.6 Hz, Aryl), 3.68 (s, 3 H, -O<u>Me</u>), 3.67 (s, 2 H, -C<u>H$_2$</u>Ar), 2.94 (s, 6 H, -N<u>Me$_2$</u>), 2.65-2.72 (m, 2 H, -SC<u>H$_2$</u>CH$_2$CO$_2$Me), 2.52-2.60 (m, 2 H, -SCH$_2$C<u>H$_2$</u>CO$_2$Me).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 129.6, 112.7, 51.7, 40.7, 35.7, 34.4, 26.0.

HRMS: EIMS (M^+) calcd for $C_{13}H_{19}NO_2S$ 253.1136, found 253.1342.

24. **3-((4-(Dimethylamino)benzyl)thio)cyclohexanone**



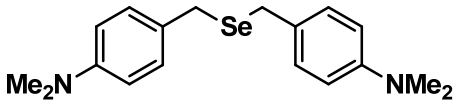
468

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, 2 H, *J* = 8.6 Hz, Aryl), 6.68 (d, 2 H, *J* = 8.3 Hz, Aryl), 3.72 (d, 1 H, *J* = 13.4 Hz, H^a), 3.68 (d, 1 H, *J* = 13.4 Hz, H^a), 2.94 (s, 6 H, -N<u>Me$_2$</u>), 2.89-2.96 (m, 1 H, Cy), 2.67 (dd, 1 H, *J* = 14.3, 4.6 Hz, H^b), 2.28-2.42 (m, 3 H, Cy), 2.03-2.15 (m, 2 H, Cy), 1.61-1.77 (m, 2 H, Cy).

^{13}C NMR (125 MHz, $CDCl_3$): δ 208.9, 149.5, 129.5, 125.6, 112.7, 47.9, 41.7, 40.9, 40.6, 34.4, 31.3, 24.2.

HRMS: EIMS (M^+) calcd for $C_{15}H_{21}NOS$ 263.1344, found 263.1349.

25. **4,4'-(Selenobis(methylene))bis(*N*,*N*-dimethylaniline)**



474

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (t from d and d overlap, 4 H, *J* = 8.1 Hz, Aryl), 6.74 (d, 2 H, *J* = 8.1 Hz, Aryl), 6.72 (d, 2 H, *J* = 8.1 Hz, Aryl), 3.94 (s, 2 H, -C$\underline{H}_2$Ar), 3.74 (s, 2 H, -C$\underline{H}_2$Ar), 2.98 (s, 12 H, 2 × -N$\underline{Me}_2$)

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 149.2, 129.7, 129.6, 126.5, 126.5, 112.6, 112.3, 40.6, 40.5, 32.8, 27.1.

HRMS: EIMS (M^+) calcd for $C_{18}H_{24}N_2Se$ 348.1105, found 348.1111

CHAPTER 6

Synthetic Study Toward Neutral Glycosylation

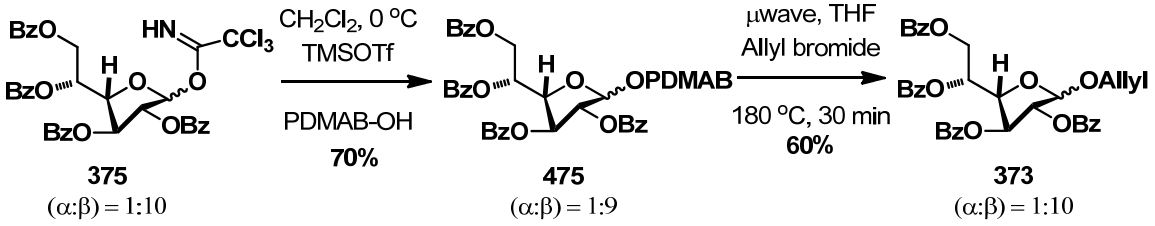
6. Introduction

In recent years, a significant amount of biological studies involving naturally occurring products such as membranes, cell walls, and antibiotics as well as the mechanisms of these substances, made clear the biological significance of the glycons of glycoconjugates (e.g., glycoproteins, glycolipids) in molecular recognition for the exchange of biological information.[278] The *O*-glycosylation method, which is a crucial synthetic methodology to attach carbohydrate to other carbohydrate moieties or other molecules (aglycon), is continuously becoming more and more important. Several synthetic methodologies have been developed in the last decade for this purpose, however many of these requires costly, and toxic reagents.[278] Toward this end, there are few literature reports available that describe glycosylation under nearly neutral or mild conditions. For example, glycosylation using promoter $LiClO_4$,[279] LiOTf,[280] and others.[281] Jensen and co-workers have reported an inter- and intramolecular glycosylation using DISAL (dinitro salisylate derivatives) donors under neutral conditions and .[282] Recently, microwave irradiation has become an alternative choice to perform glycosylation.[281, 283]

Phenols are known to undergo glycosylation with glycosyl halides under mild basic conditions *via* phenoxide ions.[284] Following this observation, we embarked on devising a strategy for neutral glycosylation encompassing the ability of PDMAB group to form alkoxide ion under μwave irradiation.

6.1. A microwave-influenced neutral glycosylation *via* alkoxide

We envisioned that installation of PDMAB group at the anomeric position on carbohydrates followed by subsequent microwave irradiation in the presence of a suitable electrophile might enable us to perform alkoxide-based neutral glycosylation. Thus compound **375** was synthesized from **374** following a previous procedure (Chapter 4, Scheme 88). Glycosylation of **375** in the presence of PDMAB-OH using promoter TMSOTf provided 70% of the desired product **475**. With **475** in hand, we decided to subject it to microwave irradiation in THF in presence of allyl bromide. Gratifyingly, the reaction afforded 60% desired product **373** as a 1:10 mixture of α and β anomers (Scheme 109). The ^{1}H and ^{13}C NMR spectra of the product were in excellent agreement with our previously obtained product **373**.

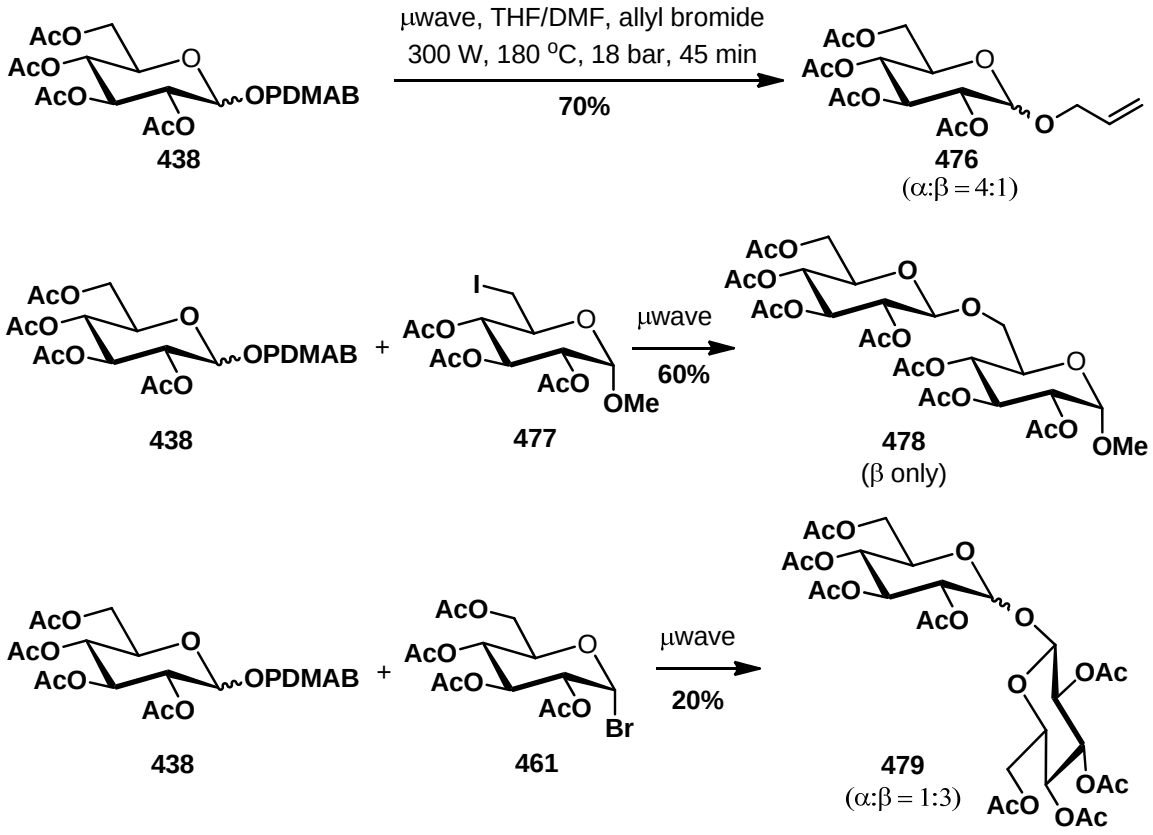


Scheme 109. Microwave-influenced neutral glycosylation *via* alkoxide

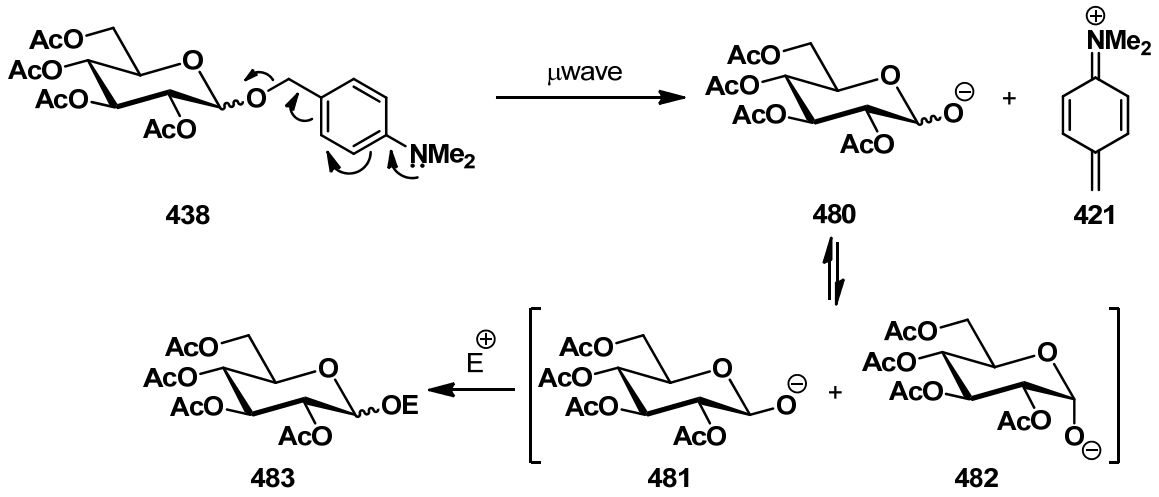
Following this result, our lab was encouraged to apply the methodology using other glycosides. To date, we have been successful in showing that the methodology can provide utility to perform glycosylation to synthesize monosaccharides as well as disaccharides as shown in scheme **134**.[285]

A proposed mechanism for the alkoxide-based neutral glycosylation is shown in scheme **135**. As shown previously (Scheme 97, 101), microwave irradiation promotes the formation alkoxide **480** *via* the formation of the well known aza-quinone methide

421. Intermediate **480** might be in equilibrium with **481** and **482**; in the presence of suitable electrophiles, they undergo S_N2 or S_N2' displacement reactions to afford the final product **483**.



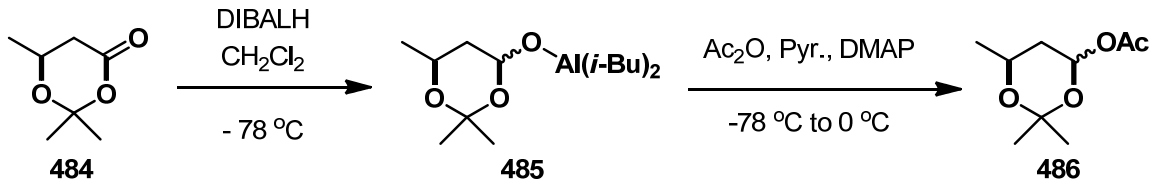
Scheme 110. Application of alkoxide-based neutral glycosylation.



Scheme 111. Proposed mechanism of the alkoxide-based neutral glycosylation.

6.2. Approach Toward an Entirely Neutral Glycosylation *via* Oxocarbenium Ion

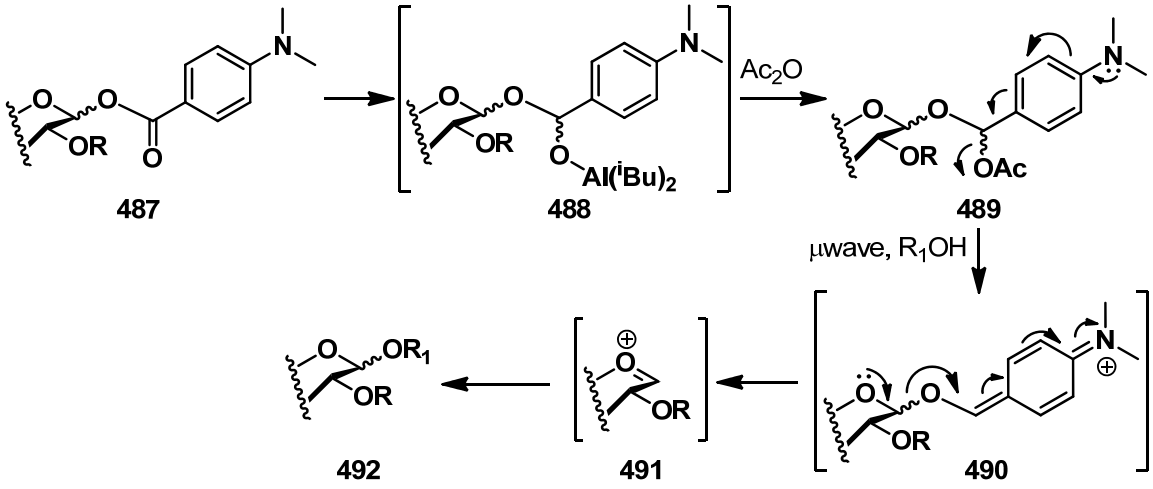
Recently, Rychnovski and co-workers reported a clever method of synthesizing α-acetoxy ethers *via* DIBALH reduction and in situ acetylation of esters (Scheme 112). In presence of DIBALH, the ester **484** forms aluminate **485** that was trapped by acetic anhydride to obtain α-acetoxy ethers **486** as synthetically useful intermediates.[286]



Scheme 112. Rychnovsky's method of preparing α-acetoxy ethers

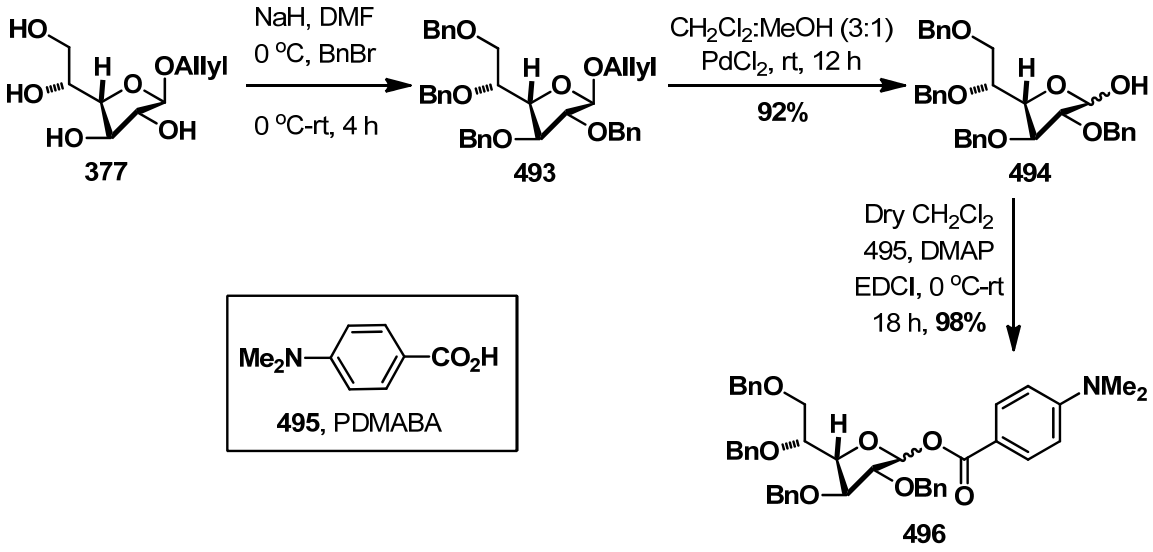
Based on Rychnovsky's method, our hypothesis was that a carbohydrate moiety **487** having an ester group at the anomeric carbon that contains a masked PDMAB group which could be revealed upon DIBALH reduction and in situ trapping with Ac_2O would provide **489** (Scheme 113). Since the α-acetoxy group is an activated leaving group, we

speculated that microwave irradiation would promote the formation of the aza-quinone methide intermediate **490** that would then be eliminated *via* electron donation from the ring oxygen to form the oxocarbenium intermediate **491**. In presence of a suitable acceptor, the donor **491** would be glycosylated to afford **492**.



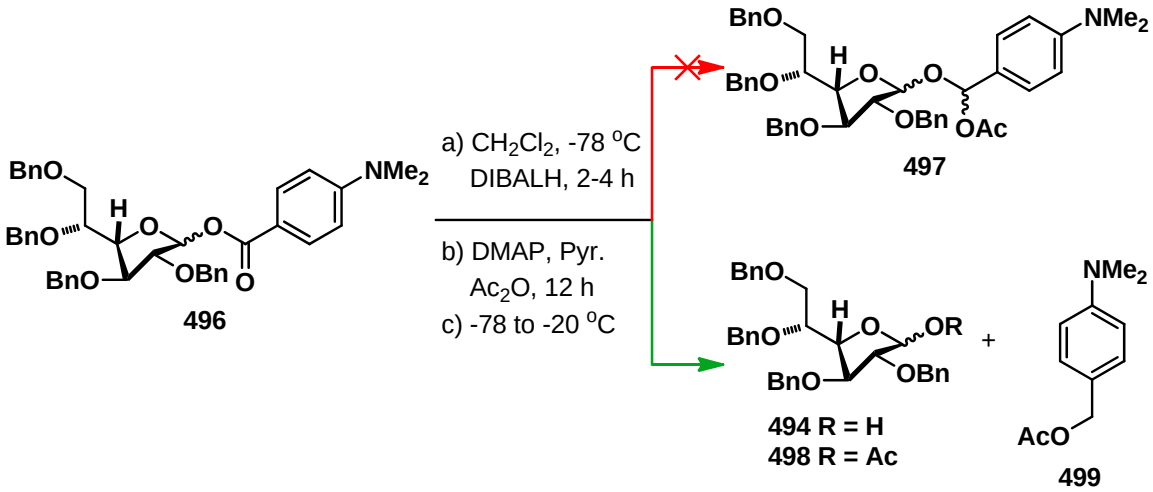
Scheme 113. Working hypothesis toward neutral glycosylation *via* oxocarbonium ion.

With this working hypothesis in mind, we attempted to synthesize the ester **495** *via* a Mitsunobu reaction[287] of the hemiacetal **494** with *p*-(*N*,*N*-dimethylamino)benzoic acid (**495**, PDMABA). However, the reaction provided moderate yield and we chose to use EDCI (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide), DMAP. The EDCI method provided quantitative yield of the desired product **495** (Scheme 114).



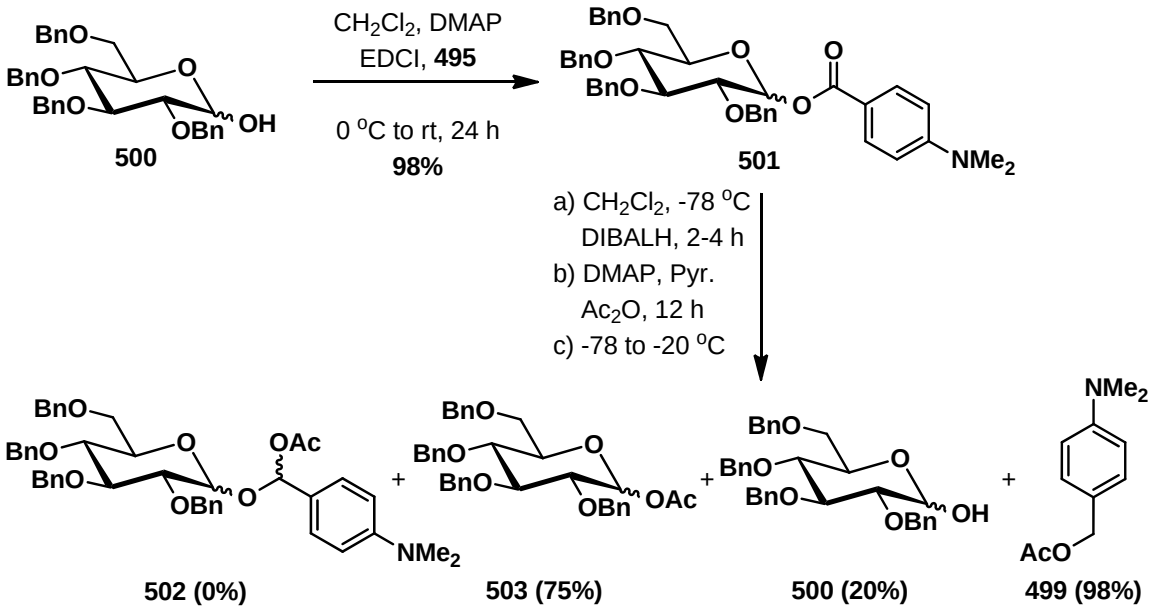
Scheme 114. Synthesis of the PDMABA ester **496**.

When the ester **496** was subjected to Rychnovsky's conditions, the expected product **497** was not obtained (Scheme 115). Instead, a mixture of the hemiacetal **494**, acetate **498** and **499** were obtained. Running the reaction repeatedly under extremely dry solvents, reagents as well as air and moisture free schlenk line, did not provide the desired product

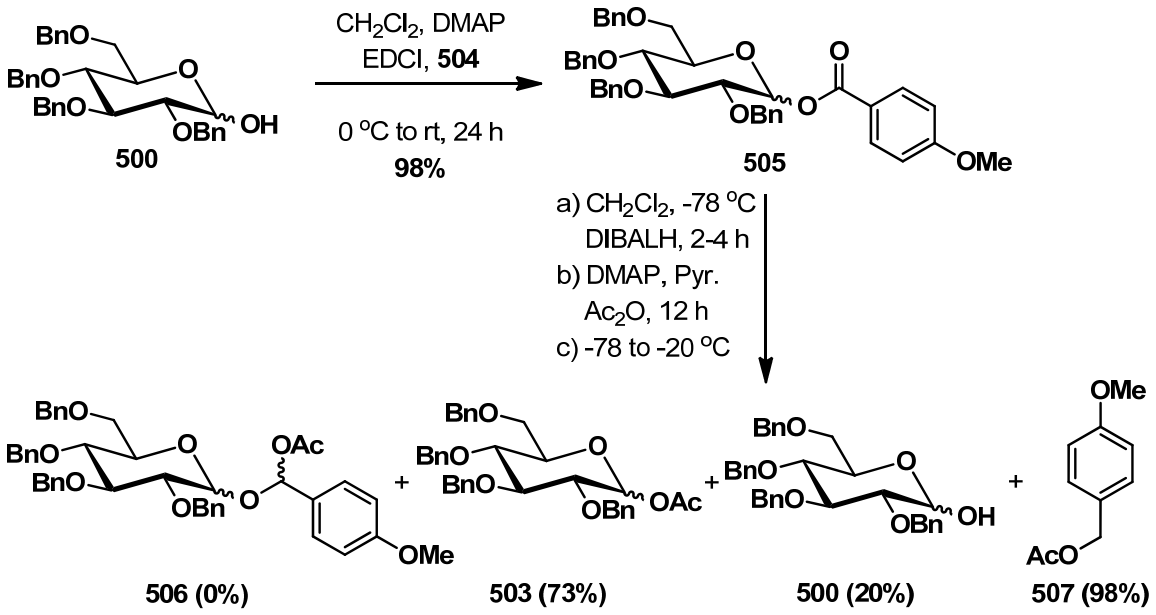


Scheme 115. Attempted synthesis of α-acetoxy ether **497**.

We reasoned that the intermediate of the type **488** is not stable due to the presence of very strong electron-donating *N*,*N*-dimethyl amino group. Also, we speculated that the furanoside ring might not permit the formation of stable oxocarbenium intermediate. Thus, we decided to synthesize the glucoside ester **501** from commercially available hemicaetal **500** *via* EDCI coupling in excellent yield. Unfortunately, when prior conditions of reduction and trapping were employed, the expected product **502** was not obtained again. Instead, the hemiacetal **500**, acetates **503** and **499** were obtained (Scheme 116).

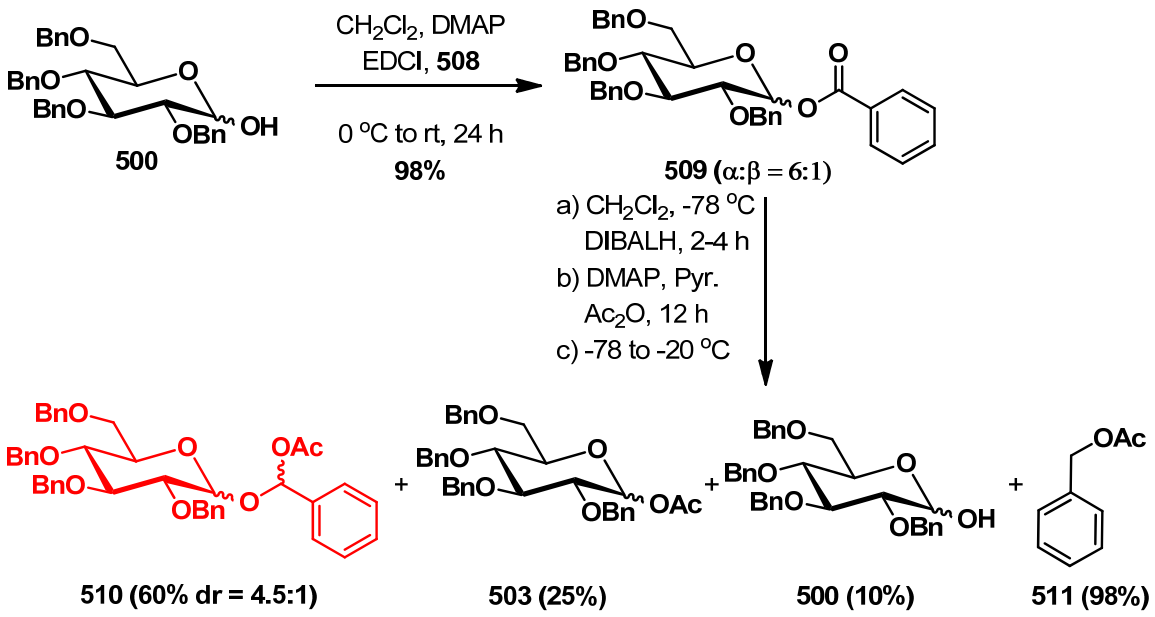


Scheme 116. Attempted synthesis of the ester **502**.



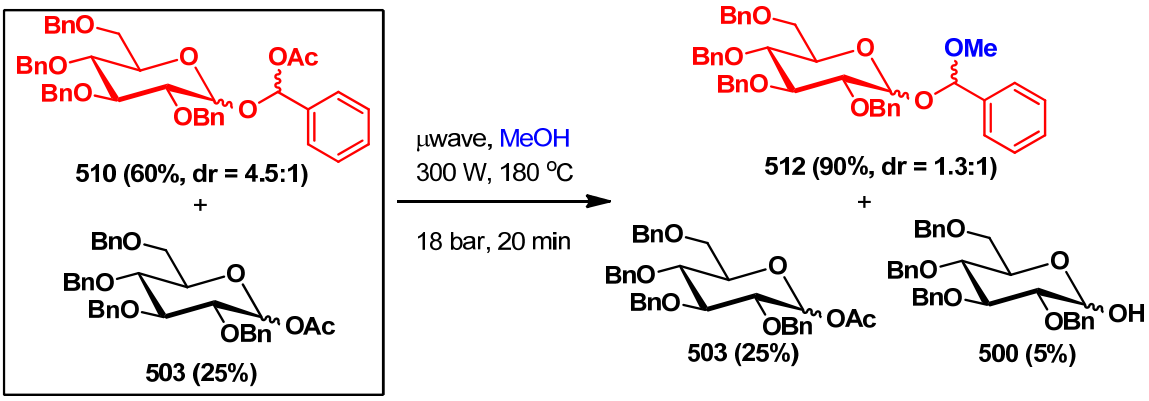
Scheme 117. Attempted synthesis of ester **506**.

Next, we decided to use *p*-methoxy benzoic acid **504** (PMBA) in the EDCI coupling reaction with **500**. The PMBA ester **505** was obtained in excellent yield. Unfortunately, again, when prior conditions were employed, the desired product **506** was not obtained. Instead, the hemiacetal **500**, acetates **507** and **508** were obtained (Scheme 117)

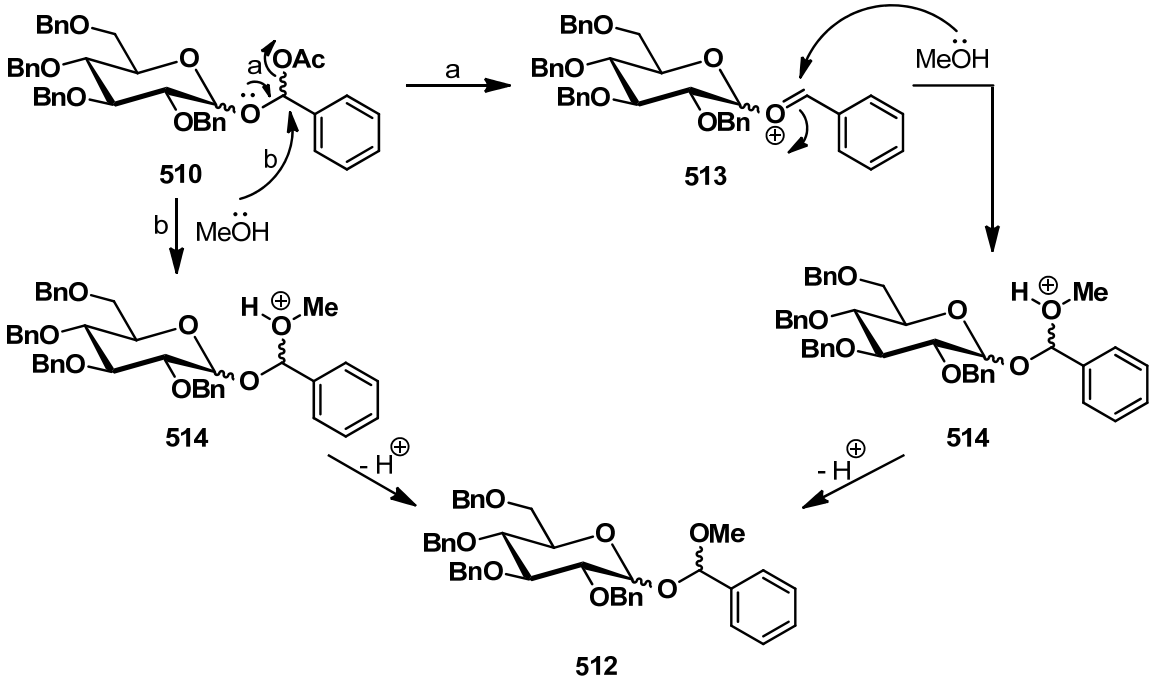


Scheme 118. Synthesis α-acetoxy ether **510** of the benzoic ester **509**.

We then synthesized the benzoic ester **509** from the hemiacetal **500** in excellent yield. Gratifyingly, the ester **509** provided the desired product **510** under Rychnovsky's conditions (Scheme 118). However, **510** was inseparable from the acetate **503** and due to sensitivity of the α-acetoxy ether **510**, we decided to use it as a mixture for the next step. When the ester was irradiated under microwave using methanol as solvent, to our surprise, the α-methoxy ether **512** was obtained as a 1:3 mixture of diastereomers which was separated from the acetate *via* preparative TLC (Scheme 119).



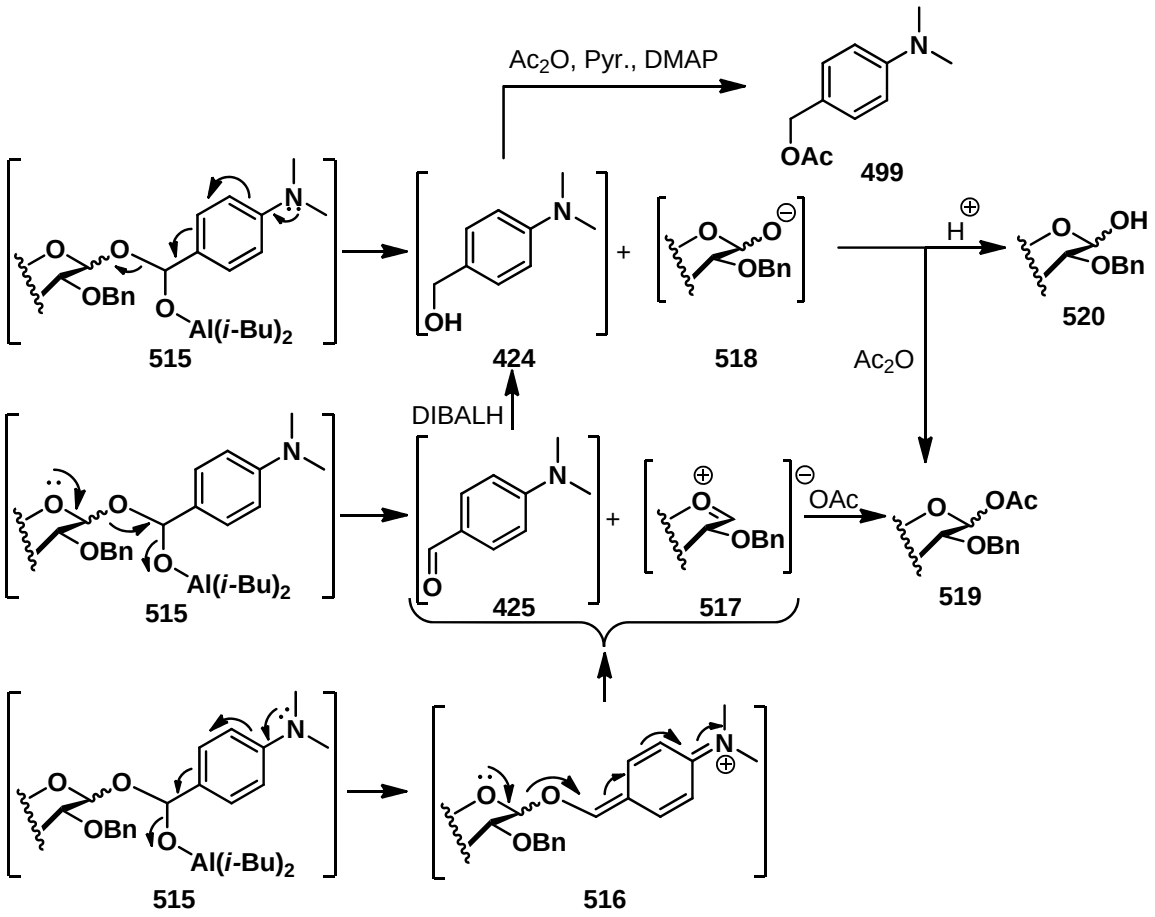
Scheme 119. Formation of α-methoxy ether from α-acetoxy ether under μwave irradiation.



Scheme 120. Proposed mechanism for the formation of α-methoxy ether **512**.

A proposed mechanism for the formation of α-methoxy ether **512** is depicted in Scheme 120. Under microwave irradiation, the lone pair of electrons on the exocyclic anomeric oxygen eliminates the acetate group to form the intermediate **513**. Methanol then attacks the electrophilic benzylic carbon to form the intermediate **514**.

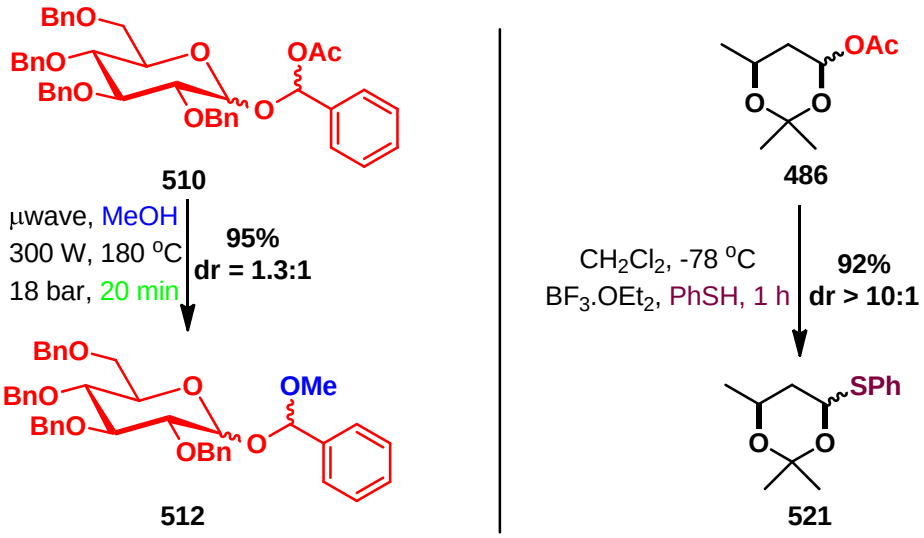
Alternatively, methanol can attack the α-carbon and eliminate the acetate group *via* an S_N2 pathway to form the intermediate **514**. Deprotonation of the intermediate **514** provides the final product **512**.



Scheme 121. Proposed mechanism for the formation of acetate side-products.

A proposed a mechanism that counts for the formation of acetates and hemiacetal from the α-acetoxy ethers is shown in Scheme 121. Electron donation from the *N*,*N*-dimethylamino group (or OMe) from the aluminate **515** under microwave irradiation allows the formation of intermediate **516**. Further electron donation from ring oxygen forms the aldehyde **425** and oxocarbenium intermediate **517**. Alternatively, electron donation from the ring oxygen can eliminate the *O*-aluminate can form the aldehyde **425**

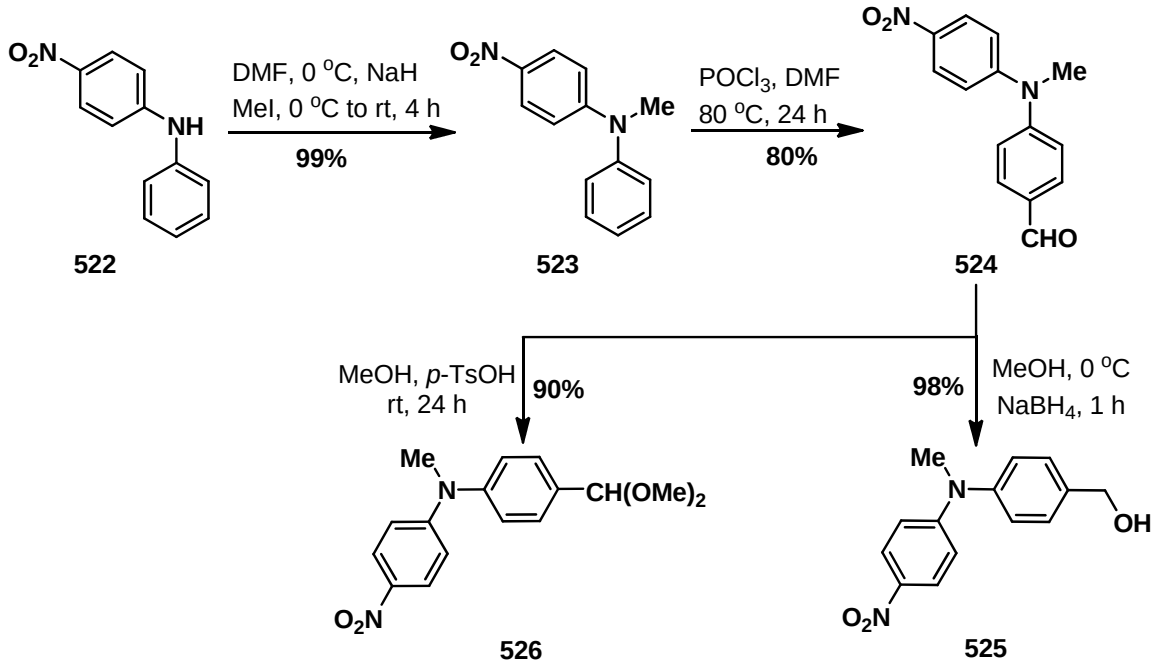
and **517**. This might possibly take place when there is no electron-donating moiety present on the phenyl ring. Reduction by DIBALH converts the aldehyde **425** into corresponding alcohol **424** which can explain the requirement of additional DIBALH during the reaction. Alternatively, electron donation from the *N*, *N*-dimethyl group (or OMe) allows the formation of alkoxide **518** and the alcohol **424** might form *via* hydride reduction. The alkoxide then may undergo protonation to provide the hemiacetal **520** or attack Ac_2O to provide the acetate **519**. The oxocarbenium ion intermediate then undergoes glycosylation with the acetate ion to afford **519**. In the presence of Ac_2O, pyridine and DMAP, the alcohol **424** forms the acetate **499** (or **507** and **511**)



Scheme 122. Comparison of our method with Rychnovsky's method.

It is quite noteworthy that we were able to create a new carbon-hetero atom bond without any external additives from the α-acetoxy ether **510** under entirely neutral conditions utilizing microwave irradiation. On the other hand, Rychnovsky and co-workers have utilized costly additives to obtain similar results as shown in Scheme 122.

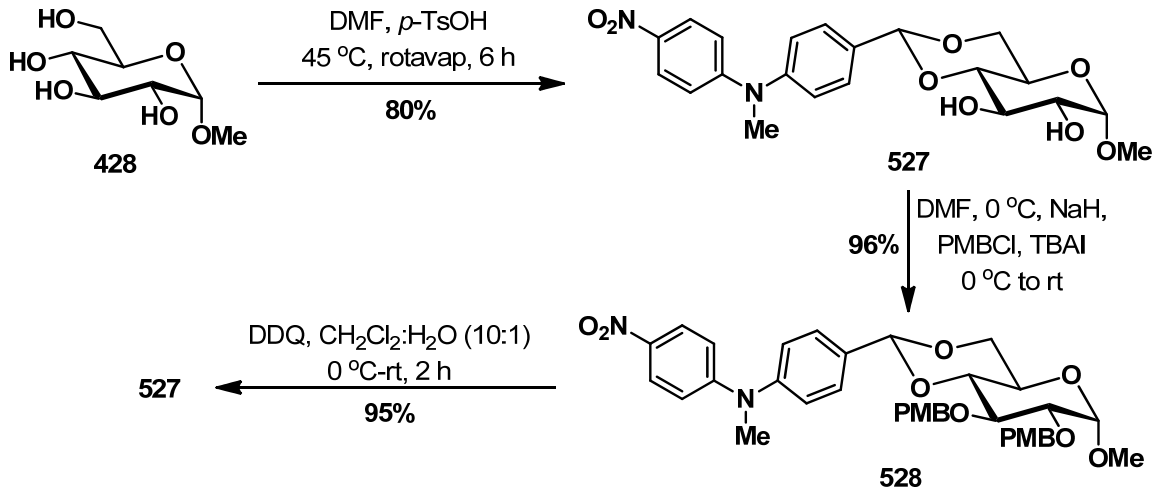
We speculated that with some fine tuning of the electronic property of the PDMAB group, we would be able to achieve our initial goal. Thus, the aldehyde **524** was synthesized from the commercially available *p*-nitrodiphenylamine **522** *via* methylation using NaH and MeI followed by formylation *via* Vilsmeyer-Hack reaction using $POCl_3$.[288] The aldehyde was then converted into the corresponding *p*-(*N*-methyl-*p*-nitophenylamino)benzyl alcohol **525** (PMNPAB) using $NaBH_4$ and then to the dimethoxy PMNPAB using *p*-TsOH in methanol; all with excellent yields (Scheme 123).



Scheme 123. Synthesis of PMNPAB alcohol **525** and PMNPAB α,α-dimethoxy ether **526** from amine **522**.

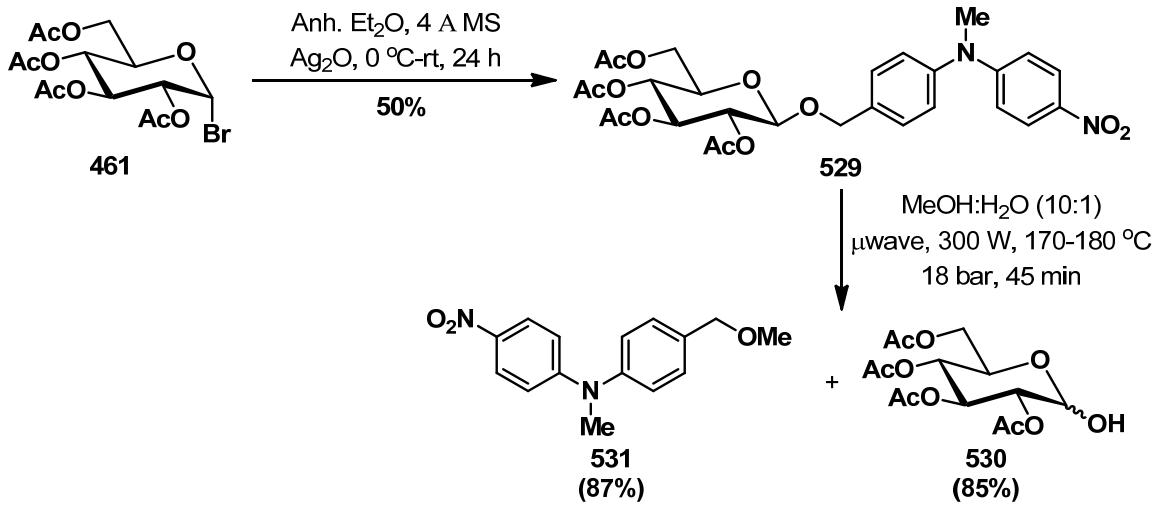
Next, we decided to examine the stability of the PMNPAB group under common oxidative removal conditions normally used for the PMB group. Thus, we synthesized the 4,6-bezylidine acetal **527** from **428** and **526** in presence of *p*-TsOH in excellent yield

(Scheme 124). The C-2 and C-3 hydroxyl groups were then protected with PMB groups in the presence of NaH and *p*-methoxybenzyl chloride to obtain **528**. When compound **528** was treated with DDQ in a mixture of CH_2Cl_2/water for 2 h at 0 ^oC, gratifyingly the PMNPAB group remained intact, whereas the PMB groups were removed. Thus, we were able to conclude that the PMNPAB group is orthogonal to the PMB under DDQ removal conditions.



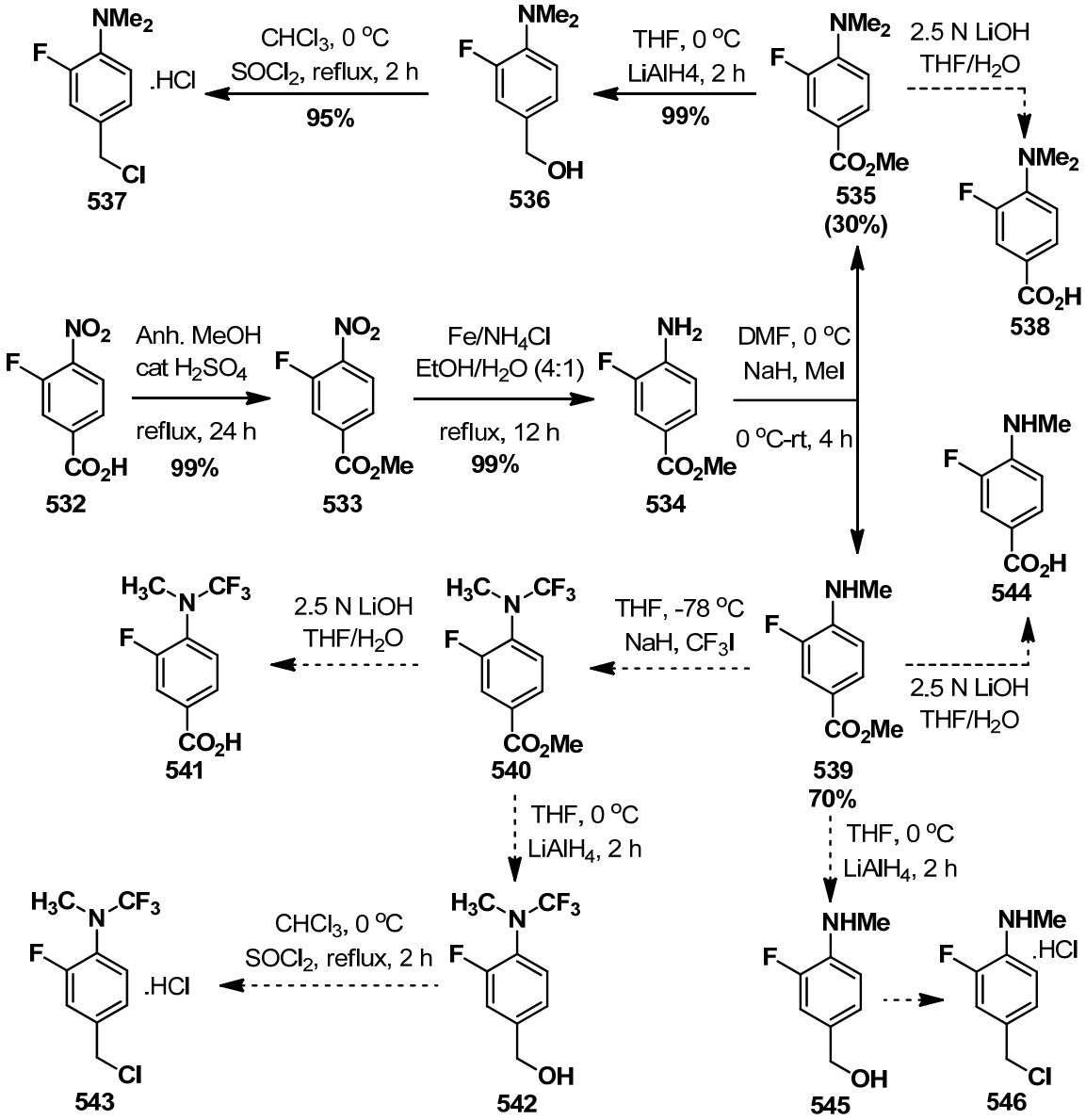
Scheme 124. PMNPAB group is orthogonal to PMB group under DDQ removal conditions.

In order to investigate the effect of microwave irradiation on this newly developed PMNPAB group of the originally discovered PDMAB group, we installed the PMNPAB group *via* Ag_2O mediated glycozylation with the glycosyl bromide donor **461** to obtain **529**. Gratifyingly, microwave irradiation of **529** in a 10:1 mixture of methanol/water was able to remove the PMNPAB group to afford the hemicaetal **530** and by-product **531** (Scheme 125)..



Scheme 125. PMNPAB group is cleavable under microwave irradiation.

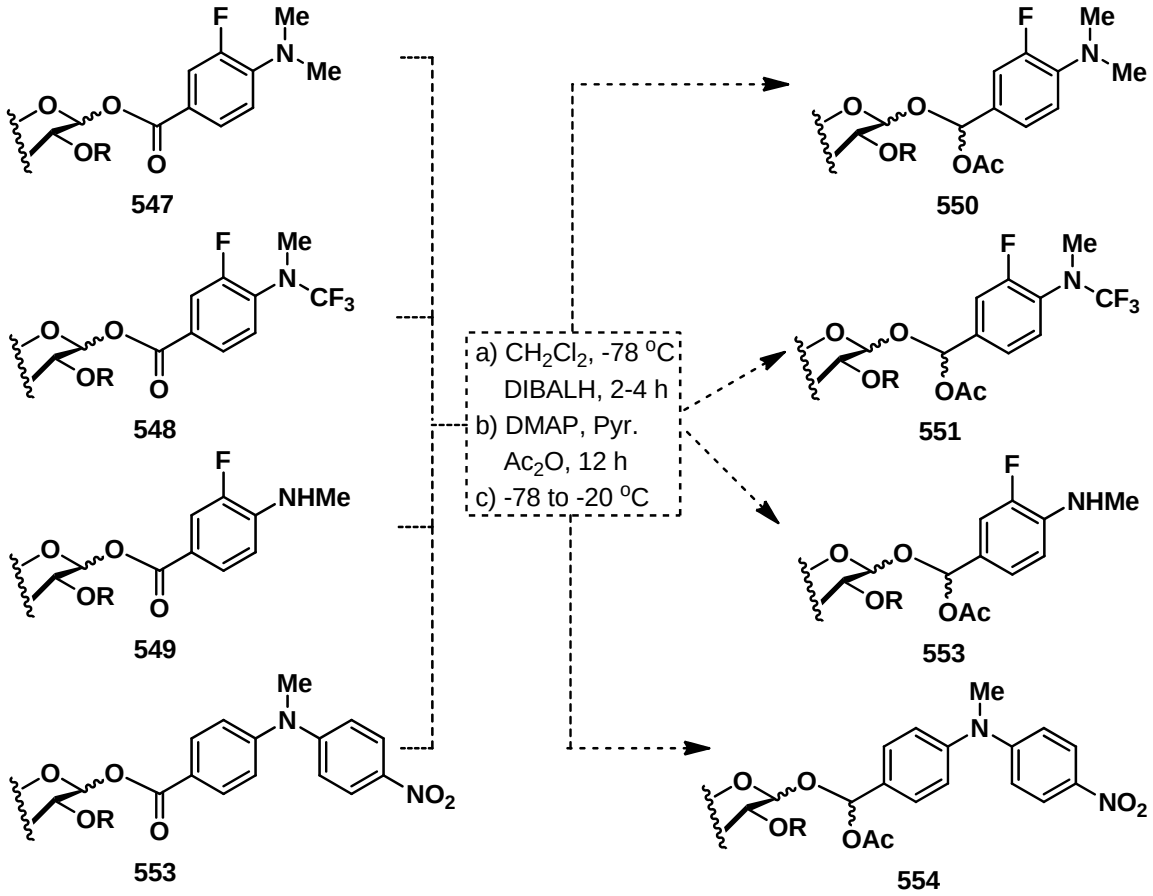
Next, we decided to synthesize a few more derivatives of PDMAB to test them using Rychnovsy's conditions to obtain α-acetoxy ethers like **502**. Thus, commercially available 3-fluoro-4-nitro benzoic acid (**532**) was esterified to obtain **533** which was reduced by Fe(0)/NH_4Cl in a 4:1 mixture of ethanol/water to afford the aniline derivative **534** in quantitative yield. Methylation of **534** with 0.99 equivalent of MeI in presence of NaH in dry DMF provided 30% of the dimethylated aniline derivative **535** and 70% of the mono-methylated aniline derivative **539**. Lithium aluminum hydride (LAH) reduction of the ester **535** provided corresponding alcohol **536** in excellent yield. The alcohol **536** was then converted to the HCl salt of the chloride **537** by refluxing with $SOCl_2$ in chloroform. Saponification of **535** in the presence of 2.5 M LiOH in a mixture of THF/water can provide the acid **538** (Scheme 127).



Scheme 126. Synthesis of fluoro-derivatives of PDMAB.

The mono-methylated aniline derivative **539** can be converted into the corresponding *N*-methyl-*N*-trifluromethane derivative **540** by treating with trifluoromethane iodide (CF_3I) and NaH at -78 °C. LAH reduction of **540** followed by halogenation can provide the salt **543**. Saponification of **540** and **539** by 2.5 N LiOH in a mixture of THF/water can provide corresponding acids **541** and **544** respectively. The

alcohols (**539**, **542**, **545**) and the corresponding chloride salts (**537**, **543**, **546**) can be used to test their feasibility as protecting groups in carbohydrate, peptide and amino acid synthesis. The acids **538**, **541** and **544** can be used to synthesize esters **547**, **548** and **549** respectively and will be subjected to Rychnovsky's conditions to examine the feasibility of obtaining α-acetoxy ethers **550**, **551**, **552** respectively. In a similar fashion, compound **524** and **525** can be converted into the corresponding acid that can be used to synthesize ester **553** and will be subjected to Rychnovsky's conditions to examine the feasibility of obtaining α-acetoxy ether **554**.



Scheme 127. Proposed synthetic route for new α-acetoxy ethers having *para*-substituents with varying electronic nature.

6.3. Materials and Methods

All Reagents were purchased from Aldrich unless otherwise noted. EDCI was purchased from Alfa Aesar. Anhydrous methanol, tetrahydrofuran, acetone and dichloromethane were purchased from Alfa Aesar. Anhydrous methanol was purchased from EMD chemicals (DriSolv). *p*-Toluene sulfonic acid was purchased from Acros organics. Except as otherwise indicated, reactions were carried out under Argon. Microwave reactions were conducted using a capped *via*l on CEM Discover System. All reactions were monitored by thin layer chromatography using 0.25 mm Dynamic Adsorbents, L.L.C. precoated silica gel (particle size 0.03-0.07 mm, catalog no. 84111). Column chromatography was performed using Whatman Purasil 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise noted. Diastereomeric ratios were determined from ^{1}H NMR spectra of non-purified reaction mixtures. Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Unity 500 and Varian 500 Direct Drive System spectrometers. The residual $CDCl_3$ singlet at δ 7.26 ppm and δ 77 ppm were used as the standard for ^{1}H NMR and ^{13}C NMR spectra respectively. Mass spectra were recorded on Micromass GCT at 70 eV.

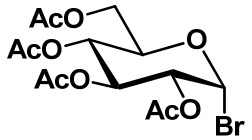
6.3.1. DDQ-mediated deprotection of PMB group in presence of PMNPAB group:

To a RB flask equipped with magnetic stir bar, compound **528** (0.071 g, 0.106 mmol) was taken and dissolved in CH_2Cl_2 (2.2 mL). To the solution, water (0.22 mL) was added and the solution was cooled to 0 ^{o}C. DDQ (0.051 g, 0.226 mmol) was added

in portion and the solution was stirred for 2 h at 0 ^{o}C. Next, the solution was slowly warmed to room temperature and the solution was concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:2 to 3:1) as the eluent.

6.4. Experimental Data

1. **1-Bromo-2,3,4,6-tetraacetate-α-D-glucopyranoside**



461

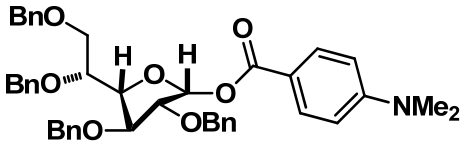
To an oven dried RB flask equipped with magnetic stir bar under Argon, 1,2,3,4,6-pentacaetate-D-glucopyranose (4.31 g, 11.04 mmol) was taken and dissolved in anhydrous CH_2Cl_2 (25 mL). The solution was then cooled to 0 ^{o}C and 45% HBr in glacial acetic acid (16 mL) was added dropwise. The flask was then covered with aluminum foil and resulting mixture was stirred at 0 ^{o}C until TLC showed (2 h) complete consumption of starting material. The reaction was then quenched with saturated $NaHCO_3$ (20 mL), washed with brine (20 mL) and extracted with CH_2Cl_2 (2 ×20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue sufficiently pure and was used directly without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (d, 1 H, *J* = 4.0 Hz, H-1), 5.54 (t, 1 H, *J* = 9.8 Hz, H-3), 5.15 (t, 1 H, *J* = 9.8 Hz, H-2), 4.82 (dd, 1 H, *J* = 10.1, 4.0 Hz, H-5), 4.25-4.35 (m, 2 H, H-4 and H-6 overlap), 4.94-4.14 (m, 1 H, H-6), 2.09 (s, 3 H, -COC$\underline{H}_3$), 2.08 (s, 3 H, -COC$\underline{H}_3$), 2.04 (s, 3 H, -COC$\underline{H}_3$), 2.02 (s, 3 H, -COC$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.8, 169.7, 169.4, 86.6, 86.4, 72.1, 70.7, 70.4, 70.1, 70.0, 67.3, 66.9, 60.9, 20.7, 20.6, 20.5, 20.4.

HRMS (EIMS, M^+): calcd for $C_{14}H_{19}BrO_9$ 410.0212, found 410.0216

2.



496 (α anomer)

To an oven dried RB flask equipped with magnetic stir bar under Argon, NaH (60% in mineral oil) was added followed by anhydrous DMF (4 mL). After stirring the solution for 10 min at room temperature, a solution of allyl-α-D-galactofuranoside (0.645 g, 2.93 mmol) in anhydrous DMF (5.6 mL) was added dropwise at 0 ^{o}C. The reaction mixture was slowly warmed to room temperature and stirred for 15 min. Next benzyl chloride (3.14 mL, 27 mmol) was added slowly and the reaction was allowed to stir for 6 h at room temperature. The reaction was then cooled to 0 ^{o}C and quenched with methanol (6 mL). After diluting the reaction mixture with water (50 mL), it was extracted with dichloromethane (3 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:20 to 1:10) as the eluent.

Allyl 2,3,4,6-tetrabenzyl-α-D-galactofuranoside (0.847 g, 1.46 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, anhydrous CH_2Cl_2 (13.5 mL) and methanol (7.3 mL) were added respectively. After

dissolving the starting material, $PdCl_2$ (0.03 g, 0.17 mmol) was added and the reaction mixture was stirred at room temperature for 4-6 h. The reaction mixture was then concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent.

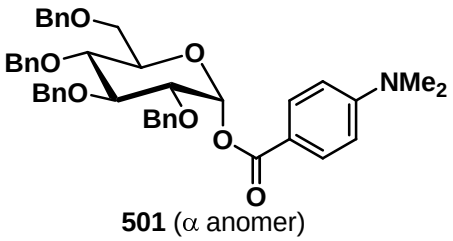
The hemiacetal (0.42 g, 0.78 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous CH_2Cl_2 (2 mL). After cooling the flask to 0 ^oC, EDCI (2.25 g, 14.49 mmol) followed by DMAP (0.036 g, 0.295 mmol) and *p*-*N*,*N*-dimethylbenzoic acid (0.25 g, 1.51 mmol) was added to the mixture and allowed to warm to room temperature slowly over a period of 30 min. After stirring 16 h at room temperature, the solution was diluted with water (30 mL) and the organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent.

^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 2 H, J = 8.6 Hz, aryl), 7.09-7.48 (m, 20 H, Ph), 6.53 (d, 2 H, 8.6 Hz, aryl), 4.40-4.81 (m, 10 H), 4.23-4.34 (m, 1 H), 4.09-4.21 (m, 1 H), 3.56-3.90 (m, 3 H), 3.03 (s, 6 H, NMe_2)

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 153.5, 138.6, 138.2, 138.1, 137.4, 131.8, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 127.3, 116.6, 110.7, 100.0, 93.7, 87.2, 83.9, 81.7, 80.3, 78.4, 73.3, 70.4, 40.0.

HRMS (EIMS, M^+): cacld for $C_{43}H_{45}NO_7$ 687.3196, found 687.3199.

3.



501 (α anomer)

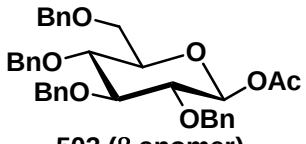
Starting from commercially available 2,3,4,6-tertabenzyl-D-glucopyranose, **501** was synthesized *via* EDCI coupling as described for **496**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, 2 H, J = 8.9 Hz, aryl), 7.20-7.41 (m, 20 H, Ph), 7.16 (m, 2 H, aryl), 6.9 (d, 1 H, *J* = 6.7 Hz), 5.88 (d, 1 H, *J* = 6.1 Hz, H-1), 4.93 (d, 1 H, -C$\underline{H}_2$Ph), 4.85 (d, 3 H, *J* = 11.0 Hz, -C$\underline{H}_2$Ph), 4.77 (d, 1 H, *J* = 11.0 Hz, -C$\underline{H}_2$Ph), 4.64 (d, 1 H, *J* = 12.2 Hz, -C$\underline{H}_2$Ph), 4.57 (d, 1 H, *J* = 11.0 Hz, -C$\underline{H}_2$Ph), 4.49 (d, 1 H, *J* = 12.2, -C$\underline{H}_2$Ph), 3.75-3.86 (m, 5 H), 3.64-3.70 (m, 1 H), 3.10 (s , 6 H, NMe_2)

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.6, 138.5, 138.1, 137.9, 132.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 113.2, 113.1, 94.5, 84.9, 81.0, 75.7, 75.5, 74.9, 73.5, 68.1, 41.5

HRMS (EIMS, M^+): cacld for $C_{43}H_{45}NO_7$ 687.3196, found 687.3192.

4.



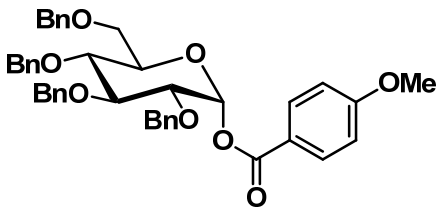
503 (β anomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.37 (m, 18 H, Ph), 7.12-7.17 (m, 2 H, Ph), 5.61 (d, 1 H, *J* = 7.9 Hz, H-1), 4.43-5.02 (m, 8 H, -C<u>H</u>$_2$Ph), 3.95 (t, 1 H, *J* = 9.2 Hz), 3.53-3.78 (m, 5 H), 2.06 (s, 3 H, -COC<u>H</u>$_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 138.6, 138.4, 138.1, 137.9, 137.8, 137.7, 137.6, 128.5, 128.4, 128.3, 128.3, 128.1, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 94.0, 84.8, 81.0, 77.2, 75.7, 75.0, 73.5, 68.1, 21.1

HRMS (EIMS, M^+): cacld for $C_{36}H_{38}O_7$ 582.2618, found 582.2620.

5.



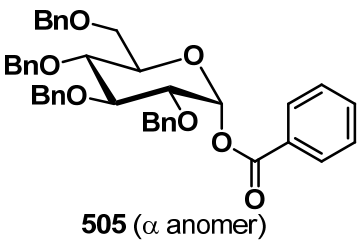
505 (α anomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04-8.12 (m, 2 H, aryl), 7.18-7.44 (m, 20 H, Ph), 6.92-6.71 (m, 2 H, aryl), 6.64 (d, 1 H, *J* = 3.7 Hz, H-1), 5.92 (m, 1 H), 4.78-5.07 (m, 6 H), 4.56-4.72 (m, 2 H), 4.49-4.55 (m, 1 H), 4.12 (t, 1 H, *J* = 9.5 Hz), 4.0-4.04 (m, 1 H), 3.90 (s, 3 H, OMe), 3.79-3.88 (m, 1 H0, 3.68-3.73 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 163.8, 138.5, 138.1, 137.9, 132.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 121.6, 113.7, 94.5, 84.9, 80.9, 75.6, 75.0, 74.9, 73.5, 68.1, 55.4.

HRMS (EIMS, M^+): cacld for $C_{42}H_{42}O_8$ 674.2880, found 674.2883.

6.



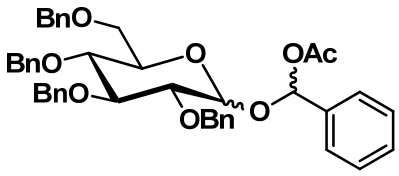
505 (α anomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07-8.17 (m, 2 H, aryl), 7.59-7.66 (m, 1 H, aryl), 7.45-7.54 (m, 2 H, aryl), 7.17-7.43 (m, 20 H, Ph), 6.66 (d, 1 H, *J* = 3.7 Hz, H-1), 4.49-5.07 (m, 8 H, -C<u>H</u>$_2$Ph), 4.12 (t, 1 H, *J* = 9.2 Hz), 3.77-3.92 (m, 5 H), 3.62-3.74 (m, 1 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 138.5, 138.1, 137.9, 132.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 94.7, 84.9, 81.8, 78.9, 75.7, 75.4, 73.5, 73.0, 68.0,

HRMS (EIMS, M^+): cacld for $C_{41}H_{40}O_7$ 644.2774, found 644.2771.

7.



510 (dr = 4.5:1)

The benzoic ester **505** (0.044 g, 0.067 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon (*via* Schlenk line) and anhydrous CH_2Cl_2 (0.34 mL) was added to the flask. After cooling the solution to -78 ^{o}C, 1.0 M DIBAL-H in cyclohexane (0.08 mL, 0.08 mmol) was added dropwise. The solution was then stirred for 2-4 h until TLC showed complete consumption of starting material. Next, pyridine (0.016 mL, 0.197 mmol) was added followed by Ac_2O (0.025 mL, 0.26 mmol) and the resulting mixture stirred at -78 ^{o}C for 12 h, then slowly warmed to -20 ^{o}C. The reaction

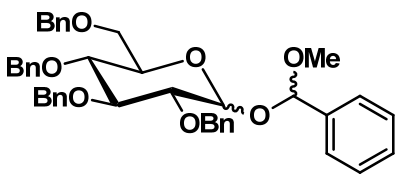
was then quenched with saturated Rochelle's salt solution (0.4 mL), stirred for 30 min and allowed to reach room temperature. The solution was then extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under pressure on rotavap. The residue was rapidly purified *via* gradient column chromatography using pre-neutralized (by 0.1% NEt_3) silica gel as the stationary phase and a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent. The desired product **510** and the undesired side product **503** had similar R_f values and seemed difficult to separate. Due to the sensitivity and stability of **510**, further purification was not attempted and used directly in the next step.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14-7.49 (m, 25 H, Ph), 6.89 (s, 1 H, -C<u>H</u>(OAc)Ph), 5.58 (d, 1 H, *J* = 3.7 Hz, H-1), 4.41-5.05 (m, 8 H, -C<u>H</u>$_2$Ph), 3.93-4.02 (m, 1 H), 3.51-3.83 (m, 5 H), 2.16 (s, 3 H, -COC<u>H</u>$_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 169.6, 139.1, 138.9, 138.6, 138.4, 138.2, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 96.4, 95.4, 85.1, 81.9, 81.3, 79.5, 77.5, 75.9, 75.7, 75.3, 73.8, 73.1, 68.3

HRMS (EIMS, M^+): cacld for $C_{43}H_{44}O_8$ 688.3036, found 688.3033.

8.



512 (dr = 1.3:1)

To a 10 mL CEM Discover microwave vial equipped with magnetic stir bar under Argon, **510** (0.01 mg, 0.015 mmol) was taken and anhydrous methanol (1.5 mL) was

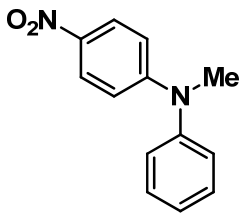
added. The perforated septum was replaced with new septum quickly, capped according to the manufacturer direction and placed into microwave reaction cavity. The microwave was equilibrated to 190 ^{o}C, 18 bar for 25 min. TLC of the reaction indicated the formation of new product. The solution was transferred to a 25 mL RB flask and concentrated under reduced pressure on rotavap. The residue was quickly purified *via* preparative silica gel chromatography using a 1:10 mixture of ethyl acetate and hexane as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15-7.52 (m, 25 H, Ph), 5.57 (s, 1 H, -C<u>H</u>(OMe)Ph), 5.40 (d, 1 H, *J* = 3.7 Hz, H-1), 4.98-5.07 (m, 1 H, -C<u>H</u>$_2$Ph), 4.78-4.89 (m, 3 H, -C<u>H</u>$_2$Ph), 4.53-4.62 (m, 1 H), 4.38-4.52 (m, 3 H, -C<u>H</u>$_2$Ph), 4.08 (t, 1 H, *J* = 9.8 Hz), 3.53-3.73 (m, 5 H), 3.48 (s, 3 H, OMe)

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1, 138.9, 138.6, 138.4, 138.2, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 103.1, 93.8, 82.0, 79.9, 77.7, 75.6, 73.5, 73.0, 71.0, 68.4

HRMS (M^{+}+ Na, EIMS): calcd for $C_{42}H_{44}NaO_7$ 683.2985, found 683.2983

9. ***N*-methyl-4-nitro-*N*-phenylaniline**



523

To an oven dried RB flask equipped with magnetic stir bar under Argon, *p*-nitrodiphenylamine (0.5 g, 2.35 mmol) was taken and dissolved in anhydrous DMF (4.5

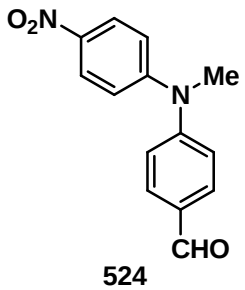
mL) at room temperature. To the solution, NaH (60% in mineral oil, 0.21 g, 4.7 mmol) was added in protion. After stirring 15 min at room temperature, the solution was cooled to 0 ^{o}C and methyl iodide (0.51 mL, 3.53 mmol) was added dropwise. The resulting solution was stirred for 2-4 h at 0 ^{o}C and then quenched with cold water. The reaction mixture was then diluted with water (50 mL) and extracted with ethyl acetate (4 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The crude product was spectroscopically pure enough and used in the preceding step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96-8.11 (m, 3 H, aryl), 7.45 (t, 2 H, *J* = 7.6 Hz, aryl), 7.27-7.34 (m, 1 H, aryl), 7.18-7.25 (m, 2 H, aryl), 6.61-6.71 (m, 2 H, aryl), 3.4 (s, 3 H, NMe)

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 153.7, 146.3, 138.1, 130.2, 126.8, 126.7, 125.7, 112.4, 40.5.

HRMS (EIMS, M^+): cacld for $C_{13}H_{12}N_2O_2$ 228.0899, found 228.0895.

10. ***p*-(methyl(4-nitrophenyl)amino)benzaldehyde**



524

Anhydrous DMF (1.11 mL, 14.3 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and cooled to 0 ^{o}C. To the cooled solution, $POCl_3$ (1.3 mL, 14.3 mmol) was added dropwise (caution: generates heat!!). After a

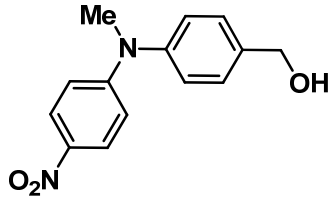
while, the reaction mixture solidifies and the ice-bath was removed, warmed with a heat gun. The flask was cooled to 0 ^{o}C again. The process was repeated 3/4 times over 1 h and then the reaction mixture turns into brick color. Then, a solution of 523 (1.09 g, 4.77 mmol) in anhydrous DMF (3 mL) was added slowly *via* syringe at 0 ^{o}C. The resulting solution was then heated to 95 ^{o}C and allowed to stir for 4 h after which TLC showed complete consumption of starting material. The reaction mixture was then cooled to room temperature and poured into ice-water, neutralized with NaOH pellets. The solution was extracted with CH_2Cl_2 (2× 20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL), brine (20 mL) and dried over Na_2SO_4. The organic layer was then concentrated under reduced pressure on rotavap and the residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:1:5 to 1:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.94 (s, 1 H, -C<u>H</u>O), 8.14 (d, 2 H, J = 9.2 Hz, aryl), 7.88 (d, 2 H, *J* = 8.5 Hz, aryl), 7.28 (d, 2 H, *J* = 8.5 Hz, aryl), 7.04 (d, 2 H, *J* = 9.2 Hz, aryl), 3.49 (s, 3 H, NMe)

^{13}C NMR (125 MHz, $CDCl_3$): δ 190.5, 152.6, 151.9, 140.9, 132.0, 131.5, 125.6, 122.6, 117.7, 40.3

HRMS (EIMS, M^+): cacld for $C_{14}H_{12}N_2O_3$ 256.0848, found 256.0851.

11. ***p*-(methyl-*N*-(4-nitrophenyl)amino)benzyl alcohol**



525

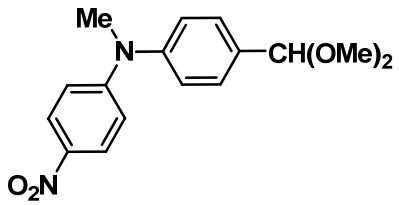
To an oven dried RB flask equipped with magnetic stir bar under Argon, aldehyde **524** (0.437 g, 1.71 mmol) was dissolved in anhydrous methanol (6.7 mL). The solution was cooled to 0 ^{o}C and $NaBH_4$ (0.105 g, 2.77 mmol) was added in portion. The reaction mixture was then stirred for 40 min at 0 ^{o}C and quenched with water (0.5 mL). After dilution with water (10 mL), the solution was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4. The crude residue was purified rapidly *via* gradient silica gel (neutralized with 0.1% NEt_3) column chromatography using a 1:3 mixture of ethyl acetate/hexane as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 2 H, *J* = 9.2 Hz, aryl), 7.46 (d, 2 H, *J* = 8.5 Hz, aryl), 7.25 (d, 2 H, *J* = 8.5 Hz, aryl), 6.64 (d, 2 H, *J* = 9.5 Hz, aryl), 4.74 (s, 2 H, -C$\underline{H_2}$Ar), 3.40 (s, 3 H, NMe), 1.90 (bs, 1 H, OH)

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 145.7, 139.4, 138.2, 128.8, 126.7, 125.8, 112.5, 64.7, 40.5.

HRMS (EIMS, M^+): cacld for $C_{14}H_{14}N_2O_3$ 258.1004, found 258.1008.

13. ***p*-*N*-methyl-*N*-(4-nitrophenyl) α,α-dimethoxybenzaldehyde**



526

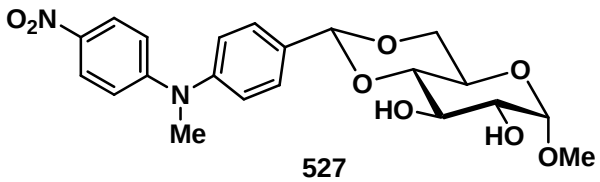
To an oven dried RB flask equipped with magnetic stir bar under Argon, the aldehyde **524** (0.3 g, 1.17 mmol) was taken and dissolved in anhydrous methanol (10 mL). The solution was cooled to 0 ^{o}C and catalytic *p*-TsOH was (0.019 g, 0.1 mmol) was added. The resulting solution was slowly warmed to room temperature and stirred for 4 h. The reaction mixture was then concentrated and used directly in the next step.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 2 H, *J* = 9.2 Hz, aryl), 7.46 (d, 2 H, *J* = 8.5 Hz, aryl), 7.25 (d, 2 H, *J* = 8.5 Hz, aryl), 6.64 (d, 2 H, *J* = 9.5 Hz, aryl), 5.42 (s, 2 H, -C$\underline{H_2}$Ar), 3.40 (s, 3 H, NMe), 3.38 (s, 6 H, OMe and OMe overlap)

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 146.7, 138.6, 136.9, 128.8, 126.5, 125.9, 112.9, 103.0, 53.2, 40.7

HRMS (EIMS, M^{+}): cacld for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1269.

14.



527

Methyl-α-D-glucopyranoside (0.145 g, 0.75 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, anhydrous DMF (6 mL)

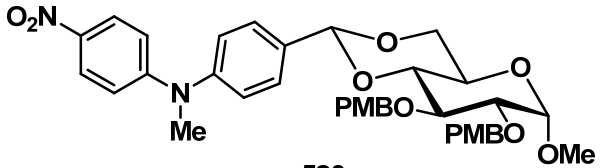
was added followed by **526** (0.271 g, 0.90 mmol). After adding catalytic amount of *p*-TsOH (0.013 g, 0.07 mmol), the reaction mixture was heated to 50 ^{o}C on a rotavap (bump trap adapter and reservoir was pre-dried in oven) under reduced for 4 h. Next, the reaction mixture was concentrated and purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:1 to 4:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, 2 H, *J* = 9.5 Hz, aryl), 7.58 (d, 2 H, J = 8.2 Hz, aryl), 7.24 (d, 2 H, J = 8.5 Hz, aryl), 6.69 (d, 2 H, J = 9.2 Hz, aryl), 5.58 (s, 1 H, -CHAr), 4.82 (d, 1 H, J = 4.0 Hz, H-1), 4.32 (dd, 1 H, J = 9.8, 4.3 Hz, H-4), 3.96 (t, 1 H, J = 9.2 Hz, H-6), 3.83 (dt, 1 H, J = 10.4, 4.9 Hz, H-3), 3.77 (t, 1 H, J = 10.1 Hz, H-6), 3.65 (dd, 1 H, J = 9.2, 4.0 Hz, H-2), 3.53 (t, 1 H, J = 9.5 Hz, H-5), 3.48 (s, 3 H, OMe), 3.39 (s, 3 H, NMe).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 147.2, 138.5, 135.4, 128.3, 126.3, 125.7, 112.9, 101.3, 99.7, 80.9, 73.0, 71.9, 68.9, 62.3, 55.7, 40.4.

HRMS (M^{+}+ Na, EIMS): calcd for $C_{21}H_{24}NaN_2O_8$ 455.1430, found 455.1424

15.



528

To an oven dried RB flask equipped with magnetic stir bar under Argon, compound **527** (0.103 g, 0.24 mmol) was taken and dissolved in anhydrous DMF (2 mL). After cooling the solution to 0 ^{o}C, NaH (60% in mineral oil, 0.04 g, 0.72 mmol) was added in portion; the reaction was slowly warmed to room temperature and stirred for 15

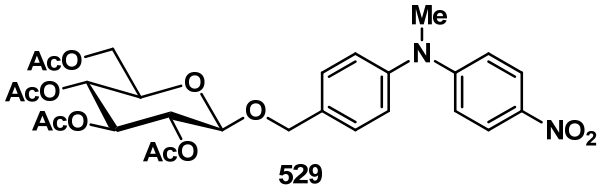
min. Then, the reaction the mixture cooled to 0 ^{o}C again and *p*-methoxybenzyl chloride (0.12 mL, 0.84 mmol) was added dropwise followed by catalytic amount of tetrabutylammonium bromide (TBAI, 0.008 g, 0.022 mmol). The resulting mixture was stirred at room temperature for 6 h. The reaction was quenched by slow addition of methanol (5 mL) at 0 ^{o}C. The reaction mixture was then diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine (30 mL). After drying on Na_2SO_4, the organic layer was concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel (neutralized with 0.1% NEt_3) column chromatography using a mixture of ethyl acetate/hexane (1:4 to 2:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03-8.10 (d, 2 H, J = 9.5 Hz, aryl), 7.56 (d, 2 H, J =9.5 Hz, aryl), 7.21-7.36 (m, 6 H, aryl), 6.87 (d, 2 H, J = 8.8 Hz, aryl), 6.85 (d, 2 H, J = 8.5 Hz, aryl), 6.70 (d, 2 H, J = 9.5 Hz, aryl), 5.57 (s, 1 H, -C<u>H</u>Ar), 4.81 (q, 2 H, J = 11.0 Hz, aryl), 4.79 (d, 1 H, J = 11.6 Hz, Bn), 4.63 (d, 1 H, J = 11.6 Hz, Bn), 4.54 (d, 1 H, J = 3.7 Hz, H-1), 4.27 (dd, 1 H, J = 10.1, 4.9 Hz, H-4), 4.01 (t, 1 H, J = 9.2 Hz, H-6), 3.81 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 3.72 (t, 1 H, J = 10.4 Hz, H-6), 3.59 (t, 1 H, J = 9.5 Hz, H-3), 3.53 (dd, 1 H, J = 9.2, 3.7 Hz, H-2), 3.41 (s, 3 H, OMe), 3.40 (s, 3 H, N<u>Me</u>)

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 159.2, 153.6, 146.9, 138.4, 135.8, 131.6, 130.9, 130.2, 129.7, 129.6, 127.9, 126.2, 125.7, 125.6, 122.5, 117.7, 113.8, 113.7, 112.8, 100.5, 99.3, 82.0, 78.8, 78.2, 75.0, 73.4, 69.1, 62.2, 55.2, 40.4

HRMS (M^{+}+ Na, EIMS): calcd for $C_{37}H_{40}N_2NaO_{10}$ 695.2581, found 695.2583.

16.



529

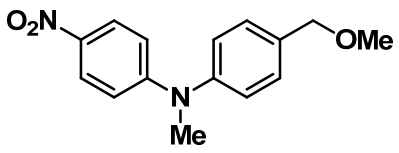
1-Bromo-2,3,4,6-tertaacetate-α-D-glucopyranoside (**461**) (0.085 g) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, 4 Å MS (oven dried 24 h followed by heat gun dried under high vacuum) was added followed by anhydrous diethyl ether (3 mL). The mixture was then stirred for 30 min at room temperature and then Ag_2O was added. The resulting solution was stirred at room temperature for 24 h. Next, the reaction mixture was concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel (neutralized with 0.1% NEt_3) column chromatography using a mixture of ethyl acetate/hexane (1:2 to 2:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03-8.11 (m, 2 H, aryl), 7.33-7.42 (m, 2 H, aryl), 7.16-7.24 (m, 2 H, aryl), 6.64-6.74 (m, 2 H, aryl), 5.22 (t, 1 H, J = 9.5 Hz, H-2), 5.06-5.17 (m, 2 H), 4.92 (d, 1 H, J = 12.2 Hz, -C$\underline{H}_2$Ar), 4.52-4.68 (m, 2 H), 4.29 (dd, 1 H, J = 12.5, 4.9 Hz, H-6), 4.16-4.24 (m, 2 H), 3.40 (s, 3 H, -NMe), 2.11 (s, 3 H, -COC$\underline{H}_3$), 2.04 (s, 3 H, -COC$\underline{H}_3$), 2.03 (s, 3 H, -COC$\underline{H}_3$), 2.01 (s, 3 H, -COC$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.3, 169.4, 169.3, 153.6, 146.1, 135.2, 130.1, 129.4, 126.5, 125.8, 112.7, 99.6, 72.7, 71.9, 71.3, 70.1, 68.4, 61.9, 60.4, 40.5, 20.7, 20.6, 20.5, 20.4.

HRMS (M^++ Na, EIMS): calcd for $C_{28}H_{32}NaN_2O_{12}$ 611.1853, found 611.1842

17.



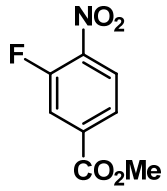
531

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, 2 H, J = 9.2 Hz, aryl), 7.43 (d, 2 H, J = 8.2 Hz, aryl), 7.21 (d, 2 H, J = 8.2 Hz, aryl), 6.68 (d, 2 H, J = 9.2 Hz, aryl), 4.48 (s, 2 H, -C$\underline{H_2}$OMe), 3.45 (s, 3 H, OMe), 3.39 (s, 3 H, NMe)

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 145.8, 136.9, 129.5, 126.6, 125.8, 112.5, 74.1, 58.4, 40.5

HRMS (M^++ Na, EIMS): calcd for $C_{15}H_{16}N_2NaO_3$ 295.1059, found 295.1063

18.



533

3-Fluro-4-nitrobenzoic acid (2.0 g, 10.8 mmol) was taken in an oven dried RB flask and dissolved in anhydrous methanol (34.8 mL) under Argon. To the stirring solution concentrated H_2SO_4 (0.35 mL) and the reaction was refluxed for 24 h. The reaction mixture was then cooled to room temperature and small amount of solid K_2CO_3 (0.03 g) was added. The solution was then concentrated under reduced pressure on rotavap to afford a yellow residue. The residue was dissolved on CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (17 mL). The organic layer was separated and the

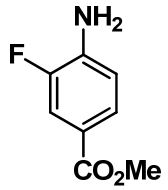
aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap to afford a yellow solid. The crude product was sufficiently pure and used directly in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06-8.11 (m, 1 H, aryl), 7.90-7.97 (m, 2 H, aryl), 3.97 (s, 3 H, -CO_2Me)

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 156.1, 153.9, 136.6, 126.1, 125.4, 119.7 ($J_{C\text{-}F}$ = 88.5 Hz), 53.1

HRMS (EIMS, M^+): calcd for $C_8H_6FNO_4$ 199.0281, found 199.0285.

19.



534

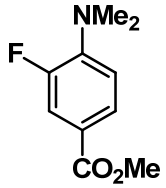
Methyl 3-fluoro-4-nitrobenzoate (2.27 g, 11.4 mmol) was taken in a 250 mL RB flask equipped with magnetic stir bar. To the flask, Fe (40 mesh) powder (9.72 g, 170.99 mmol) and solid NH_4Cl (0.613 g, 11.46 mmol) were added. Ethanol (100 mL) and water (33 mL) were added. The resulting mixture was refluxed at 80 ^oC for 18 h and after cooling to room temperature, filtered through celite. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The yellow residue was sufficiently pure and used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.6-7.71 (m, 2 H, aryl), 6.74 (t, 1 H, J = 8.5 Hz, aryl), 4.15 (bs, 2 H, -N$\underline{H_2}$), 3.86 (s, 3 H, -$CO_2\underline{Me}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 151.2, 149.3, 139.3, 126.9, 120.0, 116.6, 115.2, 51.9

HRMS (M^+, EIMS): calcd for $C_8H_8FNO_2$ 169.0539, found 169.0542.

20.



535

To an oven dried RB flask equipped with magnetic stir bar under Argon, the amine **534** (0.632 g, 3.74 mmol) was taken and dissolved in anhydrous DMF (8 mL). The solution was then cooled to 0 ^{o}C and NaH (60% in mineral oil, 0.15 g, 3.74 mmol) was added in portion. After stirring the solution at room temperature for 20 min, it was cooled to 0 ^{o}C again. To the cooled reaction mixture, MeI (0.53 mL, 3.74 mmol) was added dropwise over 15 min. The resulting mixture was then allowed to reach room temperature slowly and stirred additional 18 h. The reaction was quenched by the addition of methanol (5 mL) at 0 ^{o}C and then diluted with water (80 mL). The solution was then extracted with ethyl acetate (3 × 20 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were dried over Na_2SO_4 and combined. Concentration of the organic layer under reduced pressure on rotavap, afforded a mixture of mono-methylated, di-methylated and unreacted starting material.

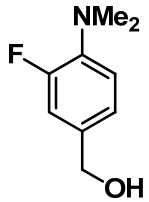
Purification of the crude residue *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:40 to 1:10) as the eluent afforded the mono-methylated compound as the major and the di-methylated compound as the mior product.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, 1 H, J = 8.5, 2.1 Hz, aryl), 7.64 (dd, 1 H, J = 14.7, 2.1 Hz, aryl), 6.78 (t, 1 H, J = 8.9 Hz, aryl), 3.87 (s, 3 H, -CO_2Me), 2.98 (s, 6 H, NMe_2)

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 153.8, 151.8, 144.13, 126.4, 120.7, 117.5, 116.1, 51.9, 42.2

HRMS (M^+, EIMS): calcd for $C_{10}H_{12}FNO_2$ 198.0930, found 198.0928

21.



536

Methyl 3-fluoro-4-*p*-(*N*,*N*-dimethylamino)benzoate (0.907 g, 4.6 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, anhydrous diethyl ether (10 mL) was added and the stirred solution was cooled to 0 ^{o}C. Next, $LiAlH_4$ (0.174 g, 4.6 mmol) was added slowly in portion. The reaction was then monitored *via* TLC. When TLC showed the completion of the reaction, the reaction was quenched with methanol (3 mL). The reaction was then diluted with water (10 mL) and extracted with diethyl ether (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The yellow residue

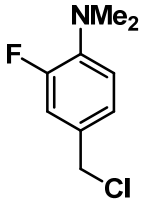
was rapidly purified *via* gradient silica gel (pre-neutralized with 0.1% NEt_3) column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95-7.02 (m, 2 H, aryl), 6.84 (t, 1 H, J = 8.5 Hz, aryl), 4.53 (s, 2 H, -C$\underline{H_2}$Ar), 2.80 (s, 6 H, NMe_2), 2.70 (bs, 1 H, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 153.9, 139.8, 134.5, 122.7, 118.1, 115.0, 64.0, 42.8.

HRMS (M^+, EIMS): calcd for $C_9H_{12}FNO$ 170.0981, found 170.0983.

22.



537

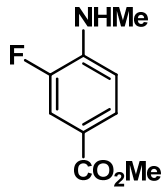
The alcohol **536** (0.958 g, 5.66 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, anhydrous $CHCl_3$ (24 mL) was added and the stirred solution was cooled to 0 ^oC. Next, $SOCl_2$ (0.79 mL, 6.59 mmol) was added dropwise to the cooled solution over 15 min. The reaction mixture was then slowly warmed to room temperature, stirred for 10 min and then refluxed for 1 h. The solution was then concentrated under reduced pressure on rotavap. For spectroscopic data, 100 mg of the crude salt was treated with saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96-7.06 (m, 2 H, aryl), 6.83-6.90 (m, 1 H, aryl), 4.36 (s, 2 H, -C$\underline{H_2}$Cl), 2.94 (s, 6 H, NMe_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 154.0, 140.2, 131.3, 123.7, 117.9, 115.7, 57.9, 42.8

HRMS (M^+, EIMS): calcd for $C_9H_{11}ClFN$ 187.0564, found 187.0569.

23.



539

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.79 (m, 1 H, aryl), 7.61 (dd, 1 H, J = 2.5, 1.8 Hz, aryl), 6.62 (t, 1 H, J = 8.6 Hz, aryl), 4.44 (bs, 1 H, -N$\underline{H}$), 3.86 (s, 3 H, $CO_2\underline{Me}$), 2.92 (s, 3 H, -NH$\underline{Me}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 151.2, 149.3, 141.8, 127.3, 117.9, 115.2, 109.7, 51.7, 29.7

HRMS (M^+, EIMS): calcd for $C_9H_{10}FNO_2$ 184.0774, found 184.0777

CHAPTER 7

Synthetic Study Toward The Total Synthesis Of The Repeating Tetrasaccharide Unit Of The Zwitterionic Polysaccharide PS A1

7. Introduction

Zwitterionic polysachharides (ZPSs) (Figure 37) are characterized by the presence of positive and negative charges on adjacent monosaccharides. Although, the majority of polysaccharides in pathogenic bacteria commonly have either negatively charged groups or no charged groups at all; the capsular polysaccharides PS A1 (**359**) and PS A2 (**555**) from *Bacterorides fragilis 9343*, Sp 1 (**556**) from *strepcoccus pneumoniae* are the few naturally occurring ZPSs.

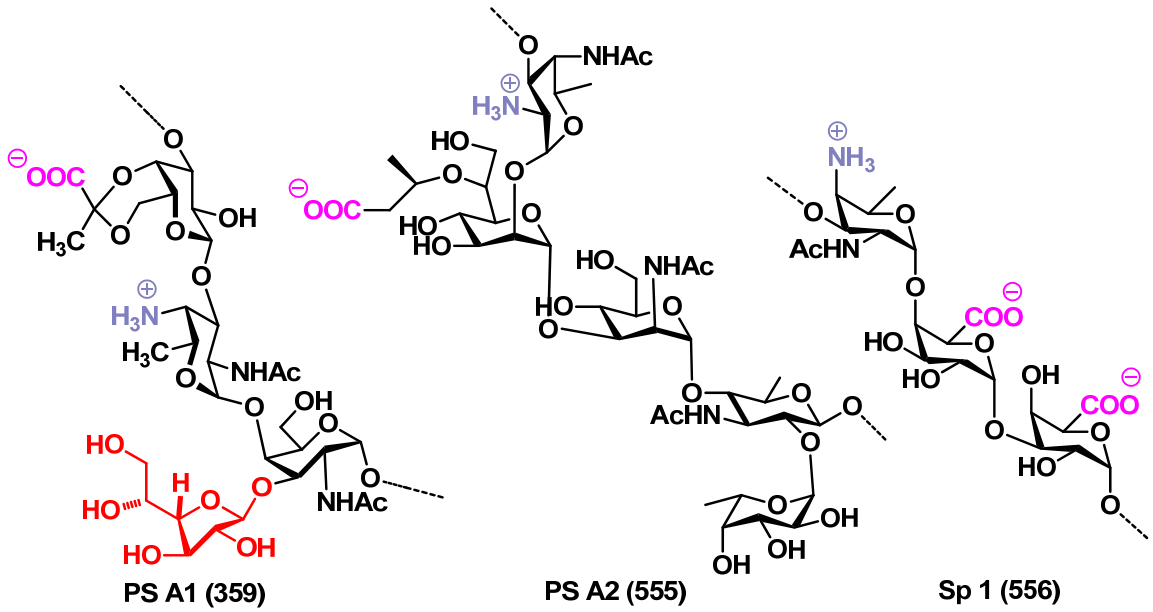


Figure 37. Naturally occurring zwitterionic polysaccharides.

PS A1 which was isolated from pathogenic gram-negative anaerobic bacteria *Bacterorides fragilis* by fermentation, is a clear example of zwitterionic characharacter.[198] It has size of 100-120 kDa which correlates to 100-120 repeating units. PS A1 is composed of a repeating tetrsaccharide unit with antigenic carboxylate of pyruvate ketal spanning C4-C6 in the D-galactopyranosyl mopiety, 2-acetamido-4-amino-L-fucose moiety, 2-acetamido-D-galactopyranosyl moiety in the polymer backbone and antigenic galactofuranosyl moiety in the side chain. The ZPS PS A1 has the following sequence: [→3)-β-D-Gal*p*-(1→3)-α-D-Sug*p*-(1→4)[β-D-Gal*f*-(1→3)]-α-D-Gal*p*NAc-(1→] (where Sug = 2-acetamido-4-amino-2,4,6-trideoxygalactose).[289] Spectroscopic data (e.g. NMR, CD) have indicated that the average solution structure of ZPS-PS A1 is composed of helical conformation with repeating units per turn and a pitchof 20 Å.[290] The zwitterionic charges which are exposed toward the outer-surface of the polymer favor interaction with other molecules. In contrast to majority of pathogenic polysaccharides, they are known to have the ability to modulate the cellular immune system by eliciting an MHC-II T-cell response.[291] This discovery was noted when studies were conducted for abscess formation.[198b] The underlying cellular mechanism for abscess formation requires T-cell activation.[291a] Conversely, abscess formation can be prevented by prophylactic subcutaneous injection of purified ZPS-PS A1 alone. Experimental Studies have proven that the unusual immunologic property of PS A1 is likely to be caused by its zwitterionic character. Neutralization of either the positively charged amino groups or the negatively charged carboxyl groups show strongly reduced biological activity as compared to the unmodified polysaccharide.[292] It is noteworthy that isolation of PS A1 from *Bacterorides fragilis* is cumbersome and only milligram

quantities can be obtained. Recently, we have shown that chemically modified PS A1 with a cancer antigen (Tn-PS A1) can elicit MHC-II mediated immune response that specifically targets the conjugated antigen.[293]

7.1. Retrosynthetic Analysis of ZPS PS A1

Our retrosynthetic analysis indicates that the ZPS PS A1 the protected repeating unit of the tetrasaccharide can be assembled *via* three separate ways: (a) convergent, (b) linear approach, (c) divergent approach, from protected monosaccharides **559-565** following the sequence of glycosylation events depicted in Figure 38-40.

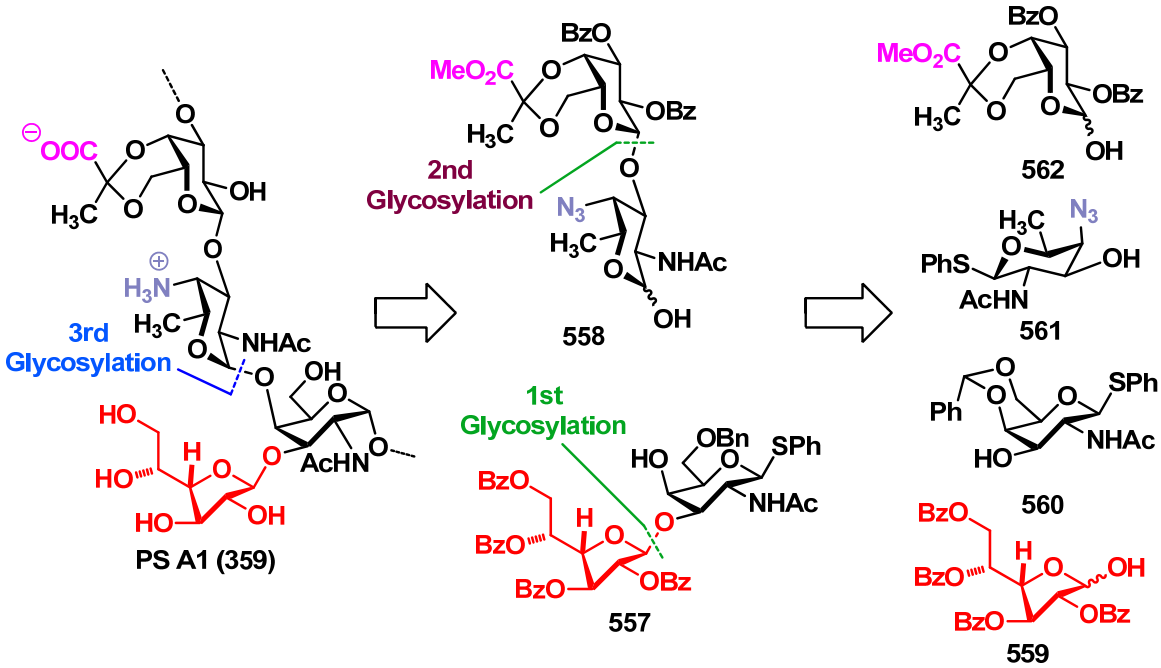


Figure 38. Convergent approach for the repeating tetrasaccharide unit of ZPS PS A1.

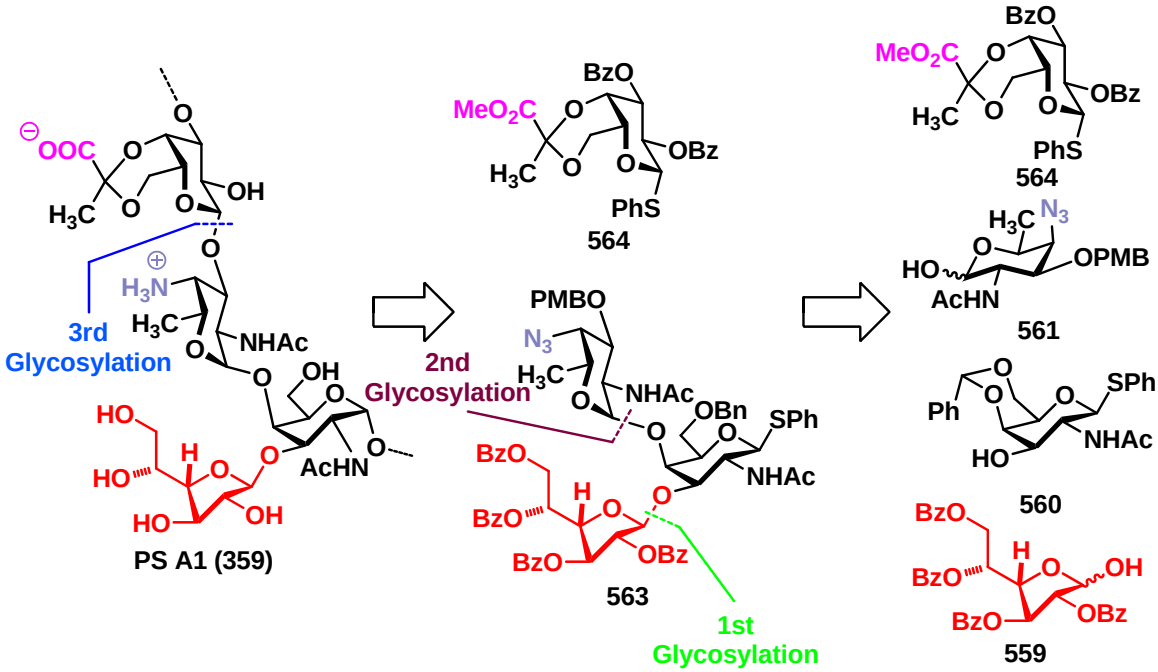


Figure 39. Linear approach for the repeating tetrasaccharide unit of ZPS PS A1.

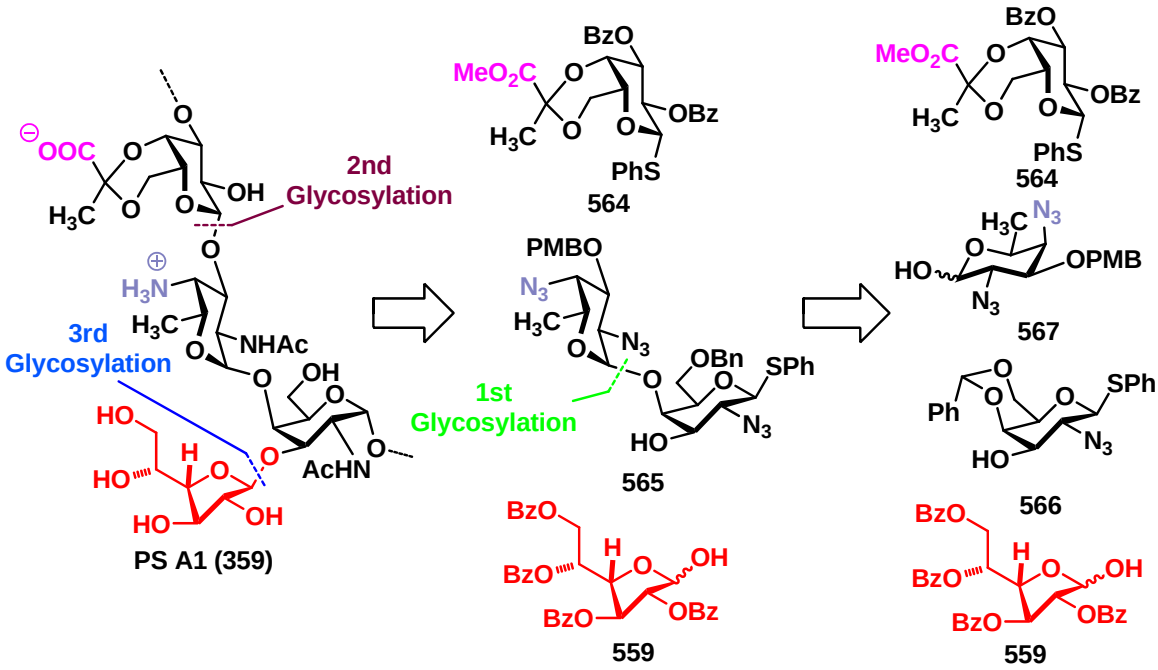


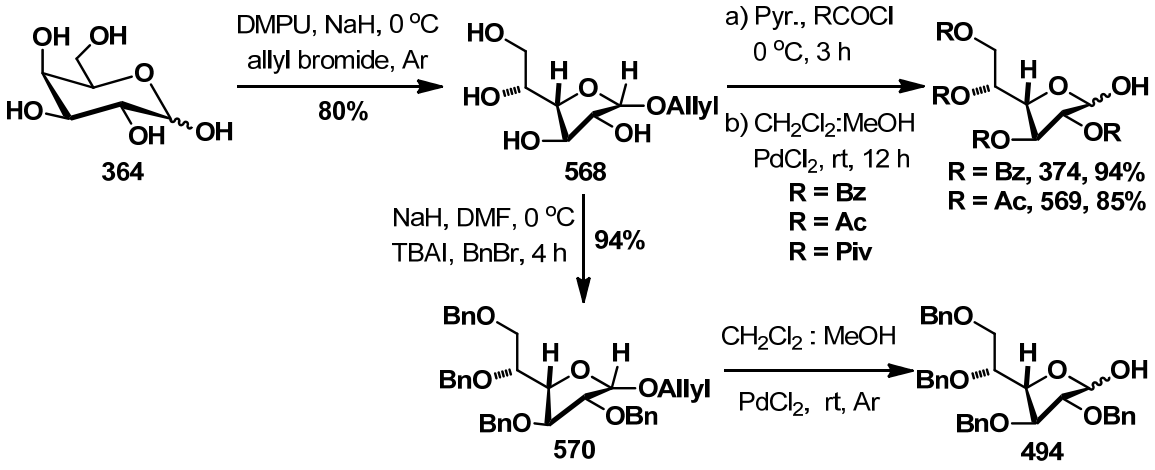
Figure 40. Divergent approach for the repeating tetrasaccharide unit of ZPS PS A1.

7.2. Forward Synthesis of the Tetrasaccharide Unit *via* Linear Approach

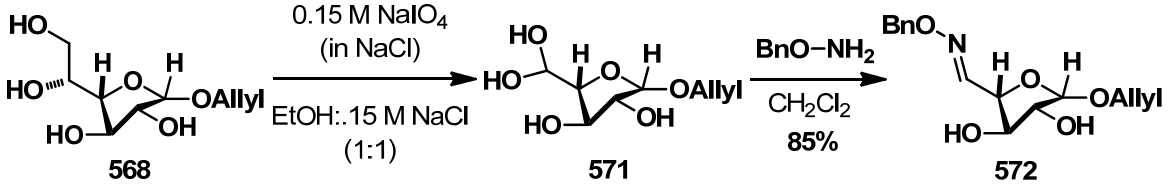
Our group has previously studied the assembly of disaccharide units **557** and **558**[294] (retrosynthetic analysis-I, Figure 38) employing the Kahne[295] as well as the Schmidt[216] glycosylation methods. Unfortunately, the desired tetrasaccharide unit **359** was not obtained. In lieu of these initial attempts, we decided to pursue the lineas approach (Figure 39).

7.2.1. Synthesis of the D-galactofuranoside unit 559

In order to synthesize 2,3,5,6-tetrabenzoyl-D-galactofuranosyl hemiacetal (**374**), D-galactopyanose was converted to 1-allyl-α-D-galactofuranoside (**568**) in presence of DMPU, allyl bromide and NaH at 0 °C.[296] Benzoylation of **568** using benzoyl chloride in pyridine, followed by deallylation in the presence of palladium chloride provided the hemiacetal **374** in excellent yield. For SAR studies; bezylation, acetylation and pivoylation of **568** were also carried out following the same procedure.[294] The 1-allyl-2,3,5,6-tetrabenzyl- and 1-allyl-2,3,4,6-tetraacetyl -α-D-galactofuranoside were converted into the corresponding hemiacetals **494** and **569** respectively (Scheme 128).



Scheme 128. Synthesis of D-galactofuranosyl hemiacetals.

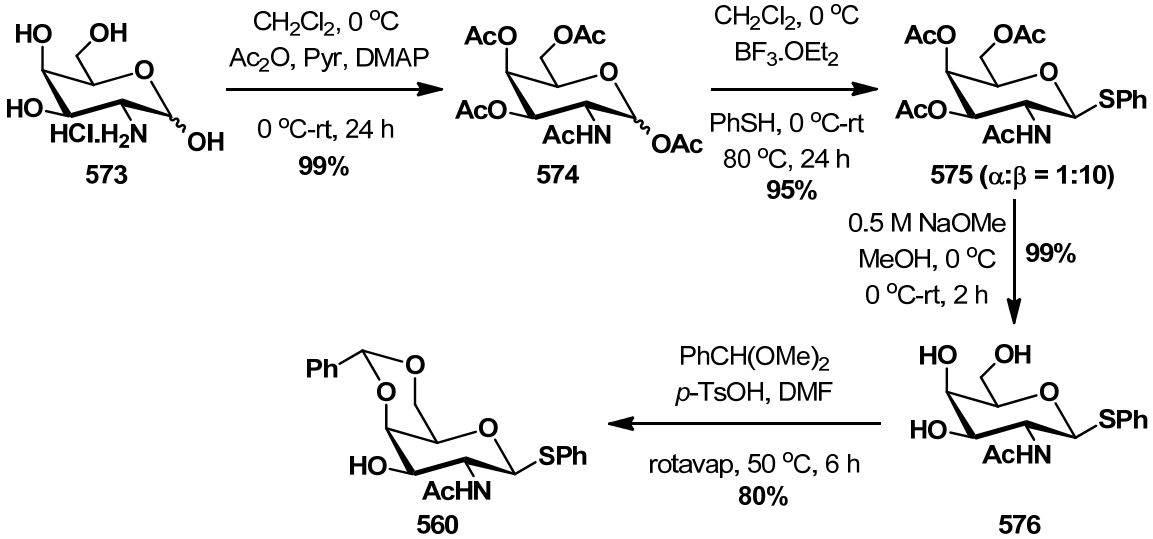


Scheme 129. Oxidative cleavage of **568** and oxime formation.

With the 1-allyl-α-D-galactofuranoside (**568**) in hand, we carried out a preliminary study to convert it into the corresponding 1-allyl-4-carboxaldehyde-α-D-galactofuranoside *via* $NaIO_4$-mediated selective oxidative cleavage of terminal diols consisting of a primary alcohol group.[297] When **568** was treated with 1.13 equivalents of $NaIO_4$ in a 1:1 mixture of ethanol/water, the reaction was completed within 15 min; on the other hand, use of less than 1 equivalent of $NaIO_4$ rendered the reaction incomplete. We also tested variation of ethanol/water in the reaction, however the use of less than 3 equivalents of ethanol led to partial solubility of **568**. Finally, we decided to test the feasibility of running the reaction under near physiological conditions. Thus, **568** was dissolved in a 1:1 mixture of ethanol and 0.15 M NaCl and a 0.15 M solution of $NaIO_4$ in NaCl was added. After stirring the reaction at room temperature for 10 min in the dark, the TLC showed complete conversion and the hydrated aldehyde **571** was obtained in excellent yield. In order to attach the Tn conjugate to the odxidized D-galactofuranoside motif of ZPS PS A1,[293] a model reaction was carried out using the hydrated aldehyde **571**. Thus, *O*-benzyl hydroxyl amine was allowed to react with **571** immediately and the expected oxime **572** was obtained in good yield as a 7:1 mixture of E/Z diastereomers. The identity of compound **572** was confirmed the ^{1}H NMR and HRMS (Scheme 129).

7.2.2. Synthesis of the 2-acetamido-D-galactopyranoside unit 560

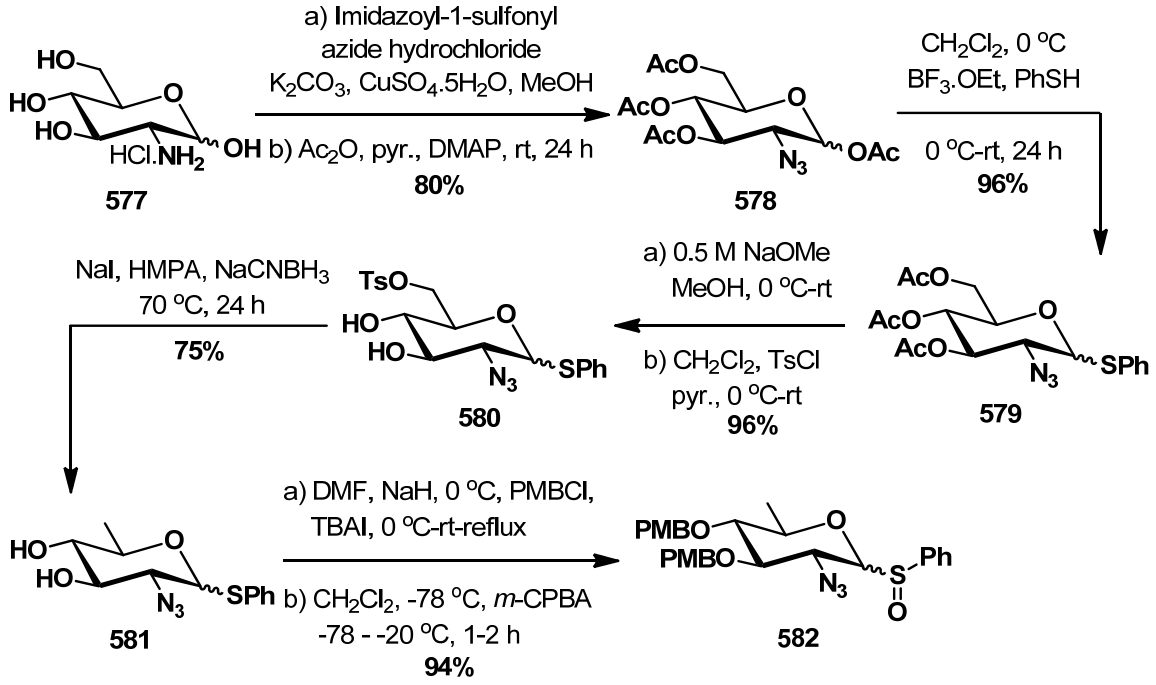
Next, we focused on synthesizing the 2-acetamido-D-galactopyranosyl hydrochloride (D-galactosamine hydrochloride) unit **560**. In the presence of acetic anhydride (Ac_2O) and pyridine, 2-amino-D-galactopyranose was converted into the corresponding peracetylated compound **574** that was thio-glycosylated in the presence of $BF_3.OEt_2$ and thio-phenol to obtain **575** as a 1:10 mixture of α/β anomers. Due to neighbouring group participation by the 2-acetamido group, the β anomer was obtained as the major product.[298] Purified β anomer of **575** was deacetylated under Zemplin conditions[299] to afford triol **576** in quantitative yield. The triol was converted into the corresponding benzylidine acetal **560** by treating with α,α-dimethoxy benzaldehyde and *p*-TsOH at 50 °C on rotavap (Scheme 130).



Scheme 130. Synthesis of the 2-acetamido-D-galactopyranoside unit **560.**

7.2.3. Synthesis of the 2-acetamido-4-amino-L-fucose unit 561

2-Acetamido-D-glucopyranosyl hydrochloride (D-glucosamine hydrochloride) **577** was converted into the corresponding peracetylated compound **578** *via* diazo transfer[300] followed by acetylation (Scheme 131). Thio-glycosylation of **578** with thio-phenol provided excellent yield of **579** as a 1:12 mixture of α/β anomers. Deprotection of the acetyl groups by NaOMe followed by tosylation of the 6-OH afforded the tosylate **580** in good yield. Reductive elimination in the presence of NaI, HMPA and sodium cyano borohydride ($NaCNBH_3$)[301] provided 1-phenylthio-6-deoxy-3,4-dihydroxy-2-acetamido-D-gluccopyranoside **581**. Protection of the diol with PMB followed by epoxidation in presence of *m*-CPBA[302] provided the desired sulfoxide derivative **582** in excellent yield.

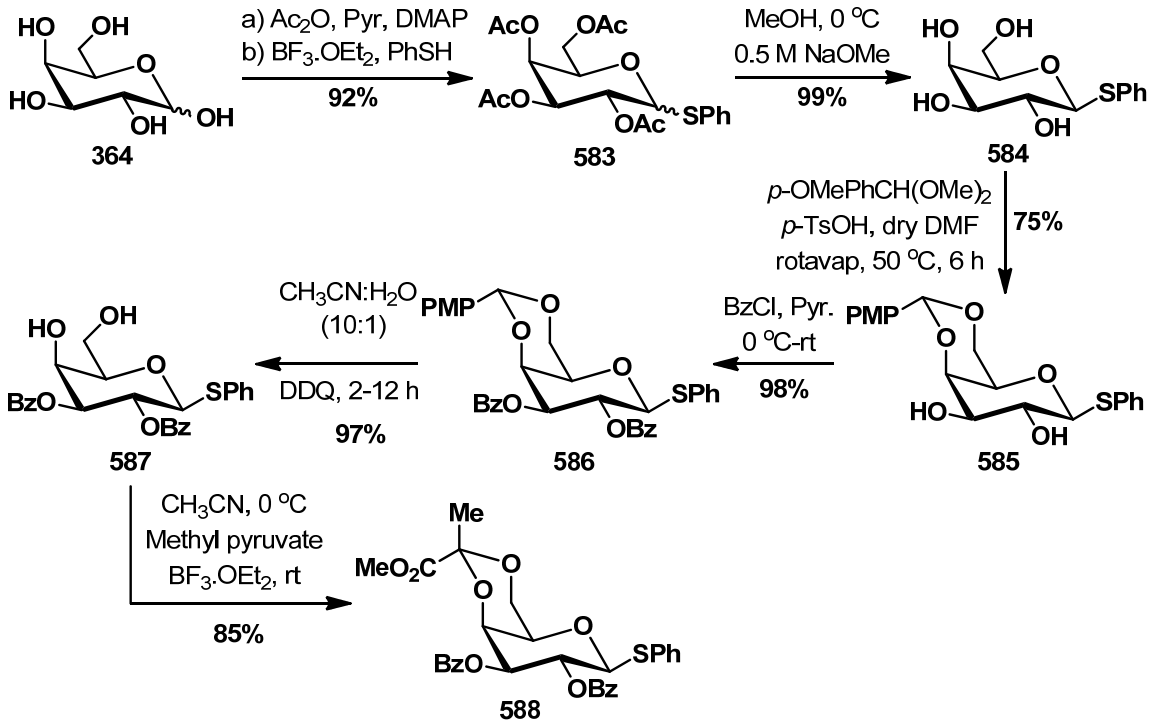


Scheme 131. Synthesis of the sulfoxide **582**.

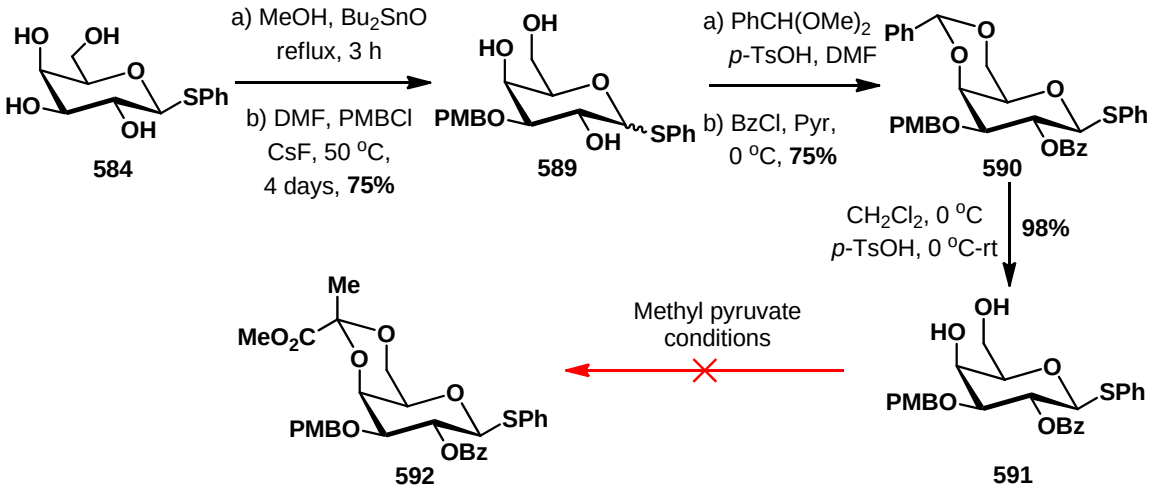
With **582** in hand our plan was to perform the 2nd glycosylation and then remove the PMB groups for the 3rd glycosylation (Figure 38). Next, our plan was to install the mesyl (Ms) group on the 4-OH and perfom a S_N2 transformation using NaN_3 to the corresponding azido derivative.

7.2.4. Synthesis of the 4,6-Pyruvate Acetal-2,3-Dibenzoyl-D-Galactopyranoside Unit 564

Peracetylation of D-galactopyranose using Ac_2O, pyridine, and DMAP followed by glycosylation in the presence of thio-phenol and boron trifluoride dietherate afforded the tetraaceate **583** in 92% yield. Deacetylation of **583** using NaOMe followed by benzylidene acetal formation using *p*-methoxyphenyl α,α-dimethoxy benzaldehyde provided **585** in good yield. Benzoylation in the presence of benzoyl chloride followed by deprotection of benzylidine acetal in the presence of DDQ afforded the diol **587** in excellent yield. Treatment of **587** with methyl pyruvate in the presence of $BF_3.OEt_2$ in CH_3CN provided the desired pyruvate acetal **588** in good yield (Scheme 132).[303]



Scheme 132. Synthesis of pyruvate acetal unit **564**.



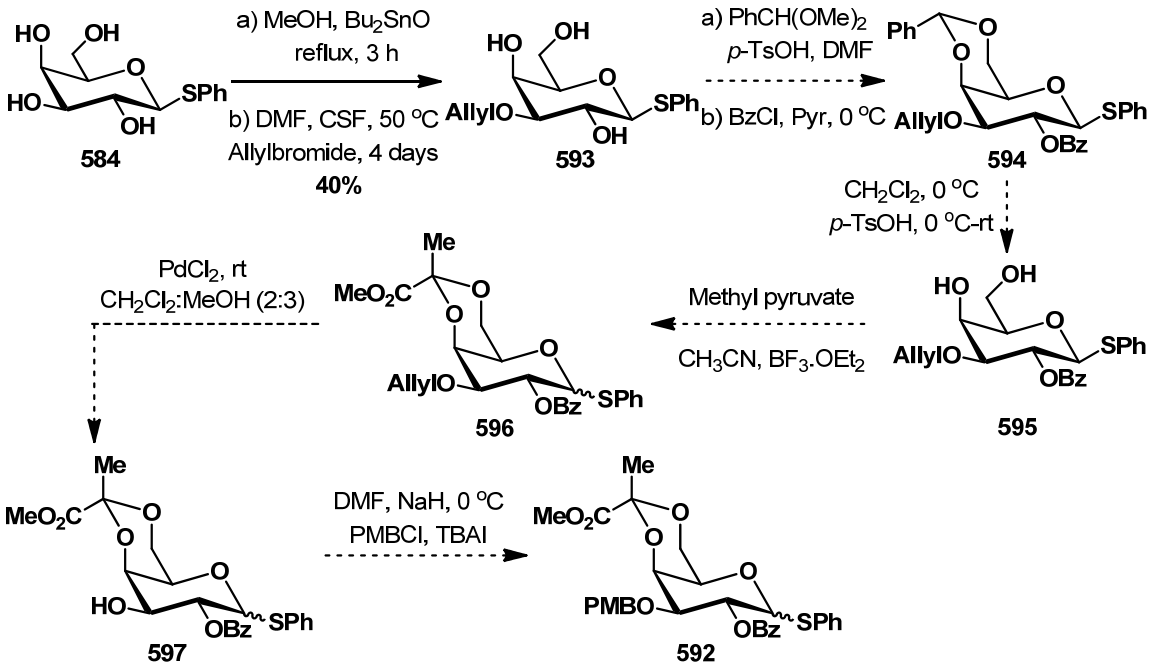
Scheme 133. Effort toward the synthesis of 3-OPMB protected pyruvate acetal **592**.

Next, we examined the synthesis of 3-OPMB protected pyruvate acetal **592** that could used to elongate the repeating tetraaccharide unit of ZPS PS A1 (Scheme 133). Thus, 1-phenylthio-β-D-galactopyranoside (**584**) was converted to 3-*p*-methoxybenzyl-1-

phenylthio-β-D-galactopyranoside **589** *via* stannylation followed by heating with *p*-methoxybenzyl chloride in the presence of CsF in DMF for 4 days. Benzylidine acetal formation of **589** followed by benzoylation afforded **590** in 75% yield.[340] Due to the presence of PMB group at the 3-position and sensitivity of PMB group towards acids, deprotection of the benzylidine acetal was carried out at 0 ^{o}C in presence of *p*-TsOH to obtain **591** in excellent yield. Next, we examined different conditions to install the methyl pyruvate group at the 4,6-positions (Table 28).[304] However, none of the conditions provided the desired pyruvate acetal **592**, either removal of the PMB group or no reaction was observed. We speculated that because of the low reactivity of methyl pyruvate, the acetal formation is not giving the desired product. Thus, we decided to synthesize methyl-2,2-bis(phenylthio)propanoate and subjected to the pyruvate acetal formation. Again, the desired product was not obtained, only removal of the PMB group was observed.

Table 28. Conditions for the synthesis of **592**.

Entry	Conditions	% Yield (**592**)
1	Methyl pyruvate, CH_3CN, $BF_3.OEt_2$, rt, 4 Å MS	0
2	Methyl pyruvate, CH_3CN, *p*-TsOH, rt, 4 Å MS	0
3	Methyl pyruvate, DMF, *p*-TsOH, rt, 4 Å MS	0
4	Methyl pyruvate, DMF, CSA, rt, 4 Å MS	0
5	Methyl pyruvate, DMF, *p*-TsOH, 60-80 oC, 4 Å MS	0
6	1, 1'-Dithiophenyl Methyl pyruvate, DMF, *p*-TsOH, 60-80 oC	0



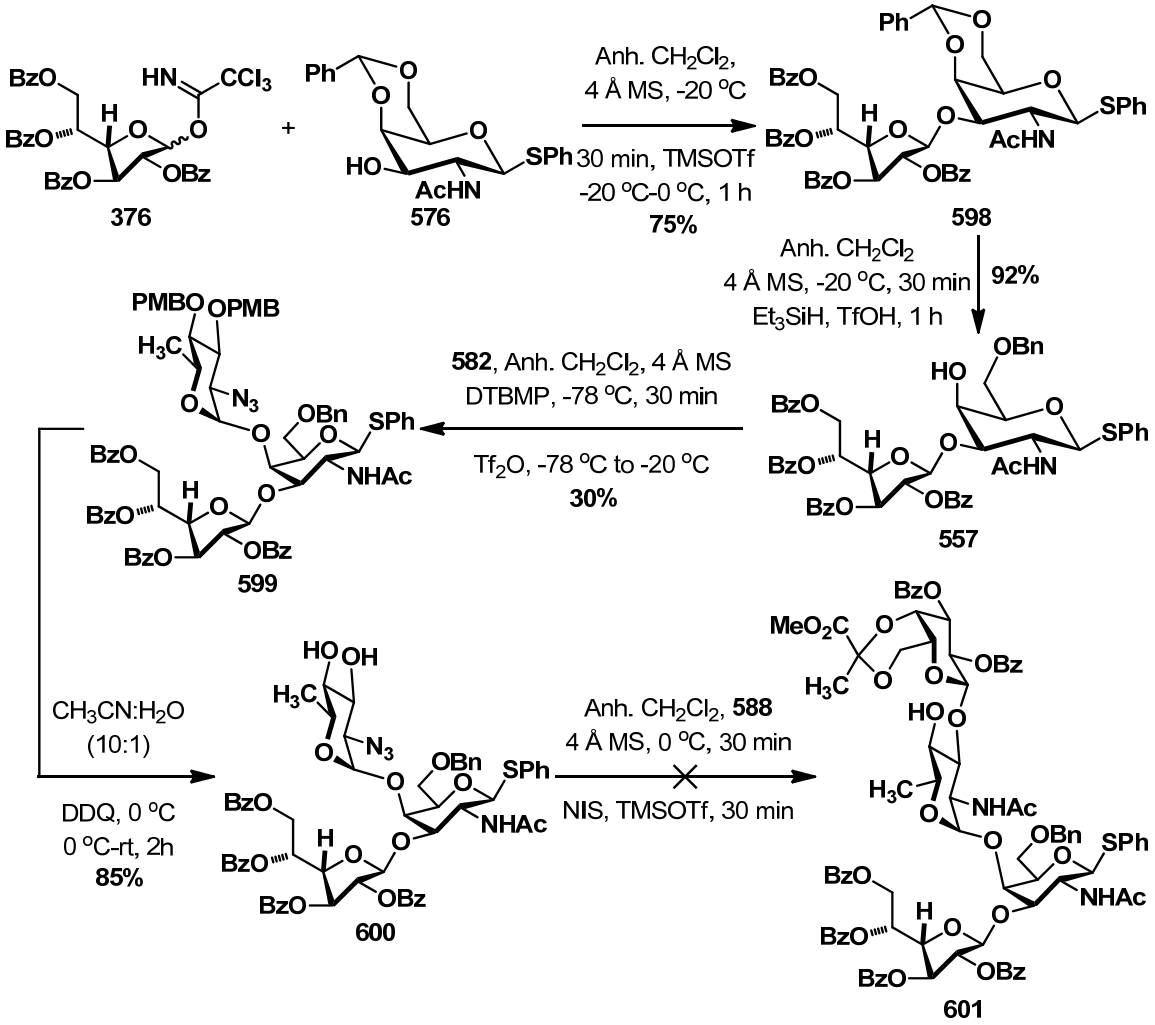
Scheme 134. Proposed synthesis of 3-OAllyl and 3-OPMB pyruvate acetals.

We speculated that a 3-OAllyl protected pyruvate acetal **596** could also be used to obtain the 3-OPMB protected pyruvate acetal **592**. Thus, stannylation using dibutyl tin oxide followed by heating in the presence of CsF and allyl bromide in DMF for 4 days afforded corresponding 1-phenylthio-3-allyl-β-D-galactopyranoside (**593**) in 40% yield.[304] Benzylidine acetal formation of **593** followed by benzoylation could be used to provide **594**. Deprotection of the benzylidine acetal followed by treatment with methyl pyruvate and $BF_3.OEt_2$ could be used to provide the desired pyruvate acetal **596**. Deallylation of **596** using $PdCl_2$ followed by protection of the 3-OH with PMB group could also provide the other desired pyruvate acetal **592** (Scheme 134).

7.2.5. Assembly of the Monosaccharide Units *via* Linear Approach

With the monosaccharide units in hand, we moved forward to assemble them *via* a sequential glycosylation strategy. Thus, 2,3,5,6-tetrabenzoyl-D-galactofuranosyl hemiacetal (**374**) was converted to the corresponding trichloroacetamidate donor **376** following a previously described methods (Scheme 88, Chapter 4). The donor **376** and acceptor **576** were dissolved in anhydrous CH_2Cl_2, stirred at -20 ^oC for 30 min in the presence of 4 Å MS (freshly dried by heat-gun under high-vacuum) followed by the addition of the activator TMSOTf[305] which provided the desired disaccharide **598** in 75% yield. Neighbouring group participation from the benzoyl group promotes formation of β configuration at the newly formed glycosidic bond. Chemoselective bezylidine acetal ring opening using triethylsilane (Et_3SiH) and triflic acid (TfOH) combination[306] afforded compound **557** in 92% yield. Next, the sulfoxide donor **582**, acceptor **557**, di-*tert*-butyl-4-methyl-pyridine (DTBMP) were dissolved in anhydrous CH_2Cl_2, stirred at -78 ^oC for 30 min in presence of 4 Å MS (freshly dried by heat-gun under high-vacuum) and then the activator triflic anhydride (Tf_2O) was added.[295] The reaction was then slowly warmed to -20 ^oC over 1 h and quenced. Gradient column chromatography using silica gel as the stationary phase and ethyl acetate/hexane (1:4 to 1:1) as mobile phase provided the desired product **599** in 30% yield (Scheme 135). Steric hindrance exerted by the furanosyl motif[307] of the acceptor **557** might be responsible for the observed low yield. Furthermore, the presence of electron withdrawing azido group at C2 disfavors the build up of any positive charge on C1, making the donor **582** somewhat disarmed and less reactive.[308] In addition, the 4-OH group of pyranoses are less reactive.[309] The

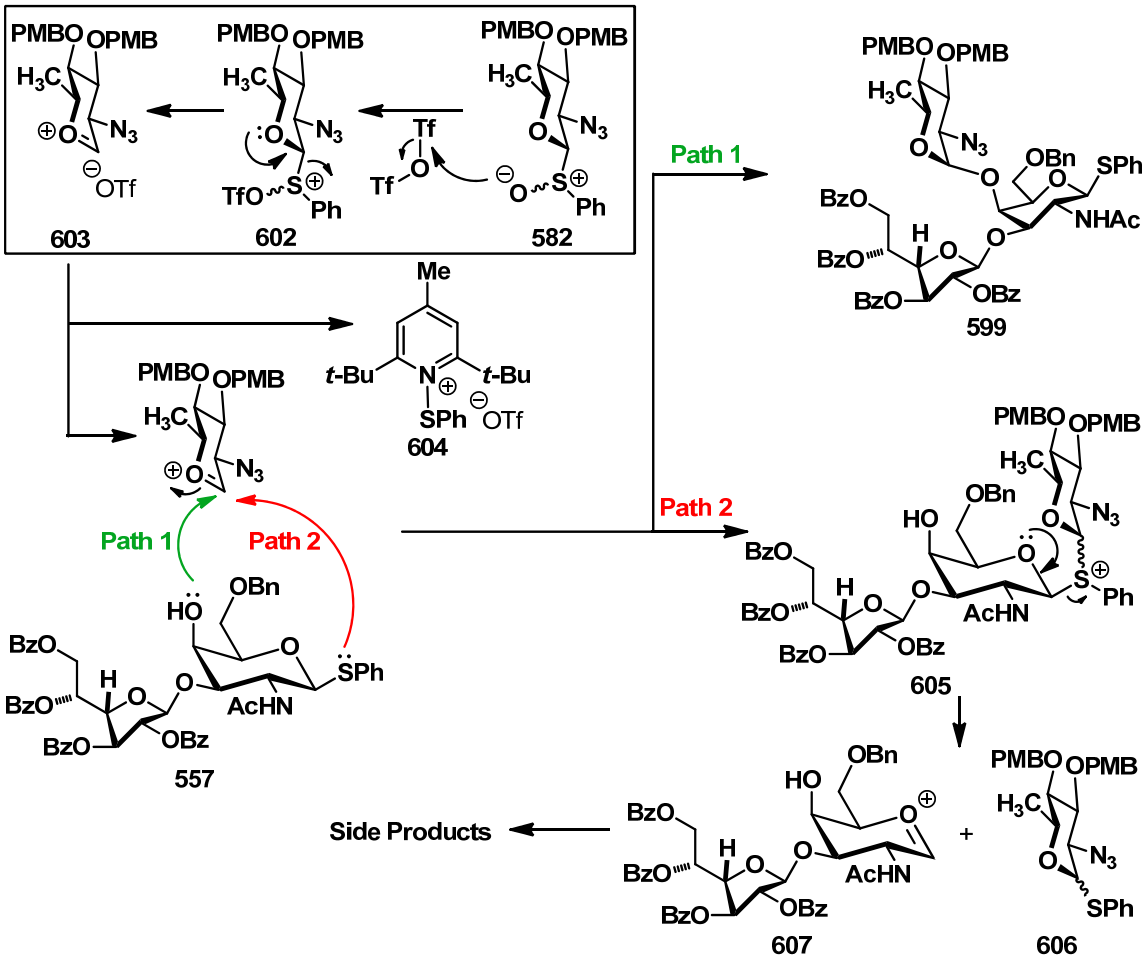
trisaccharide was inseparable from some impurity that was thought to be the aglycon transfer product **606** *via* the pathway shown in Scheme 136.[310]



Scheme 135. Assembly of the monosaccharide units.

Attempts to further purify compound **599** *via* silica gel column chromatography led to decomposition. Thus, we decided to move forward and DDQ removal of PMB groups from **509** provided the diol compound **600** in 85% yield. Pre-activation of the donor **600** by *N*-iodo-succinimide (NIS) and TMSOTf in anhydrous CH_2Cl_2 in the presence of 4 Å MS (freshly dried by heat-gun under high-vacuum) followed by addition

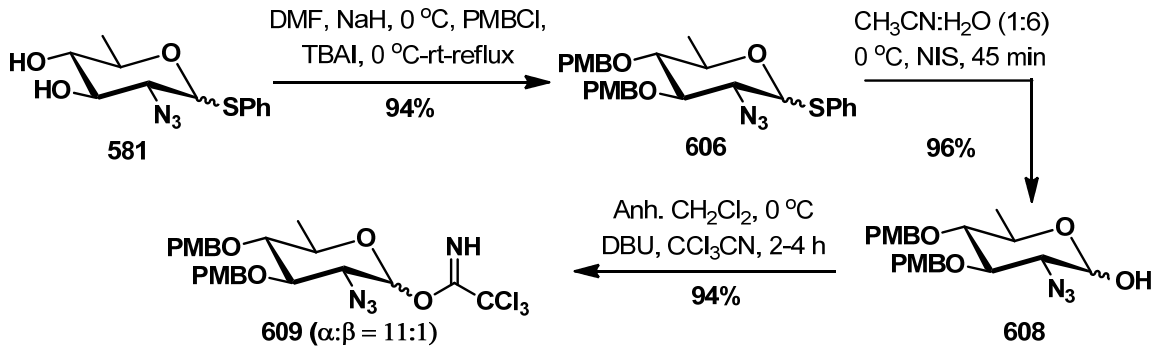
of the acceptor **588**[311] did not provide the desired tetrasaccharide **601** (Scheme 135). It is suspected that since the acceptor also contains a thiophenyl group at the anomeric position and the presence of *N*-acetyl group at C-2 favors formation of positive charge at C1, making the acceptor more reactive than donor **588** which is disarmed and less reactive due to the presence of benzoyl group at C2, which leads to unkown side reaction (Scheme 136).[308]



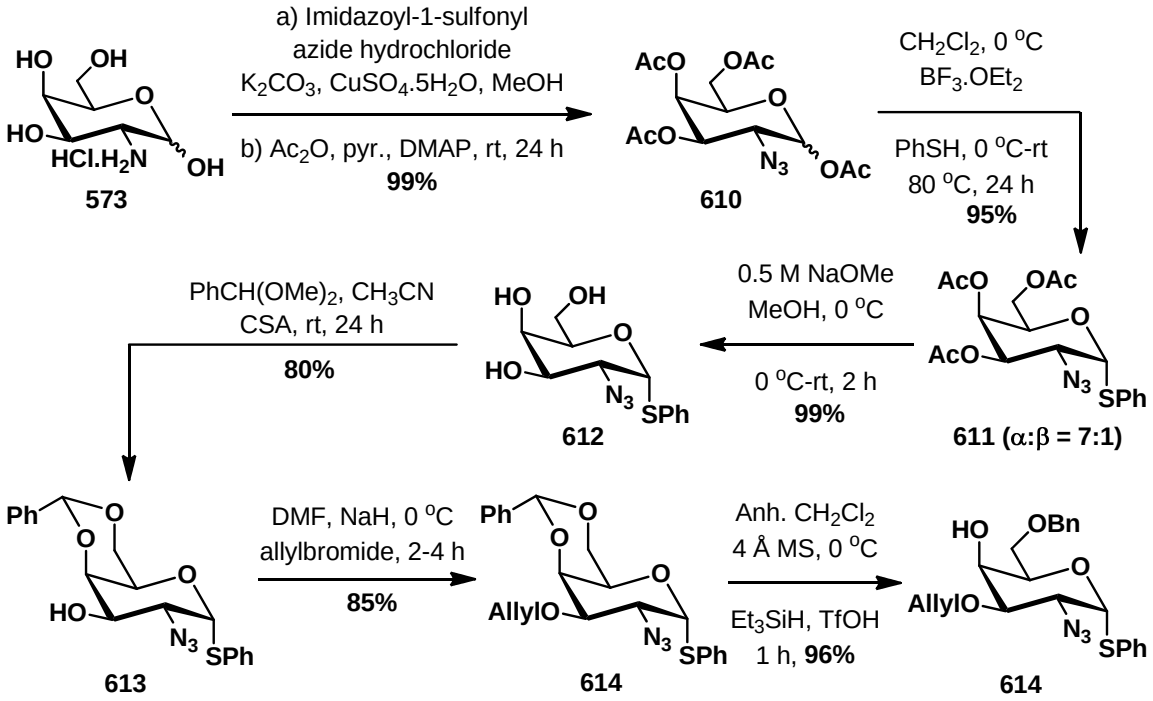
Scheme 136. Possible mechanism for the aglycon transfer pathway.

7.3. Synthetic Study *via* Divergent Approach

Being unsuccessful in the construction of the tetrasaccharide unit *via* the linear approach, we elected to examine the alternative divergent approach. We speculated that the initial construction of of the disaccharide **565** would be more feasible as it could avoid the steric hindrance of furanosyl moiety and would enable us to set the required α stereochemistry at C-1 of the 3,4-di-*p*-methoxybenzyl,-2-azido-6-deoxy fucose motif. Thus the trichloro acetamidate donor **609** was synthesized from compound **581**. Protection of the 3,4-dihydroxyl groups by PMB group afforded the corresponding di-PMB product **606** which was treated with NIS in a 1:6 mixture of CH_3CN and water to obtain the hemiacetal **608**. The trichloroacetamidate **609** was obtained by treating **608** with DBU and trichloroacetonitrile at 0 ^oC for 2-4 h (Scheme 137). Compound **609** was purified *via* gradient silica gel column (neutralized with 1% Et_3N) chromatography using ethyl acetate/hexane (1:4 to 1:1) mixture as the eluent. It is important to note that **609** is quite unstable (probably due to the presence of electron withdrawing azido group at C-2) and spontaneously converts into corresponding hemiacetal **608** at room temperature. Thus it was used directly after purification.



Scheme 137. Synthesis of di-PMB protected trichloroacetamidate **609**.

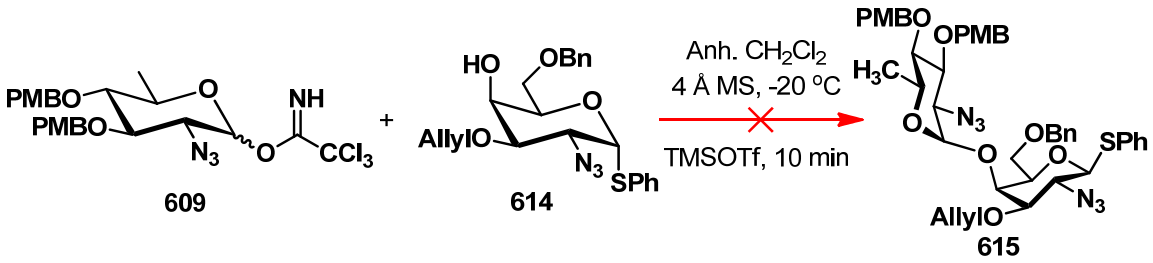


Scheme 138. Synthesis of 3-*O*allyl protected acceptor **614**.

Next, we focused on the synthesis of 3-*O*allyl protected 2-azido 4,6-benzylidine-D-galactopyranoside. Thus, 2-amino-D-galactopyranose was converted to the corresponding 2-azido,1-3,4,6-tetraacetyl-D-galactopyranoside **610** *via* diazo transfer using imidazoyl-1-sulfonyl hydrochloride in the presence of K_2CO_3, $CuSO_4.5H_2O$[300] followed by per-acetylation as described earlier (Scheme 131). Glycosylation of **610** with thio-phenol provided **611** as a 7:1 mixture of α/β anomers. Deprotection of the acetyl groups using NaOMe followed by benzylidine acetal formation in presence of α,α-dimethoxy benzaldehyde and camphor sulfonic acid (CSA) in CH_3CN afforded **613** in good yield. Allylation of **613** using allylbromide and NaH in DMF provided the 3-OAllyl product **614** (Scheme 138). As described earlier, chemoselective benzylidine acetal ring opening by Et_3SiH/TfOH[306] afforded the desired acceptor **614** in excellent

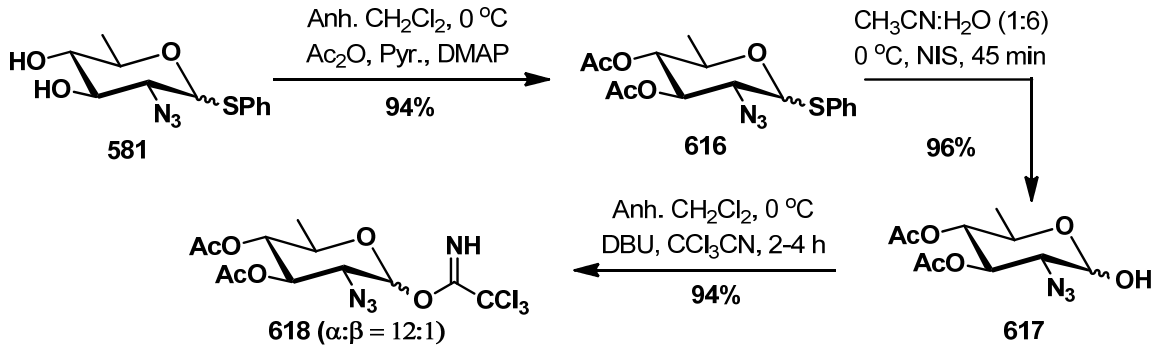
yield. Compound **614** observed to be not so stable for an extended period of time when stored at 0 °C. Thus it was prepared as required.

With the donor **609** and acceptor **614** in hand, we examined the coupling employing Schmidt's conditions. The donor **609** and acceptor **614** were dissolved in anhydrous CH_2Cl_2 in presence of 4 Å MS (freshly dried by heat-gun under high-vacuum) for 1 h at 0 °C and then the activator TMSOTf was added. However, the expected disaccharide **615** was not obtained even after use of 0.3-0.5 equiv. of the activator TMSOTf (Scheme 139). Probably, the 4-OH of the acceptor is unreactive and requires a longer reaction time. Moreover, the PMB groups of the donor **609** might render some steric hindrance during glycosylation. Furthermore, the presence of azido group at C2 disfavors the build up of any positive charge at C1, making it somewhat disarmed and less reactive.[308]



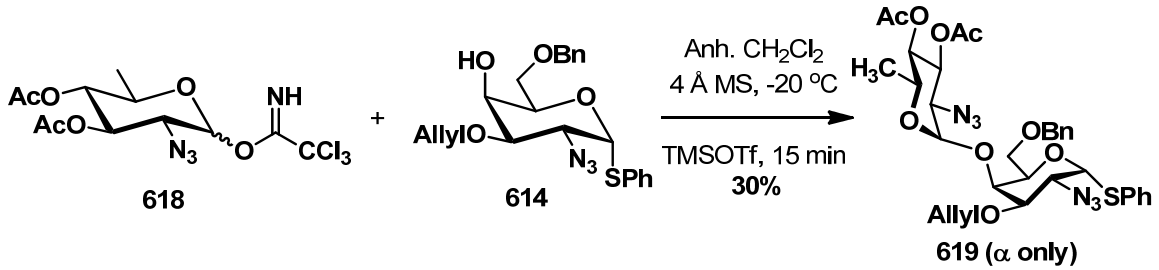
Scheme 139. Coupling of donor **609** and acceptor **614**.

Hence, we revised our synthetic strategy and decided to replace PMB with acetate groups. Thus, acetylation of **581** followed by the steps described previously (Scheme 141) afforded the desired trichloroacetamidate **618** in excellent yield (Scheme 140).

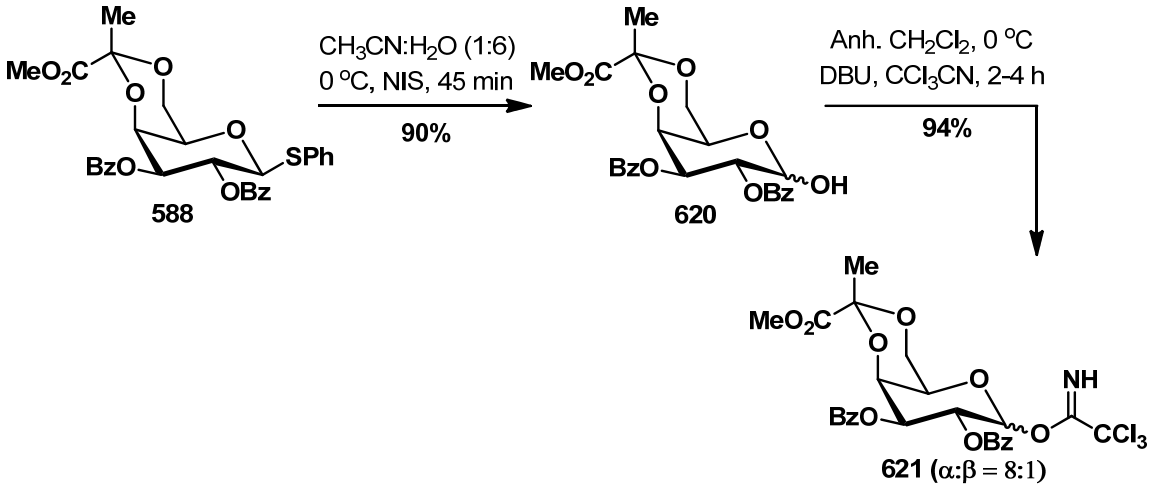


Scheme 140. Synthesis of di-acetate protected trichloroacetamidate **618**.

With **618** in hand, we performed the glycosylation with the acceptor **614** as described for **615**. Gratifyingly, the desired disaccharide **619** was obtained in 30% yield along with the aglycon transfer product **616** (Scheme 141). Unreacted **614** was recovered *via* gradient silica gel column chromatography. It is noteworthy to mention that, the coupling provides exclusively α-product which was confirmed by ^{1}H and ^{13}C NMR. Our result is also in good aggrement with literature precedence on similar couplings.[310e, 312] The indentity of compound **619** was further confirmed by ^{1}H-^{1}H GDQFCOSY, GHMQC and GHMBC.

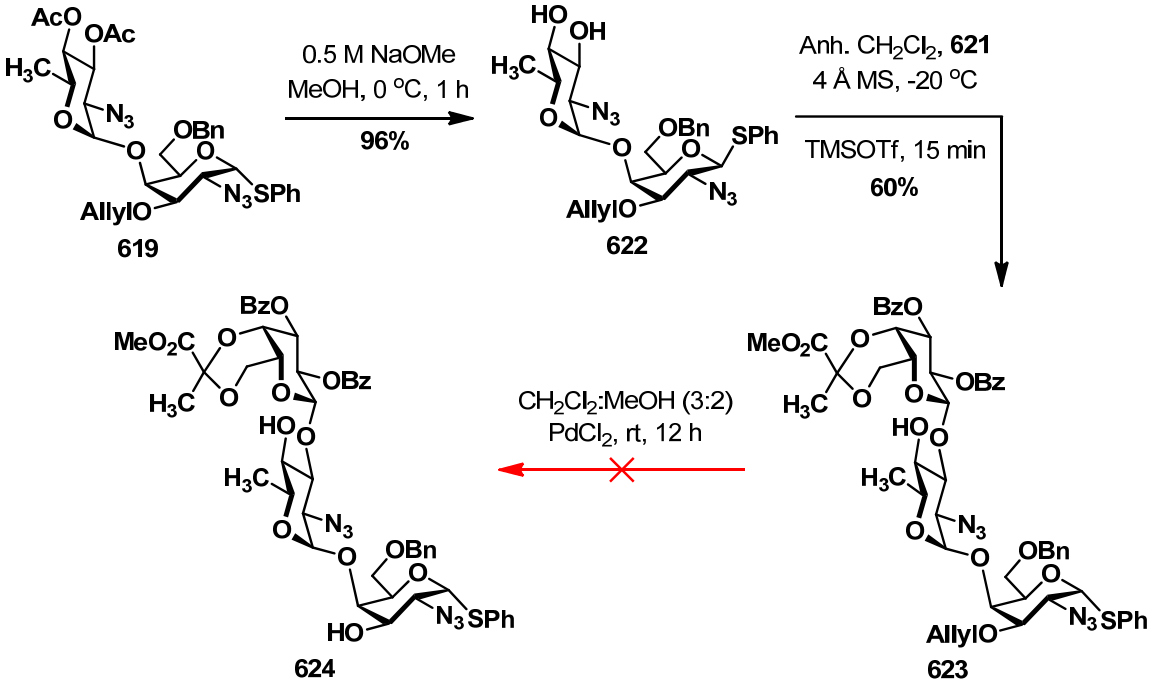


Scheme 141. Synthesis of disaccharide **619**.



Scheme 142. Synthesis of trichloroacetamidate **621** of the pyruvate acetal **588**.

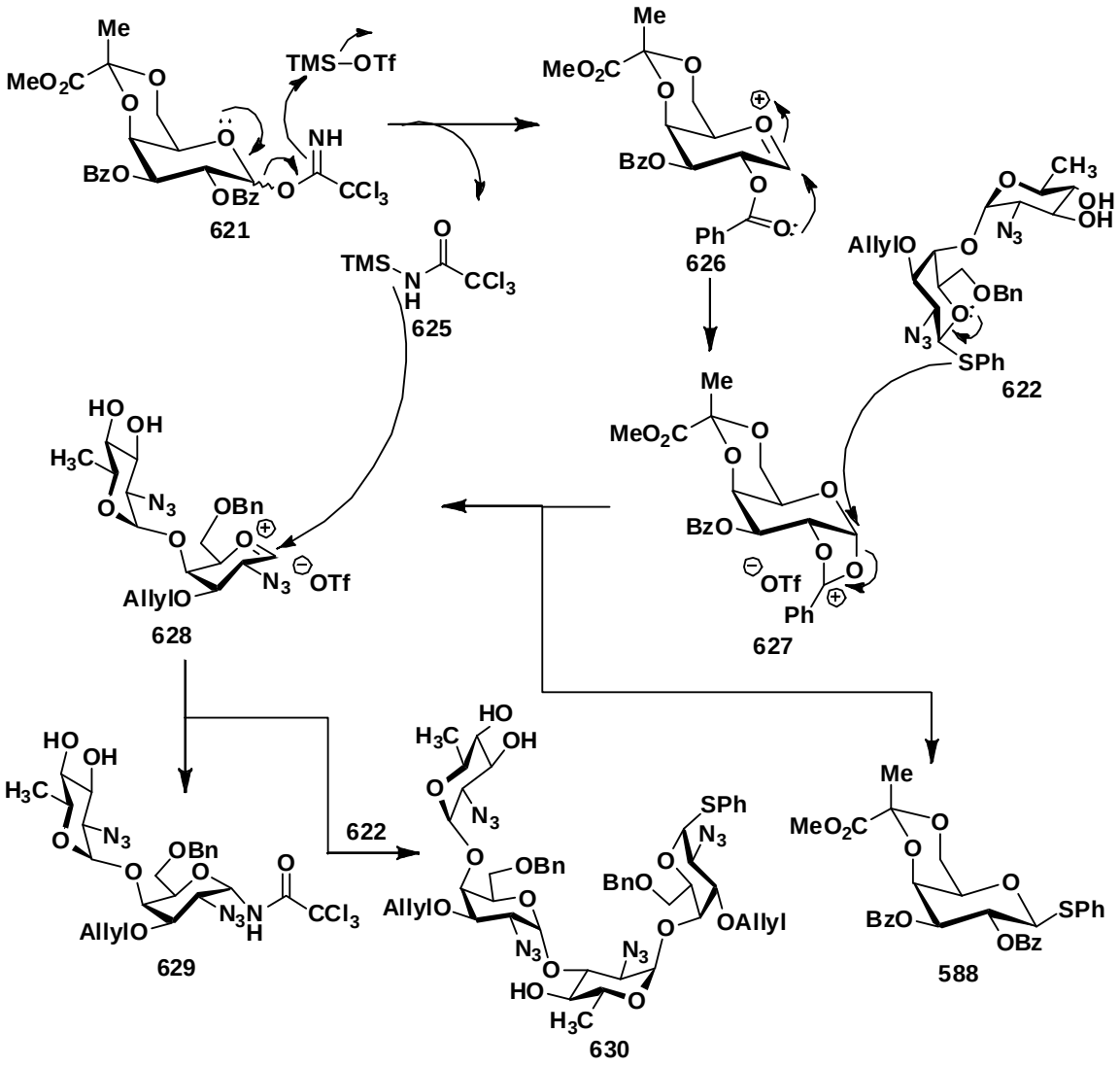
Next, we decided to couple disaccharide **619** with the trichloroacetamidate of the benzoyl protected pyruvate acetal **588**. Thus, **588** was converted to the corresponding hemiacetal **620** which was converted to trichloroacetamidate **621** following the procedure as described earlier (Scheme 142).



Scheme 143. Synthesis of trisaccharide **623**.

With **621** in hand, we carried out the glycosylation with the acceptor **622** following the procedure described for **619**. The desired trisaccharide **623** was obtained in good yield along with the aglycon transfer[310] product **588** which was inseparable. Thus, we decided to use **623** without further purification. The idenity of compound **623** was confirmed by ^{1}H, ^{13}C, ^{1}H-^{1}HGDQFCOSY. Lower yield could be due to the presence of benzoyl group at C2 which makes the donor **621** somewhat disarmed and less reactive. Furthermore, the pyruvate acetal locks the ring in a specific conformation that might also disfavor the formation of planner oxocarbonium ion due to torsional strain.[313] Next, **623** was subjected to deallylation in presence of $PdCl_2$,[296] after 4 h TLC showed 50% conversion. However, after 12 h, unfortunately decomposition of the starting material was observed (Scheme 143).

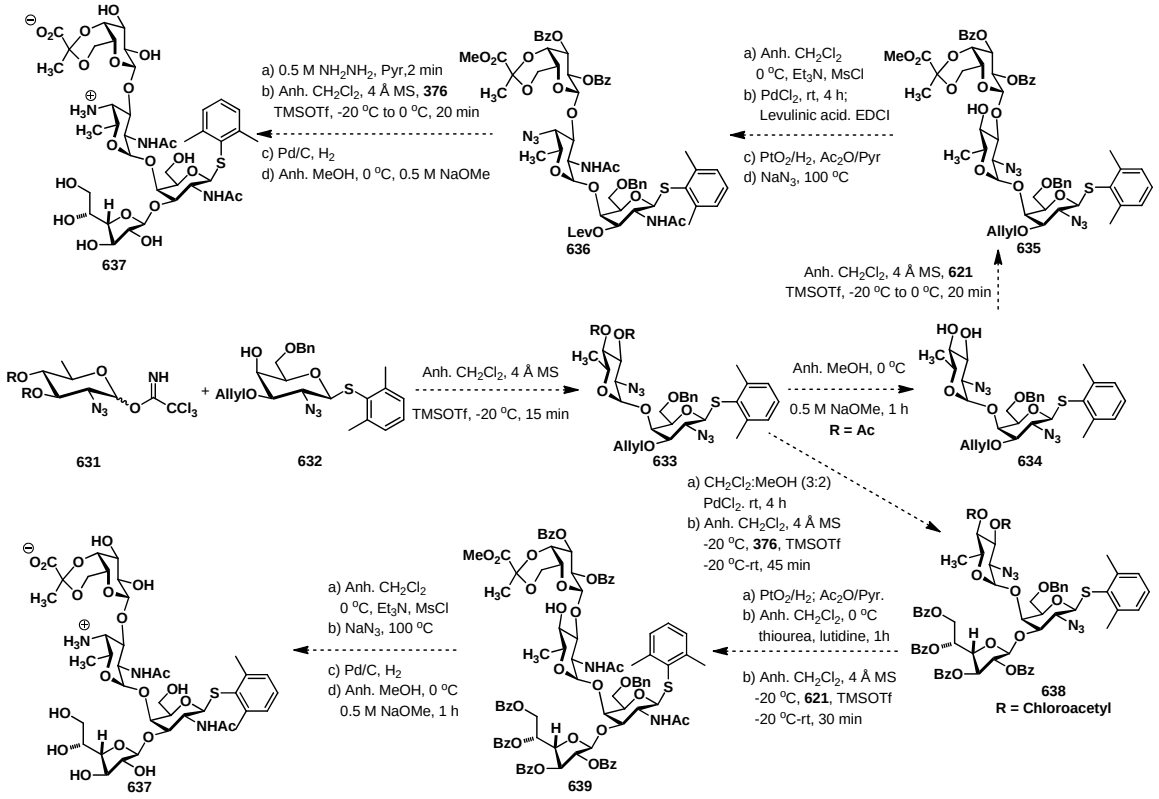
A probable mechanism for the formation of aglycon transfer product **588** and side products is shown in scheme 145.[310d] Activation of the donor **621** by TMSOTf forms 2,2,2-trichloro-*N*-trimethylsilylacetamide (**625**)and the benzoxonium ion **626**. The thiophenol group at anomeric position of the acceptor **622** then attack on the C1 of **626** and forms the β-thioplycoside **588** *via* sulfonium intermediate as shown in Scheme 160. The reactive intermediate **628** can either be trapped be a nucleophile or will decompose. Thus either **625** or the 3-OH (more reactive than 4-OH) of the acceptor **622** can serve as nucleophile and provide the trichloroacetamide derivative **629** or the polymerization product **630** respectively (Scheme 144).



Scheme 144. Probable mechanism for the formation of trichloroacetamide and polymerization product.

7.4. Future Direction

Since we have observed aglycon transfer during the synthesis of **619** (Scheme 141), the future strategy would be to prevent this side reaction. Gildersleeve and co-workers have shown that use of 2,6-dimethylphenylthio group at the anomeric position of the acceptor **614** was effective to prevent aglycon transfer during TMSOTf-mediated glycosylation.[310] Thus, the 2,6-dimethylphenylthio group protected accetor **632** can be synthesized following the procedure outlined in Scheme 138.



Scheme 145. Future direction toward the synthesis of repeating tetrasachharide unit of ZPS PS A1.

Coupling of the acetate (or cloroacetate) protectecd donor **631** with 2,6-dimethylphenylthio protected acceptor **632** *via* Schmidt glycosylation can provide the disachharide **633**. Deprotection of the acetyl groups in presence of NaOMe can provide

the diol **634**. Schmidt glycosylation with the donor **621** in presence of TMSOTf can afford the trisachharide **635**. Mesylation of **635** followed by deallylation, protection with levulinic group, reduction of the azido group (by Adam's catalyst) and finally S_N2 displacement of OMs group by azide can provide the trisachharide **636**. Removal of the levulinic group by thiourea followed by Schmidt glycosylation with the donor **376**, debenzylation in presence of Pd/C and global deprotection of benzoyl groups as well as the ester group can provide the desired tetrasachharide **637**.

Alternatively, the chloroacetyl protected disachharide **633** can be subjected to deallylation followed by Schmidt glycosylation with donor **376** to obtain trisachharide **638**. The chloroacetyl group can deprotected by thiourea and the acceptor can be subjected to Schmidt glycosylation with the donor **621** to access the tetrasachharide **639**. Mesylation of **638** followed by S_N2 displacement by NaN_3, debenzylation and global deprotection can provide the tetrasachharide **637**.

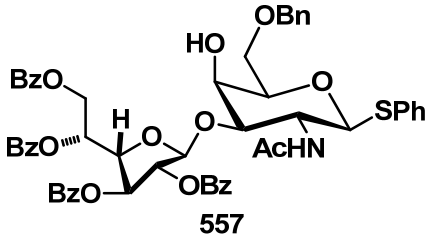
In case, the deallylation in presence of $PdCl_2$ fails, the iridium based catalyst $[Ir(COD)(PMePh_2)]PF_6$ in presence of H_2 in THF followed by treatment with $HgCl_2$ and HgO in acetone/H_2O can be employed. Then the steps described above can be followed.

7.5. Materials and Methods

All Reagents were purchased from Aldrich unless otherwise noted. Anhydrous methanol, tetrahydrofuran, acetone and dichloromethane were purchased from Alfa Aesar. Anhydrous methanol was purchased from EMD chemicals (DriSolv). *p*-Toluene sulfonic acid and TMSOTf were purchased from Acros organics. Thiophenol, Allyl bromide, methyl pyruvate, DMPU and NIS were purchased from Alfa Aesar. Palladium chloride was purchased from Stream Chemicals. Except as otherwise indicated, reactions were carried out under Argon. All reactions were monitored by thin layer chromatography using 0.25 mm Dynamic Adsorbents, L.L.C. precoated silica gel (particle size 0.03-0.07 mm, catalog no. 84111). Column chromatography was performed using Whatman Purasil 60 Å (230-400 mesh ASTM) silica gel. Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise noted. Diastereomeric ratios were determined from ^{1}H NMR spectra of non-purified reaction mixtures. Proton and carbon-13 NMR spectra were recorded on Varian Mercury 400, Varian Unity 500 and Varian 500 Direct Drive System spectrometers. The residual $CDCl_3$ singlet at δ 7.26 ppm and δ 77 ppm were used as the standard for ^{1}H NMR and ^{13}C NMR spectra respectively. Mass spectra were recorded on Micromass GCT at 70 eV.

7.5. Experimental Data

1.



557

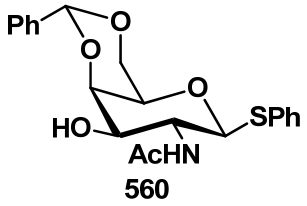
To an oven dried RB flask equipped with magnetic stir bar under Argon, compound **598** (0.145 g, 0.148 mmol) was taken and 4 Å MS (0.042 g, oven dried for 24 h followed by heat gun under high vacuum) was added to the flask. After adding anhydrous CH_2Cl_2 (2 mL), the flask was stirred for 1 h at room temperature and then cooled to -78 ^oC. To the stirred solution, Et_3SiH (8 μL, 0.488 mmol) was added followed by TfOH (4 μL, 0.444 mmol). The resulting solution was stirred at -78 ^oC for 1 h and then neutralized by the addition of Et_3N (0.3 mL) followed by methanol (0.5 mL). The mixture was then diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (10 mL). The aqueous layer was washed with CH_2Cl_2 (5 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The crude residue was purified *via* gradient silica gel (neutralized with 0.1% Et_3N) column chromatography using a mixture of ethyl acetate/hexane (1:3 to 1:1) as the eluent to afford 0.134 g (92%) of **557** as a white solid.

^1H NMR (500 MHz, $CDCl_3$): δ 8.06-8.12 (m, 2 H, aryl), 7.95-8.03 (m, 4 H, aryl), 7.48-7.60 (m, 6 H, aryl), 7.27-7.45 (m, 14 H, aryl), 7.20-7.26 (m, 2 H, aryl), 5.96 (m, 1 H), 5.91 (d, 1 H, *J* = 7.3 Hz, H-1), 5.68 (dd,1 H, *J* = 5.6, 1.8 Hz), 5.38-5.45 (m, 3 H), 4.81 (dd, 1 H, *J* = 5.8, 3.7 Hz), 4.75 (dd, 1 H, *J* = 11.9, 4.6 Hz), 4.68 (dd, 1 H, *J* = 11.9, 6.7 Hz), 4.51 (s, 2 H), 4.47 (dd, 1 H, *J* = 10.4, 3.1 Hz), 4.16 (d, 1 H, J = 2.7 Hz), 3.62-3.77 (m, 4 H), 2.7 (bs, 1 H, 4-OH), 1.99 (s, 3 H, -NHCOC$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 166.1, 165.8, 165.7, 165.6, 137.9, 133.6, 133.5, 133.4, 133.3, 133.2, 131.9, 129.9, 129.9, 129.8, 129.4, 129.3, 128.9, 128.7, 128.5, 128.4, 128.4, 128.3, 127.7, 127.5, 107.7, 85.0, 82.9, 81.1, 77.8, 77.1, 73.6, 70.1, 69.9, 69.6, 63.1, 52.6, 46.6, 23.6.

HRMS (EIMS, M^+ +Na): cald for $C_{55}H_{50}NNaO_{14}S$ 1003.2850, found 1003.2854.

2. **1-Phenylthio-2-*N*-acetyl-4,6-benzylidene-β-D-galactopyranoside**



560

To an oven dried RB flask equipped with magnetic stir under Argon, Na (0.07 g, 3.04 mmol, washed with dry hexane) was taken and cooled to 0 ^oC. Anhydrous methanol (39 mL) was then added at ^oC; the solution was stirred for 1-2 h until all Na completely dissolved and the solution was kept at 0 ^oC. 1-Phenylthio-2-*N*-acetyl-3,4,6-triacetate-β-D-galactopyranose (**575**) (3.38 g, 7.70 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous methanol (10 mL). The flask was then cooled to 0 ^oC and freshly prepared NaOMe (39 mL, 0.08 M) was added slowly *via* a syringe. The resulting solution was then slowly warmed to room temperature and stirred for 12 h. The reaction mixture was then neutralized to pH 6 with Amberlite 120 and then filtered. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure on rotavap to afford 2.47 g (99%) of triol **576** as a colorless oil.

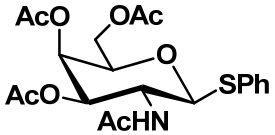
The triol **576** (2.47 g, 7.89 mmol) was dissolved in anhydrous DMF (29 mL) under Argon. To the solution, catalytic amount of *p*-TsOH was added the resulting mixture was heated to 50 ^oC on rotavap under reduced pressure for 6 h. The reaction mixture was then cooled to room temperature and diluted with water (200 mL). The solution was then then extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of

ethyl acetate/hexane (1:3 to 3:1) as the eluent to afford 2.53 g (80%)of **560** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.64 (m, 2 H, Ph), 7.40-7.49 (m, 3 H, Ph), 7.31-7.37 (m, 3 H, Ph), 7.22-7.28 (m, 3 H, Ph), 5.5 (s, 1 H, -CHPh), 4.84-4.89 (m, 1 H), 4.34 (d, 1 H, *J* = 12.5 Hz, H-6), 4.15-4.20 (m, 1 H), 4.01 (d, 1 H, *J* = 12.5 Hz, H-6), 3.81-3.86 (m, 2 H), 3.53 (s, 1 H), 2.35 (bs, 1 H, 3-OH), 2.0 (s, 3 H, -NHCOCH$_3$)

HRMS (EIMS, M^+): cald for $C_{21}H_{23}NO_5S$ 401.1297, found 401.1291.

3.



575 (β anomer)

D-Galactosamine hydrochloride (3 g, 13.91 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. Anhydrous CH_2Cl_2 (50 mL) was then added to the flask and cooled to 0 ^oC. To the solution, pyridine (16.87 mL, 208.65 mmol) was added dropwise *via* syringe followed Ac_2O (13.15 mL, 139.10 mmol) and DMAP (0.15 g, 1.23 mmol). The resulting mixture was then slowly warmed to room temperature and stirred for 18 h. The reaction was then quenched with with saturated $NaHCO_3$ (100 mL) at 0 ^oC. The solution was then extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was diluted with toluene (100 mL) and further concentrated under reduced pressure on rotavap to remove remaining AcOH and pyridine. The residue was then purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent to afford 5.85 g (99%) of **574** as a white solid.

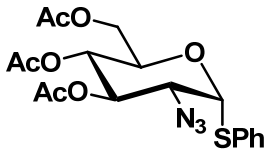
4 Å MS was dried in oven for 24 h followed by heat gun under high vacuum and then transferred to an oven dried RB flask equipped with magnetic stir bar under Argon. To the flask, **574** (3.55 g, 9.13 mmol) was added and dissolved in anhydrous CH_2Cl_2 (40 mL). The solution was then cooled to 0 ^oC and PhSH (2.82 mL, 27.38 mmol) was added followed by $BF_3.OEt_2$ (4.59 mL, 36.50 mmol). The resulting mixture was stirred at 0 ^oC for 4 h, then slowly warmed to room temperature and stirred for 4 h. TLC showed that reaction was incomplete and thus the reaction mixture was refluxed for 24 h in a silicone-based oil-bath. After cooling reaction to room temperature, the reaction was quenched with saturated $NaHCO_3$ to pH 7 and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine (50 mL) and dried over Na_2SO_4. After concentrating the organic layer under reduced pressure on rotavap, the residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 5:1) as the eluent to afford 3.48 g (95%) of **575** as a white solid.

^1H NMR (500 MHz, $CDCl_3$): δ 7.46-7.51 (m, 2 H, Ph), 7.24-7.31 (m , 3 H, Ph), 6.0 (d, 1 H, J = 9.2 Hz, H-1), 5.36 (d, 1 H, *J* = 3.4 Hz), 5.21 (dd, 1 H, *J* = 10.7, 3.4 Hz), 4.94 (d, 1 H, *J* = 10.4 Hz), 4.19 (dd, 1 H, *J* = 19.8, 10.1 Hz), 4.14 (dd, 1 H, *J* = 11.0, 7.0 Hz, H-6), 4.08 (dd, 1 H, *J* = 11.1, 5.8 Hz, H-6), 3.94 (t, 1 H, *J* = 6.7 Hz), 2.10 (s, 3 H, -COC$\underline{H}_3$), 2.0 (s, 3 H, -COC$\underline{H}_3$), 1.96 (s, 3 H, -COC$\underline{H}_3$), 1.95 (s, 3 H, -COC$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.3, 170.2, 133.1, 131.8, 128.8, 127.7, 86.9, 74.3, 71.0, 66.9, 61.9, 49.6, 23.3, 20.6

HRMS (EIMS, M^+): cald for $C_{20}H_{25}NO_8S$ 439.1301, found 439.1298.

4.



579 (α anomer)

D-Glucosamine hydrochloride (3 g, 13.92 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and anhydrous methanol (75 mL) was added. To the solution, K_2CO_3 (4.65 g, 33.63 mmol) and $CuSO_4.5H_2O$ (0.06 g, 0.27 mmol) and imidazole-1-sulfonyl azide (3.51 g, 16.68 mmol) were added respectively. The resulting mixture was stirred at room temperature for 18 h and then diluted with MeOH (25 mL). The solution was then filtered, the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure on rotavap.

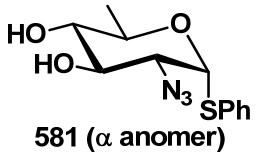
To the peracetylated residue was dissolved in anhydrous CH_2Cl_2 (25 mL) and Ac_2O (10.5 mL, 111 mmol), pyridine (17 mL, 210.19 mmol) were added followed by catalytic amount of DMAP (0.17 g, 1.39 mmol) at 0 ^oC. The resulting mixture was then slowly warmed to room temperature and stirred for 18 h. The reaction was then cooled to 0 ^oC and quenched with saturated $NaHCO_3$ to pH 7. The solution was then extracted with CH_2Cl_2 (3 × 20 mL) and the aqueous layer was washed with additional CH_2Cl_2 (20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was diluted with toluene (100 mL) and further concentrated under reduced pressure on rotavap to remove remaining AcOH and pyridine. The syrup was then purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:6 to 1:1) as the eluent to obtain 4.16 g (80%) of **578** a white solid.

2-azido-1,3,4,6-tetraacetate-D-glucopyranoside (3.0 g, 8.04 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon. 4 Å MS (0.1 g, oven dried for 24 h followed by heat gun dried under high vacuum) was added to the flask. The mixture was stirred in anhydrous CH_2Cl_2 for 30 min at room temperature. After cooling to 0 ^oC, PhSH (1.66 mL, 16.07 mmol) and $BF_3.OEt_2$ (3.03 mL, 24.12 mmol) were added respectively. The resulting mixture was slowly warmed to room temperature over 2 h and then stirred for 18 h. The reaction was then quenched with saturated $NaHCO_3$ to pH 7 and extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was washed with additional CH_2Cl_2 (20 mL). The organic layer were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:6 to 1:1) as the eluent to afford **575** as a white solid.

^1H NMR (400 MHz, $CDCl_3$): δ 7.45-7.53 (m, 2 H, Ph), 7.27-7.38 (m, 3 H, Ph), 5.62 (d, 1 H, *J* = 4.9 Hz, H-1), 5.32 (t, 1 H, *J* = 9.3 Hz, H-3), 5.03 (t, 1 H, J = 10.5 Hz, H-4), 4.54-4.64 (m, 1 H), 4.28 (dd, 1 H, *J* = 17.0, 4.9 Hz), 4.06 (dd, 1 H, *J* = 10.5, 5.7 Hz), 4.01 (dd, 1 H, *J* = 2.5, 1.6 Hz), 2.09 (s, 3 H, –COC$\underline{H}_3$), 2.04 (s, 3 H, –COC$\underline{H}_3$), 2.01 (s, 3 H, –COC$\underline{H}_3$)

HRMS (EIMS, M^+): cald for $C_{20}H_{25}NO_8S$ 439.1301, found 439.1298.

5.



581 (α anomer)

1-Phenylthio-2-azido-3,4,6-triacetate-D-glucopyranoside (2.8 g, 7.38 mmol) was taken in an oven dired RB flask equipped with magnetic stir bar under Argon, dissolved in anhydrous MeOH (8 mL) and cooled to 0 ^{o}C. To the flask, freshly prepared NaOMe solution (0.067 g in 37 mL anhydrous MeOH) at 0 ^{o}C was added dropwise. The resulting solution was then slowly warmed to room temperature and stirred for 18 h. The raction was then neutralized with amberlite IR-120 to pH 6 and filtered. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The triol was used directly without further purification.

1-Phenylthio-2-azido-D-glucopyranoside (1.2 g, 4.04 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous CH_2Cl_2 (30 mL). Pyrdine (1.31 mL, 16.16 mmol) was added and the solution was cooled 0 ^{o}C. Next, TsCl (0.79 g, 4.12 mmol) was added dropwise *via* syringe. The resulting mixture was then slowly warmed to room temperature and stirred for 6 h. The reaction was quenched with 1 N HCl (5 mL), the organic layer was washed with brine (2 × 20 mL). The organic layers were combined and dried over Na_2SO_4. After concentrating the organic layer under reduced pressure on rotavap, the residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:3 to 2:1) as the eluent.

1-Phenylthio-2-azido-6-*O*-tosylate-D-glucopyranoside (1.0 g, 2.22 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in HMPA (40 mL). To the solution, NaI (0.49 g, 3.32 mmol) and $NaCNBH_3$ (1.67 g, 26.59 mmol) were added respectively. The resulting solution was then heated to 70 ^{o}C for 18 h. The reaction was then cooled to 0 ^{o}C and diluted with water (20 mL).

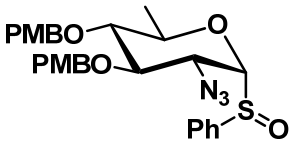
The solution was then extracted with diethyl ether (3 × 20 mL) and the organic layers were separated. The aqueous layer was further washed with diethyl ether (20 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure on rotavap and purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.57 (m, 2 H, Ph), 7.27-7.37 (m, 3 H, Ph), 5.54 (d, 1 H, *J* = 5.6 Hz, H-1), 4.19-4.30 (m, 1 H), 3.84 (dd, 1 H, *J* = 10.8, 5.6 Hz), 3.76 (t, 1 H, *J* = 9.4 Hz), 3.28 (dt, 1 H, *J* = 10.0, 2.4 Hz), 2.71 (bs, 1 H, OH), 2.38 (bs, 1 H, OH), 1.32 (d, 3 H, *J* = 6.4 Hz, C$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.1, 170.0, 134.4, 132.4, 129.5, 128.3, 86.7, 72, 2, 68.9, 68.7, 62, 1, 61.8, 21.0, 20.9, 20.8

HRMS (EIMS, M^+ + Na): cald for $C_{12}H_{15}N_3NaO_3S$ 304.0732, found 304.0729.

6.



582 (α anomer)

1-Phenylthio-2-azido-6-deoxy-D-glucopyranoside (0.072 g, 0.26 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Agron and dissolved in anhydrous DMF (1.5 mL). After cooling the solution to 0 ^{o}C, NaH (0.04 g, 0.78 mmol, 60% in mineral oil) was added in portion, then the mixture was allowed to warm to room temperature and stirred for 15 min. The reaction was again cooled to 0 ^{o}C and PMBCl (0.12 mL, 0.89 mmol) was added followed by catalytic amount of TBAI.

The resulting mixture was then slowly warmed to room temperature, stirred for 4 h and heated to 60 ^{o}C until TLC showed complete consumption of starting material. After cooling the flask to 0 ^{o}C, the reaction was quenched with methanol (5 mL) and diluted with water (50 mL). The solution was then extracted with CH_2Cl_2 (3 × 20 mL), the organic layers were combinbed, dried over Na_2SO_4. The organic layer was concentrated under reduced pressure on rotavap and purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:20 to 1:6) as the eluent.

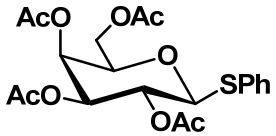
The di-PMB protected compound (0.042 g, 0.081 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous CH_2Cl_2 (3.2 mL). After cooling the solution to -78 ^{o}C, *m*-CPBA (0.019 g, 0.11 mmol) was added in portion and stirred for 1 h. The reaction was then quenched with saturated $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.76 (m, 2 H, aryl), 7.48-7.57 (m, 3 H, aryl), 7.29 (d, 2 H, *J* = 8.6 Hz, -CH_2PMP), 7.21 (d, 2 H, *J* = 8.6 Hz, -CH_2PMP), 6.9 (d, 2 H, *J* = 8.6 Hz, aryl), 6.87 (d, 2 H, *J* = 8.6 Hz, aryl), 4.79 (d, 1 H, *J* = 10.7 Hz, -C<u>H</u>$_2$PMP), 4.72 (d, 1 H, *J* = 10.7 Hz, -CH_2PMP), 4.69 (d, 2 H, *J* = 10.7 Hz, -CH_2PMP), 4.55 (d, 1 H, *J* = 4.9 Hz, H-1), 4.50 (d, 1 H, *J* = 10.7 Hz, -CH_2PMP), 4.19 (dd, 1 H, *J* = 7.6, 4.9 Hz), 4.14 (dd, 1 H, *J* = 7.6, 4.9 Hz), 3.87 (q, 1 H, *J* = 6.1 Hz, H-5), 3.81 (s, 6 H, OMe, OMe), 3.18 (dd, 1 H, *J* = 8.5, 6.7 Hz, H-2), 1.02 (d, 3 H, *J* = 6.4 Hz, -C<u>H</u>$_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 159.4, 141.6, 131.5, 129.8, 129.6, 129.5, 129.4, 128.9, 125.5, 113.9, 113.8, 94.3, 81.3, 79.1, 74.2, 73.9, 73.1, 61.2, 55.3, 17.7

HRMS (EIMS, M^+): cald for $C_{28}H_{31}N_3O_6S$ 537.1934, found 537.1938.

7. **1-Phenylthio-2,3,4,6-tetraacetate-β-D-galactopyranoside**



583

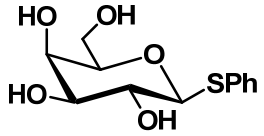
It was synthesized following the procedure described for compound **575**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.53 (m, 2 H, Ph), 7.28-7.33 (m, 3, Ph), 5.4 (d, 1 H, J = 3.4, 0.6 Hz), 5.22 (t, 1 H, J = 10.1 Hz), 5.04 (dd, 1 H, J = 9.8, 3.4 Hz), 4.71 (d, 1 H, J = 10.1 Hz, H-1), 4.17 (dd, 1 H, J = 11.6, 7.0 Hz, H-6), 4.10 (dd, 1 H, J = 11.3, 6.1 Hz, H-6), 3.93 (t, 1 H, J = 7.0 Hz), 2.10 (s, 3 H, Me), 2.08 (s, 3 H, Me), 2.02 (s, 3 H, Me), 1.96 (s, 3 H, Me).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.1, 169.9, 169.3, 132.5, 132.4, 128.8, 128.1, 86.5, 74.3, 71.9, 67.2, 67.1, 61.6, 20.8, 20.6, 20.5, 20.4

HRMS (EIMS, M^+): cald for $C_{20}H_{24}O_9S$ 440.1141, found 440.1138.

8.



584

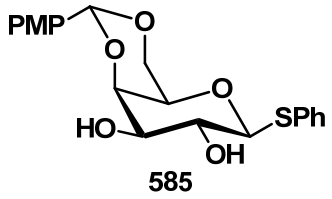
It was synthesized from compound **583** by treating with NaOMe solution as described previously for compound **575**.

^{1}H NMR (500 MHz, CD_3OD): δ 7.44-7.52 (m, 2 H, Ph), 7.12-7.25 (m, 3 H, Ph), 4.51 (d, 1 H, *J* = 9.8 Hz, H-1), 3.82 (dd, 1 H, *J* = 3.4, 0.6 Hz), 3.68 (dd, 1 H, *J* = 11.6, 7.0 Hz, H-6), 3.63 (dd, 1 H, *J* = 11.3, 5.2 Hz, H-6), 3.53 (t, 1 H, *J* = 9.5 Hz), 3.48 (m, 1 H), 3.42 (dd, 1 H, *J* = 9.2, 3.4 Hz)

^{13}C NMR (125 MHz, CD_3OD): δ 164.1, 160.1, 156.0, 118.3, 108.6, 104.3, 99.0, 98.4, 90.6.

HRMS (EIMS, M^+): cald for $C_{12}H_{16}O_5S$ 272.0718, found 272.0722.

9.



585

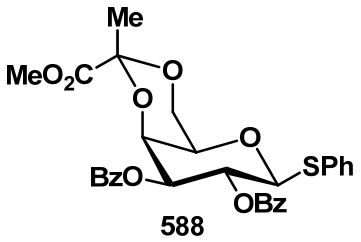
It was synthesized from compound **584** following the procedure described previously for compound **560**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 2 H, J = 6.7 Hz, aryl), 7.27-7.37 (m, 5 H, Ph), 6.88 (d, 2 H, *J* = 6.7 Hz, aryl), 5.46 (s, 1 H, -CHPMP), 4.5 (q, 1 H, *J* = 4.9 Hz), 4.36 (dd, 1 H, *J* = 12.5, 1.2 Hz), 4.19 (d, 1 H, *J* = 1.6 Hz, H-1), 4.01 (dd, 1 H, *J* = 12.5, 1.5 Hz), 3.82 (s, 3 H, Ome), 3.64-3.72 (m, 2 H), 3.53 (d, 1 H, *J* = 0.9 Hz), 2.6 (bs, 2 H, 2-OH, 3-OH),

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 133.9, 132.7, 131.0, 130.4, 129.4, 129.2, 128.4, 128.1, 113.8, 101.5, 87.2, 75.6, 74.0, 70.3, 69.5, 69.1, 55.6.

HRMS (EIMS, M^+ + Na): cald for $C_{20}H_{22}NaO_6S$ 413.1035, found 413.1036.

11.



588

Compound **585** (1.4 g, 3.59 mmol) was taken in oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous CH_2Cl_2 (10 mL). After cooling the solution to 0 ^oC, pyridine (1.45 mL, 17.95 mmol) and Benzoyl (Bz) chloride (3.35 mL, 17.95 mmol) were added followed by catalytic amount of DMAP. The resulting solution was slowly warmed to room temperature and stirred for 18 h. The reaction was cooled to 0 ^oC and quenched with saturated $NaHCO_3$ (10 mL). The solution was then extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (50 mL) and combined organic layer was dried over Na_2SO_4. After concentrating the organic layer under reduced pressure on rotavap, the residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent.

Compound **586** (2.5 g, 4.18 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar and dissolved in CH_2Cl_2 (30 mL). Water (3 mL) was added and the solution was then cooled to 0 ^oC. To the solution, DDQ (1.42 g, 6.26 mmol) was added in portion, the resulting mixture was slowly warmed to room temperature and stirred for 18 h. The reaction was then diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer was washed additional CH_2Cl_2 (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified

via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 2:1) as the eluent to afford **587** as a white solid.

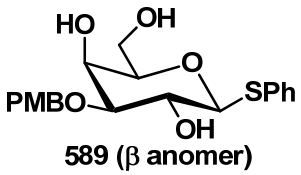
1-Phenylthio-2,3-di-O-benzoyl-β-D-galactopyranoside (0.118 g, 0.246 mmol) was taken in an oven dried RB flask and dissolved in anhyrous CH_3CN. To the solution, methyl pyruvate (51 μL, 0.492 mmol) was added followed by $BF_3.OEt_2$ (62 μL, 0.492 mmol) at room temperature. The resulting mixture was stirred for 48 h at room temperature. The reaction was then cooled to 0 ^oC and quenched with saturated $NaHCO_3$ (5 mL). The solution was then extracted with CH_2Cl_2 (2 × 10 mL) and the aqueous layer was further extracted with additional CH_2Cl_2 (10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 ro 1:1) as the eluent to obtain **588** as a white solid.

^1H NMR (500 MHz, $CDCl_3$): δ 7.93-8.30 (m, 4 H, Bz), 7.29-7.64 (m, 11 H, Aryl), 5.77 (t, 1 H, *J* = 10.1 Hz, H-2), 5.29 (s, 1 H), 5.22 (dd, 1 H, *J* = 9.8, 3.4 Hz), 4.92 (d, 1 H, *J* = 10.1 Hz, H-1), 4.57 (d, 1 H, *J* = 3.4 Hz), 4.20 (dd, *J* = 12.8, 1.2 Hz, H-6), 4.03 (dd, 1 H, *J* = 12.8, 1.2 Hz, H-6), 3.64 (s, 3H, CO_2Me), 1.54 (s, 3 H, Me).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 166.4, 165.3, 133.9, 133.5, 133.4, 131.8, 130.1, 130.0, 129.9, 129.5, 129.0, 128.6, 128.6, 128.5, 98.9 (C-1), 85.9, 74.2, 69.4, 69.3, 67.2, 52.7, 25.8.

HRMS (EIMS, M^+ + Na): cald for $C_{30}H_{28}NaO_9S$ 587.1352, found 587.1349.

12.



589 (β anomer)

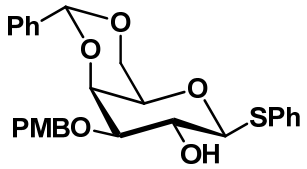
1-Phenylthio-β-D-galactopyranoside (0.05 g, 0.184 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous MeOH (2 mL). To the solution, Bu_2SnO (0.046 g, 0.184 mmol) was added and the resulting mixture was refluxed for 2-3 h (until a clear solution appears). The reaction mixture was then concentrated under reduced pressure on rotavap (rotavap bump trap and reservoir was oven dried). The residue was dissolved in anhydrous DMF (2 mL) under Argon and PMBCl (27 μL, 0.189 mmol) was added followed by CsF (0.029 g, 0.19 mmol). The resulting mixture was heated to 50 ^oC for 4 days. The reaction was then diluted with toluene and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of MeOH/CH_2Cl_2 (1:60 to 1:10) as the eluent.

^1H NMR (500 MHz, CD_3OD): δ 7.49 (d, 2 H, J = 7.0 Hz, aryl), 7.13-7.33 (m, 5 H, aryl), 6.82 (d, 2 H, *J* = 8 Hz, aryl), 4.63 (d, 1 H, *J* = 11.3 Hz, -C$\underline{H}_2$PMP), 4.56 (d, 1 H, *J* = 11. 6 Hz, -C$\underline{H}_2$PMP), 4.53 (d, 1 H, *J* = 9.8 Hz, H-1), 3.98 (d, 1 H, *J* = 2.7 Hz), 3.72 (s, 3 H, OMe), 3.61-3-74 (m, 3 H), 3.44 (t, 1 H, *J* = 6.4 Hz), 3.33 (dd, 1 H, *J* = 9.2, 3.4 Hz),

^{13}C NMR (125 MHz, CD_3OD): δ 160.6, 135.7, 132.2, 131.6, 130.6, 129.7, 127.9, 124.6, 90.1, 83.2, 80.3, 72.4, 70.1, 67.4, 62.5, 55.6.

HRMS (EIMS, M^+ + Na): cald for $C_{20}H_{24}NaO_6S$ 415.1191, found 415.1195.

13.



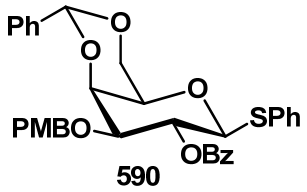
Compound **589** (0.217 g, 0.553 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous DMF (5 mL) and α,α-diemthoxy benzaldehyde (0.168 mL, 1.11 mmol) was added followed by catalytic amount of *p*-TsOH. The resulting mixture was heated to 50 ^{o}C under reduced pressure on rotavap (bump trap and reversoir was dried in oven) for 6 h. The reaction was diluted with toluene (20 mL) and concentrated under reduced pressure on rotavap. The residue was purified *via* silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 2:1) as the eluent to afford 1-Phenylthio-3-*p*-methoxylbenzyl-4,6-benzylidine-β-D-galactopyranoside.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 2 H, *J* = 7.3 Hz, aryl), 7.19-7.48 (m, 10 H, aryl), 6.84 (d, 2 H, *J* = 8.5 Hz, aryl), 5.54 (s, 1 H, -C<u>H</u>Ph), 4.66 (dd, 2 H, *J* = 24.7, 12.4 Hz, -C<u>H$_2$</u>Ph), 4.53 (d, 1 H, *J* = 9.5 Hz), 4.35 (d, 1 H, *J* = 12.2 Hz, H-6), 4.17 (d, 1 H, *J* = 3.1 Hz), 3.98 (d, 1 H, *J* = 12.2 Hz, H-6), 3.94 (t, 1 H, *J* = 9.5 Hz), 3.80 (s, 3 H, OMe), 3.50 (dd, 1 H, *J* = 9.2, 3.1 Hz), 3.44 (s, 1 H), 2.54 (s, 1 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 137.8, 133.7, 130.7, 129.9, 129.5, 128.9, 128.8, 128.0, 126.5, 113.8, 101.1, 86.9, 79.8, 73.2, 71.1, 70.0, 69.3, 67.1, 55.2.

HRMS (EIMS, M^+ + Na): cald for $C_{27}H_{28}NaO_6S$ 503.1504, found 503.1501.

14.



590

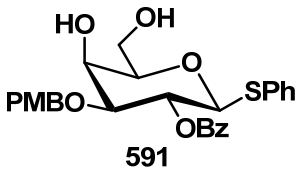
1-Phenylthio-3-*p*-methoxybenzyl-4,6-benzylidine-β-D-galactopyranoside (0.124 g, 0.258 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous CH_2Cl_2 (3 mL). After cooling the solution to 0 ^oC, pyridine (0.3 mL, 1.29 mmol) was added followed by benzoyl chloride (0.11 mL, 0.774 mmol). The resulting mixture was then slowly warmed to room temperature and stirred for 6 h. The reaction was diluted with toluene (20 mL) and concentrated under reduced pressure on rotavap. The residue was was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent to afford **590** as a white solid.

^1H NMR (500 MHz, $CDCl_3$): δ 8.01-8.09 (m, 2 H, aryl), 7.57-7.67 (m, 3 H, aryl), 7.43-7.53 (m, 4 H, aryl), 7.34-7.42 (m, 3 H, aryl), 7.2-7.33 (m, 3 H, aryl), 7.12 (d, 2 H, *J* = 8.6 Hz, aryl), 6.68 (d, 2 H, *J* = 8.6 Hz, aryl), 5.56 (t, 1 H, *J* = 9.8 Hz), 5.51 (s, 1 H, -C<u>H</u>Ph), 4.82 (d, 1 H, *J* = 9.8 Hz, H-1), 4.58 (d, 1 H, *J* = 12.5 Hz, -C<u>H</u>$_2$Ph), 4.50 (d, 1 H, *J* = 12.2 Hz, -C<u>H</u>$_2$Ph), 4.39 (dd, 1 H, *J* = 12.5, 1.2 Hz, H-6), 4.24 (d, 1 H, *J* = 3.1 Hz), 4.04 (dd, 1 H, *J* = 12.2, 1.2 Hz, H-6), 3.77 (dd, 1 H, *J* = 9.8, 3.36 Hz), 3.74 (s, 3 H, OMe), 3.50 (s, 1 H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9, 159.2, 137.6, 133.6, 132.9, 131.6, 130.2, 129.8, 129.7, 129.3, 128.9, 128.7, 128.3, 128.1, 126.6, 113.6, 101.2, 85.4, 77.7, 73.2, 70.6, 70.1, 69.2, 69.0, 55.1.

HRMS (EIMS, M^+ + Na): calcd for $C_{34}H_{32}NaO_7S$ 607.1766, found 607.1769.

15.



591

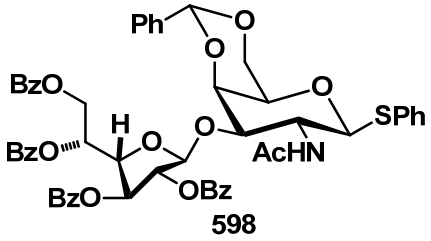
Compound 590 (0.22 g, 0.377 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous methanol (11 mL). Catalytic amount of *p*-TsOH (0.006 g, 0.03 mmol) was added and the solution was stirred at room temperature for 5 days. The reaction mixture was then concentrated under reduced pressure on rotavap and purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:2 to 4:1) as the eluent to afford **591** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98-8.04 (m, 2 H, aryl), 7.58-7.64 (m, 1 H, aryl), 7.4-7.5 (m, 4 H. Aryl), 7.22-7.29 (m, 3 H, aryl), 7.02-7.09 (m, 2 H, aryl), 6.63-6.69 (m, 2 H, aryl), 5.47 (t, 1 H, *J* = 9.8 Hz, H-2), 4.77 (d, 1 H, *J* = 10.1 Hz, H-1), 4.58 (d, 1 H, *J* = 12 Hz), 4.44 (d, 1 H, *J* = 12 Hz), 4.12 (dd, 1 H, *J* = 3.4, 0.9 Hz), 4.06 (dd, 1 H, *J* = 11.9, 7.0 Hz, H-6), 3.84 (dd, 1 H, *J* = 11.6, 4.6 Hz, H-6), 3.72 (s, 3 H, OMe), 3.66 (dd, 1 H, *J* = 9.2, 3.4 Hz), 3.61 (m, 1 H), 2.3 (bs, 2 H, 4-OH, 6-OH)

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 159, 4, 133.1, 133.0, 132.2, 129.9, 129.6, 128.9, 128.8, 128.4, 127.7, 113.8, 86.5, 78.7, 78.4, 71.1, 69.6, 66.8, 62.5, 55.2.

HRMS (EIMS, M^+ + Na): calcd for $C_{34}H_{32}NaO_7S$ 607.1766, found 607.1769.

16.



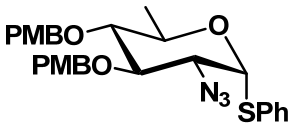
598

To an oven dried RB flask equipped with magnetic stir bar under Argon, the donor **376** (0.055 g, 0.074 mmol) and acceptor **576** (0.029 g, 0.074 mmol) were taken. To the flask, 4 Å MS (0.02 g, freshly dried by heat-gun under high-vacuum) was added followed by anhydrous CH_2Cl_2 (3 mL) and the flask was cooled to -20 ^oC for 30 min. Next, the activator TMSOTf (12 μL, 0.067 mmol) was added and the reaction was stiired at -20 ^oC for 1.5 h. The reaction mixture was then slowly warmed to -10 ^oC and quenched by the addition of solid $NaHCO_3$ (0.02 g). The solution was then filtered through a celite pad and the filtrate was concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent to afford disaccharide **598** in 75% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 8.03-8.11 (m, 2 H, aryl), 7.95-8.02 (m, 2 H, aryl), 7.77-7.87 (m, 4 H, aryl), 7.62-7.69 (m, 2 H, aryl), 7.45-7.58 (m, 4 H, aryl), 7.15-7.44 (m, 16 H, aryl), 6.0 (m, 1 H), 5.74 (d, 1 H, *J* = 7.0 Hz), 5.64 (d, 1 H, *J* = 5.8 Hz), 5.59 (d, 1 H, *J* = 10.1 Hz), 5.48 (s, 1 H, -C<u>H</u>Ph), 5.38 (s, 1 H), 5.34 (d, 1 H, *J* = 1.2 Hz), 4.81 (dd, 1 H, *J* = 10.4, 3.4 Hz), 4.77 (dd, 1 H, *J* = 11.9, 4.6 Hz), 4.80 (dd, 1 H, *J* = 5.5, 3.4 Hz), 4.68 (dd, 1 H, *J* = 11.6, 6.4 Hz), 4.33 (d, 1 H, *J* = 3.1 Hz), 4.30 (d, 1 H, *J* = 12.5 Hz), 3.85 (d, 1 H, *J* = 12.5 Hz), 3.47-3.57 (m, 2 H), 2.05 (s, 3 H, -NHCOC<u>H</u>$_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 166.4, 165.9, 165,8, 162,8, 138.3, 133.7, 133.7, 133.6, 133.4, 132.2, 130.2, 130.0, 129.9, 129.7, 129.6, 129.1, 129.0, 128.9, 128.9, 128.8, 128.7, 128.7, 128.6, 128.3, 127.9, 126.5, 107.8, 100.8, 83.5, 82.9, 81.2, 77.4, 76.3, 75.6, 70.3, 70.0, 69.6, 63.6, 52.6, 36.7, 23.9.

HRMS (EIMS, M^+ + Na): calcd for $C_{55}H_{48}NNaO_{14}S$ 1001.2693, found 1001.2695.

17.



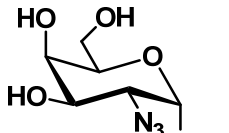
606 (α anomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.53 (m, 2 H, aryl), 7.22-7.39 (m , 7 H, aryl), 6.80-6.96 (m, 2 H, aryl), 5.51 (d, 1 H, *J* = 5.5 Hz, H-1), 4.77-4.92 (m, 4 H, -C$\underline{H}_2$PMP), 4.50-4.66 (m, 1 H), 4.25-4.33 (m, 1 H, H-5), 3.88-3.93 (m, 1 H), 3.83 (s, 6 H, OMe, OMe), 3.78 (dd, 1 H, *J* = 9.6, 8.9 Hz), 3.32 (t, 1 H, *J* = 9.5 Hz), 1.27 (d, 3 H, *J* = 6.4 Hz, -C$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 159.4, 133.8, 133.5, 132.0, 130.0, 129.9, 129.5, 129.1, 129.0, 127.6, 113.9, 87.0, 83.9, 81.4, 75.4, 75.0, 68.5, 64.4, 55.3, 55.2, 17.7.

HRMS (EIMS, M^+ + Na): calcd for $C_{28}H_{31}N_3NaO_5S$ 544.1882, found 544.1881.

18.



612 (α anomer)

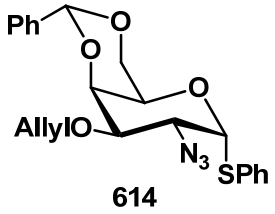
Starting from D-galactosamine hydrochloride, compound 612 was synthesized following the procedure described for compound **581**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.52 (m, 2 H, Ph), 7.17-7.26 (m, 3 H, Ph), 5.6 (d, 1 H, *J* = 5.5 Hz, H-1), 4.39-4.47 (m, 1 H), 4.25 (t, 1 H, *J* = 6.4 Hz), 4.02 (dd, 1 H, *J* = 11.0, 5.2 Hz), 3.86-3.90 (m, 1 H), 3.60-3.74 (m, 2 H, H-6)

^{13}C NMR (125 MHz, $CDCl_3$): δ 133.7, 133.0, 129.9, 128.6, 88.1, 80.7, 75.2, 69.7, 64.5, 62.6.

HRMS (EIMS, M^+ + Na): calcd for $C_{12}H_{15}N_3NaO_4S$ 320.0681, found 320.0683.

19.



614

Compound **612** (0.5 g, 1.68 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and 4 Å MS (freshly dried by heat gun under high vacuum). To the flask, anhydrous CH_3CN (15 mL) was added and the solution was cooled to 0 ^{o}C. α,α-Dimethoxy benzaldehyde (0.51 mL, 3.36 mmol) was added followed by catalytic amount of CSA (0.008 g, 0.34 mmol). The resulting solution was slowly warmed to room temperature and stirred for 24 h. The reaction mixture was then concentrated under reduced pressure on rotavap and the residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:4 to 2:1) as the eluent to afford 1-phenylthio-2-azido-4,6-benzylidine-α-D-galactopyranoside (**613**) as a white solid.

Compound **613** (0.2 g, 0.52 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous DMF (10 mL). After cooling the solution to 0 ^{o}C, NaH (0.032g, 0.78 mmol, 60% in mineral oil) was added in

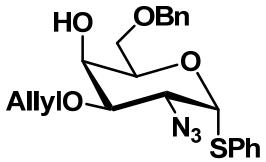
portion. The reaction mixture was then slowly warmed to room temperature and stirred for 15 min. Freshly distilled allyl bromide (0.07 mL, 0.78 mmol) was added at 0 ^{o}C, then the solution was slowly warmed to room temperature and stirred for 6 h. The reaction was then quenched by addition of methanol (2 mL) at 0 ^{o}C and then diluted with water (10 mL). The solution was then extracted with CH_2Cl_2 (3 × 20 mL) and the aqueous layer was further extracted with CH_2Cl_2 (10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* sgradient silica gel (neutralized with 0.1% NEt_3) column chromatography using a mixture of ethyl acetate/hexane (1:4 to 1:1) as the eluent to afford **614** as a white solid. Compound **614** found to be sensitive to column chromatography and also under decomposition when stored at 0 ^{o}C for over 3 months.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.58 (m, 4 H, Ph), 7.25-7.43 (m, 6 H, Ph), 6.03 (ddd, 1 H, *J* = 12.8, 8.0, 4.4 Hz -CH_2–C<u>H</u>=CH_2), 5.79 (d, 1 H, *J* = 5.5 Hz, H-1), 5.61 (s, 1 H, -C<u>H</u>Ph), 5.41 (m, 1 H, -CH_2–CH=C<u>H_2</u>), 5.28 (m, 1 H, -CH_2–CH=C<u>H_2</u>), 4.47 (dd, 1 H, *J* = 10.5, 5.5 Hz), 4.40 (d, 1 H, *J* = 3.5 Hz), 4.20-4.31 (m, 3 H), 4.19 (s, 1 H), 4.08-4.15 (m, 1 H), 3.82 (dd, 1 H, *J* = 10.5, 3.5 Hz, H-2)

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.7, 134.5, 134.0, 131.3, 129.4, 129.3, 128.5, 127.6, 126.5, 118.1, 101.319, 87.8, 76.3, 73.1, 70.6, 69.6, 64.1, 59.5.

HRMS (EIMS, M^+ + Na): calcd for $C_{22}H_{23}N_3NaO_4S$ 448.1307, found 448.1303.

20.



615

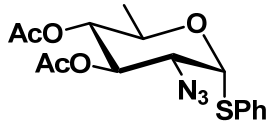
Compound **615** was obtained *via* cemoselective ring opening of benzylidine acetal in presence of TfOH as described previously for compound **557**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.59 (m, 3 H, Ph), 7.20-7.41 (m, 12 H, Ph), 6.0 (ddd, 1 H, *J* = 16.8,11.3, 5.8 Hz, -CH_2–C<u>H</u>=CH_2), 5.62 (d, 1 H , *J* = 5.4 Hz, H-1), 5.39 (d, 1 H, *J* = 7.4 Hz, -CH_2–CH=C<u>H$_2$</u>), 5.29 (d, 1 H, *J* = 10.4 Hz, -CH_2–CH=C<u>H$_2$</u>), 4.50-4.62 (m, 3 H), 4.27 (m, 2 H), 4.20 (m, 2 H), 3.81 (dd, 1 H, *J* = 10.1, 5.2 Hz), 3.74 (dd, 1 H, *J* = 10.1, 5.8 Hz), 3.68 (dd, 1 H, *J* = 10.4, 3.1 Hz, H-2), 2.72 (bs, 1 H, OH)

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 133.7, 133.2, 132.4, 132.3, 128.9, 128.4, 127.7, 127.6, 118.4, 87.4, 77.5, 73.6, 70.8, 69.7, 69.5, 66.7, 59.4.

HRMS (EIMS, M^+ + Na): calcd for $C_{22}H_{25}N_3NaO_4S$ 450.1463, found 450.1467.

21. **1-Phenylthio-2-azido-3,4-di-*O*-acetate-6-deoxy-α-D-glucopyranpside**



616 (α anomer)

1-Phenylthio-2-azido-6-deoxy-α-D-glucopyranpside (0.39 g, 1.39 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in CH_2Cl_2 (10 mL). After cooling the solution to 0 ^oC, pyridine (0.71 mL, 6.93 mmol), Ac_2O (0.71 mL, 6.93 mmol) and DMAP (0.003 g, 0.024 mmol) were added respectively. The resulting mixture was warmed slowly to room temperature and stirred for 18 h. The reaction was neutralized by slow addition of saturated $NaHCO_3$ (10 mL) at 0 ^oC. The solution was then extracted with CH_2Cl_2 (2 × 10 mL) and aqueous layer was further washed with CH_2Cl_2 (10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified

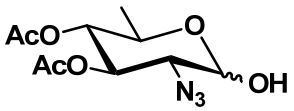
via gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:2) as the eluent to afford **616** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.48 (m, 2 H, Ph), 7.22-7.31 (m, 3 H, Ph), 5.52 (d, 1 H, *J* = 5.7 Hz, H-1), 5.26 (dd, 1 H, *J* = 10.5, 8.9 Hz, H-3), 4.76 (t, 1 H, *J* = 9.7 Hz, H-4), 4.32-4.45 (m, 1 H, H-5), 4.0 (dd, 1 H, *J* = 10.5, 5.6 Hz, H-2), 2.05 (s, 3 H, -COC$\underline{H}_3$), 2.02 (s, 3 H, -COC$\underline{H}_3$), 1.15 (d, 3 H, *J* = 6.1 Hz, C$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 169.6, 132.9, 131.9, 128.9, 127.7, 86.4, 73.7, 71.8, 66.5, 61.8, 20.5, 16.9.

HRMS (EIMS, M^+ + Na): calcd for $C_{16}H_{19}N_3NaO_5S$ 365.1045, found 365.1048.

22. **2-Azido-3,4-di-*O*-acetate-6-deoxy-α-D-glucopyranose**



617

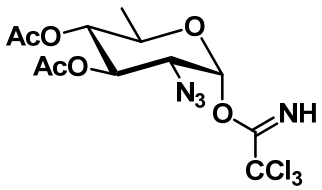
Compound **616** (0.44 g, 1.20 mmol) was taken in a RB flask equipped with magnetic stir bar and dissolved in CH_3CN (17 mL) and then water (4.2 mL) was added. The solution was then cooled to 0 ^{o}C and NIS (0.46 g, 2.05 mmol) was added in one portion. The solution was then stirred at 0 ^{o}C until TLC showed complete conversion (1-2 h). The reaction was then quenched by addition of saturated $Na_2S_2O_3$ (15 mL) solution at 0 ^{o}C. The solution was extracted with CH_2Cl_2 (3 × 20 mL) and the aqueous layer was further washed with CH_2Cl_2 (10 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent to afford **617** as a colorless syrup.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.46 (t, 1 H, *J* = 9.8 Hz, H-3), 5.31 (d, 1 H, J = 3.4 Hz, H-1), 4.96 (t, 1 H, *J* = 9.8 Hz, H-4), 4.75 (dt, 1 H, *J* = 9.5, 2.4 Hz), 4.15 (m, 1 H), 3.65 (bs, 1 H, OH), 3.38 (dd, 1 H, *J* = 10.4, 3.4 Hz, H-2), 2.07 (s, 3 H, -COC$\underline{H}_3$), 2.04 (s, 3 H, -COC$\underline{H}_3$), 1.16 (d, 3 H, *J* = 6.1 Hz, C$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.2, 91.9, 73.9, 72.6, 70.4, 65.3, 20.7, 20.6, 17.3.

HRMS (EIMS, M^+ + Na): calcd for $C_{10}H_{15}N_3NaO_6$ 296.0859, found 296.0861.

23. **1-Trichloroacetamidate-2-azido-3,4-di-*O*-acetate-6-deoxy-α-D-glucopyranoside**



618 (α anomer)

Compound 617 (0.026 g, 0.01 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and dissolved in anhydrous CH_2Cl_2 (3 mL). After cooling the solution to 0 ^{o}C, CCl_3CN (0.048 mL, 0.48 mmol) and DBU (0.022 mL, 0.14 mmol) were added respectively. The reaction was monitored *via* TLC and after 4 h the reaction mixture was concentrated under reduced pressure on rotavap. The residue was purified *via* gradient silica gel column (neutralized with 0.1% NEt_3) chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent (after certain interval 0.1% NEt_3) to afford **618** as a colorless syrup.

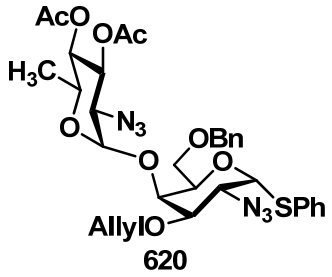
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79 (s, 1 H, N$\underline{H}$), 6.51 (d, 1 H, *J* = 3. 7 Hz, H-1), 5.48 (t, 1 H, *J* = 10.1 Hz, H-3), 4.87 (t, 1 H, *J* = 9.8 Hz, H-4), 4.11 (q, 1 H, *J* = 6.11 Hz, H-5),

3.72 (dd, 1 H, *J* = 10.7, 3.7 Hz, H-2), 2.11 (s, 3 H, -COC<u>H</u>$_3$), 2.06 (s, 3 H, -COC<u>H</u>$_3$), 1.21 (d, 3 H, *J* = 6.1 Hz, C<u>H</u>$_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 169.8, 160.7, 94.2, 73.3, 70.5, 68.2, 60.9, 20.7, 20.6, 17.3.

HRMS (EIMS, M^+ + Na): calcd for $C_{12}H_{15}Cl_3N_4NaO_6$ 438.9955, found 438.9952.

24.



620

The donor **618** (0.023 g, 0.054 mmol) and acceptor **615** (0.026 g, 0.065 mmol) was taken in an oven dried RB flask equipped with magnetic stir bar under Argon and 4 Å MS (0.12 g, freshly dried by heat gun under high vacuum after overnight over-drying at 140 ^{o}C). To the flask, anhydrous CH_2Cl_2 (4.2 mL) was added and the solution was stirred for 30 min at -20 ^{o}C. Next, TMSOTf (13 µL, 0.071 mmol) was added and the resulting mixture was monitored *via* TLC. After 15 min, the reaction was quenched solid $NaHCO_3$ (0.02 g) and filtered through a Buchner funnel. The filtrate was concentrated under reduced pressure and the residue was purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:6 to 1:2) as the eluent to afford **620** as white solid.

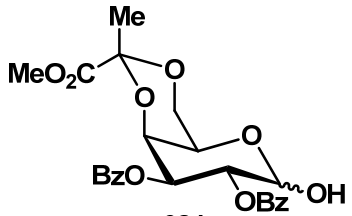
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.51 (m, 2 H, aryl), 7.29-7.41 (m, 8 H, aryl), 5.95 (ddd, 1 H, *J* = 16.8,11.3, 5.8 Hz, -CH_2–C<u>H</u>=CH_2), 5.62 (d, 1 H, *J* = 5.5 Hz, H-1), 5.33-

5.43 (m, 2 H, -CH_2–CH=C$\underline{H}_2$ overlap), 5.23-5.31 (m, 1 H, -CH_2–CH=C$\underline{H}_2$), 4.91 (d, 1 H, *J* = 3.7 Hz, H-1′), 4.73 (t, 1 H, *J* = 9.8 Hz, 4.56 (d, 1 H, *J* = 11.9 Hz, -C$\underline{H}_2$Ph), 4.48 (d, 1 H, *J* = 11.9 Hz, -C$\underline{H}_2$Ph), 4.43 (dd, 1 H, *J* = 9.2, 5.5 Hz), 4.36 (dd, 1 H, *J* = 10.4, 6.4 Hz), 4.22-4.31 (m, 2 H), 4.11 (dd, 1 H, *J* = 12.4, 5.4 Hz), 3.85 (t, 1 H, *J* = 9.4 Hz), 3.63 (dd, 1 H, *J* = 10.8, 2.9 Hz), 3.45 (dd, 1 H, *J* = 9.3, 5.7 Hz, H-2′), 3.25 (dd, 1 H, *J* = 10.7, 3.7 Hz, H-2), 2.07 (s, 3 H, -COC$\underline{H}_3$), 2.06 (s, 3 H, -COC$\underline{H}_3$), 1.12 (d, 1 H, *J* = 6.1 Hz, -C$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.1, 137.5, 134.0, 132.4, 129.3, 128.8, 128.5, 128.9, 127.9, 118.2, 98.1, 87.8, 74.2, 73.8, 72.8, 71.5, 70.8, 69.9, 66.7, 65.8, 62.0, 59.8, 20.9, 17.9.

HRMS (EIMS, M^+ + Na): calcd for $C_{32}H_{38}N_6NaO_9S$ 705.2319, found 705.2321.

25. **2,3-di-*O*-Benzoyl-4,6-pyruvate acetal-D-galactopyranose**



621

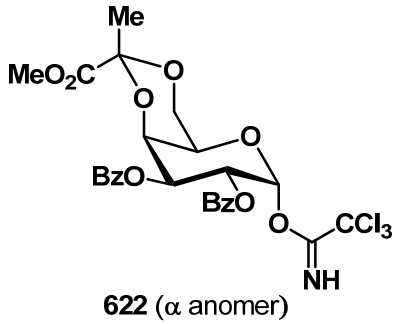
Compound **621** was obtained from **588** following the procedure as described for the synthesis of compound **617**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96-8.49 (m, 4 H, aryl), 7.48-7.55 (m, 2 H, aryl), 7.33-7.42 (m, 4 H, aryl), 5.61-5,73 (m, 2 H), 4.50-4.61 (m, 1 H), 4.02 (s, 1 H), 3.63 (s, 3 H, OMe), 3.41-3.49 (m, 1 H), 1.61 (s, 3 H, Me)

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 166.2, 165.9, 133.3, 133.1, 129.8, 129.7, 128.4, 128.3, 98.7, 91.3, 69.8, 69.1, 68.8, 68.7, 65.3, 61.4, 52.4, 25.7.

HRMS (EIMS, $M^+ + Na$): calcd for $C_{24}H_{24}NaO_{10}$ 495.1267, found 495.1269.

26.



622 (α anomer)

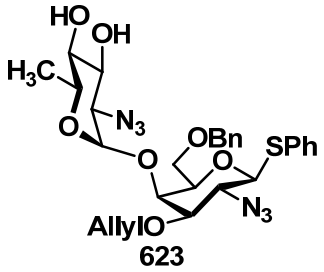
Compound **622** was obtained from compound **621** following the procedure as described for the synthesis of compound **618**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (s, 1 H, NH), 8.03 (d, 2 H, *J* = 7.3 Hz, aryl), 7.98 (d, 2 H, *J* = 7.3 Hz, aryl), 7.48-7.57 (m, 2 H, aryl), 7.41 (t, 2 H, *J* = 7.6 Hz, aryl), 7.37 (t, 2 H, *J* = 7.6 Hz, aryl), 6.83 (d, 1 H, *J* = 3.4 Hz, H-1), 6.01 (dd, 1 H, *J* = 10.7, 3.7 Hz, H-2), 5.71 (dd, 1 H, *J* = 10.7, 3.7 Hz, H-3), 4.73 (d, 1 H, *J* = 3.4 Hz, H-4), 4.14 (d, 1 H, *J* = 11.9 Hz, H-6), 4.05 (d, 1 H, *J* = 11.9 Hz, H-6), 4.04 (s, 1 H), 3.68 (s, 3 H, OMe), 1.63 (s, 3 H, Me)

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 166.2, 165.6, 160.6, 133.4, 133.3, 129.8, 129.8, 129.5, 128.9, 128.4, 128.4, 98.8, 94.5, 90.9, 69.2, 69.1, 67.1, 64.9, 64.1, 52.5, 25.6.

HRMS (EIMS, $M^+ + Na$): calcd for $C_{26}H_{24}Cl_3NNaO_{10}$ 638.0363, found 638.0367.

27.



623

To an oven dried RB flask (A) equipped with magnetic stir bar under Argon, Na (0.115 g, 0.138 mmol, washed with dry hexane) was taken and the flask was cooled to 0 ^{o}C. Anhydrous methanol (5 mL) was added to the flask slowly and stirred until all Na was completely dissolved (1-2 h). The solution was kept at 0 ^{o}C for immediate use. In a separate oven dried flask (B) equipped with magnetic stir bar under Argon, compound 620 (0.026 g, 0.039 mmol) was taken and dissolved in anhydrous methanol (5 mL). After cooling the solution (flask B) to 0 ^{o}C, freshly prepared NaOMe (flask A) was added slowly. The resulting mixture was warmed slowly to room temperature and stirred until TLC showed complete conversion (2-4 h). The reaction was then neutralized by slow addition of amberlite IR-120 (H^+ resin) to pH 6. The solution was then filter *via* Buchner funnel. The filtrate was concentrated under reduced pressure on rotavap and purified *via* gradient silica gel column chromatography using a mixture of ethyl acetate/hexane (1:5 to 1:1) as the eluent to afford **623** as a white solid.

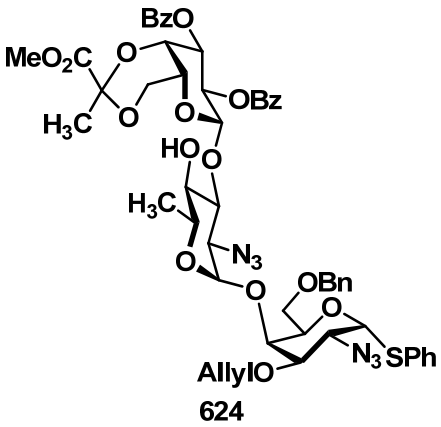
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.53 (m, 2 H, aryl), 7.21-7.41 (m, 8 H, aryl), 5.97 (ddd, 1 H, *J* = 16.8,11.3, 5.8 Hz, -CH_2–C<u>H</u>=CH_2), 5.62 (d, 1 H, *J* = 5.5 Hz, H-1), 5.38 (dd, 1 H, *J* = 17.4, 1.50 Hz, -CH_2–CH=C<u>H</u>$_2$), 5.27 (dd, 1 H, *J* = 10.7, 1.50 Hz, -CH_2–CH=C<u>H</u>$_2$), 4.91 (d, 1 H, *J* = 3.7 Hz, H-1′), 4.54 (dd, 2 H, *J* = 17.4 , 11.4 Hz, -C<u>H</u>$_2$Ph), 4.45 (dd, 1 H, *J* = 8.6, 5.8 Hz), 4.28-4.35 (m, 1 H, H-6), 4.26 (d, 1 H, *J* = 2.7 Hz), 4.20

(dd, 1 H, *J* =10.7, 5.5 Hz), 4.17 (dd, 1 H, *J* = 9.5, 6.4 Hz), 4.06-4.13 (m, 1 H), 3.98 (t, 1 H, *J* = 9.5 Hz), 3.88 (t, 1 H, *J* = 8.9 Hz), 3.64 (dd, 1 H, *J* = 10.7, 2.8 Hz), 3.50 (dd, 1 H, *J* = 9.5, 6.1 Hz), 3.19 (t, 1 H, *J* = 9.2 Hz), 3.12 (dd, 1 H, *J* = 10.7, 3.9 Hz), 2.88 (bs, 1 H, 3-OH), 2.48 (bs, 1 H, 4-OH), 1.26 (d, 1 H, *J* = 6.1 Hz, -C$\underline{H}_3$)

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 133.8, 132.5, 128.9, 128.5, 128.1, 128.0, 127.7, 117.9, 98.3, 87.6, 77.1, 76.6, 73.5, 72.0, 71.5, 70.9, 69.8, 67.6, 66.8, 63.7, 59.9.

HRMS (EIMS, M^+ + Na): calcd for $C_{28}H_{34}N_6NaO_7S$ 621.2107, found 621.2105.

28.



624

To an oven dried flask the donor **622** (0.013 g, 0.02 mmol) was taken under Agron. Freshly dried (overnight in oven at 140 ^oC followed by heat gun under high vacuum) 4 Å MS (0.011 g) was added to the flask and connected to under high vacuum for 1 h under Argon. The flask was then quickly capped and anhydrous CH_2Cl_2 (1.5 mL) was added. After cooling the solution to -20 ^oC, a solution of the acceptor **623** (0.01 g, 0.017 mmol) in anhydrous CH_2Cl_2 was slowly *via* syringe followed by TMSOTf (4 μL, 0.018 mmol). The resulting solution was stirred for 20 min at -20 ^oC and then quenched by addition of solid $NaHCO_3$ (0.01 g) and filtered *via* Buchner funnel. The filtrate was

concentrated under reduced pressure on rotavap and purified *via* preparative TLC using a 1:2 mixture of ethyl acetate/hexane as the eluent to afford **623** as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96-8.08 (m, 4 H, aryl), 7.18-7.59 (m, 14 H, aryl), 5.97 (ddd, 1 H, *J* = 16.8,11.3, 5.8 Hz, -CH_2–C<u>H</u>=CH_2), 5.81 (t, 1 H, *J* = 9.8 Hz, H-3″), 5.57 (d, 1 H, J = 5.5 Hz, H-1), 5.45 (dd, 1 H, *J* = 10.4, 3.7 Hz), 5.31-5.41 (m, 2 H), 5.21-5.30 (m, 2 H), 4.88 (d, 1 H, *J* = 7.9 Hz, H-1″), 4.56 (d, 1 H, *J* = 3.4 Hz), 4.41 (s, 2H, -C<u>H</u>$_2$Ph), 4.27-4.34 (m, 1 H, H-6), 4.03-4.22 (m, 10 H), 3.80 (dd, 1 H, *J* = 10.4, 8.5 Hz), 3.76 (s, 1 H), 3.60-3.73 (m, 9 H), 3.42 (dd, 1 H, *J* = 9.2, 6.1 Hz), 3.31 (t, 1 H, *J* = 9.5 Hz), 3.01 (dd, 1 H, *J* = 10.4, 3.7 Hz), 2.36 (t, 1 H, *J* = 7.6 Hz), 1.61 (s, 3 H, Me), 1.28 (d, 1 H, *J* = 6.1 Hz, -C<u>H</u>$_3$)

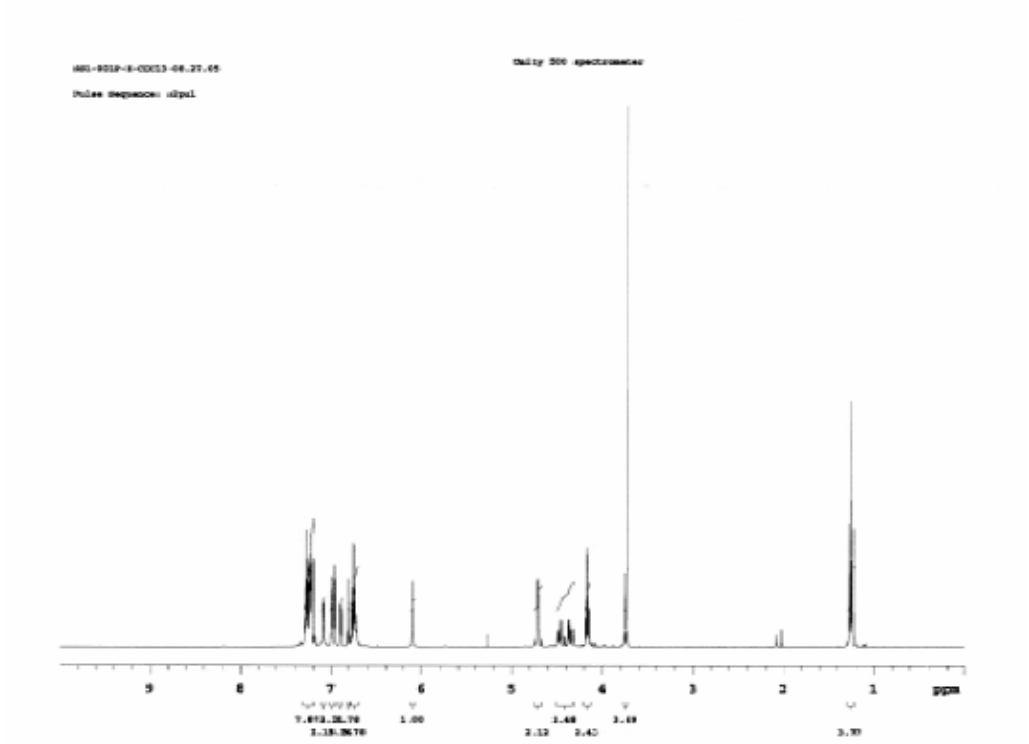
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 166.1, 165.3, 137.2, 133.7, 133.5, 133.3, 133.2, 132.9, 129.9, 129.7, 129.0, 128.6, 128.5, 128.4, 128.3, 128.0, 118.1, 101.8, 98.8, 98.4, 87.8, 82.3, 80.5, 73.4, 72.5, 71.6, 71.1, 69.7, 68.7, 67.6, 66.8, 66.0, 64.7, 62.5, 59.8, 52.4, 29.7, 25.5, 18.1, 14.1.

HRMS (EIMS, M^+ + Na): calcd for $C_{52}H_{56}N_6NaO_{16}S$ 1075.3371, found 1075.3375.

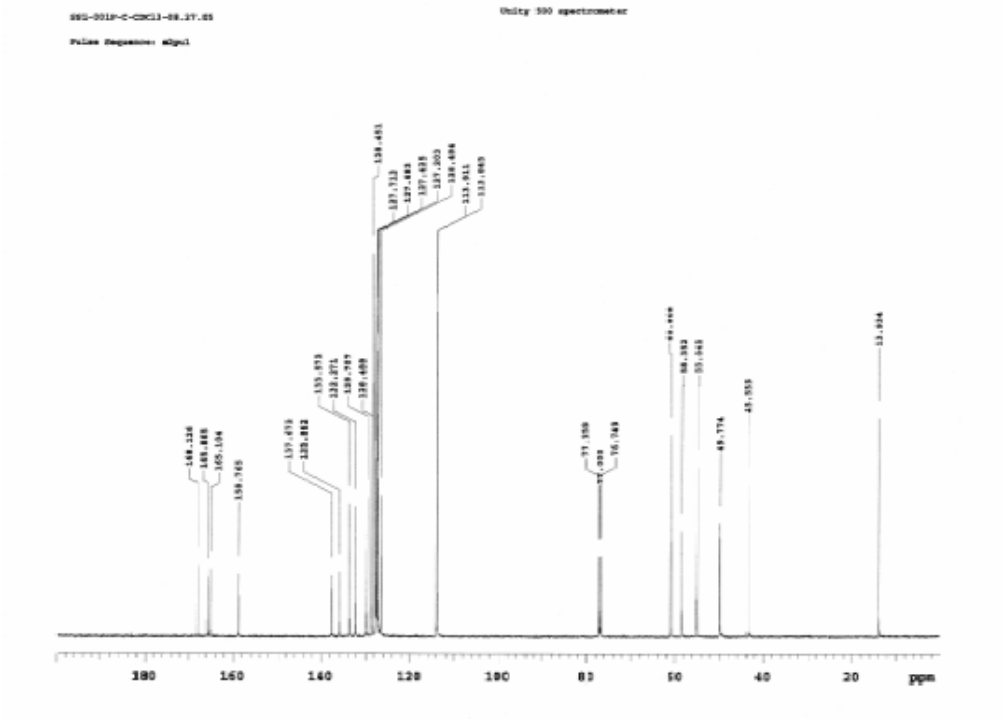
APPENDIX I

NMR Spectra of Chapter 2

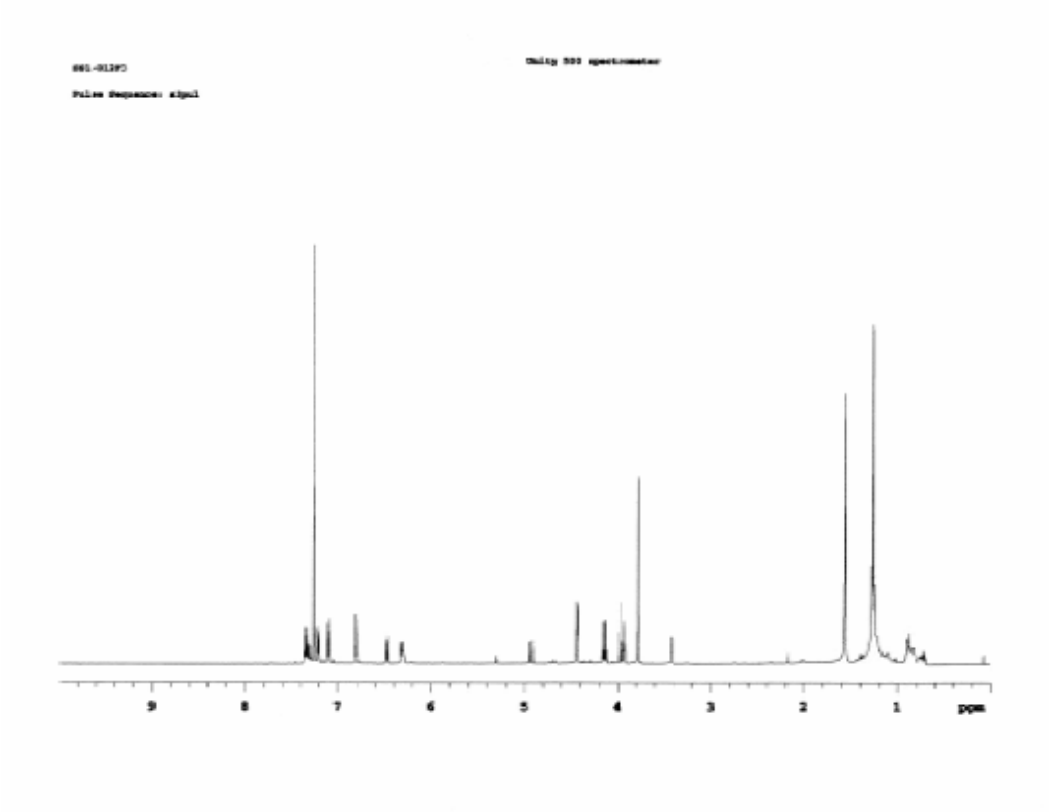
^{1}H NMR (Compound 7)



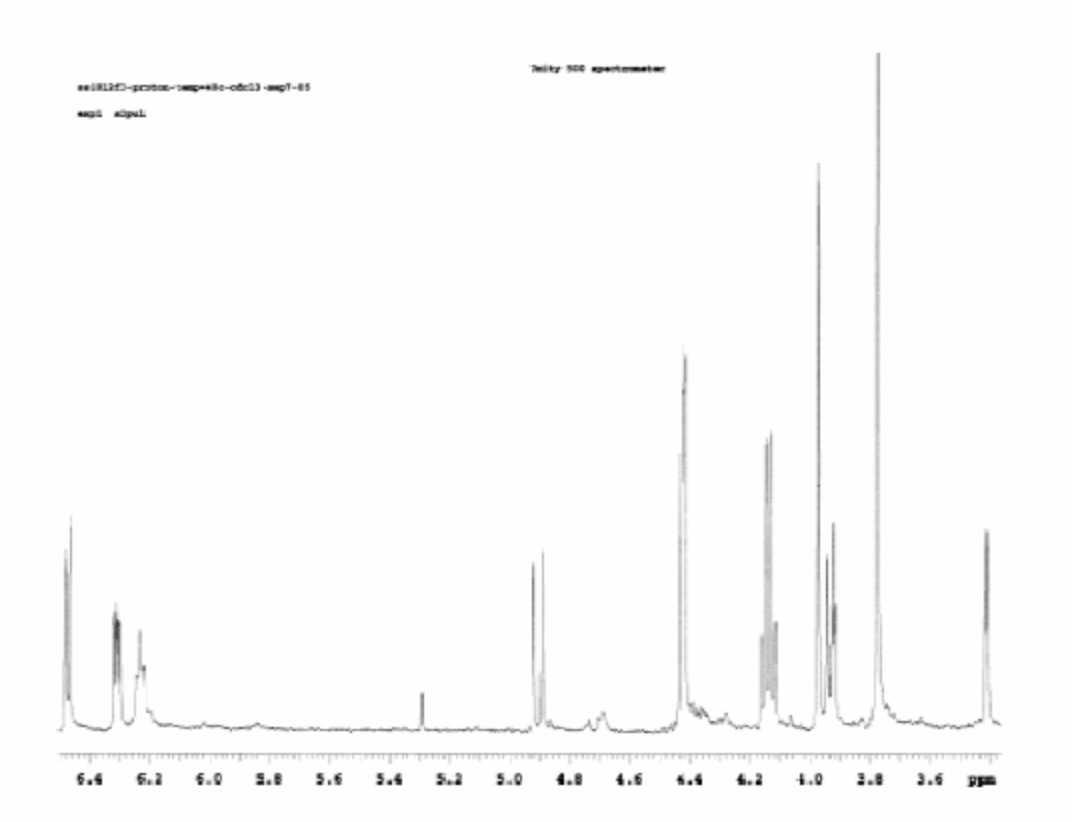
^{13}C NMR (Compound 7)



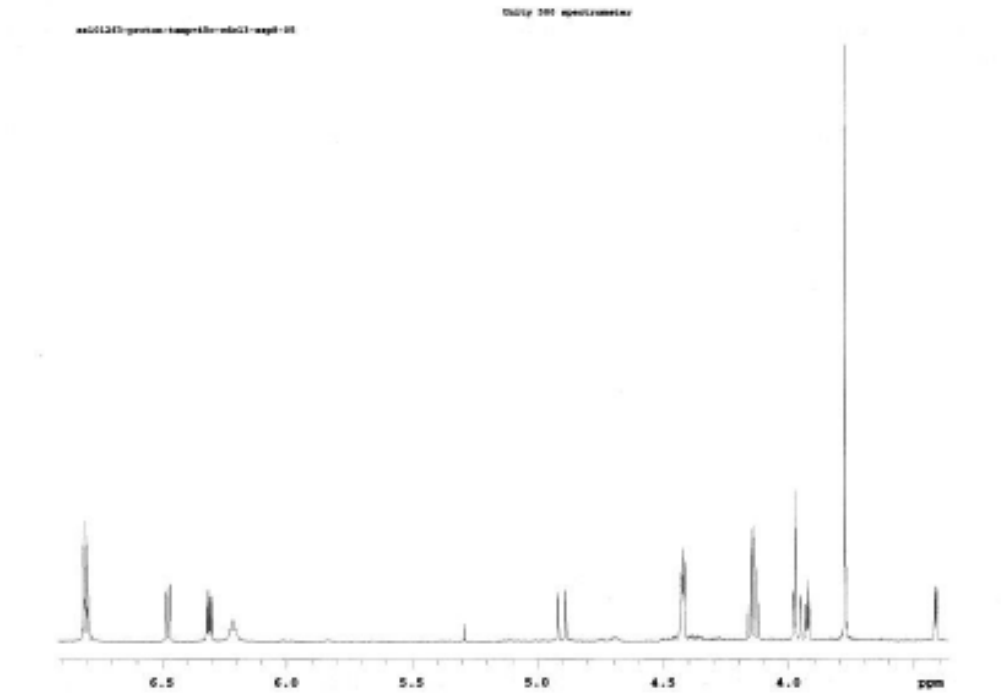
^{1}H NMR (Compound 8 at room temperature)



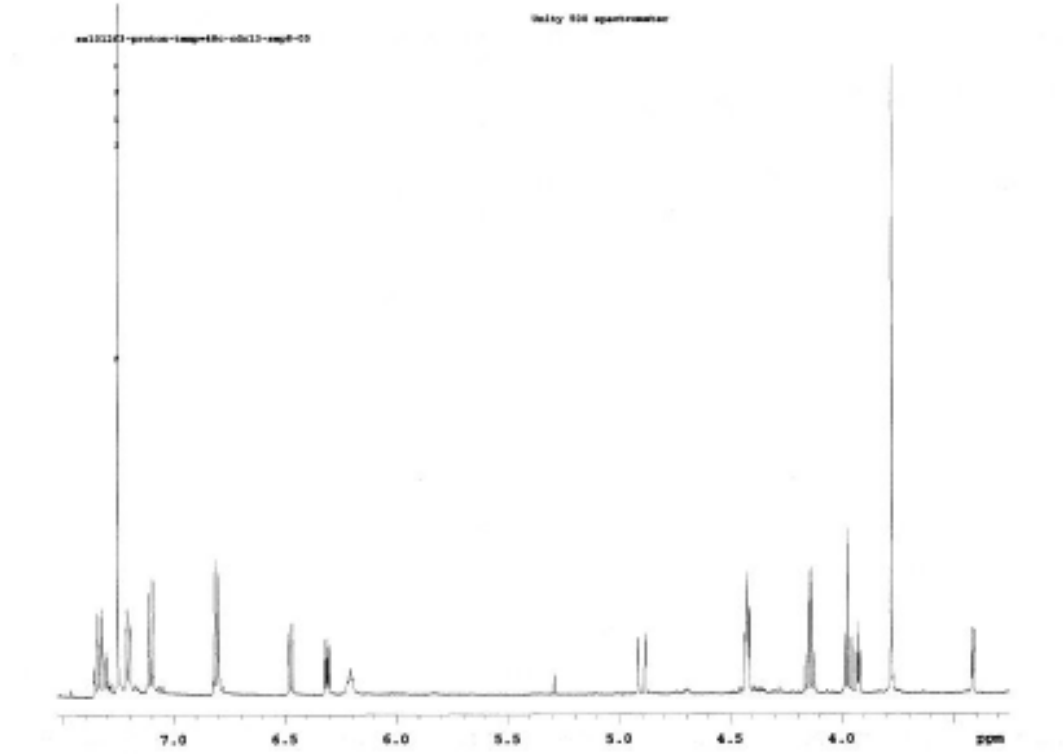
^{1}H NMR (Compound 8 at 40 ^{o}C)



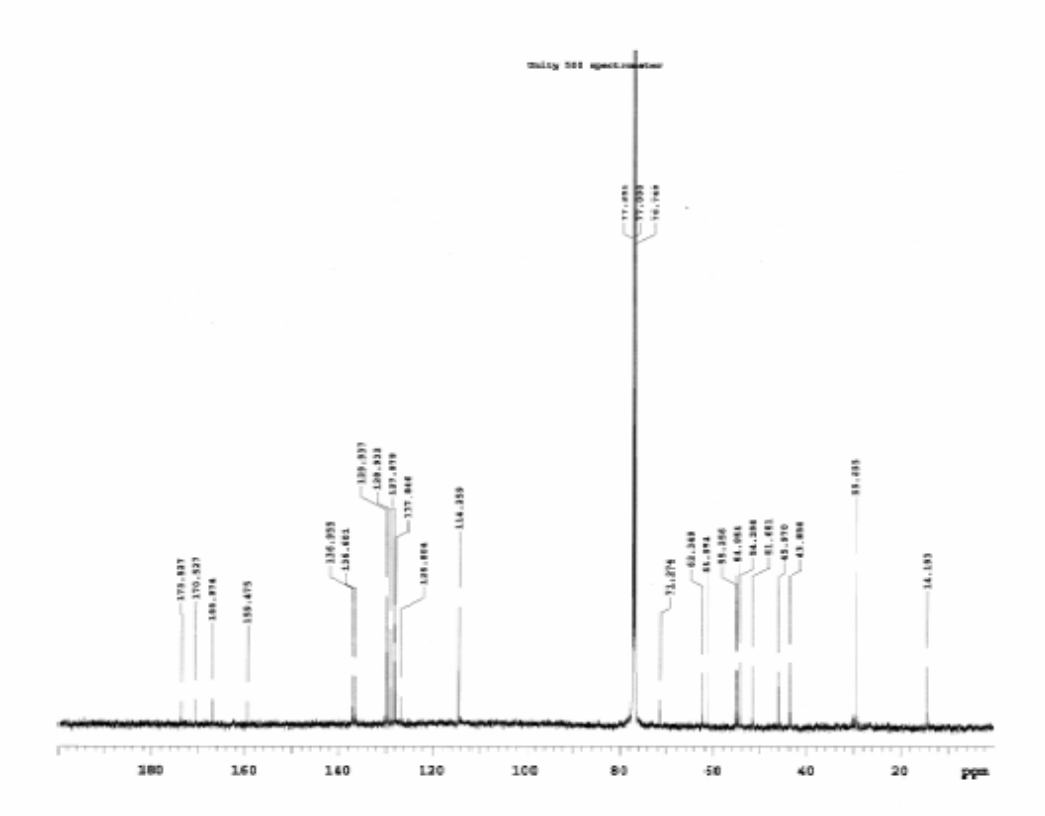
^{1}H NMR (Compound 8 at 45 ^{o}C)



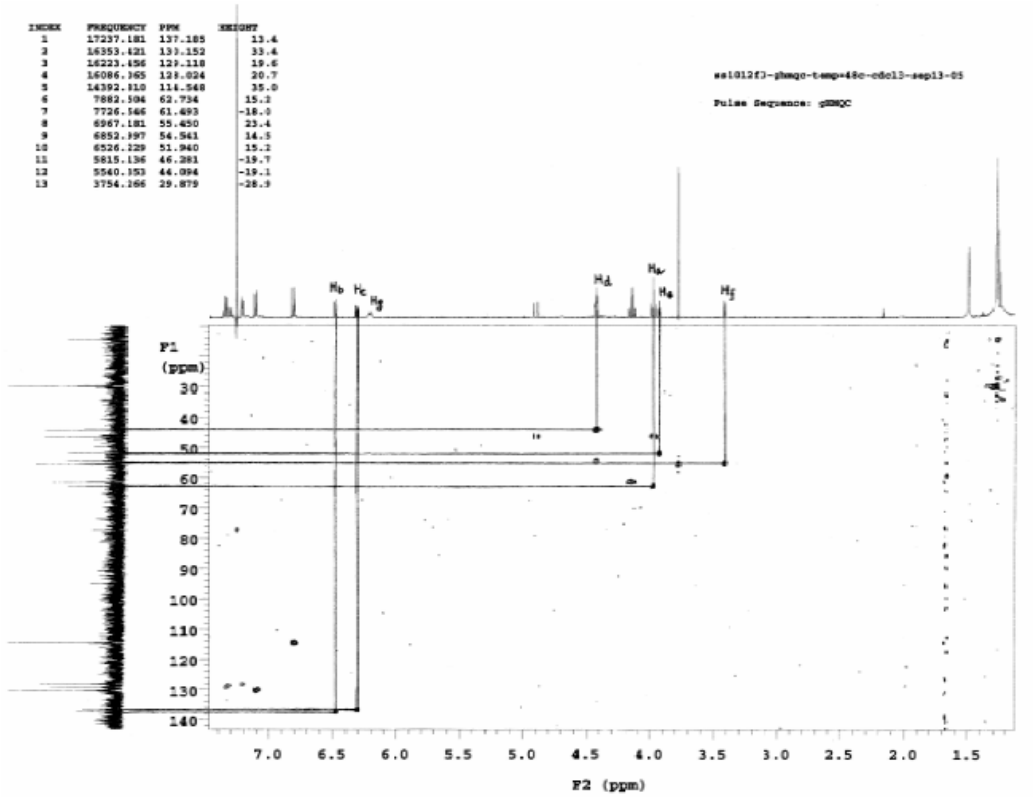
^{1}H NMR (Compound 8 at 48 ^{o}C)



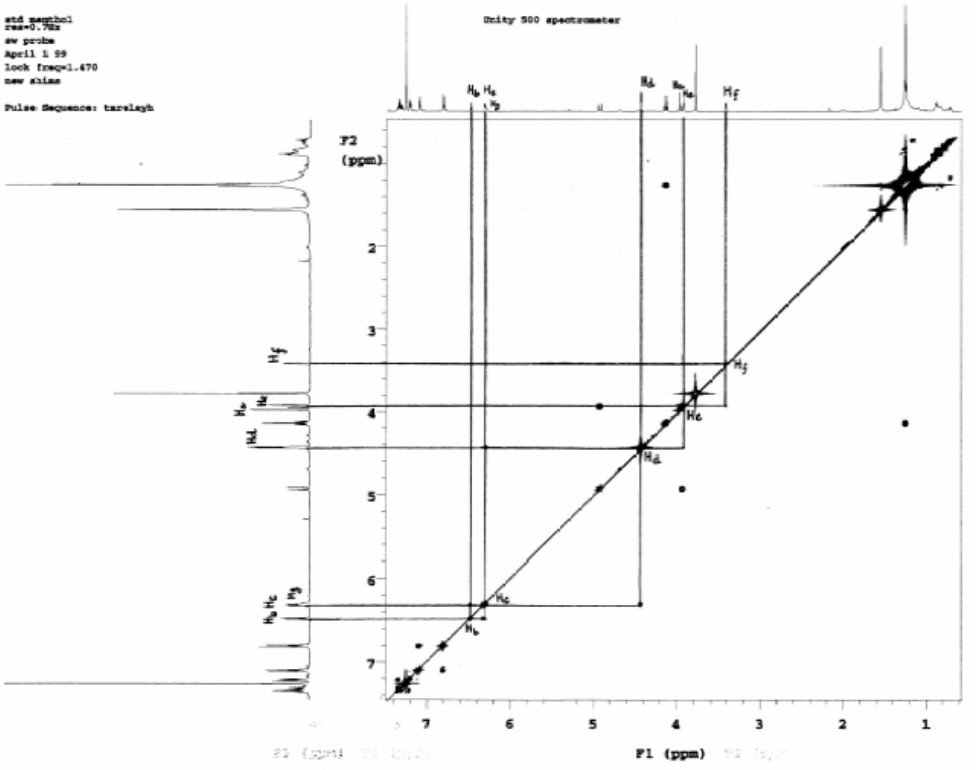
^{13}C NMR (Compound 8 at room temperature)



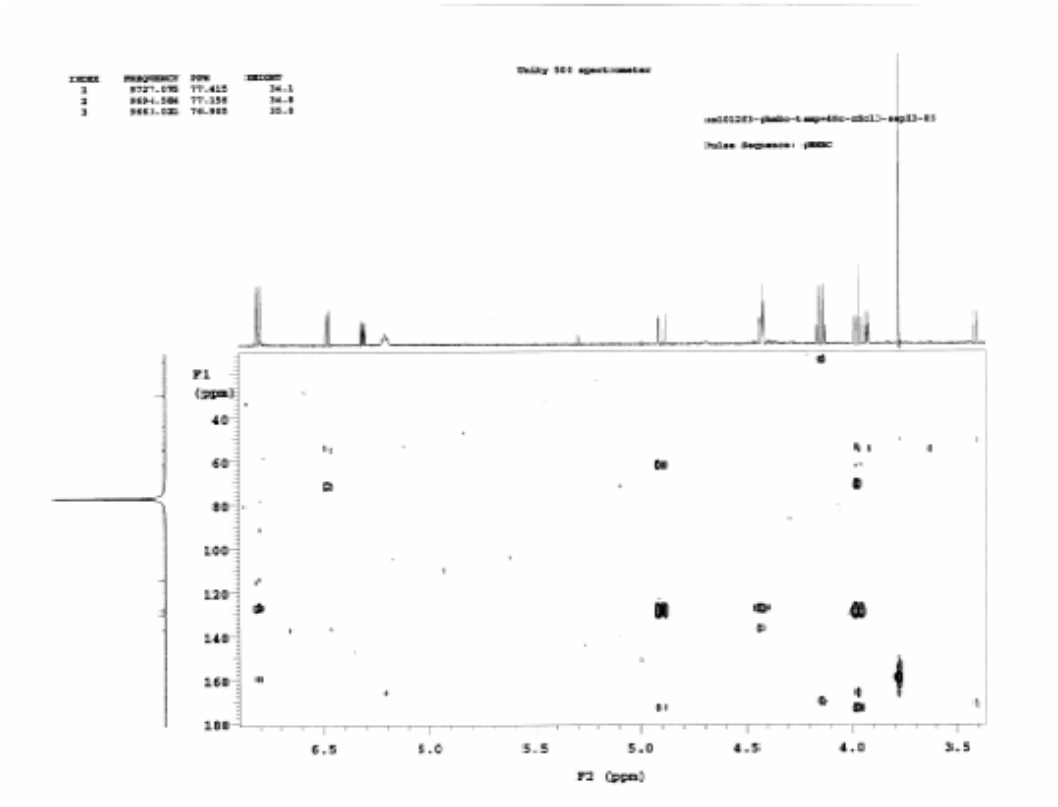
GHMQC NMR (Compound 8 at 48 ^{o}C).



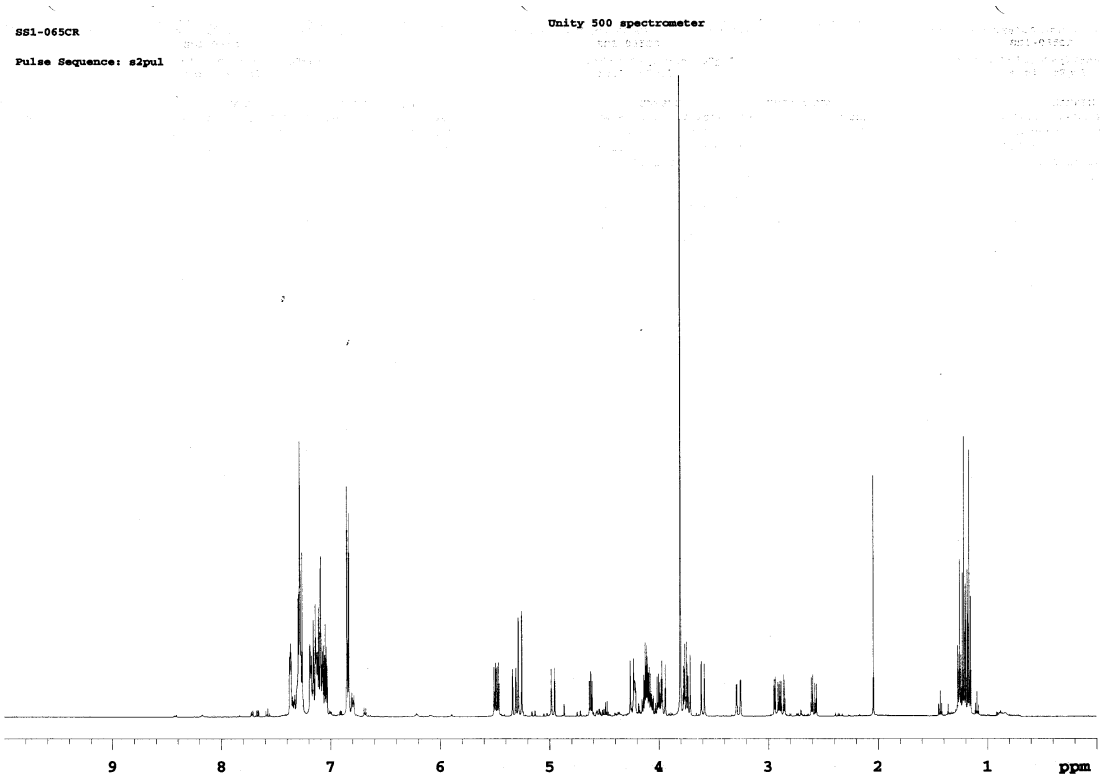
^{1}H-^{1}H GDQFCOSY NMR (Compound 8 at 48 ^{o}C)



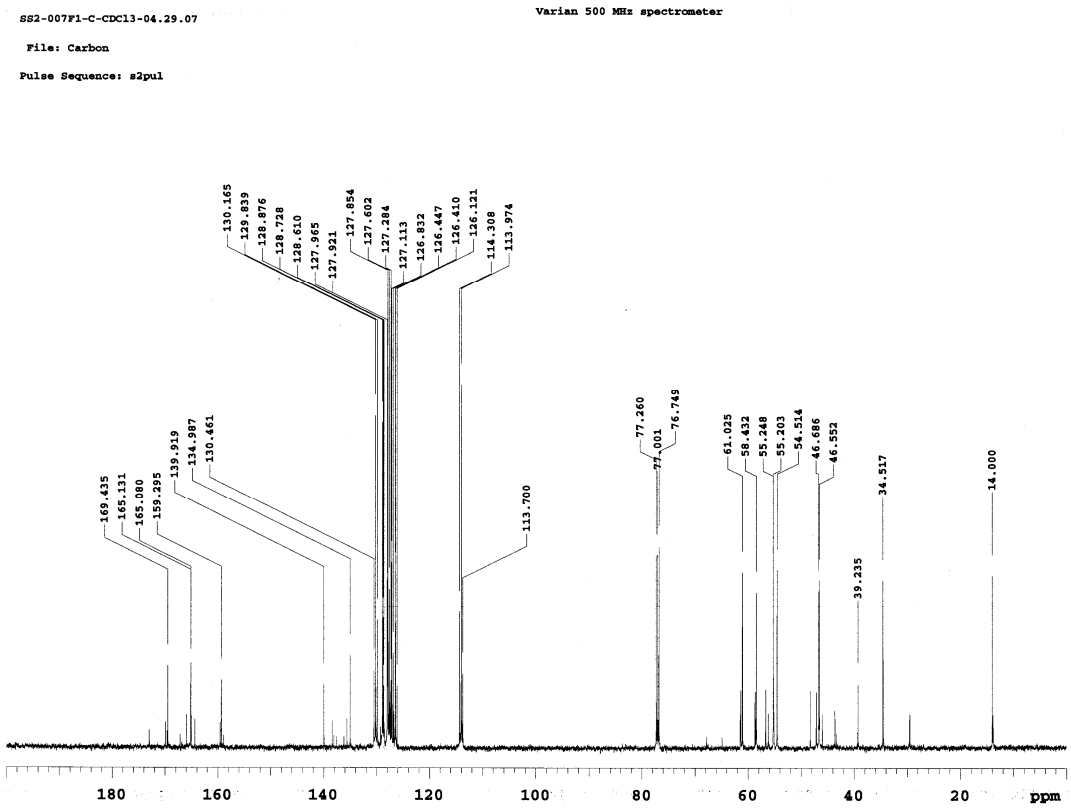
GHMBC NMR (Compound 8 at 48 ^{o}C)



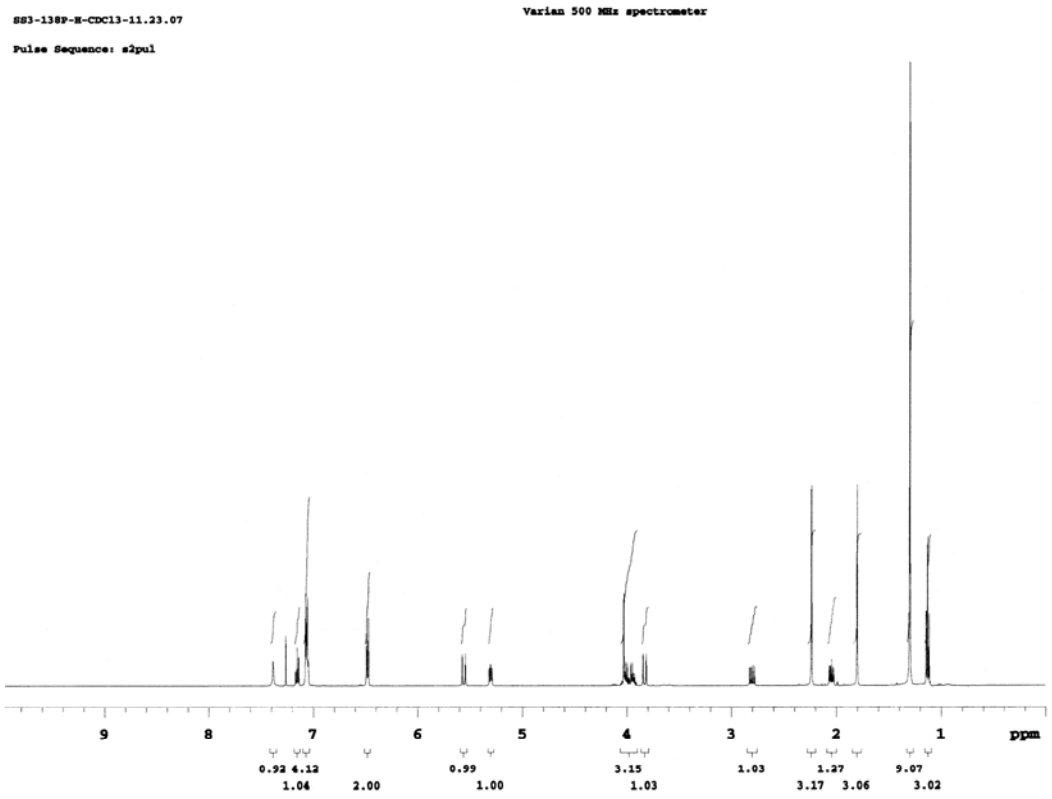
^{1}H NMR (Compound 11)



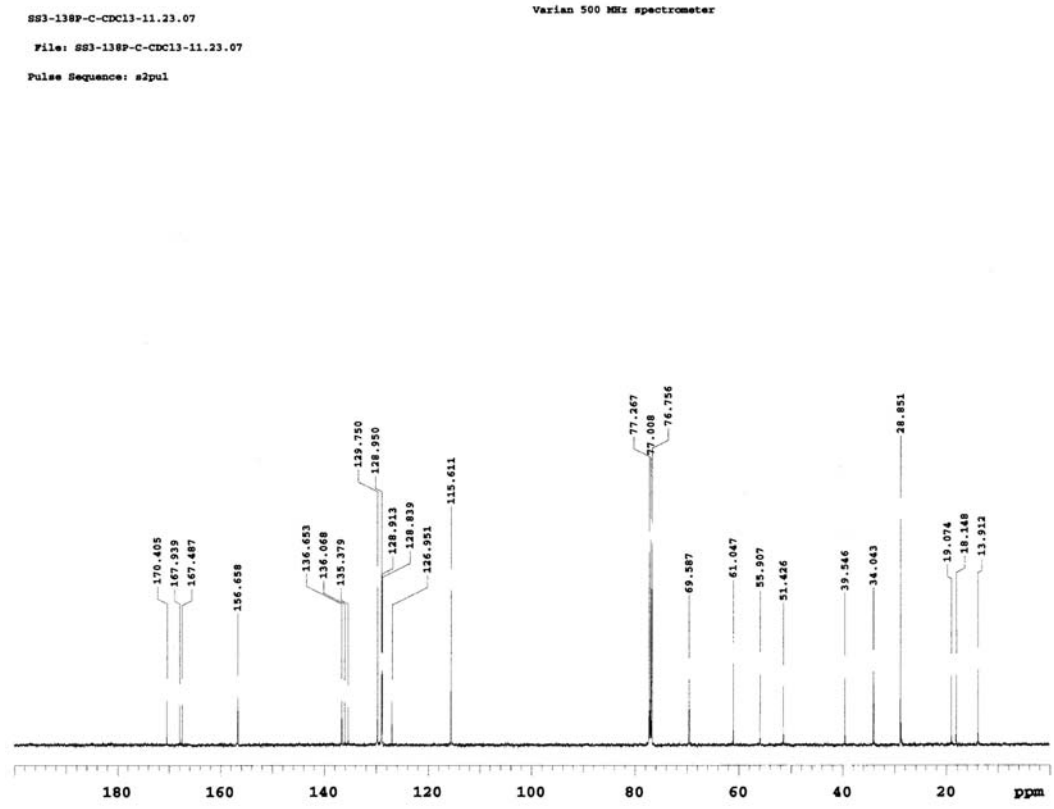
^{13}C NMR (Compound 11)



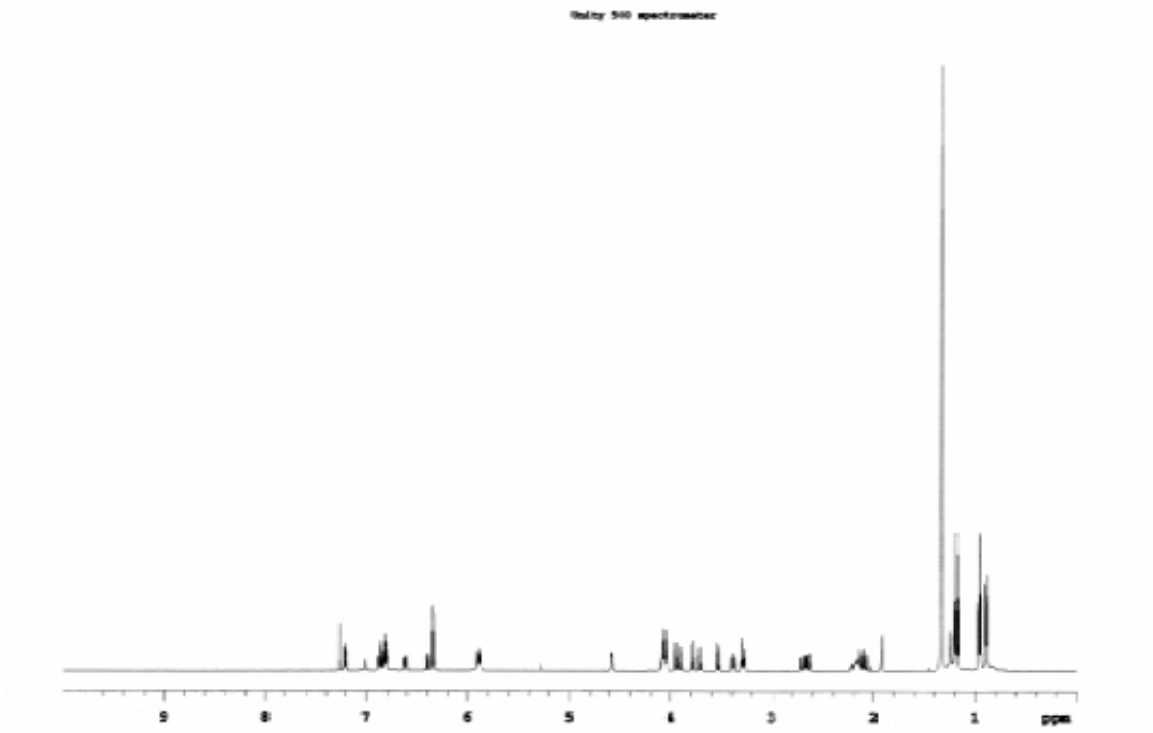
^{1}H NMR (Compound 12)



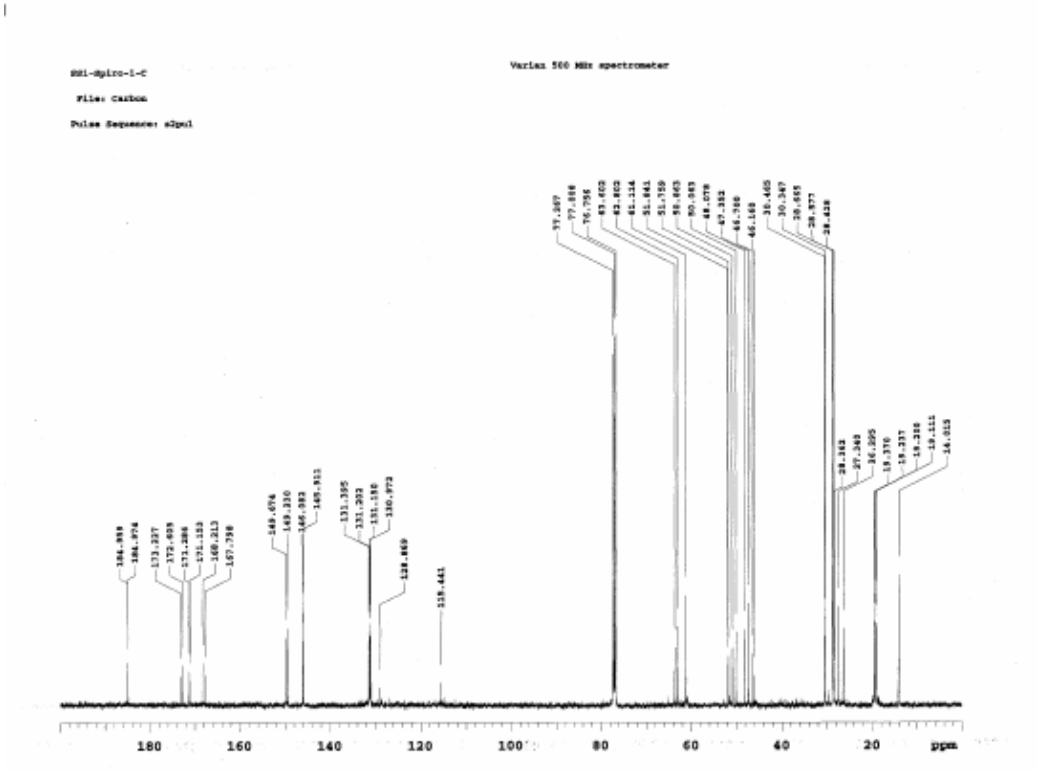
^{13}C NMR (Compound 12)



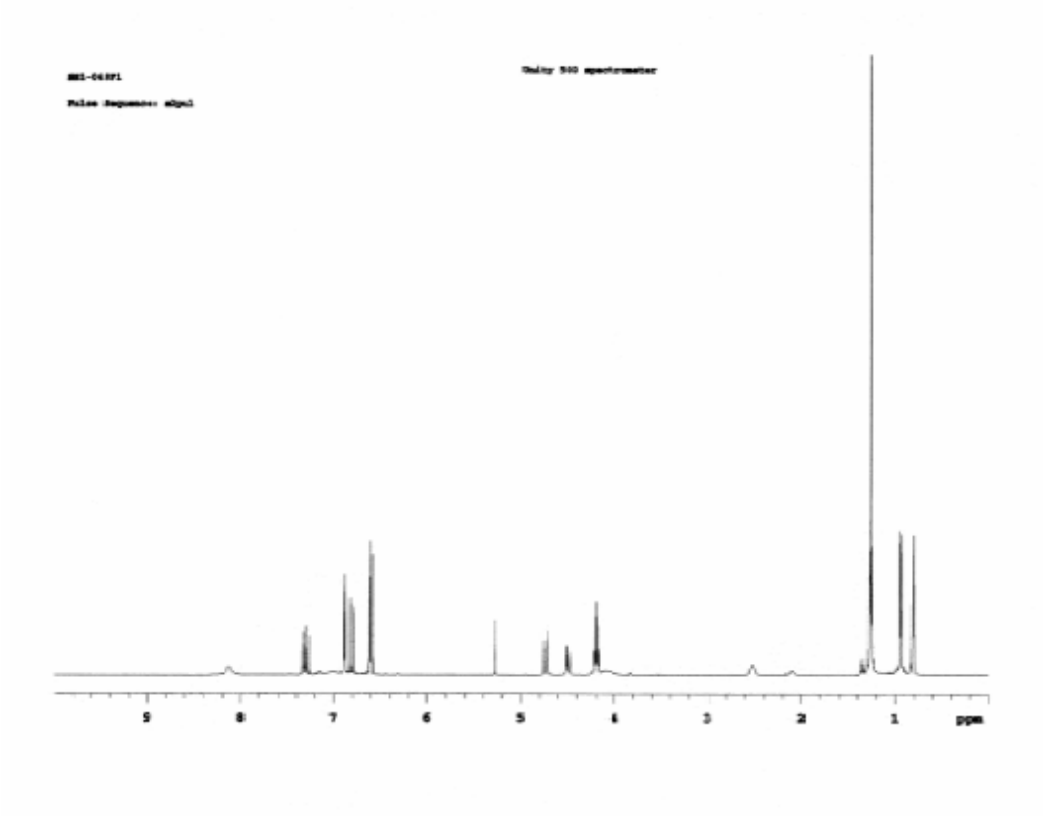
^{1}H NMR (Compound 16)



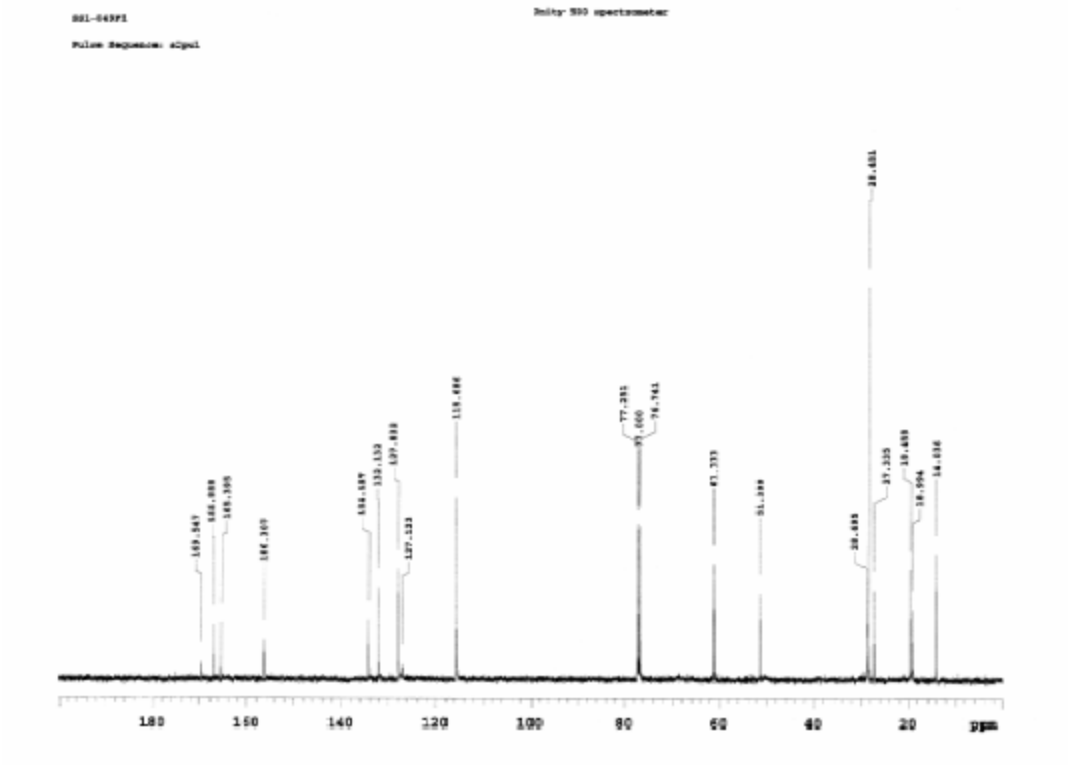
^{13}C NMR (Compound 16)



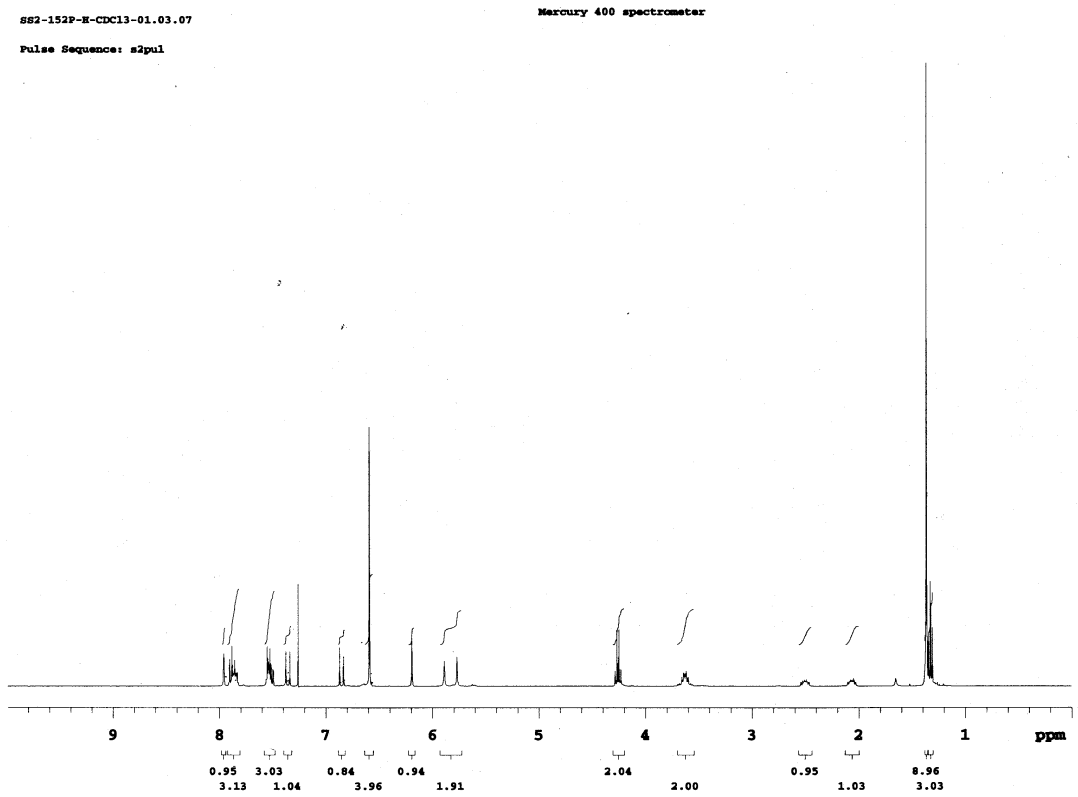
^{1}H NMR (Compound 17)



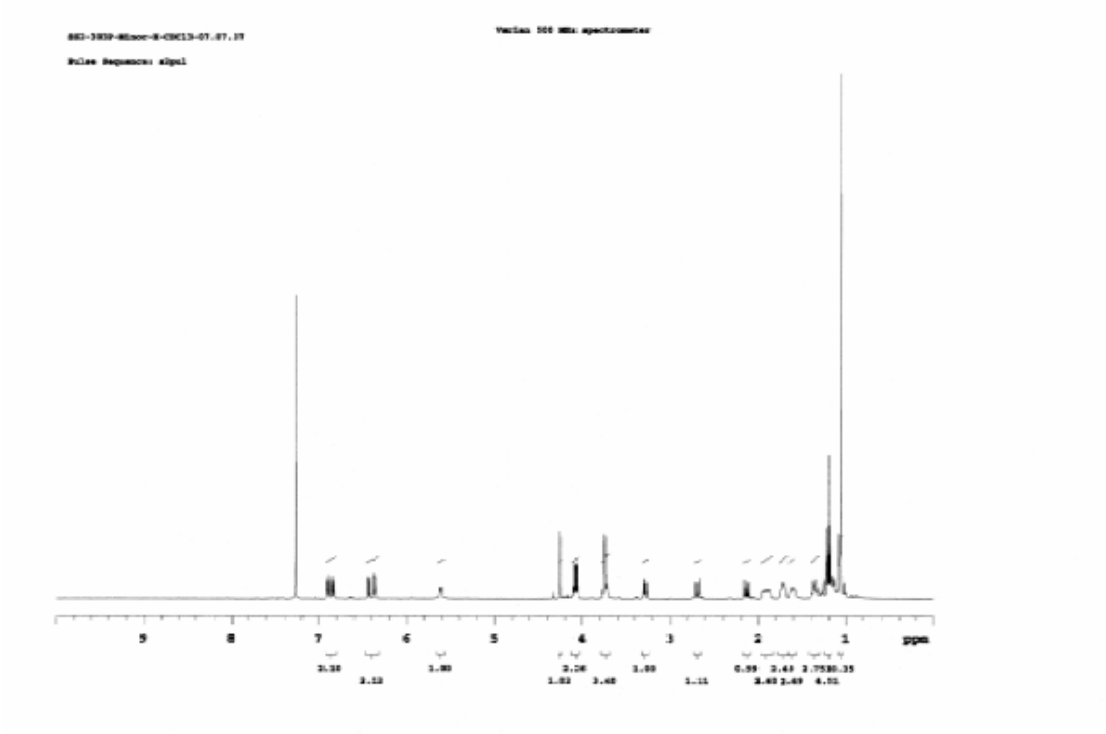
^{13}C NMR (Compound 17)



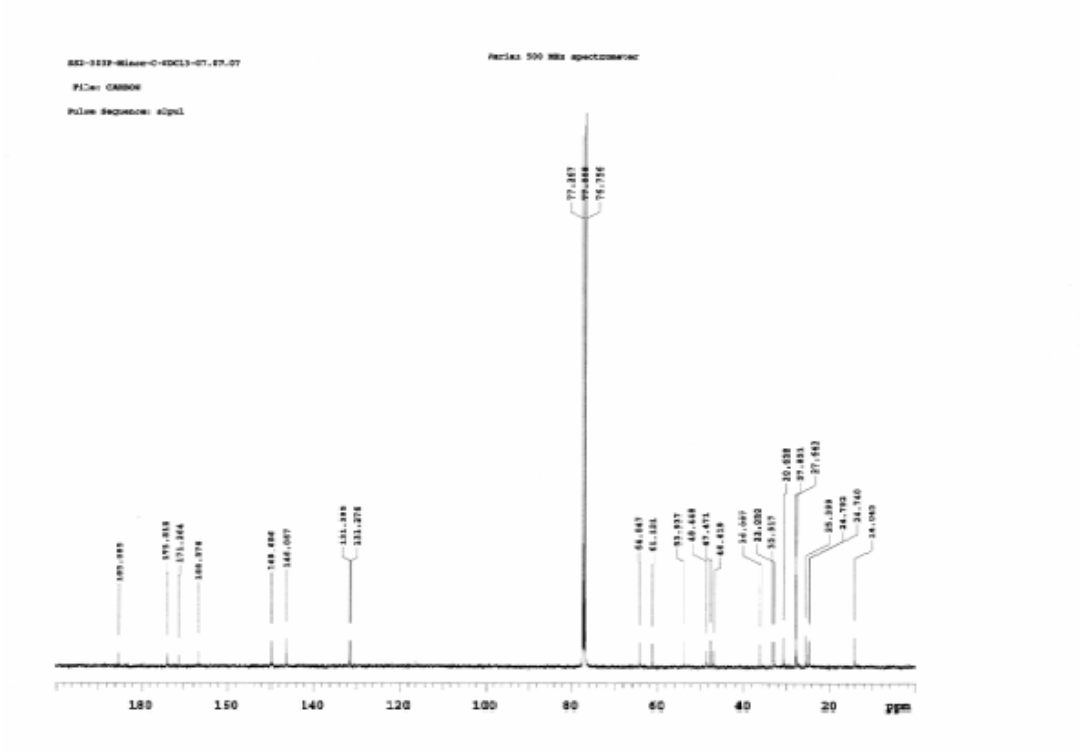
^{1}H NMR (Compound 20)



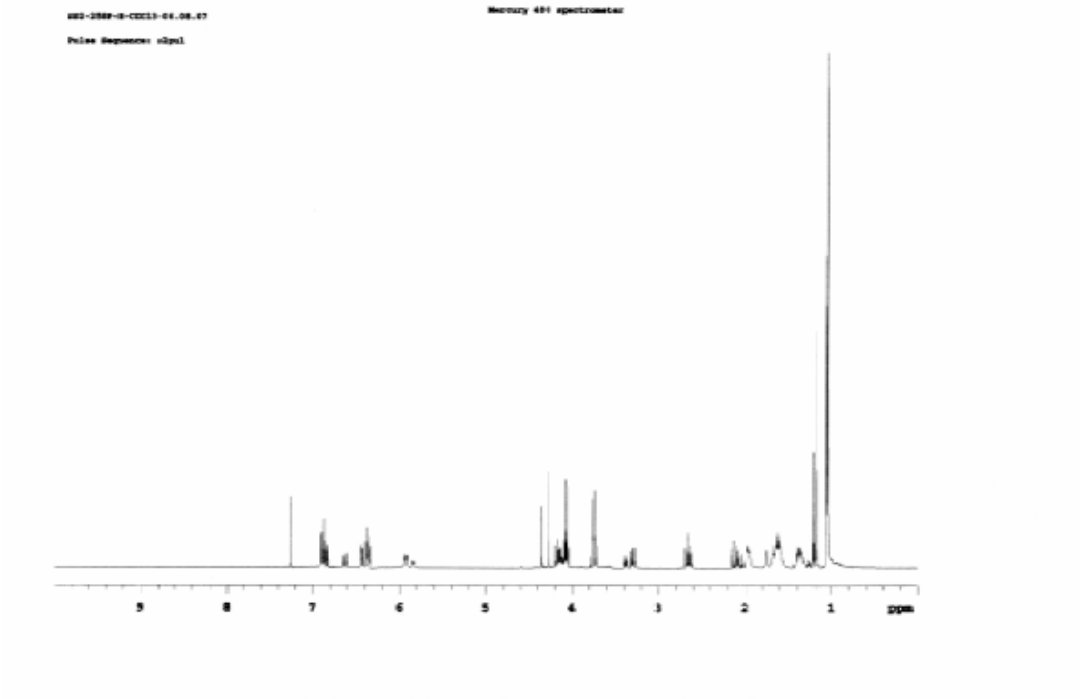
^{1}H NMR (Compound 23b)



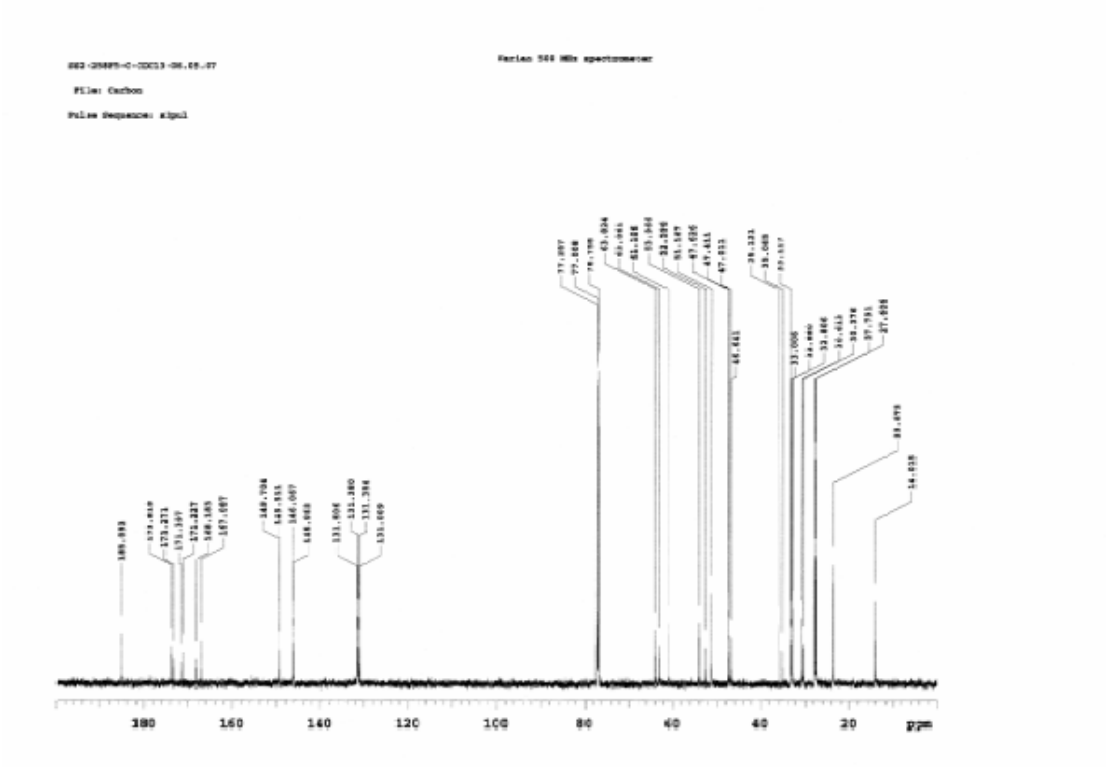
^{13}C (Compound 23b)



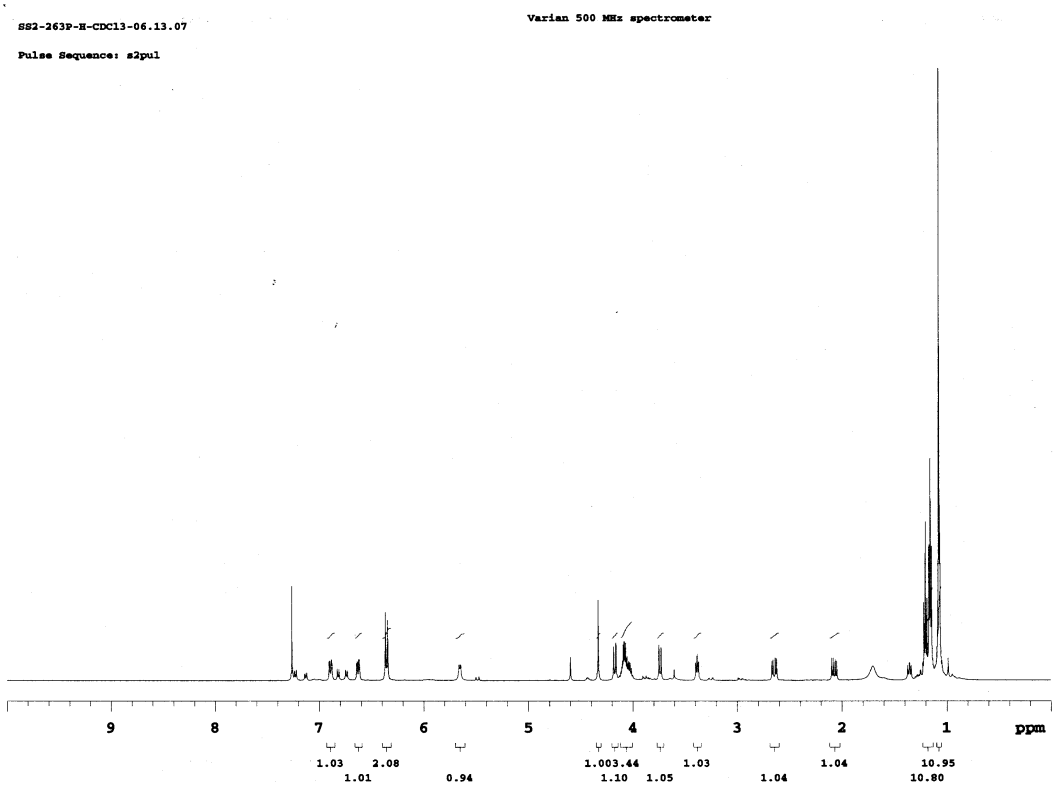
^{1}H NMR (Compound 23c)



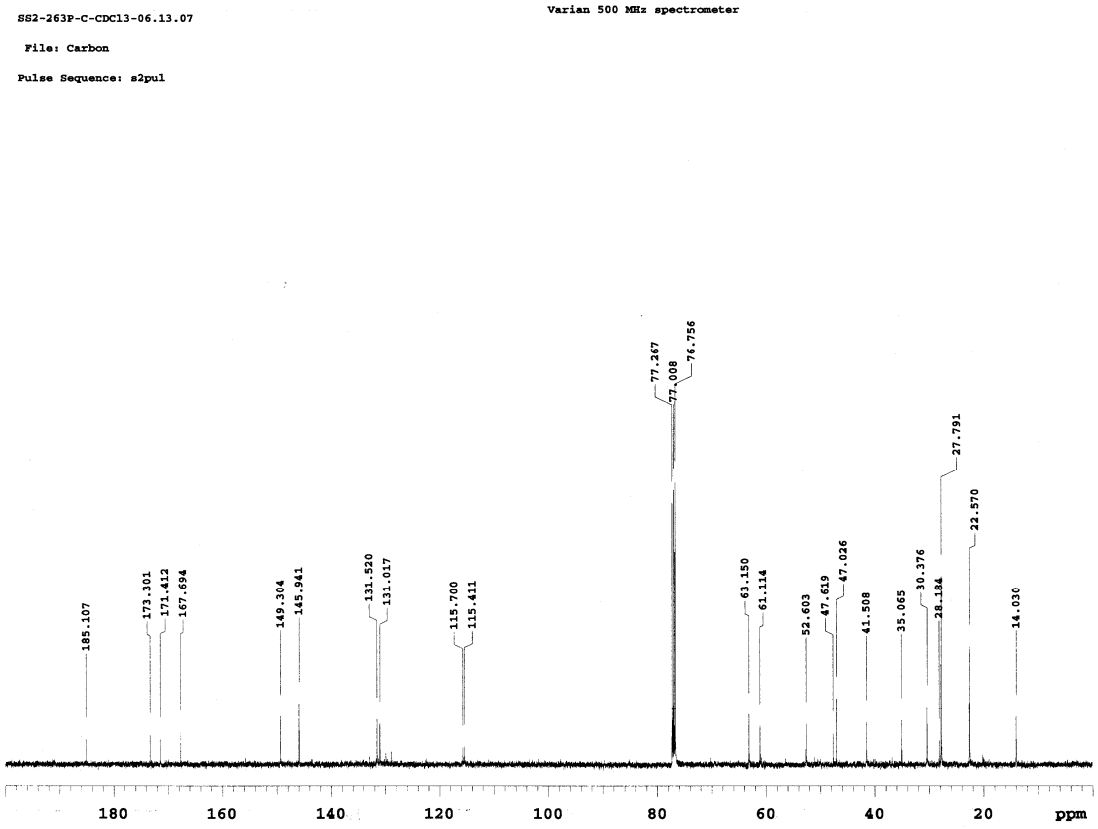
^{13}C NMR (Compound 23c)



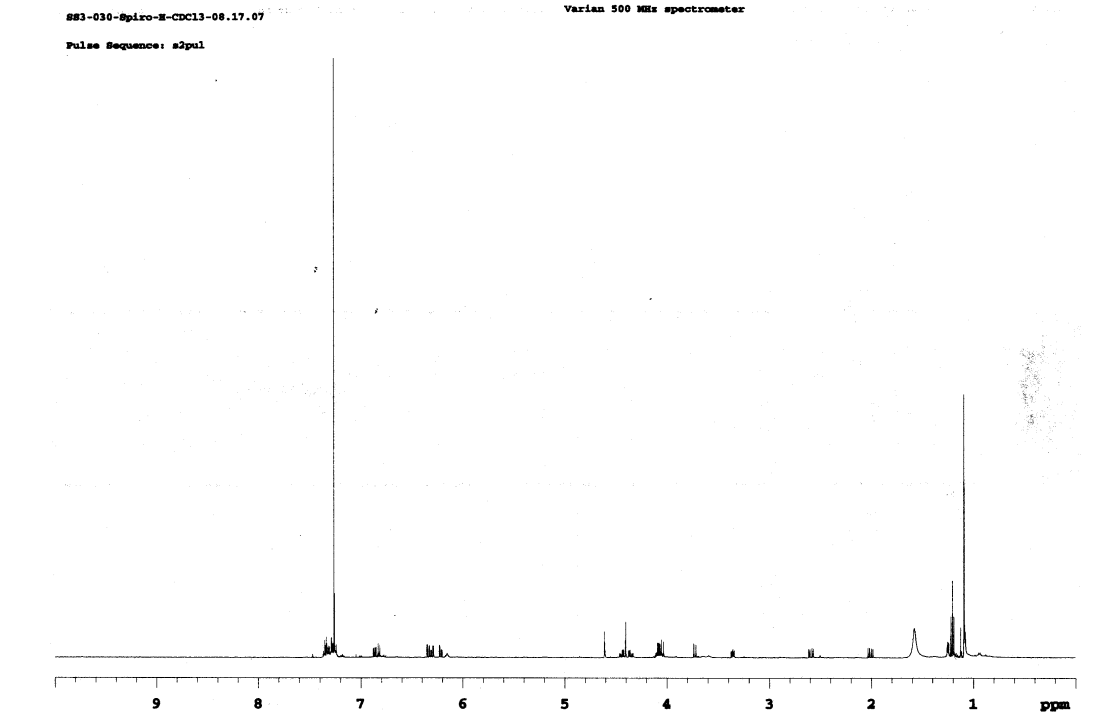
^{1}H NMR (Compound 23d)



^{13}C NMR (Compound 23d)



^{1}H NMR (Compound 23e)



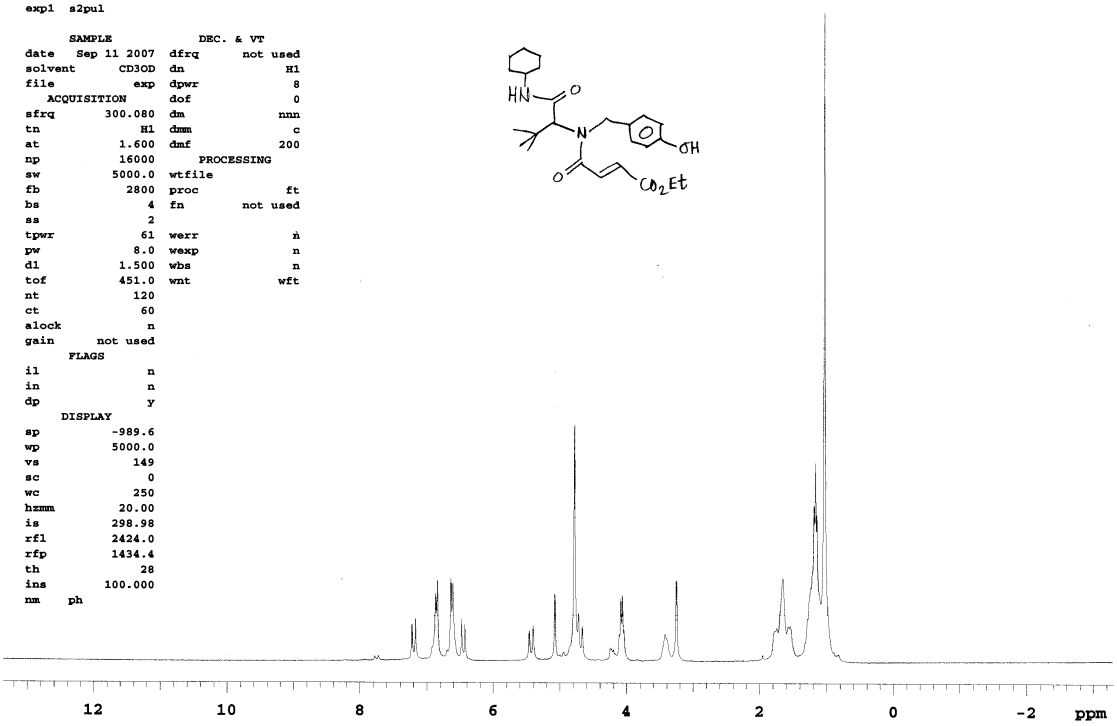
^{1}H NMR (Compound 24b)

SS2-302P-CD3OD-09.11.07
SS2-302P-CD3OD-09.11.07

exp1 s2pul

SAMPLE		DEC. & VT	
date	Sep 11 2007	dfrq	not used
solvent	CD3OD	dn	H1
file	exp	dpwr	8
ACQUISITION		dof	0
sfrq	300.080	dm	nnn
tn	H1	dmm	c
at	1.600	dmf	200
np	16000	PROCESSING	
sw	5000.0	wtfile	
fb	2800	proc	ft
bs	4	fn	not used
ss	2		
tpwr	61	werr	n
pw	8.0	wexp	n
dl	1.500	wbs	n
tof	451.0	wnt	wft
nt	120		
ct	60		
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-989.6		
wp	5000.0		
vs	149		
sc	0		
wc	250		
hzmm	20.00		
is	298.98		
rfl	2424.0		
rfp	1434.4		
th	28		
ins	100.000		
nm	ph		

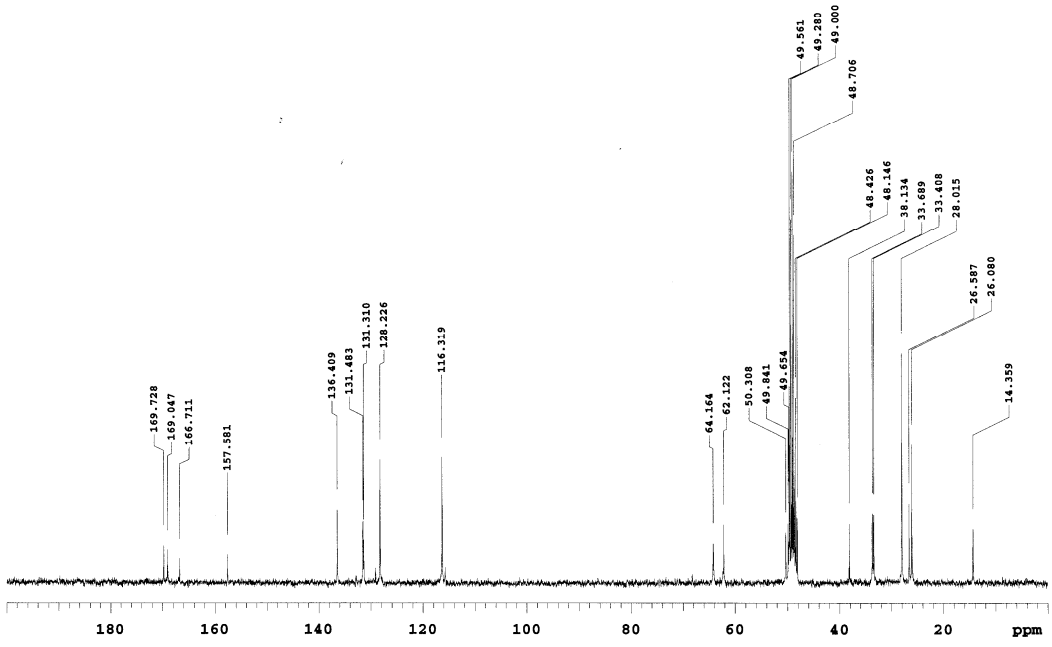
Unity 300 spectrometer



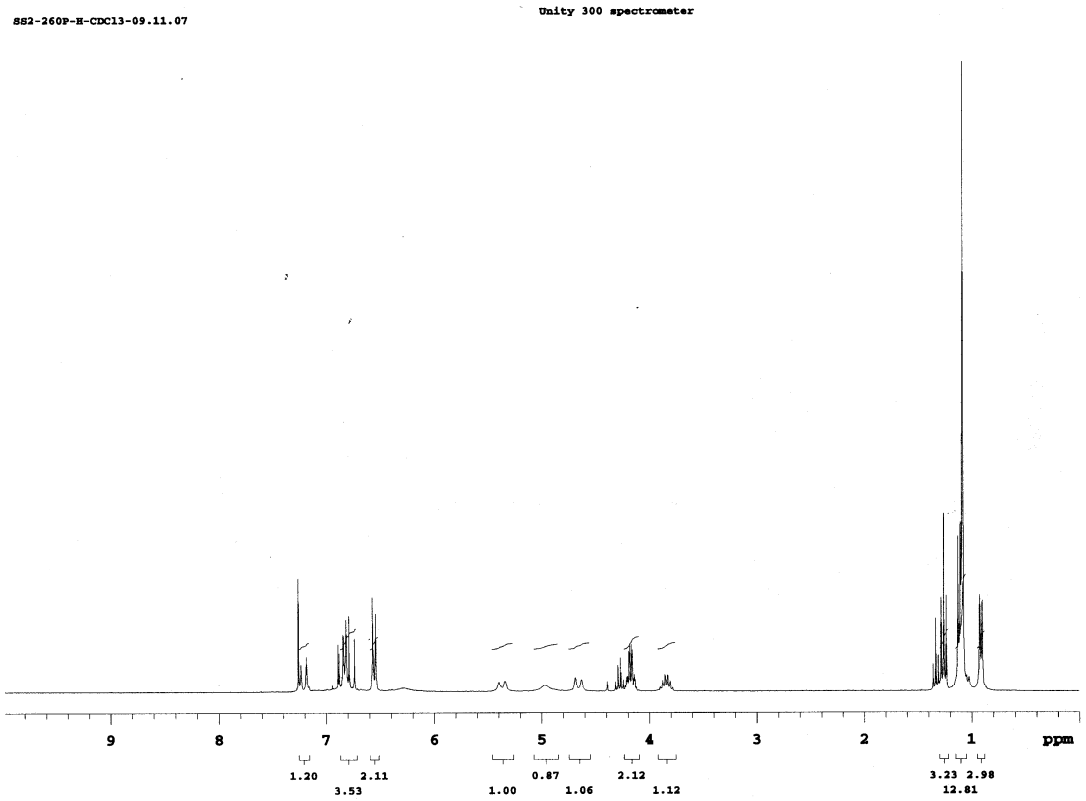
^{13}C NMR (Compound 24b)

SS2-302P-C-CD3OD-09.11.07
standard Carbon expriment

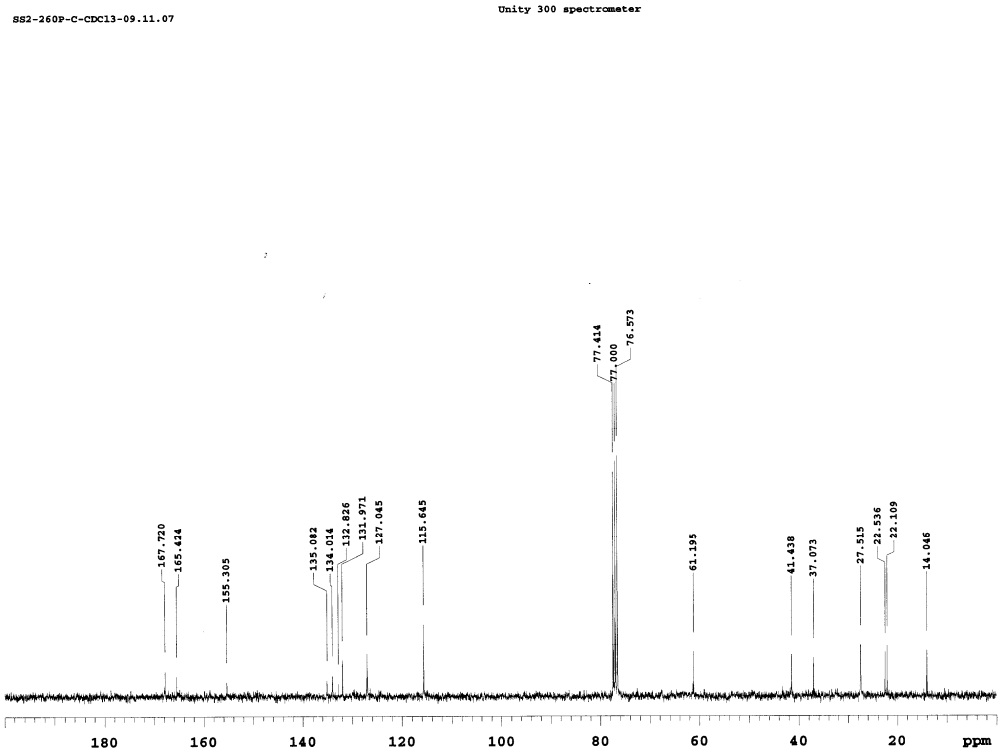
Unity 300 spectrometer



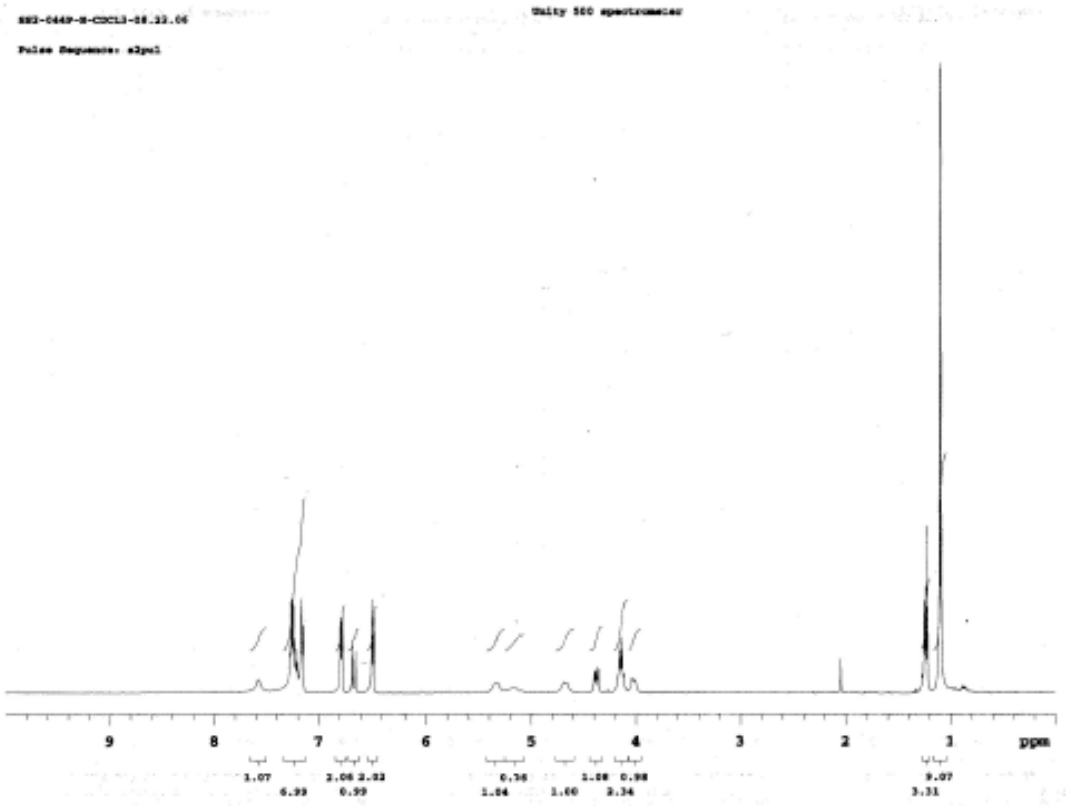
^{1}H NMR (Compound 24d)



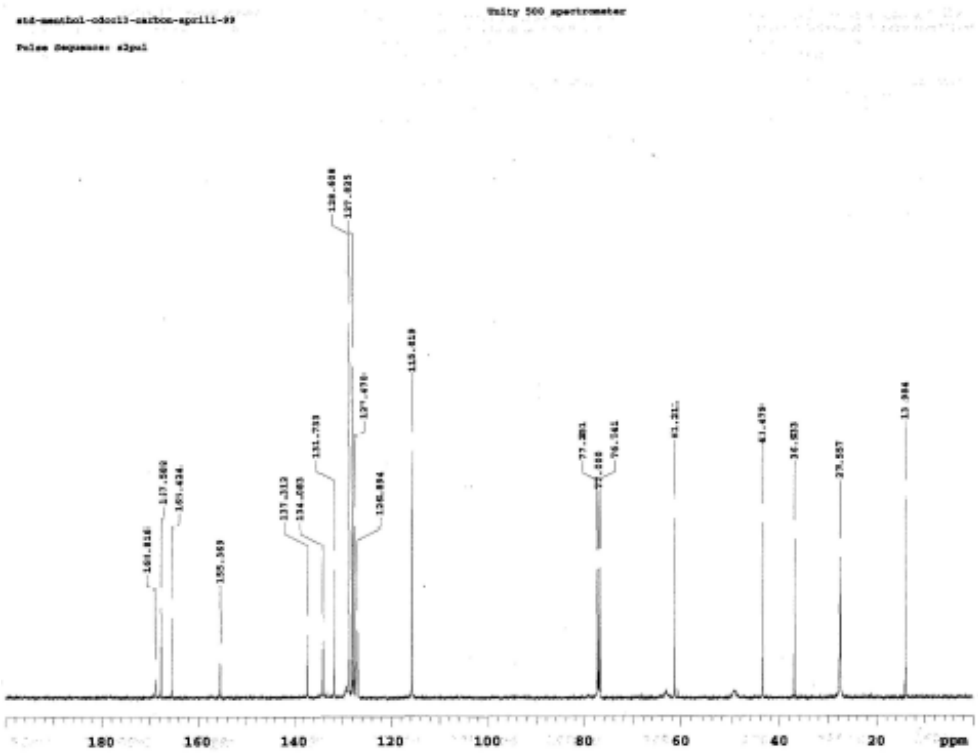
^{13}C NMR (Compound 24d)



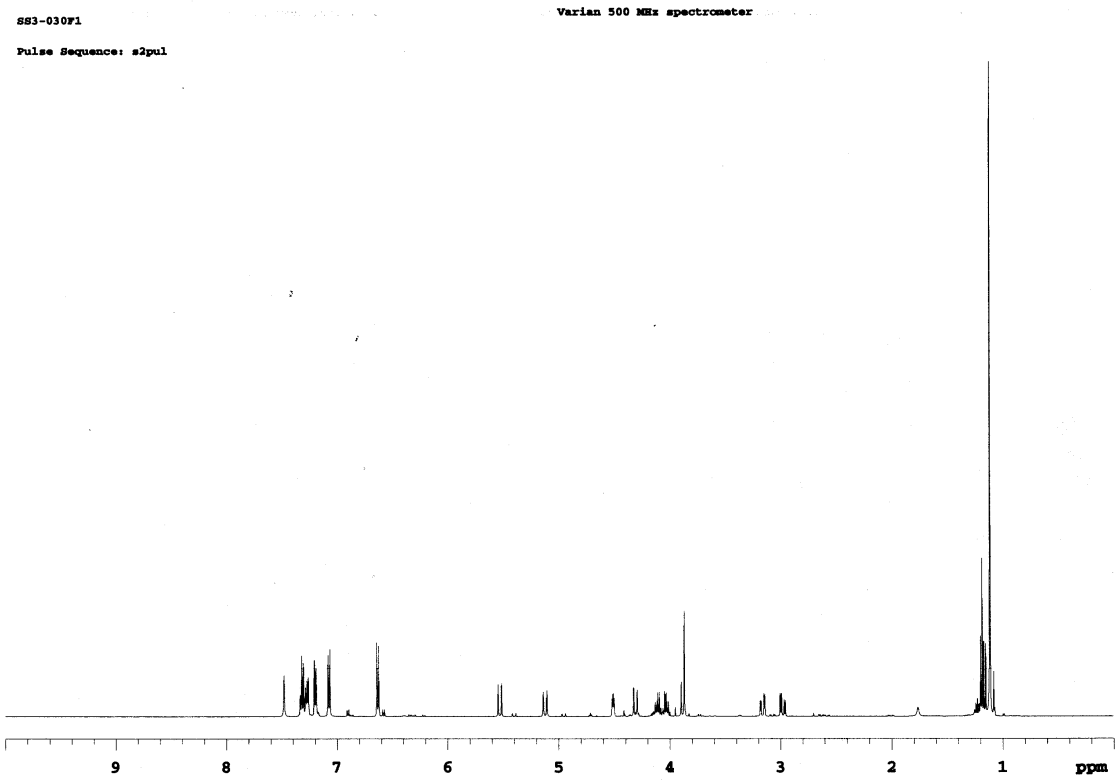
^{1}H NMR (Compound 24e)



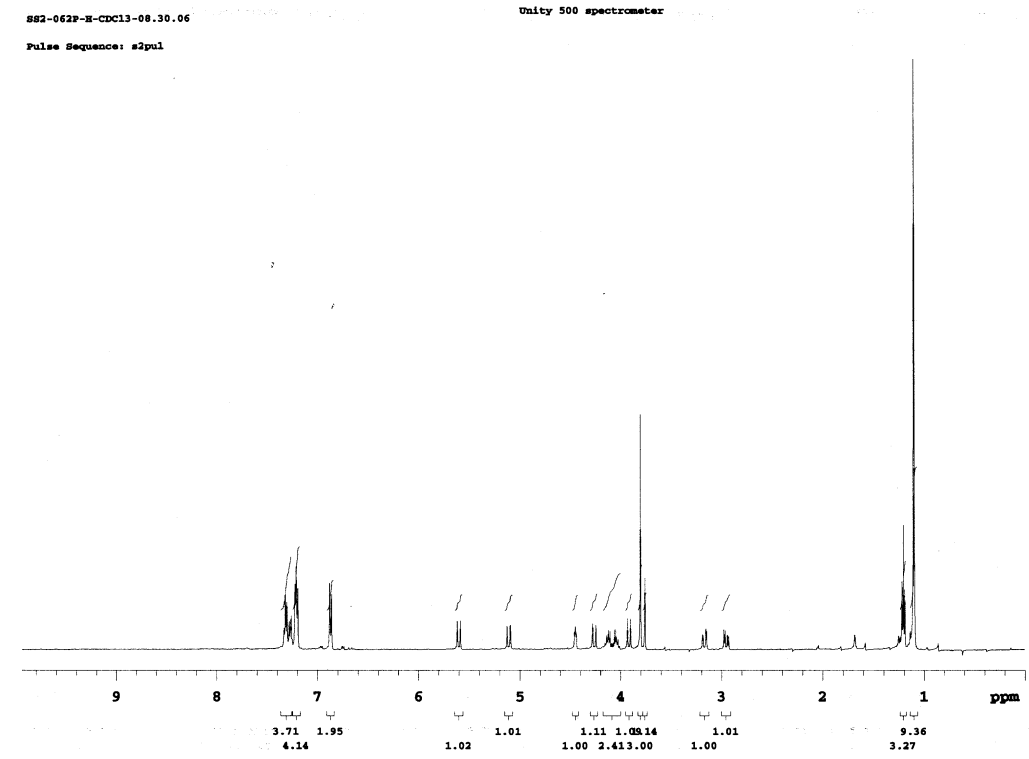
^{13}C NMR (Compound 24e)



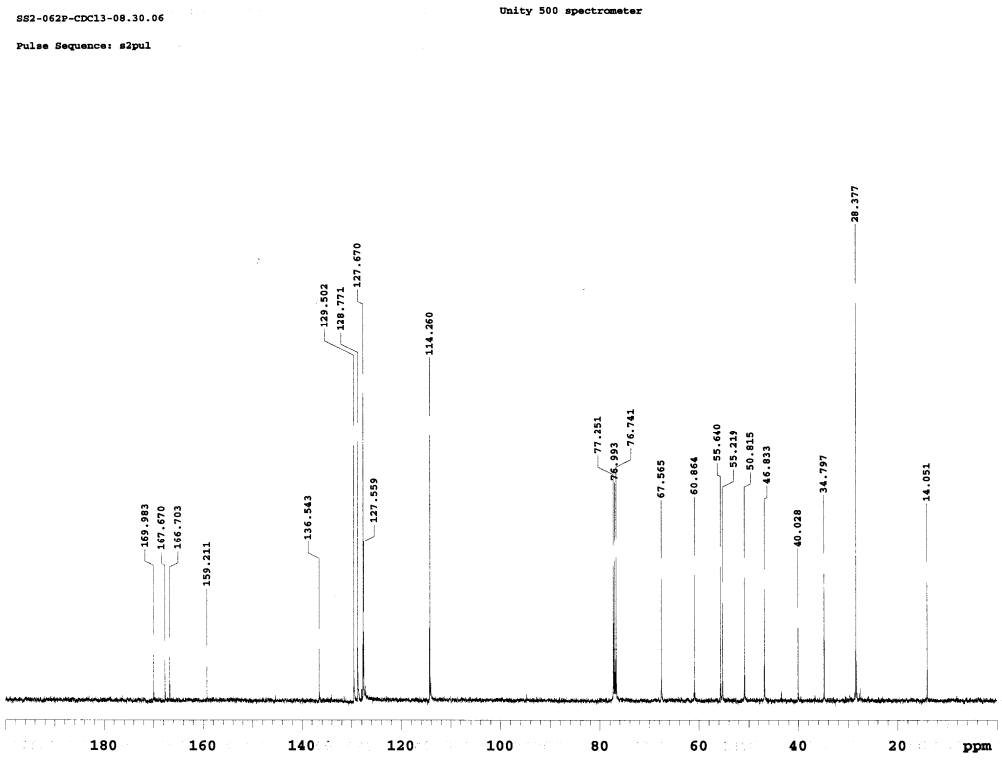
^{1}H NMR (Compound 25e)



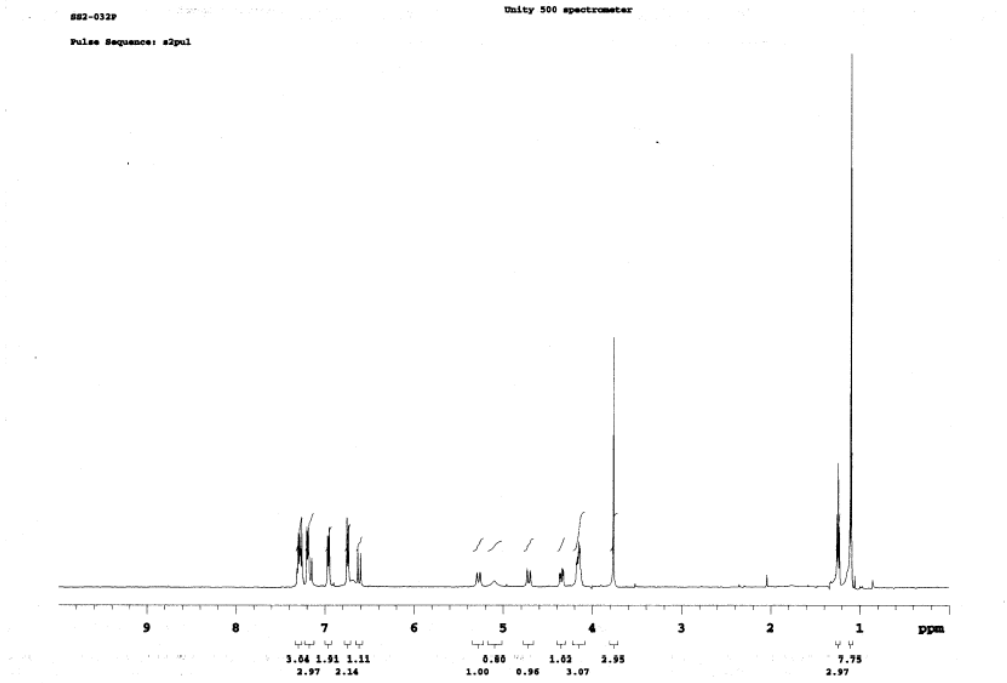
^{1}H NMR (Compound 27)



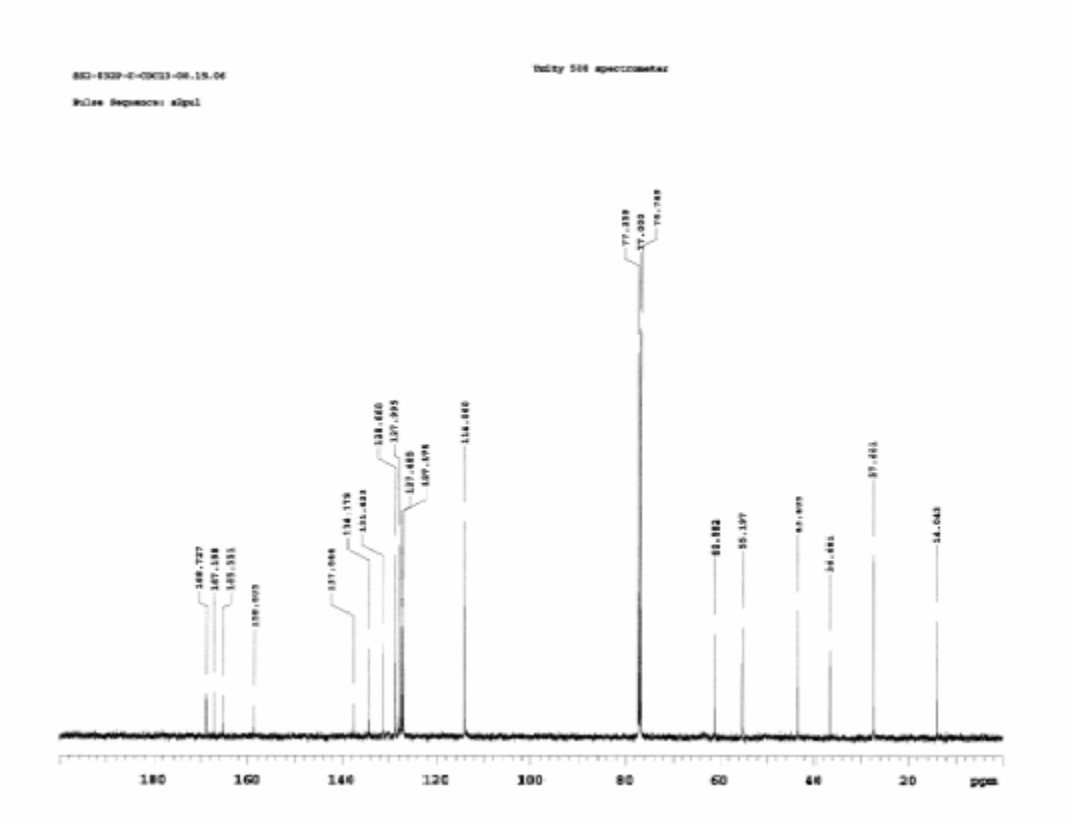
^{13}C NMR (Compound 27)



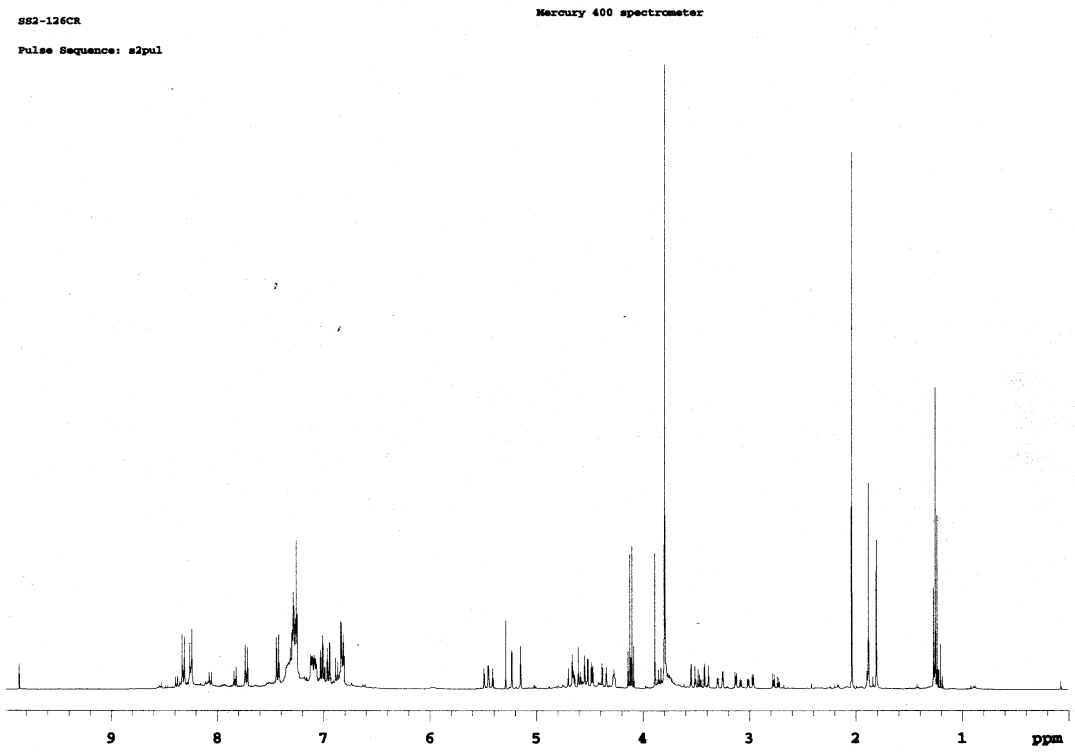
^{1}H NMR (Compound 27a)



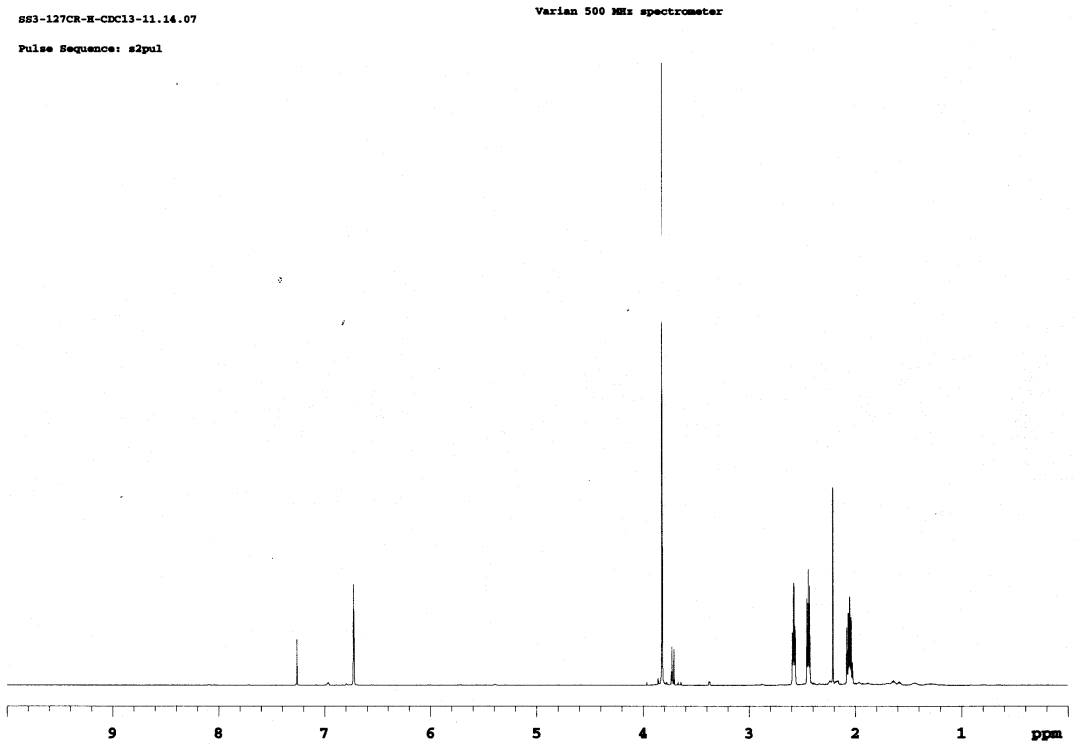
^{13}C NMR (Compound 27a)



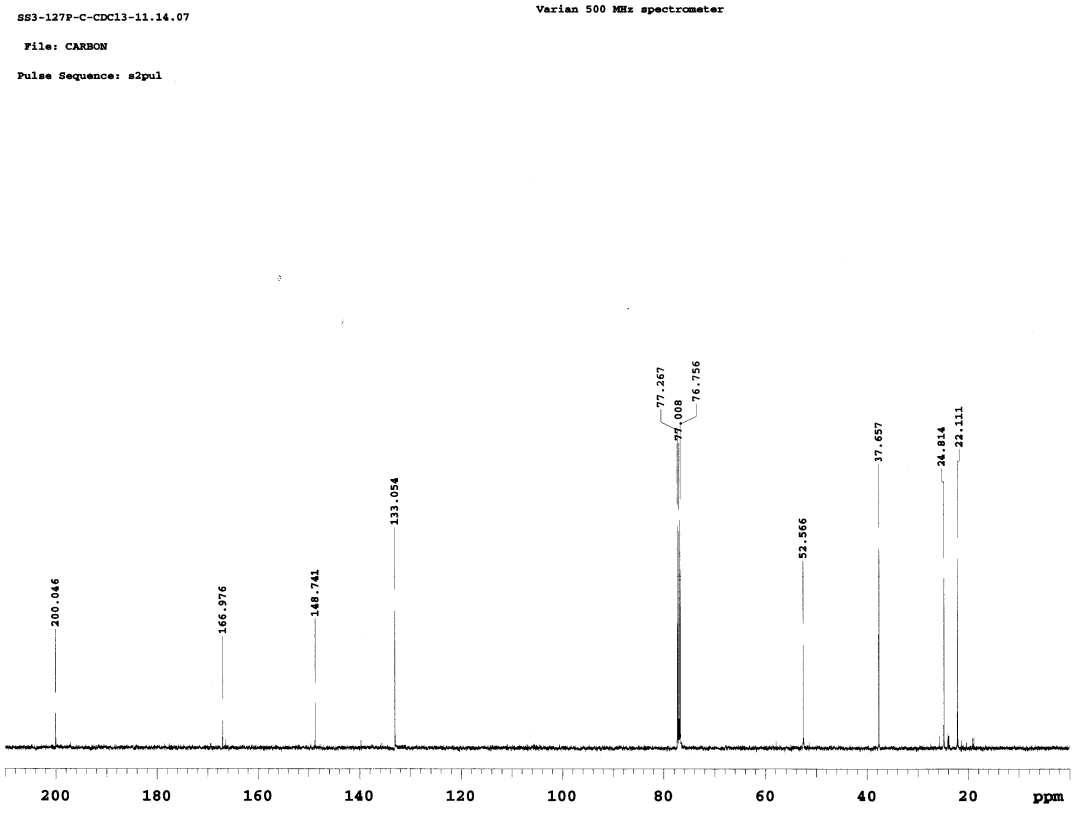
^{1}H NMR (Compound 28)



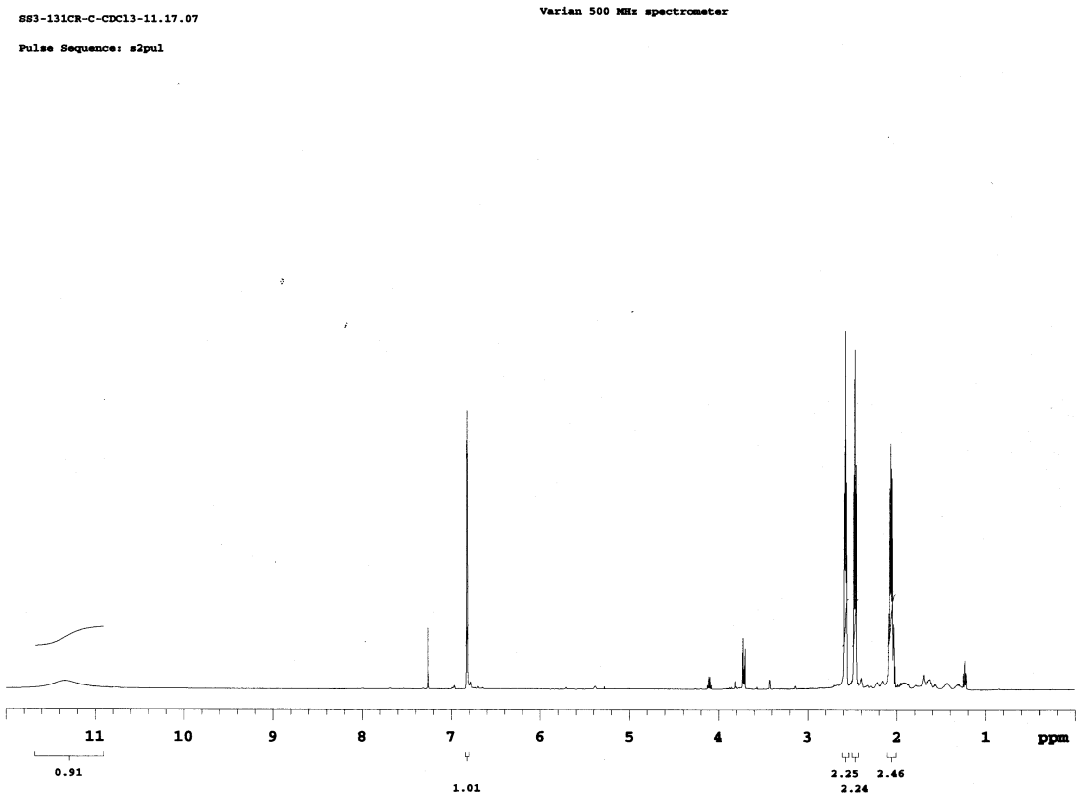
^{1}H NMR (Compound 31)



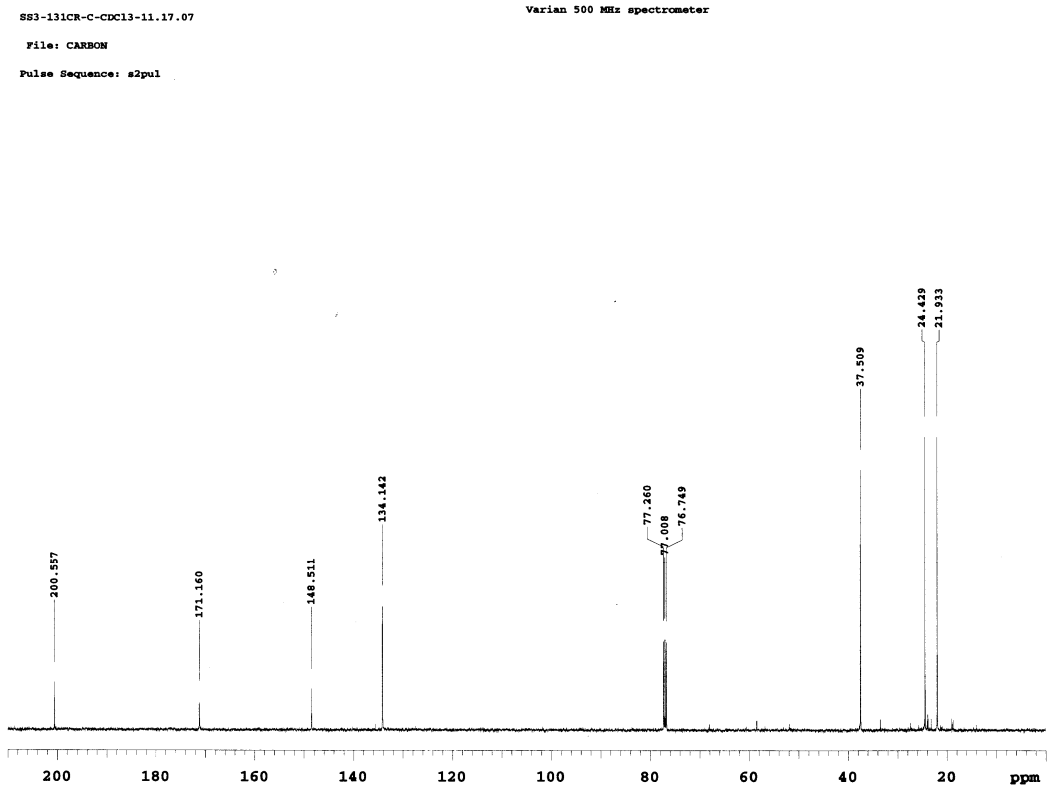
^{13}C NMR (Compound 31)



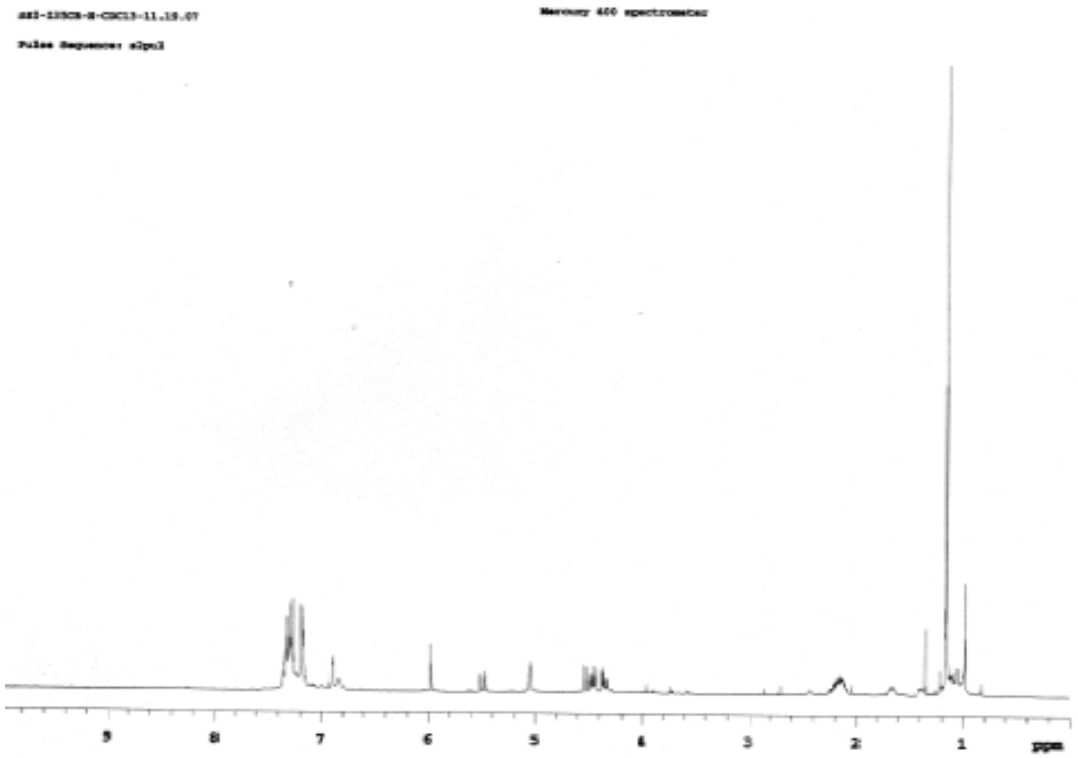
^{1}H NMR (Compound 2e)



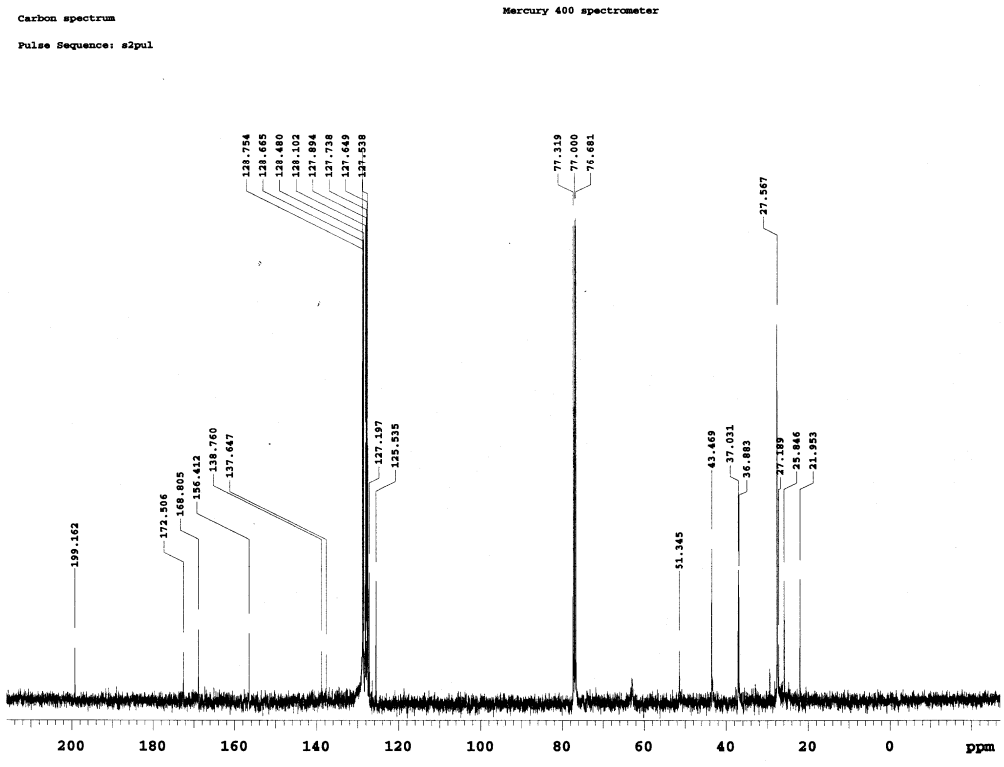
^{13}C NMR (Compound 2e)



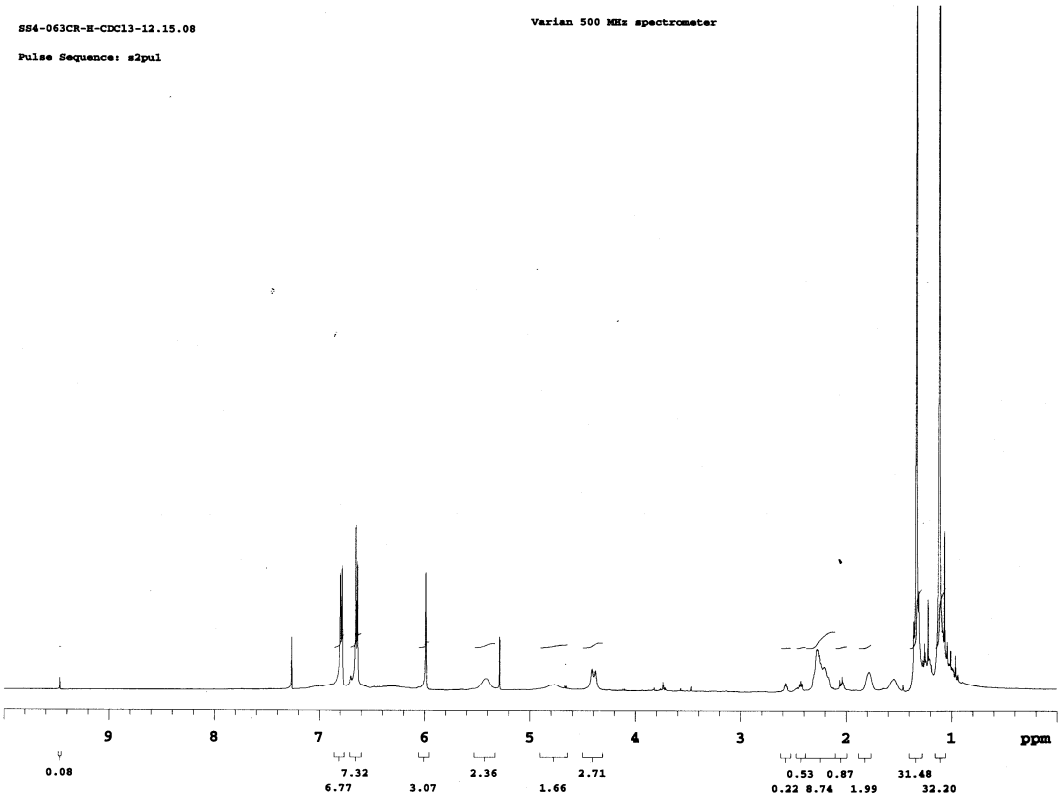
^{1}H NMR (Compound 32)



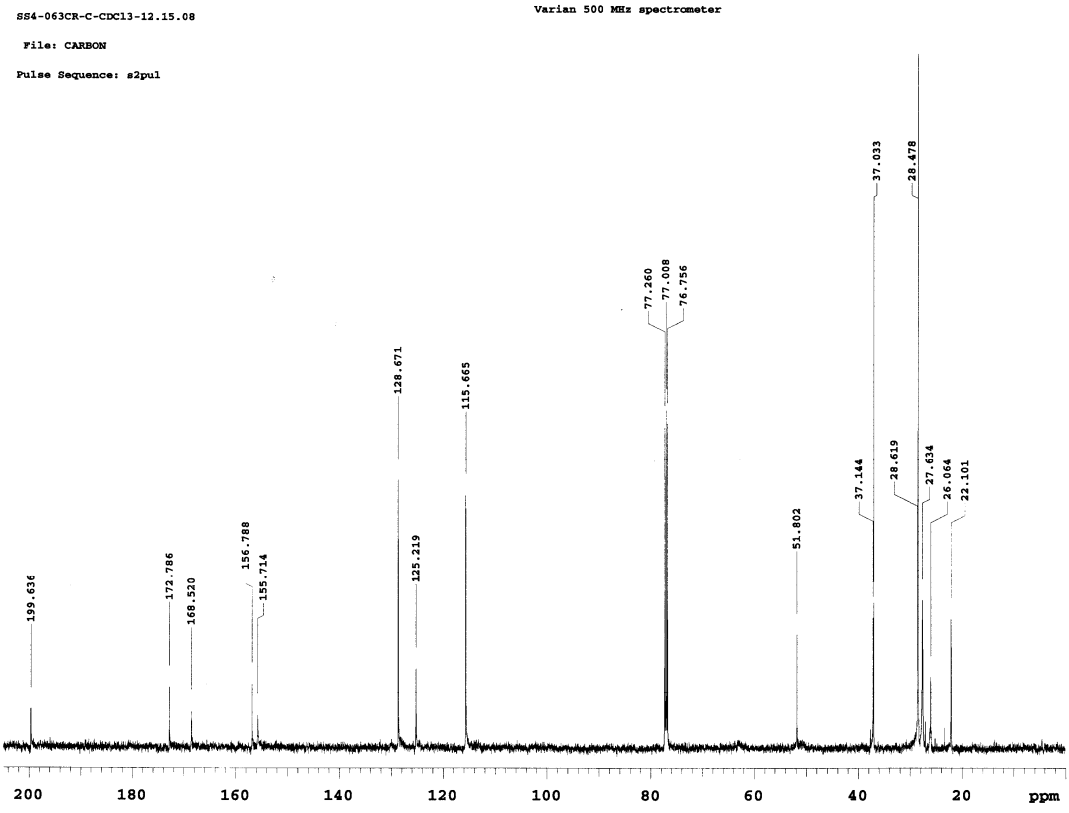
^{13}C NMR (Compound 32)



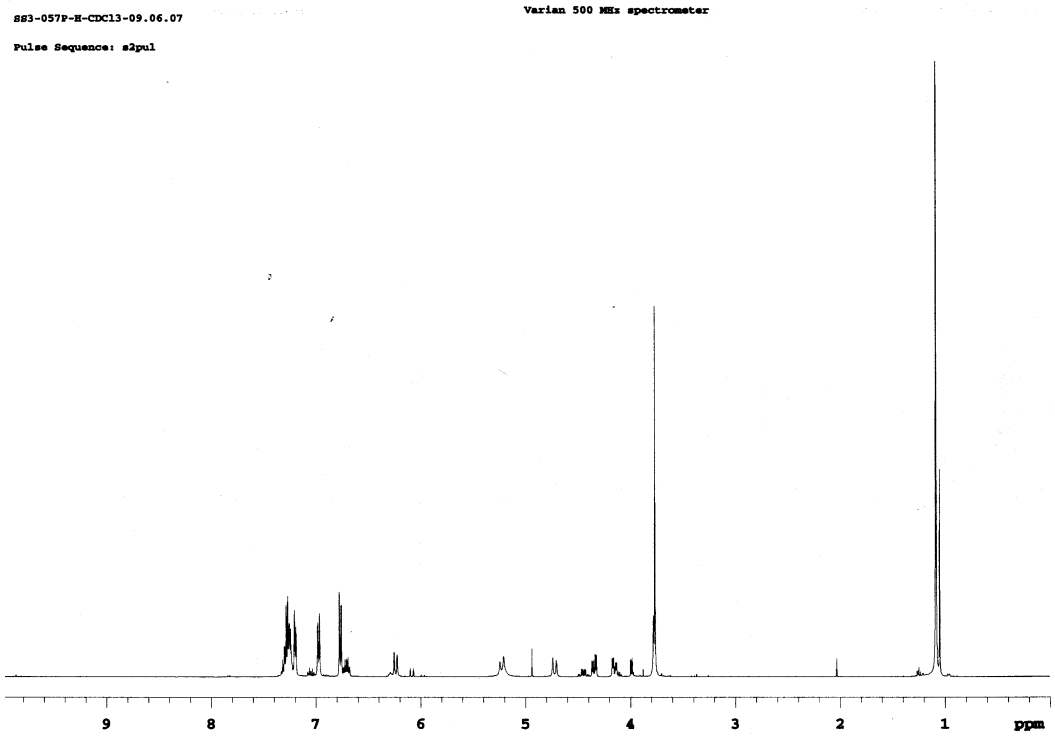
^{1}H NMR (Compound 34)



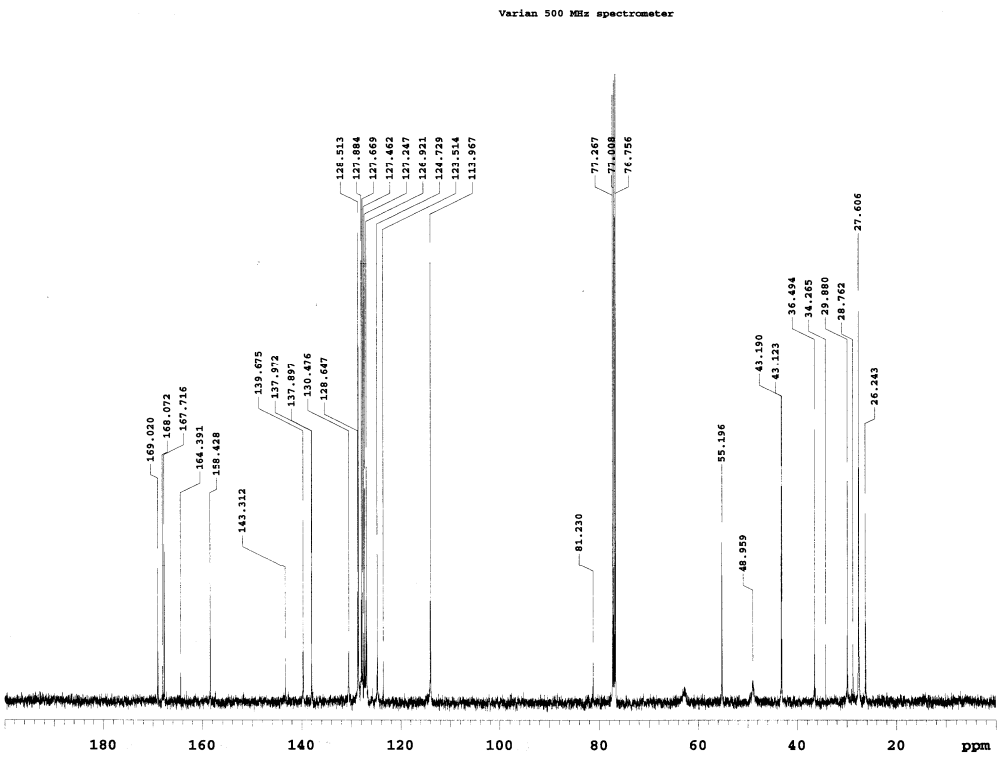
^{13}C NMR (Compound 34)



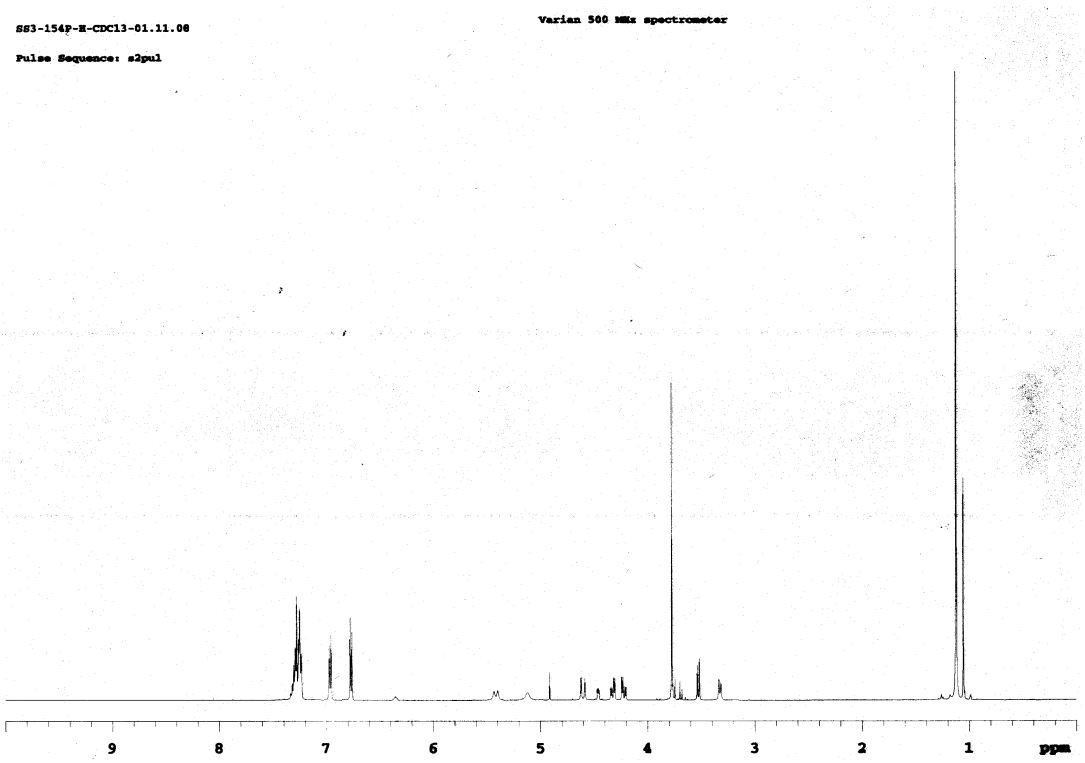
^{1}H NMR (Compound 37a)



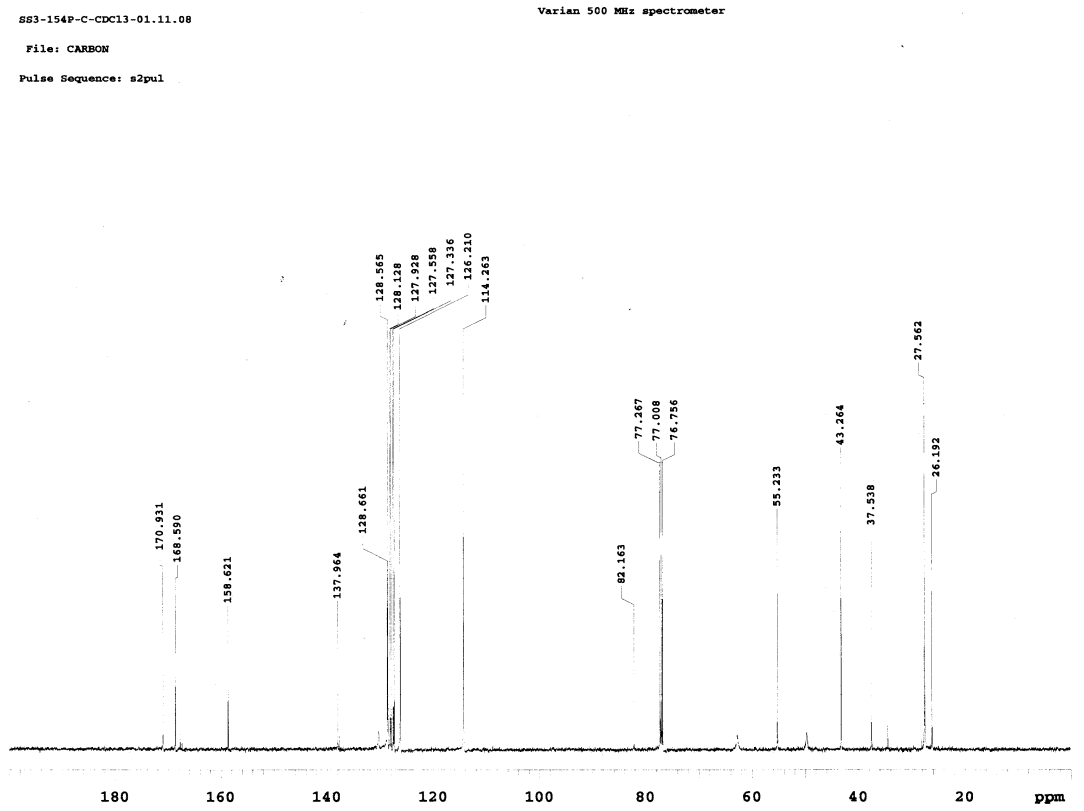
^{13}C NMR (Compound 37a)



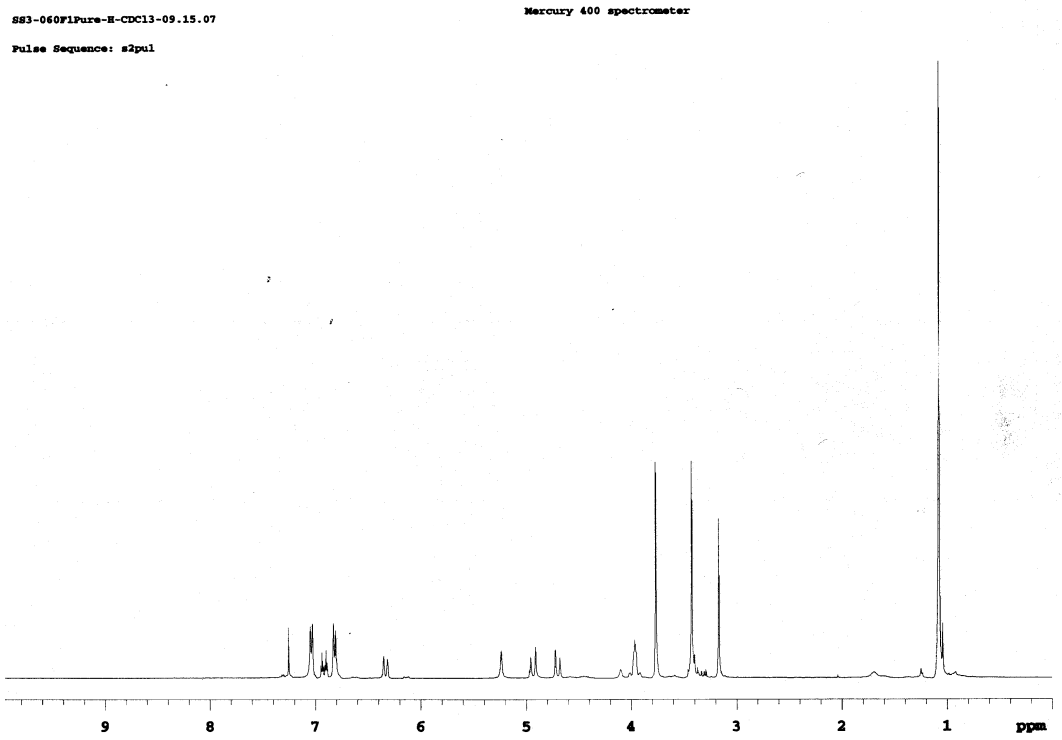
^{1}H NMR (Compound 37b)



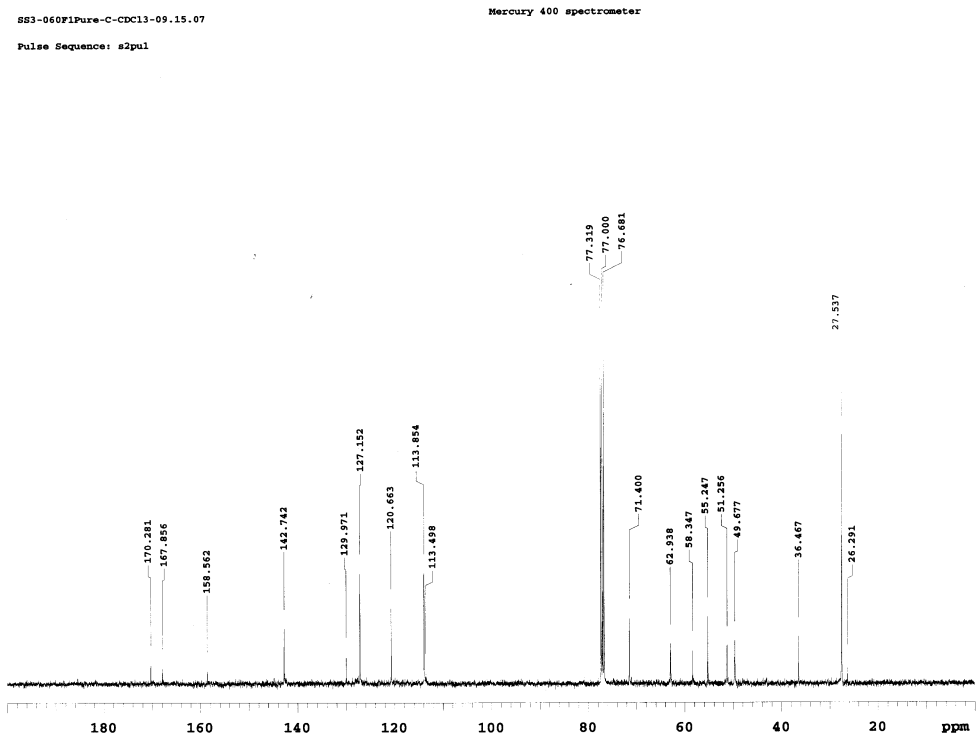
^{13}C NMR (Compound 37b)



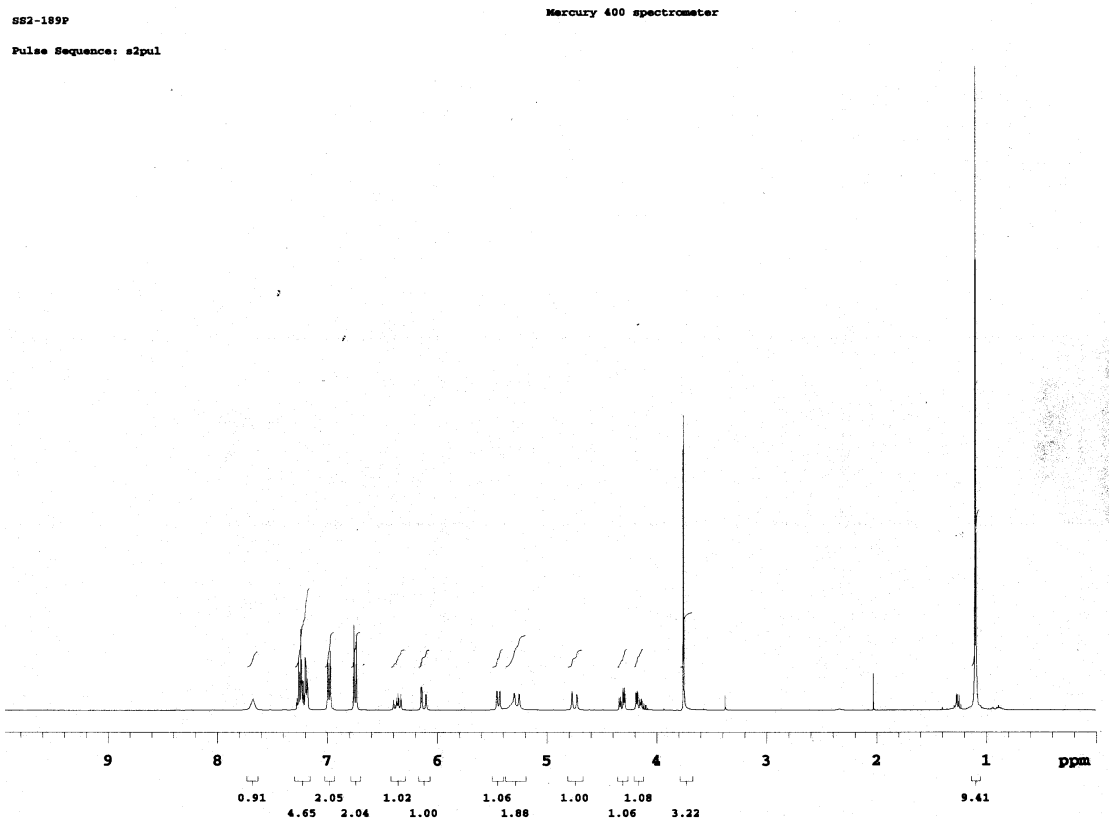
^{1}H NMR (Compound 41)



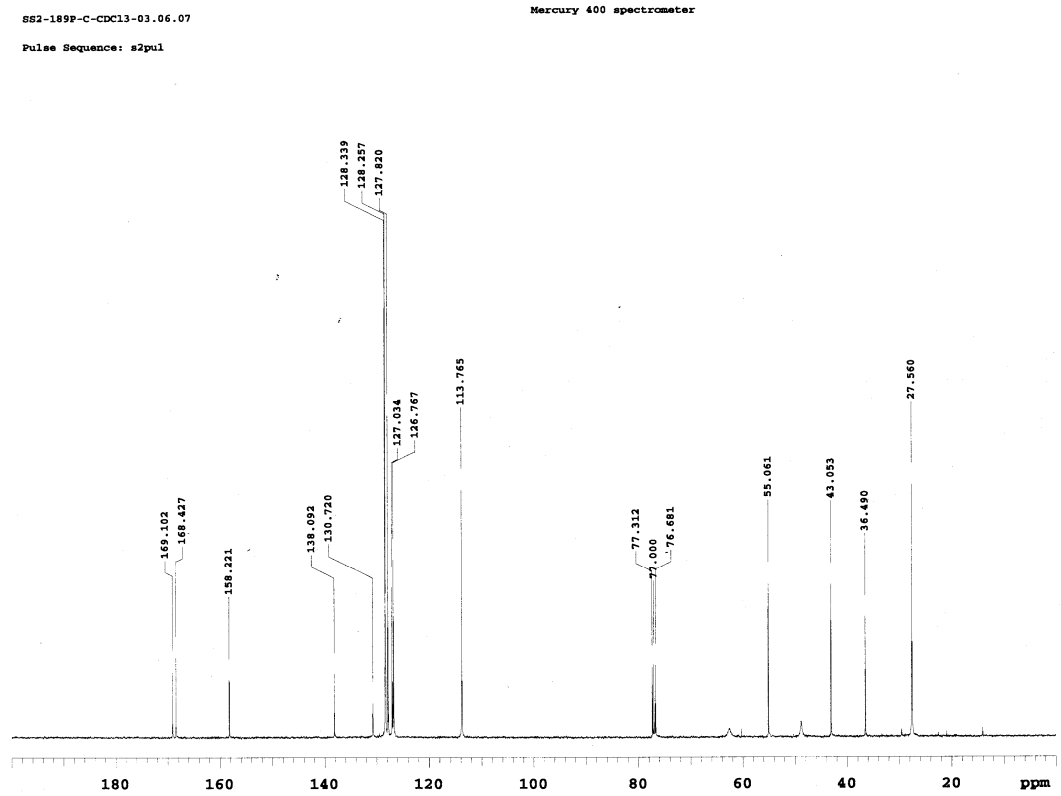
^{13}C NMR (Compound 41)



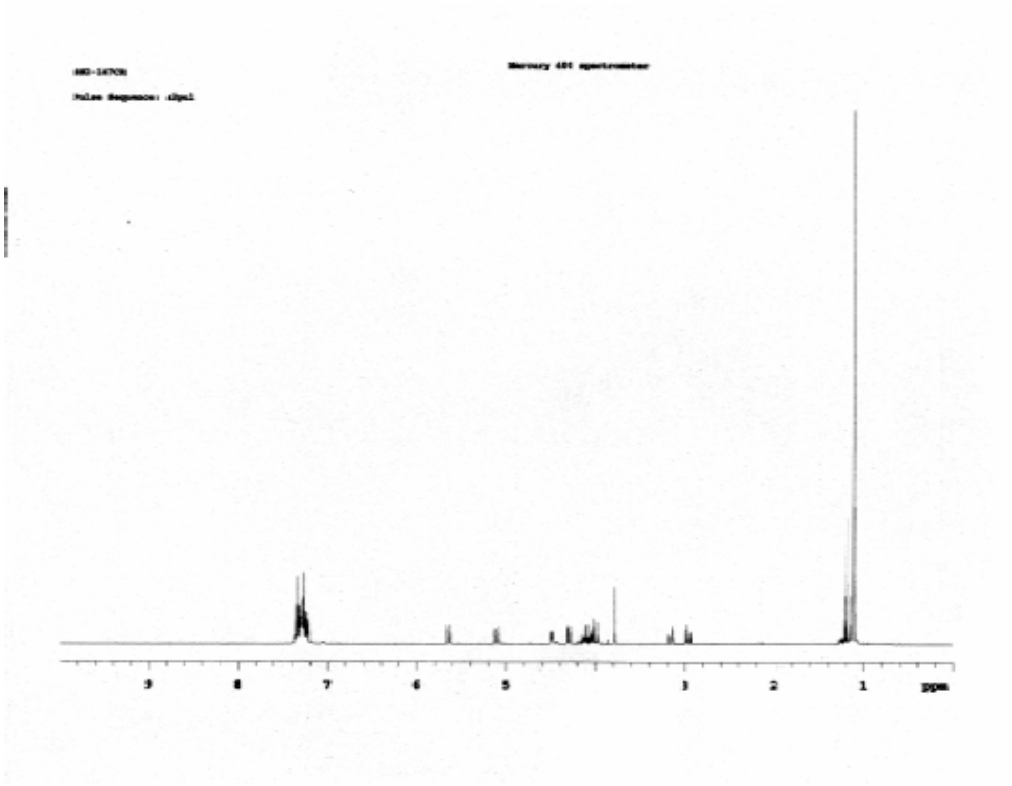
^{1}H NMR (Compound 44)



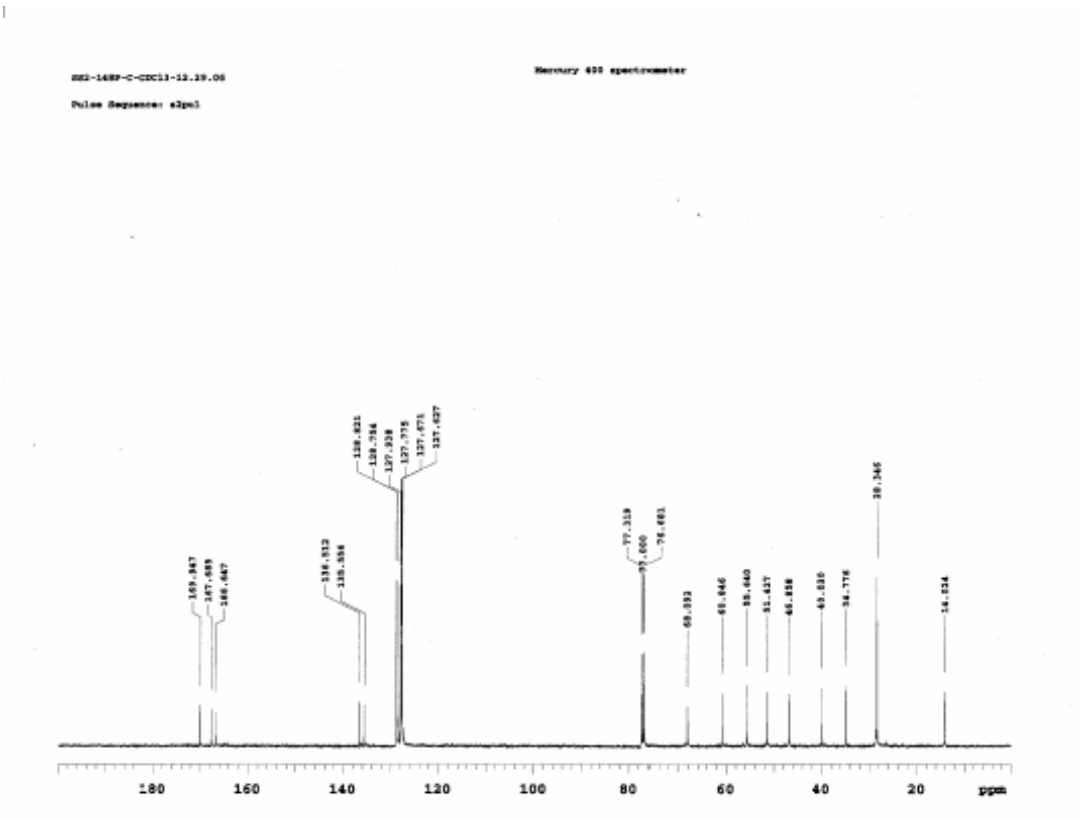
^{13}C NMR (Compound 44)



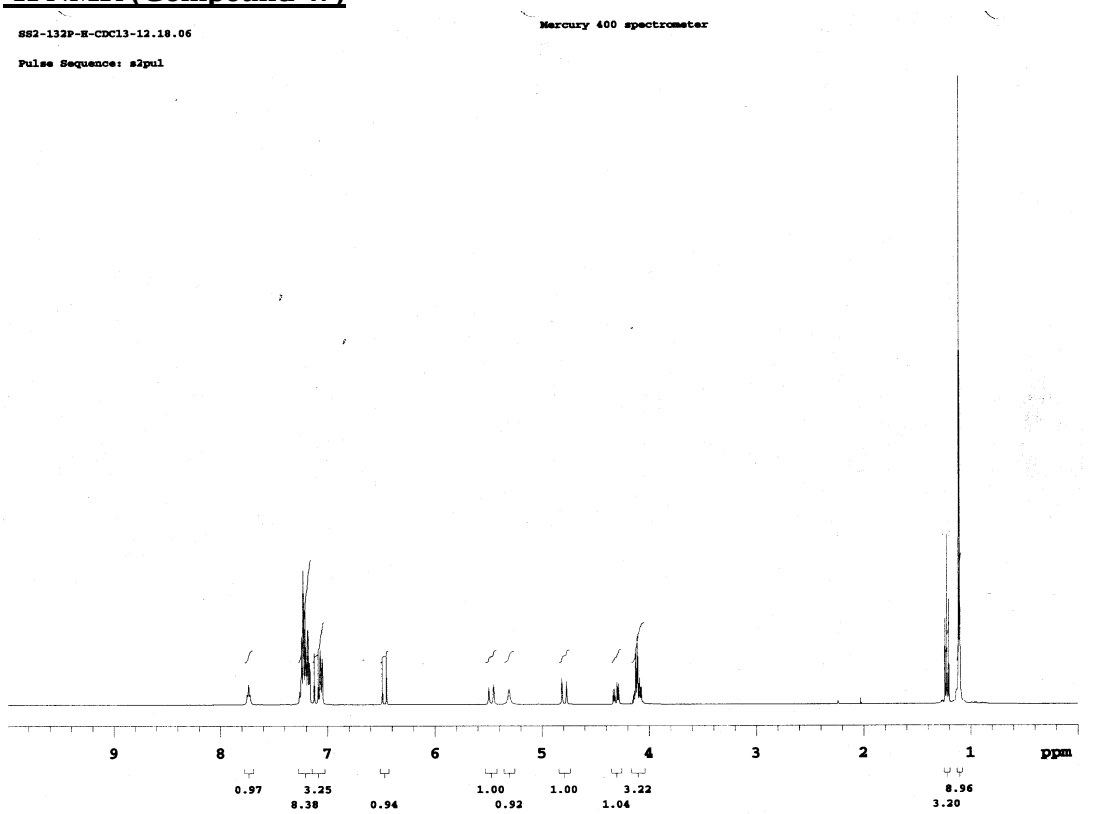
^{1}H NMR (Compound 46)



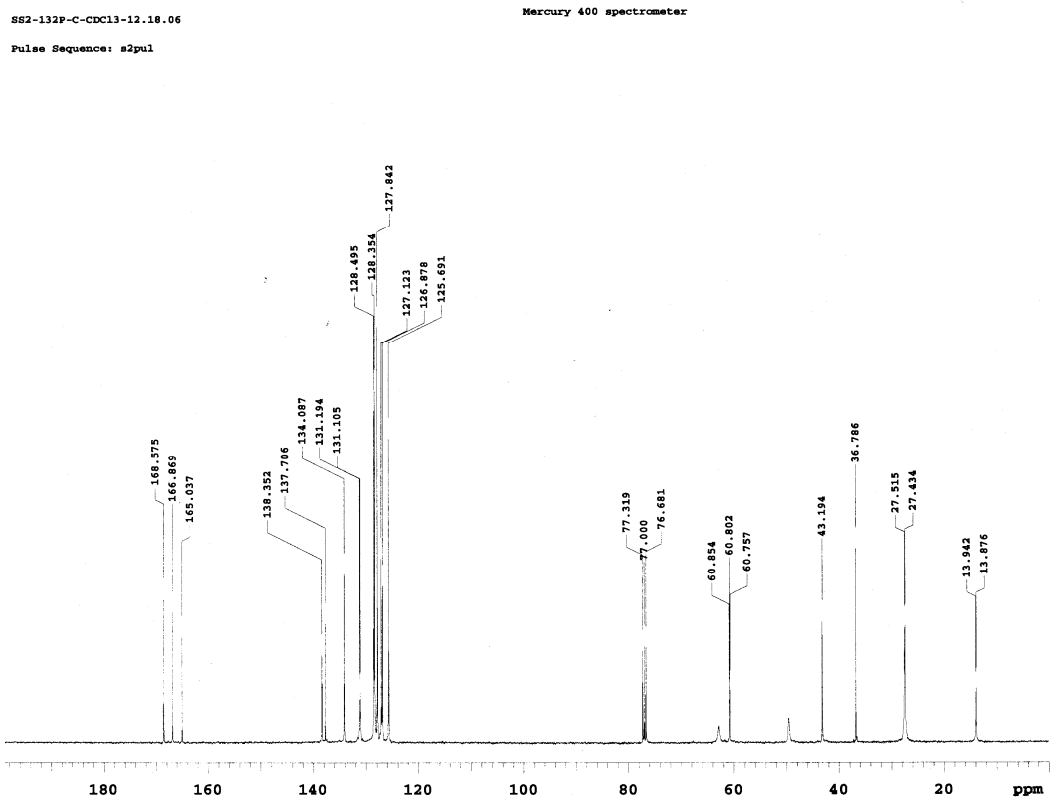
^{13}C NMR (Compound 46)



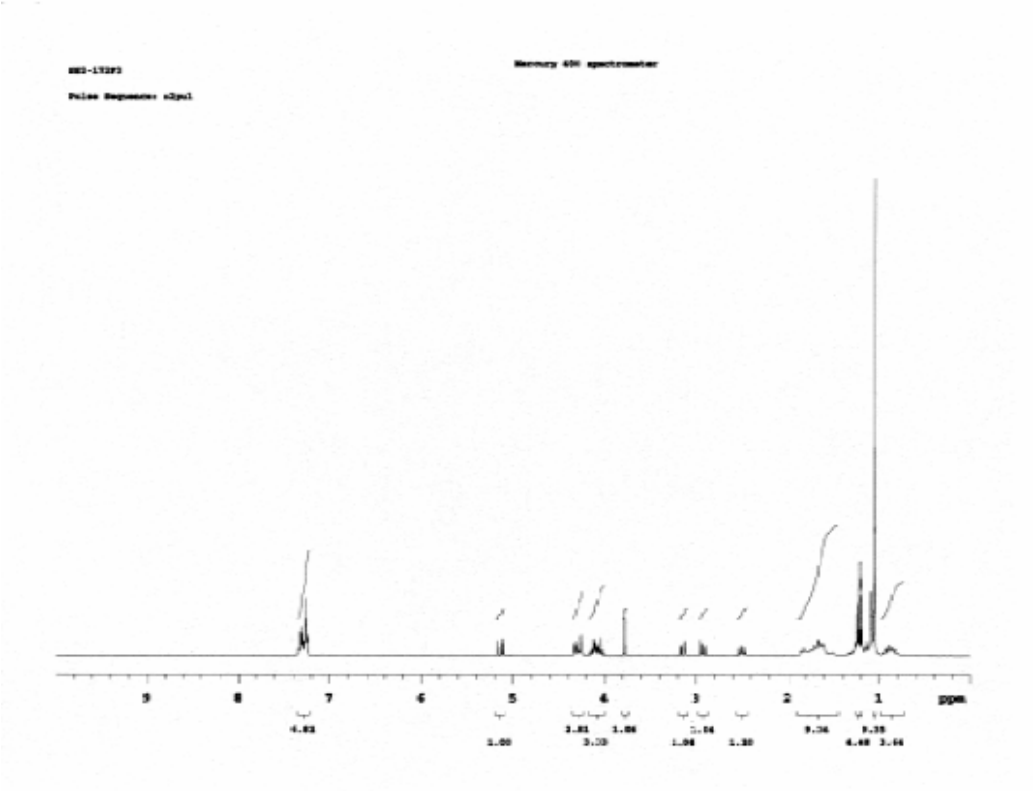
^{1}H NMR (Compound 47)



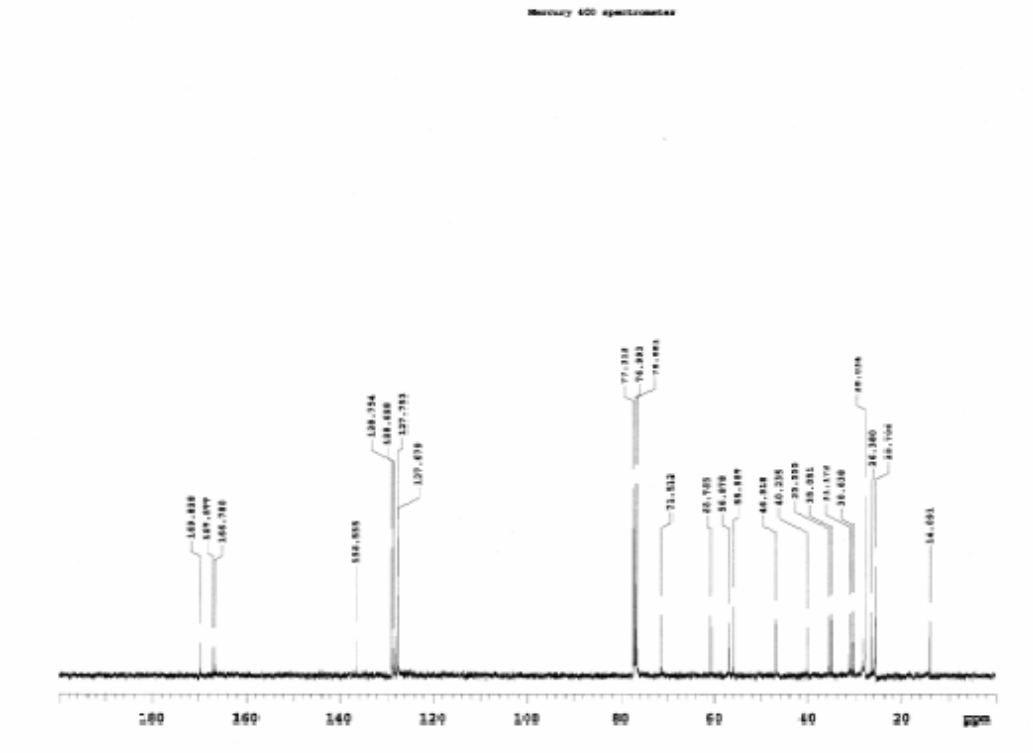
^{13}C NMR (Compound 47)



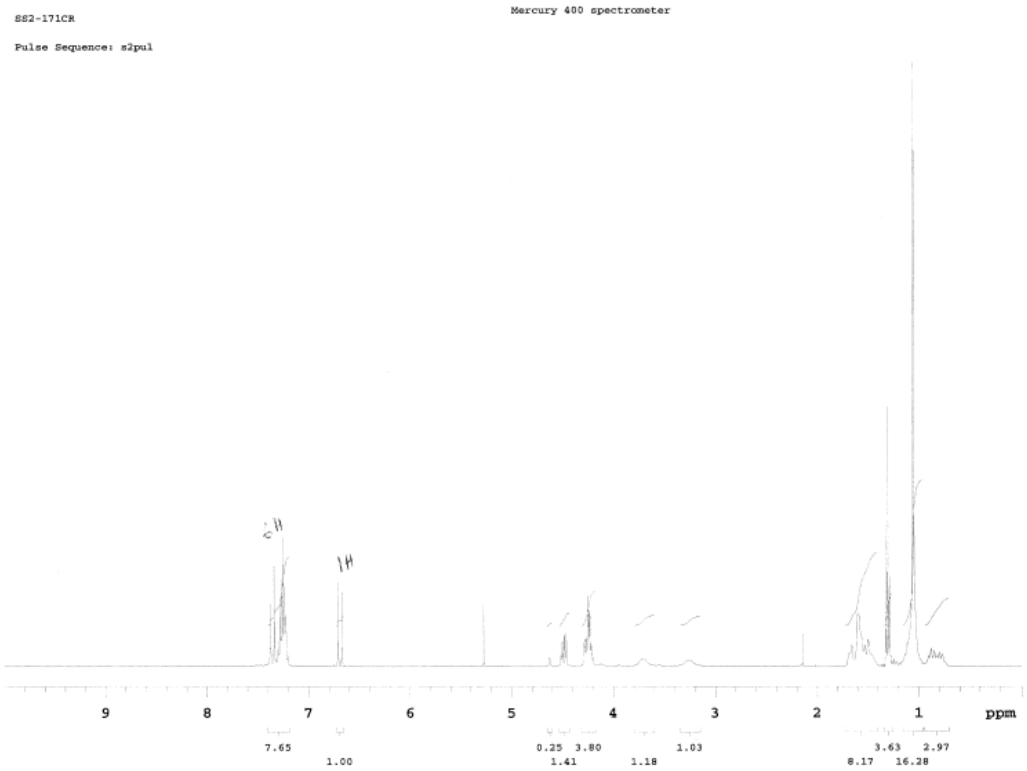
^{1}H NMR (Compound 48)



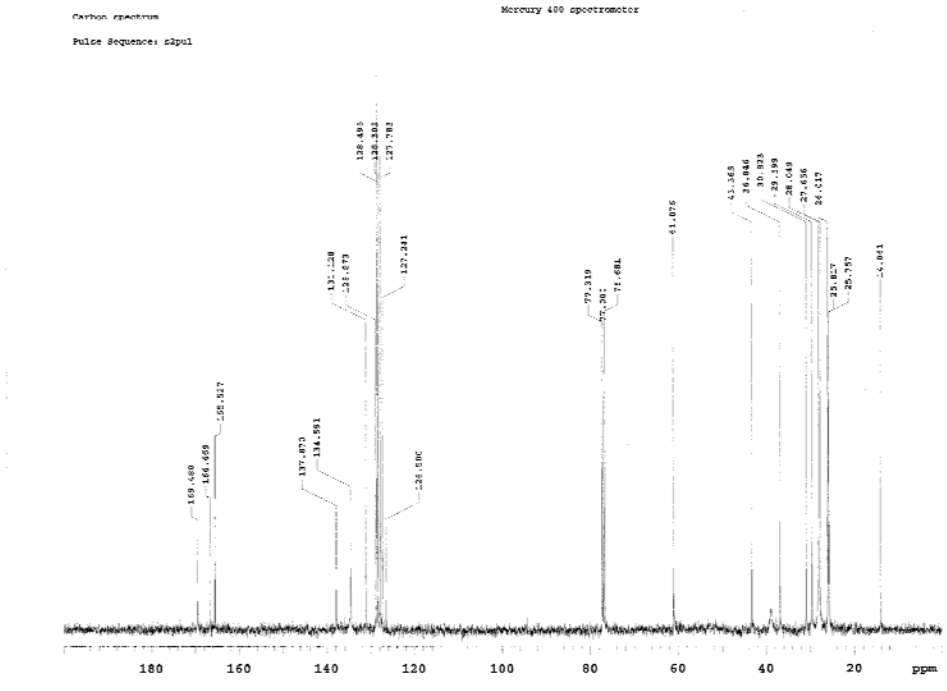
^{13}C NMR (compound 48)



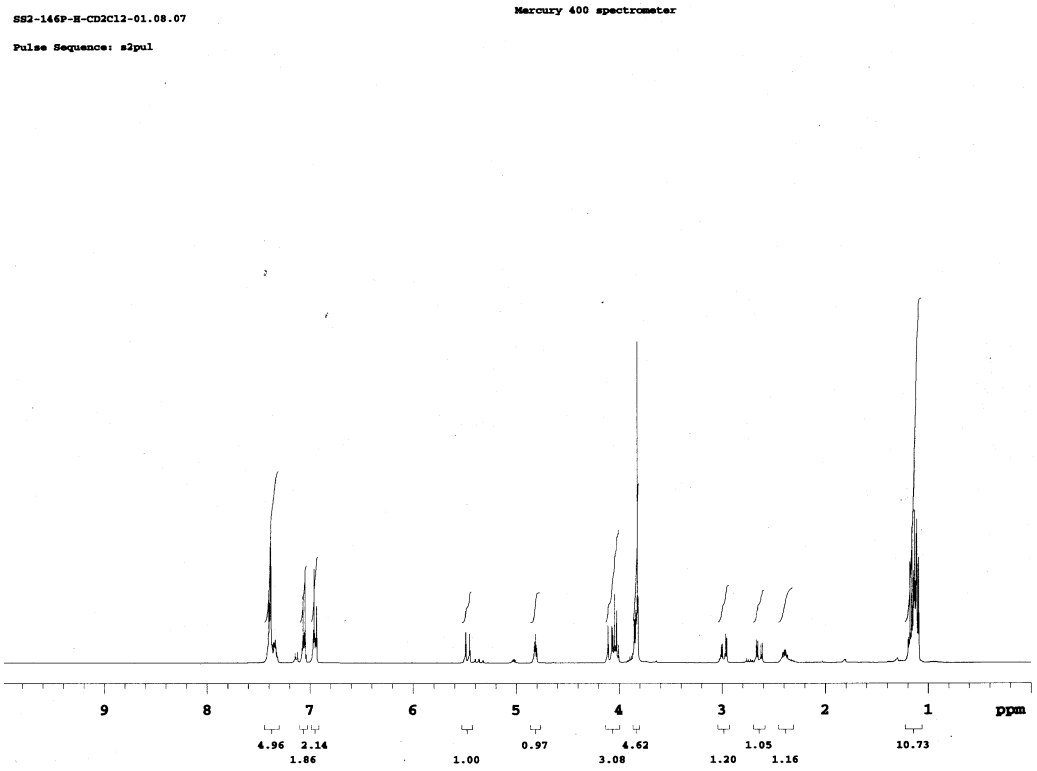
^{1}H NMR (Compound 49)



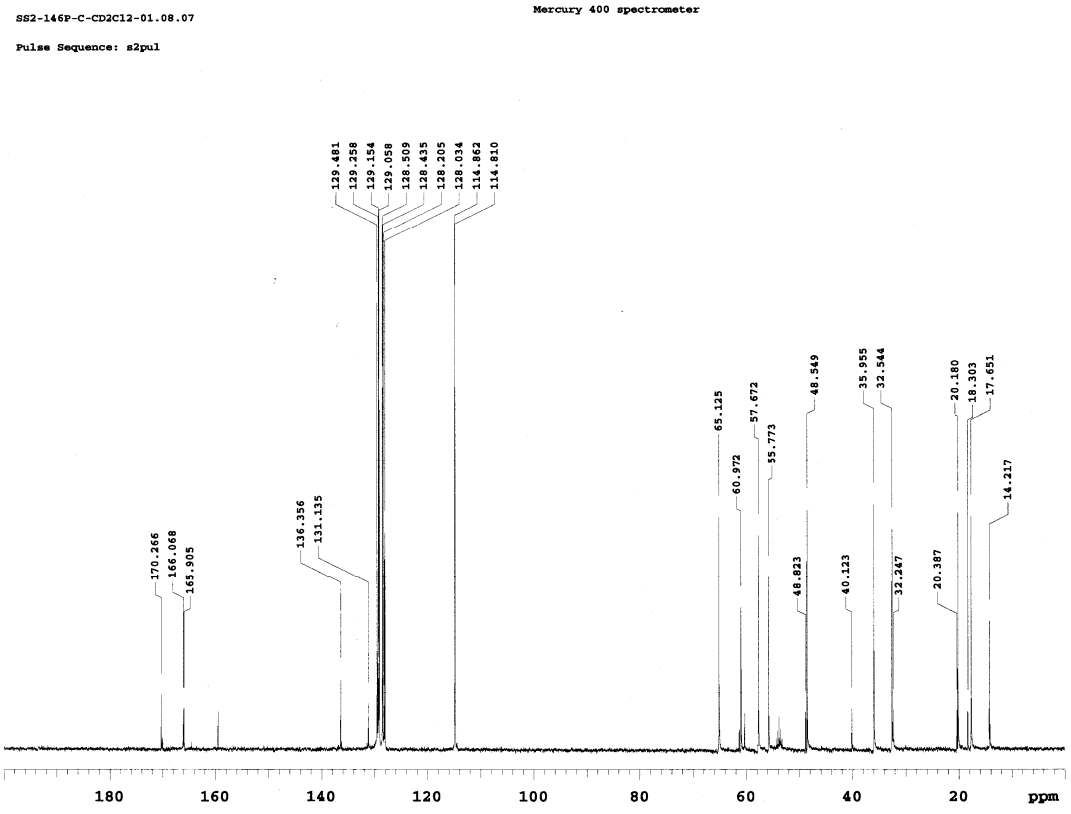
^{13}C NMR (Compound 49)



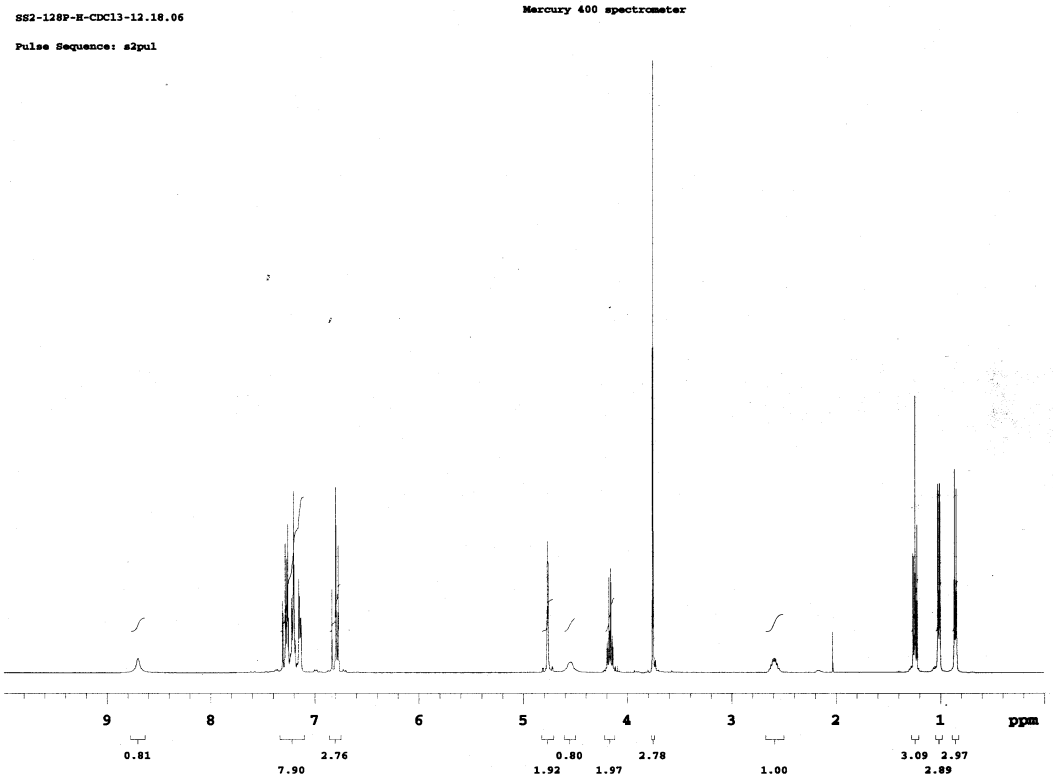
^{1}H NMR (Compound 50)



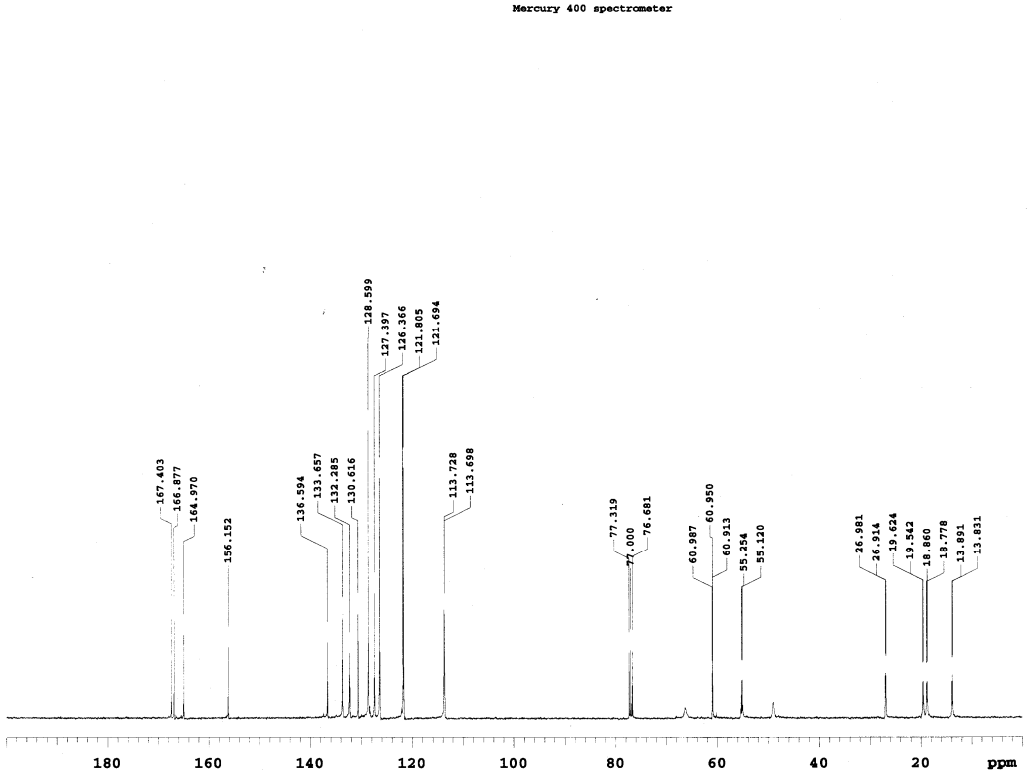
^{13}C NMR (Compound 50)



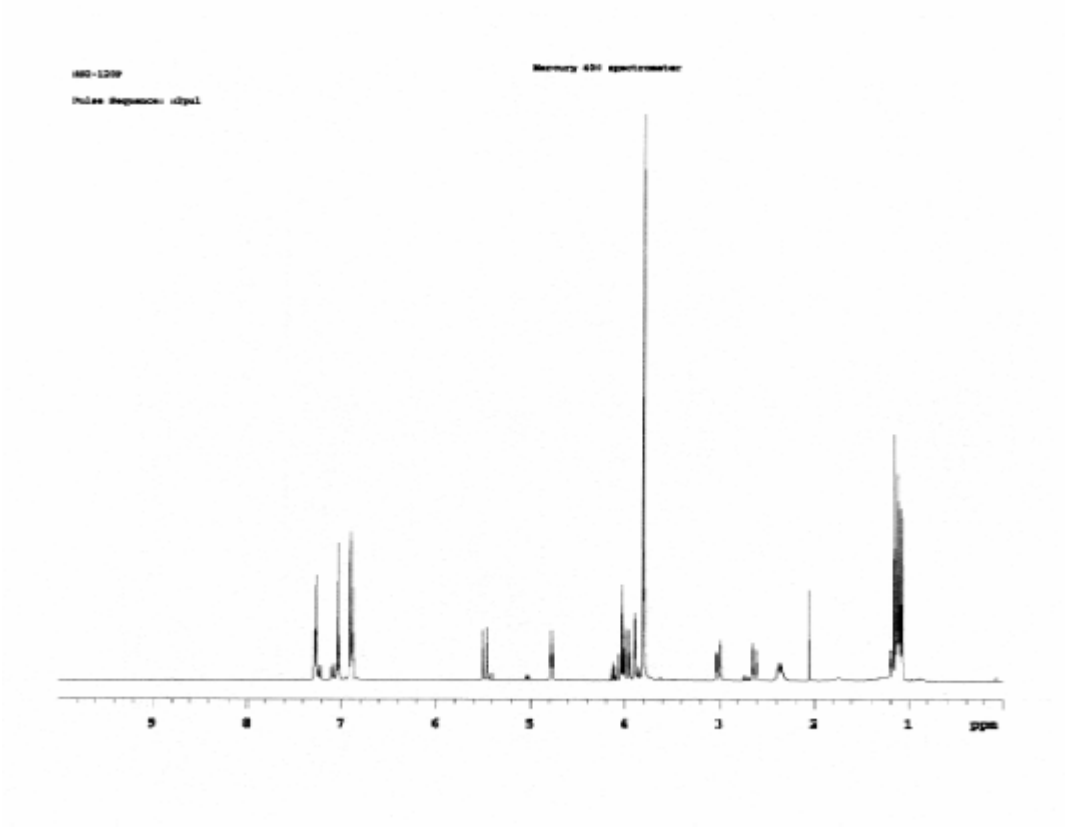
^{1}H NMR (Compound 51)



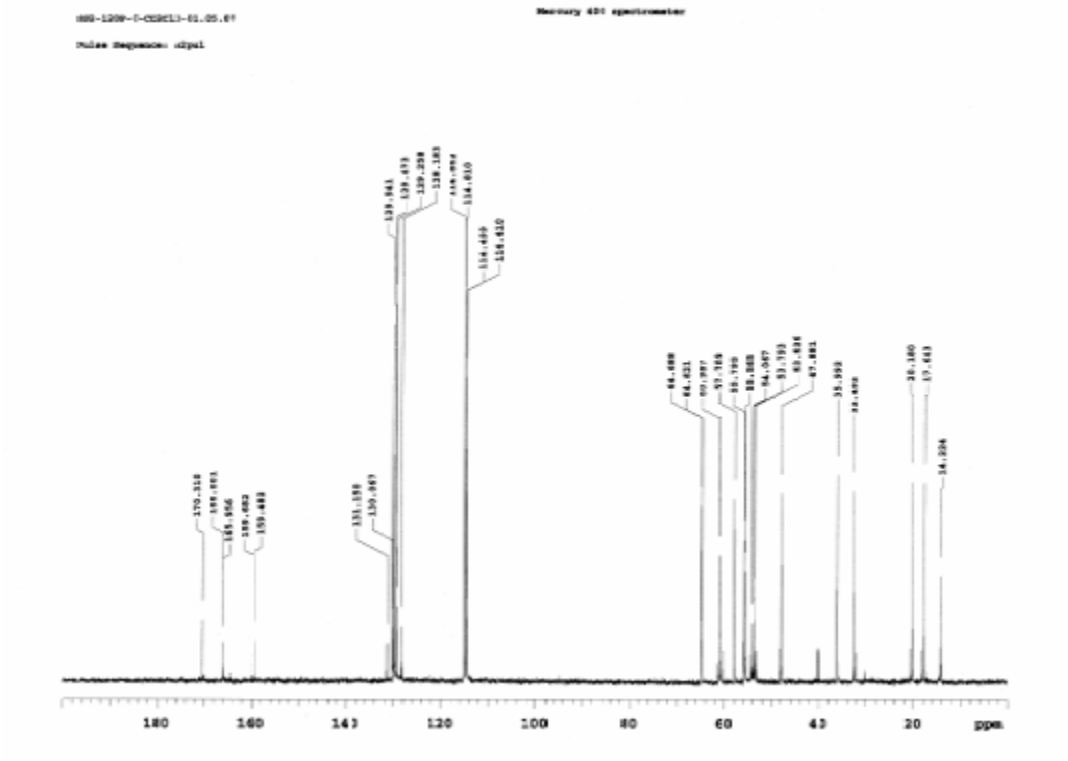
^{13}C NMR (Compound 51)



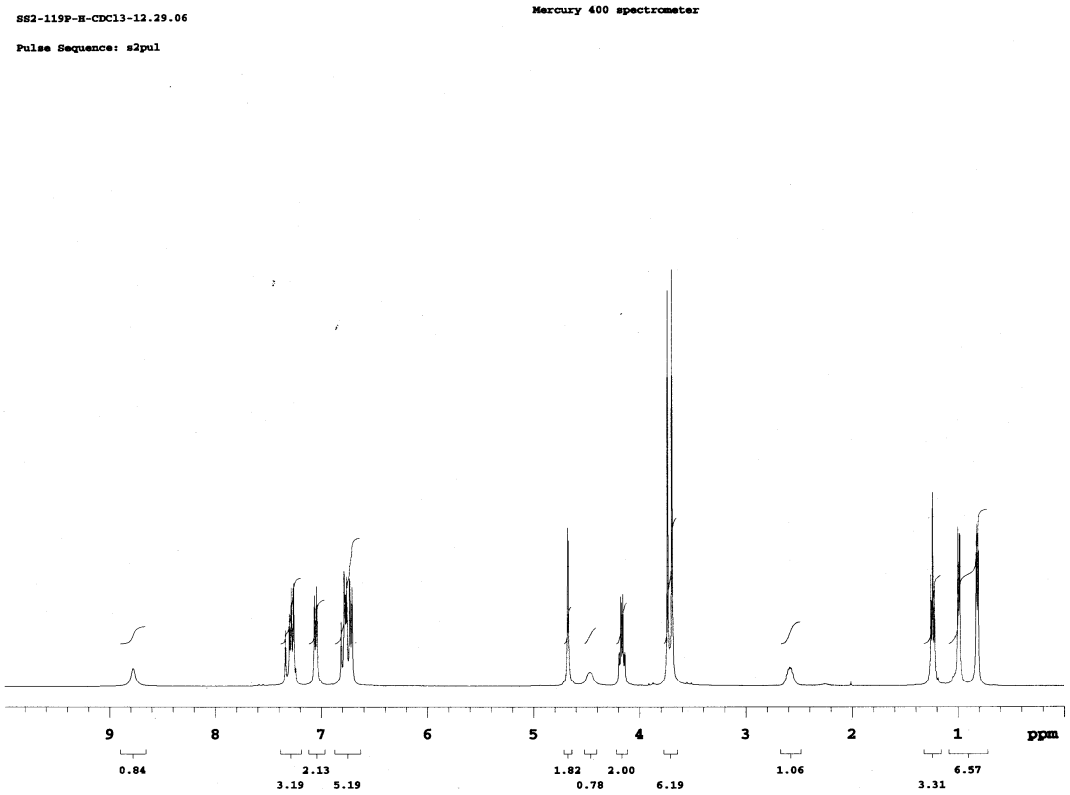
[1]H NMR (Compound 52)



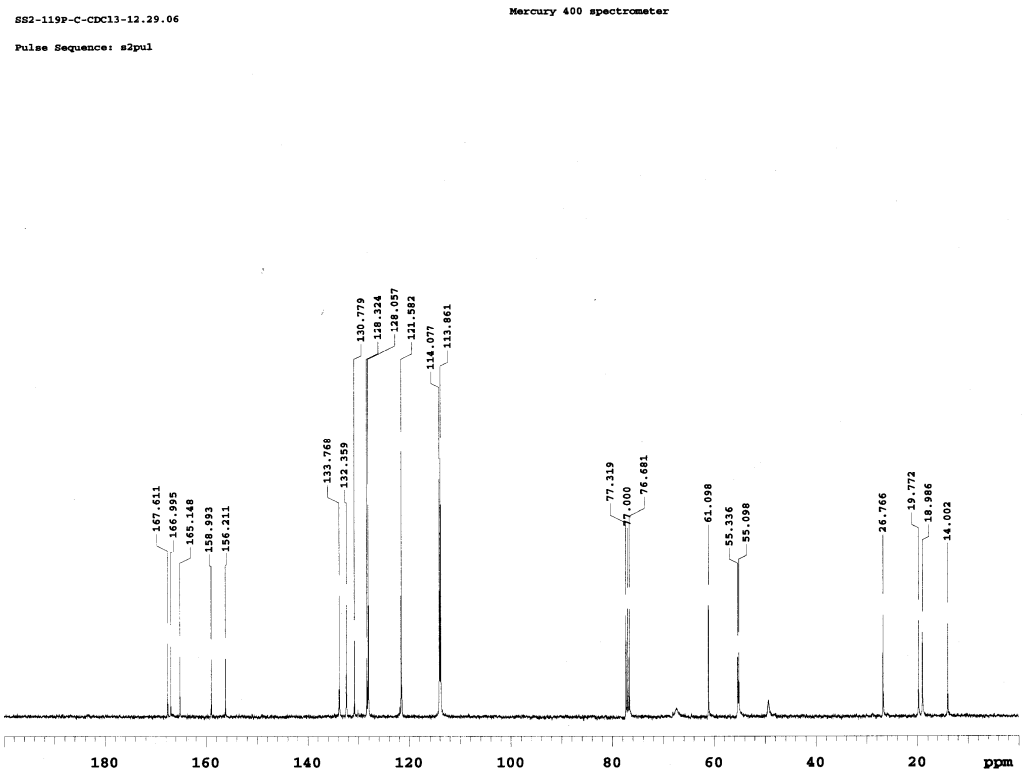
[13]C NMR (Compound 52)



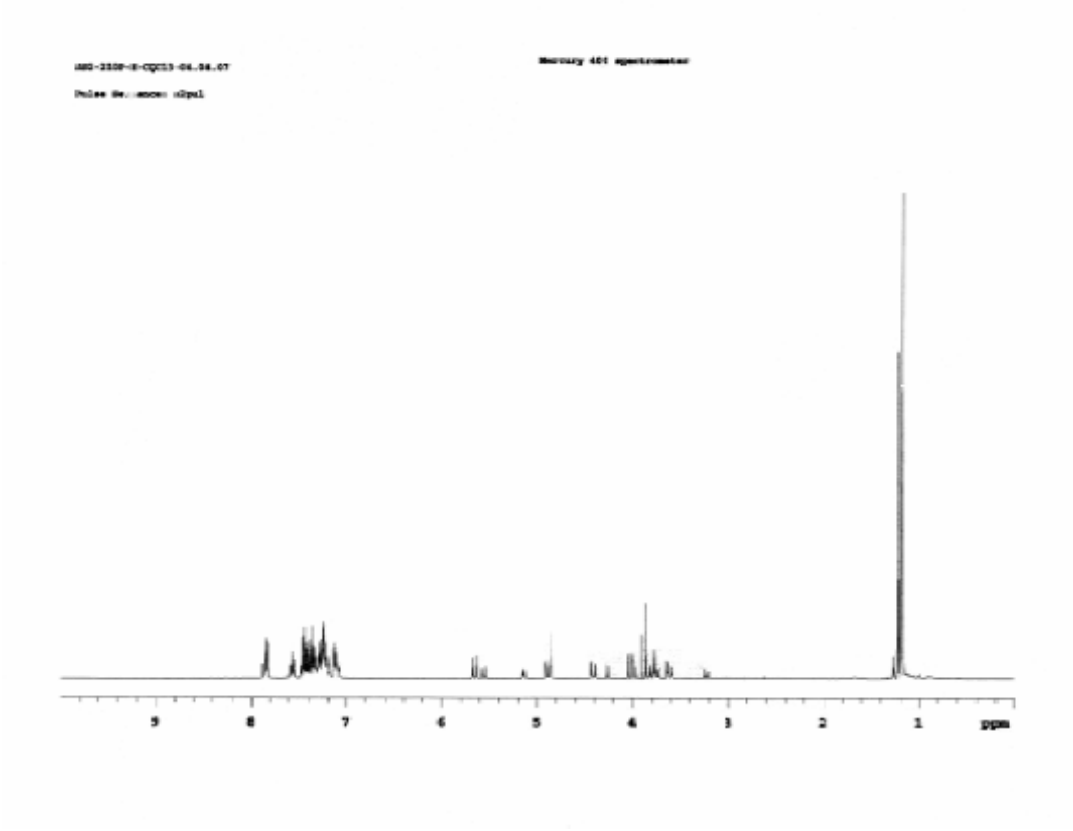
^{1}H NMR (Compound 53)



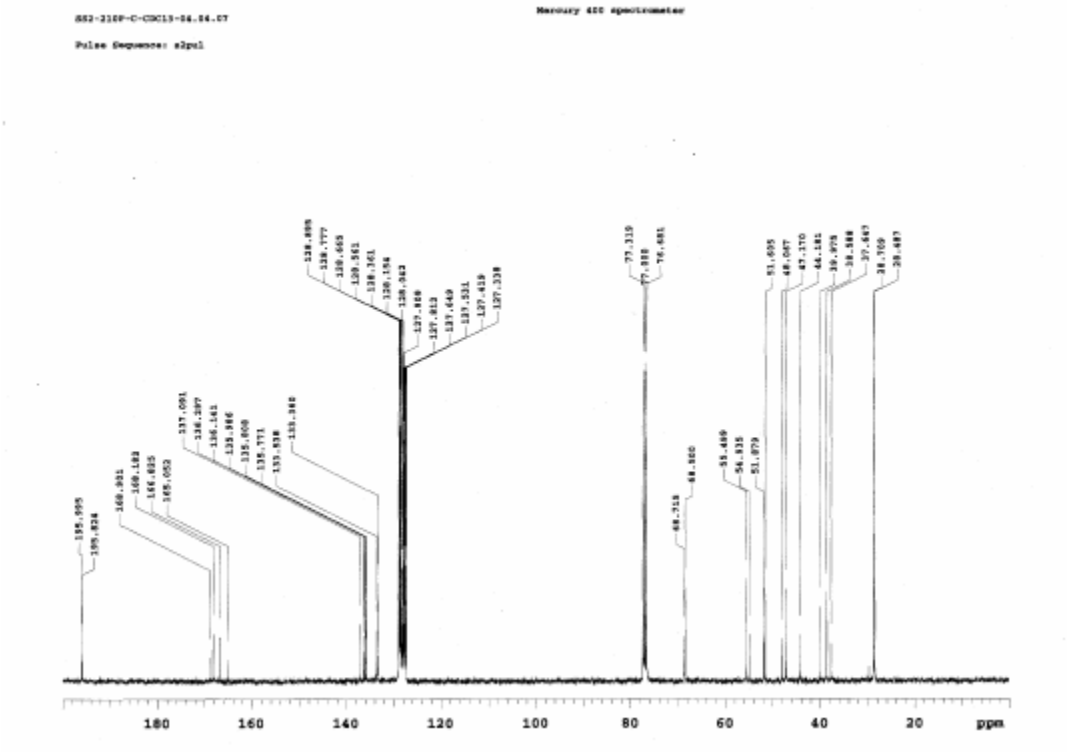
^{13}C NMR (Compound 53)



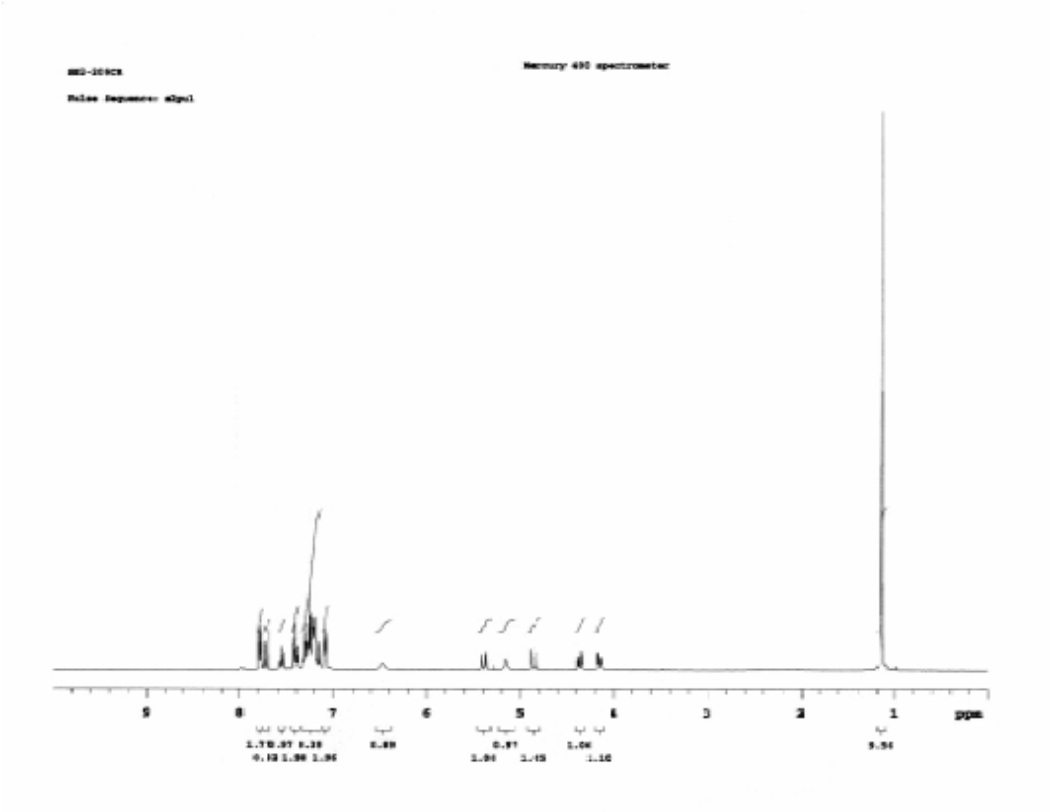
[1]H NMR (Compound 54)



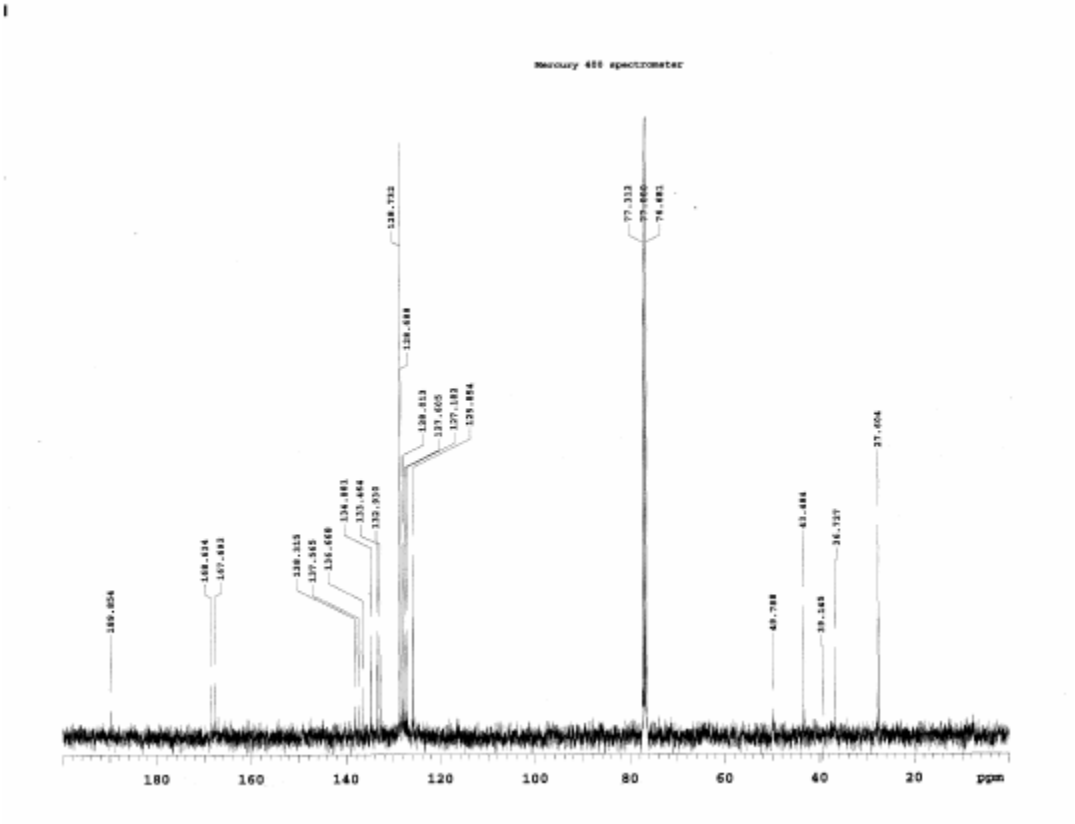
[13]C NMR (Compound 54)



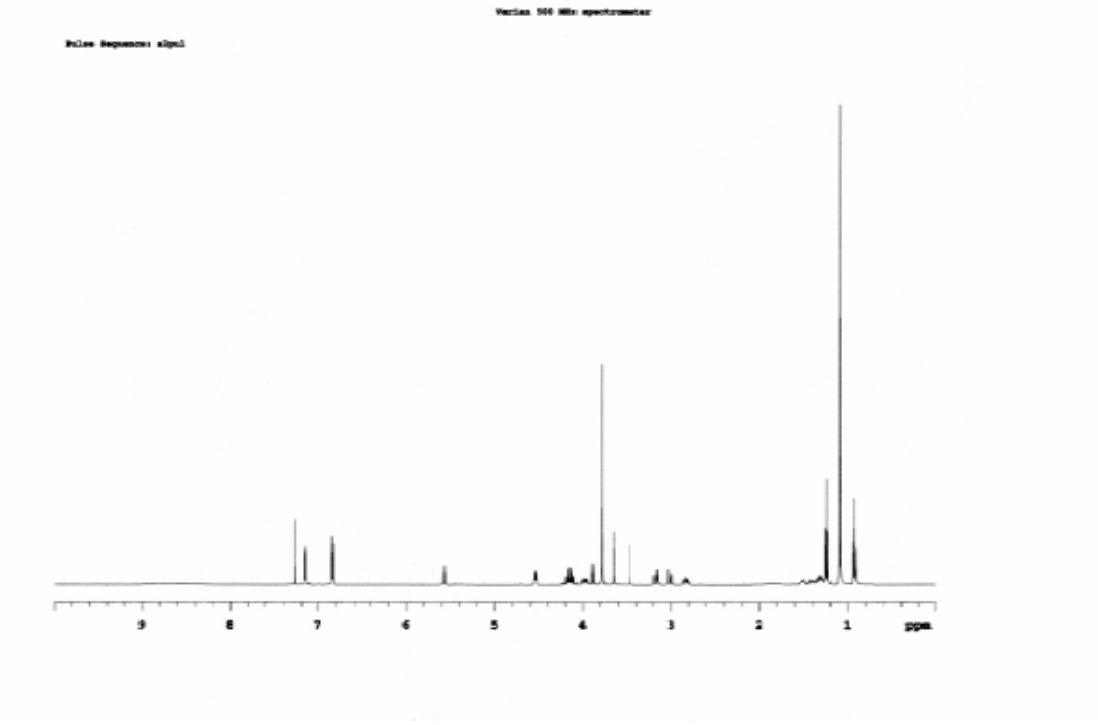
^{1}H NMR (Compound 55)



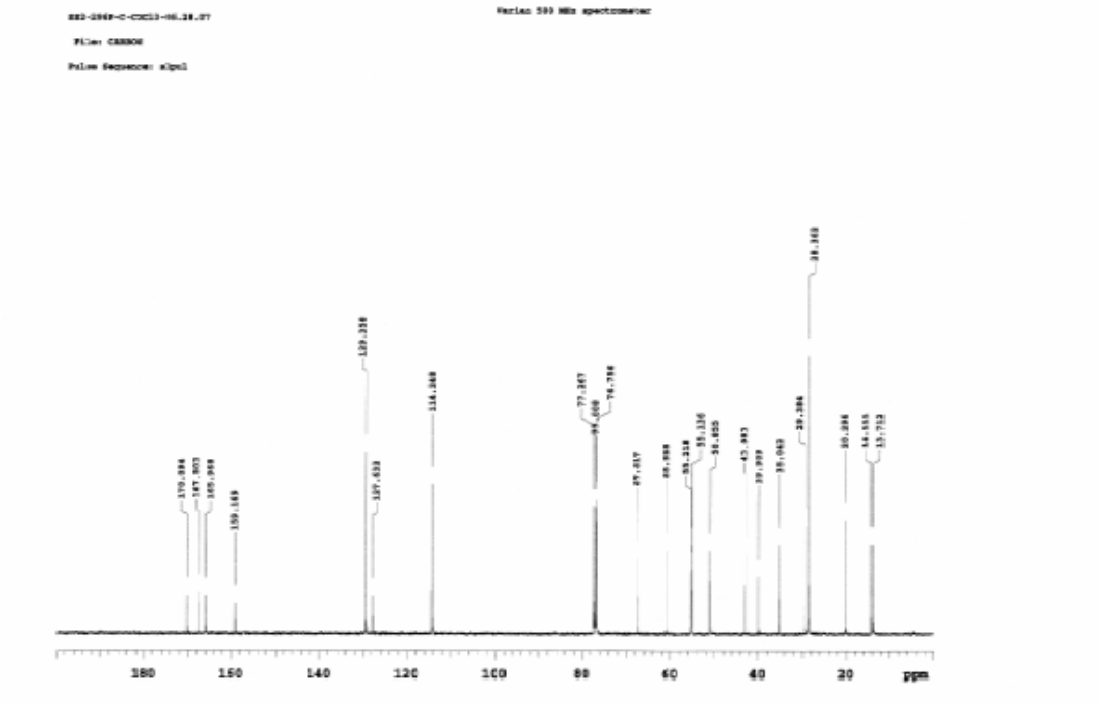
^{13}C NMR (Compound 55)



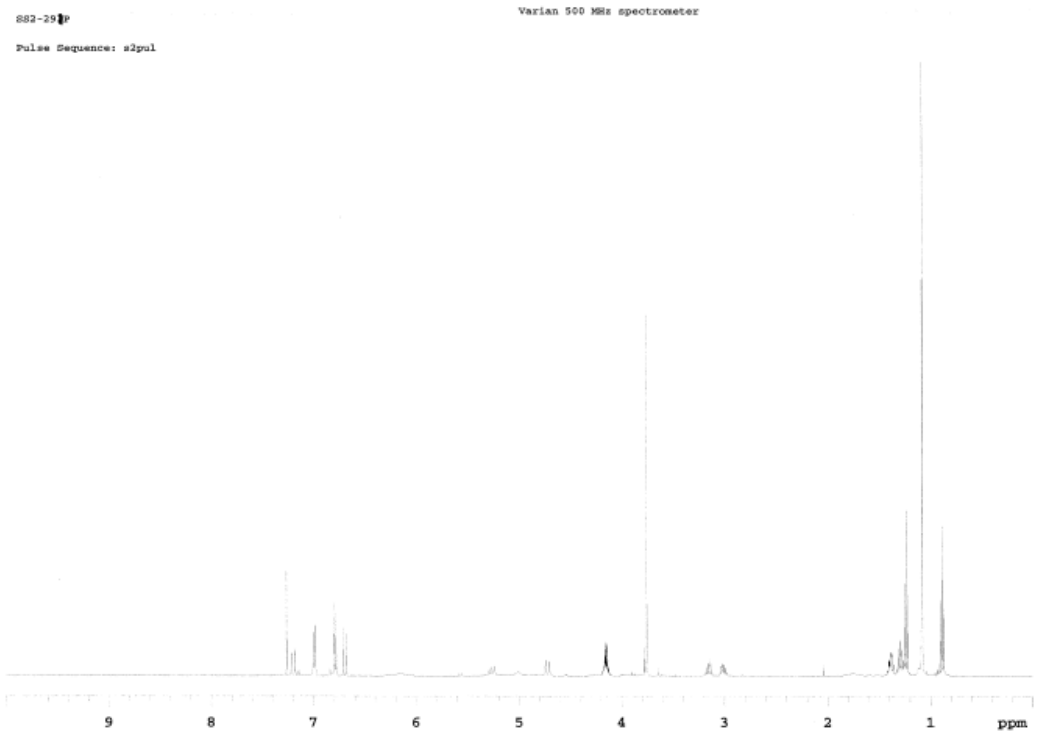
^{1}H NMR (Compound 56)



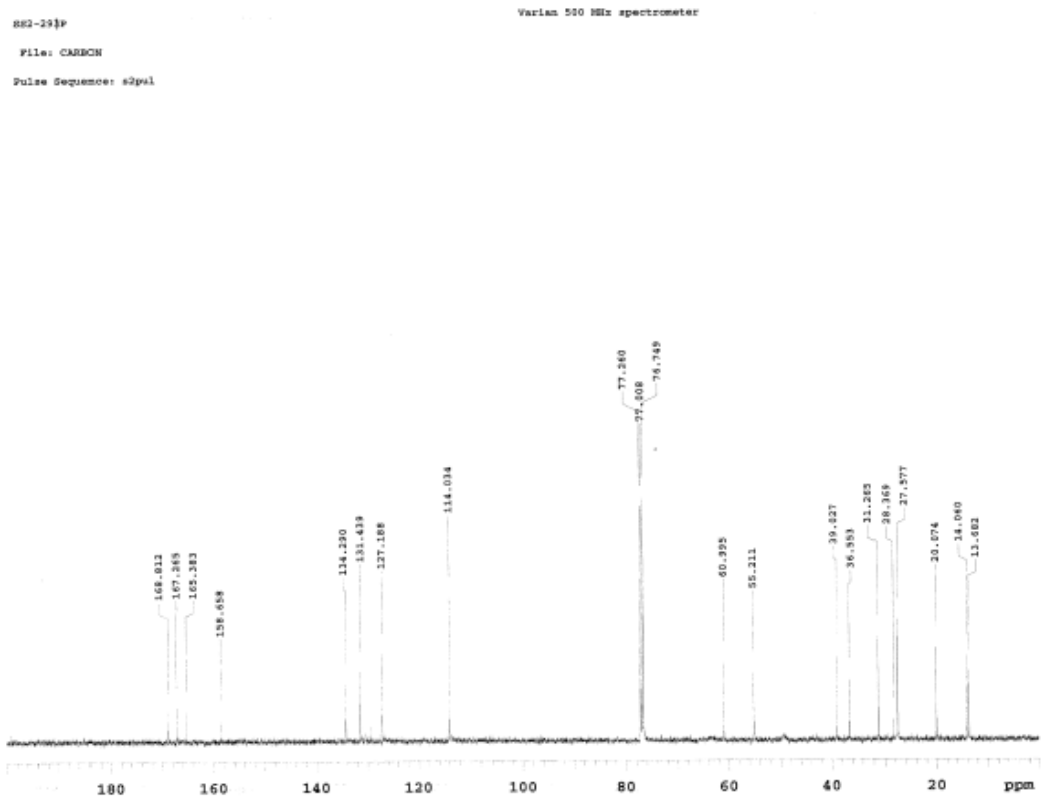
^{13}C NMR (Compound 56)



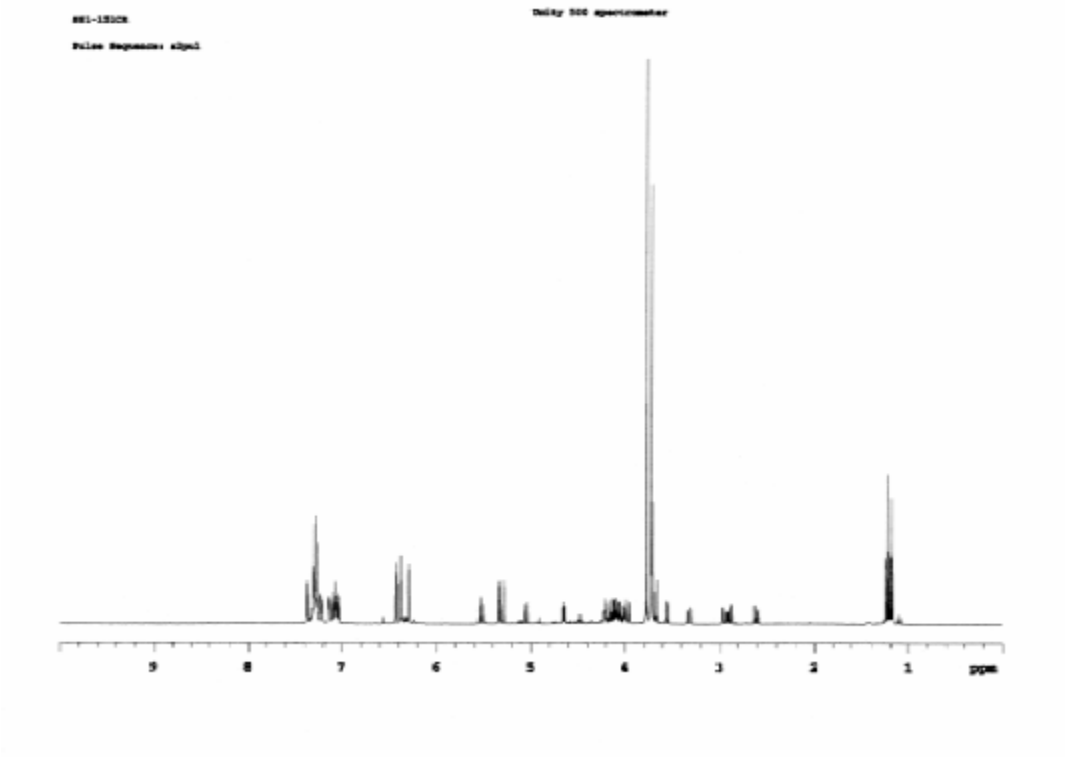
^{1}H NMR (Compound 57)



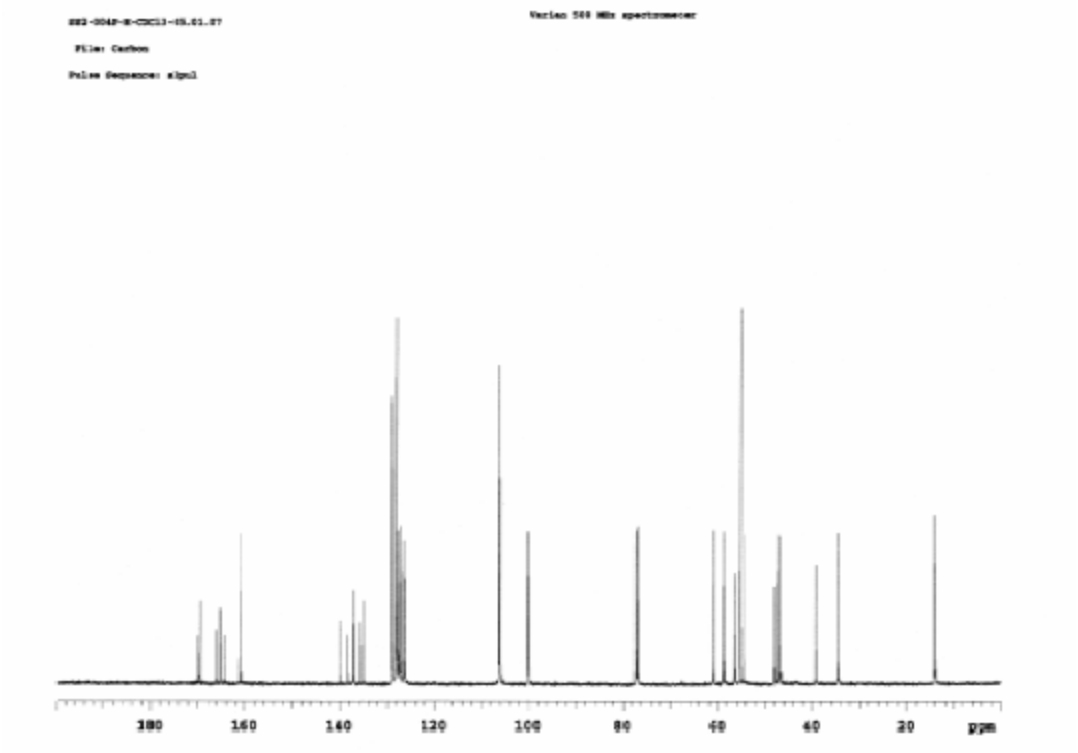
^{13}C NMR (Compound 57)



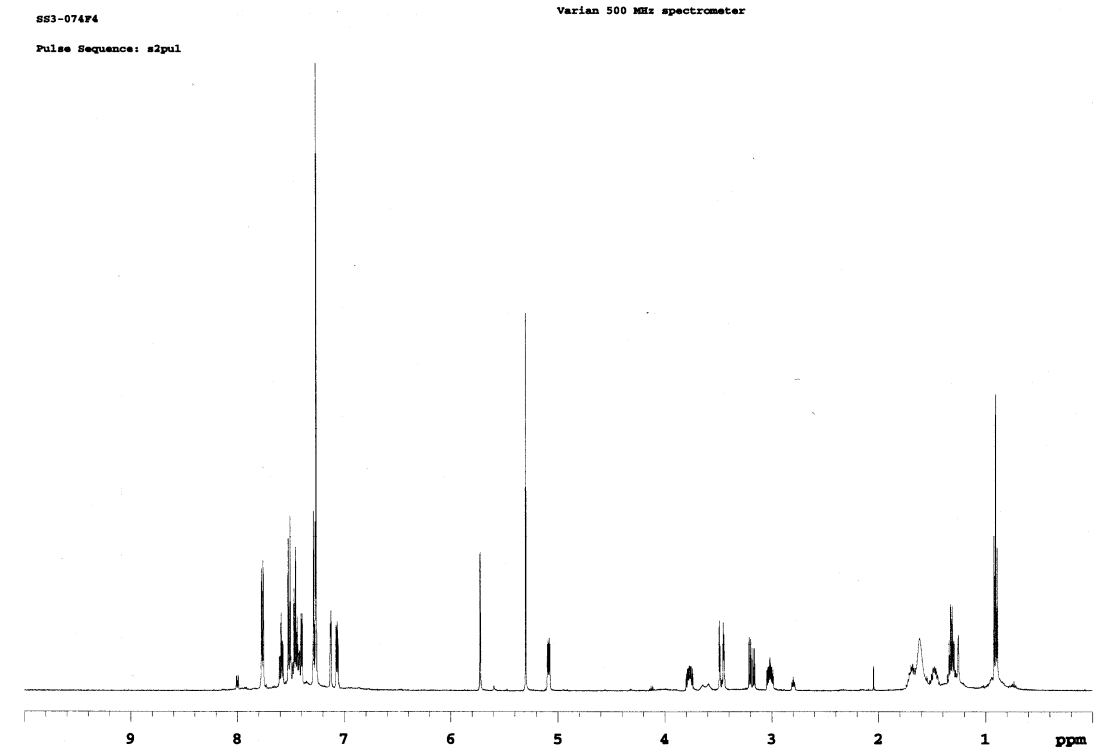
[1]H NMR (Compound 58)



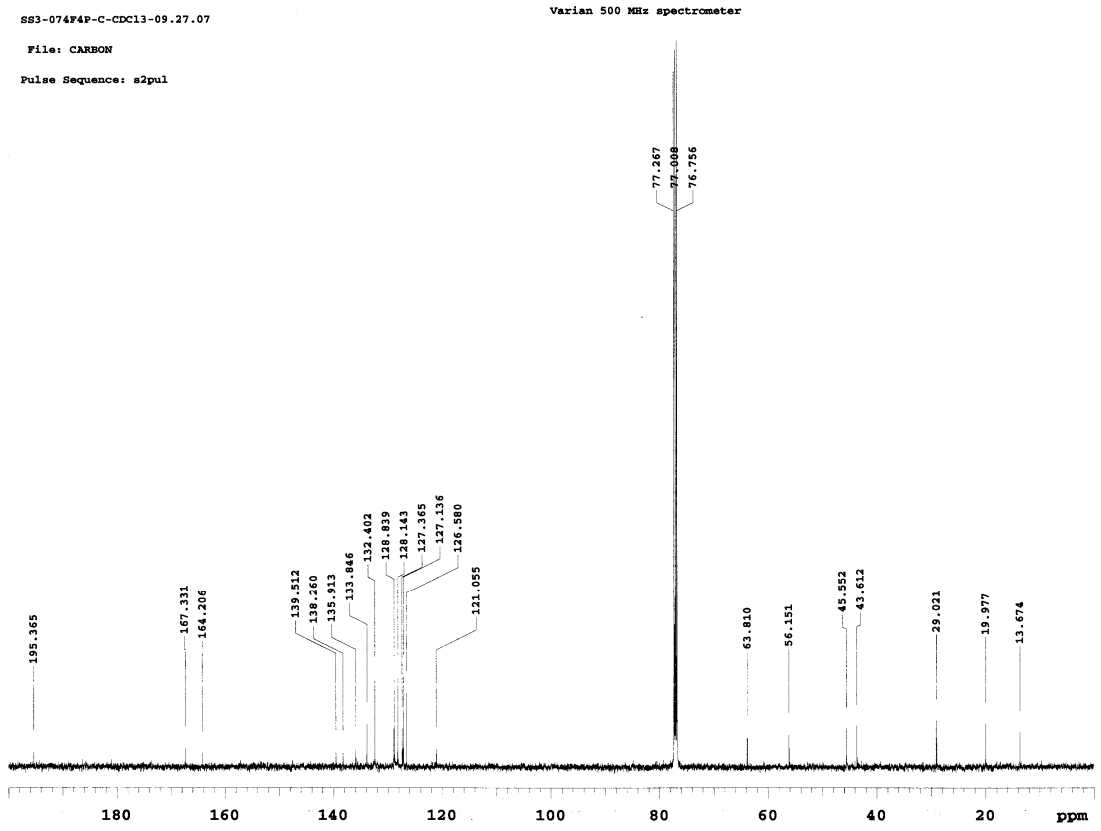
[13]C NMR (Compound 58)



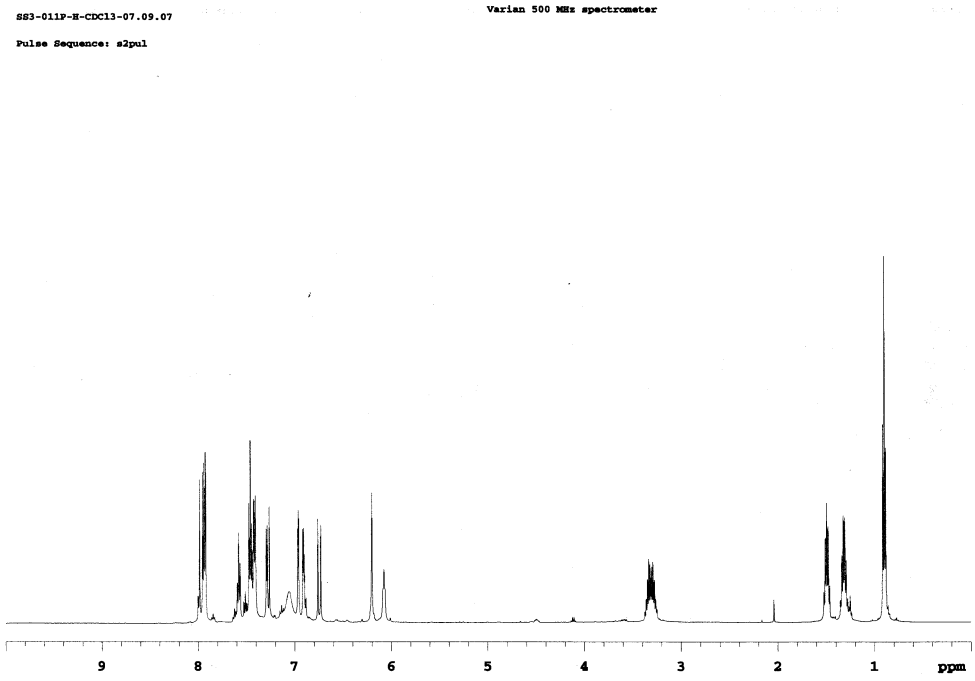
^{1}H NMR (Compound 59)



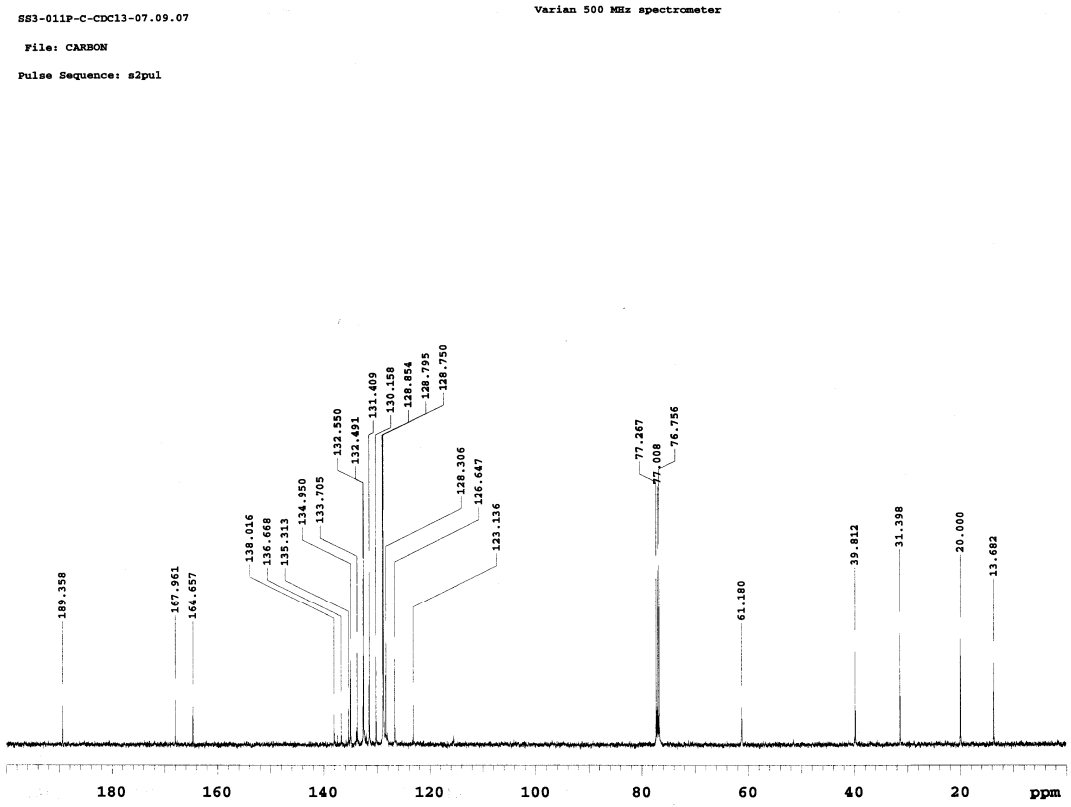
^{13}C NMR (Compound 59)



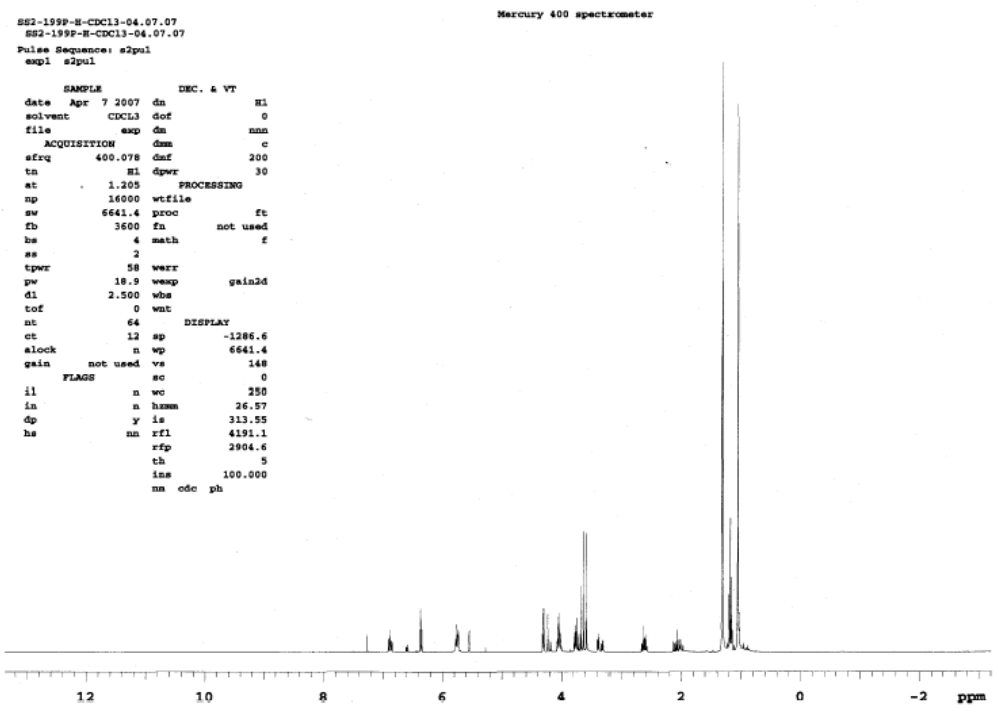
^{1}H NMR (Compound 59a)



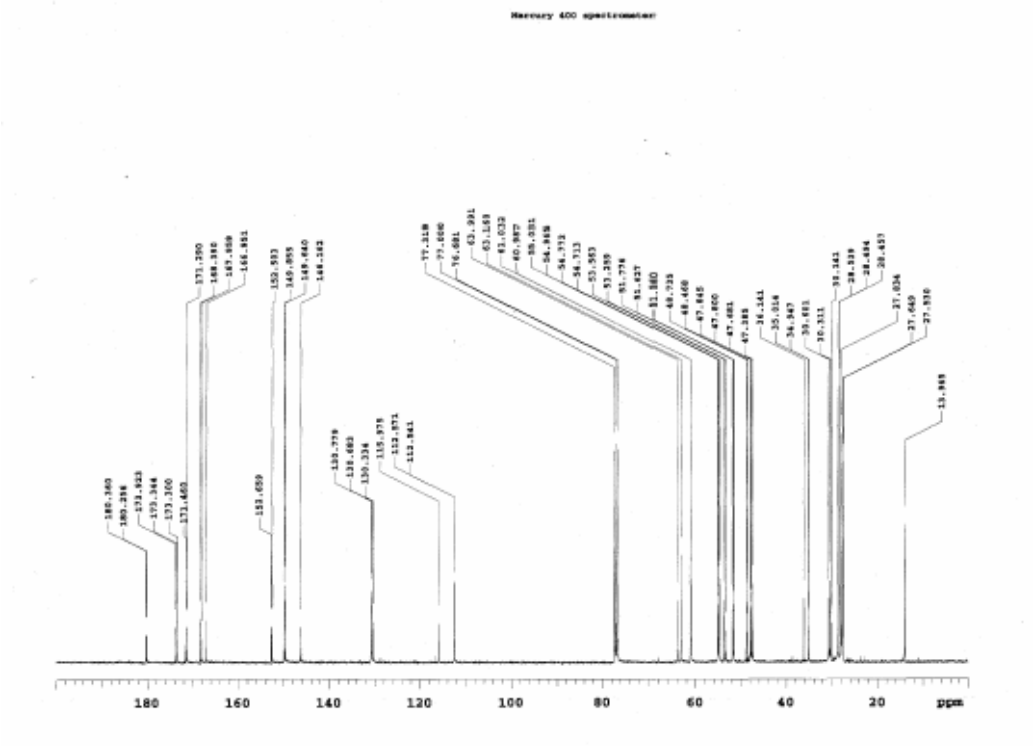
^{13}C NMR (Compound 59a)



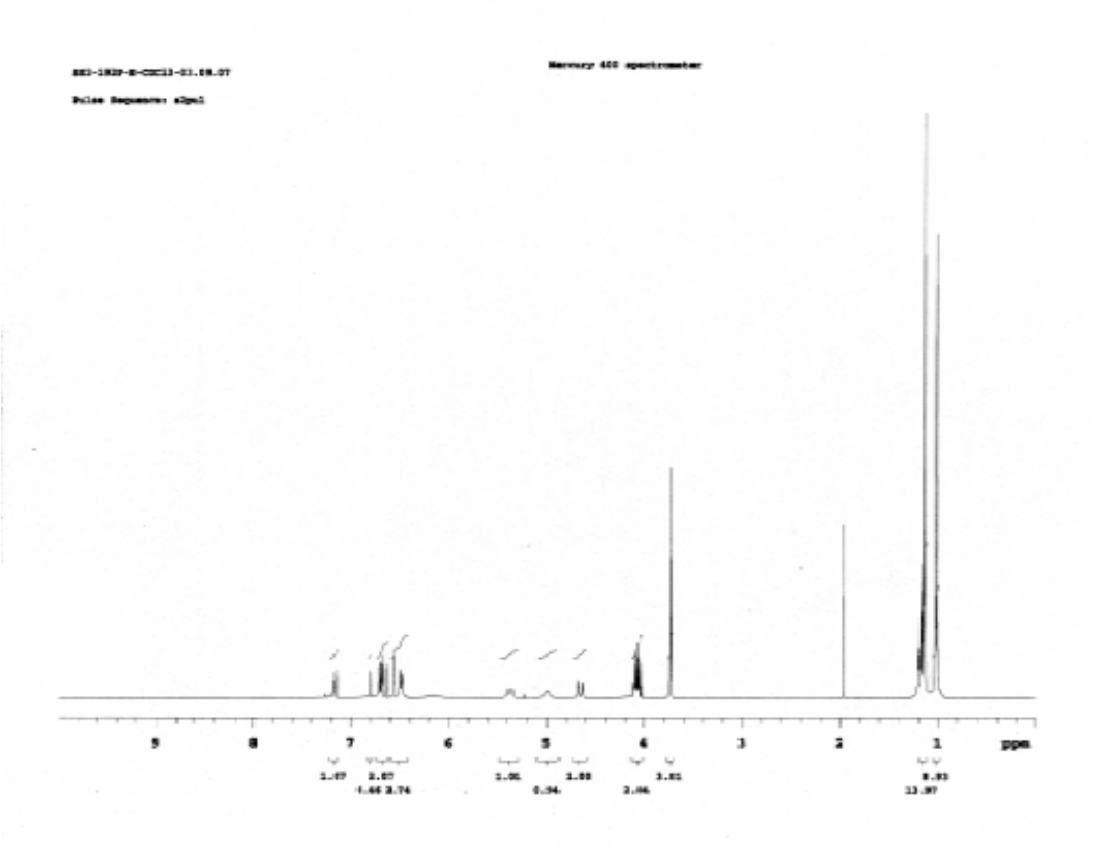
^{1}H NMR (Compound 60)



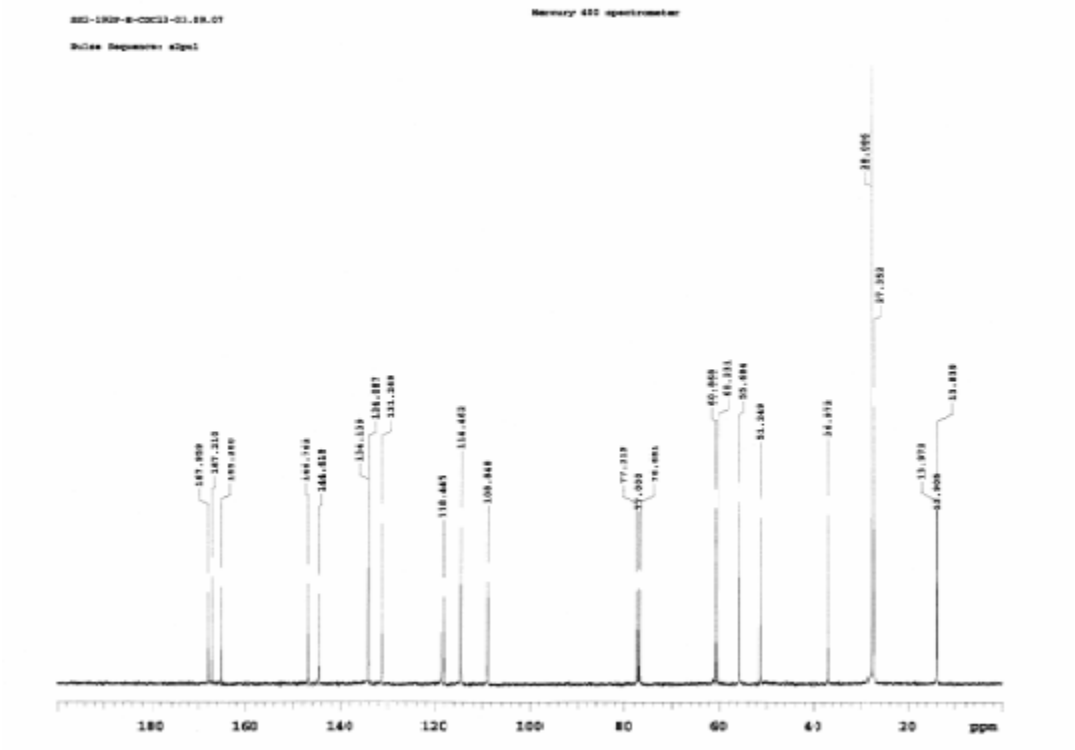
^{13}C NMR (Compound 60)



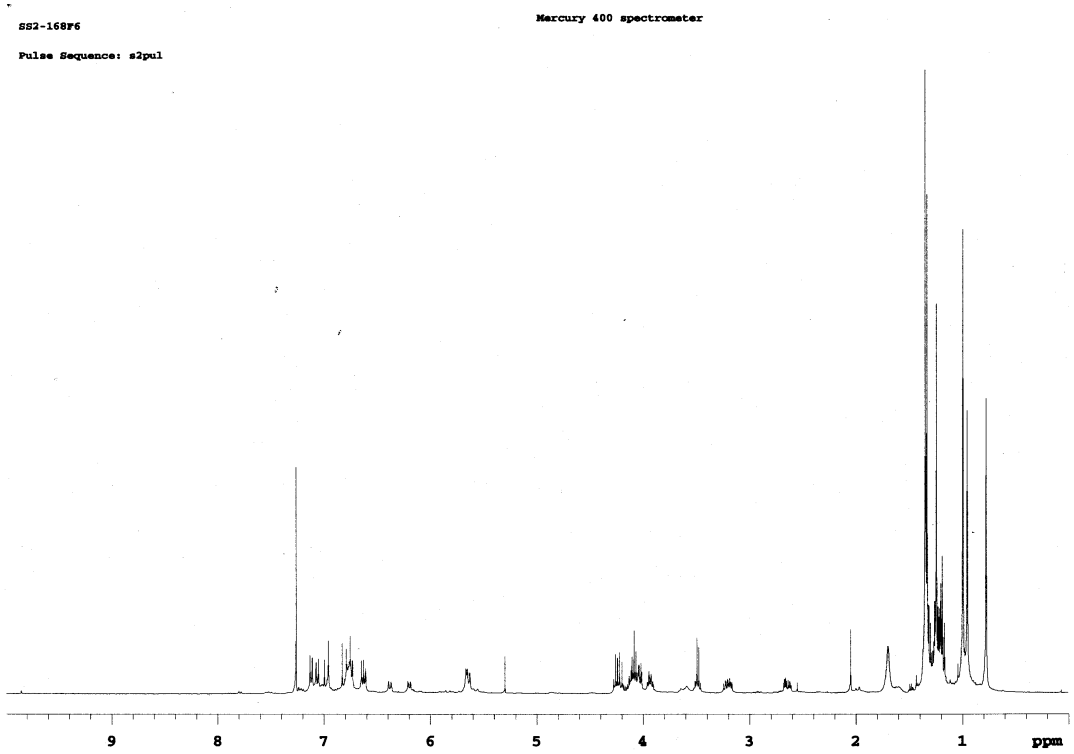
^{1}H NMR (Compound 61)



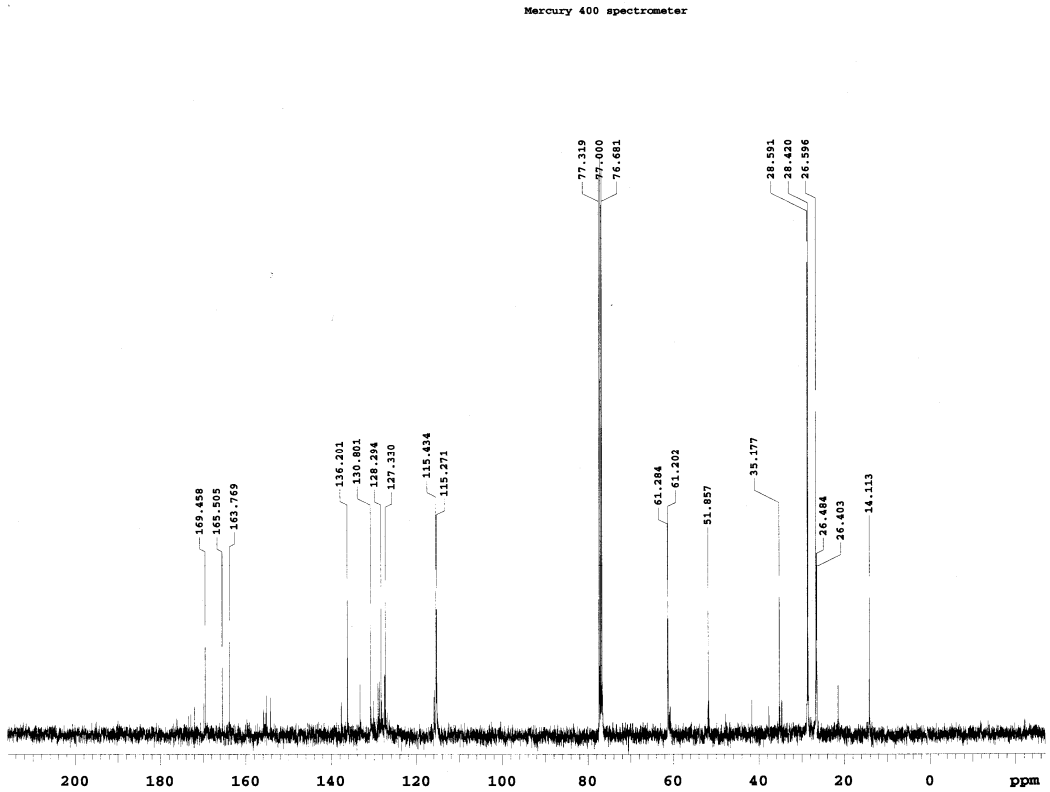
^{13}C NMR (Compound 61)



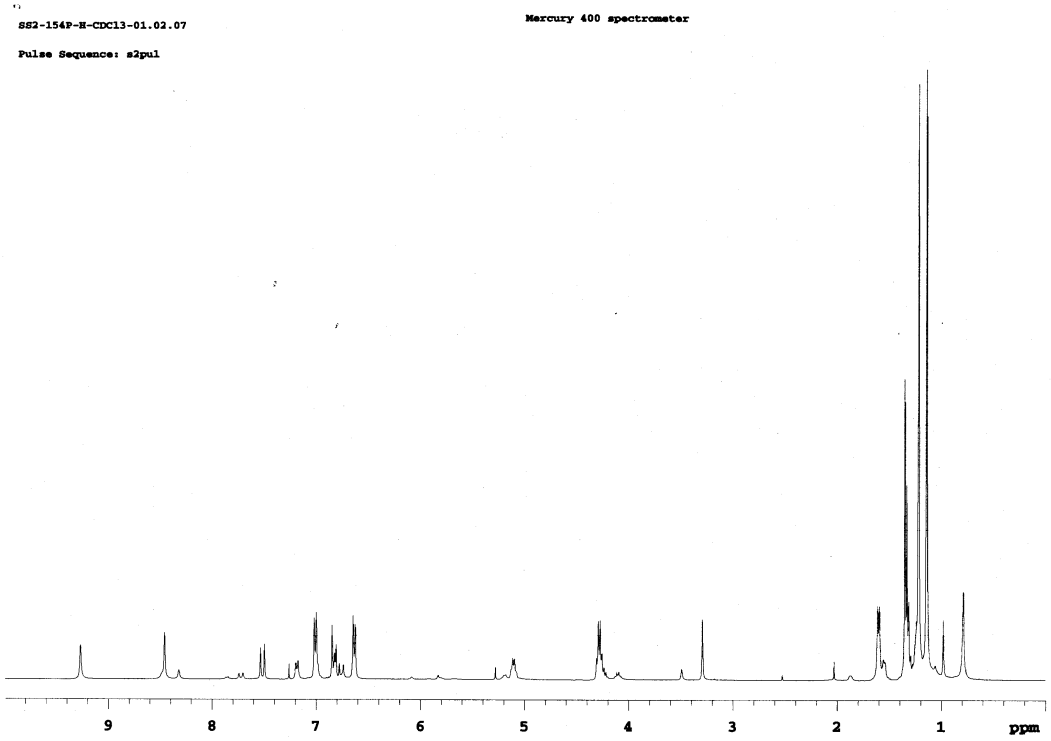
^{1}H NMR (Compound 62)



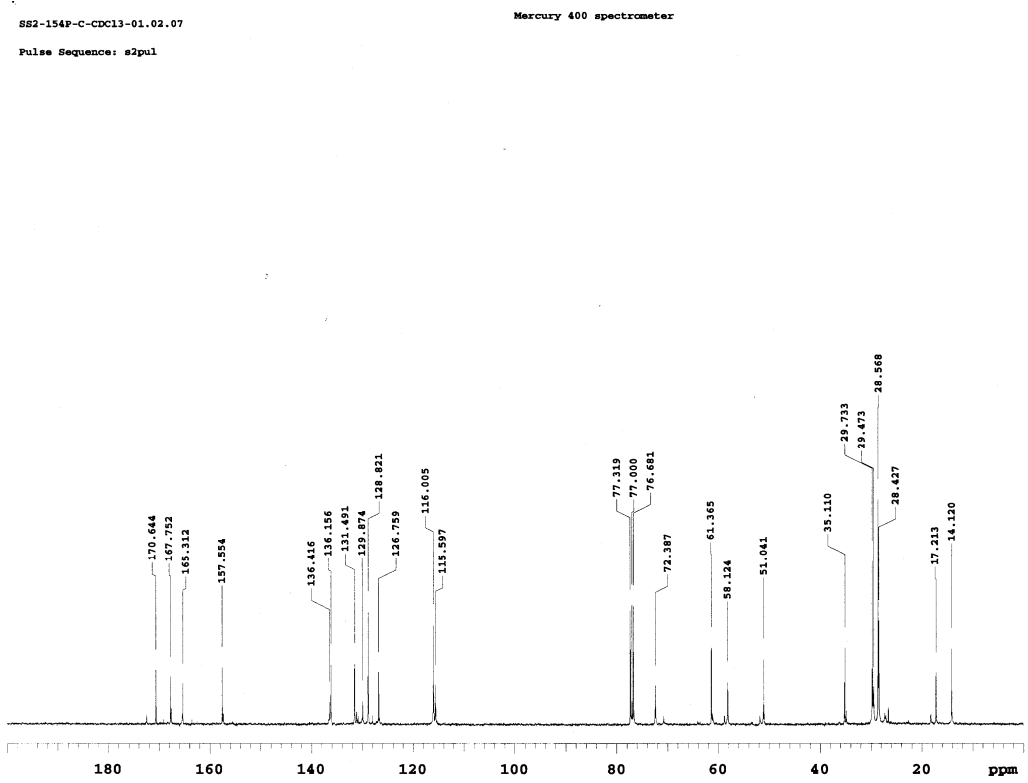
^{13}C NMR (Compound 62)



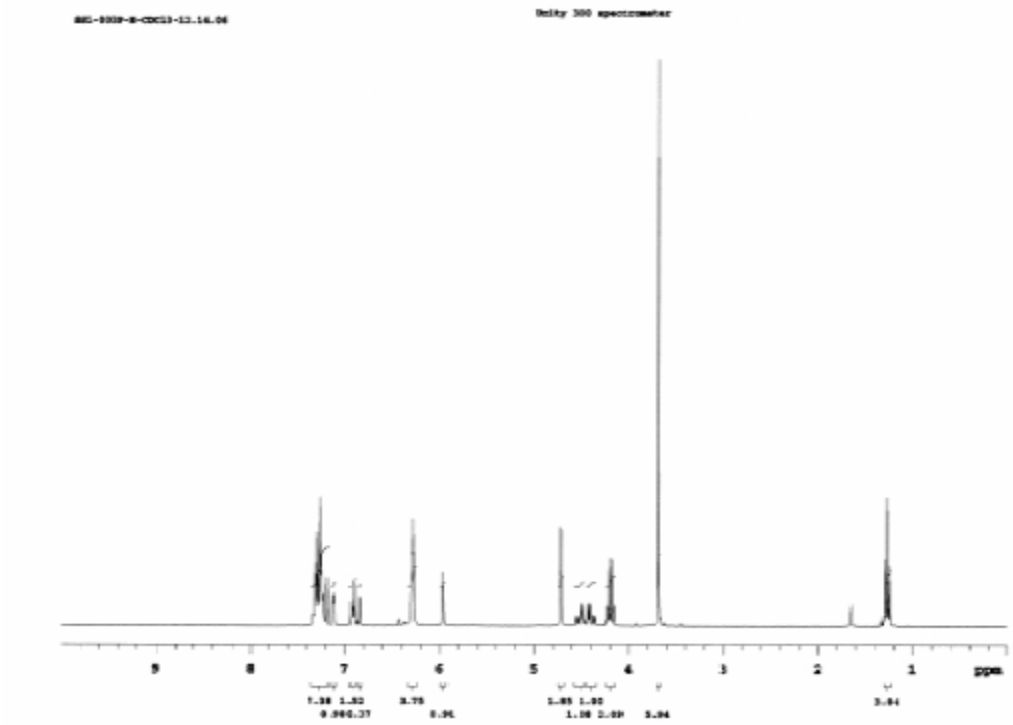
^{1}H NMR (Compound 63)



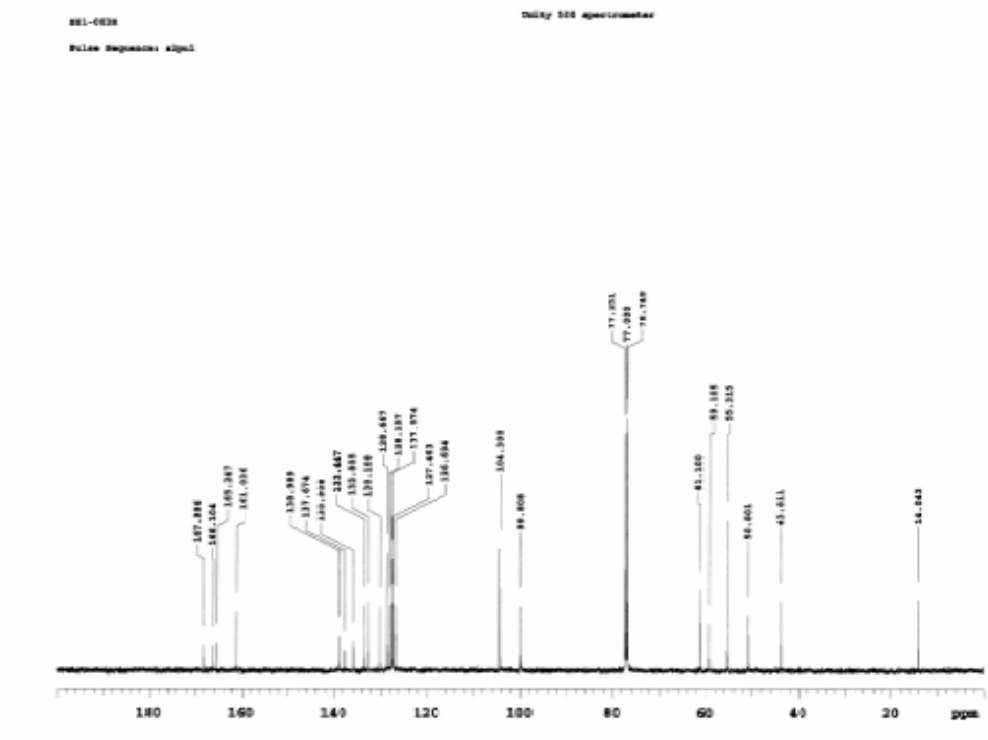
^{13}C NMR (Compound 63)



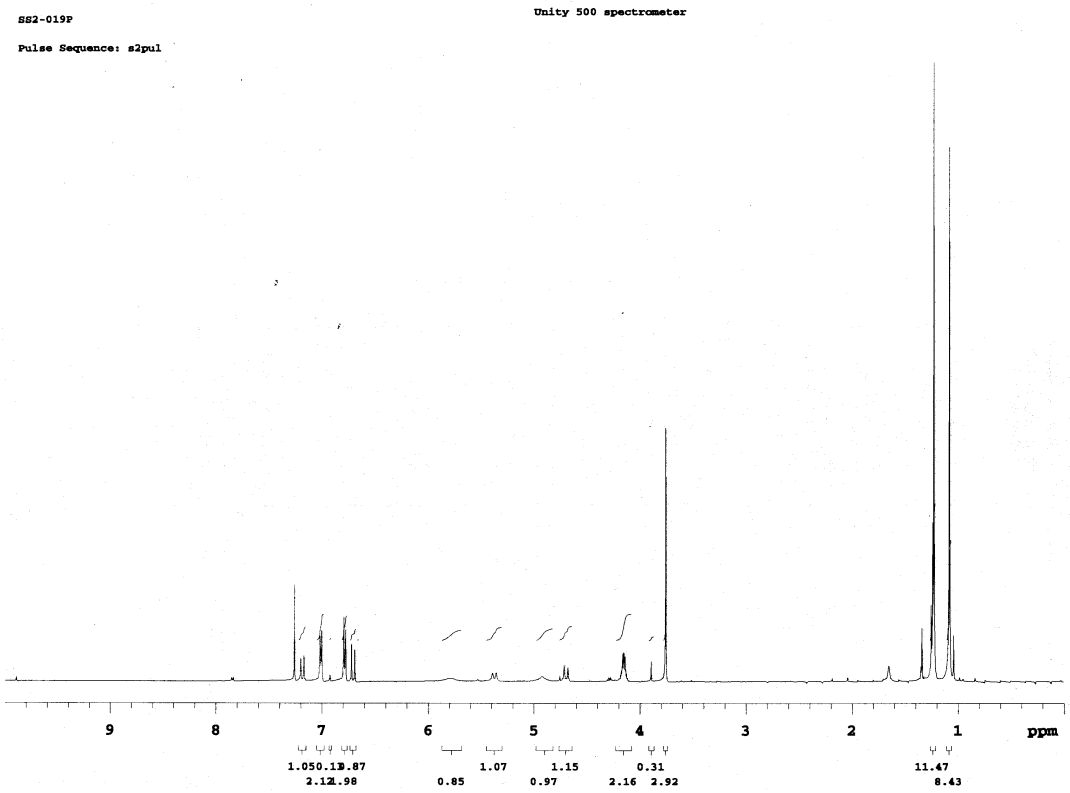
^{1}H NMR (Compound 64)



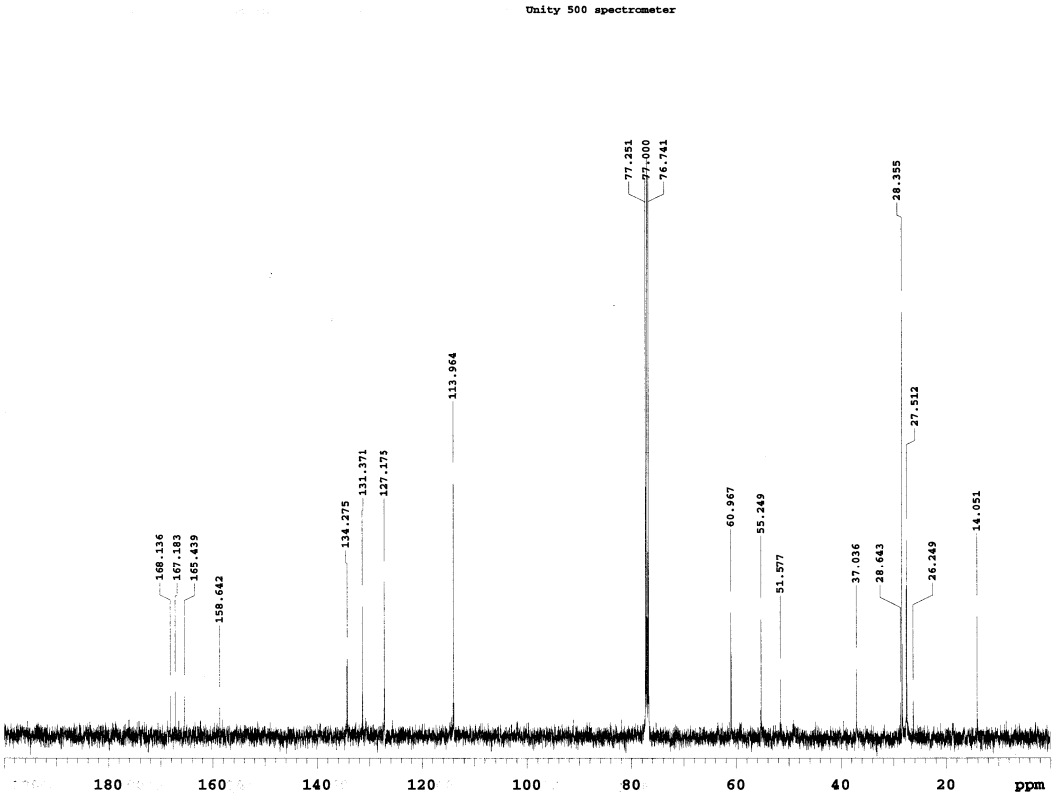
^{13}C NMR (Compound 64)



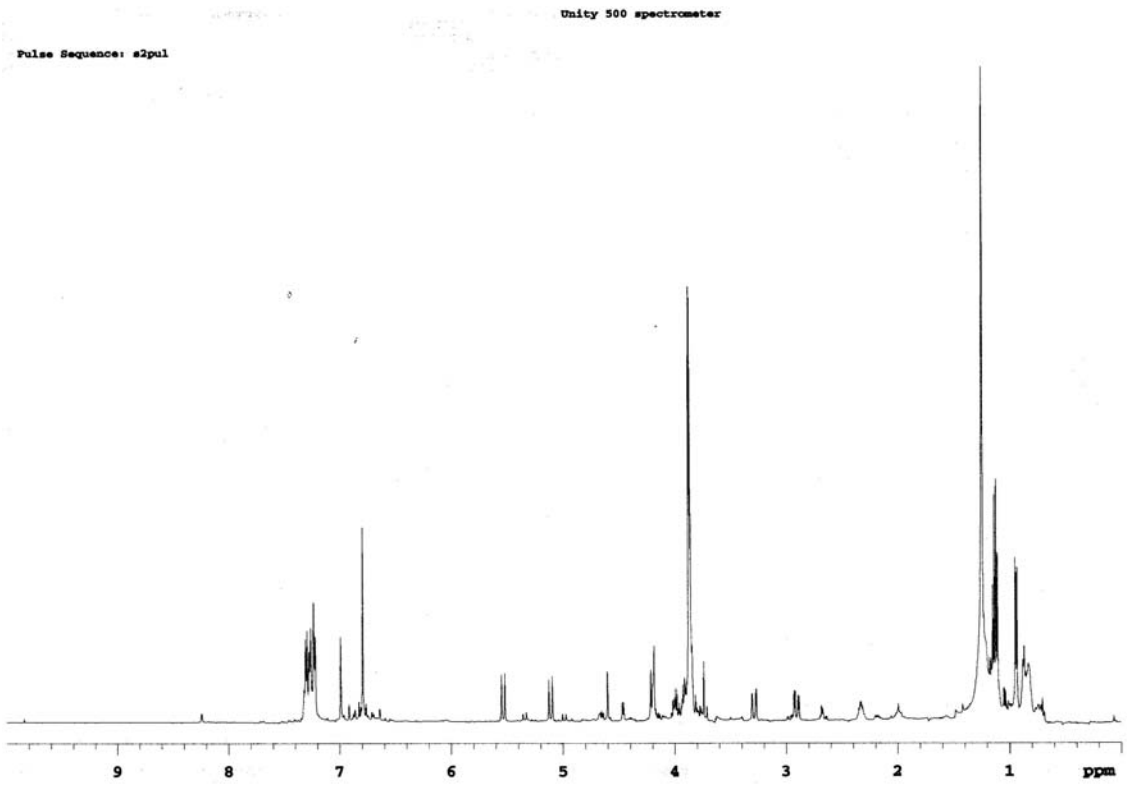
^{1}H NMR (Compound 66)



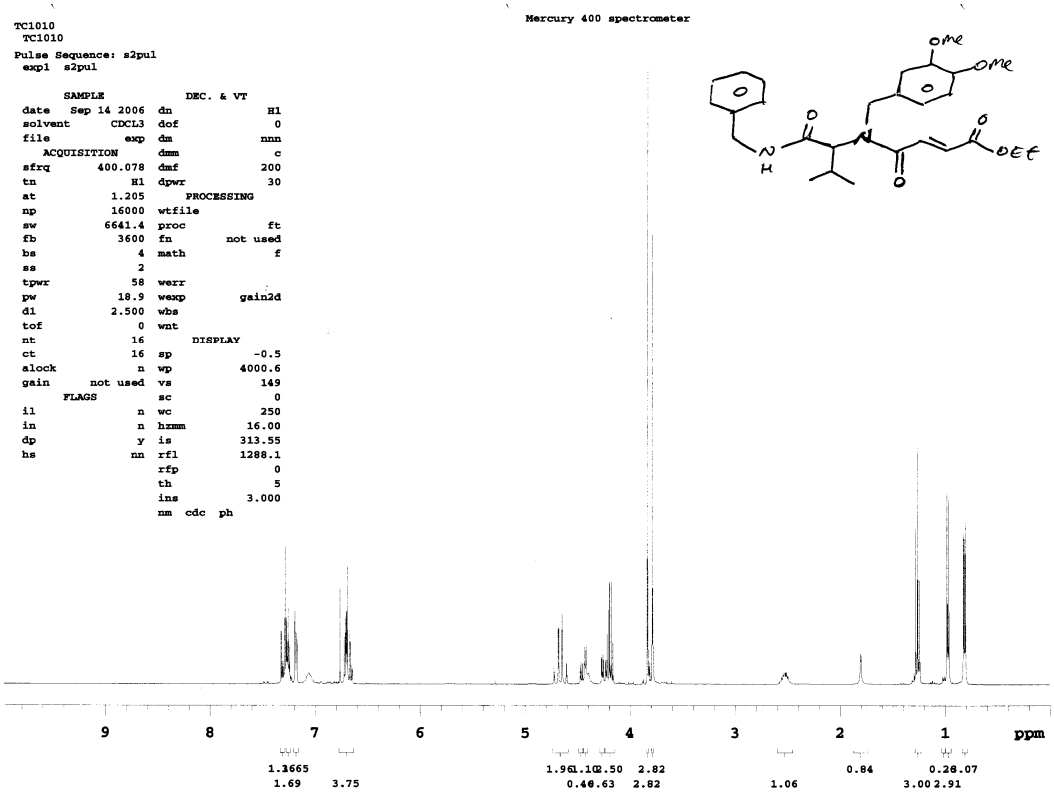
^{13}C NMR (Compound 66)



^{1}H NMR (Compound 67)



^{1}H NMR (Compound 67a)



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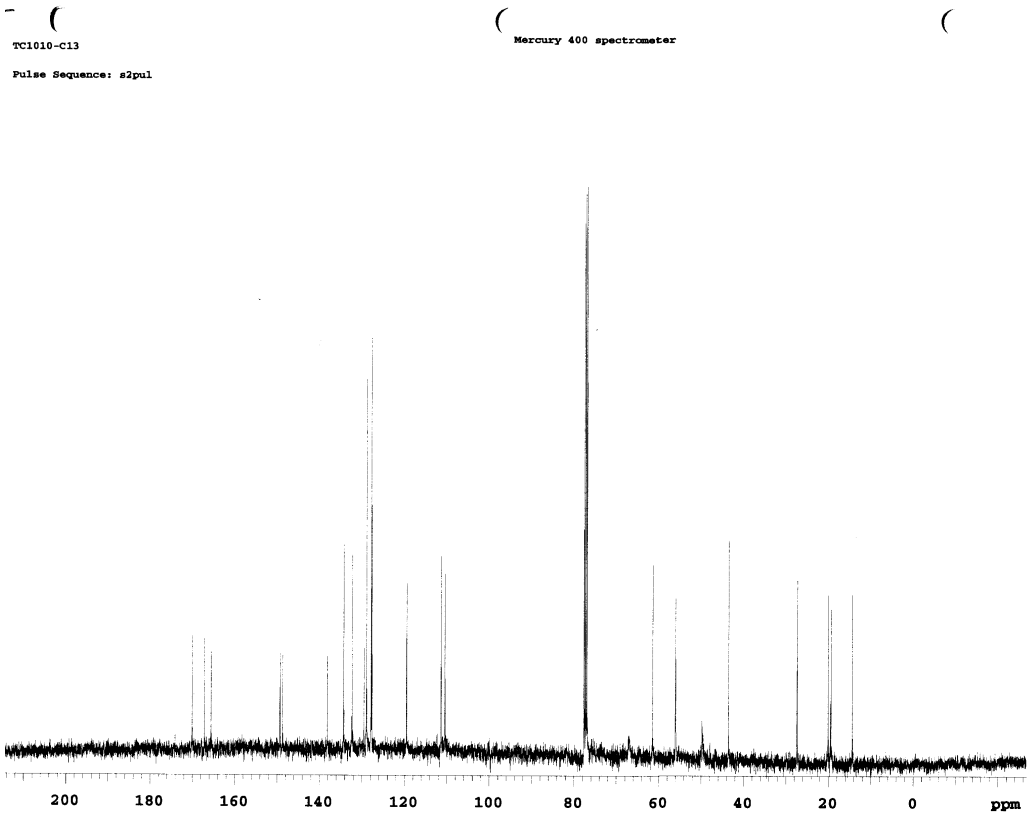
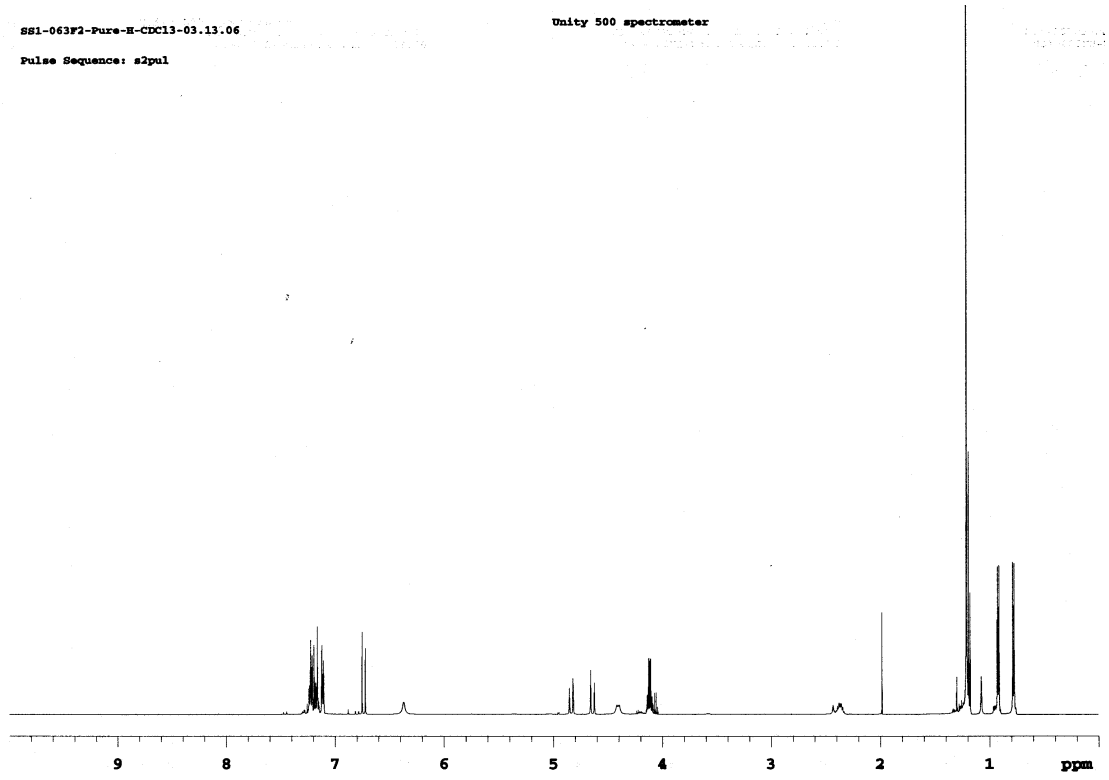
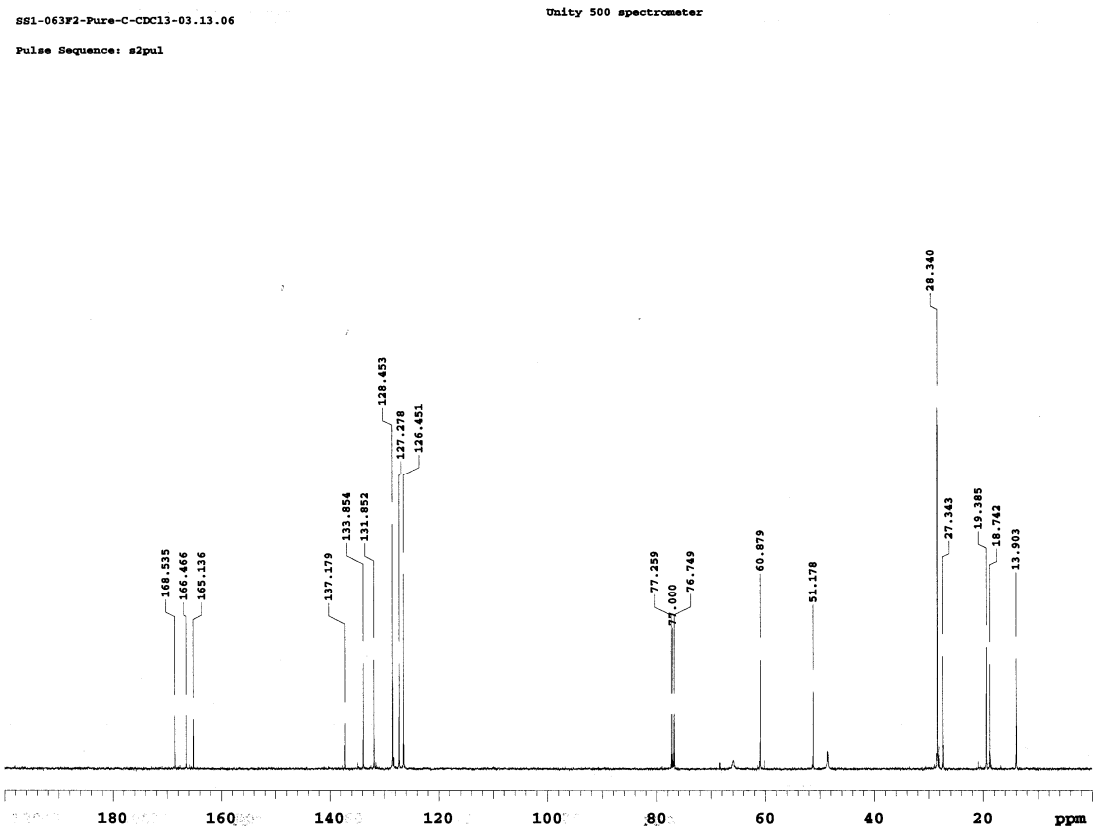


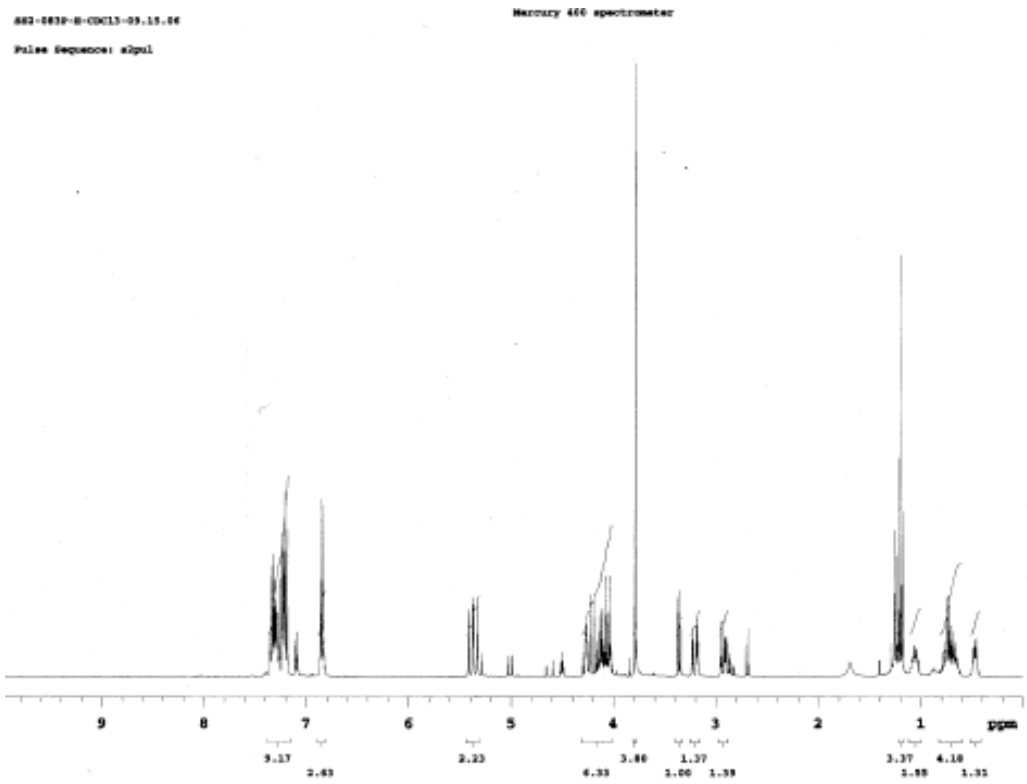
^{1}H NMR (Compound 68)



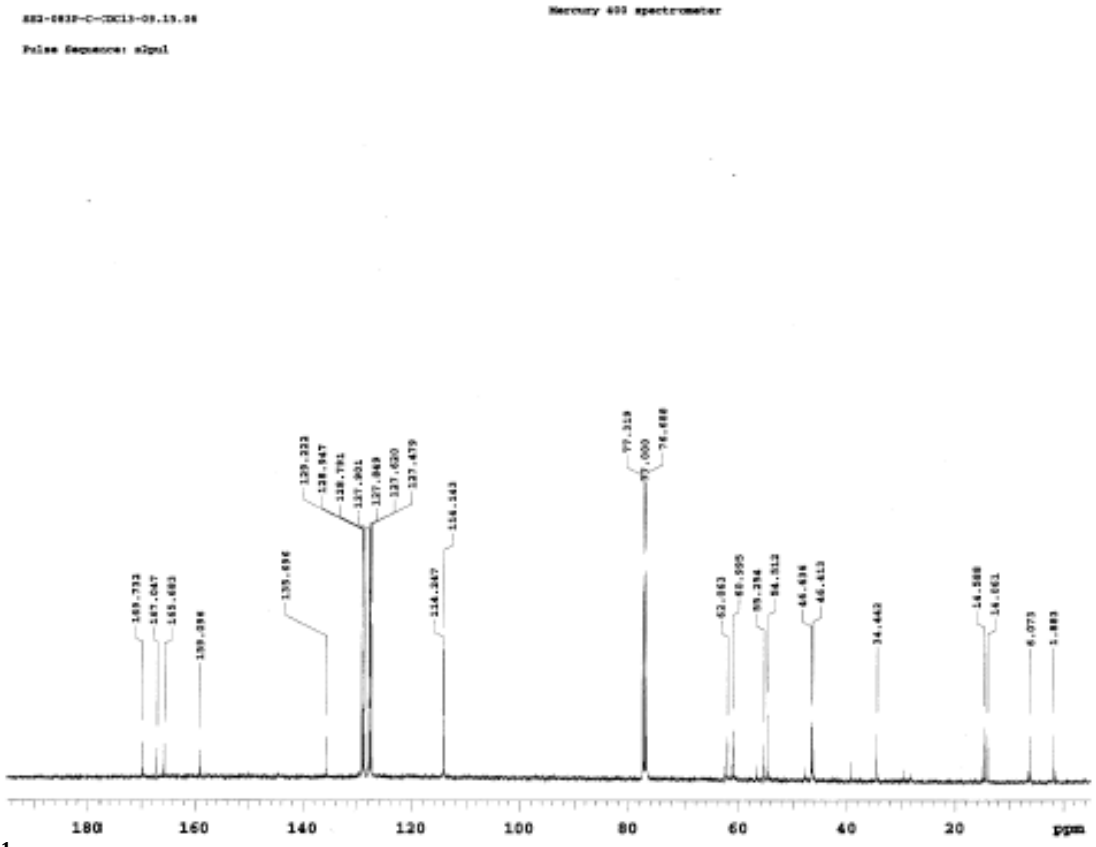
^{13}C NMR (Compound 68)



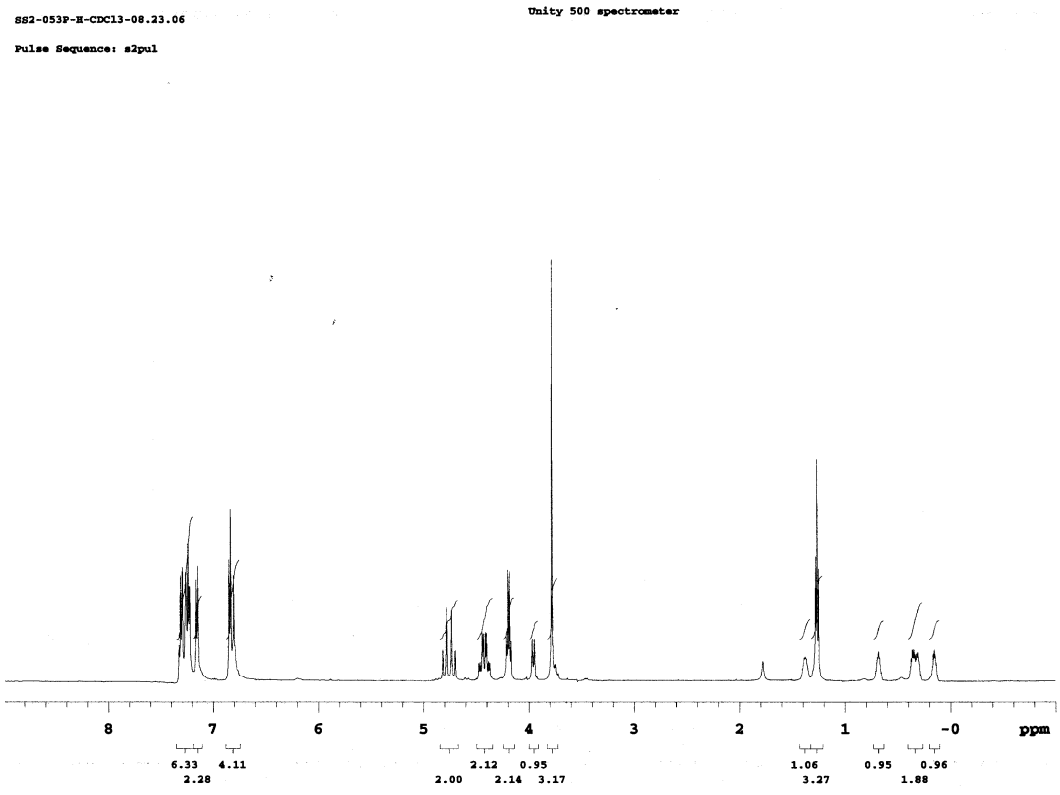
^{1}H NMR (Compound 69)



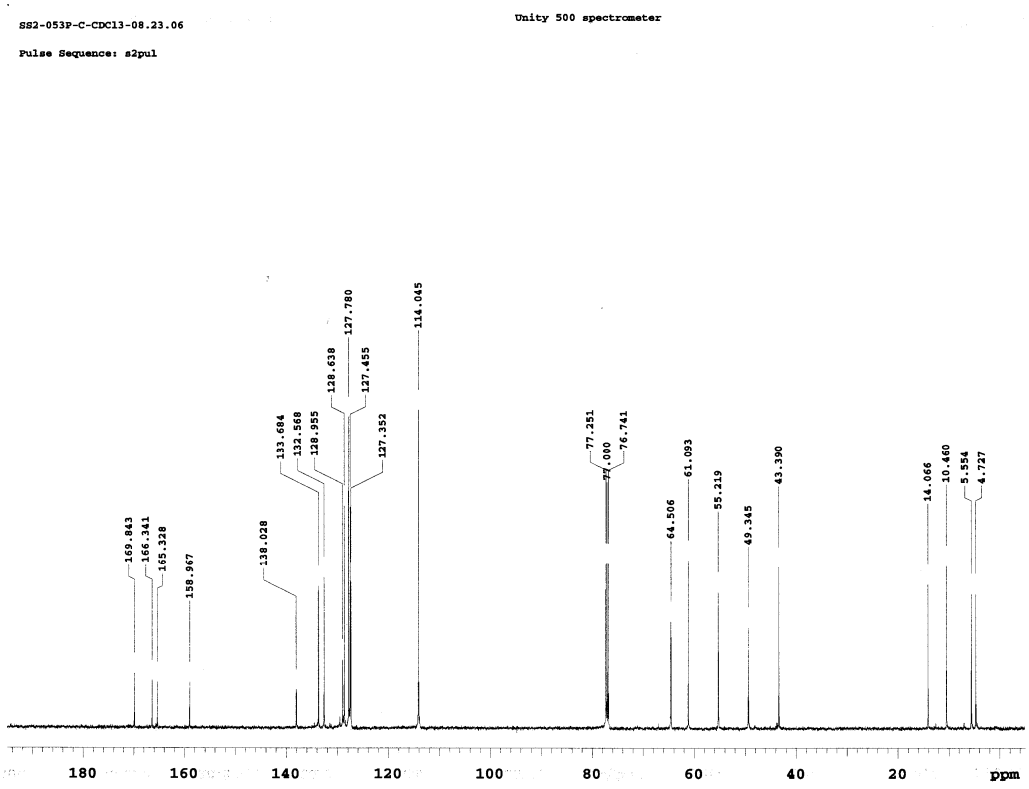
^{13}C NMR (Compound 69)



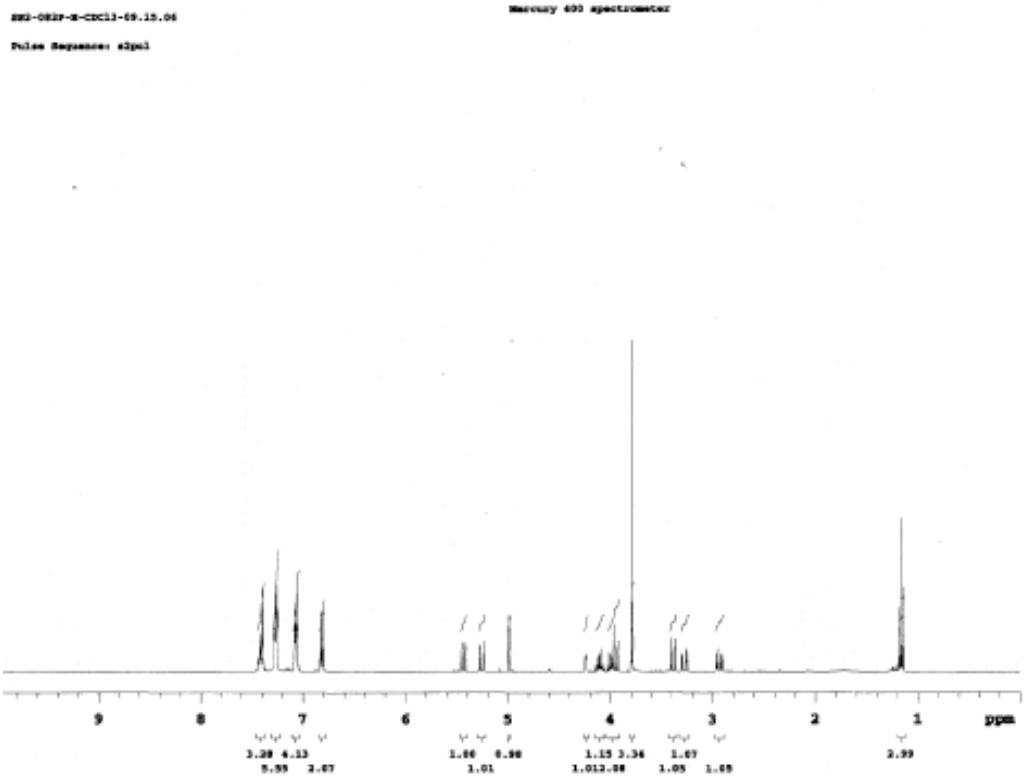
^{1}H NMR (Compound 70)



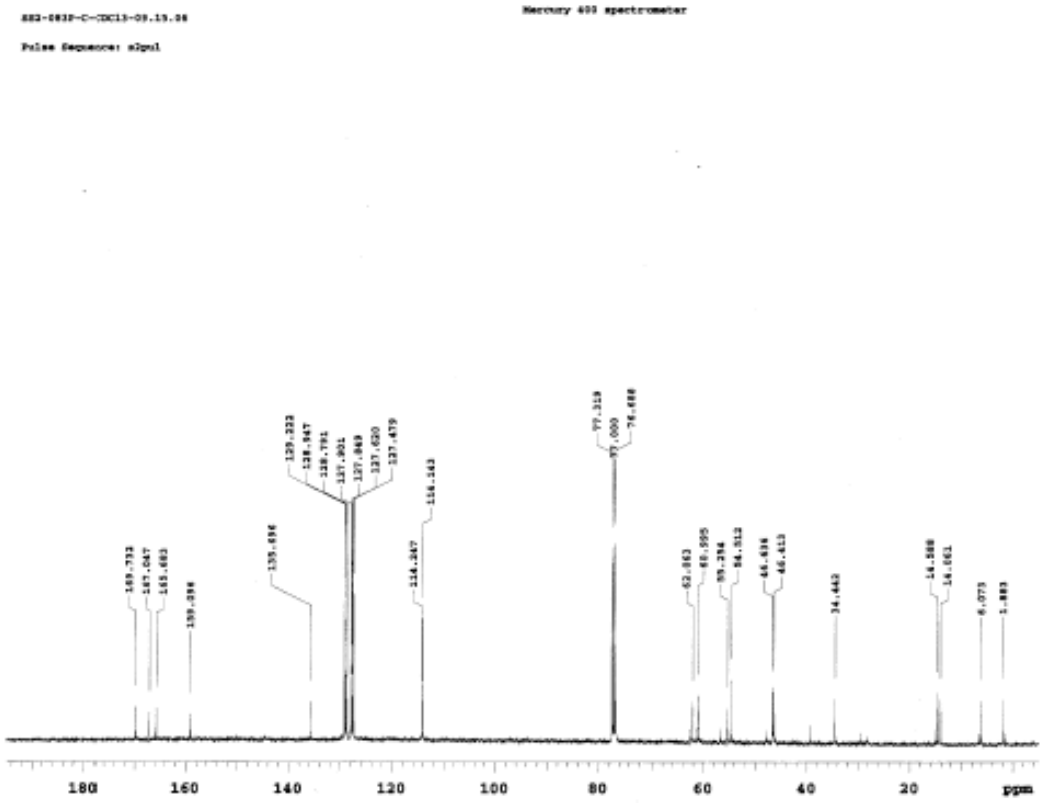
^{13}C NMR (Compound 70)



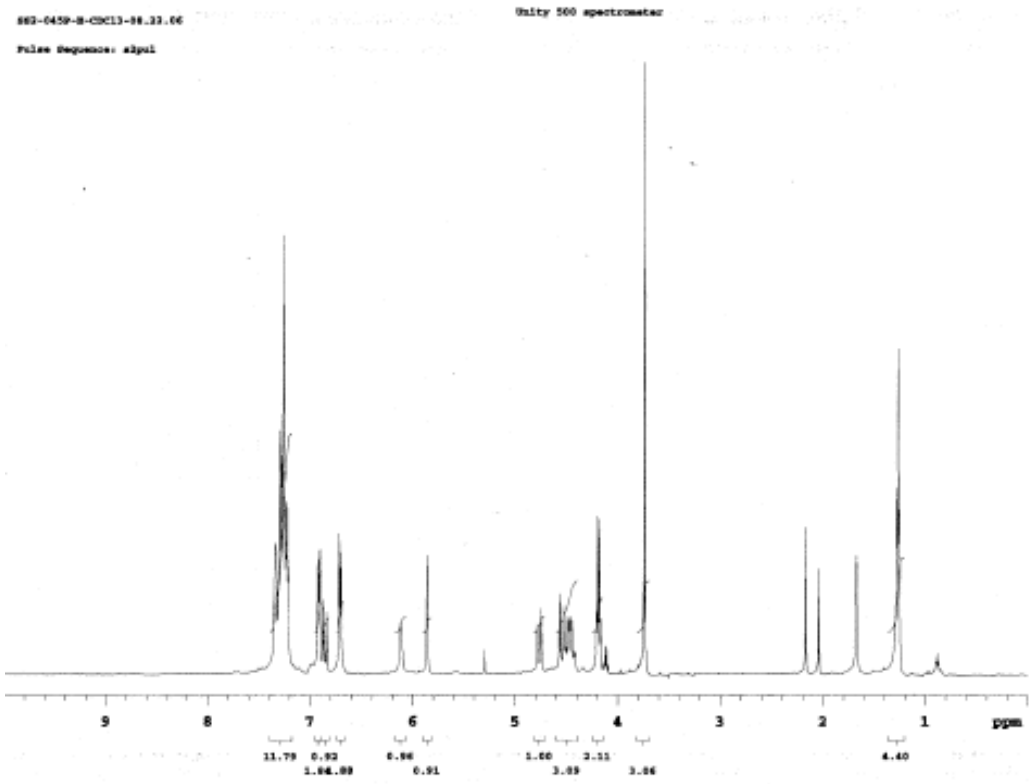
^{1}H NMR (Compound 71)



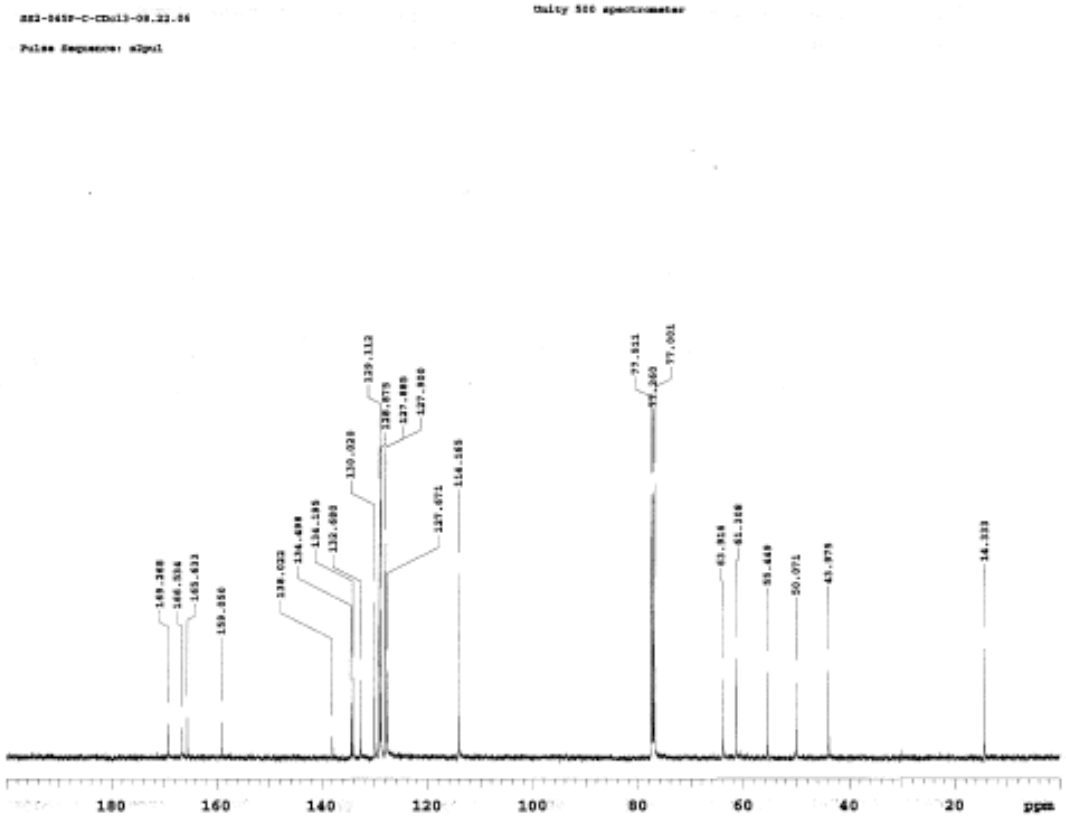
^{13}C NMR (Compound 71)



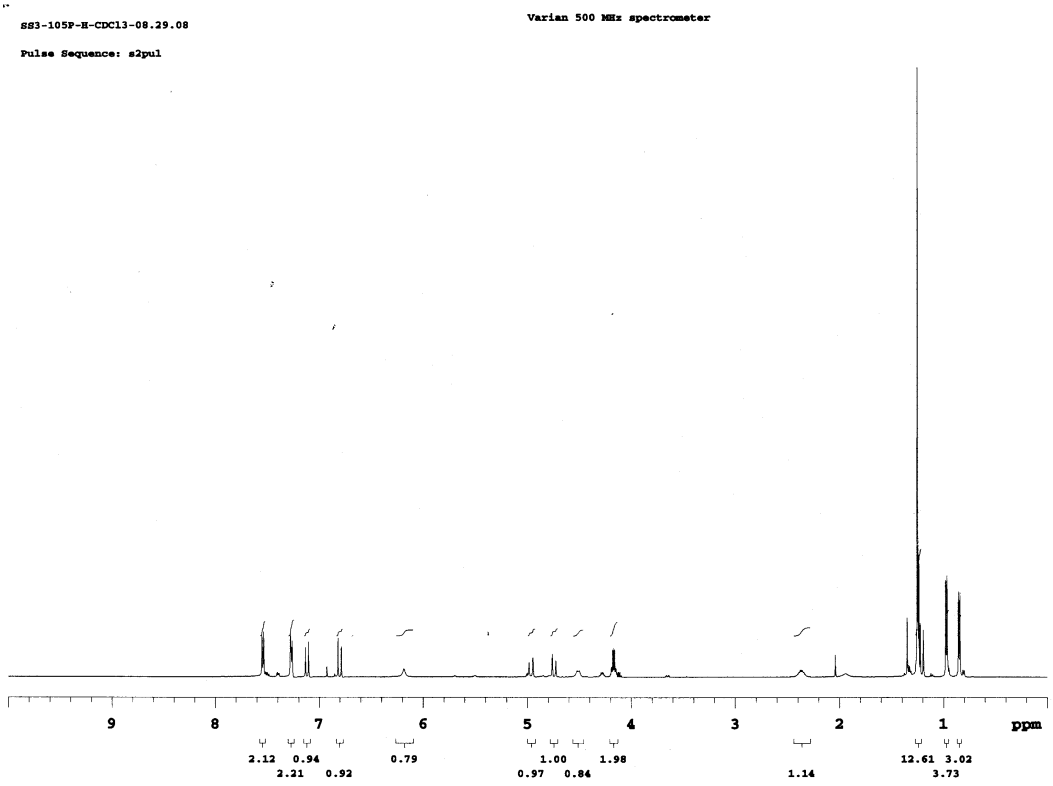
^{1}H NMR (Compound 72)



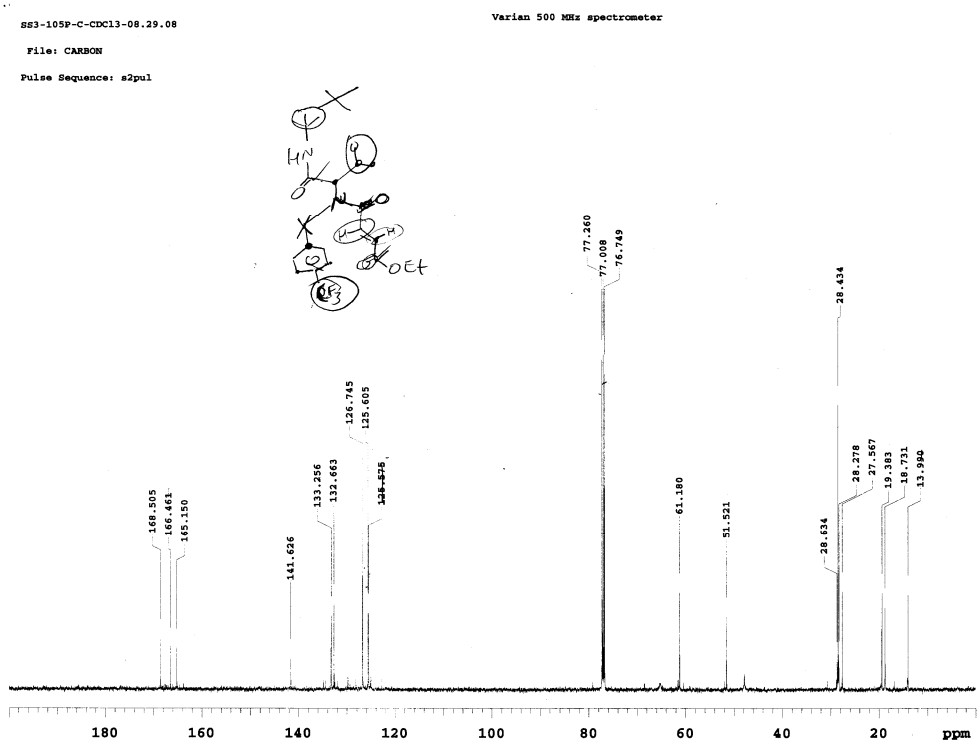
^{13}C NMR (Compound 72)



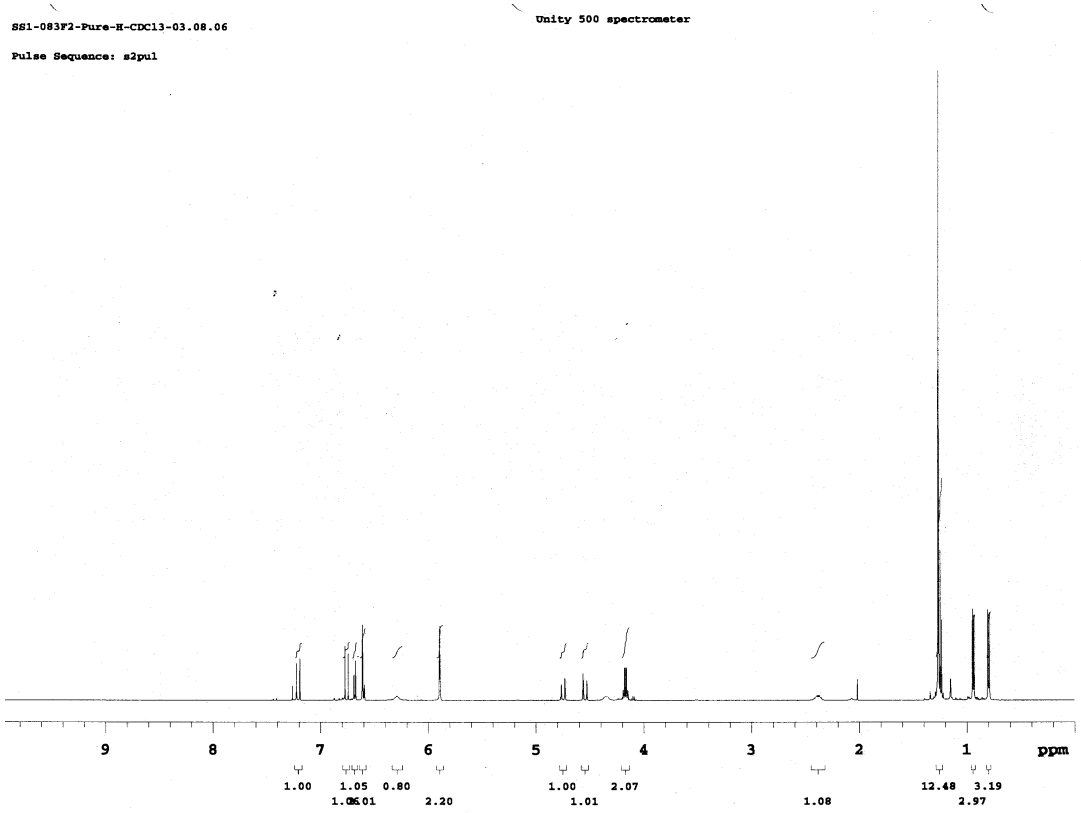
^{1}H NMR (Compound 75)



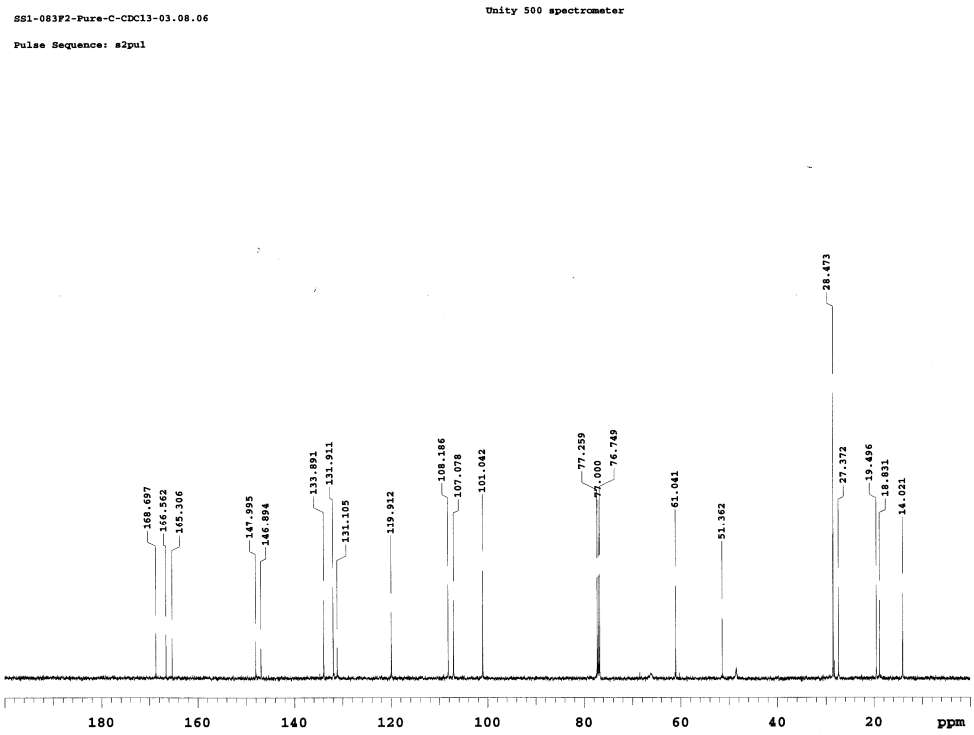
^{13}C NMR (Compound 75)



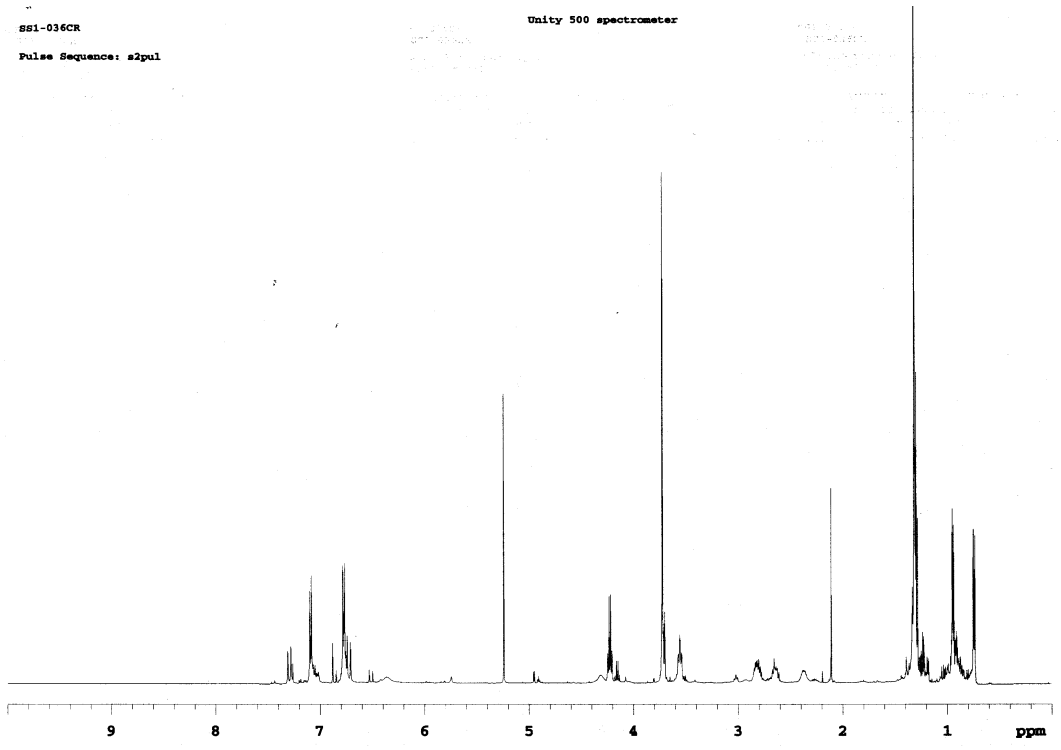
^{1}H NMR (Compound 77)



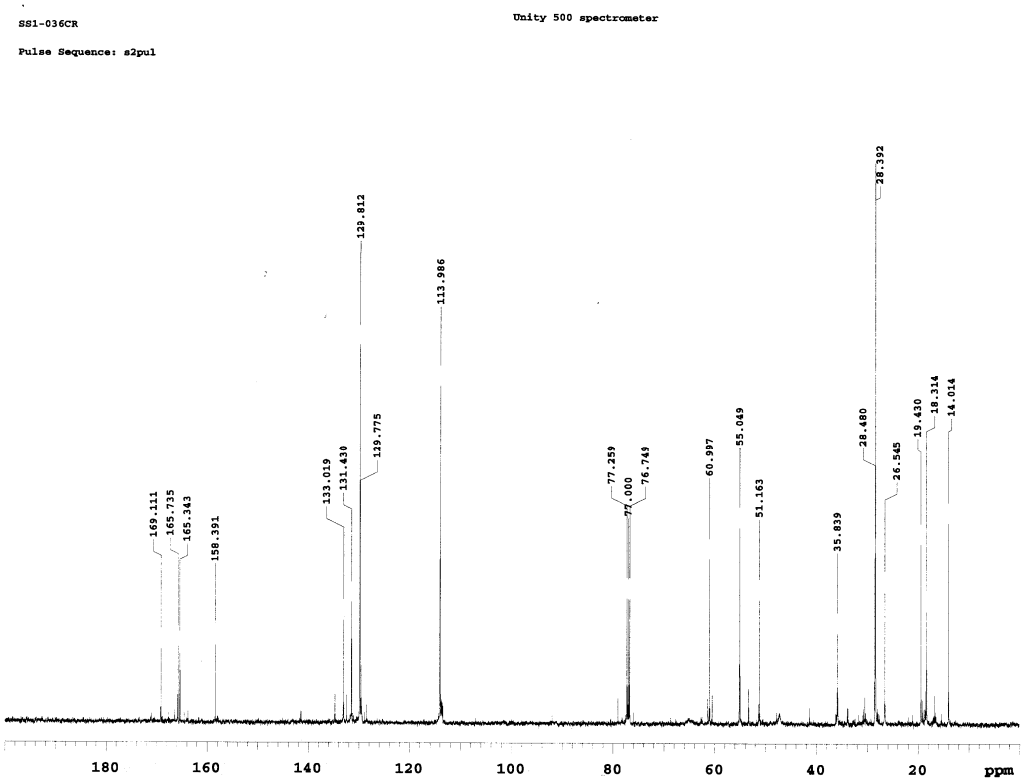
^{13}C NMR (Compound 77)



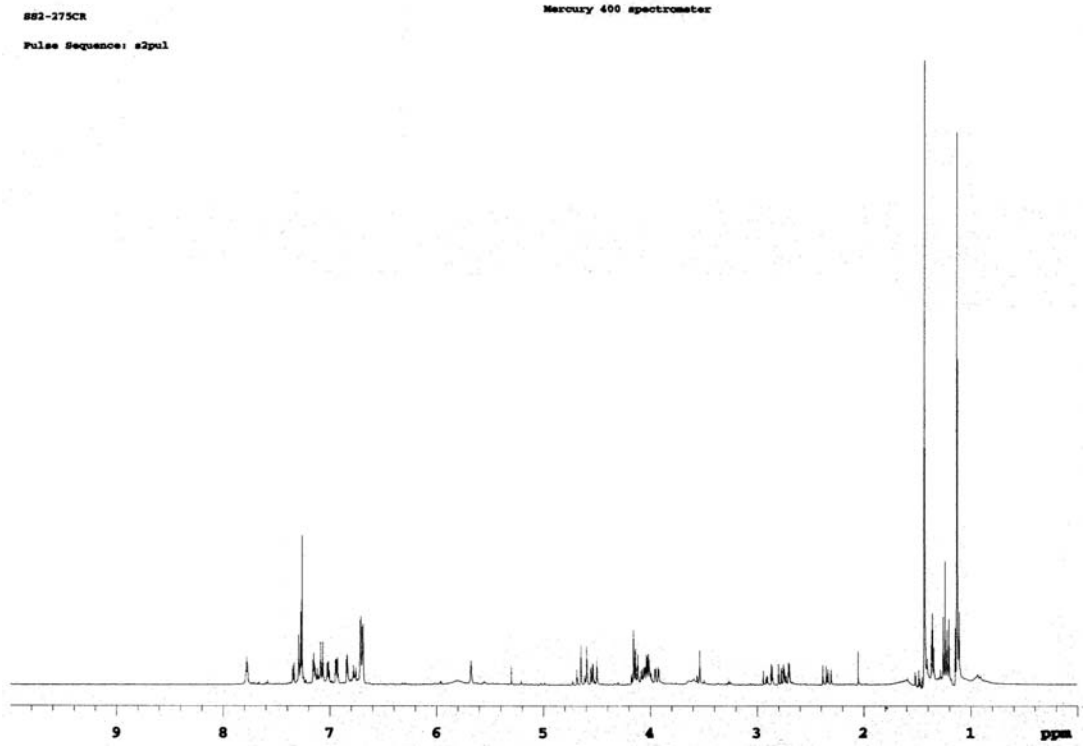
^{1}H NMR (Compound 80)



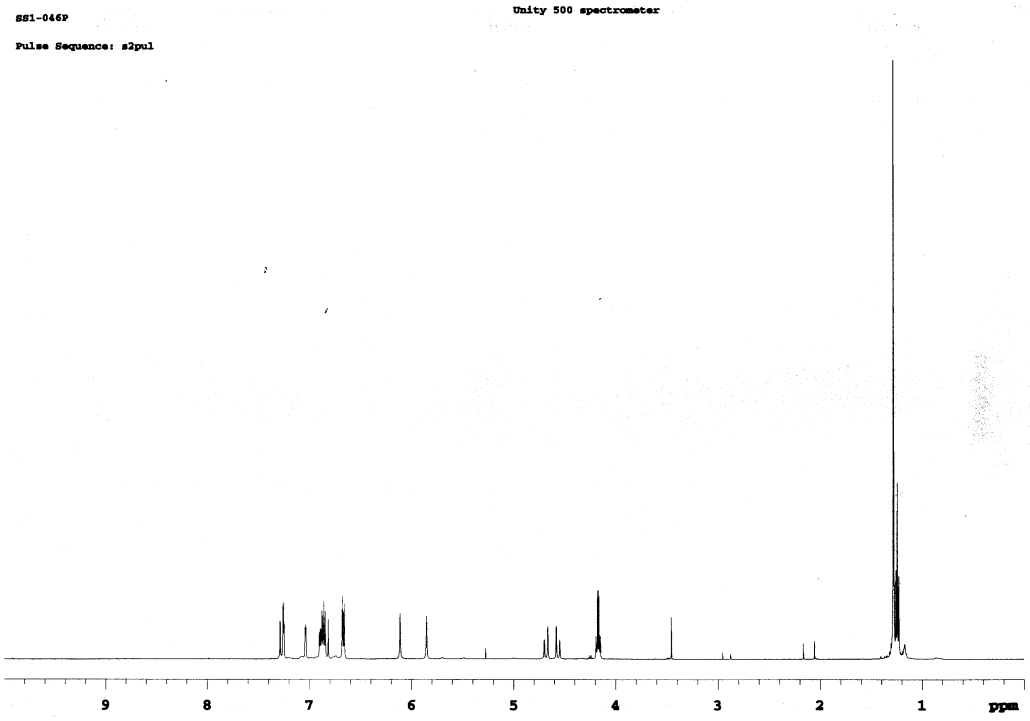
^{13}C NMR (Compound 80)



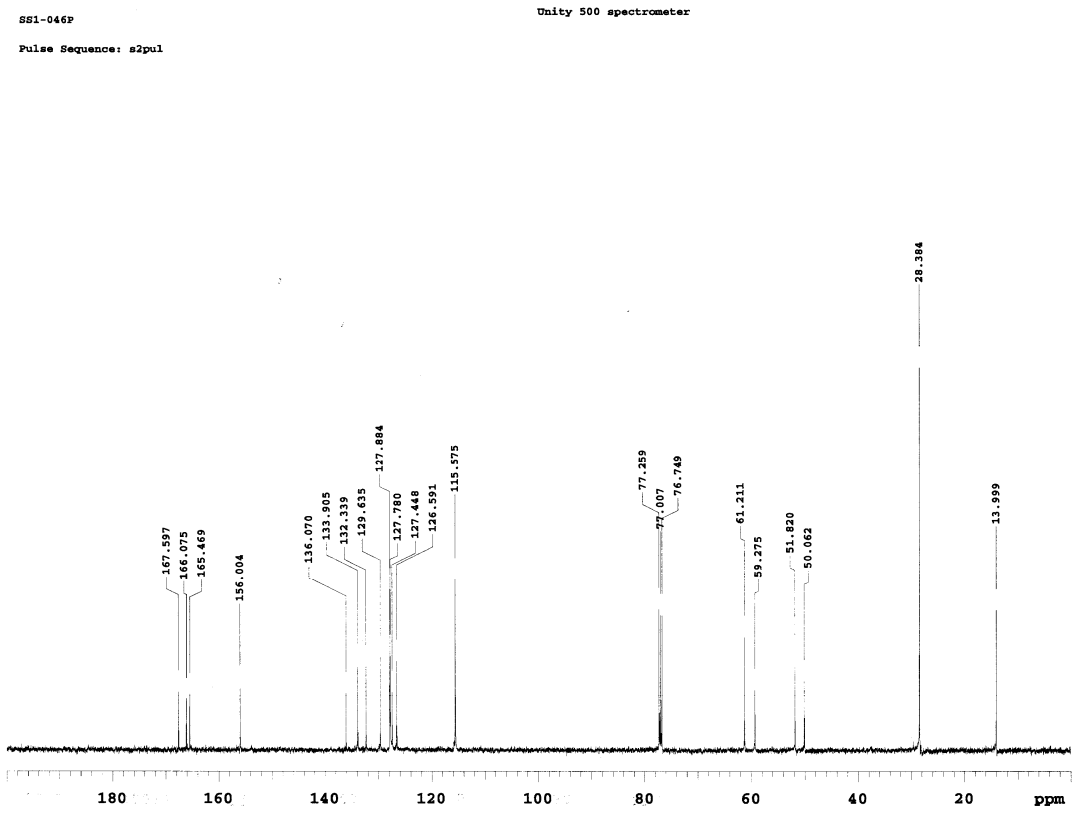
^{1}H NMR (Compound 81)



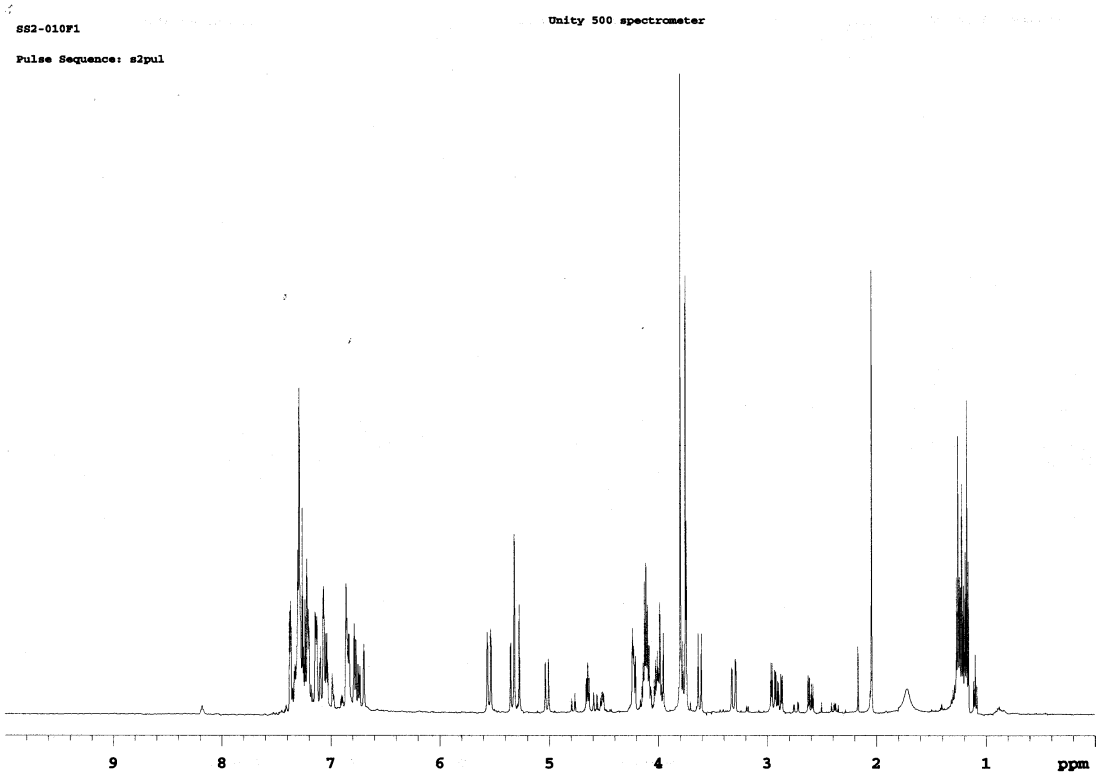
^{1}H NMR (Compound 81a)



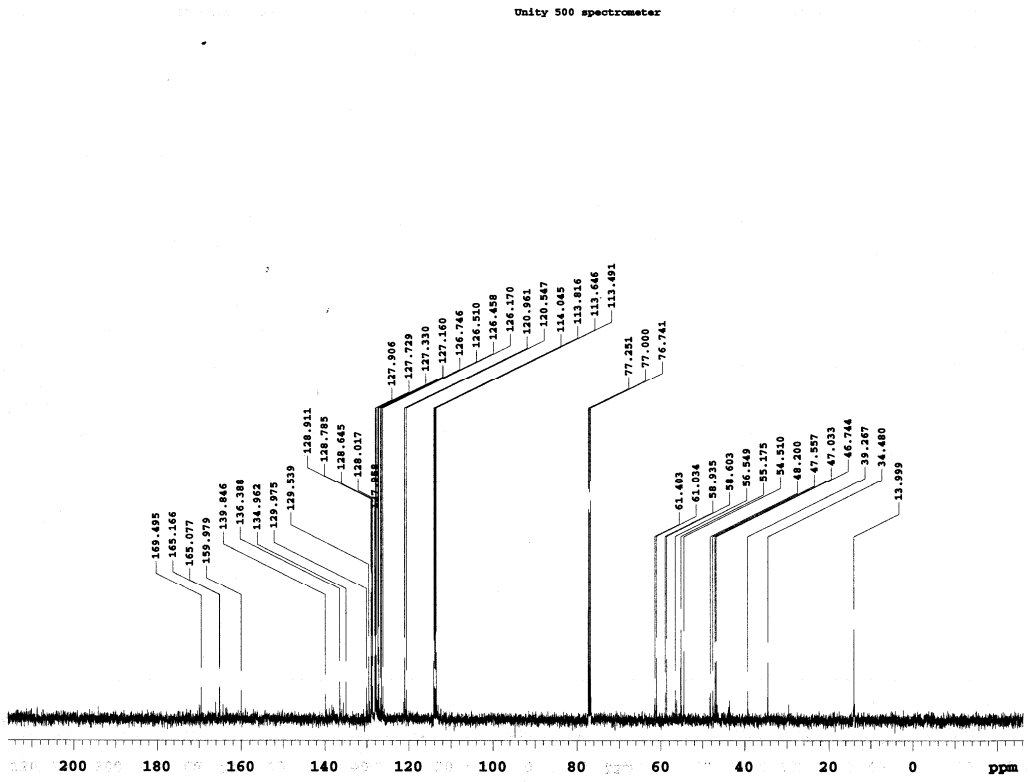
^{13}C NMR (Compound 81a)



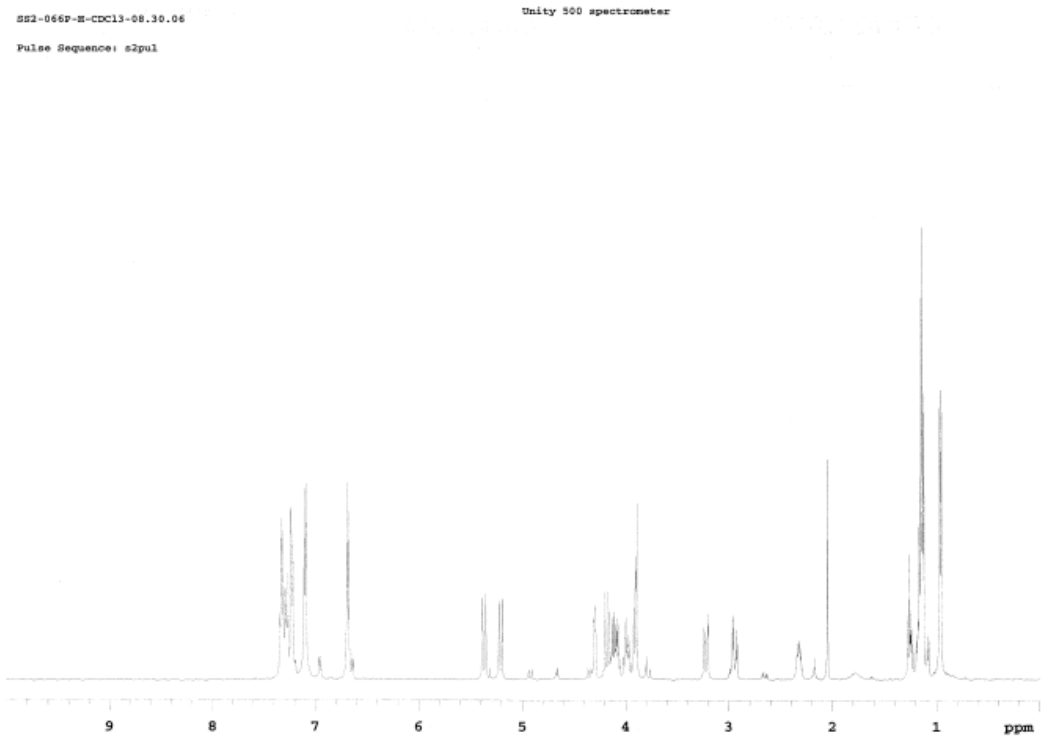
^{1}H NMR (Compound 83)



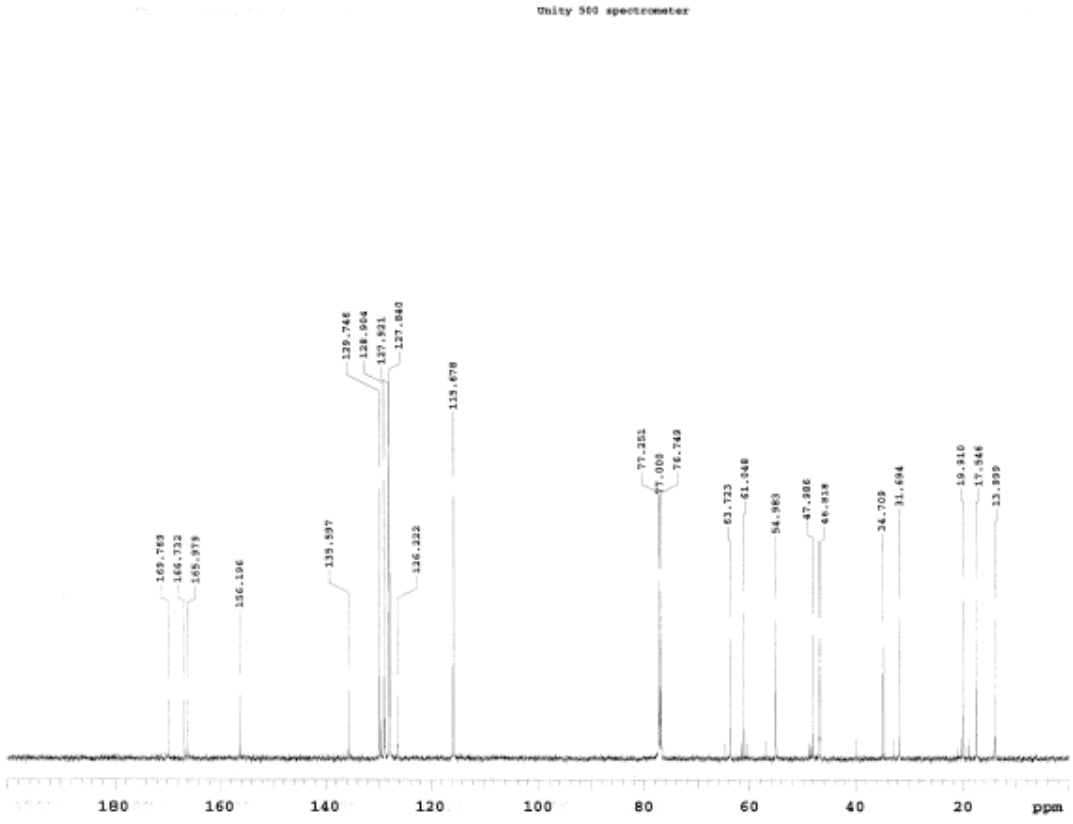
^{13}C NMR (Compound 83)



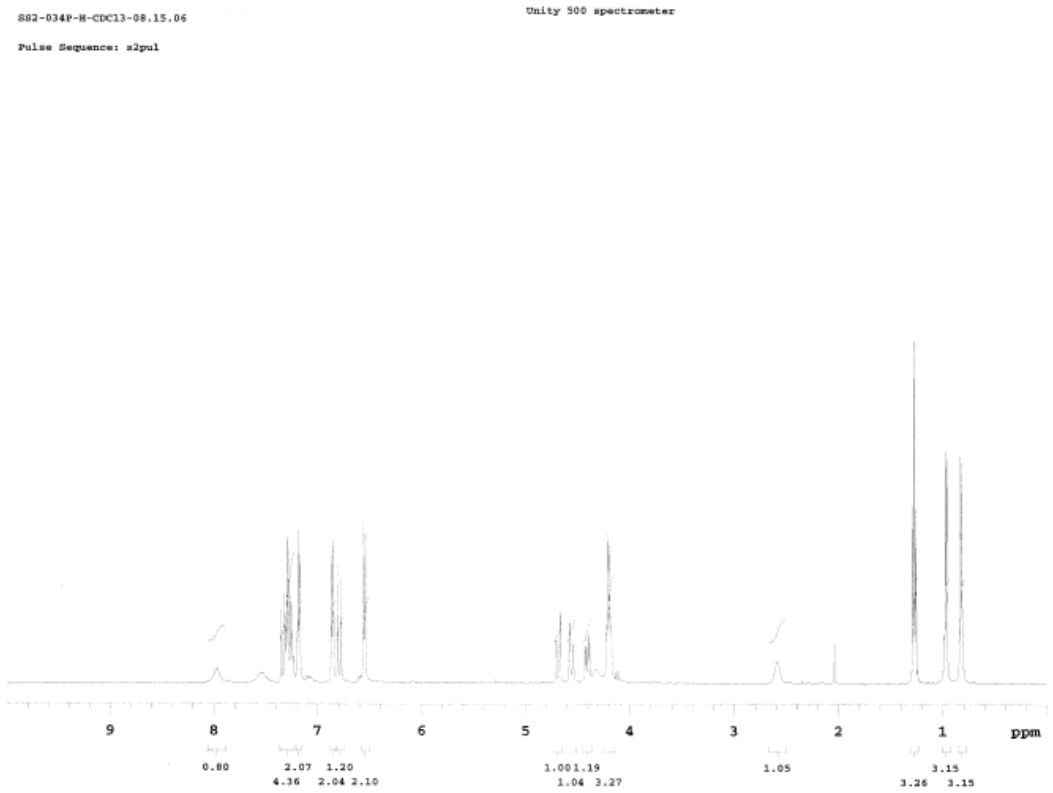
^{1}H NMR (Compound 86)



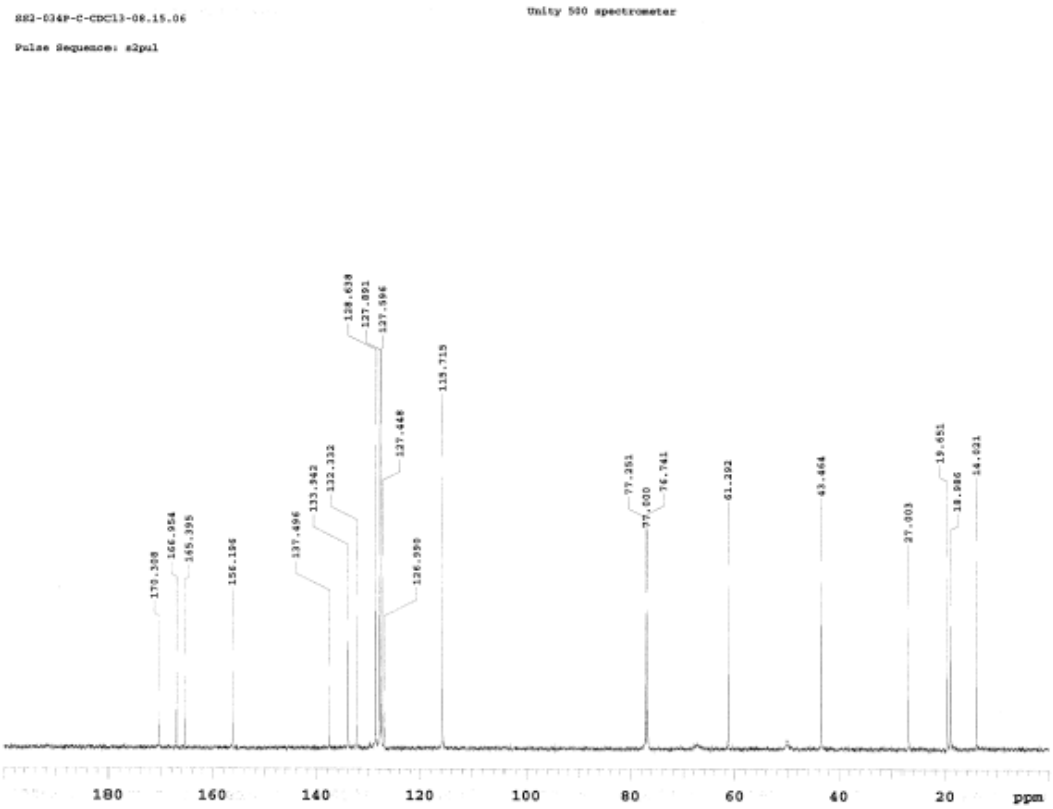
^{13}C NMR (Compound 86)



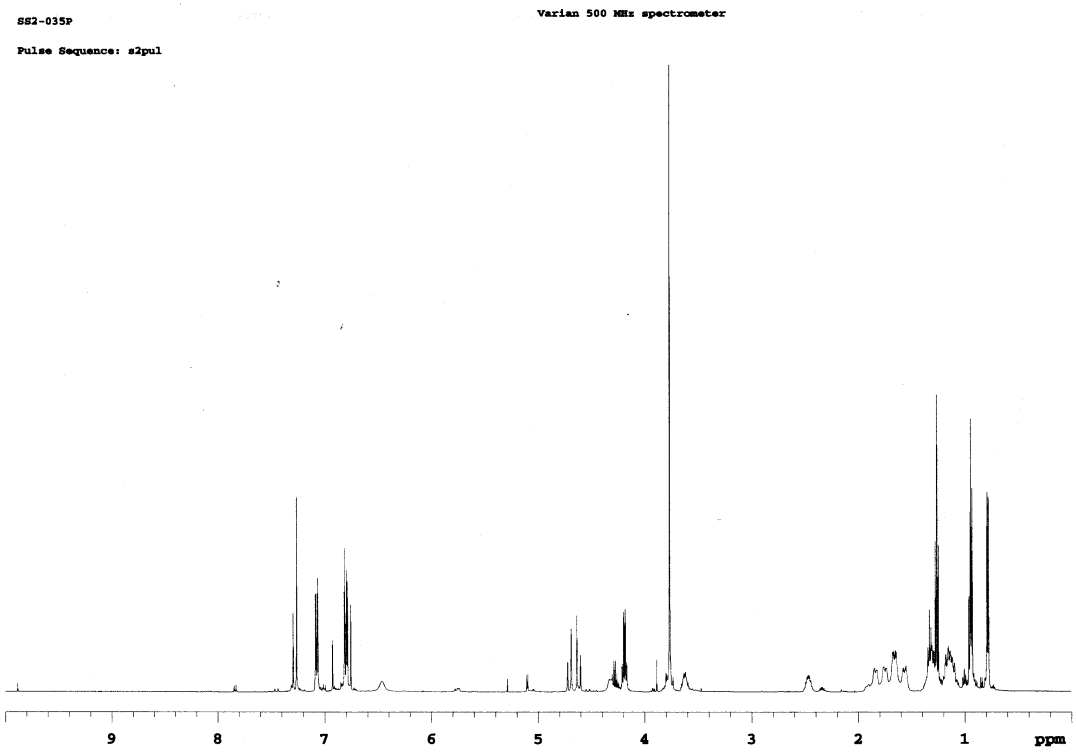
^{1}H NMR (Compound 87)



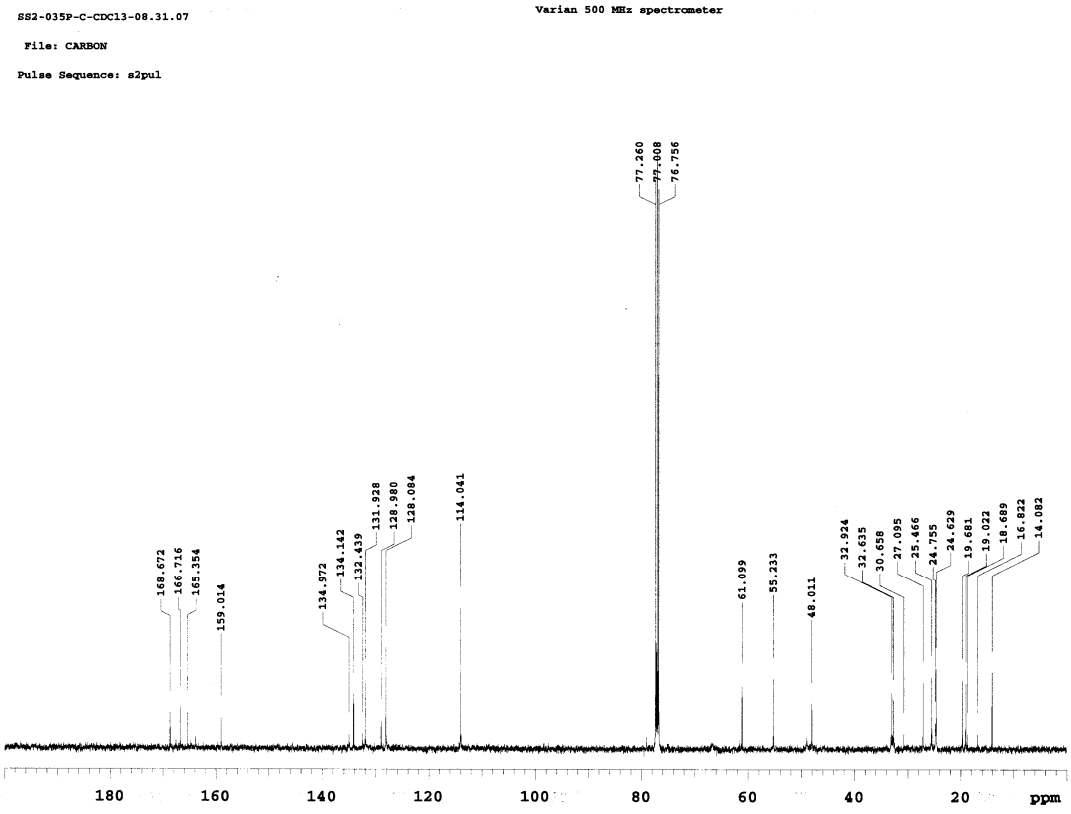
^{13}C NMR (Compound 87)



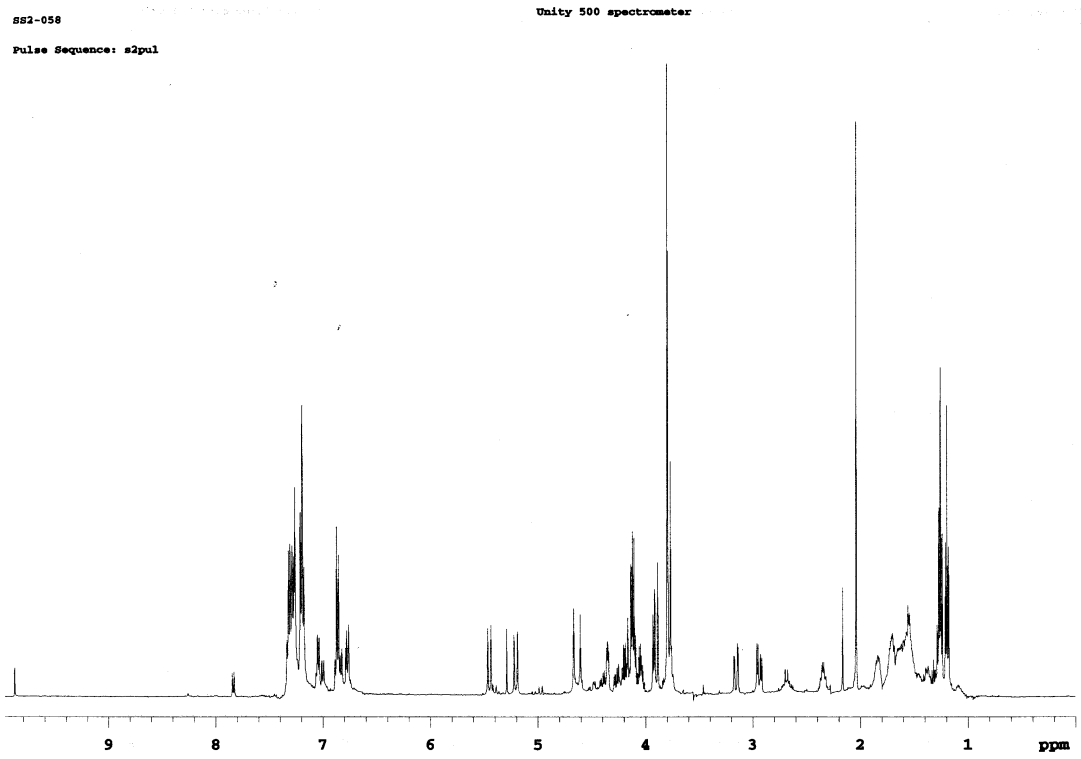
^{1}H NMR (Compound 88)



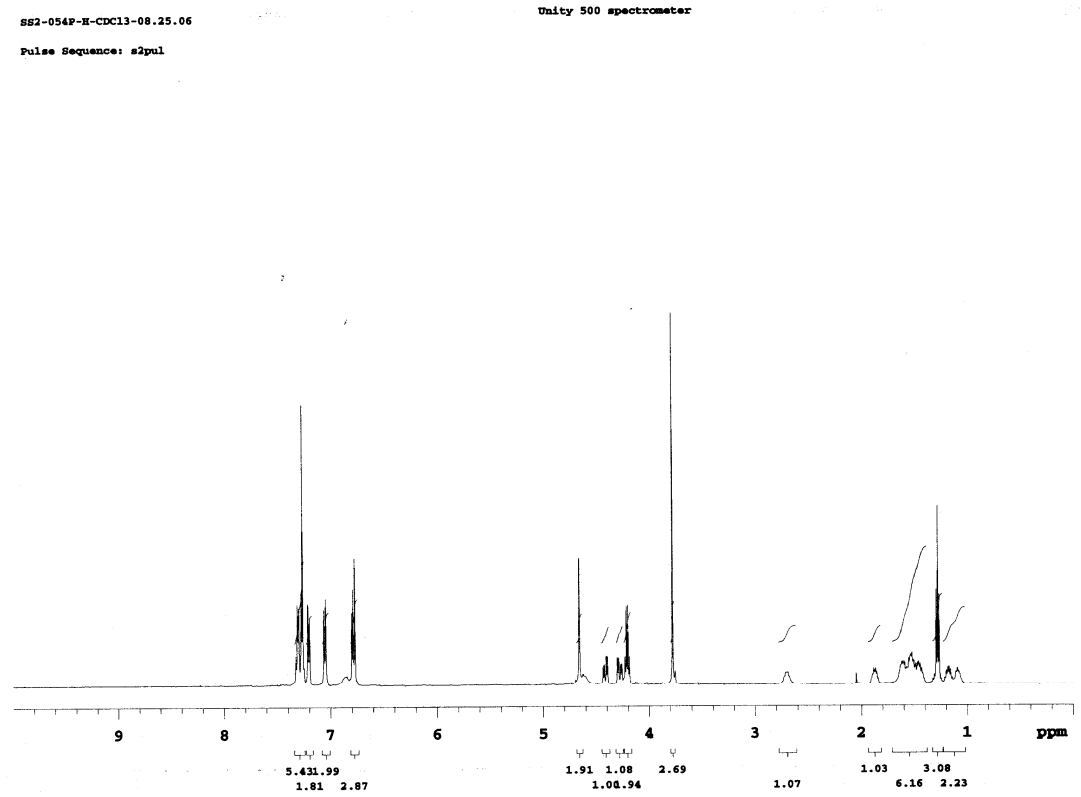
^{13}C NMR (Compound 88)



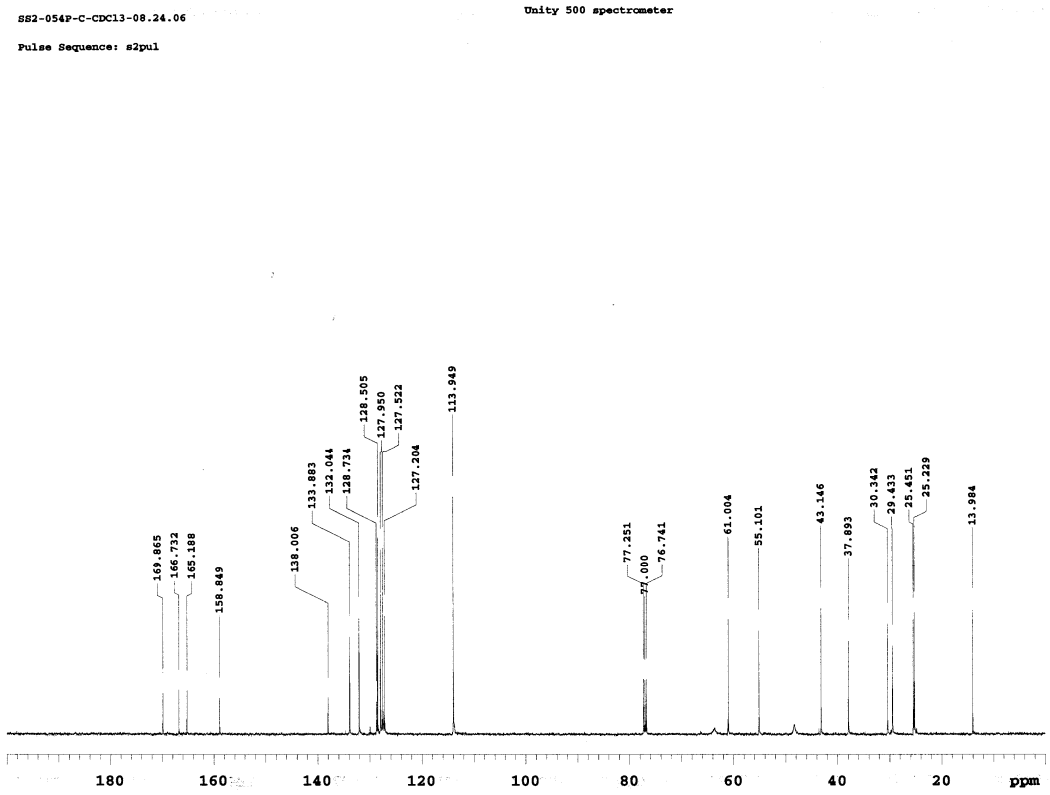
^{1}H NMR (Compound 89)



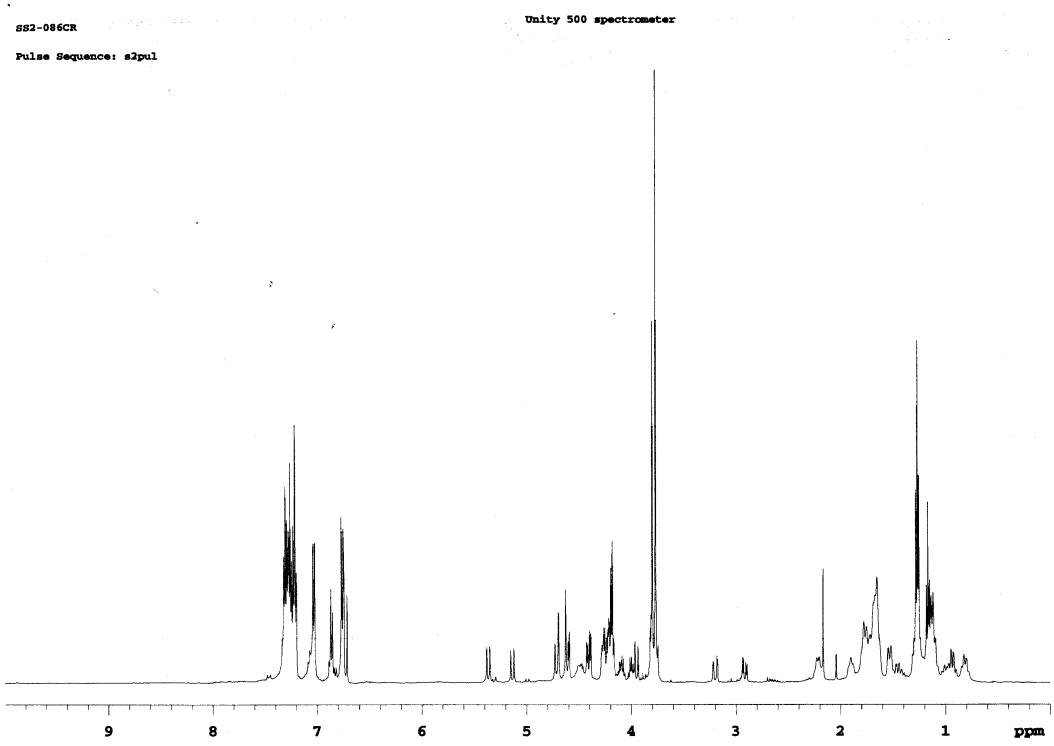
^{1}H NMR (Compound 90)



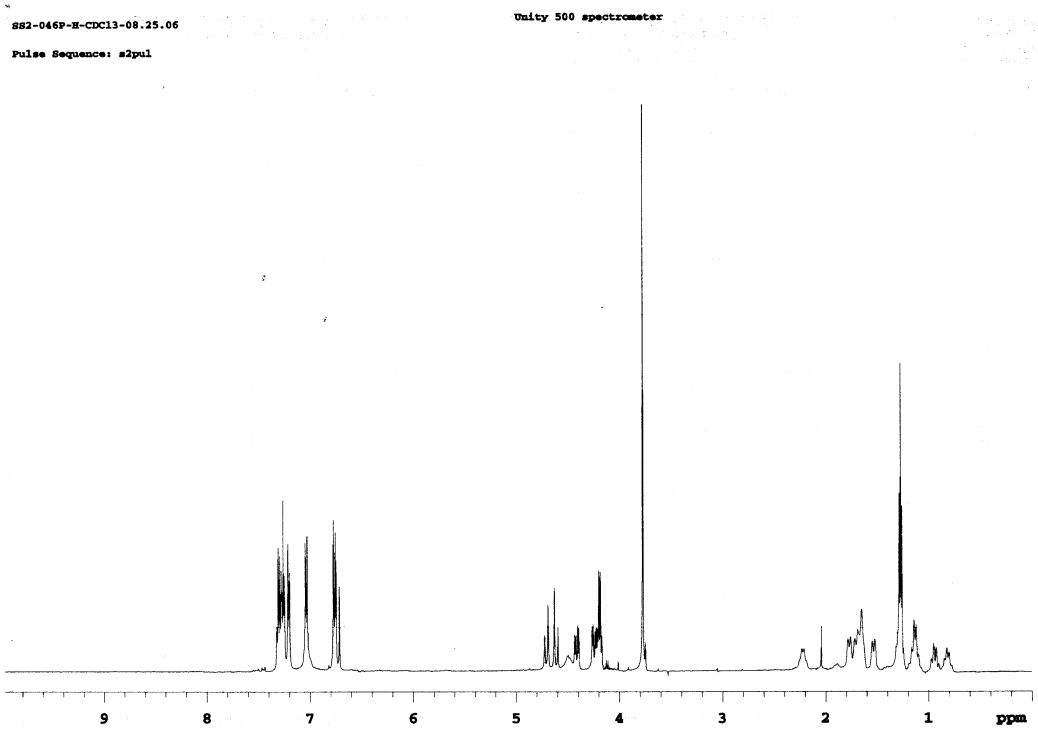
^{13}C NMR (Compound 90)



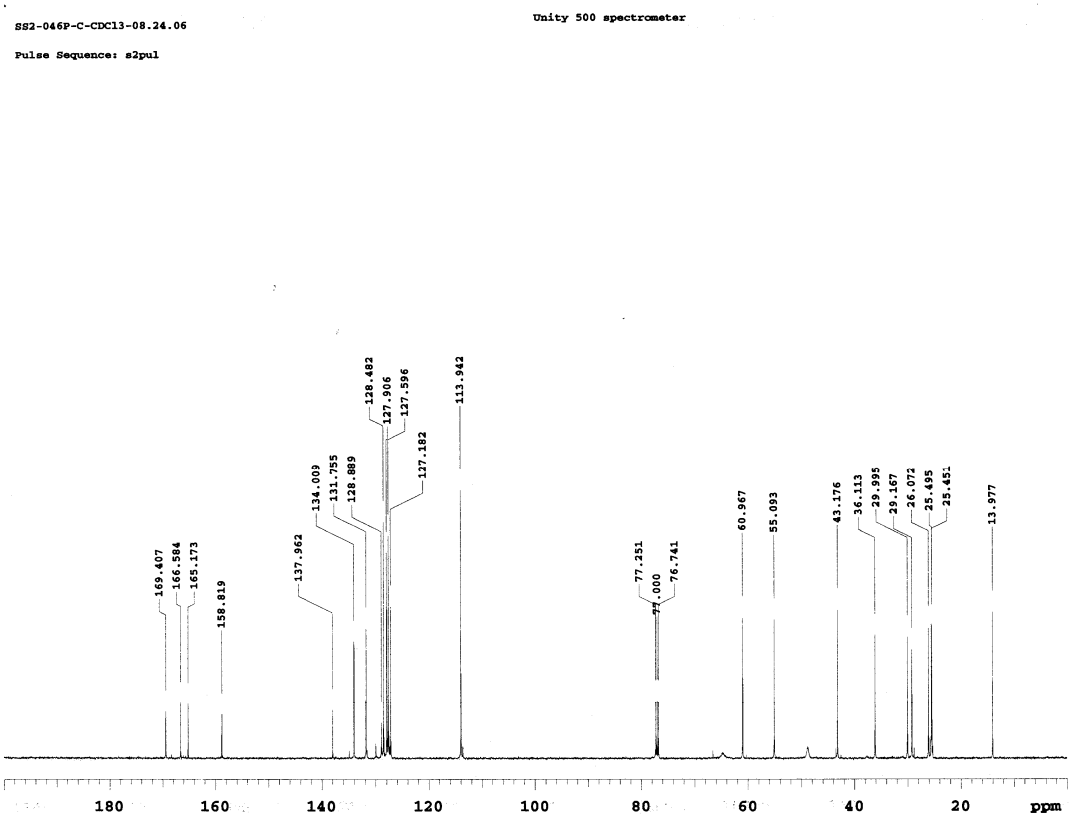
^{1}H NMR (Compound 91)



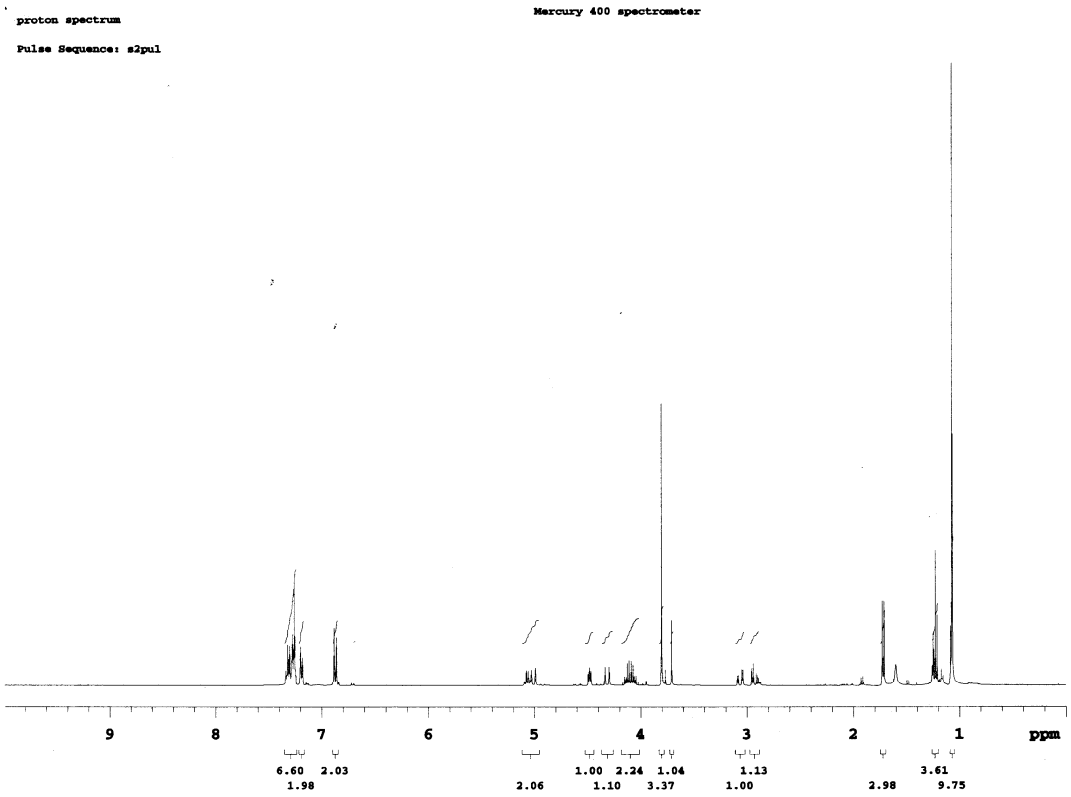
^{1}H NMR (Compound 92)



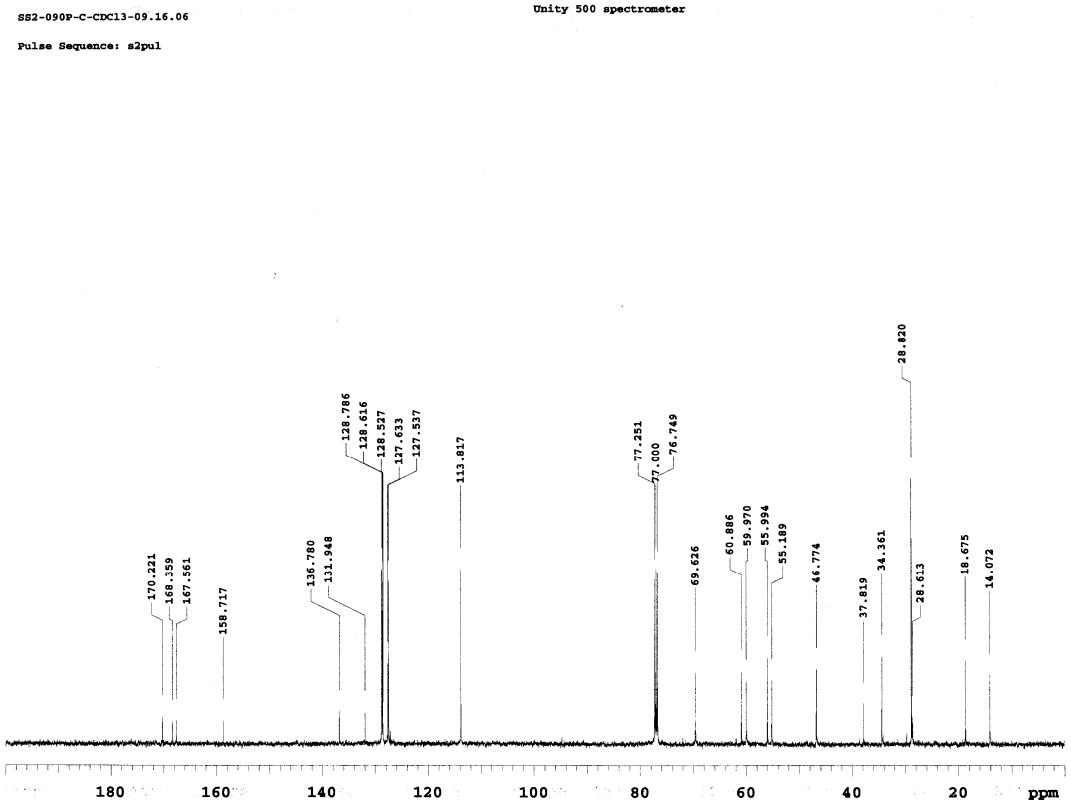
^{13}C NMR (Compound 92)



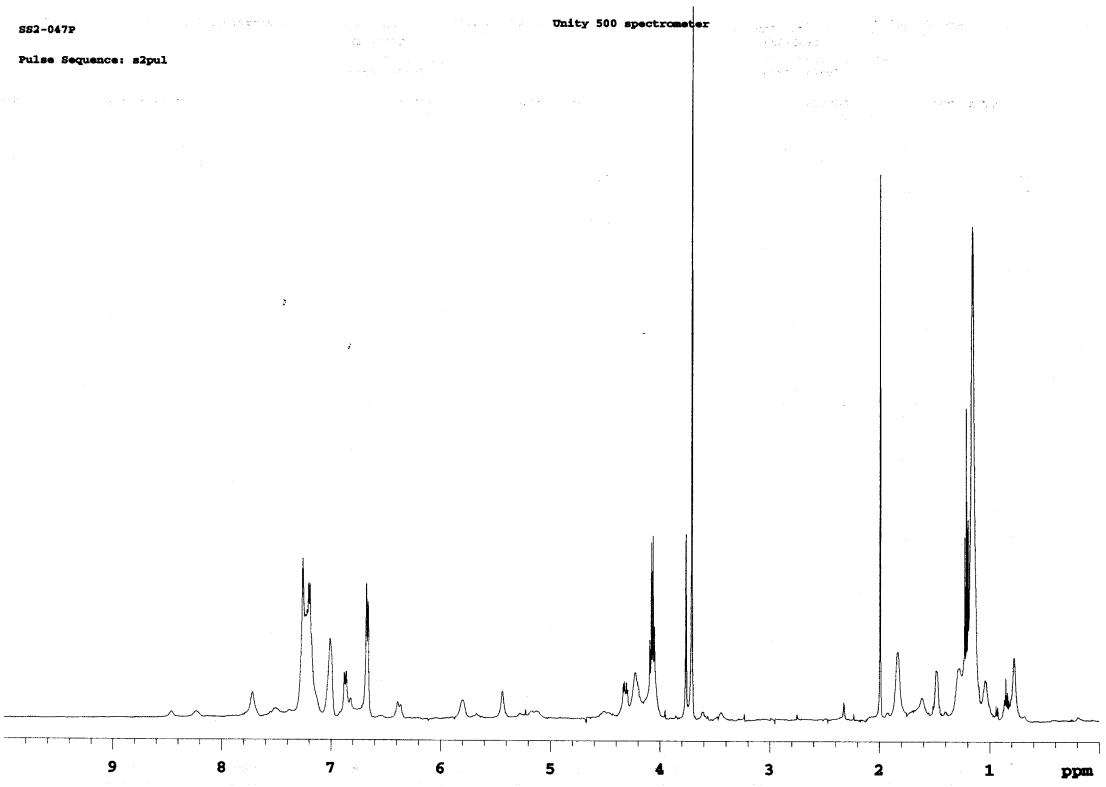
^{1}H NMR (Compound 93)



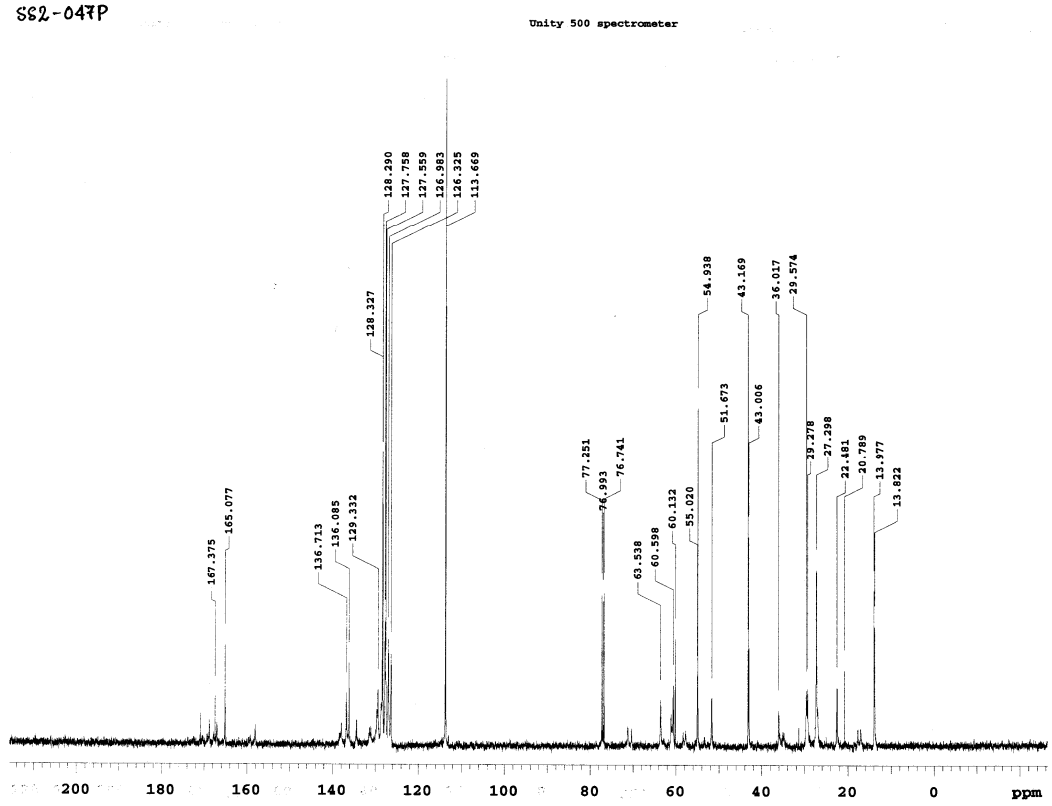
^{13}C NMR (Compound 93)



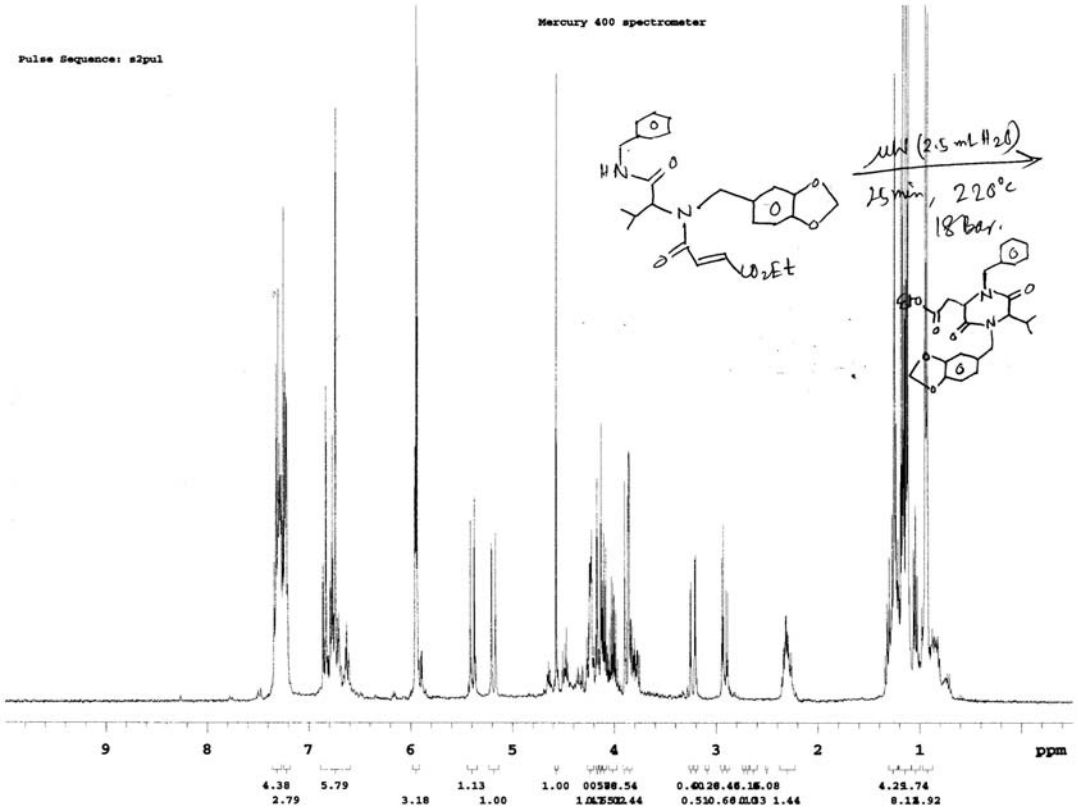
^{1}H NMR (Compound 94)



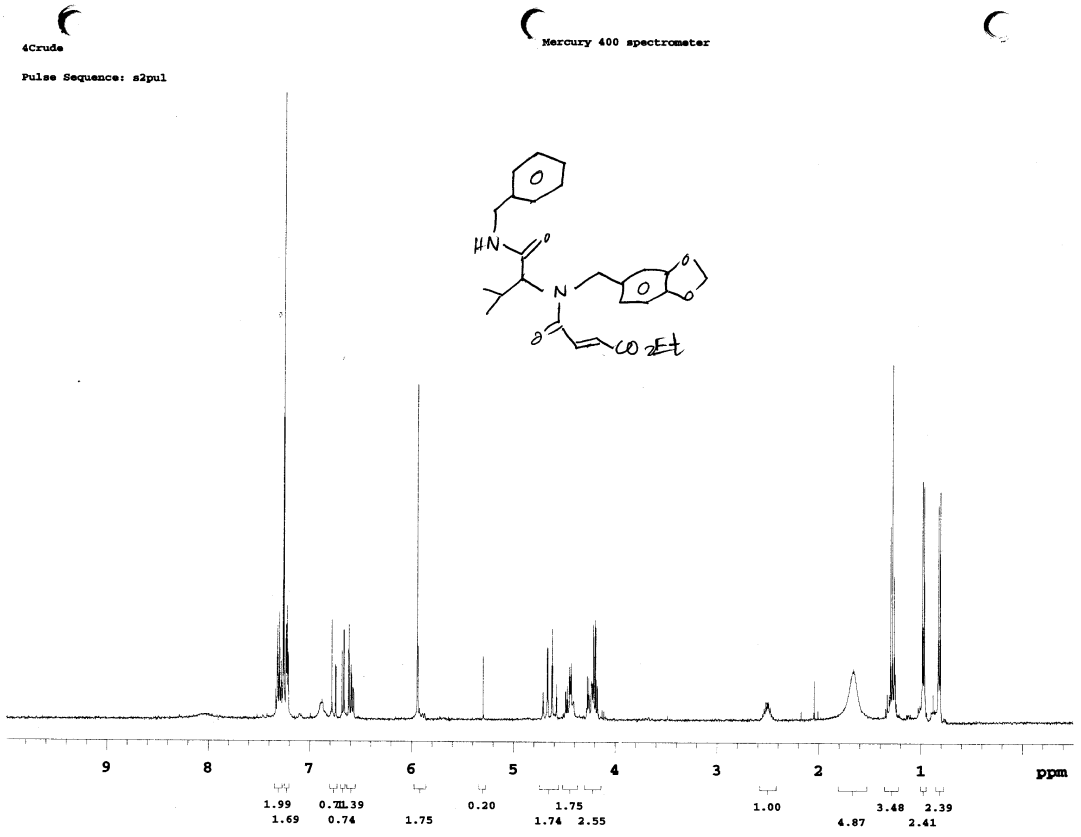
^{13}C NMR (Compound 94)



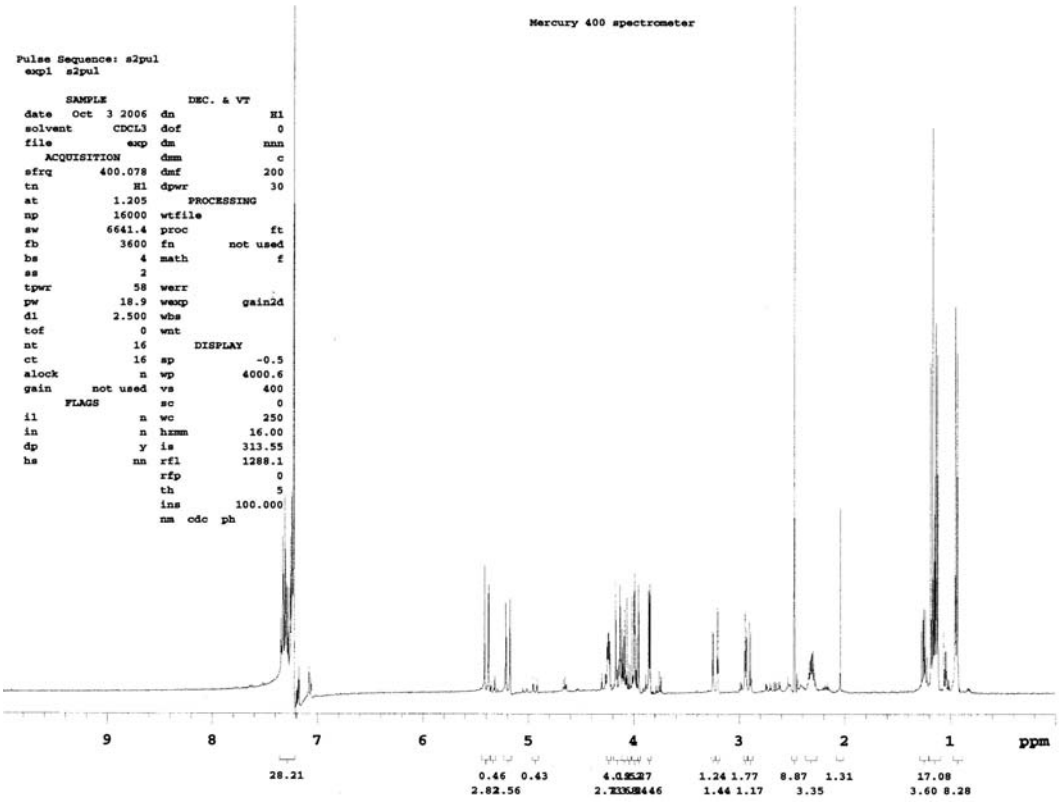
^{1}H NMR (Compound 95)



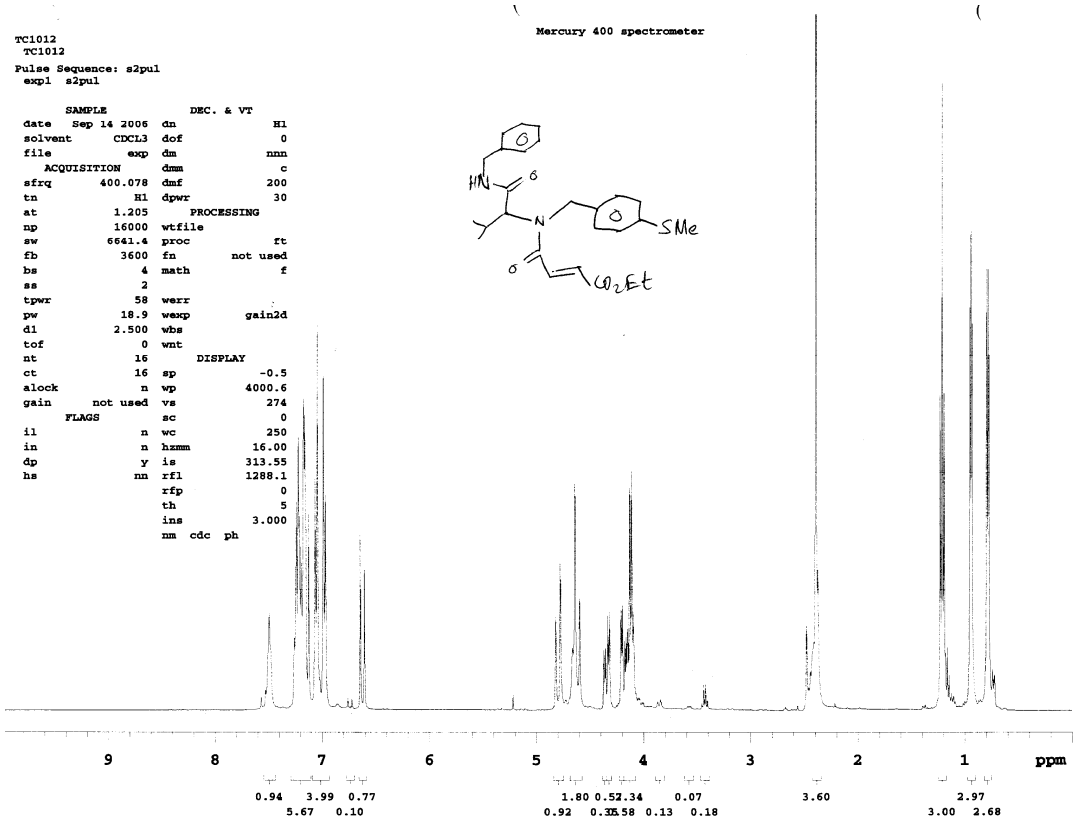
^{1}H NMR (Compound 96)



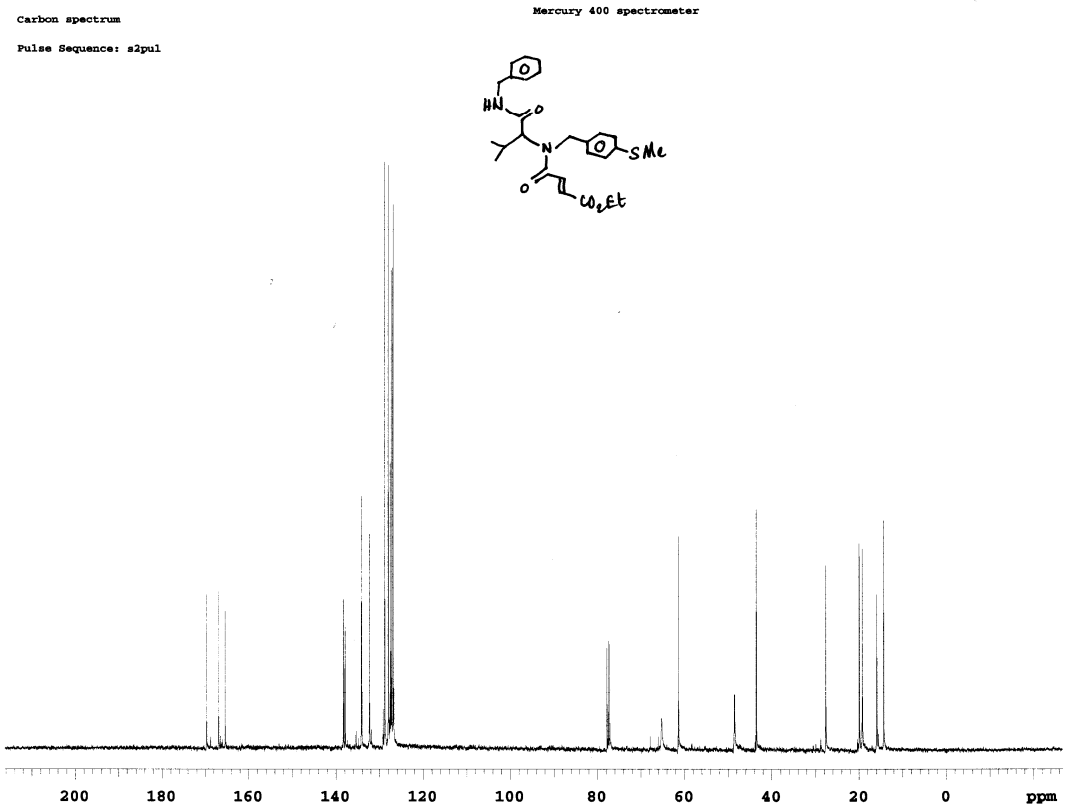
^{1}H NMR (Compound 97)



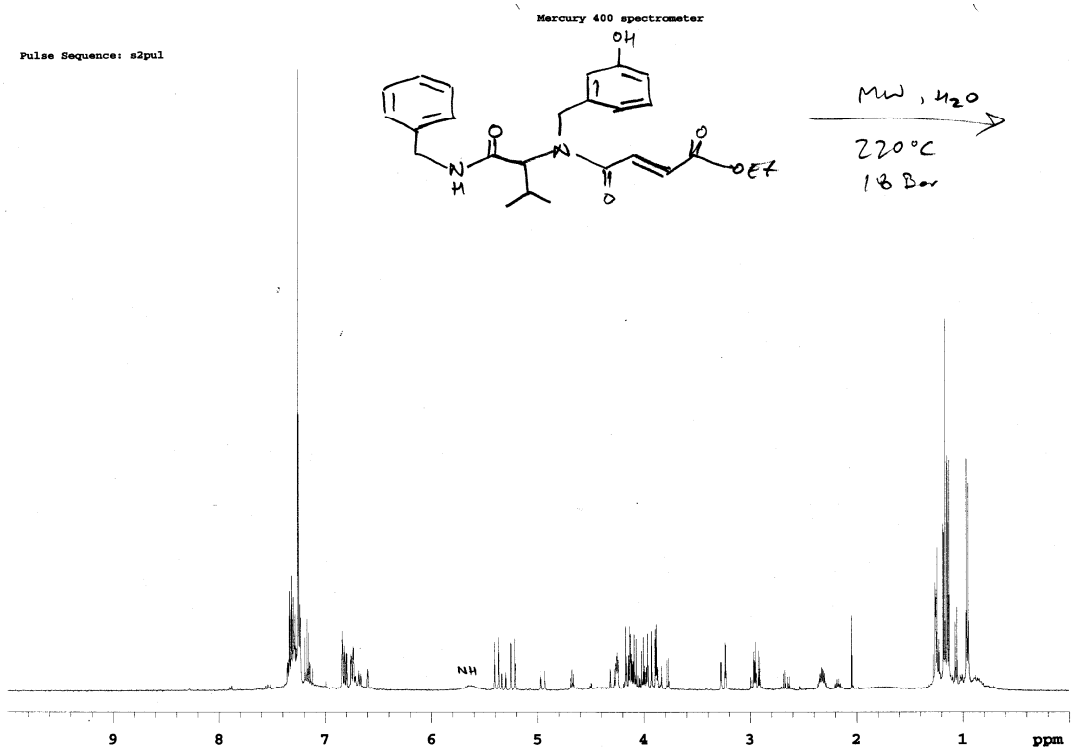
^{1}H NMR (Compound 98)



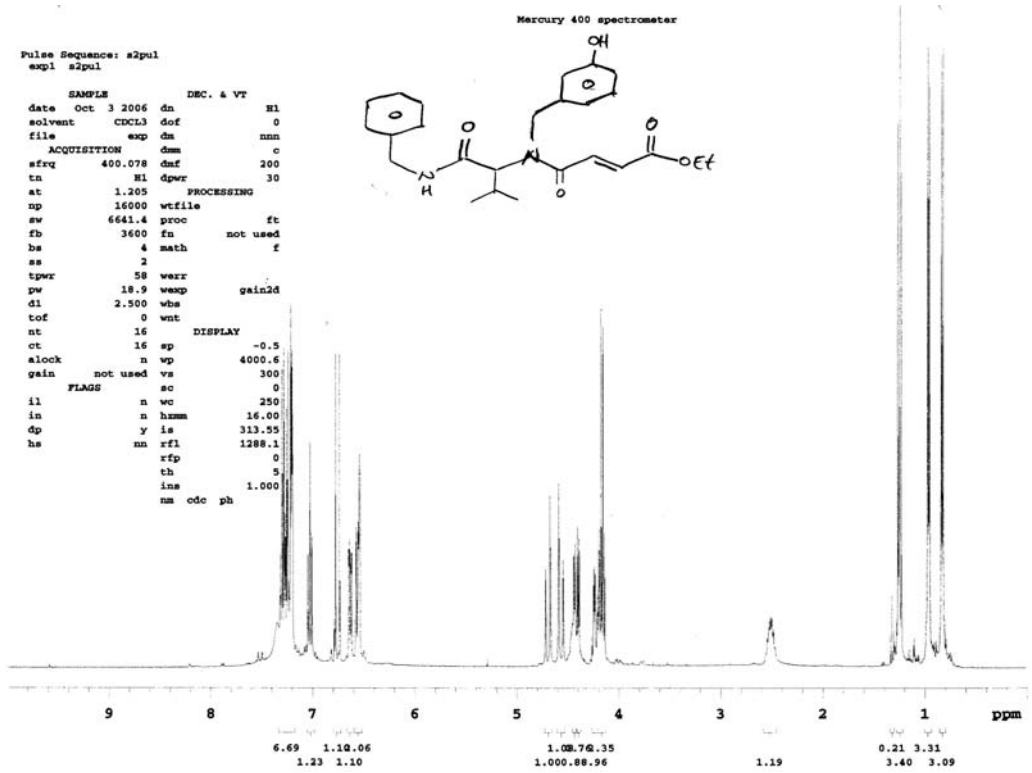
^{13}C NMR (Compound 98)



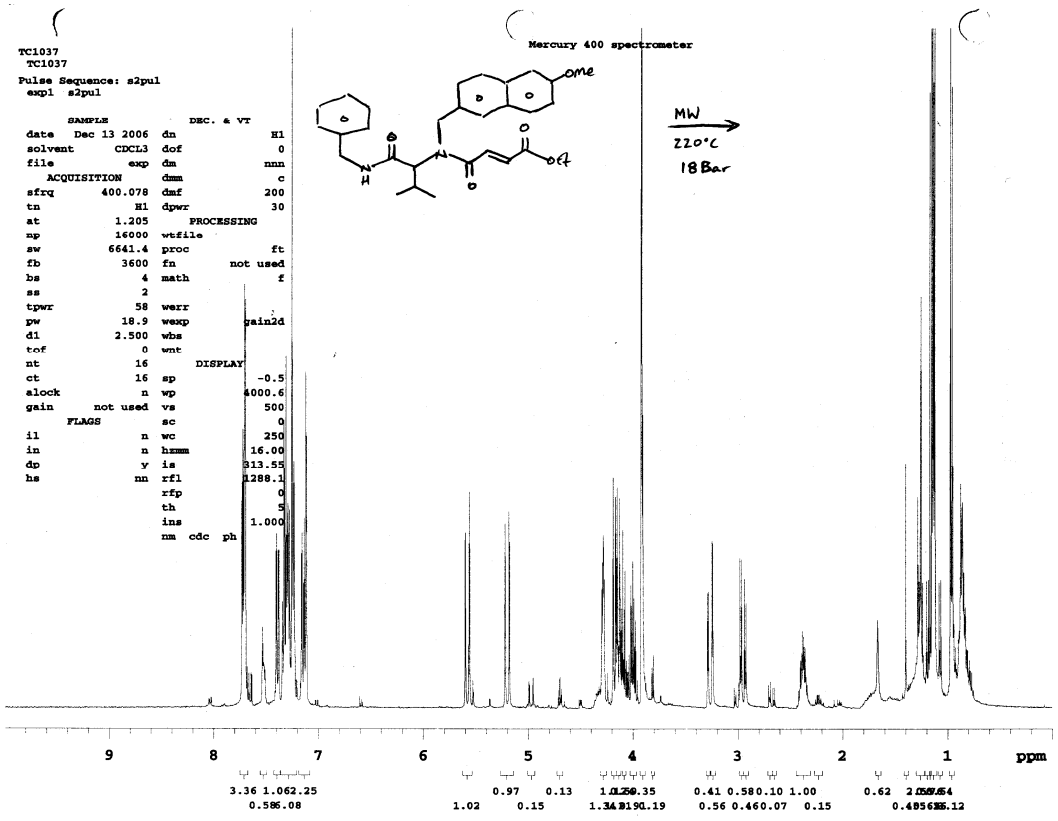
^{1}H NMR (Compound 99)



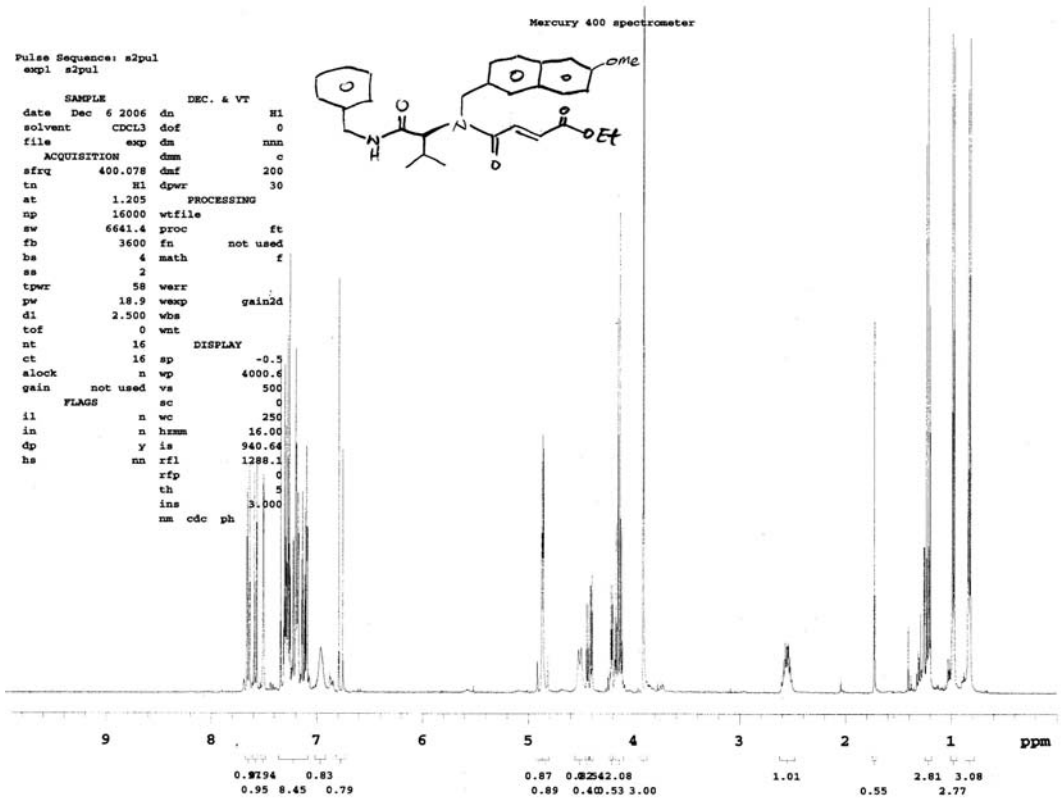
^{1}H NMR (Compound 100)



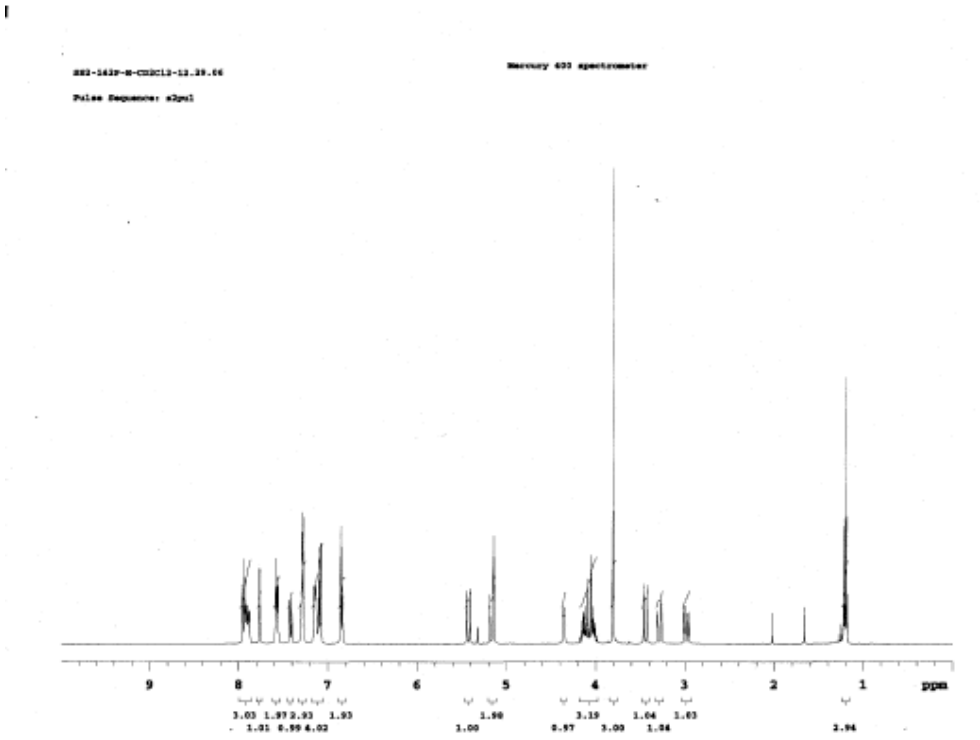
^{1}H NMR (Compound 101)



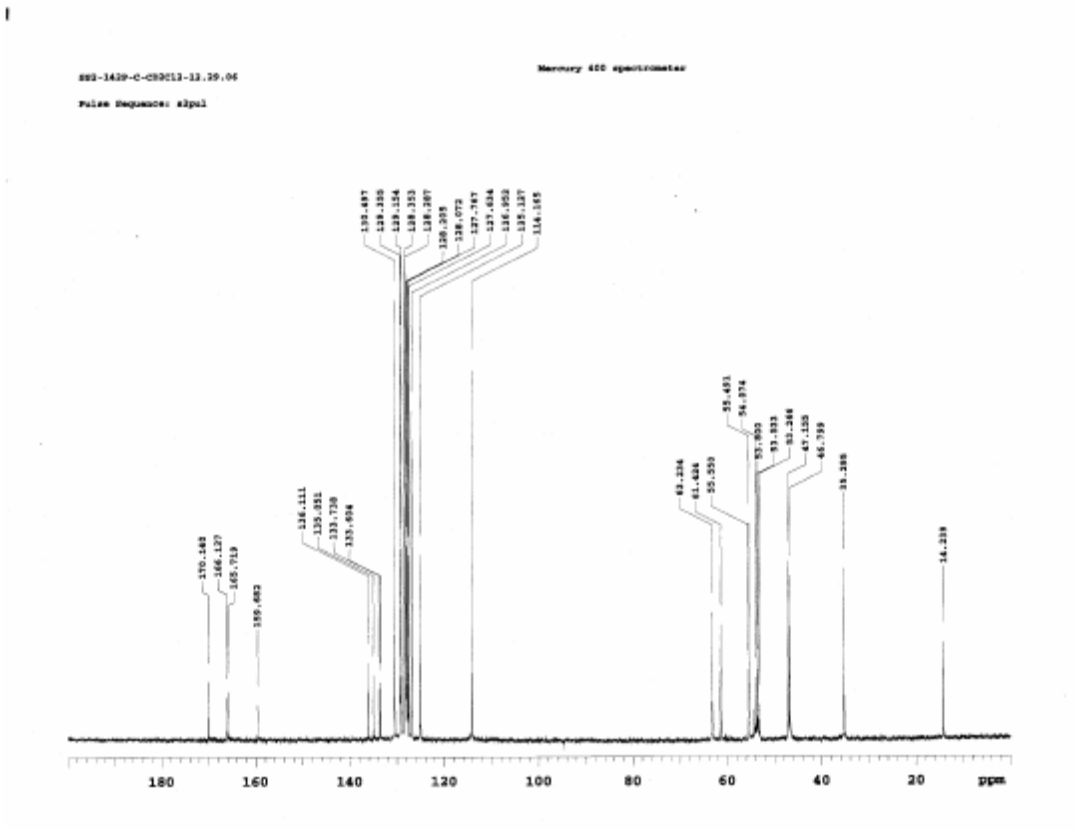
[1]H NMR (Compound 102)



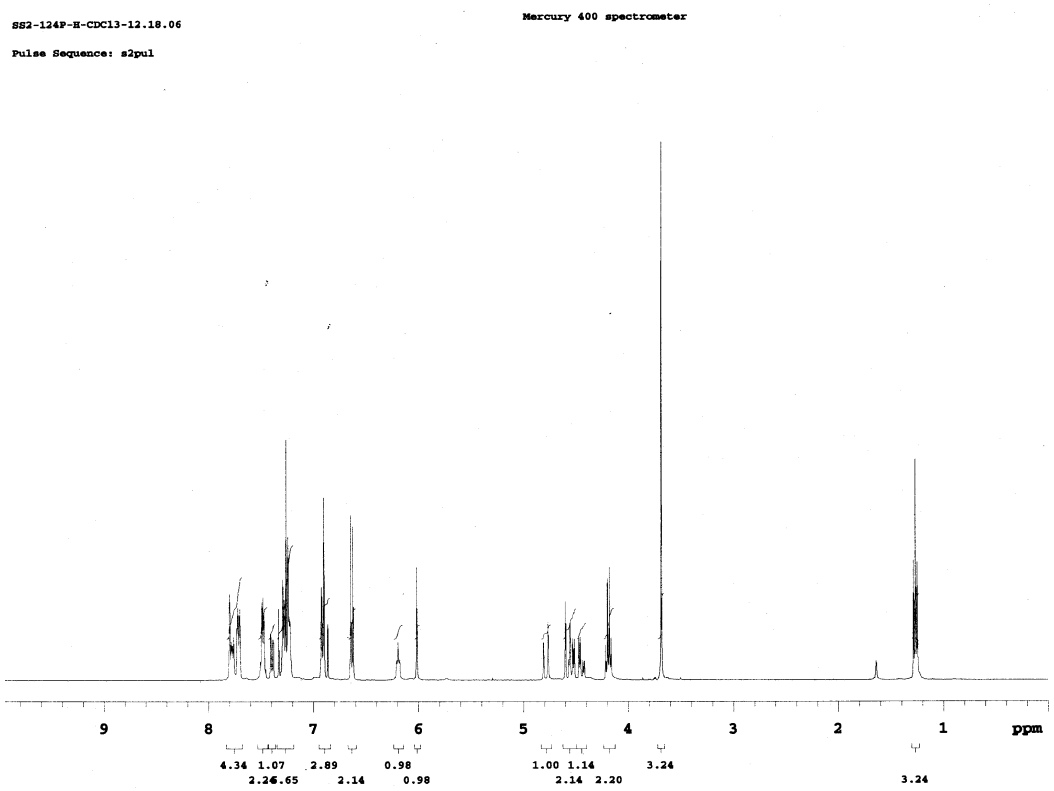
[1]H NMR (Compound 103)



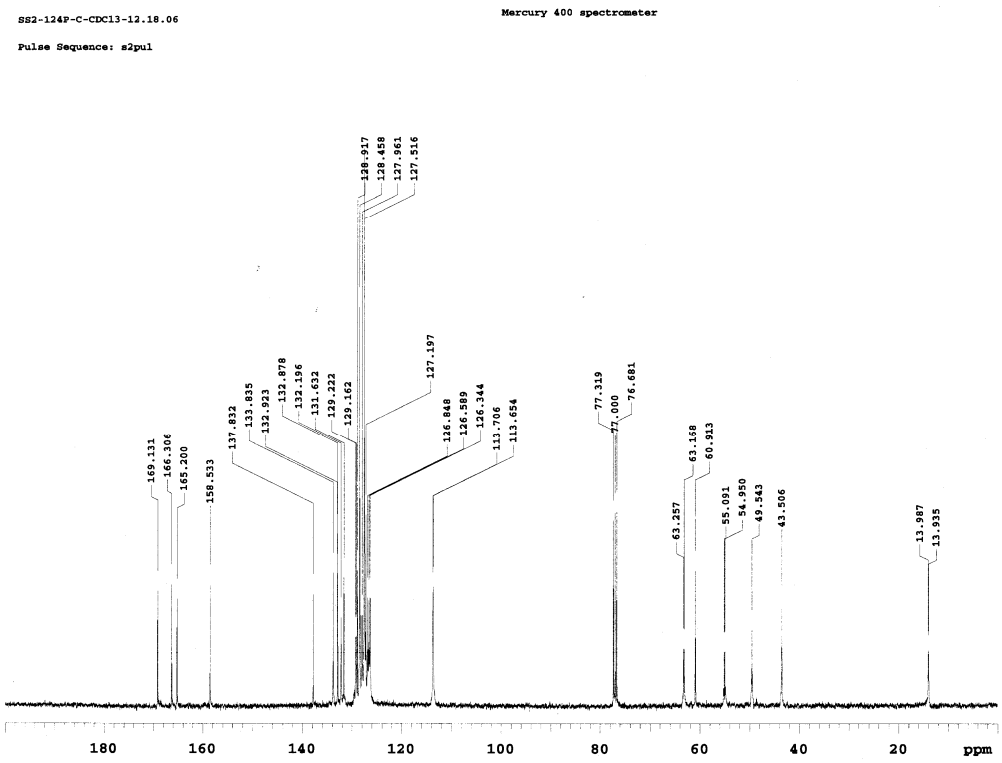
^{13}C NMR (Compound 103)



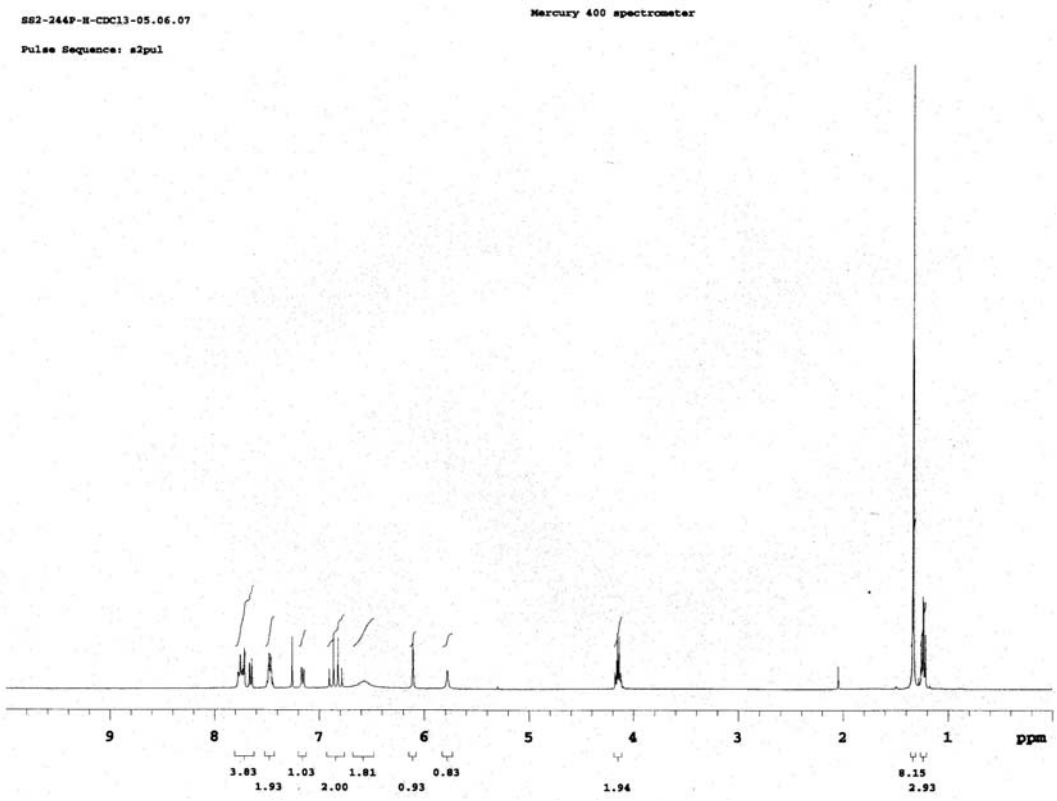
^{1}H NMR (Compound 103a)



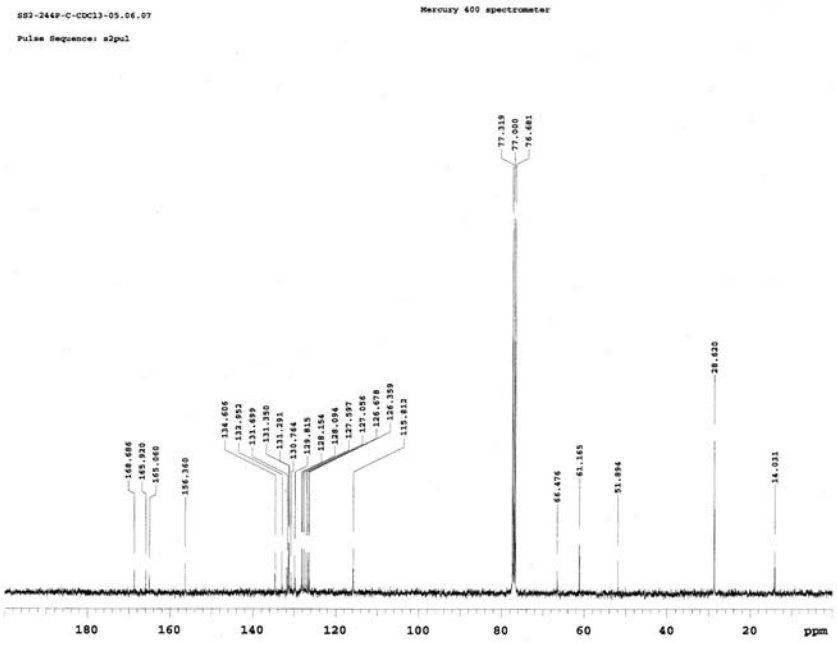
^{13}C NMR (Compound 103a)



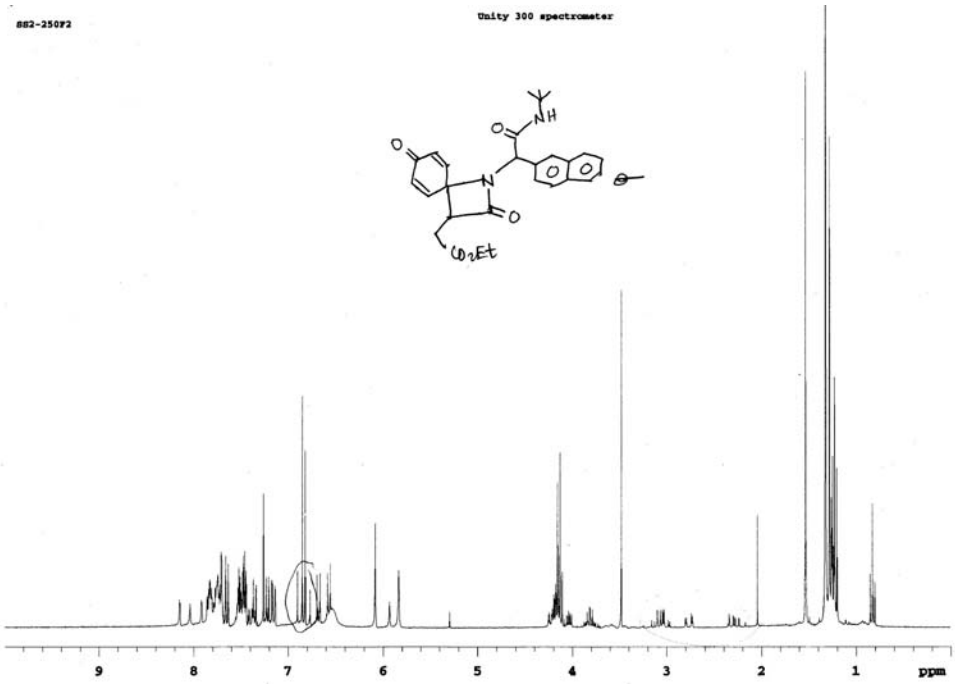
^{1}H NMR (Compound 112)



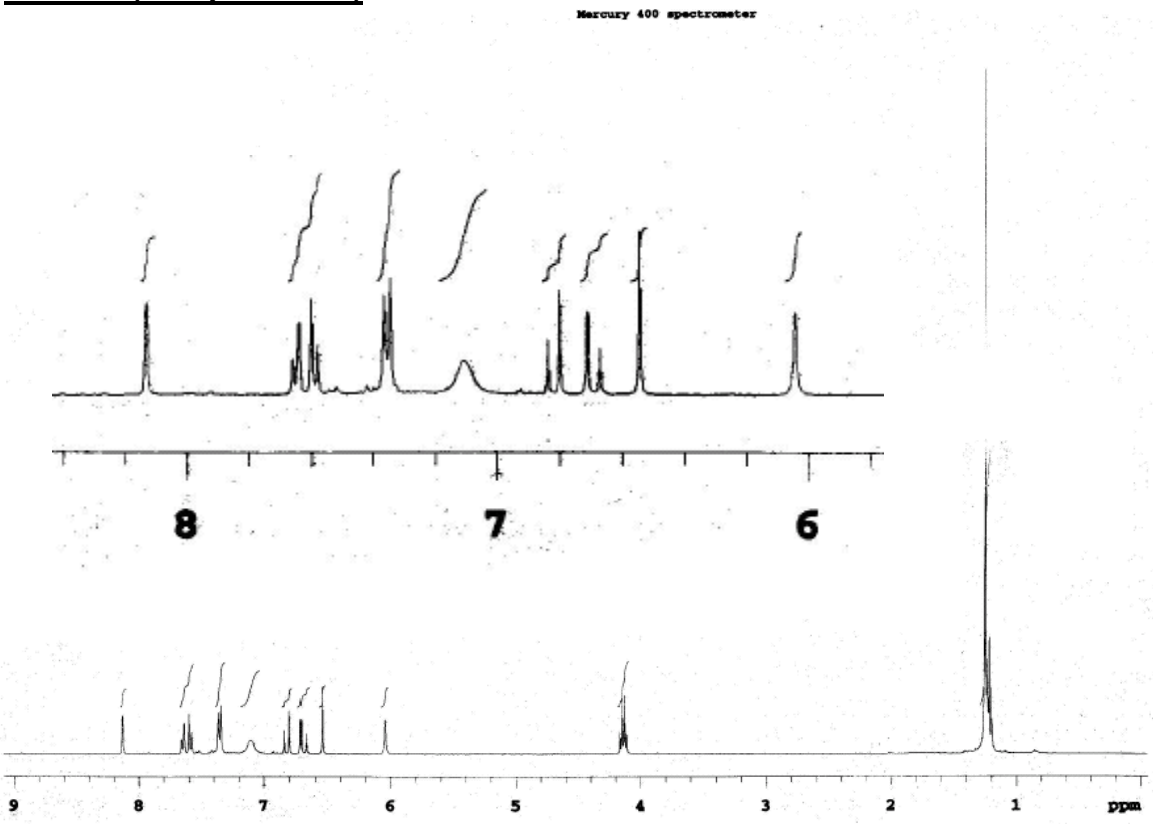
^{13}C NMR (Compound 112)



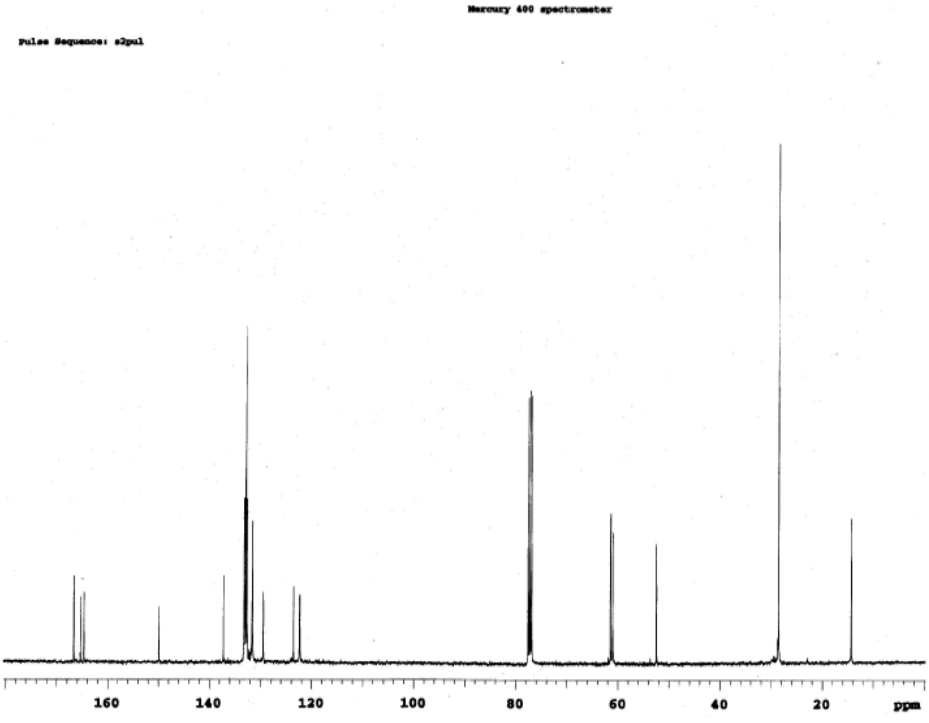
^{1}H NMR (Compound 113: inseparable from 112)



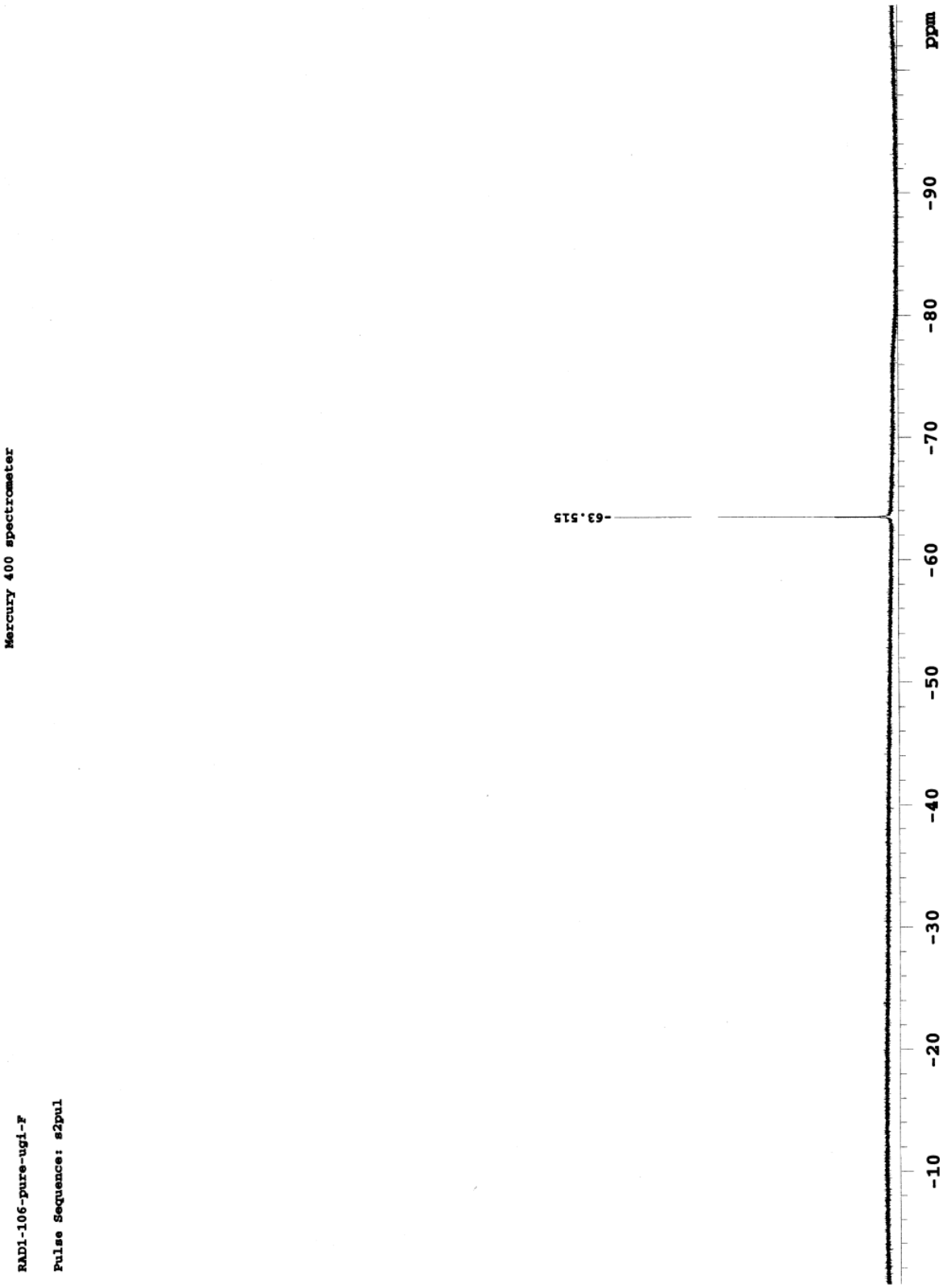
^{1}H NMR (Compound 122)



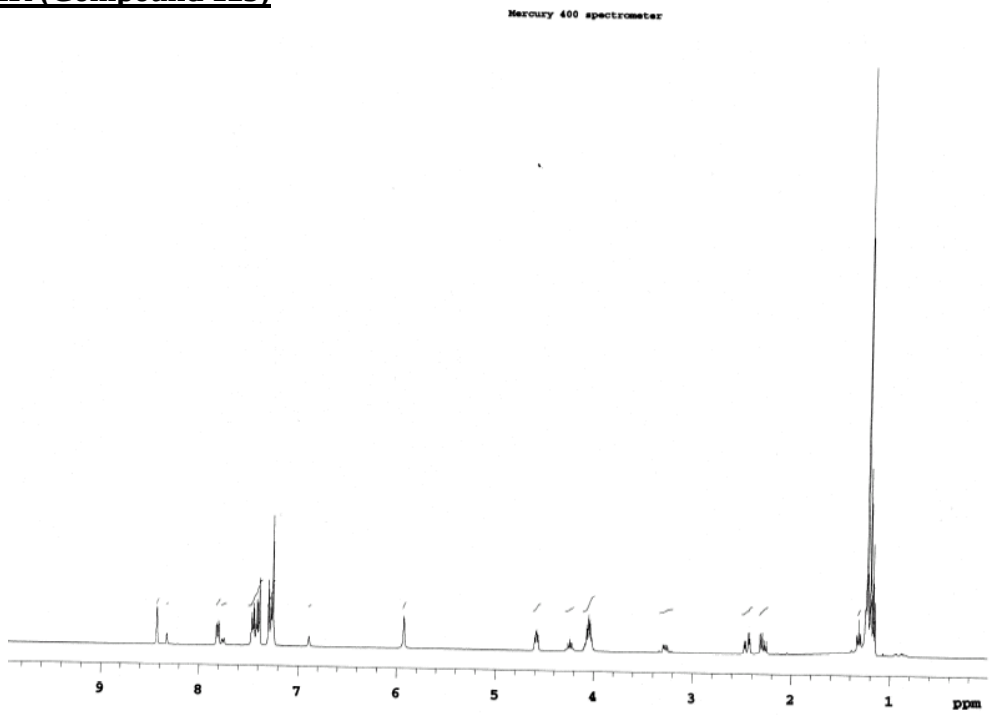
^{13}C NMR (Compound 122)



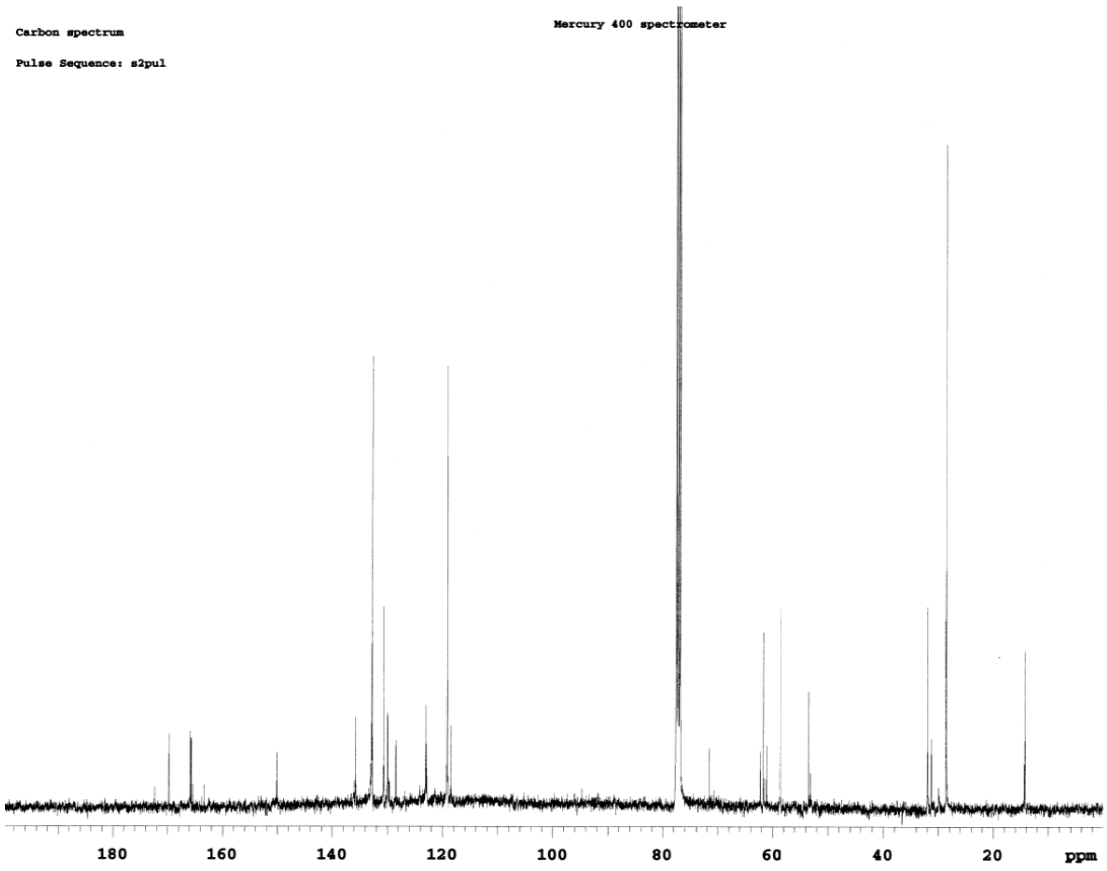
^{19}F NMR (Compound 122)



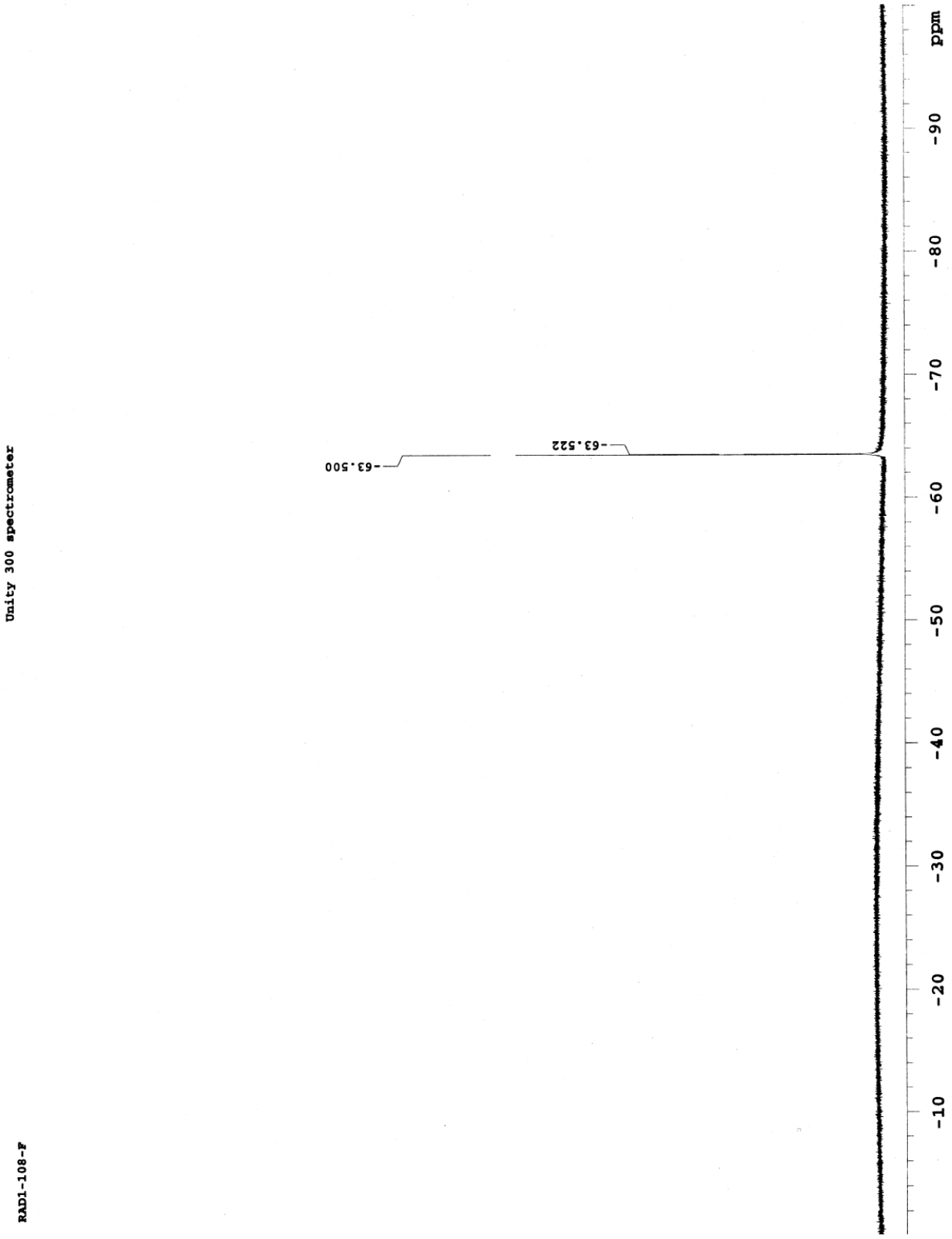
^{1}H NMR (Compound 123)



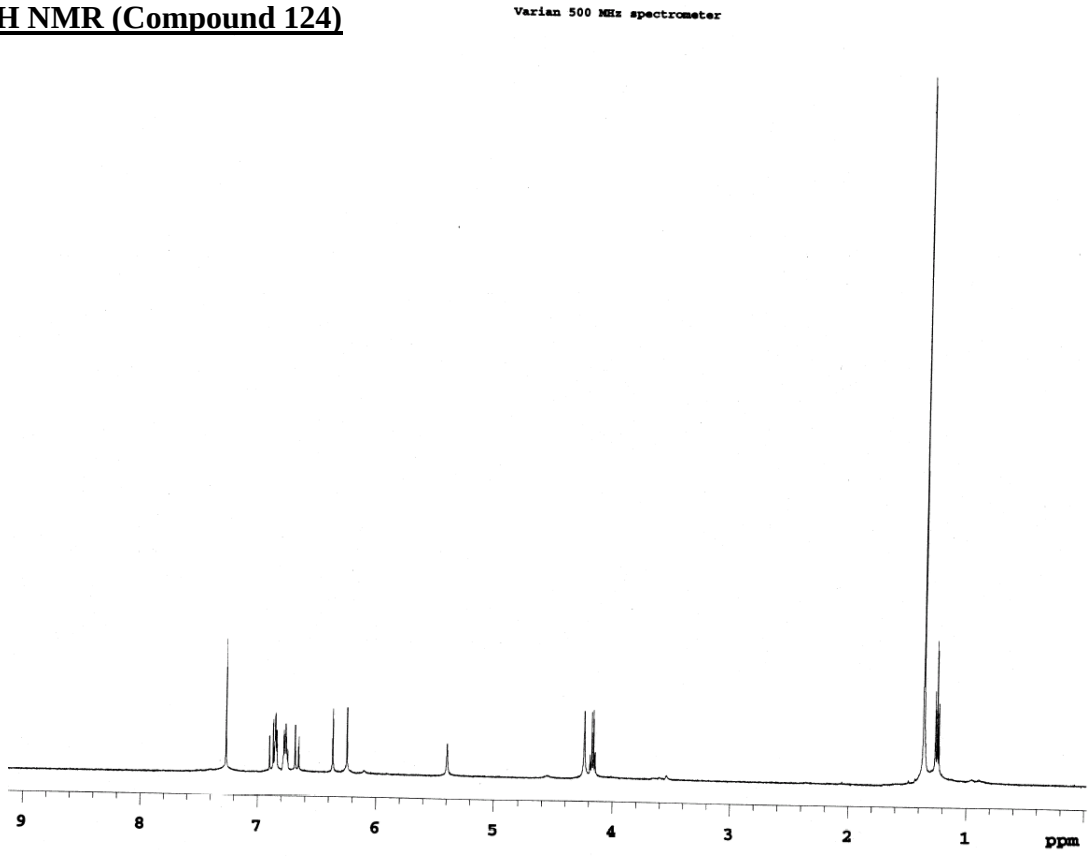
^{13}C NMR (Compound 123)



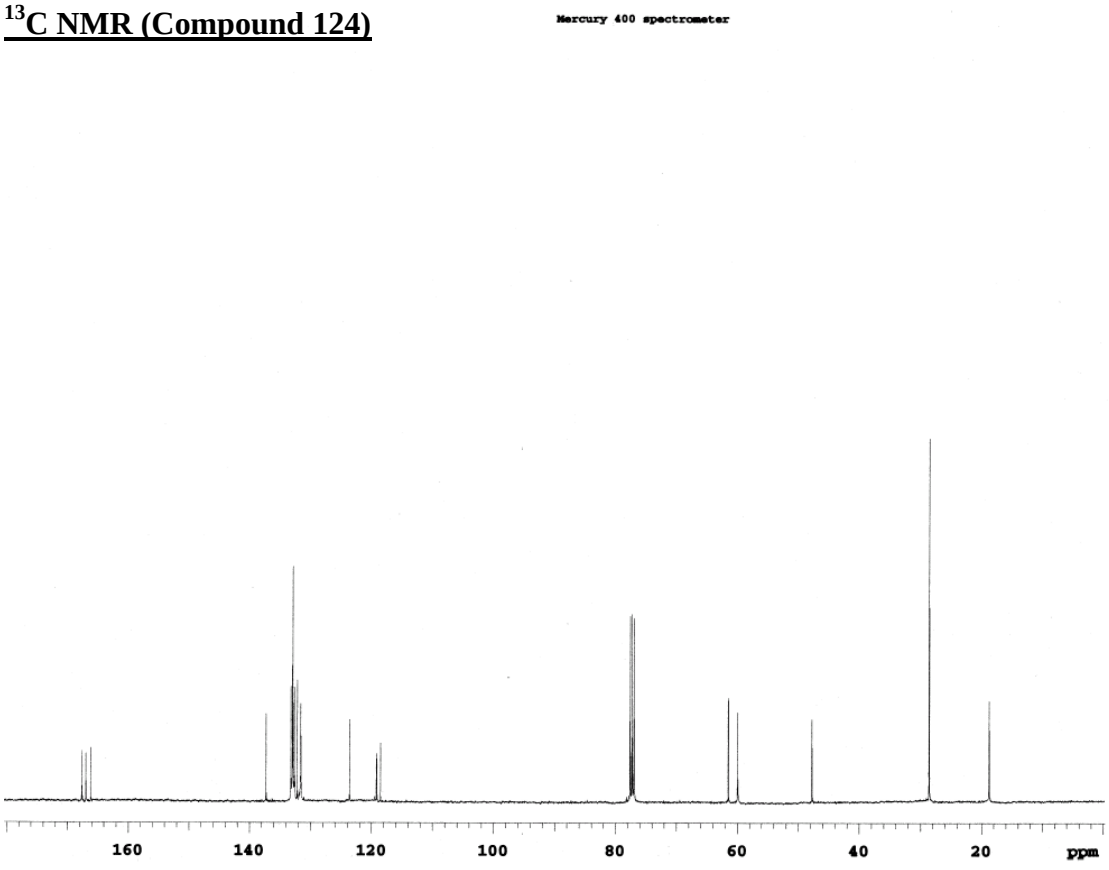
^{19}F NMR (Compound 123)



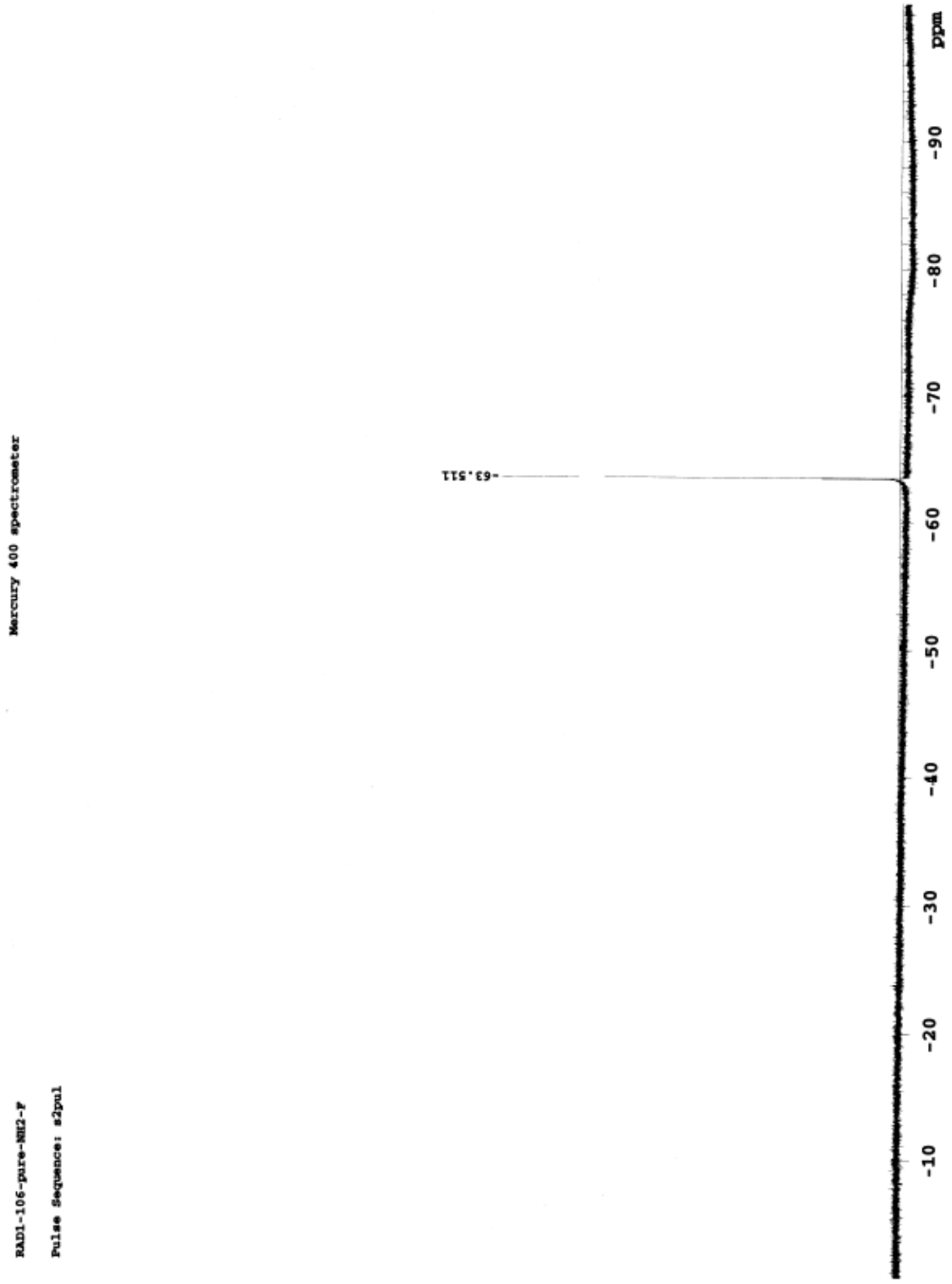
^{1}H NMR (Compound 124)



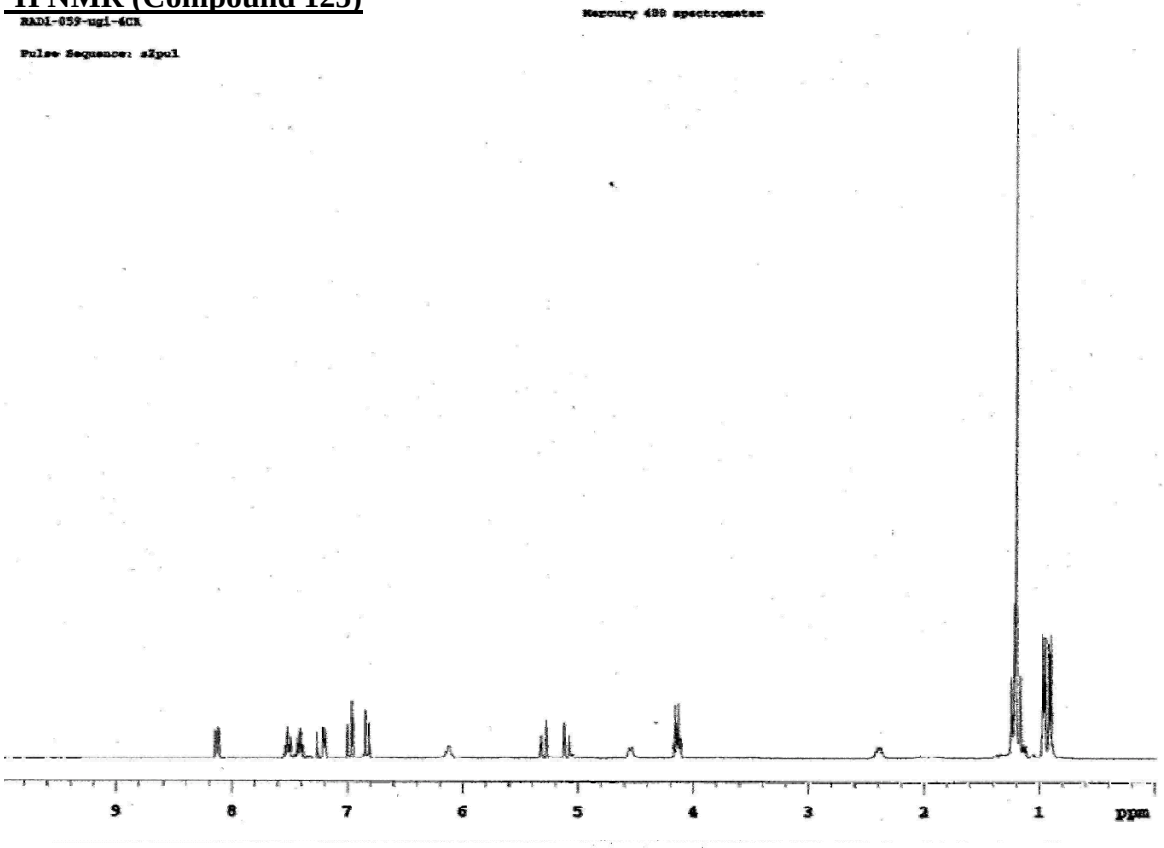
^{13}C NMR (Compound 124)



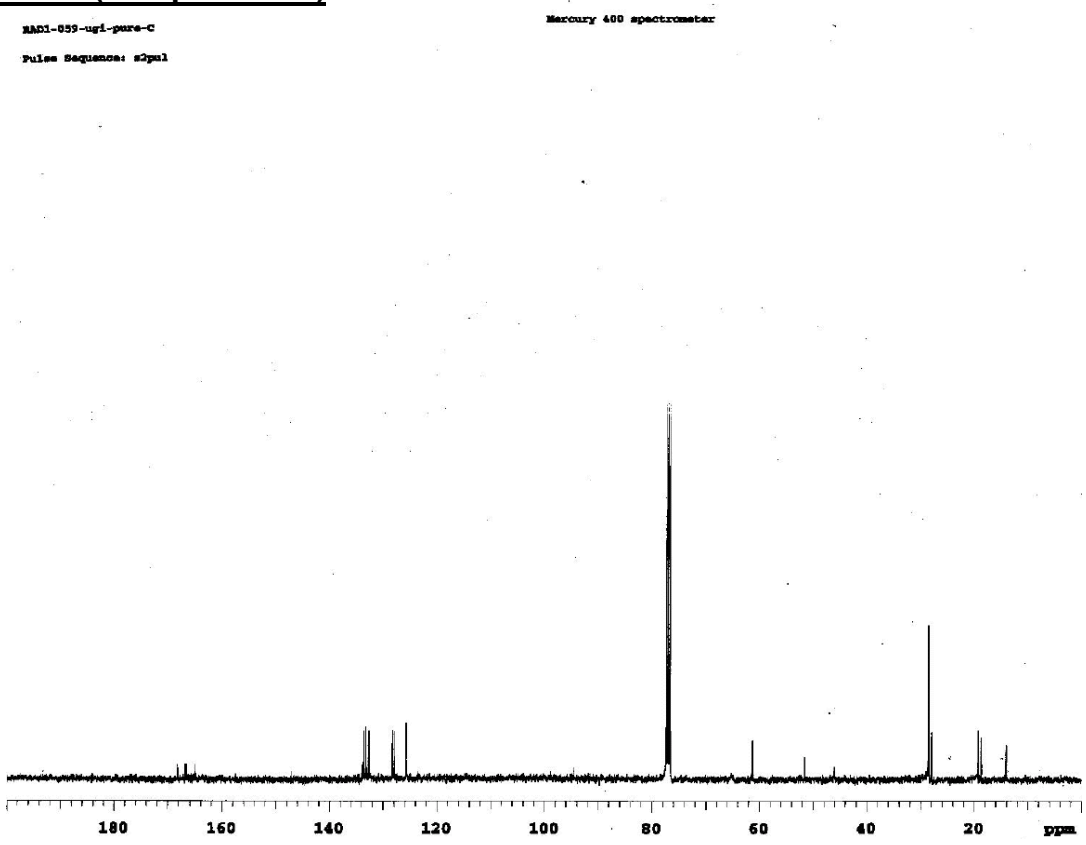
^{19}F NMR (Compound 124)

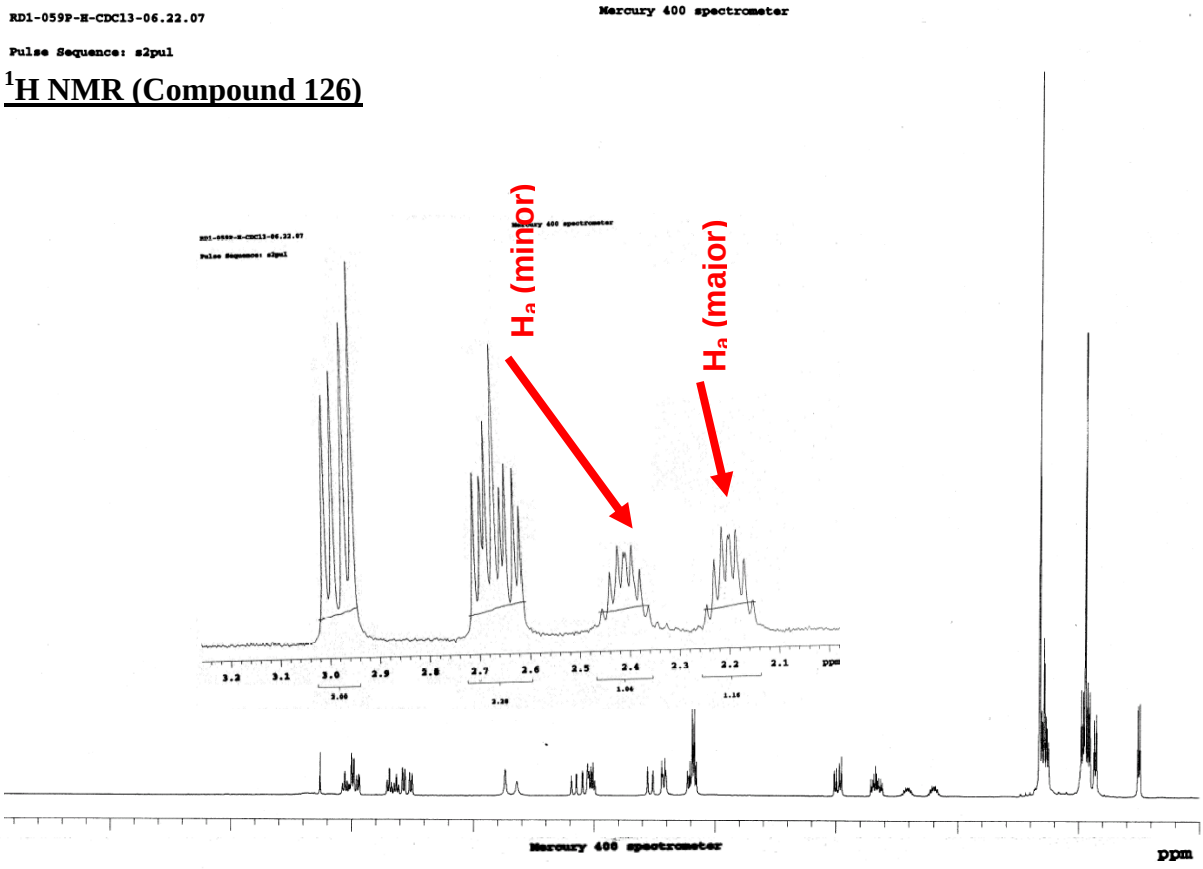


^{1}H NMR (Compound 125)



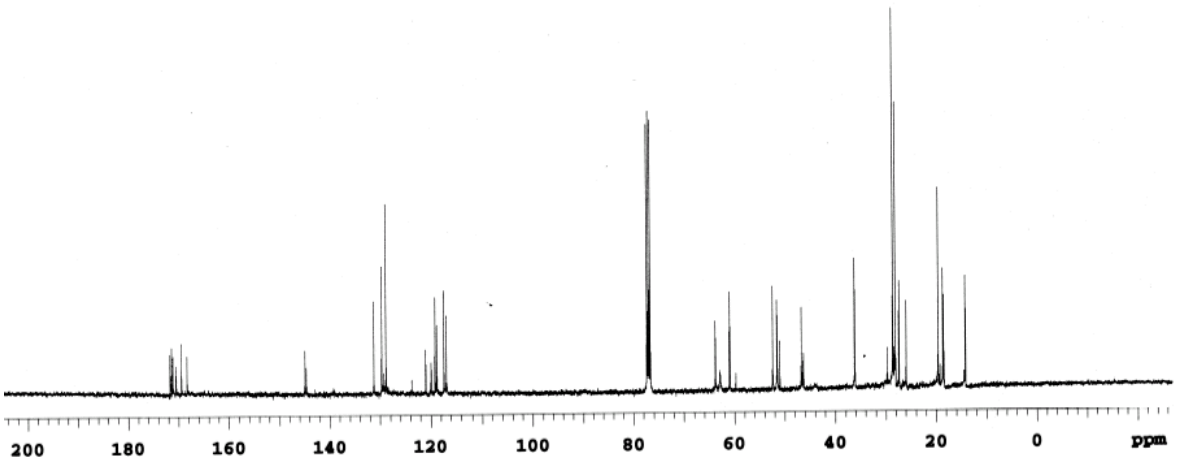
^{13}C NMR (Compound 125)



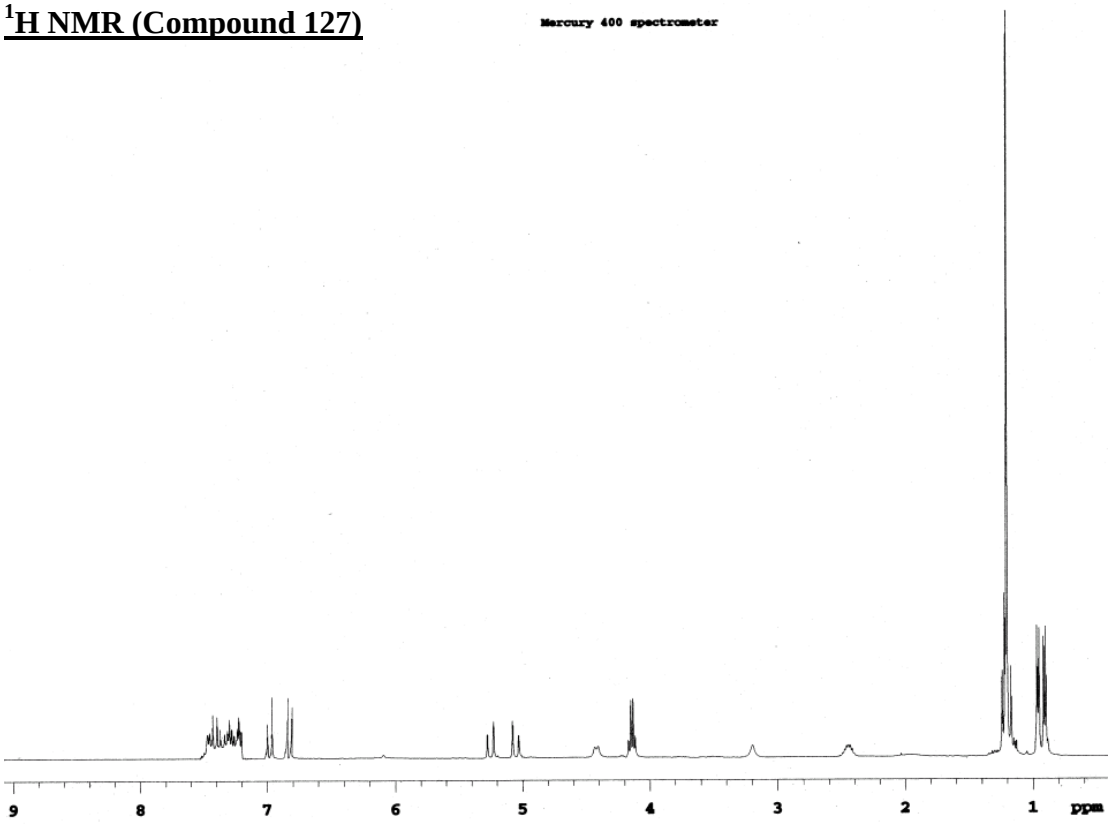


^{1}H NMR (Compound 126)

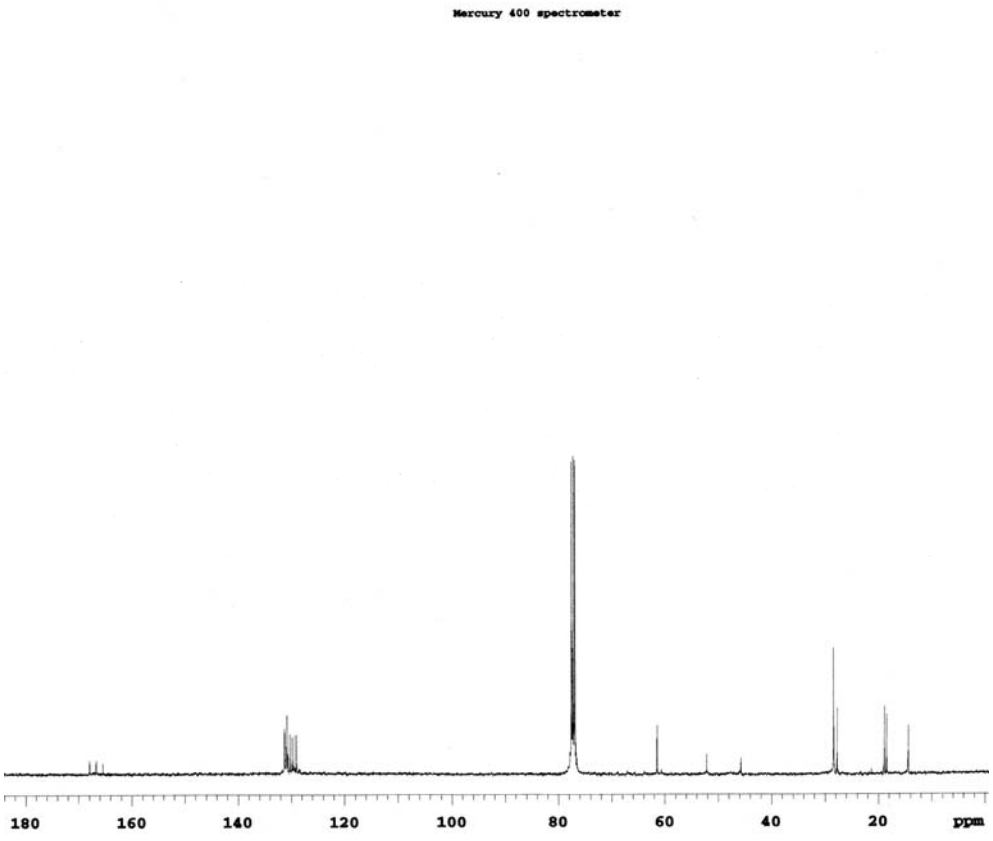
^{13}C NMR (Compound 126)



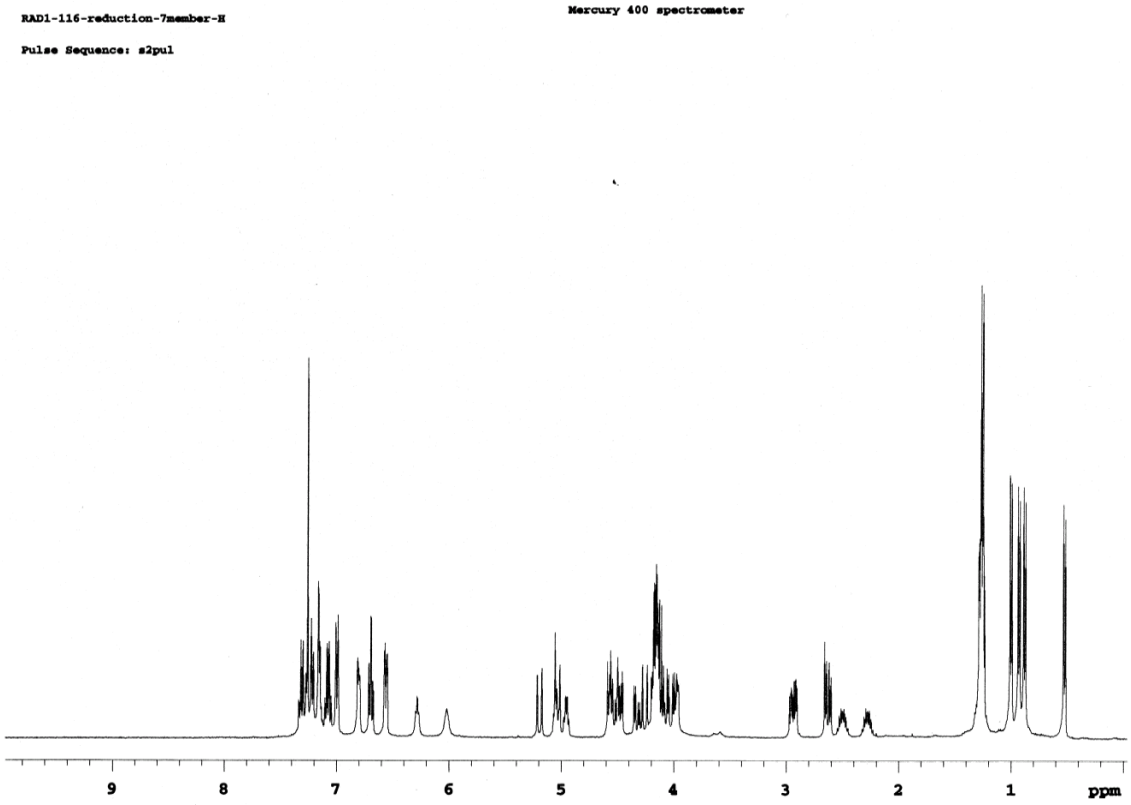
^{1}H NMR (Compound 127)



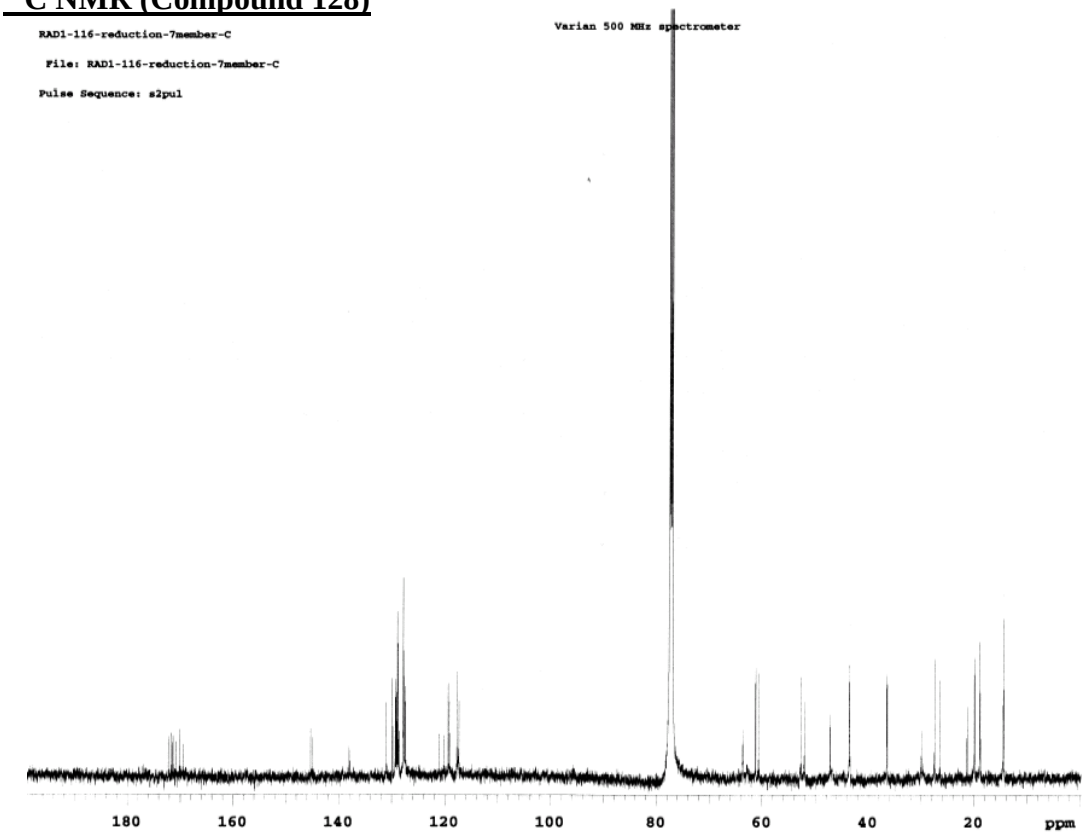
^{13}C NMR (Compound 127)



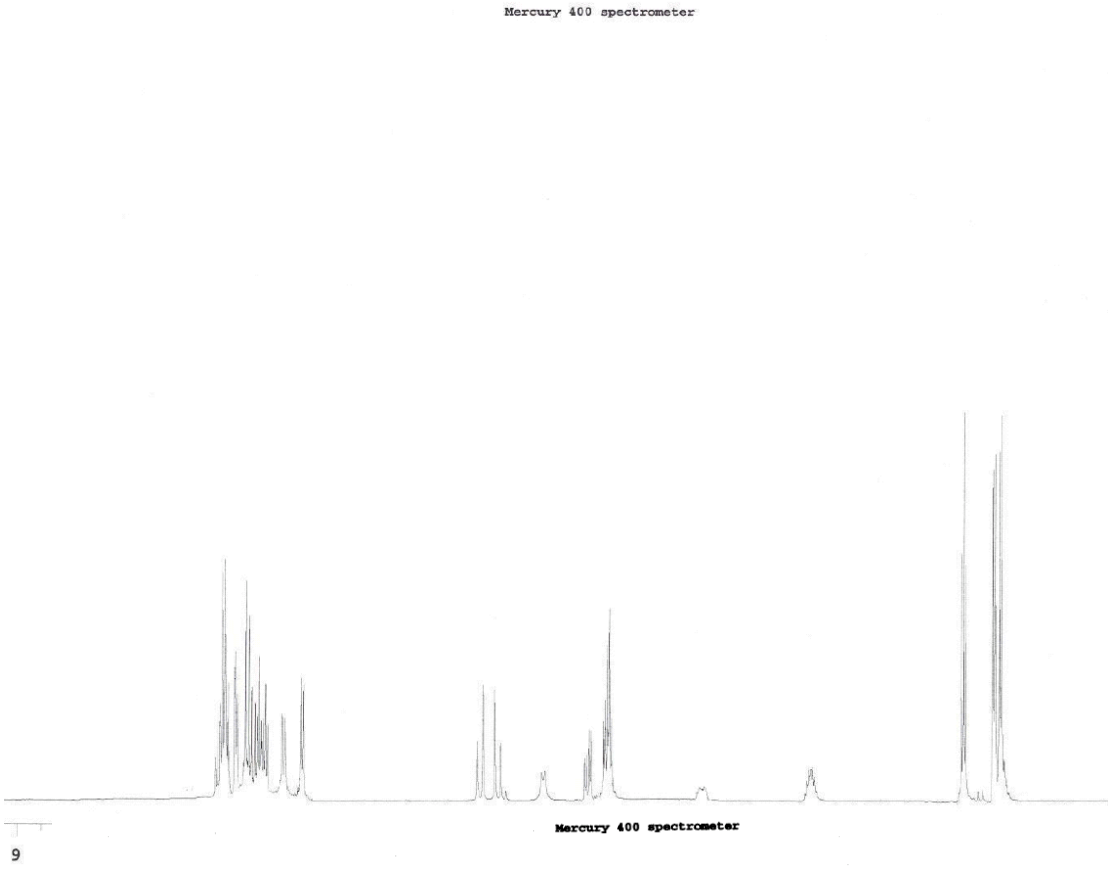
^{1}H NMR (Compound 128)



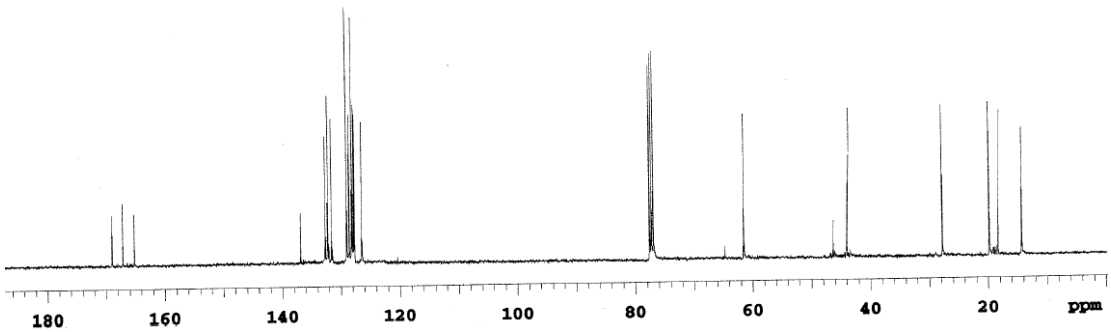
^{13}C NMR (Compound 128)



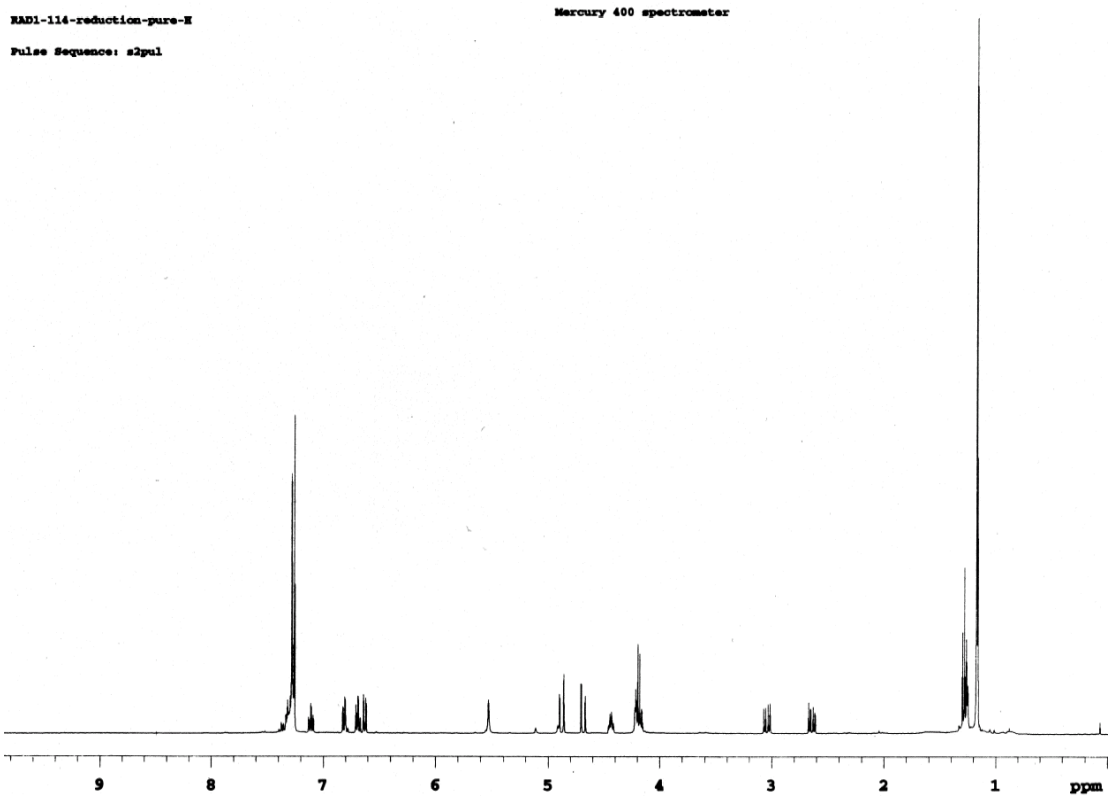
^{1}H NMR (Compound 129)



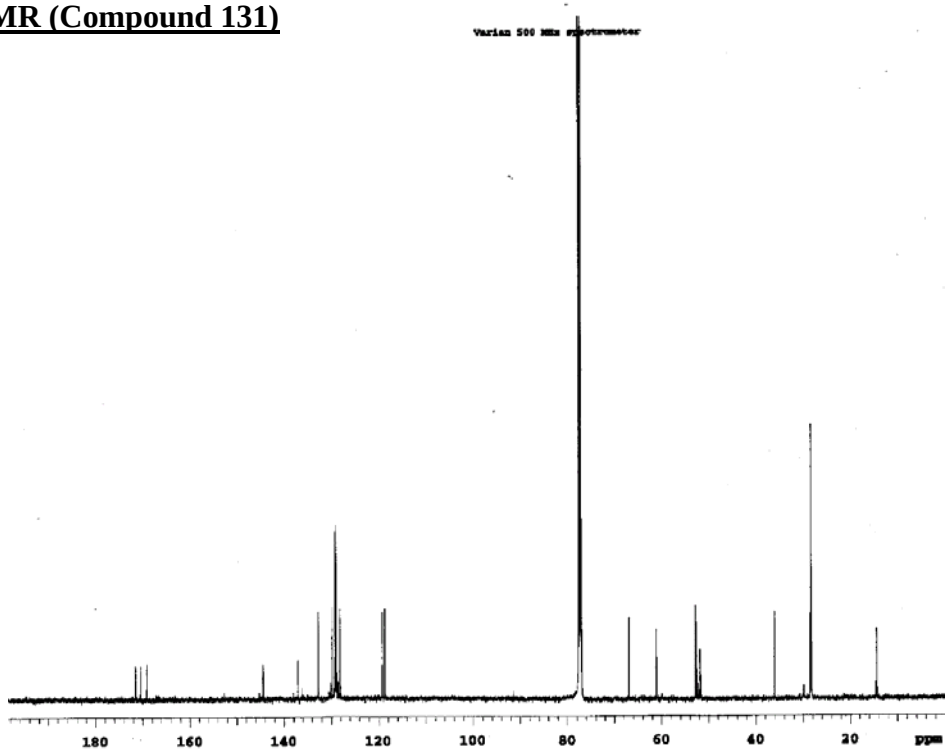
^{13}C NMR (Compound 129)



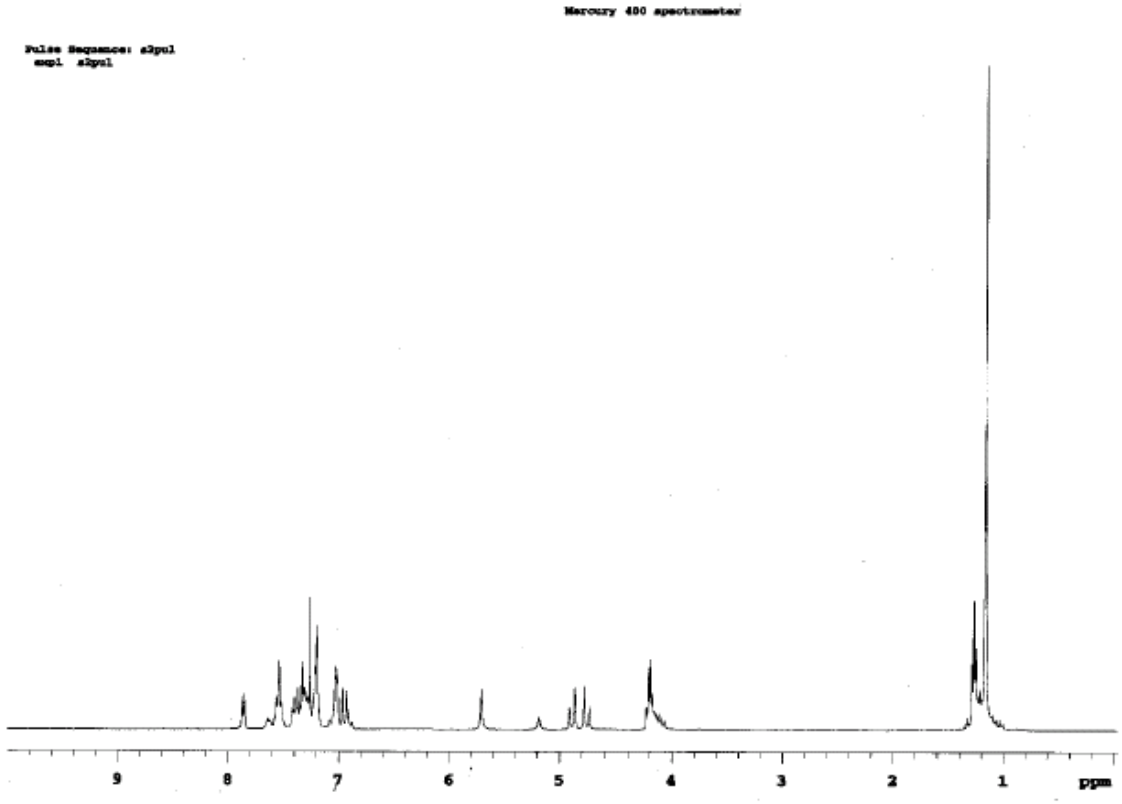
^{1}H NMR (Compound 131)



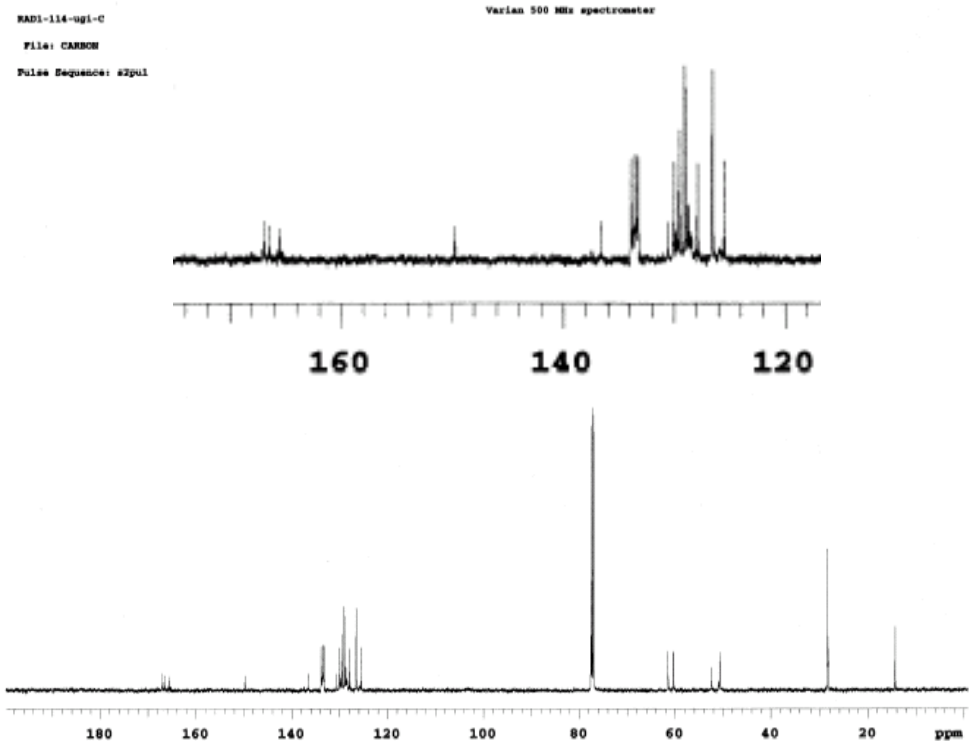
^{13}C NMR (Compound 131)



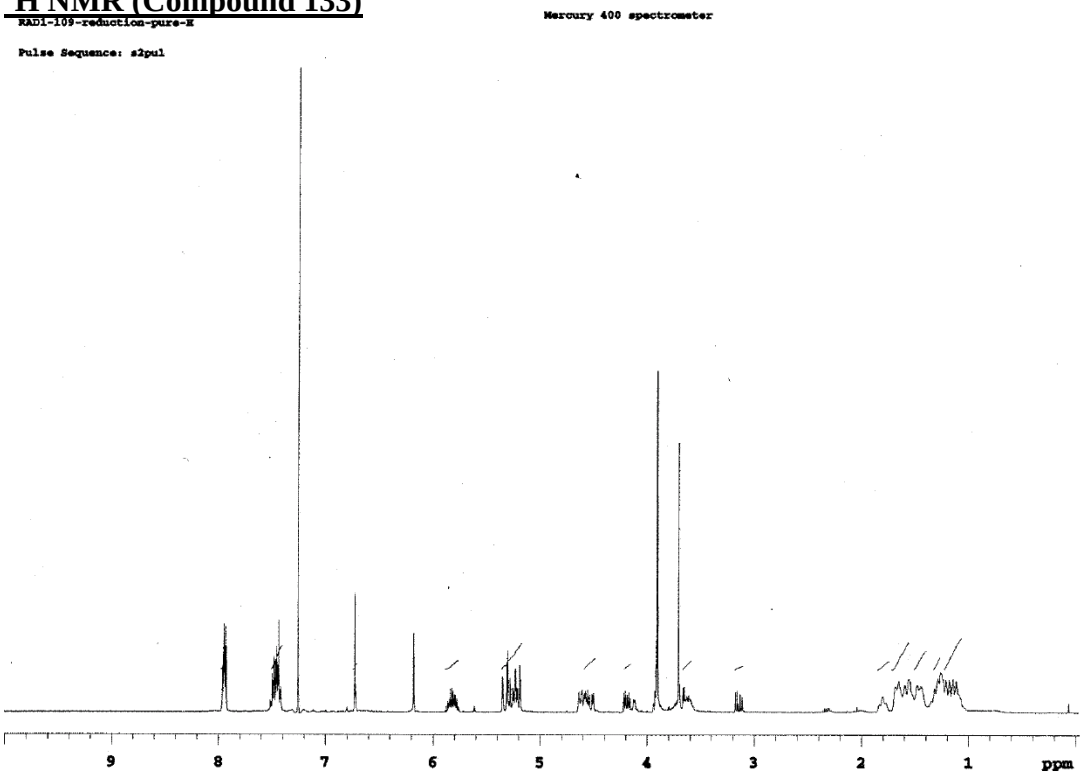
^{1}H NMR (Compound 132)



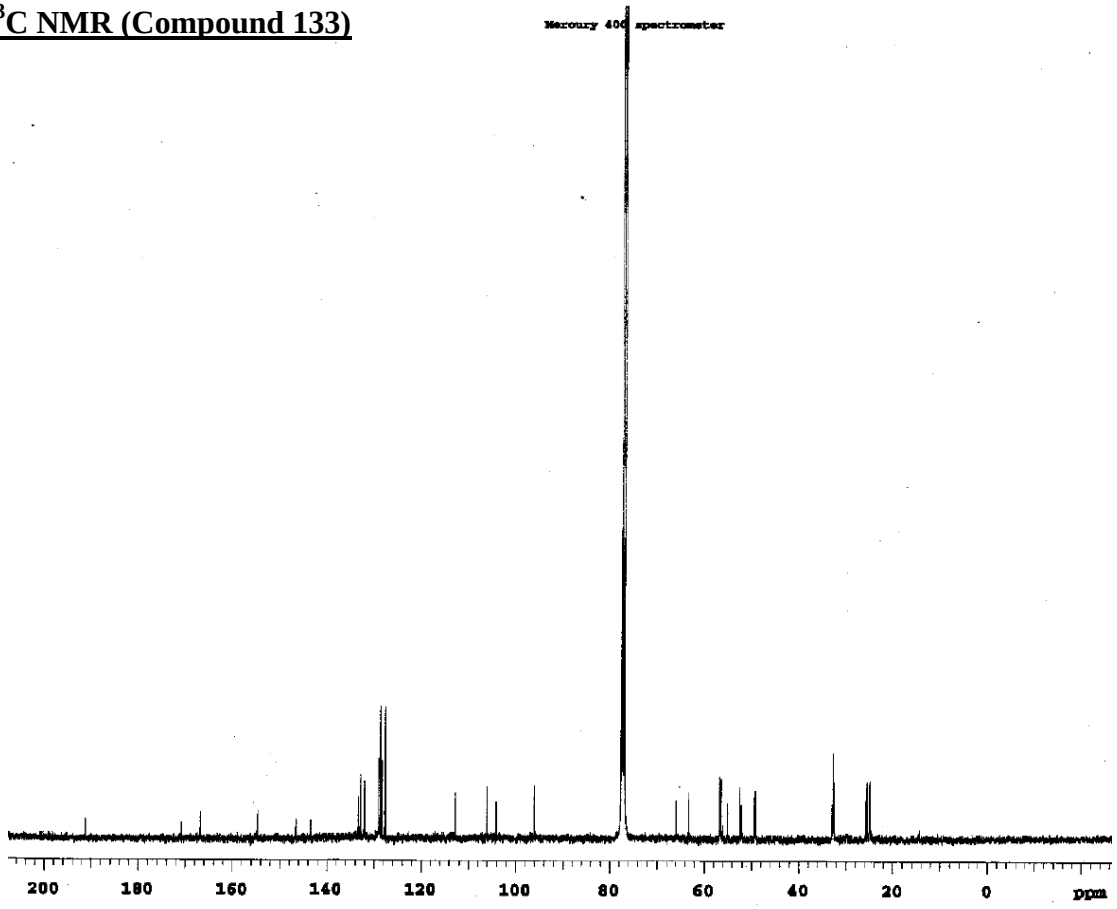
^{13}C NMR (Compound 132)



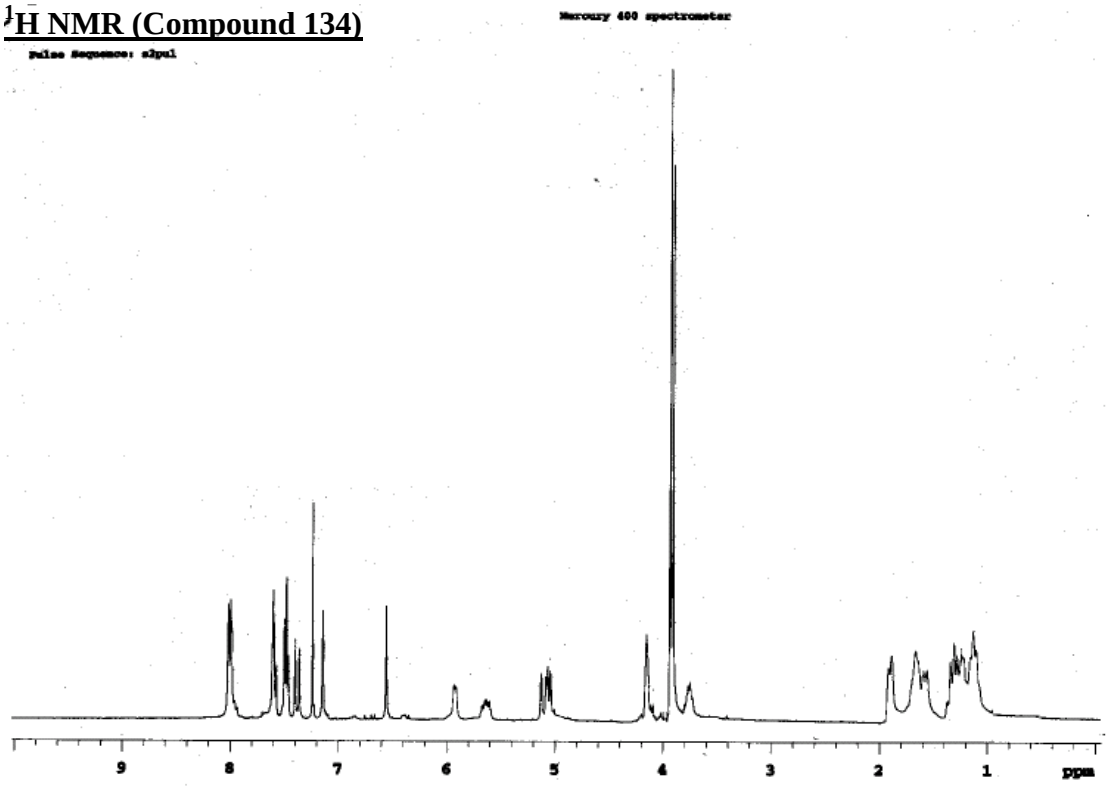
^{1}H NMR (Compound 133)



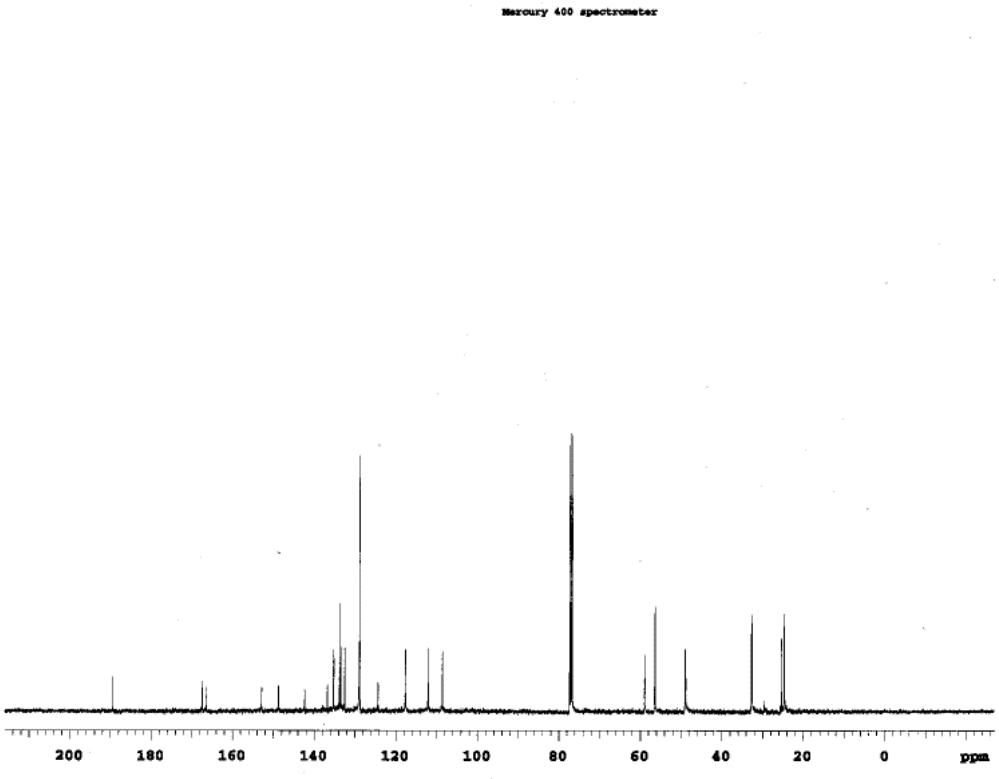
^{13}C NMR (Compound 133)



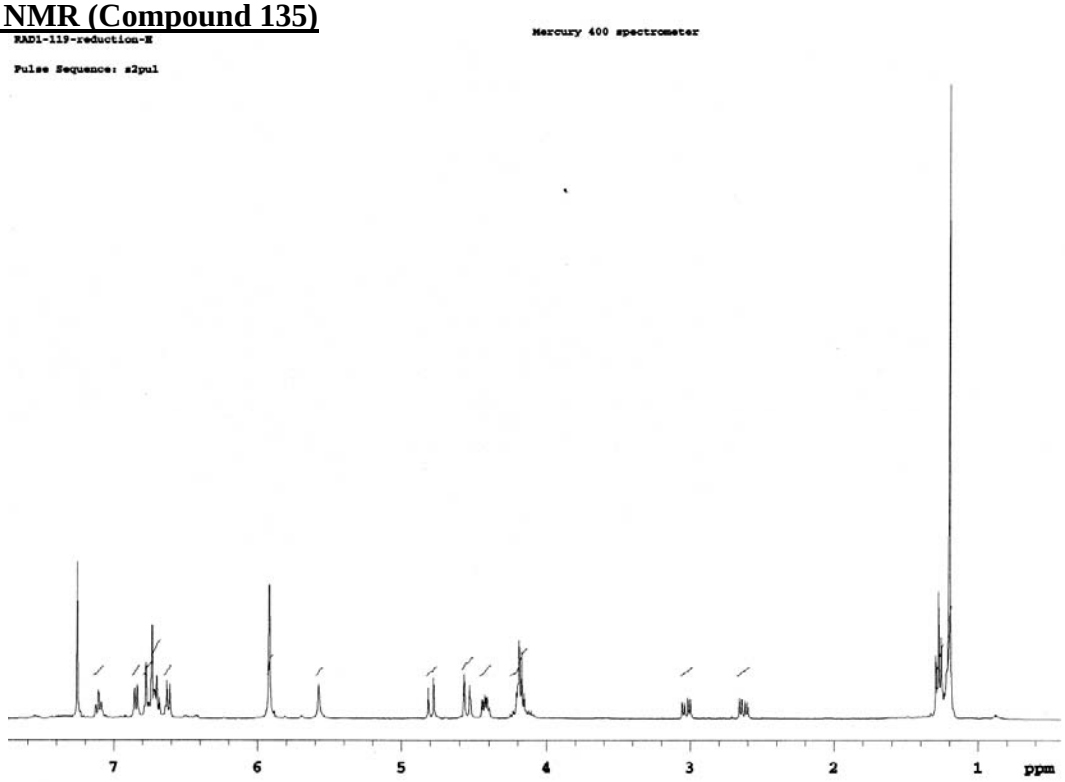
^{1}H NMR (Compound 134)



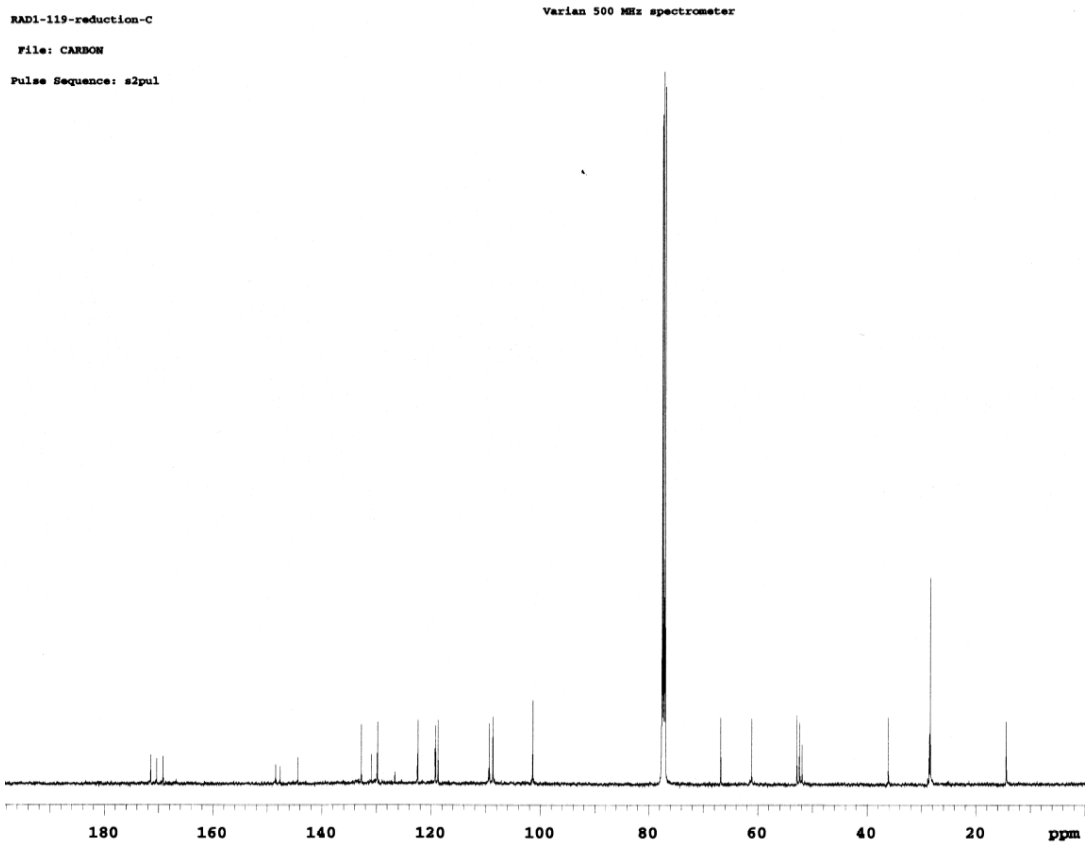
^{13}C NMR (Compound 134)



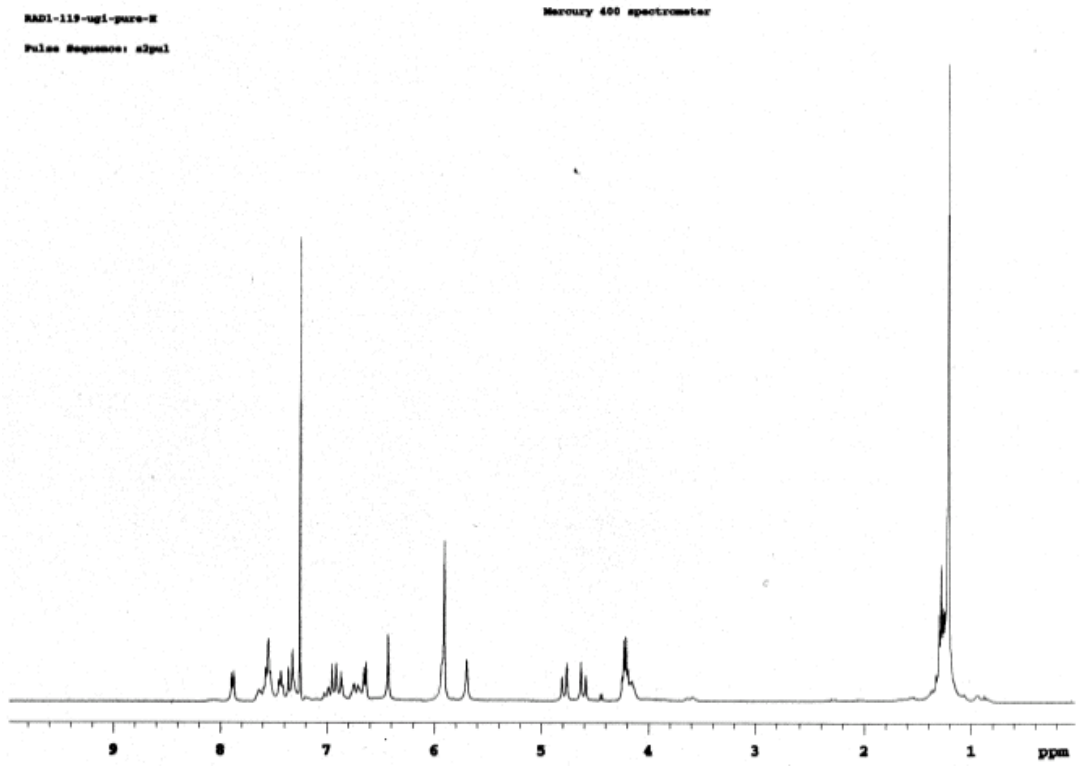
^{1}H NMR (Compound 135)



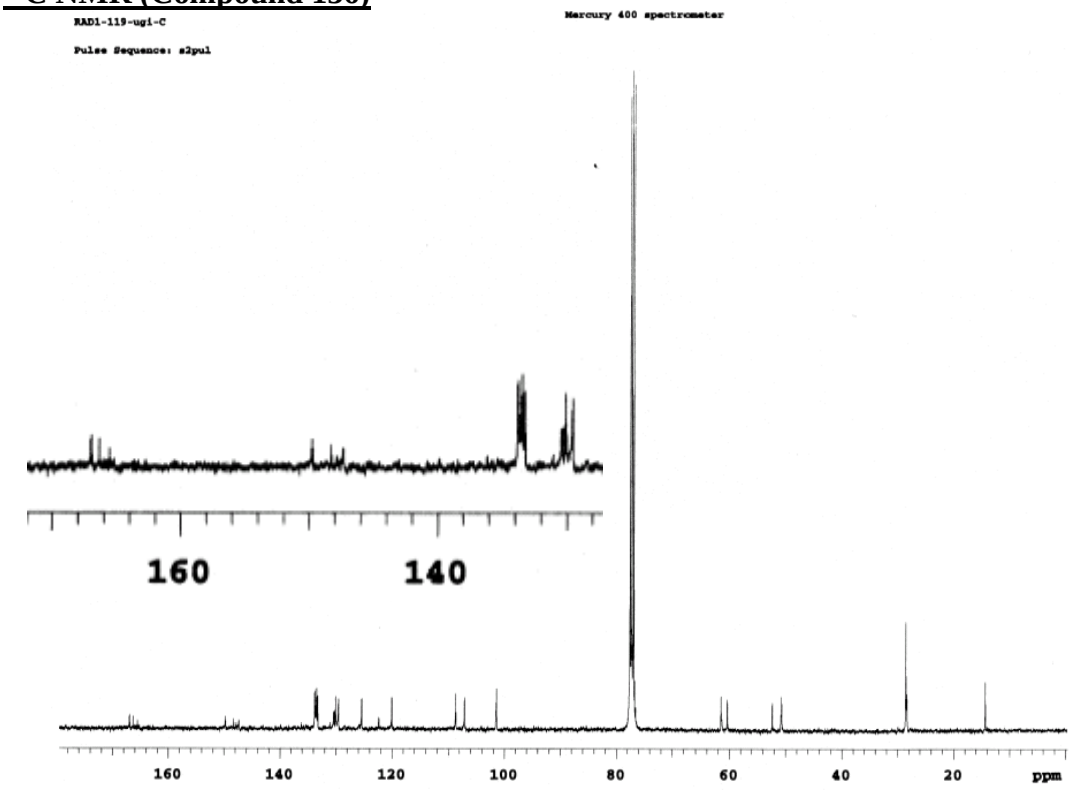
^{13}C NMR (Compound 135)



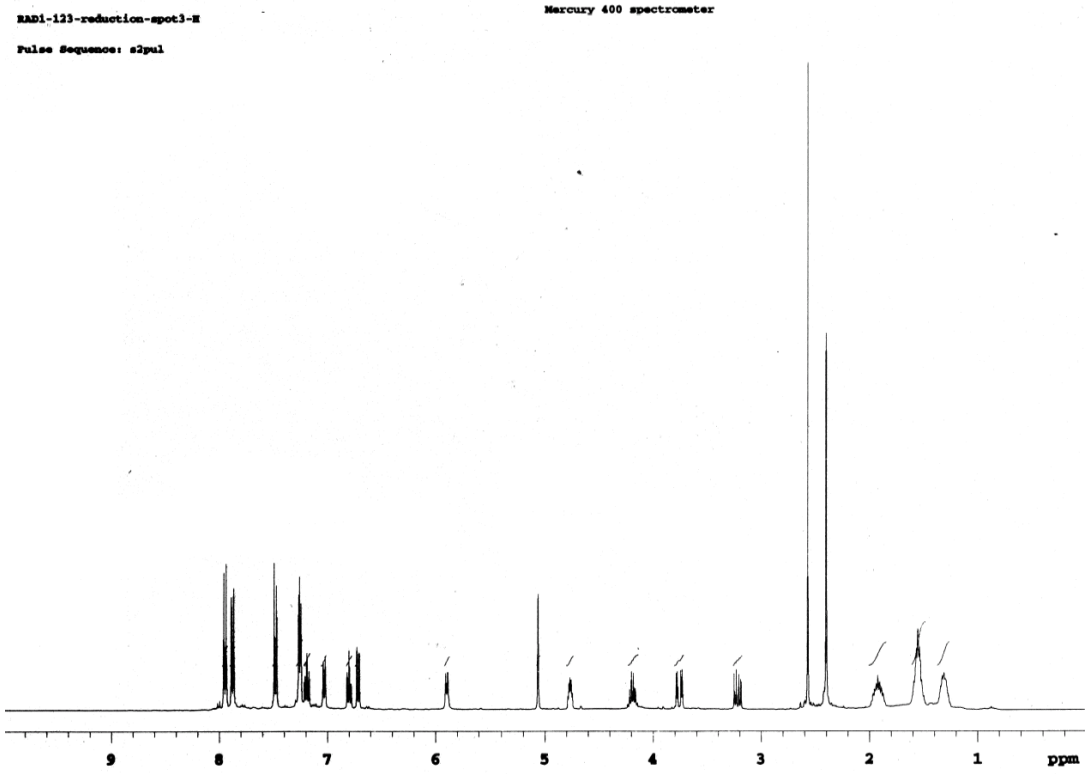
^{1}H NMR (Compound 136)



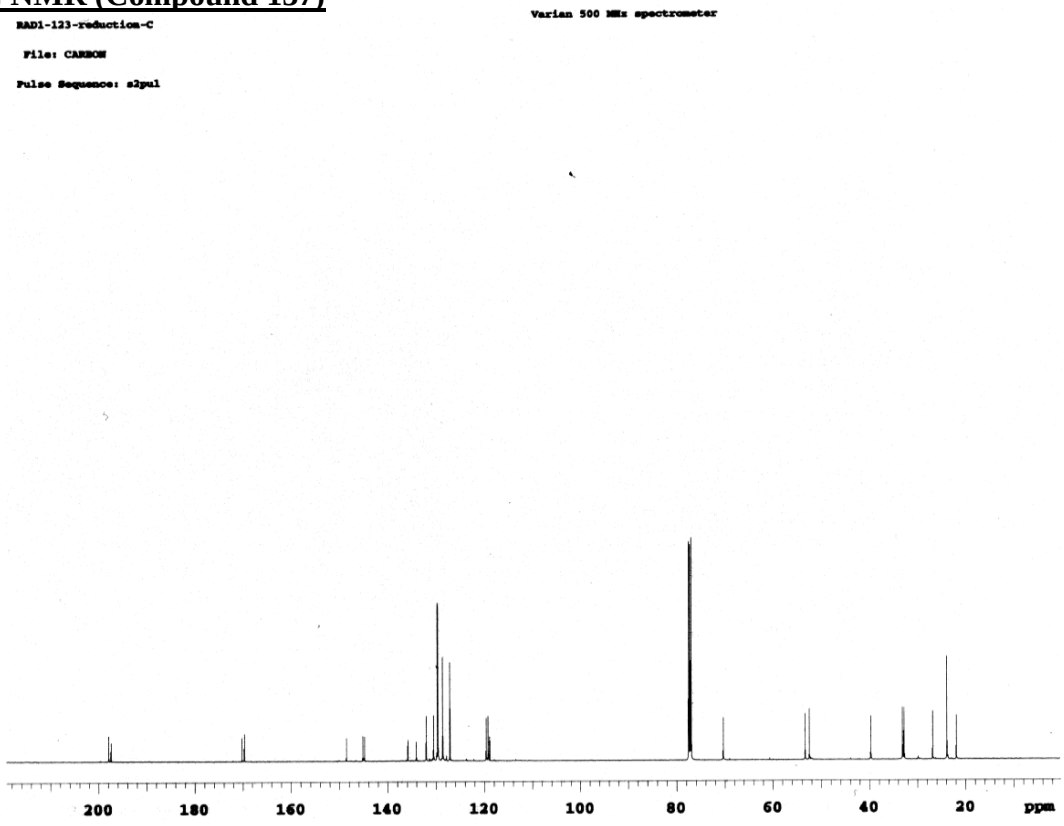
^{13}C NMR (Compound 136)



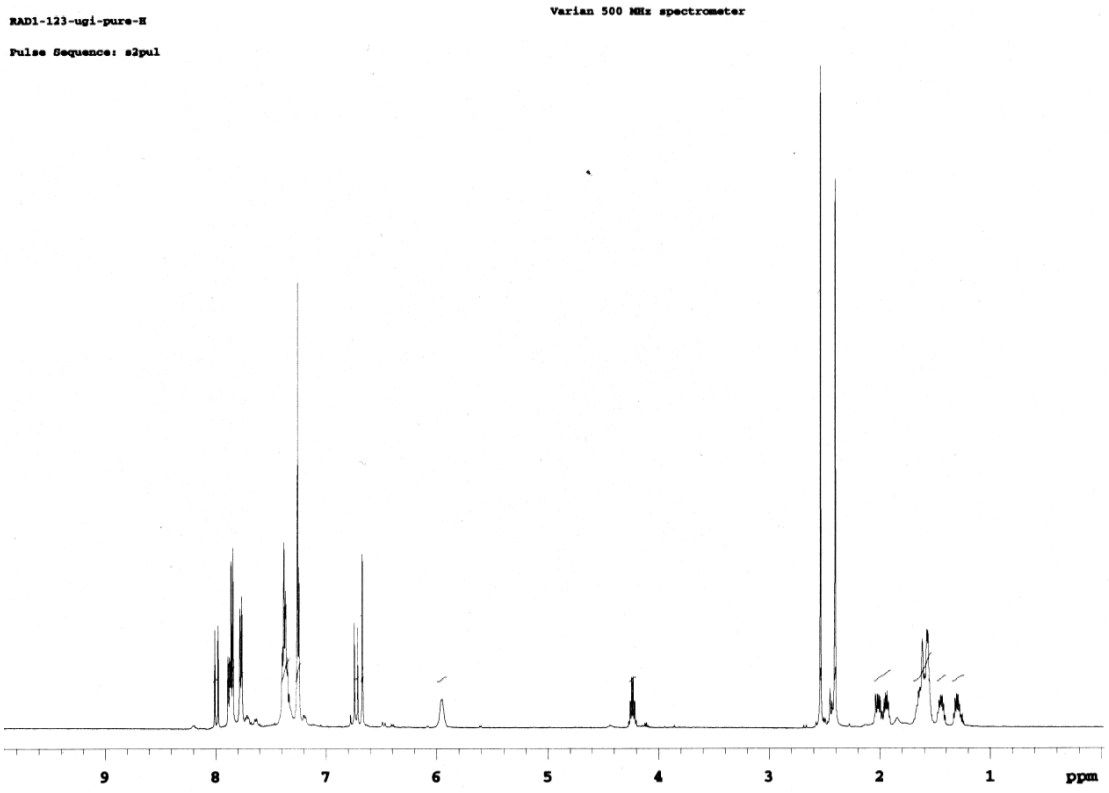
^{1}H NMR (Compound 137)



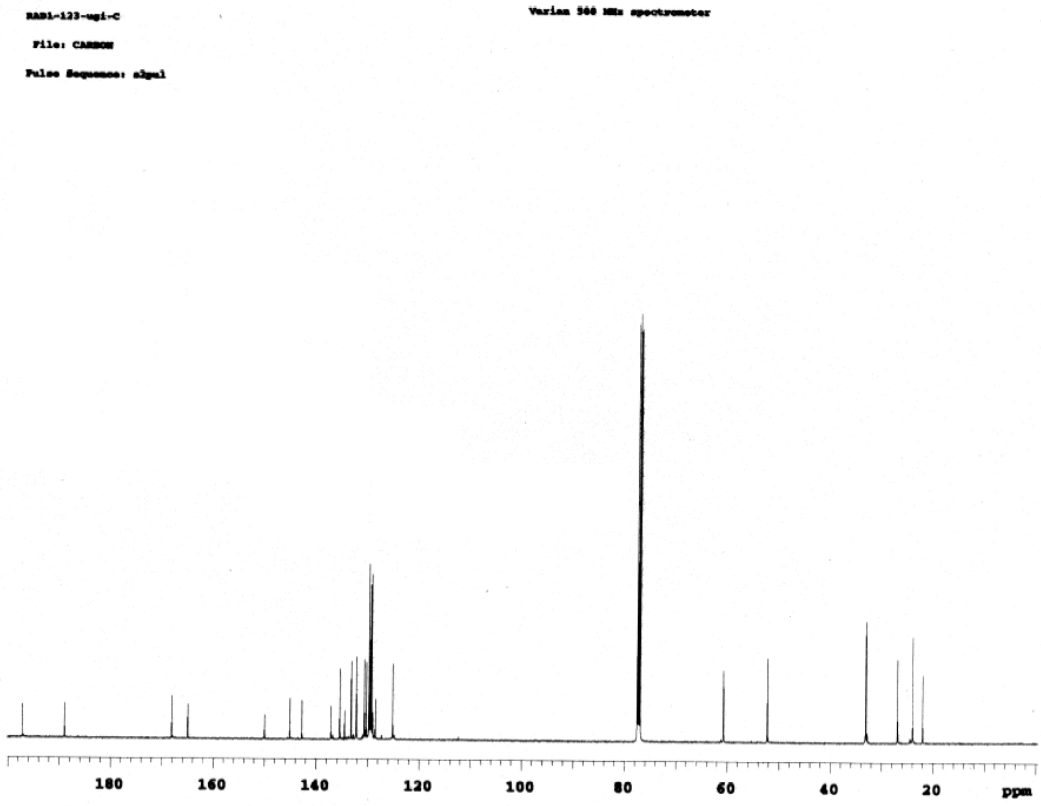
^{13}C NMR (Compound 137)



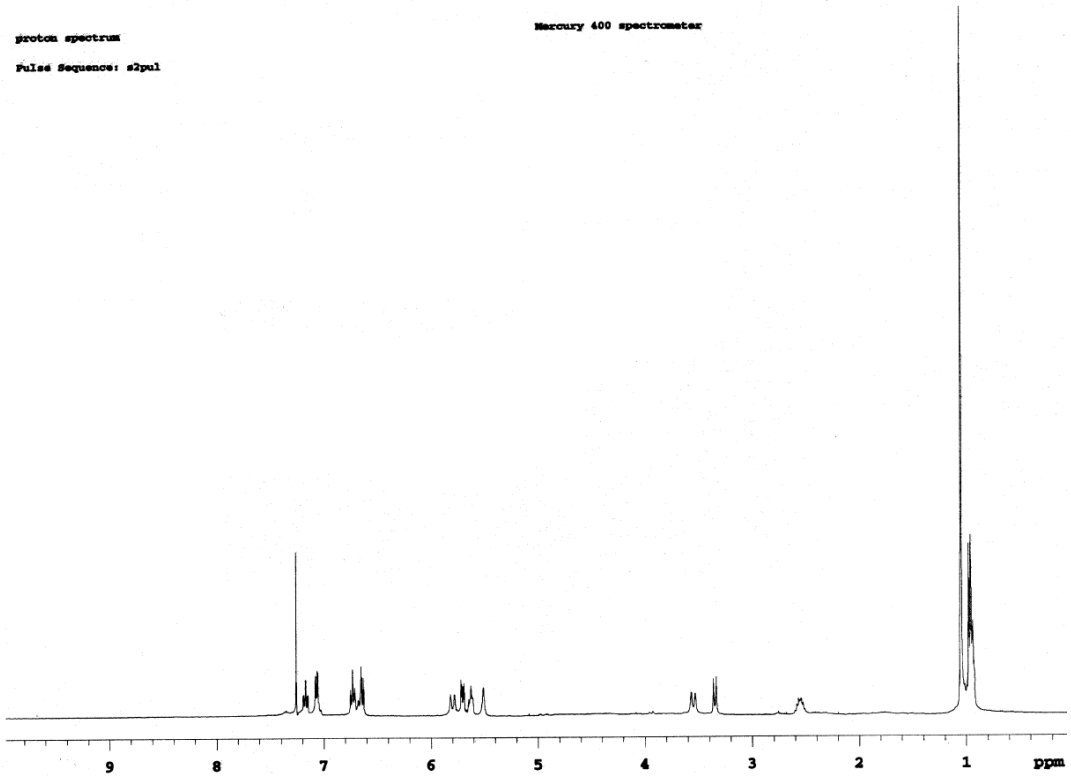
^{1}H NMR (Compound 138)



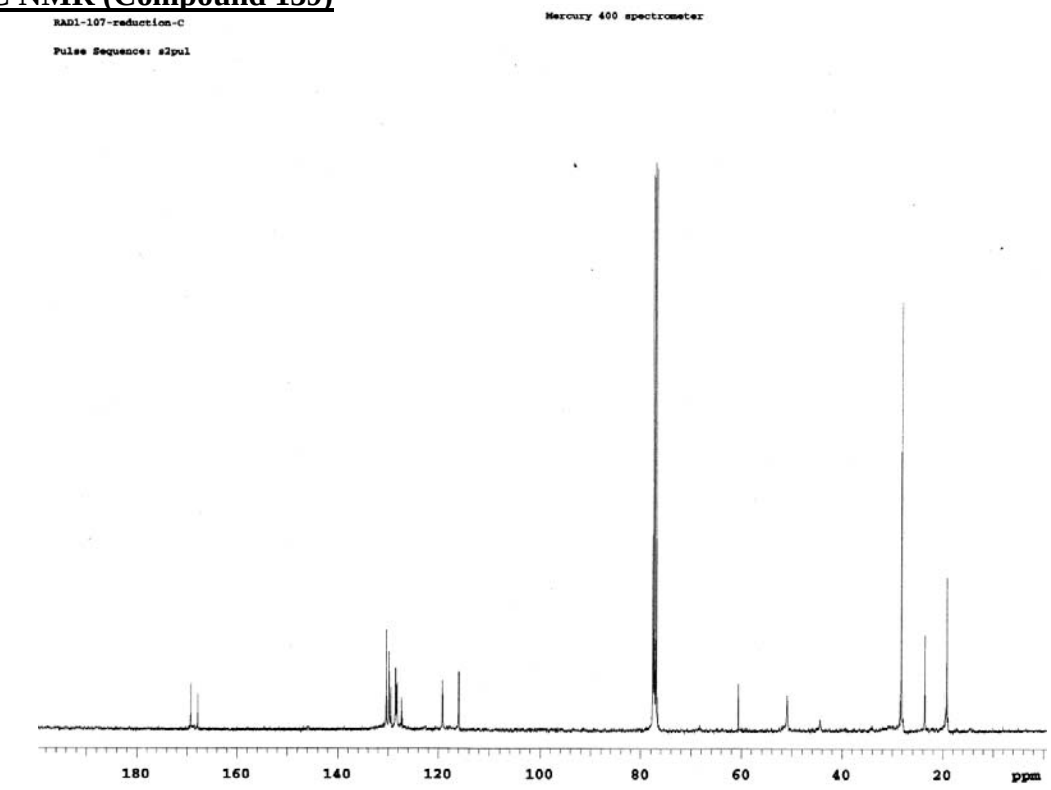
^{13}C NMR (Compound 138)



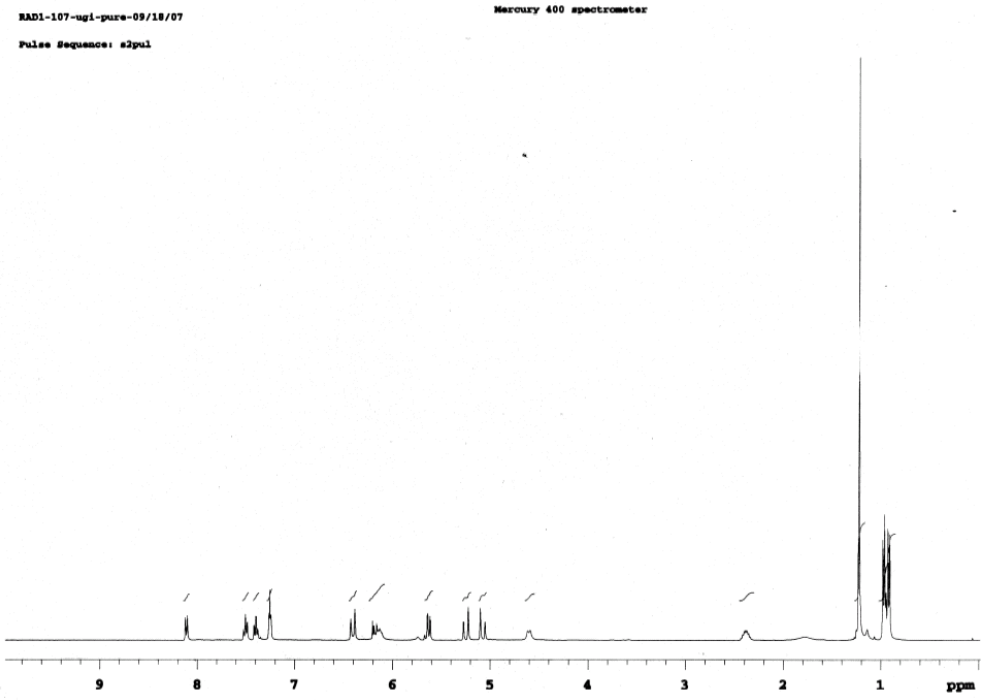
^{1}H NMR (Compound 139)



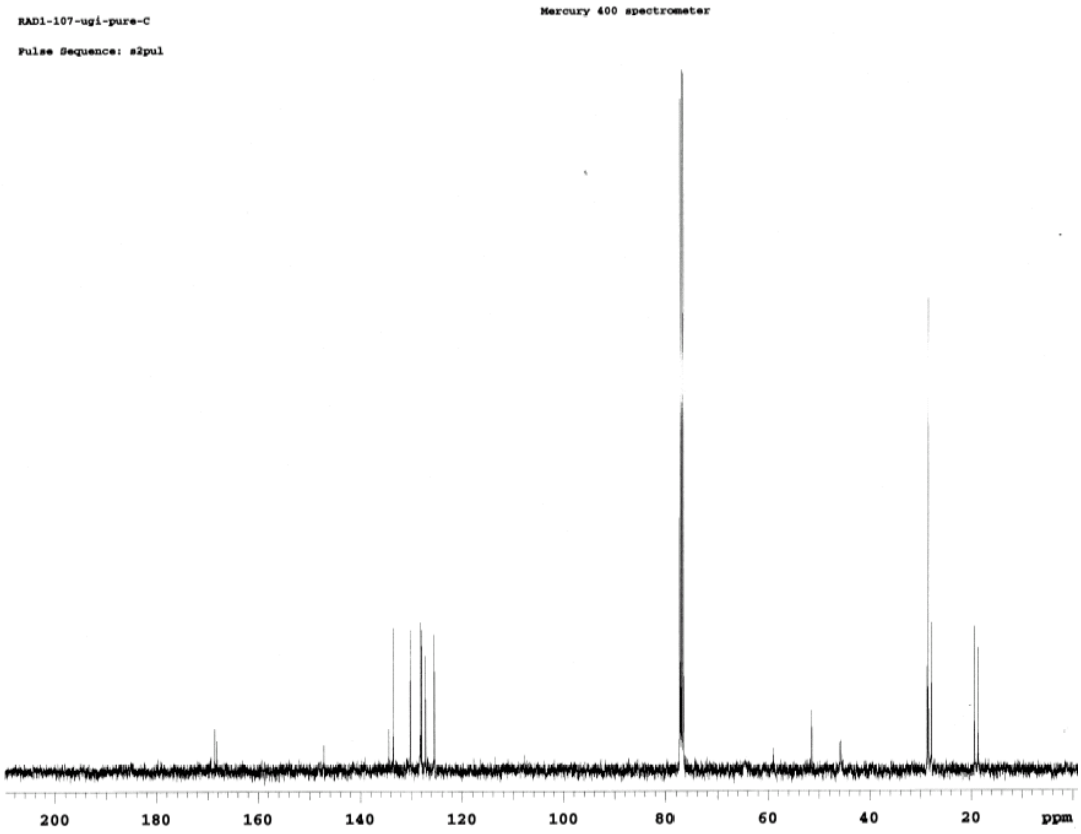
^{13}C NMR (Compound 139)



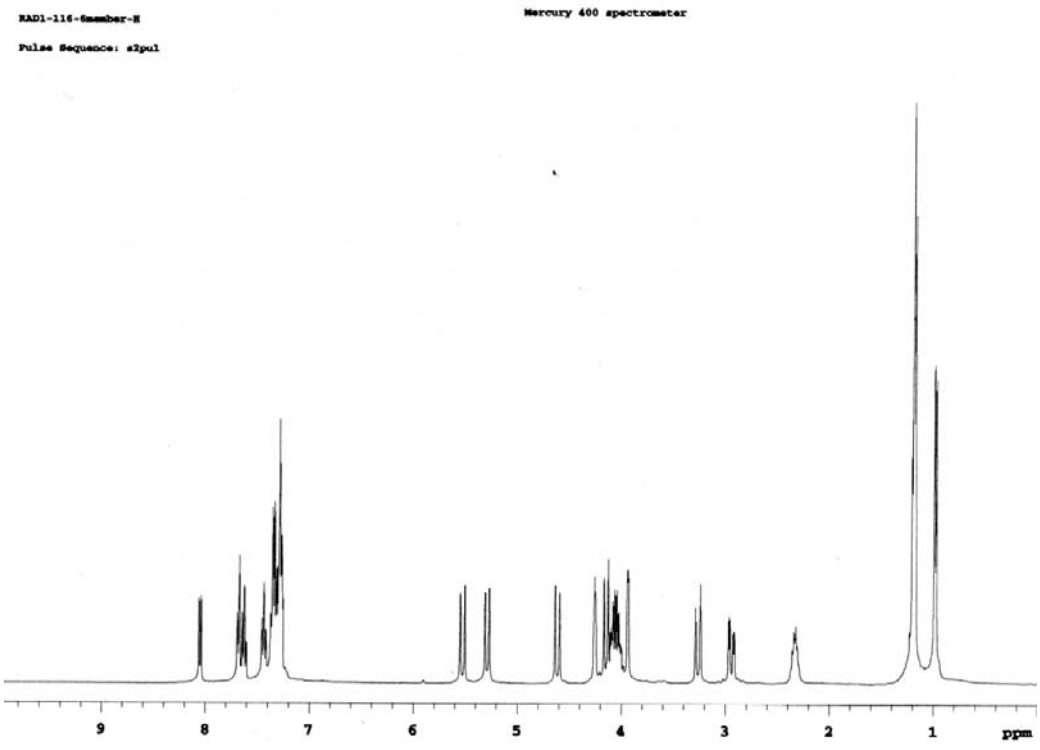
^{1}H NMR (Compound 139a)



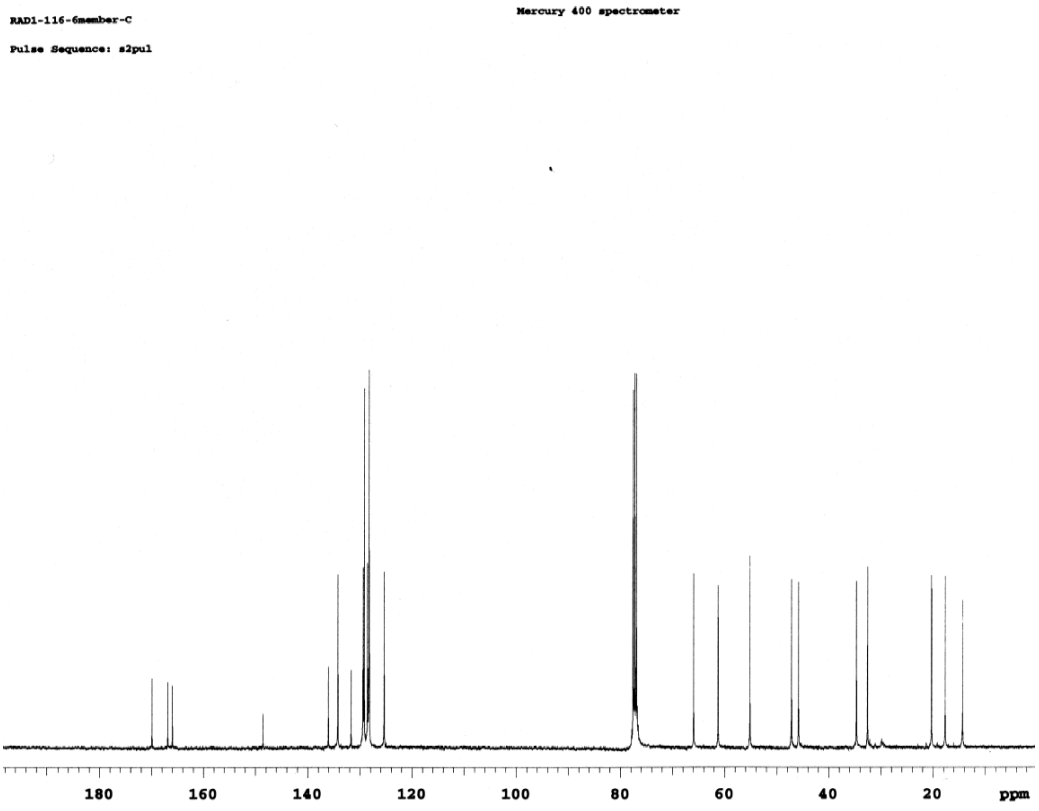
^{13}C NMR (Compound 139a)



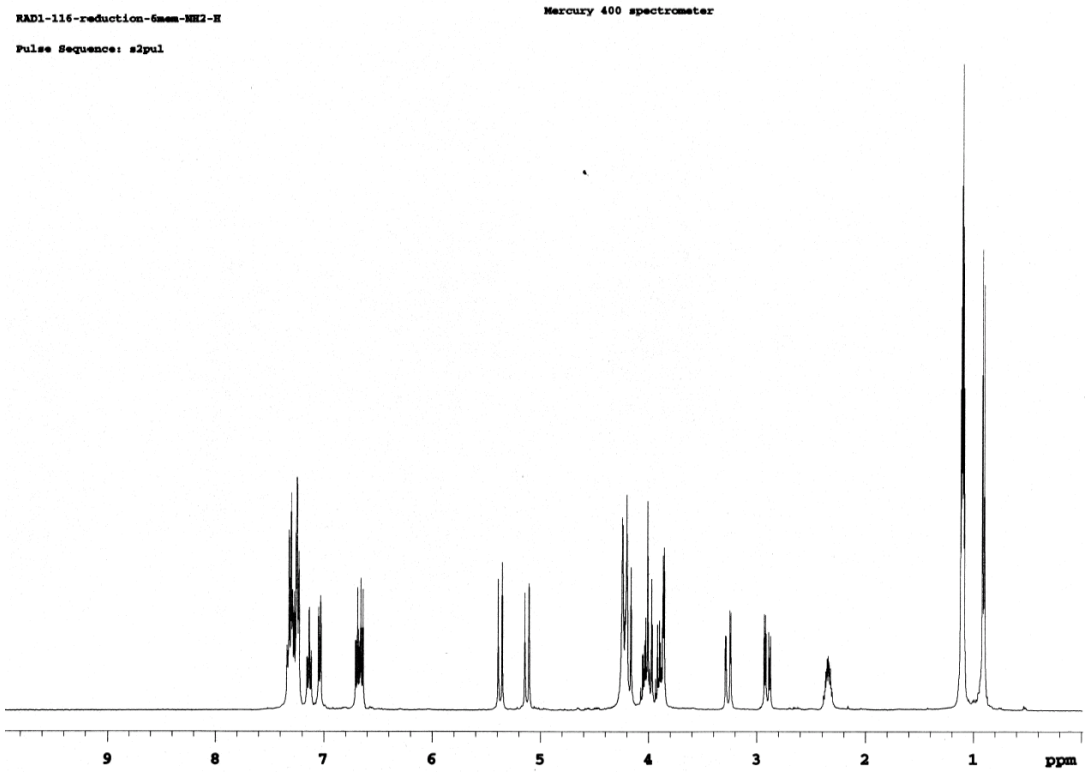
^{1}H NMR (Compound 140)



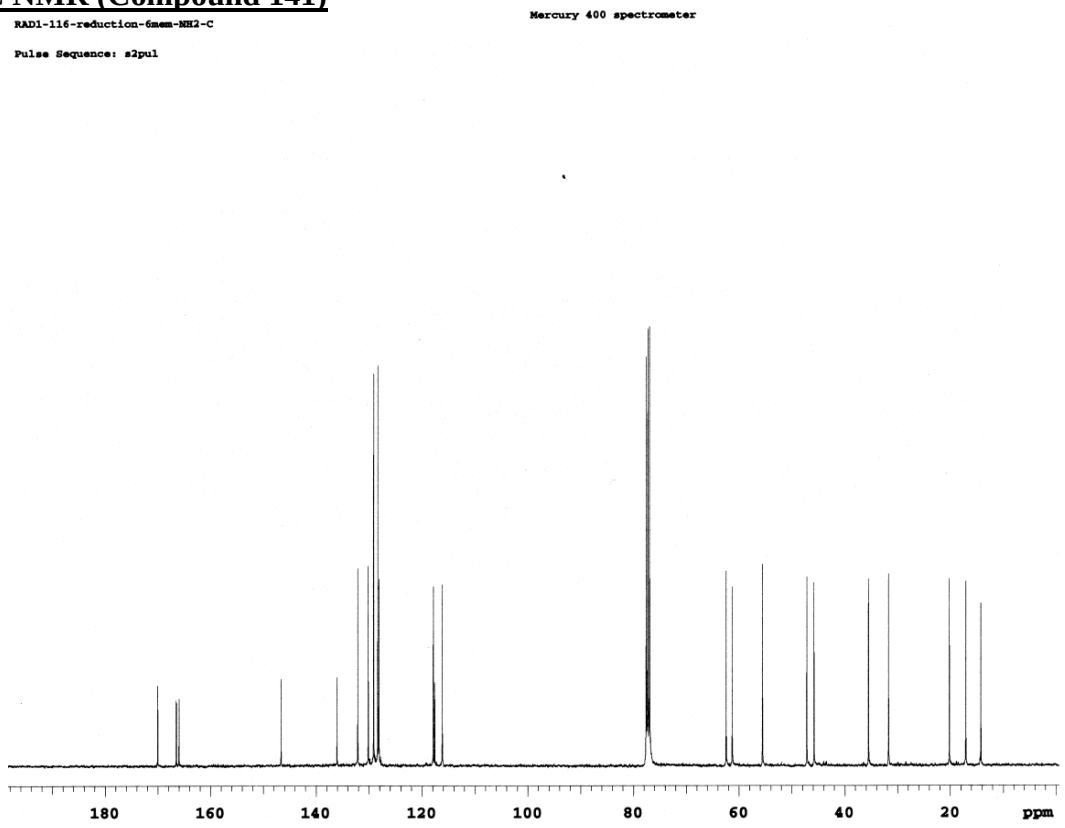
^{13}C NMR (Compound 140)



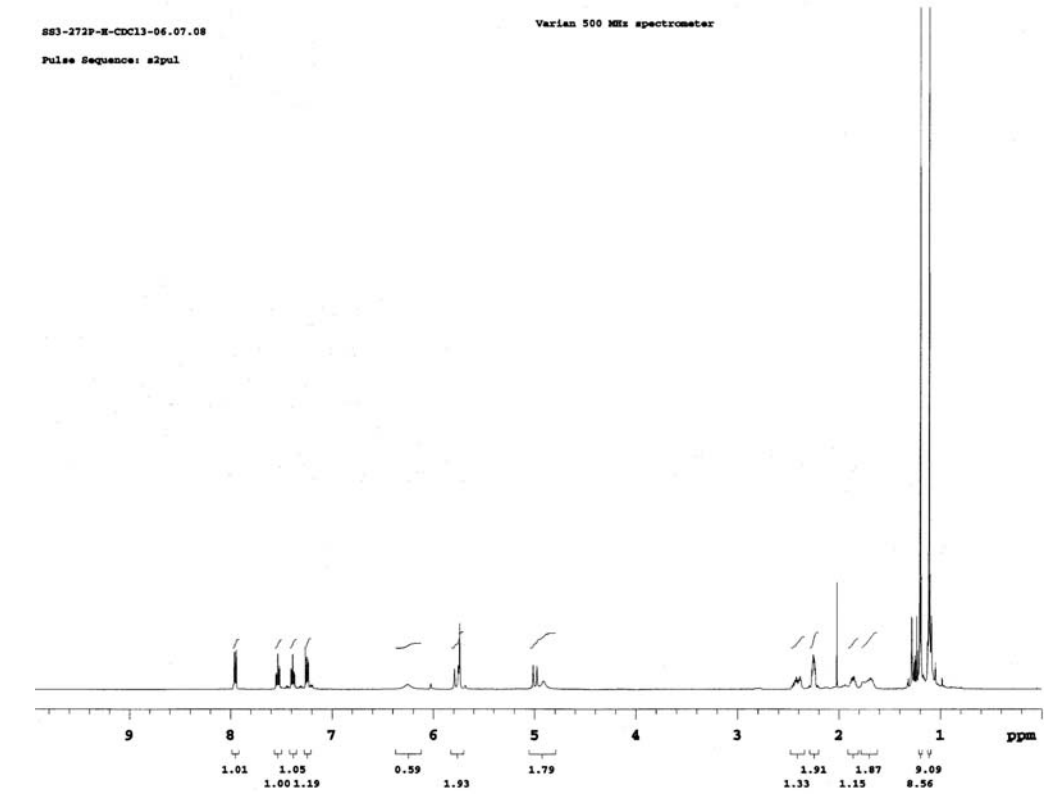
^{1}H NMR (Compound 141)



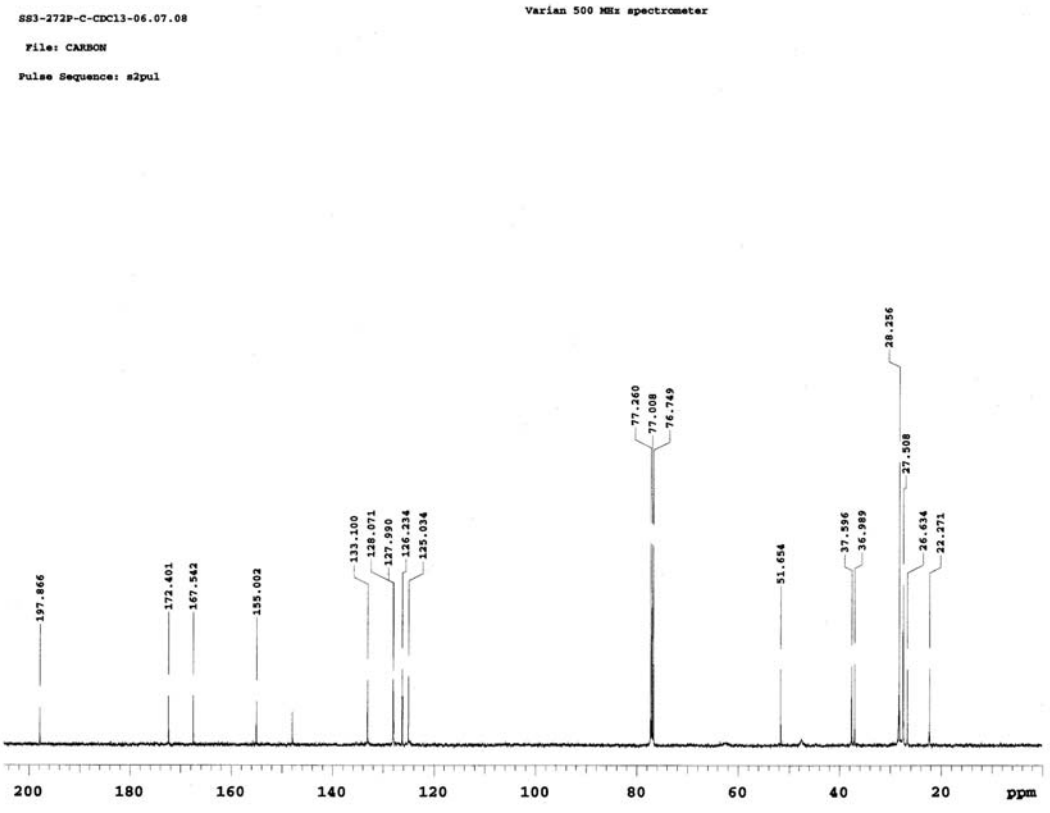
^{13}C NMR (Compound 141)



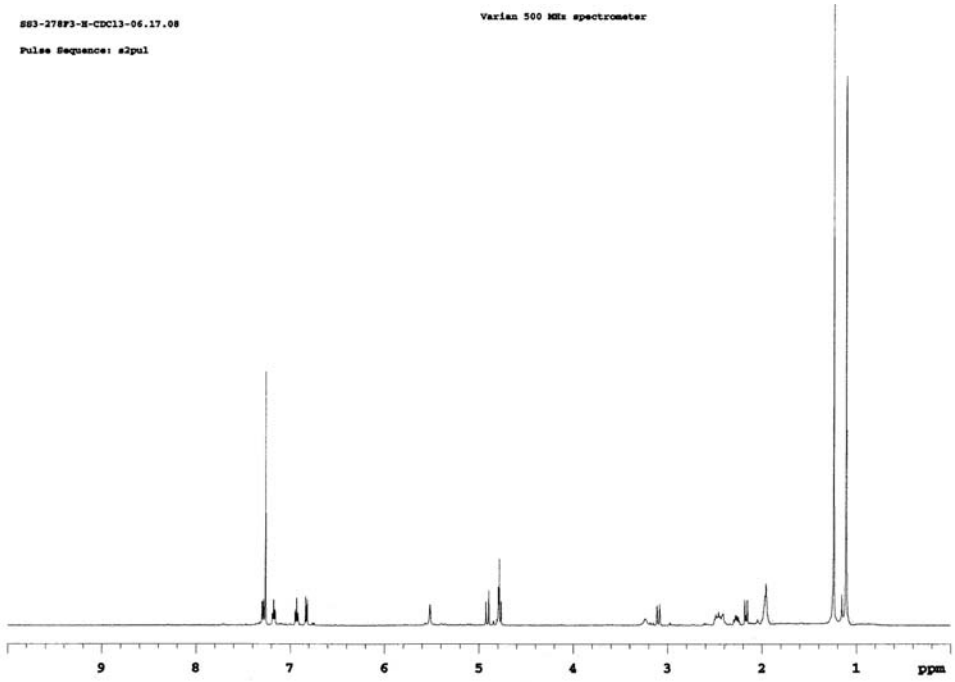
^{1}H NMR (Compound 142)



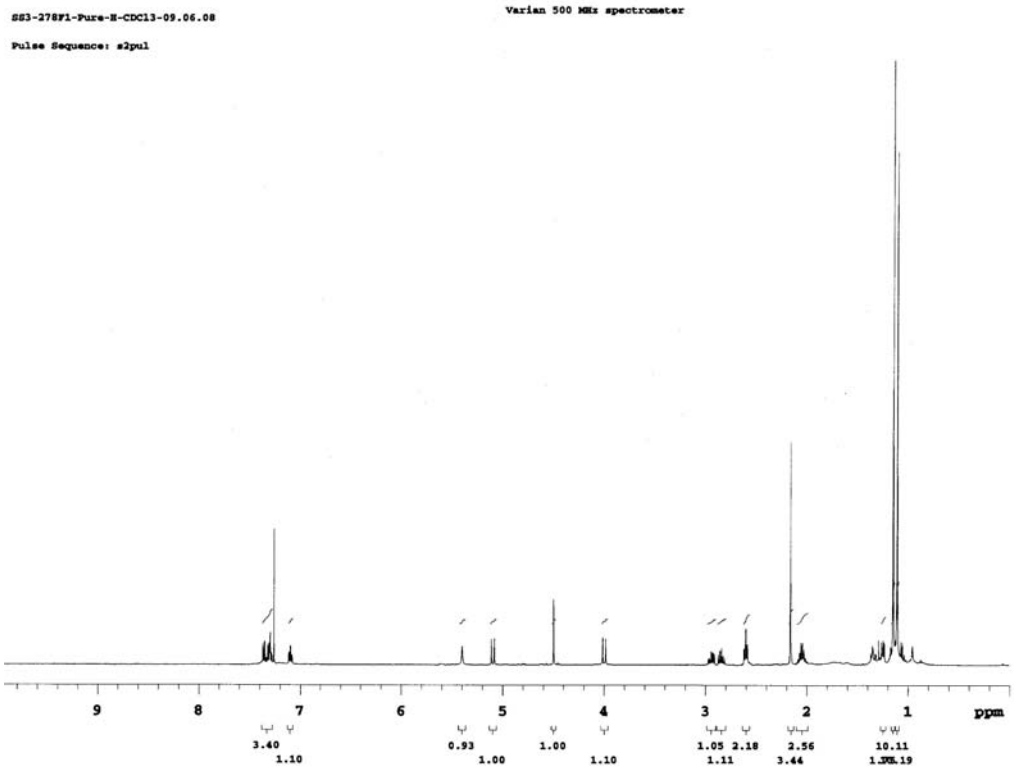
^{13}C NMR (Compound 142)



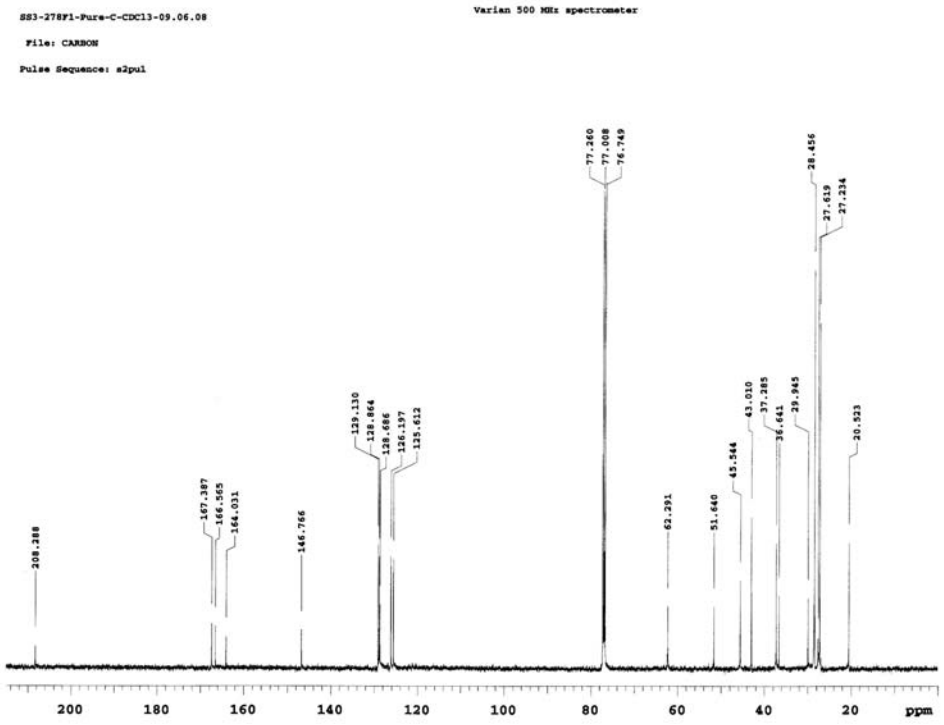
^{1}H NMR (Compound 143)



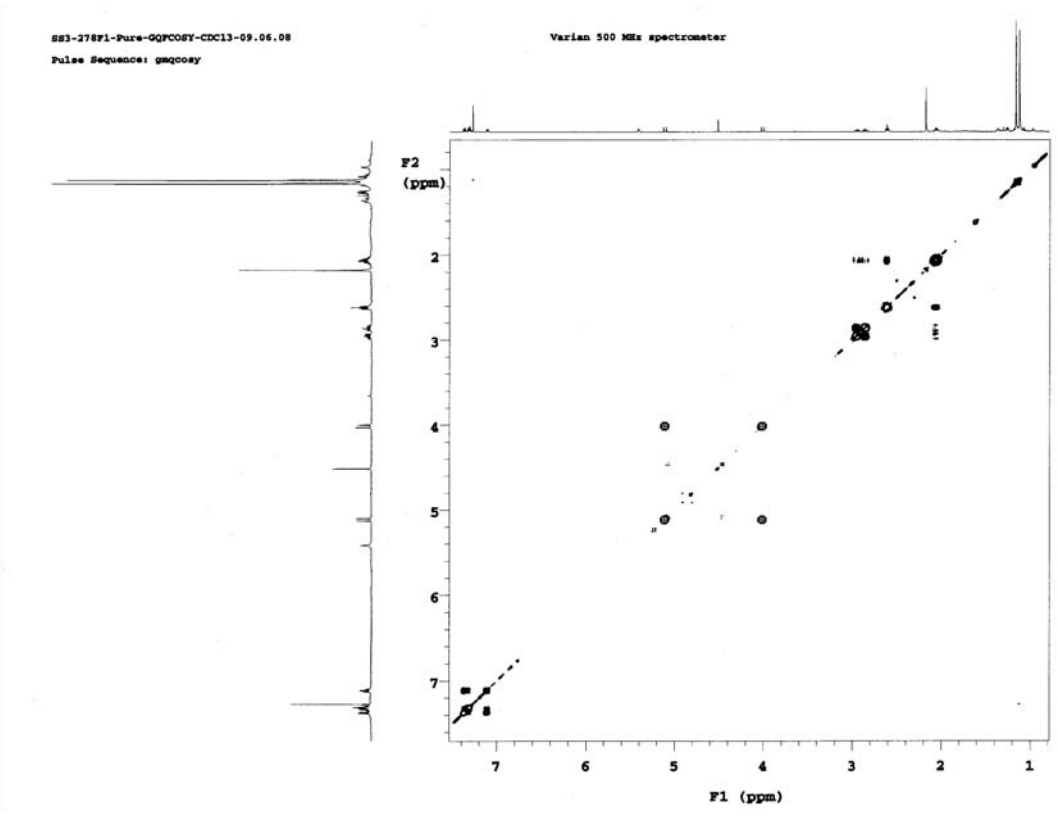
^{1}H NMR (Compound 144)



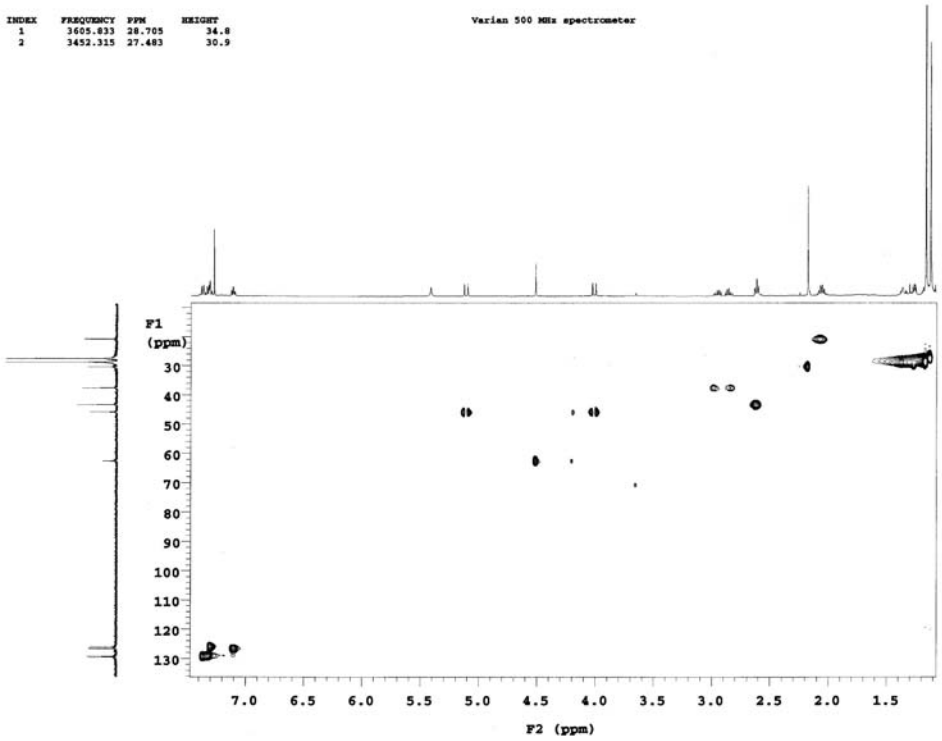
^{13}C NMR (Compound 144)



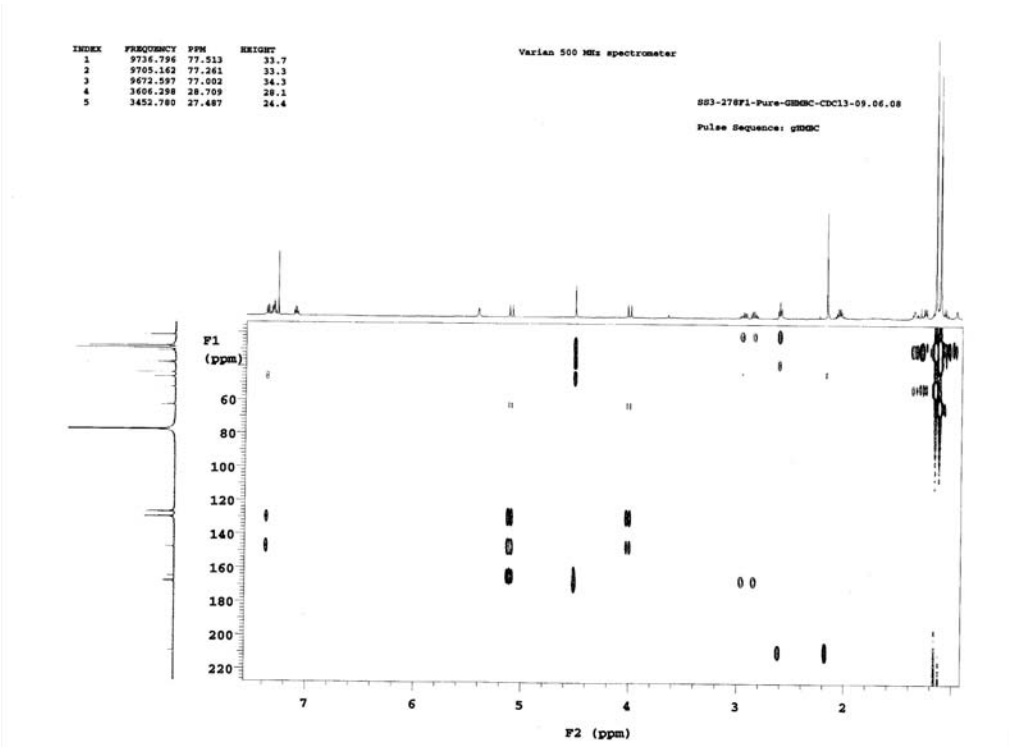
^{1}H-^{1}H GDQFCOSY NMR (Compound 144)



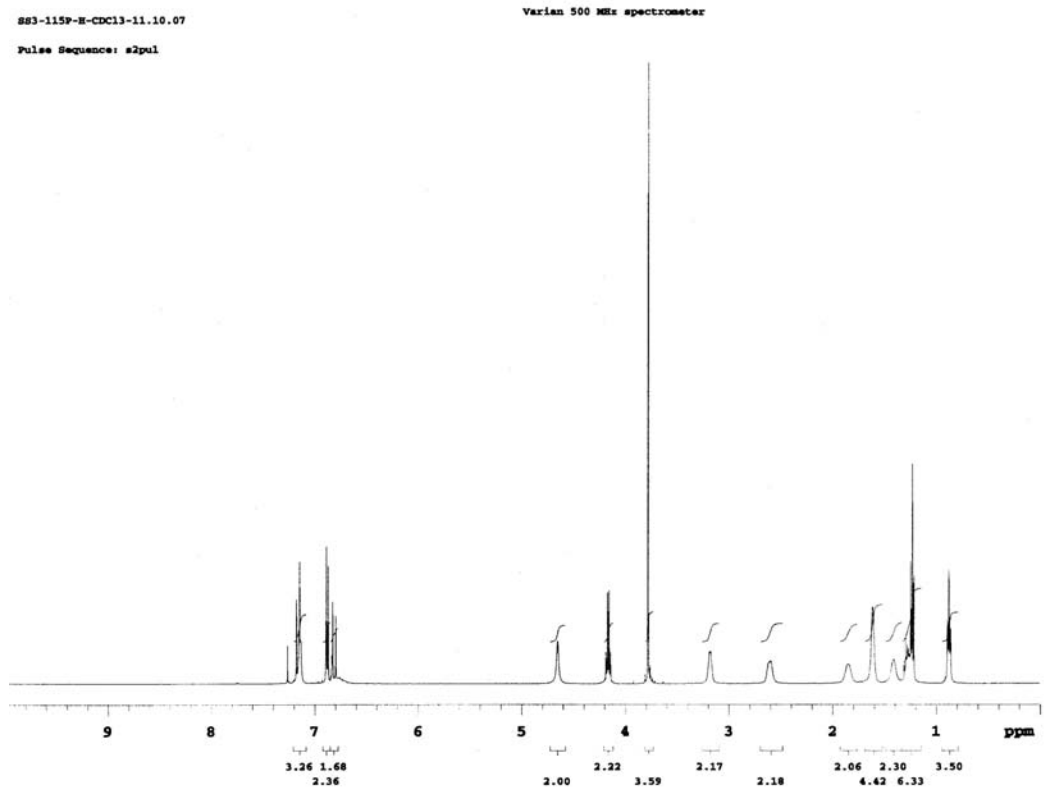
GHMQC NMR (Compound 144)



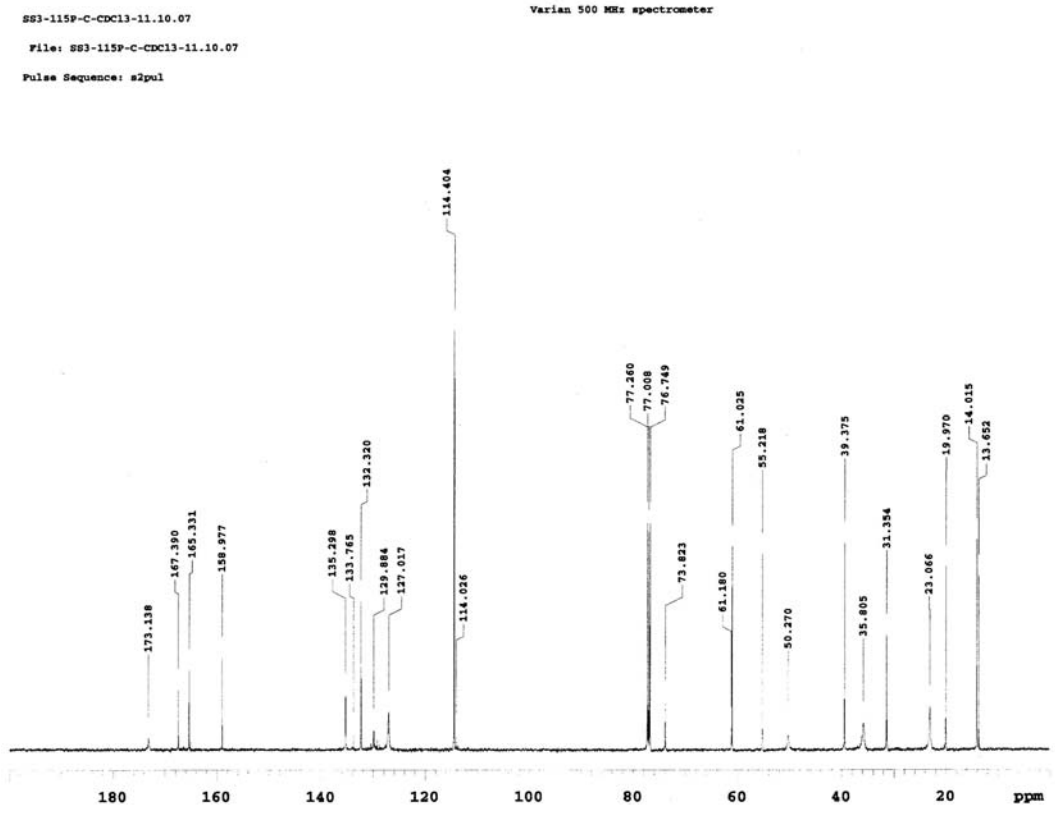
GHMBC NMR (Compound 144)



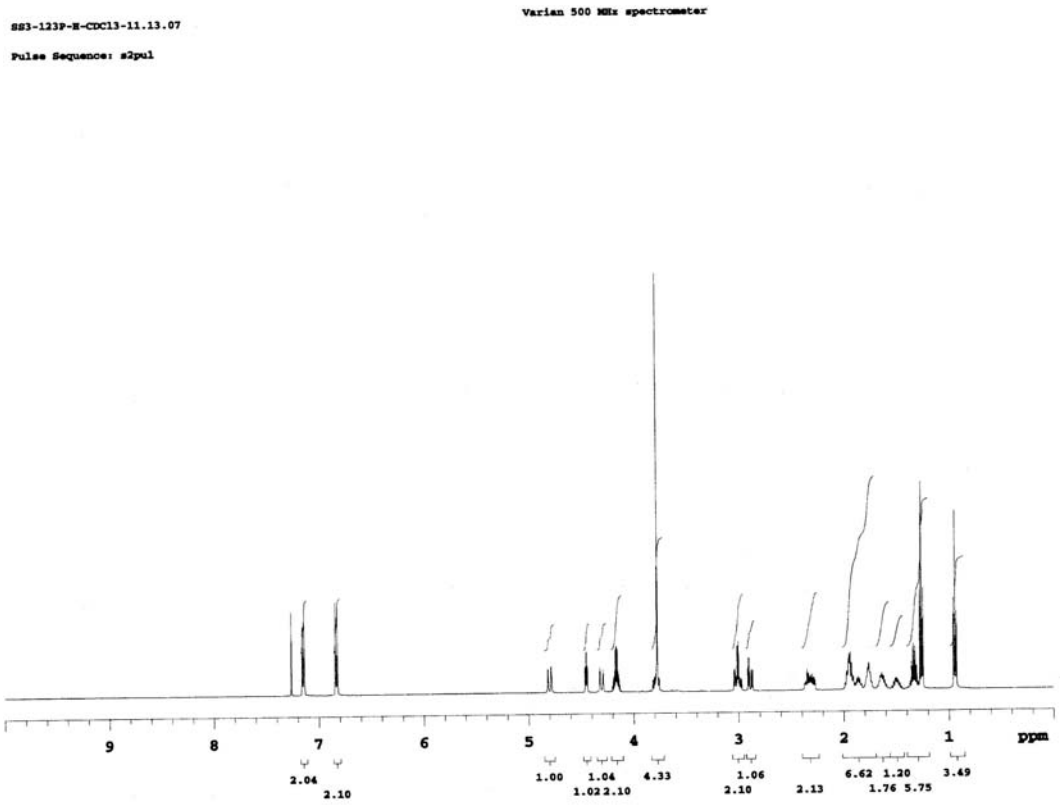
^{1}H NMR (Compound 145)



^{13}C NMR (Compound 145)



^{1}H NMR (Compound 146)



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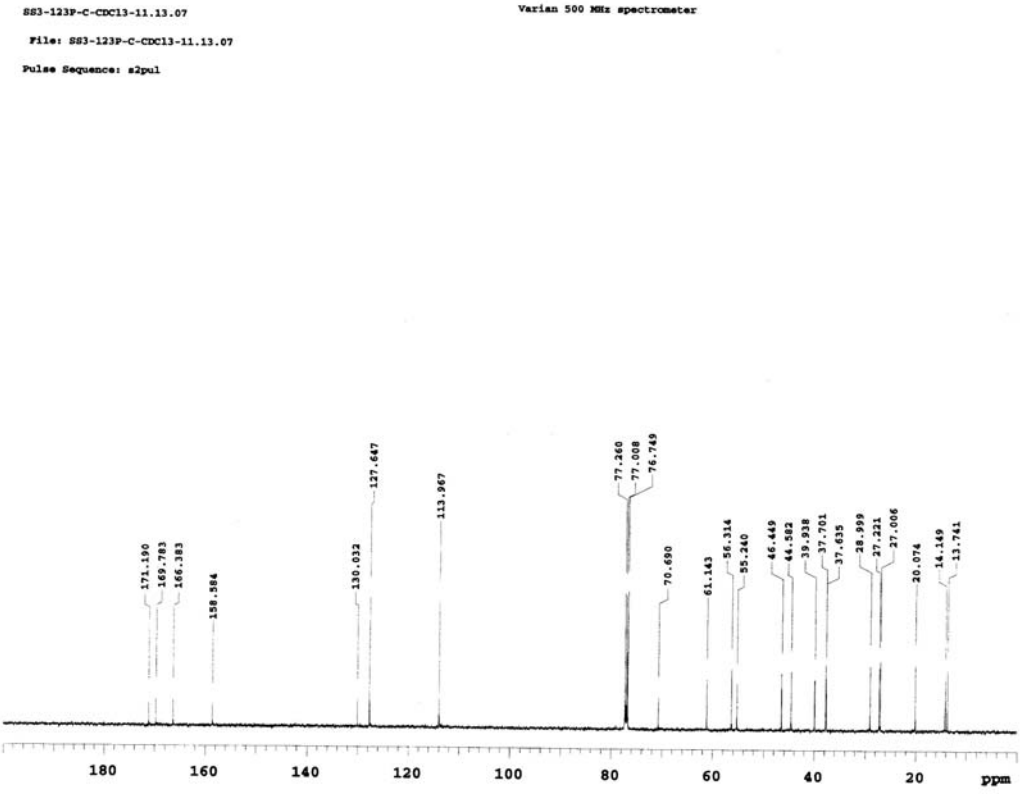
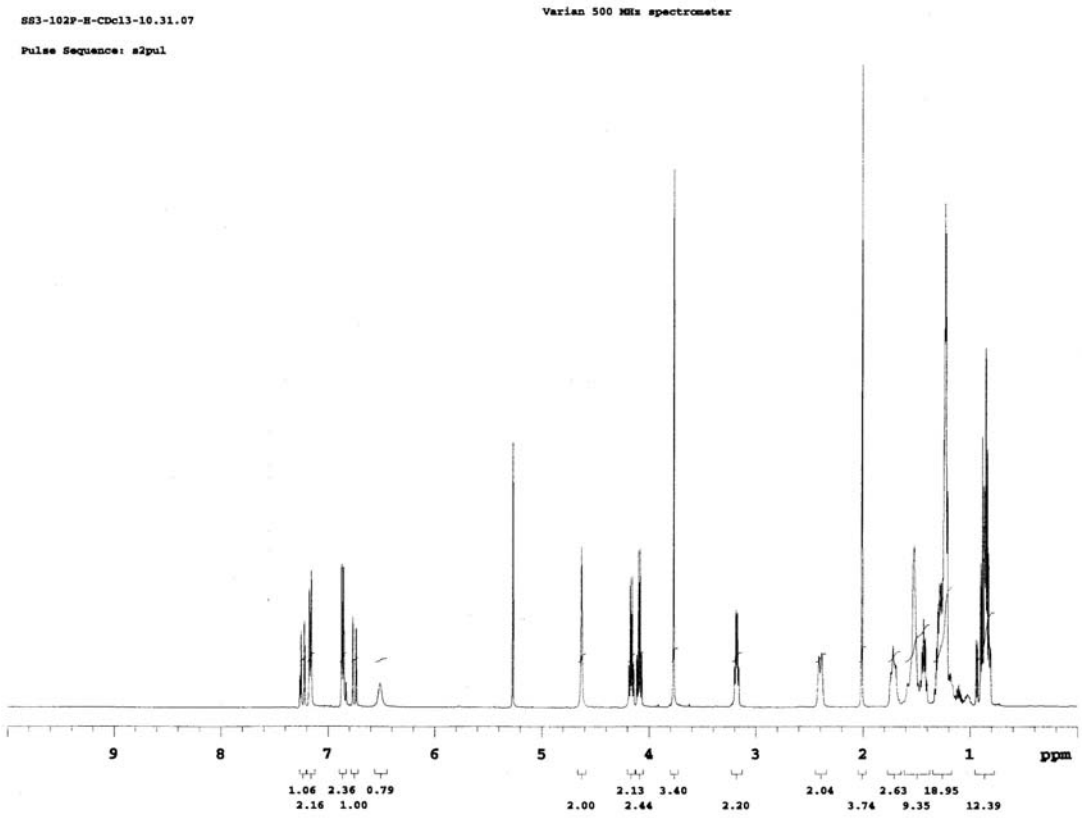
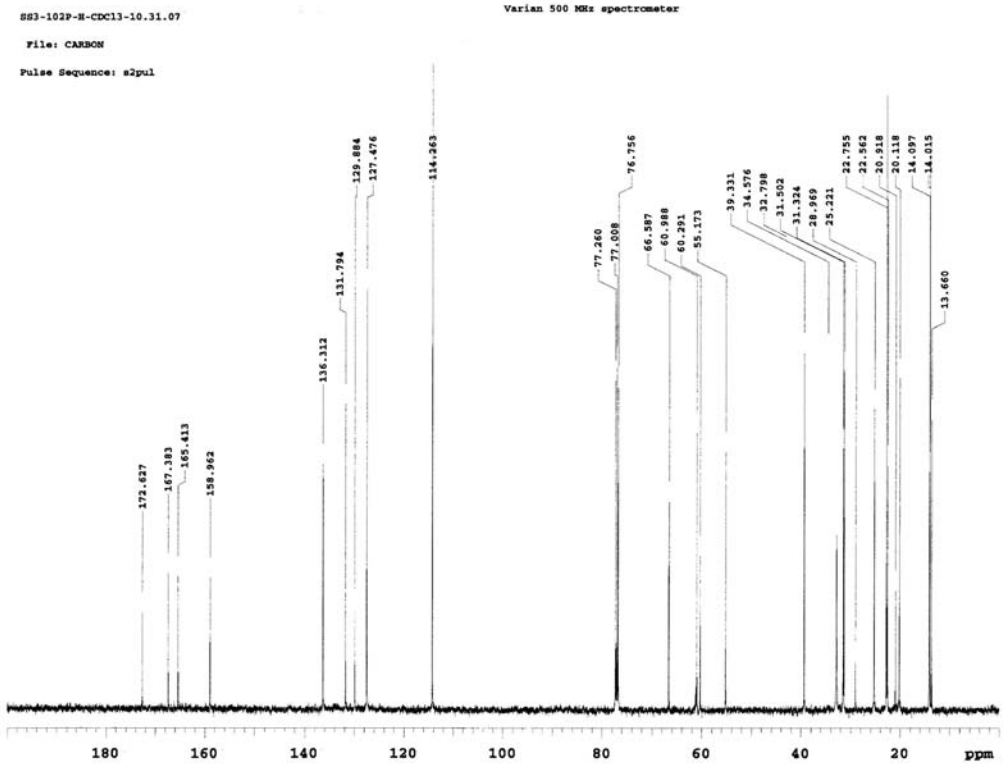
^{13}C NMR (Compound 146)



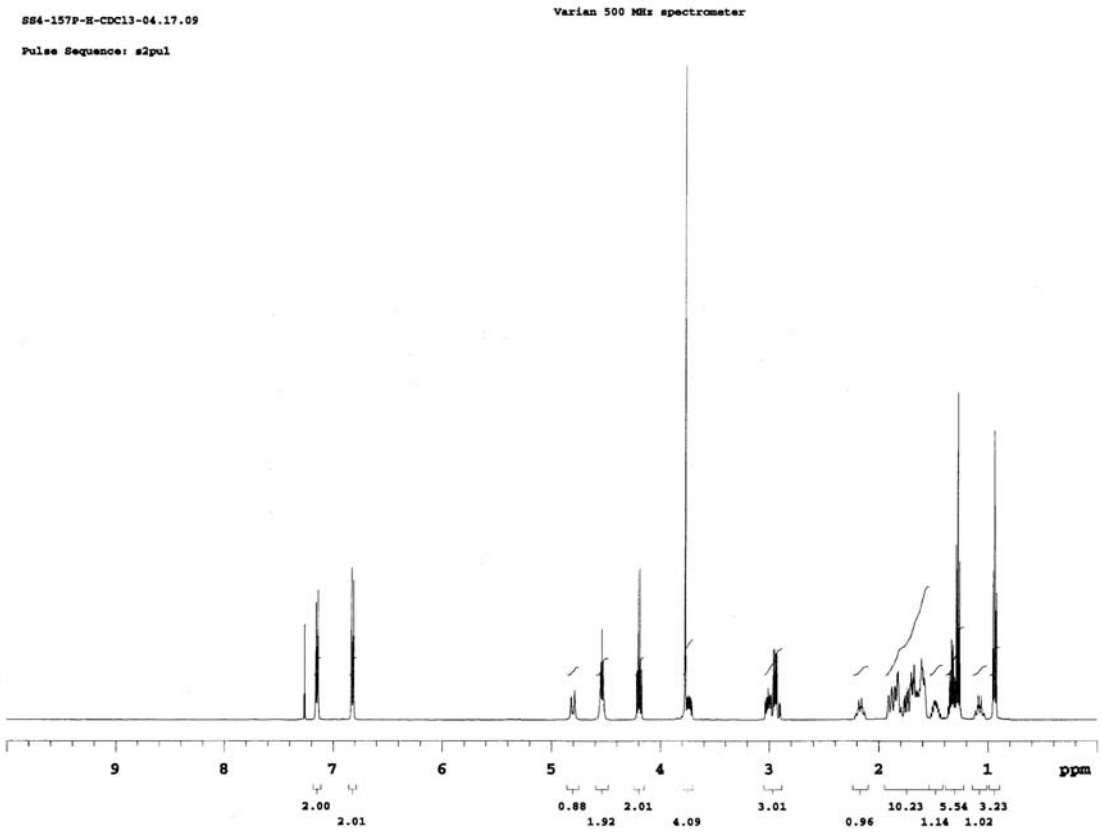
^{1}H NMR (Compound 147)



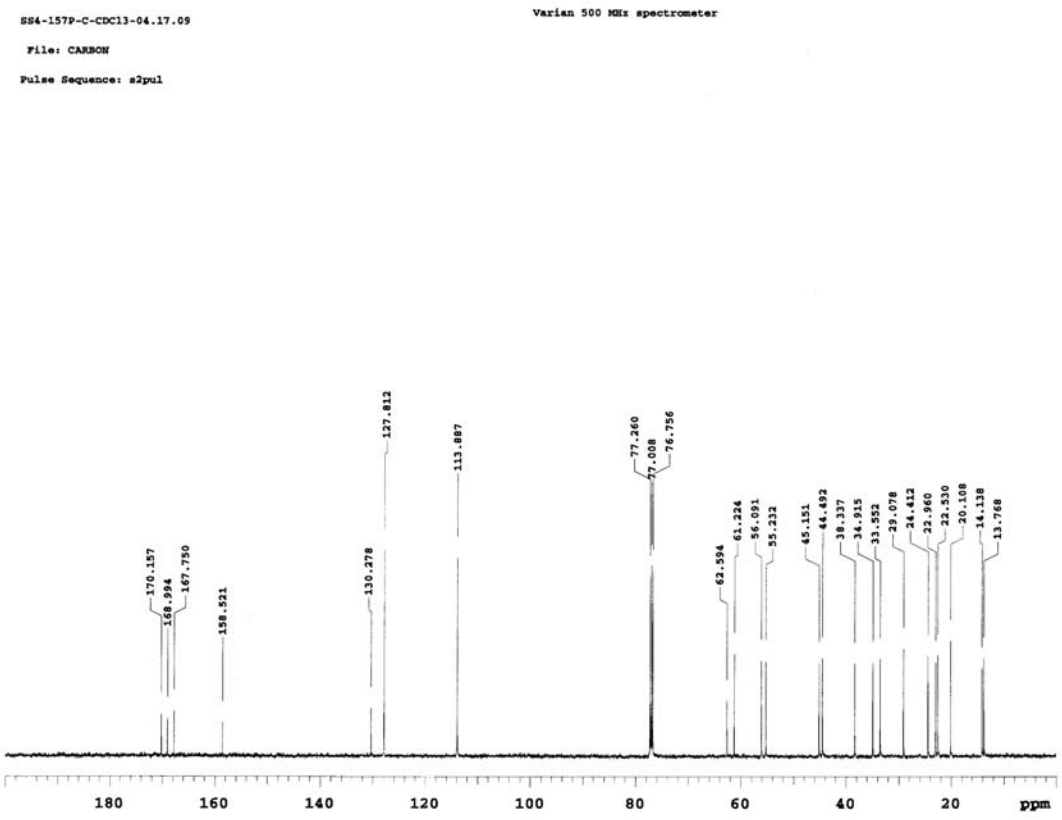
^{13}C NMR (Compound 147)



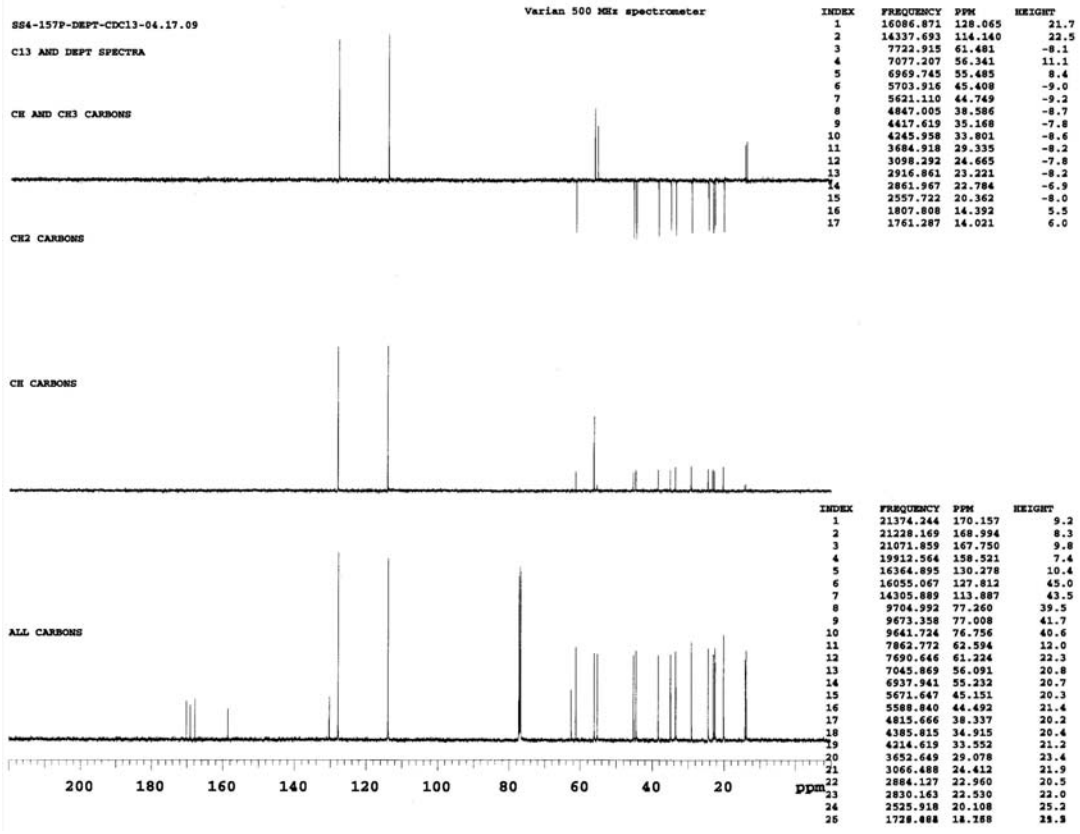
^{1}H NMR (Compound 148)



^{13}C NMR (Compound 148)



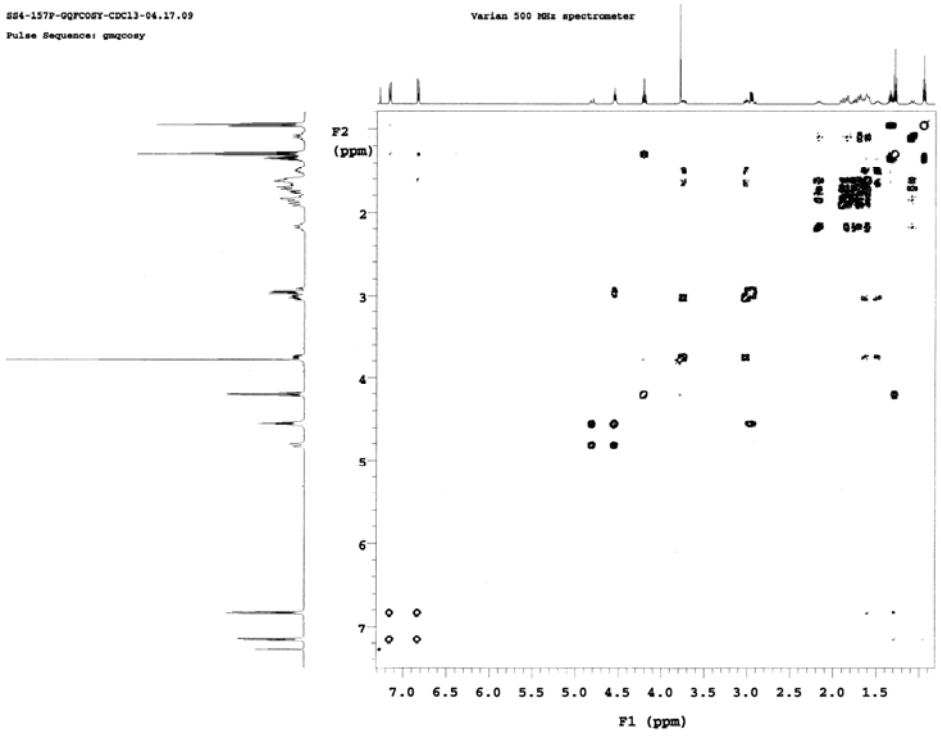
DEPT NMR (Compound 148)



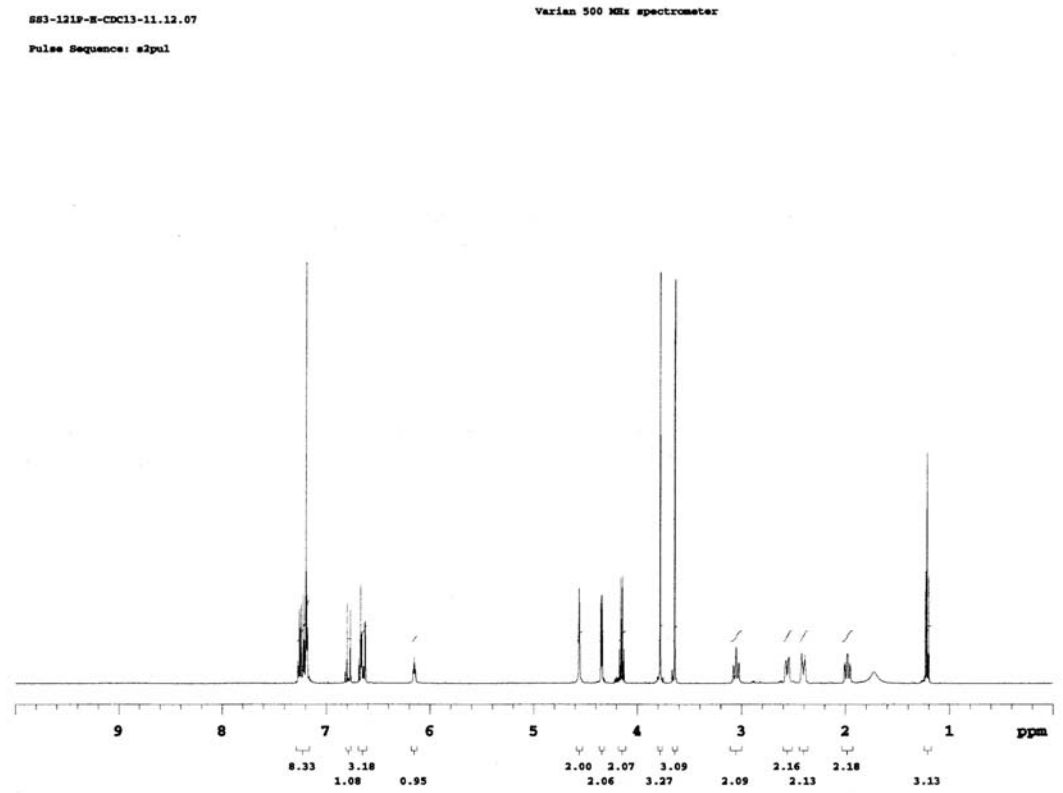
INDEX	FREQUENCY	PPM	HEIGHT
1	16086.871	128.065	21.7
2	14337.693	114.140	22.5
3	7722.915	61.481	-8.1
4	7077.207	56.341	11.1
5	6969.745	55.485	8.4
6	5703.916	45.408	-9.0
7	5621.110	44.749	-9.2
8	4847.005	38.586	-8.7
9	4417.619	35.168	-7.8
10	4245.958	33.801	-8.6
11	3684.918	29.335	-8.2
12	3098.292	24.665	-7.8
13	2916.861	23.221	-8.2
14	2861.967	22.784	-6.9
15	2557.722	20.362	-8.0
16	1807.808	14.392	5.5
17	1761.287	14.021	6.0

INDEX	FREQUENCY	PPM	HEIGHT
1	21374.244	170.157	9.2
2	21228.169	168.994	8.3
3	21071.859	167.750	9.8
4	19912.564	158.521	7.4
5	16364.895	130.278	10.4
6	16055.067	127.812	45.0
7	14305.889	113.887	43.5
8	9704.992	77.260	39.5
9	9673.358	77.008	41.7
10	9641.724	76.756	40.6
11	7862.772	62.594	12.0
12	7690.646	61.224	22.3
13	7045.869	56.091	20.8
14	6937.941	55.232	20.7
15	5671.647	45.151	20.3
16	5588.840	44.492	21.4
17	4815.666	38.337	20.2
18	4385.815	34.915	20.4
19	4214.619	33.552	21.2
20	3652.649	29.078	23.4
21	3066.488	24.412	21.9
22	2884.127	22.960	20.5
23	2830.163	22.530	22.0
24	2525.918	20.108	25.2
25	1728.488	18.758	25.5

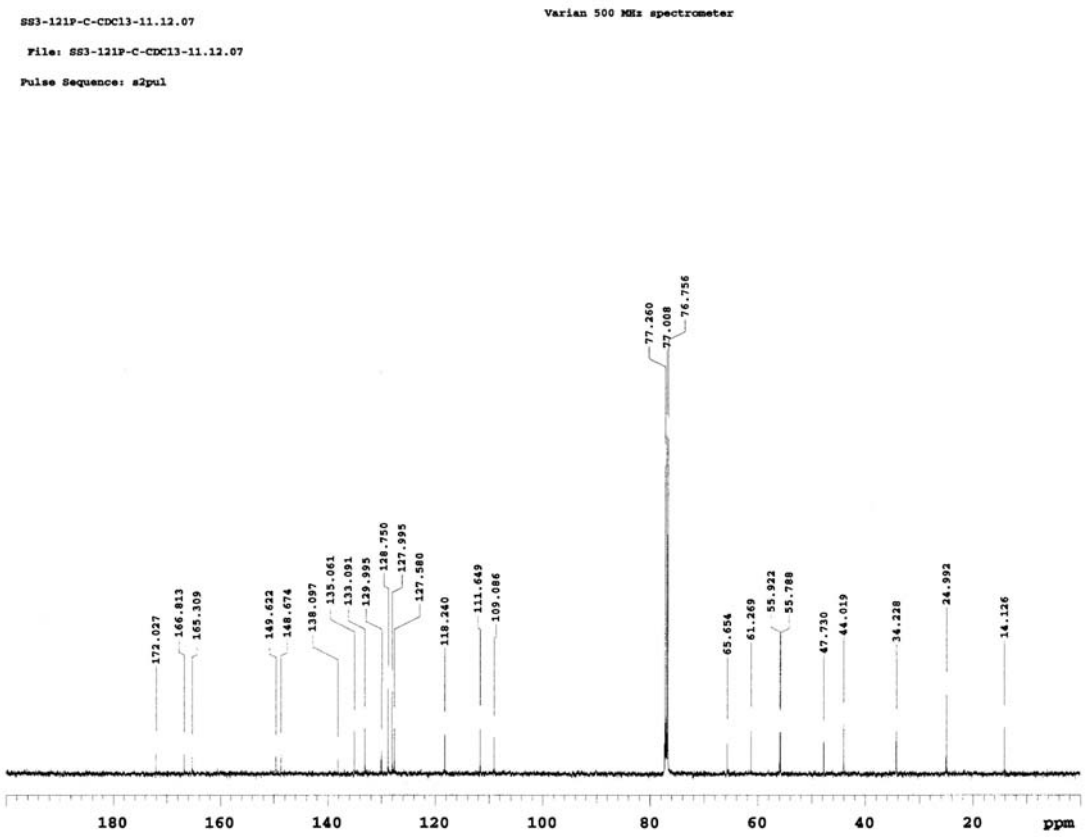
^{1}H-^{1}H GDQFCOSY (Compound 148)



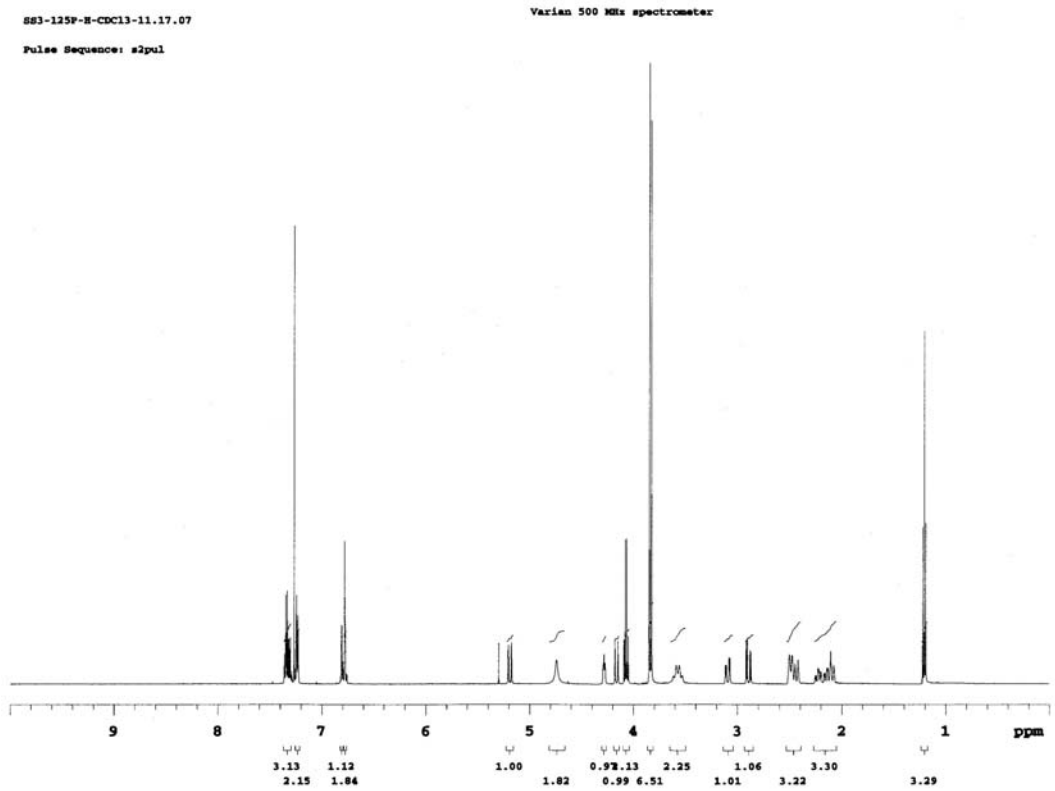
^{1}H NMR (Compound 149)



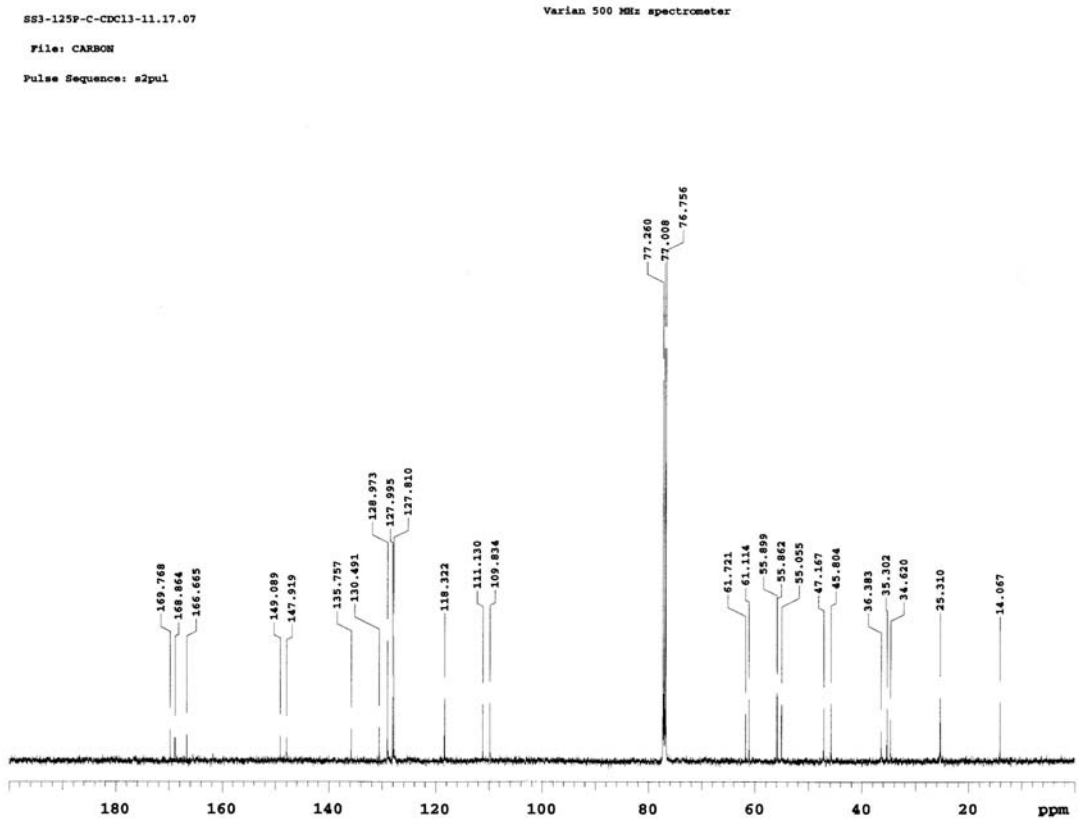
^{13}C NMR (Compound 149)



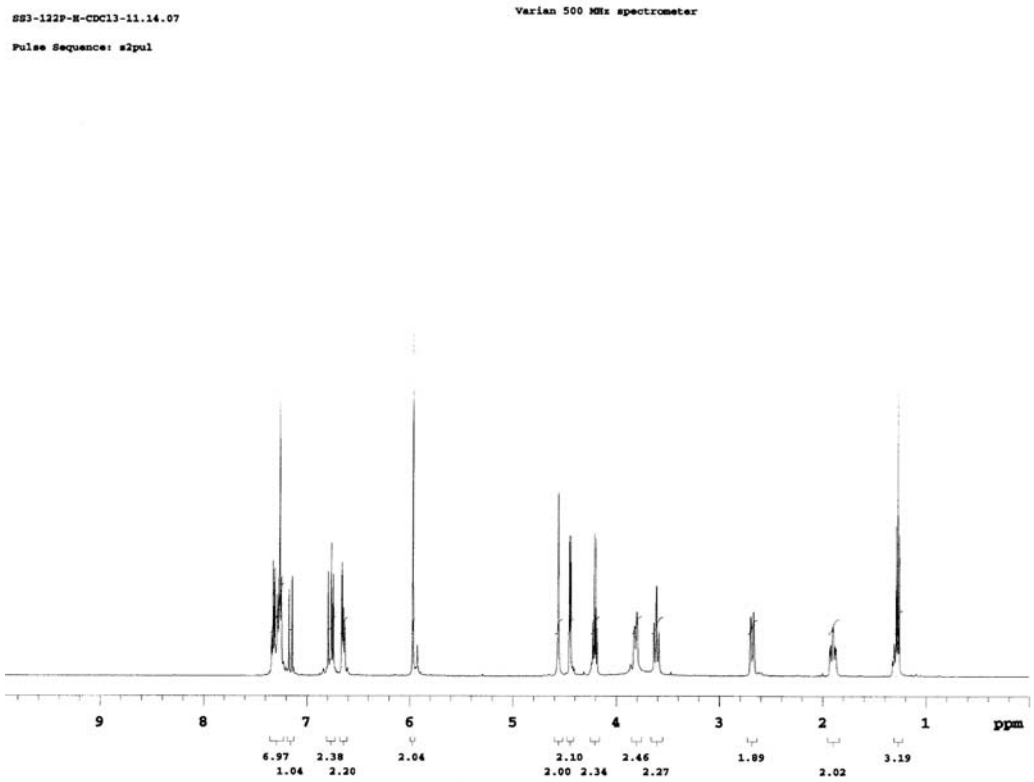
^{1}H NMR (Compound 150)



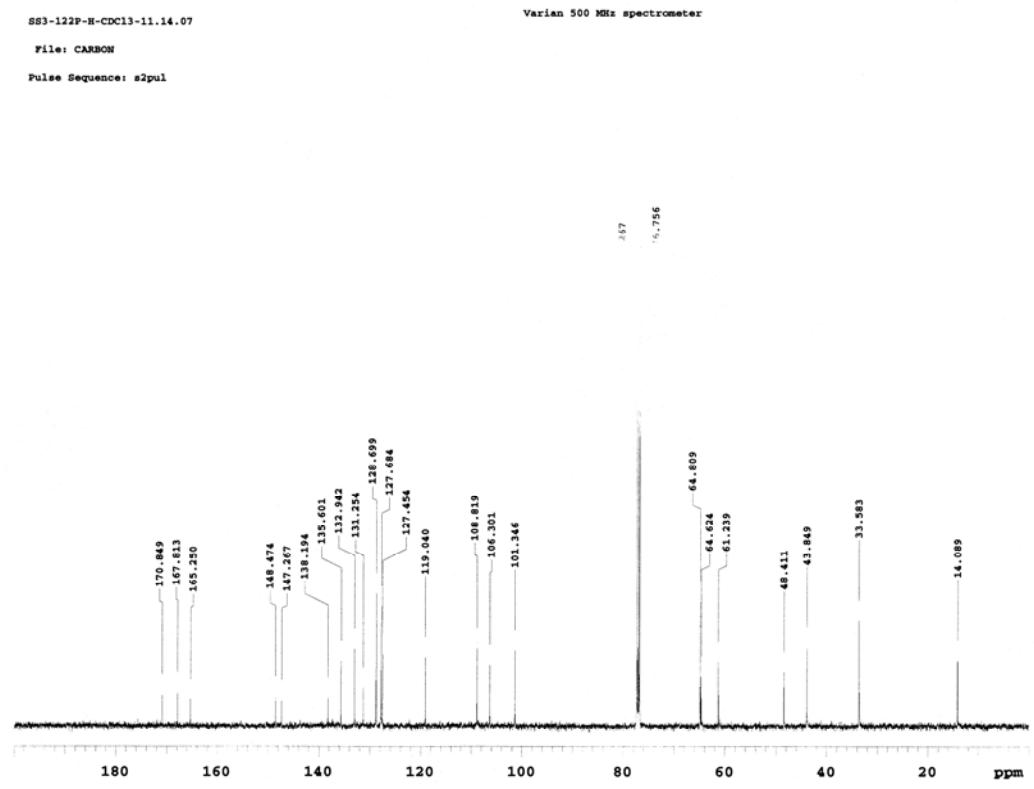
^{13}C NMR (Compound 150)



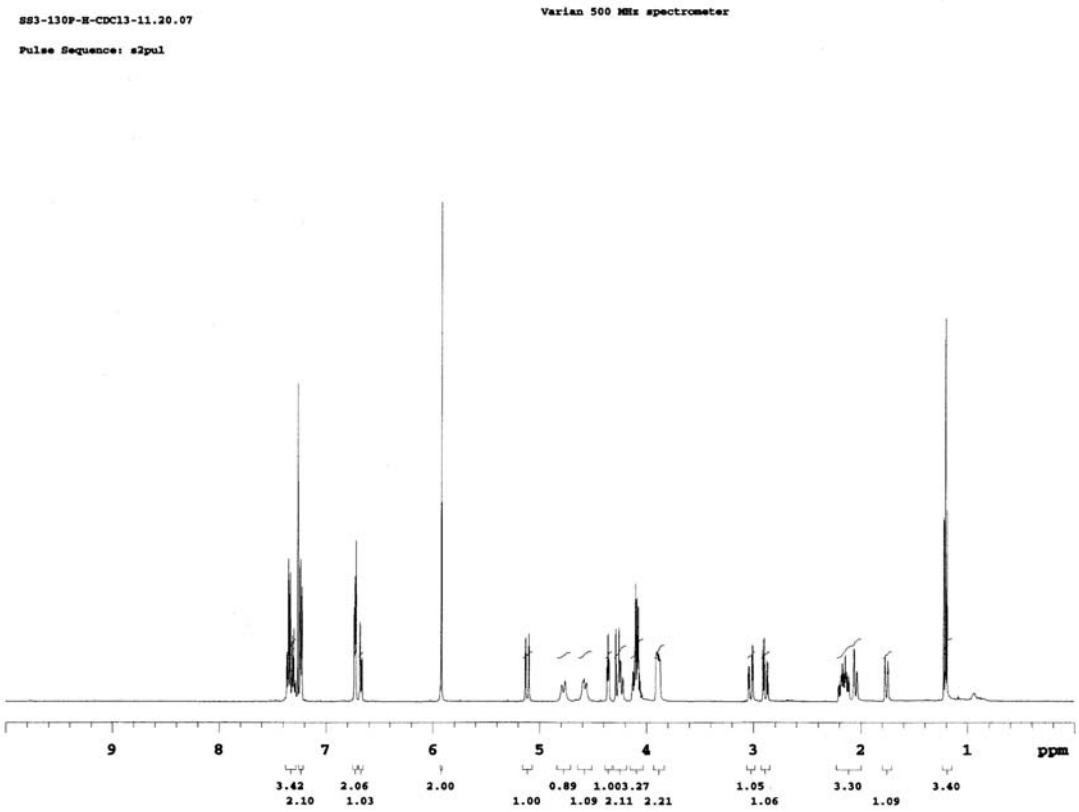
^{1}H NMR (Compound 151)



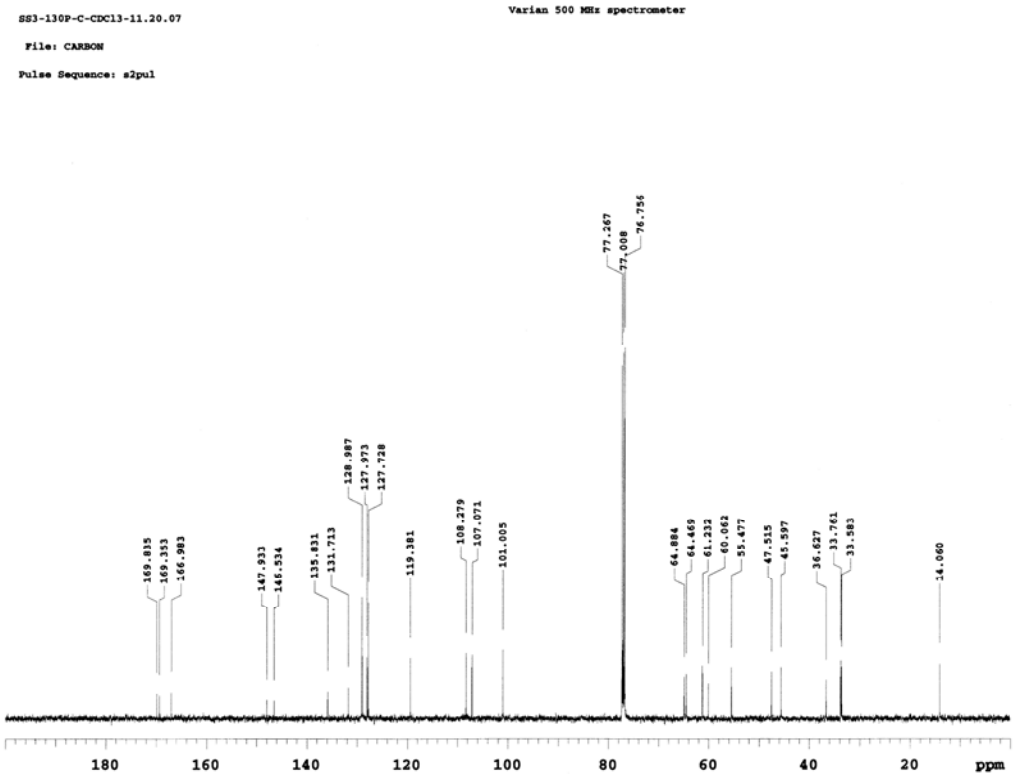
^{13}C NMR (Compound 151)



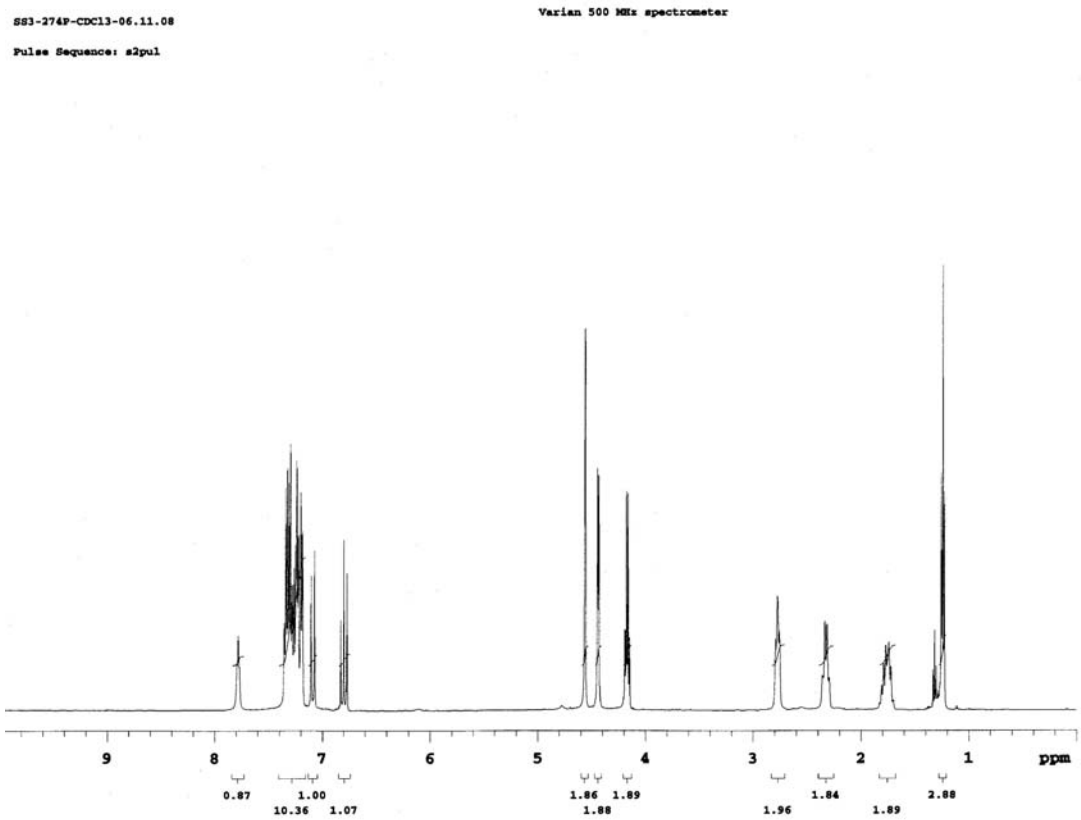
^{1}H NMR (Compound 152)



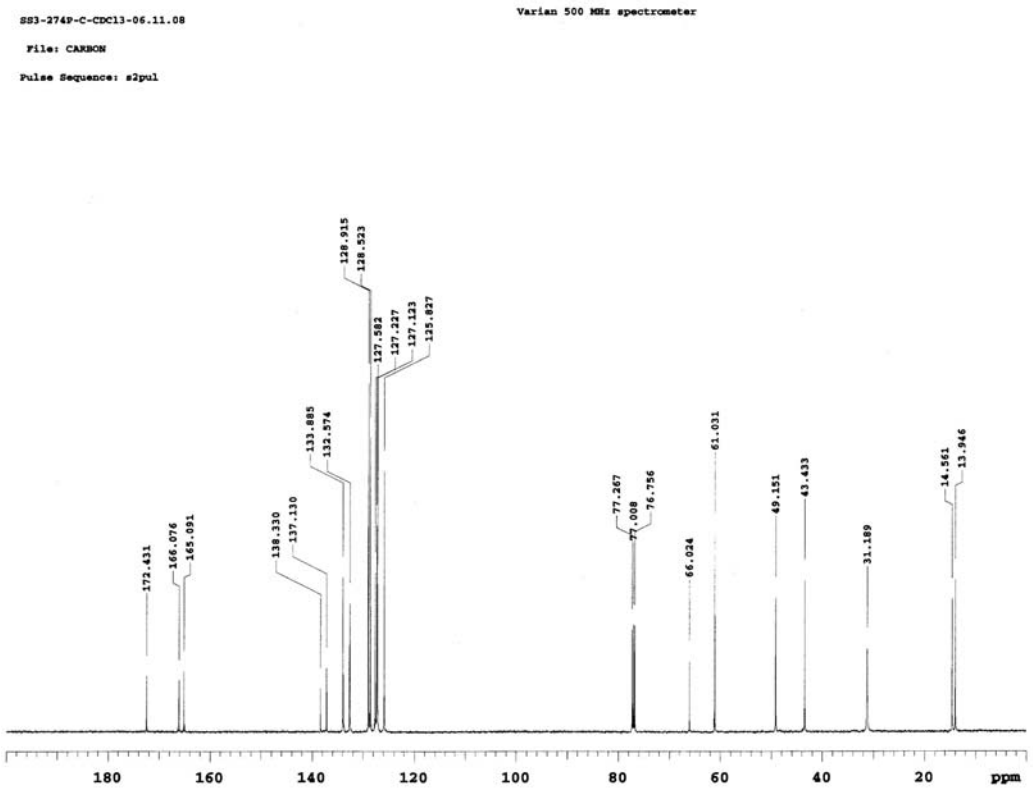
^{13}C NMR (Compound 152)



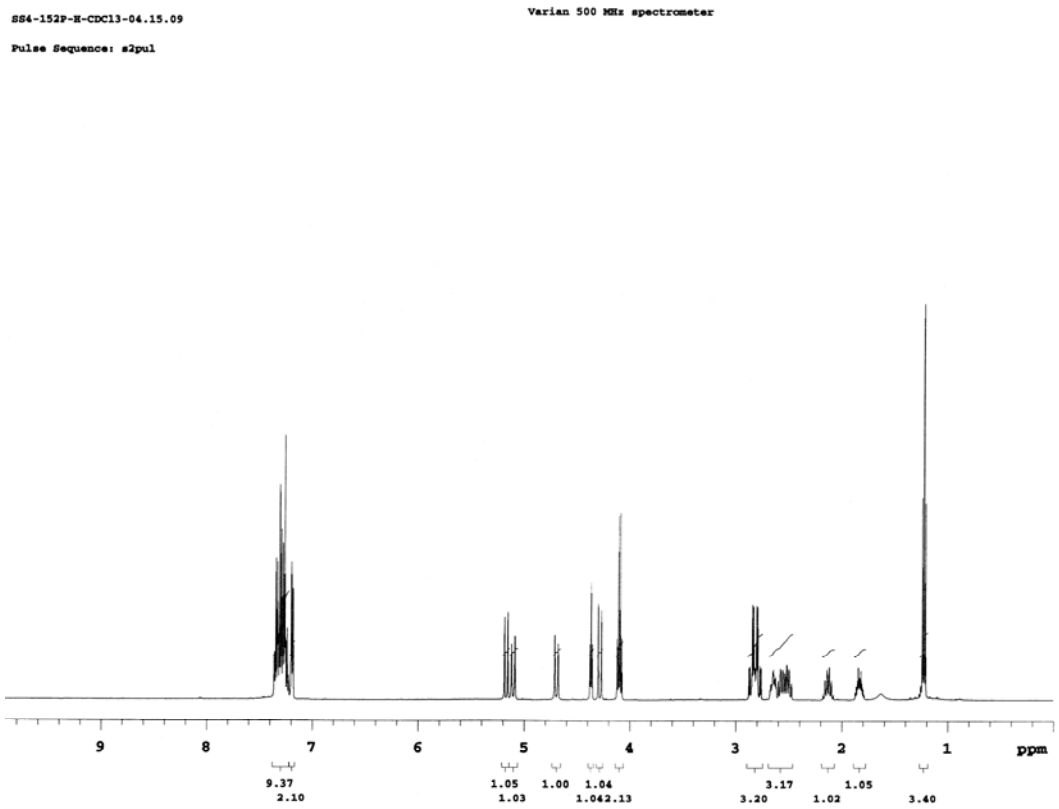
^{1}H NMR (Compound 153)



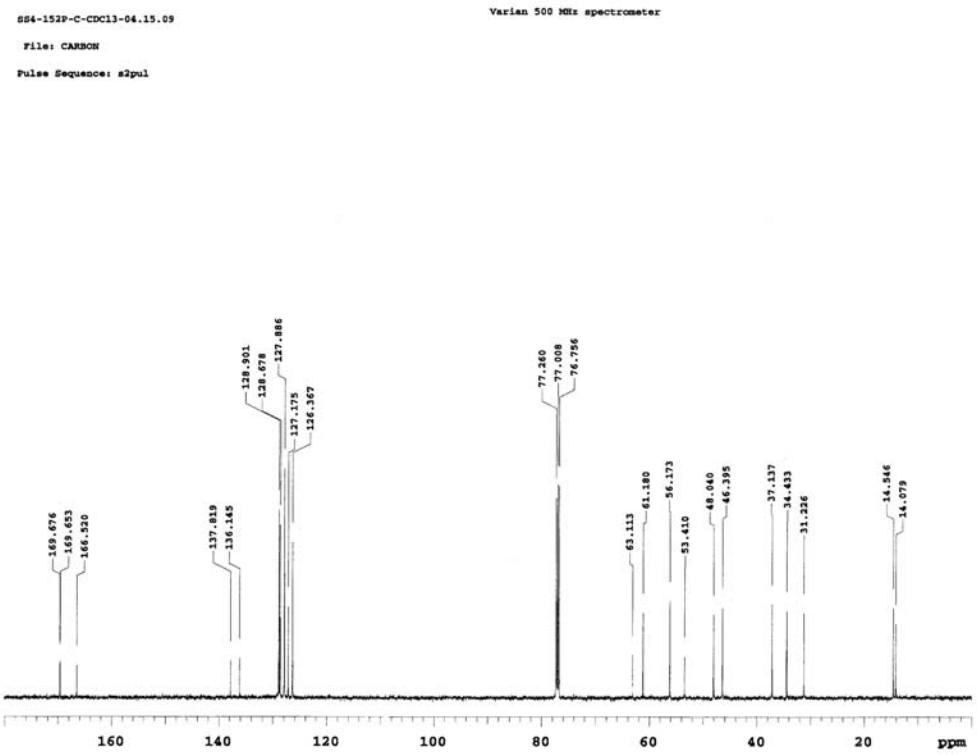
^{13}C NMR (Compound 153)



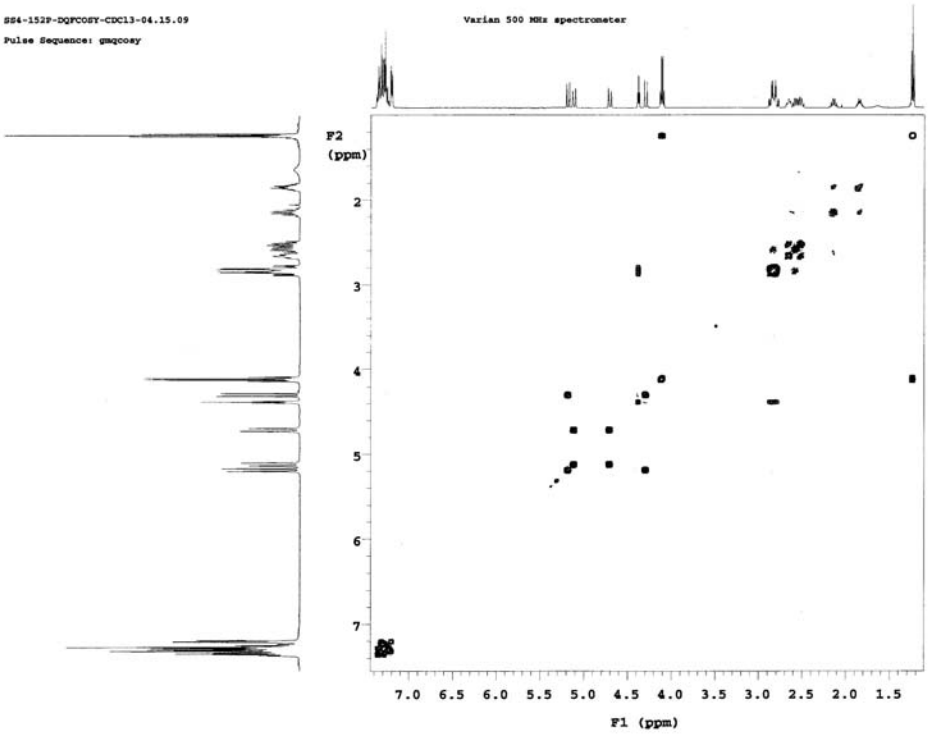
^{1}H NMR (Compound 154)



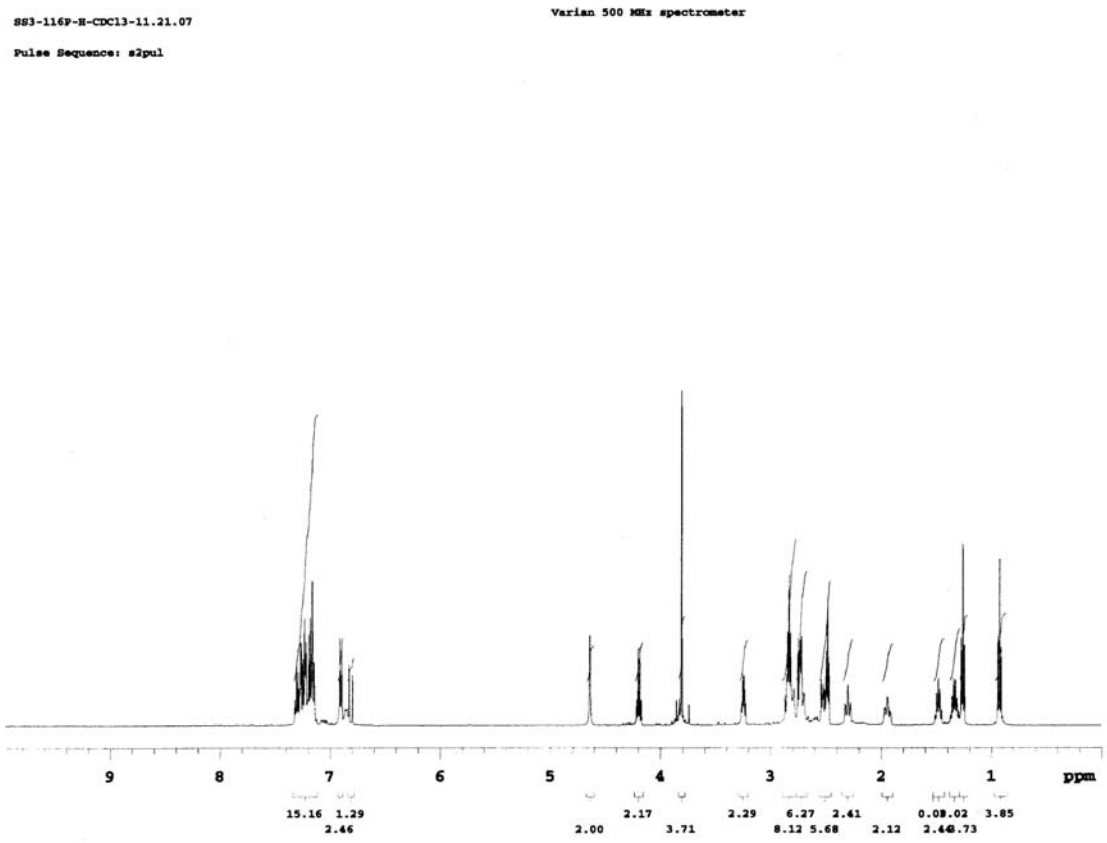
^{13}C NMR (Compound 154)



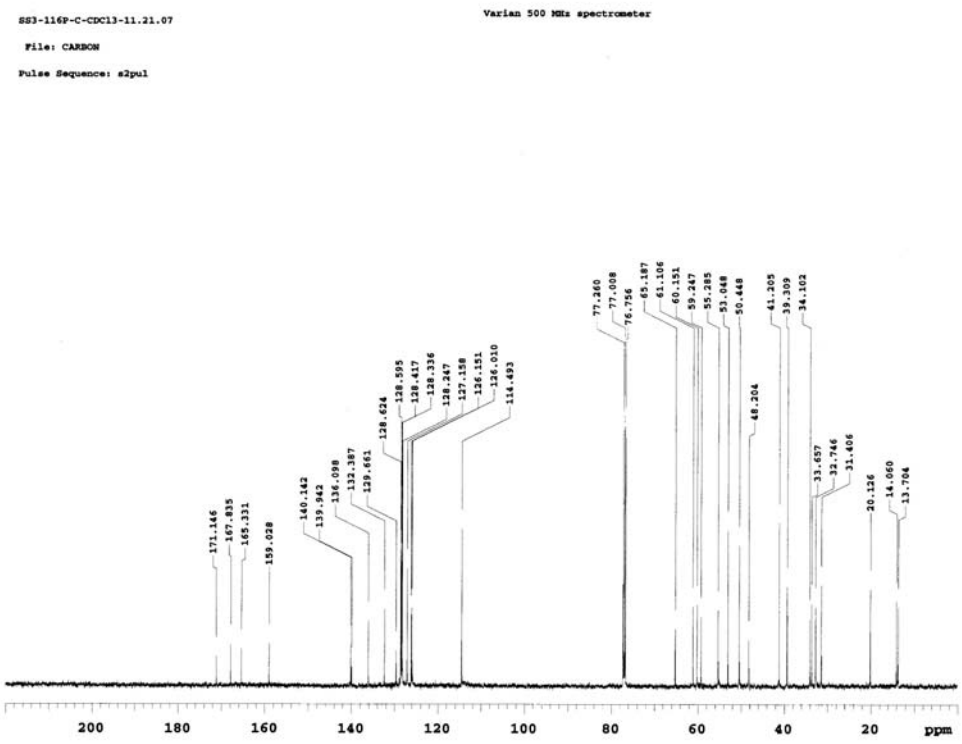
^{1}H-^{1}H GDQFCOSY NMR (Compound 154)



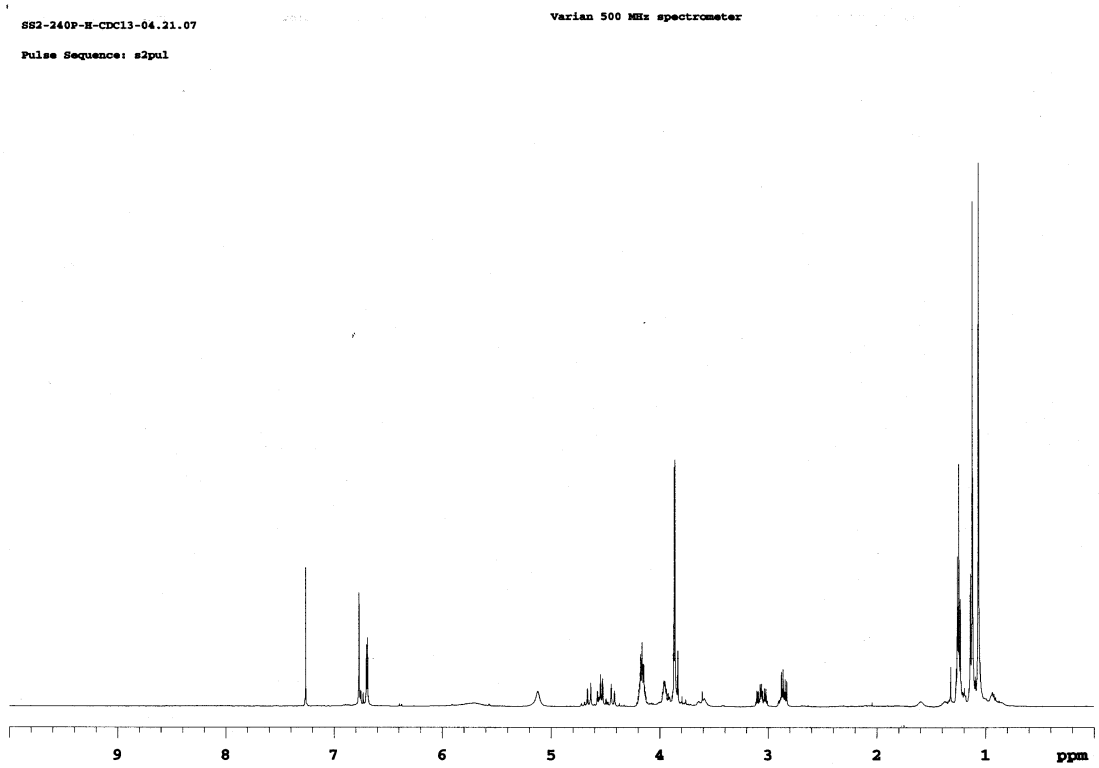
^{1}H NMR (Compound 157)



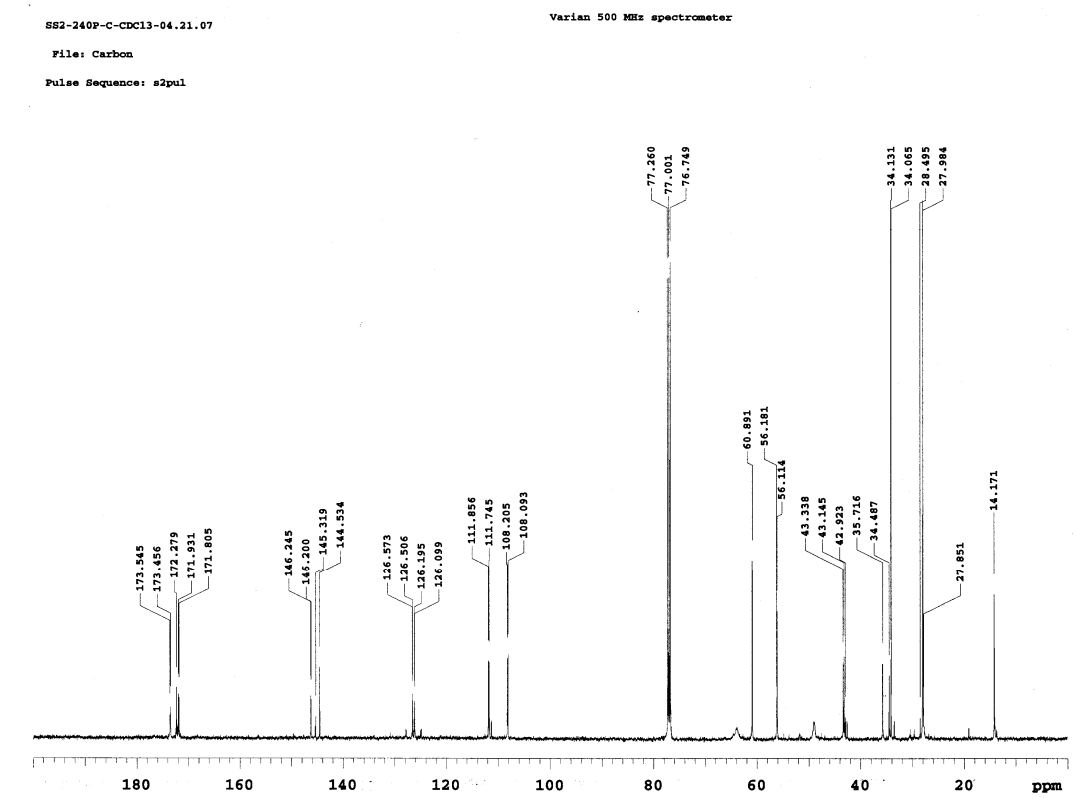
^{13}C NMR (Compound 157)



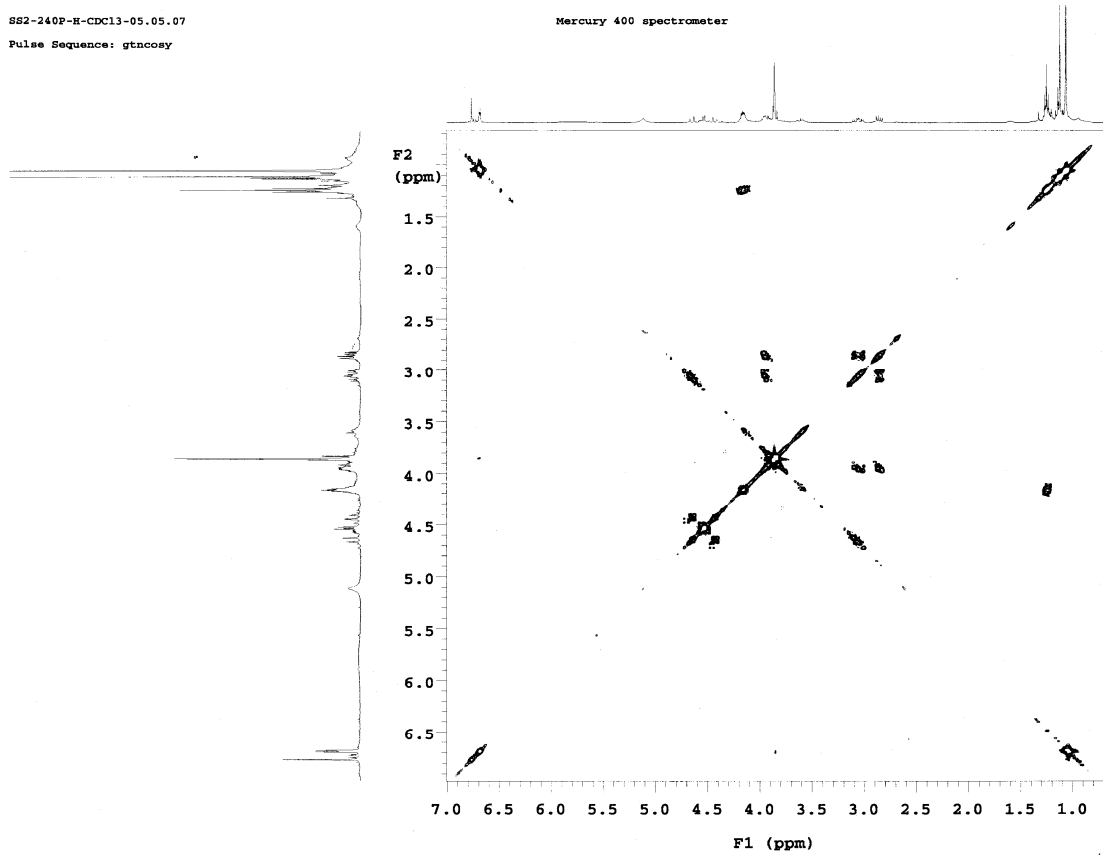
^{1}H NMR (Compound 159)



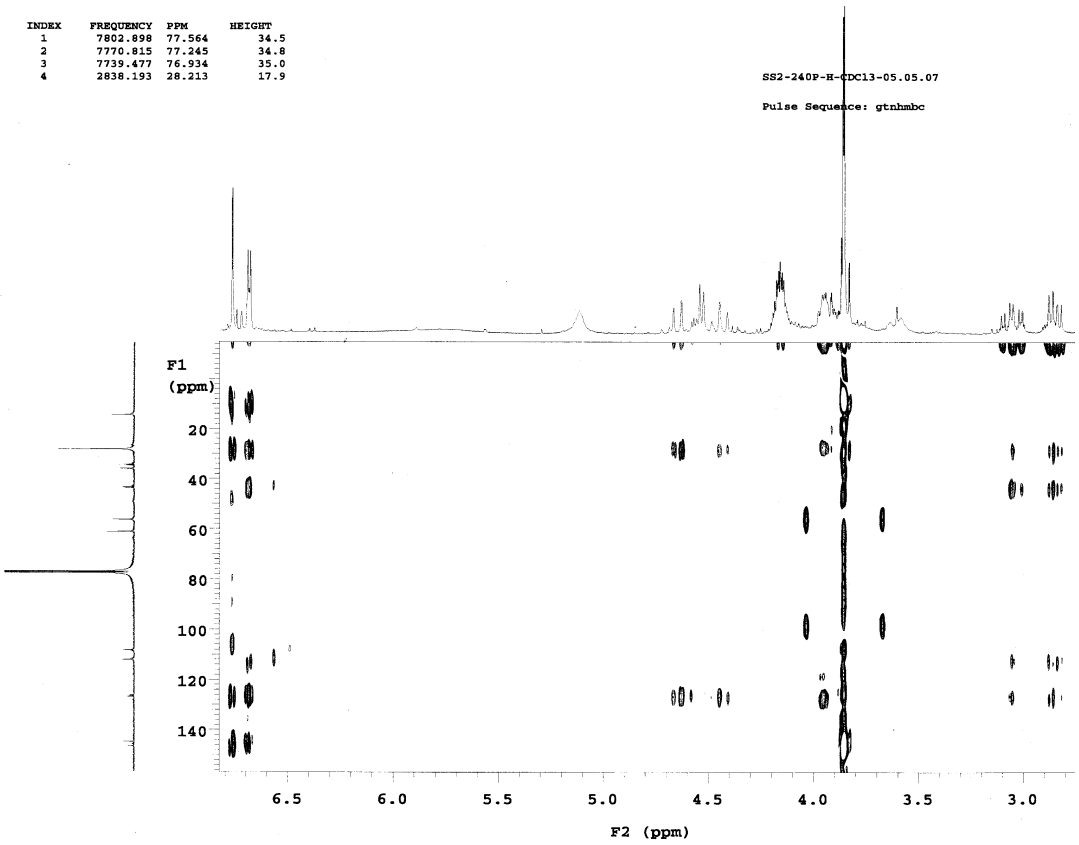
^{13}C NMR (Compound 159)



^{1}H-^{1}H GDQFCOSY NMR (Compound 159)



GHMBC NMR (Compound 159)



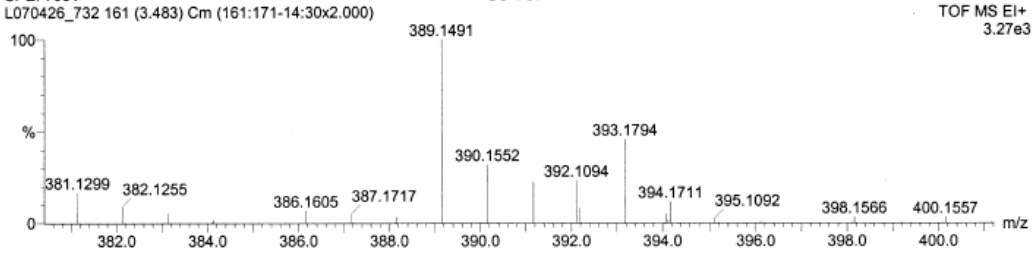
HRMS (EIMS, M^+): Compound 159

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

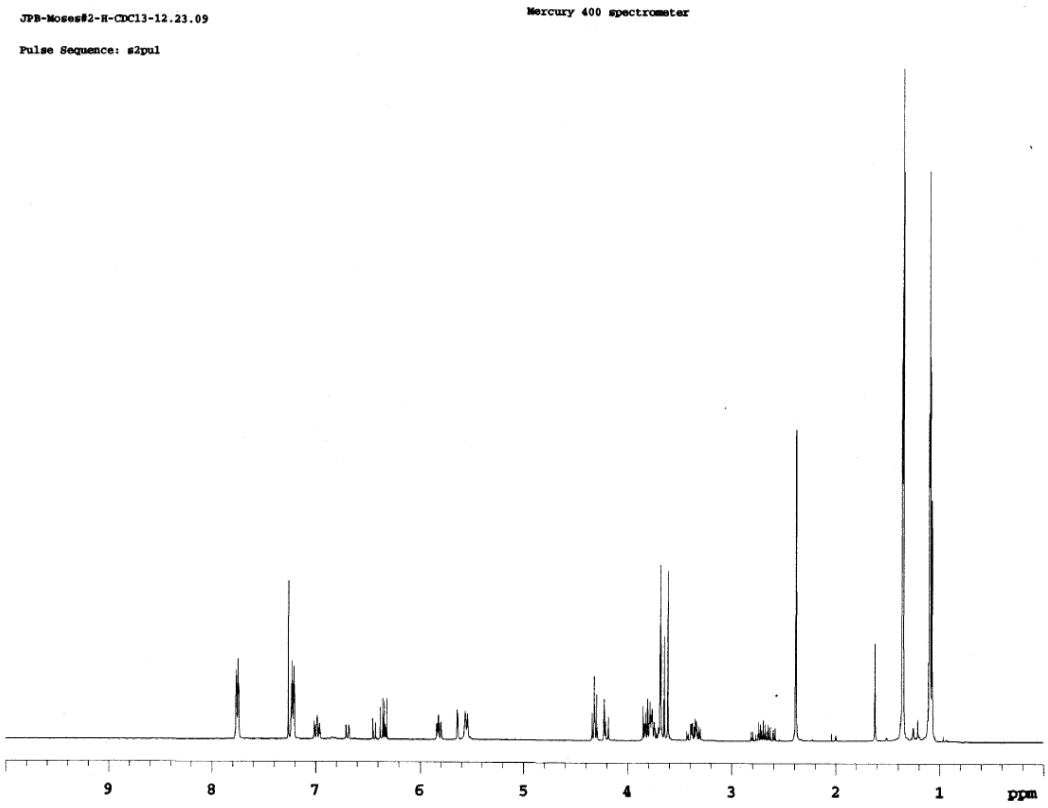
Monoisotopic Mass, Odd and Even Electron Ions
254 formula(e) evaluated with 6 results within limits (all results (up to 1000) for each mass)

Soumava Santra SS2-240P 26-Apr-2007 12:13:15
SPEI 70eV GC-TOF TOF MS EI+
L070426_732 161 (3.483) Cm (161:171-14:30x2.000) 3.27e3

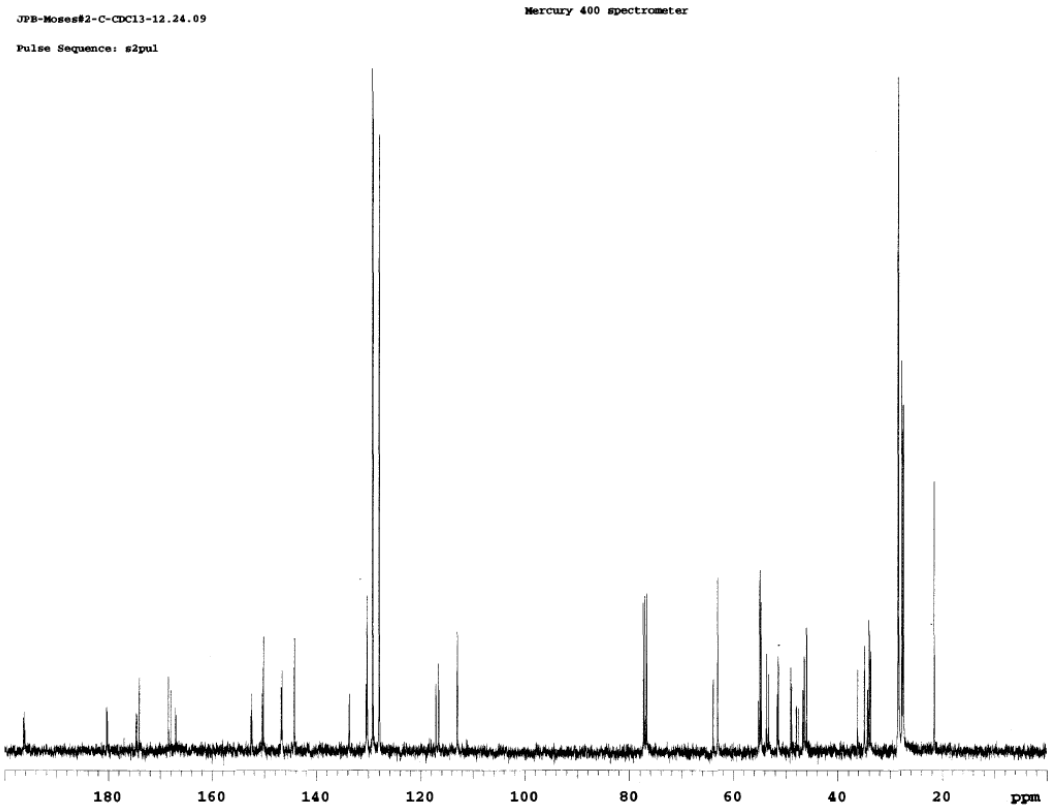


Minimum:				-1.5		
Maximum:		5.0	10.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
393.1794	393.1788	0.7	1.7	8.0	2	C20 H27 N O7
	393.1774	2.0	5.1	8.5	3	C18 H25 N4 O6
	393.1814	-2.0	-5.1	12.5	1	C23 H25 N2 O4
	393.1761	3.3	8.5	3.5	5	C17 H29 O10
	393.1747	4.7	11.9	4.0	6	C15 H27 N3 O9
	393.1841	-4.7	-12.0	17.0	4	C26 H23 N3 O

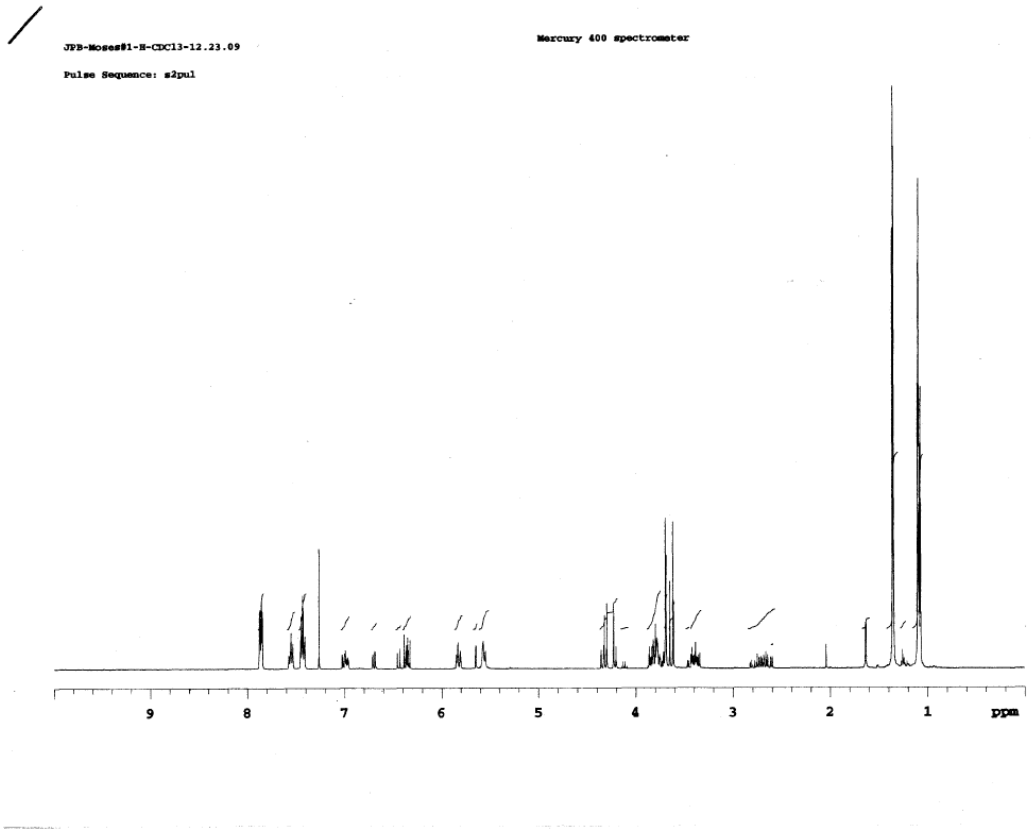
^{1}H NMR (Compound 161)



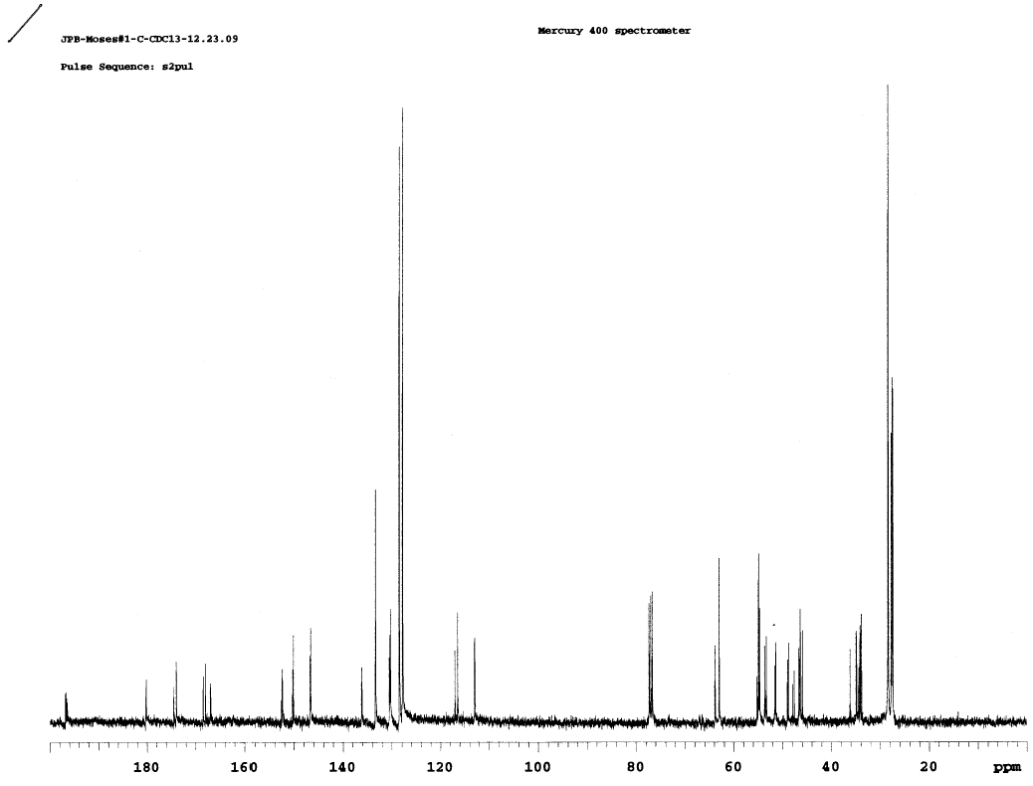
^{13}C NMR (Compound 161)



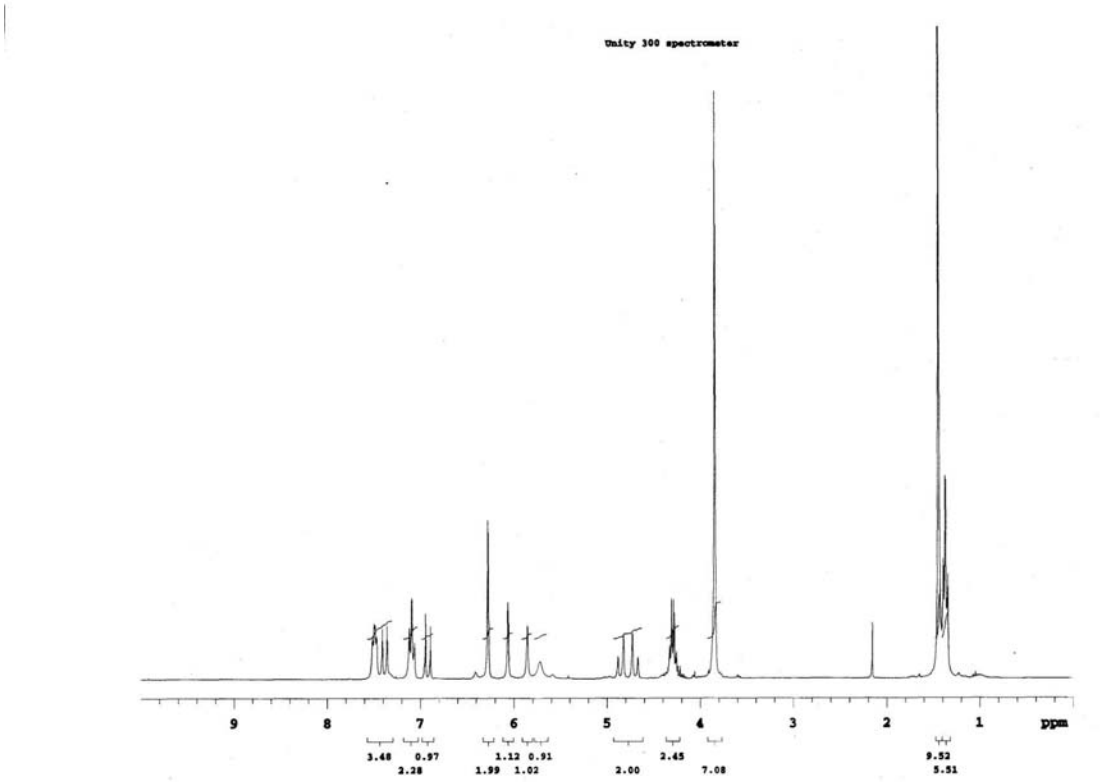
^{1}H NMR (Compound 163)



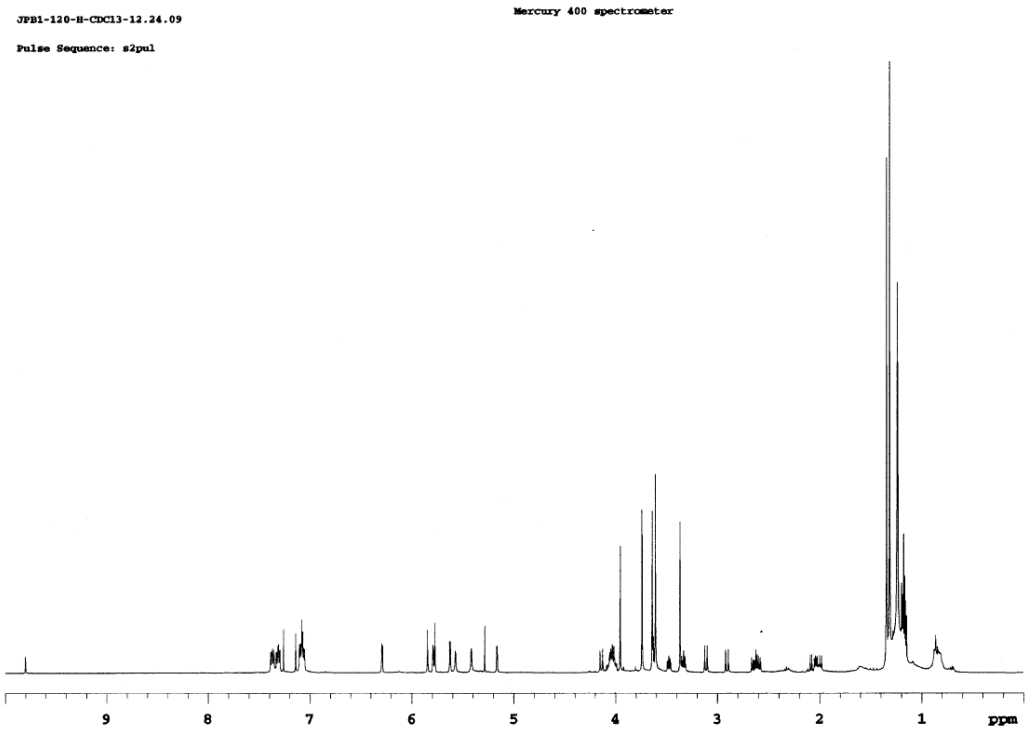
^{13}C NMR (Compound 163)



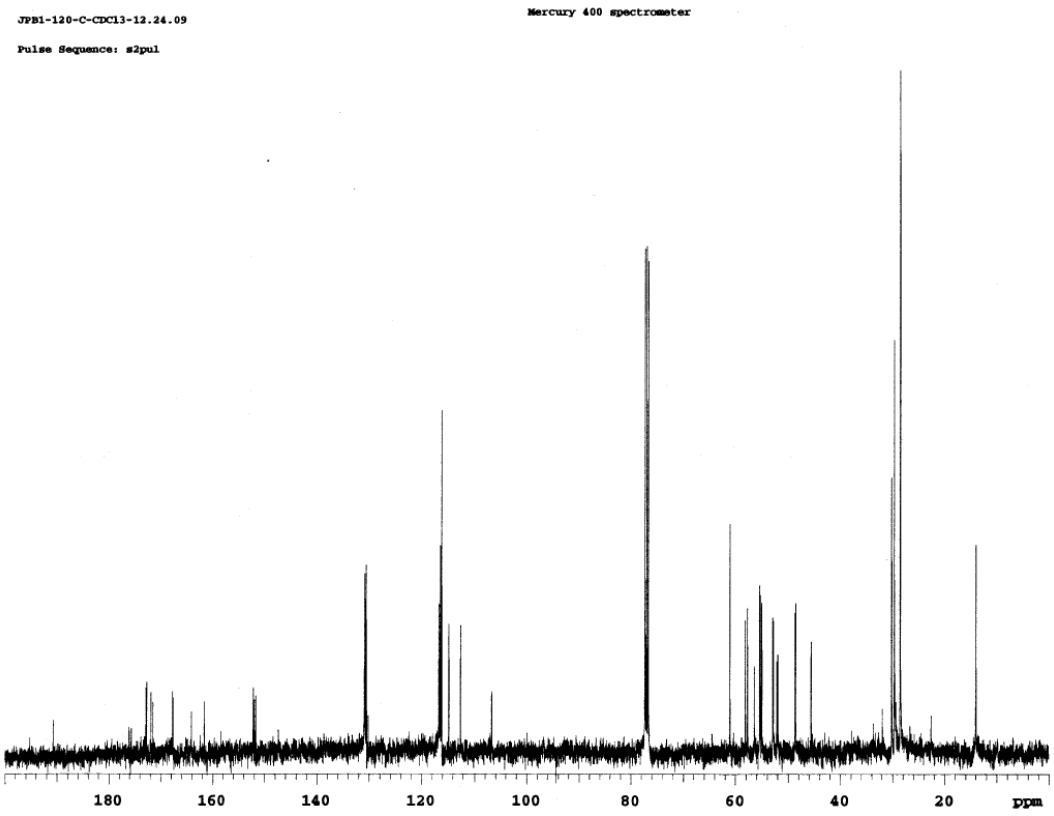
^{1}H NMR (Compound 165)



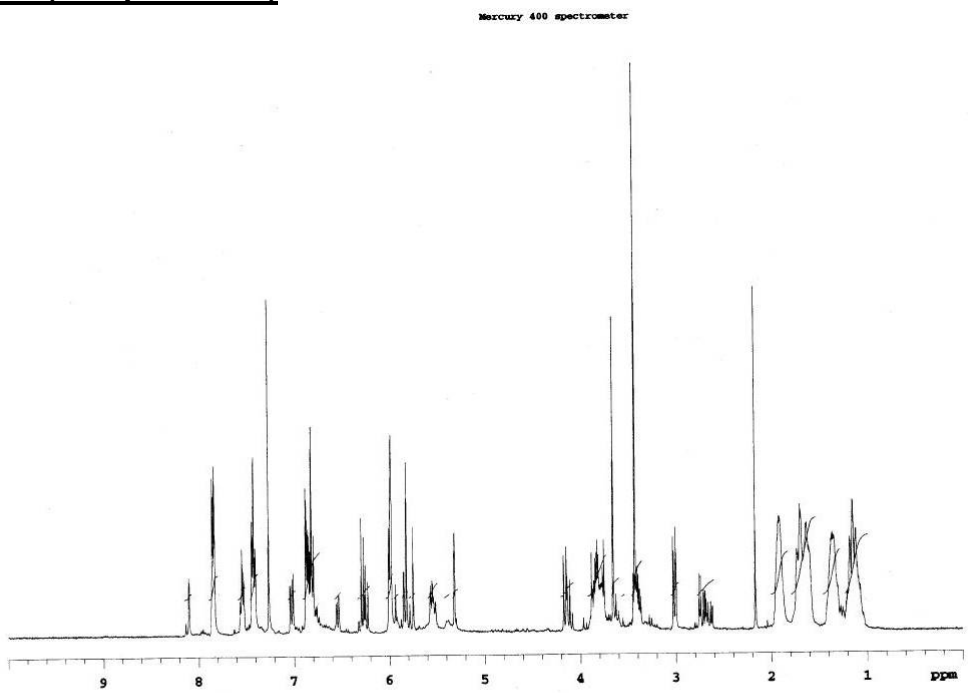
^{1}H NMR (Compound 166)



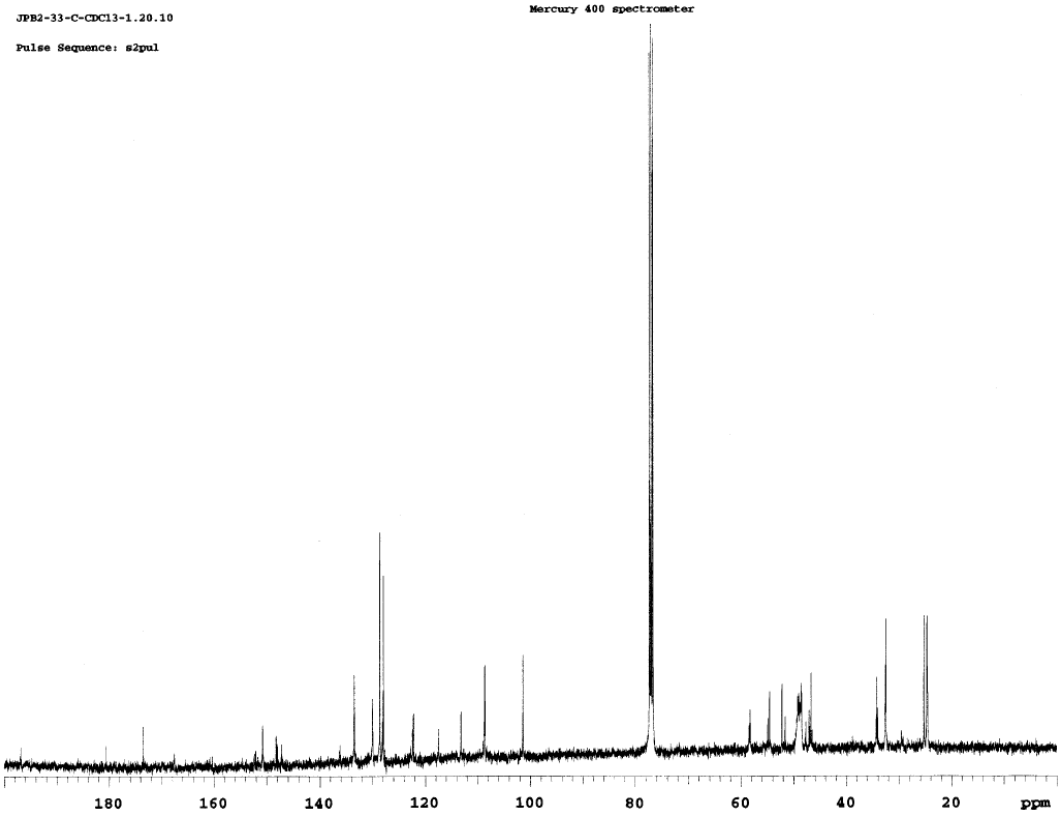
^{13}C NMR (Compound 166)



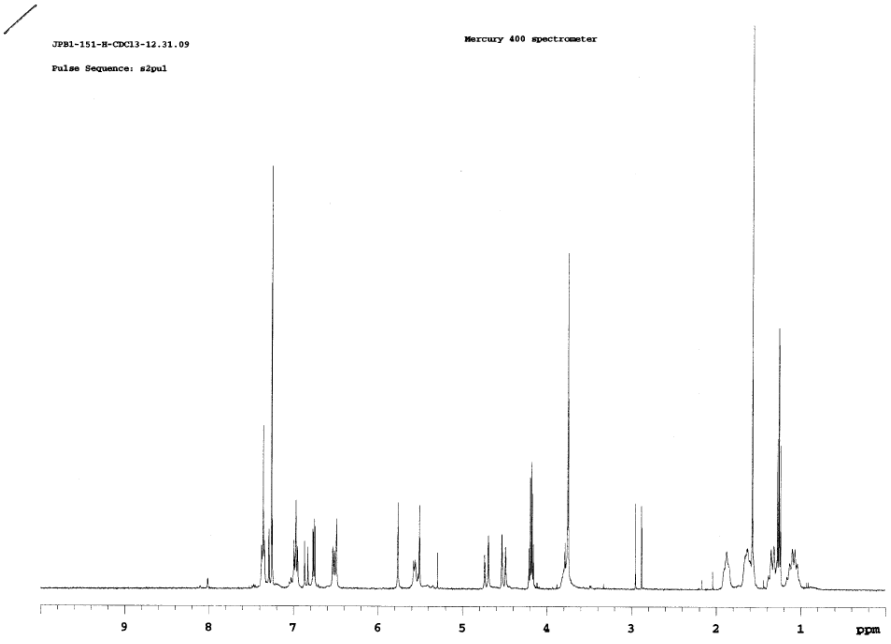
^{1}H NMR (Compound 168)



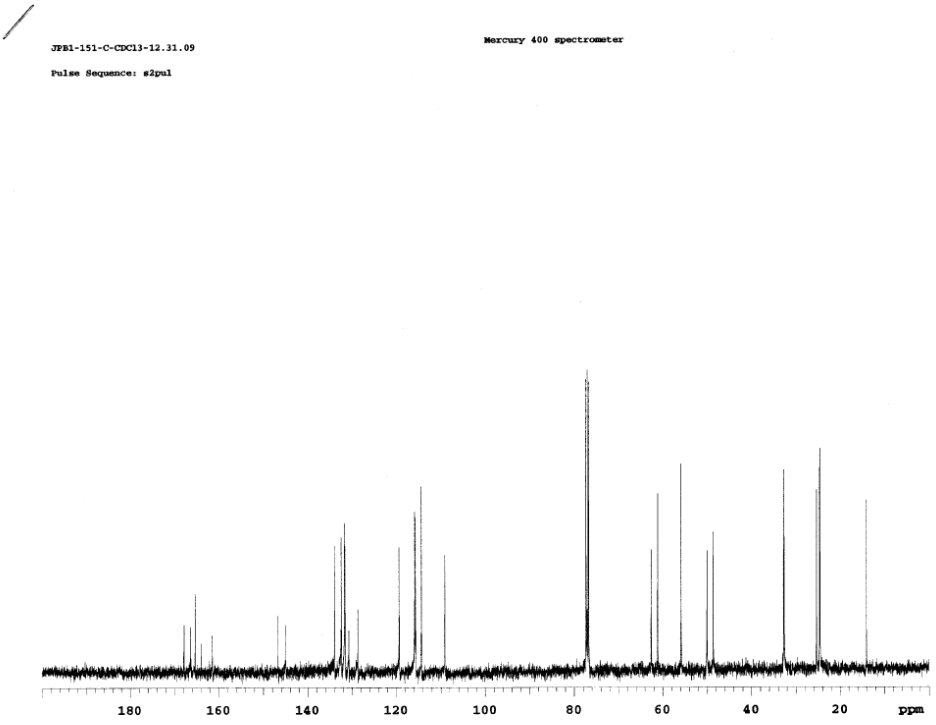
^{13}C NMR (Compound 168)



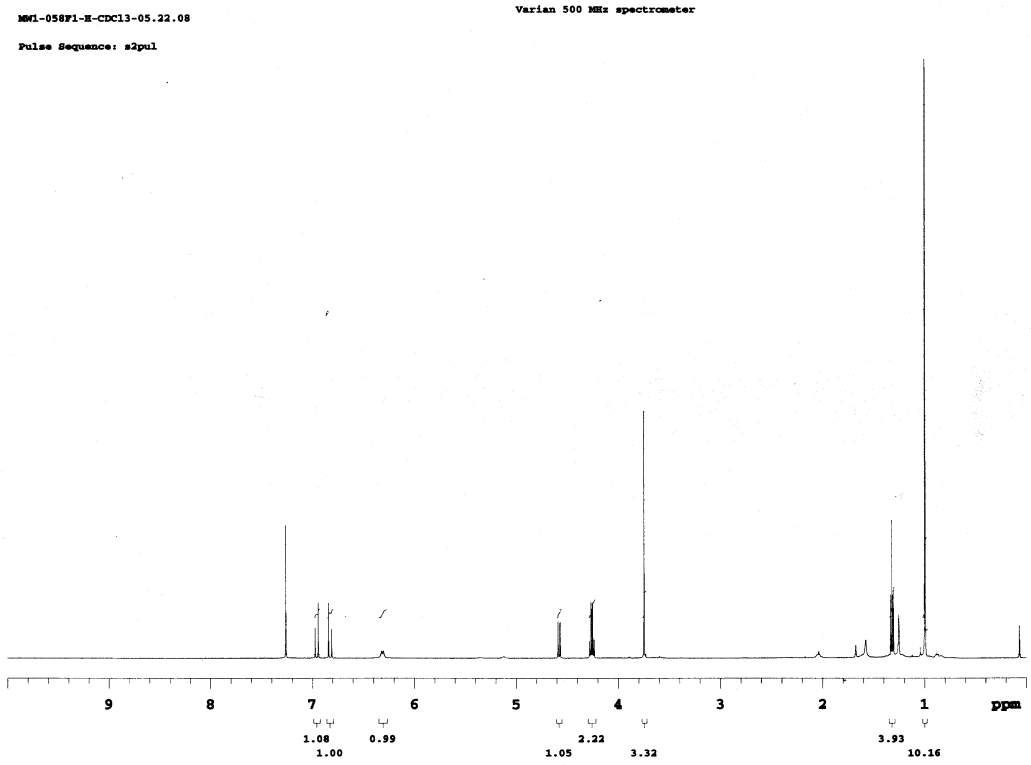
^{1}H NMR (Compound 170)



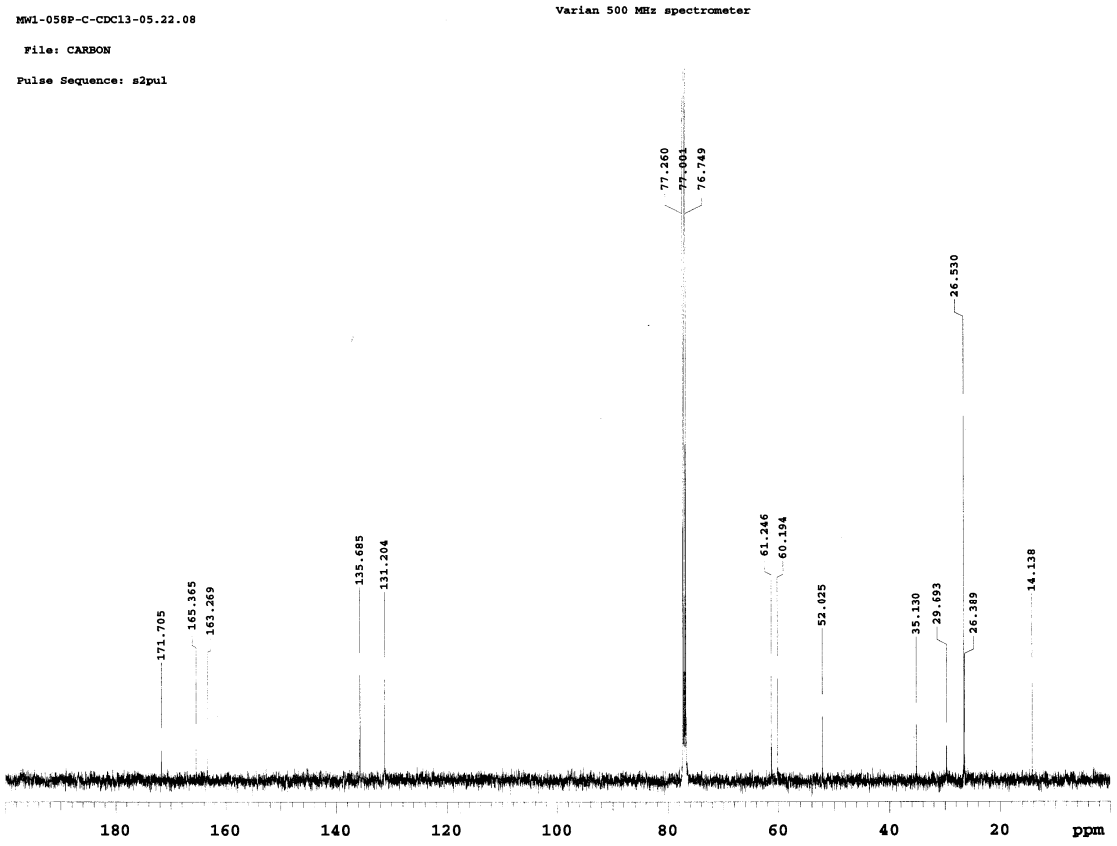
^{13}C NMR (Compound 170)



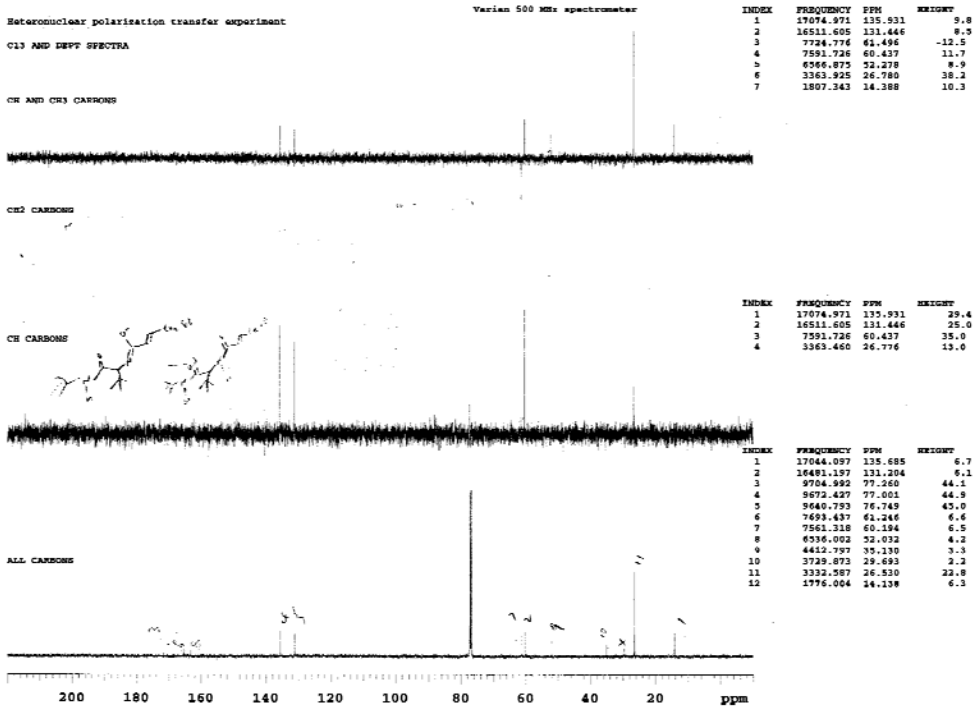
^{1}H NMR (Compound 186)



^{13}C NMR (Compound 186)



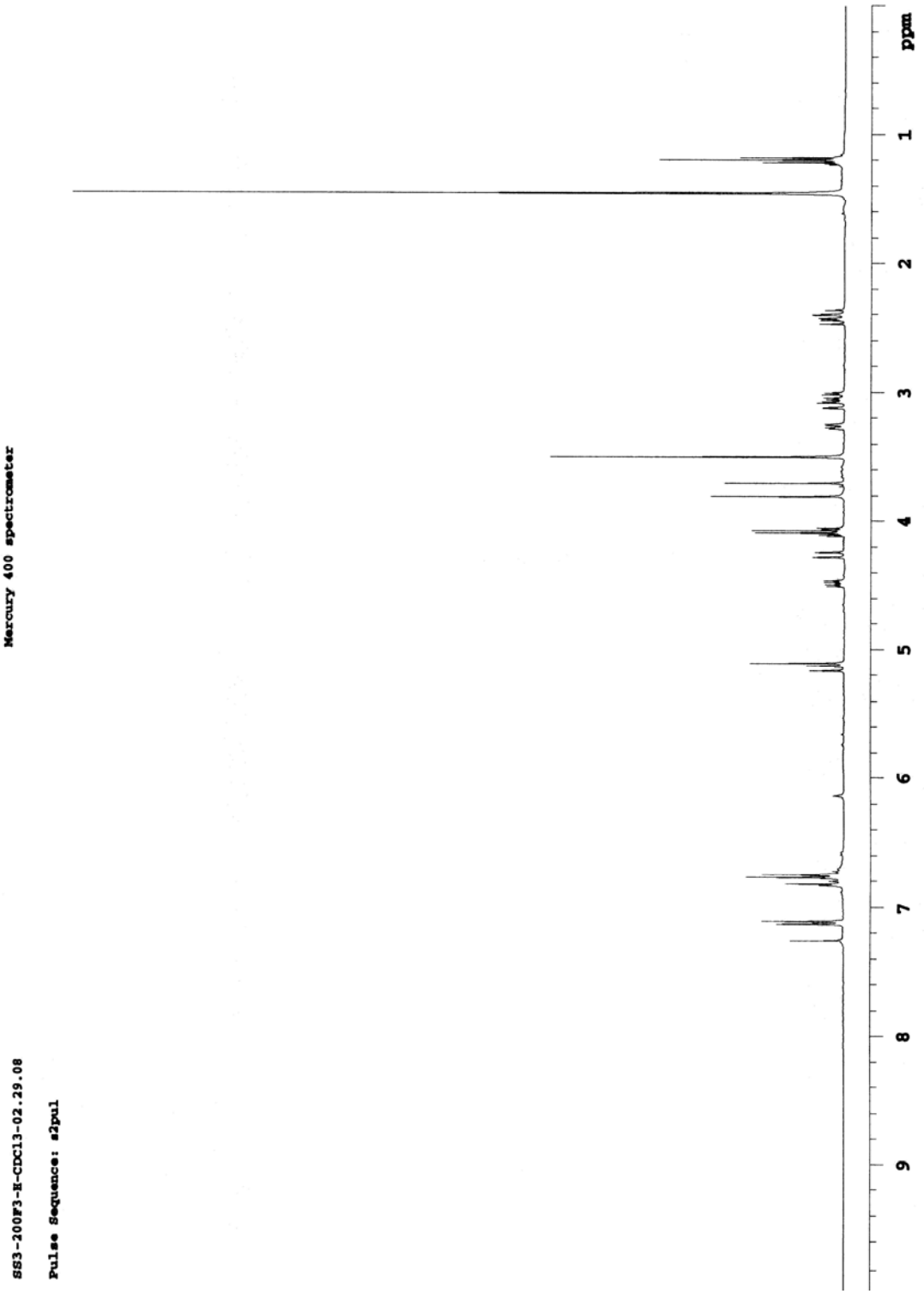
DEPT NMR (Compound 186)



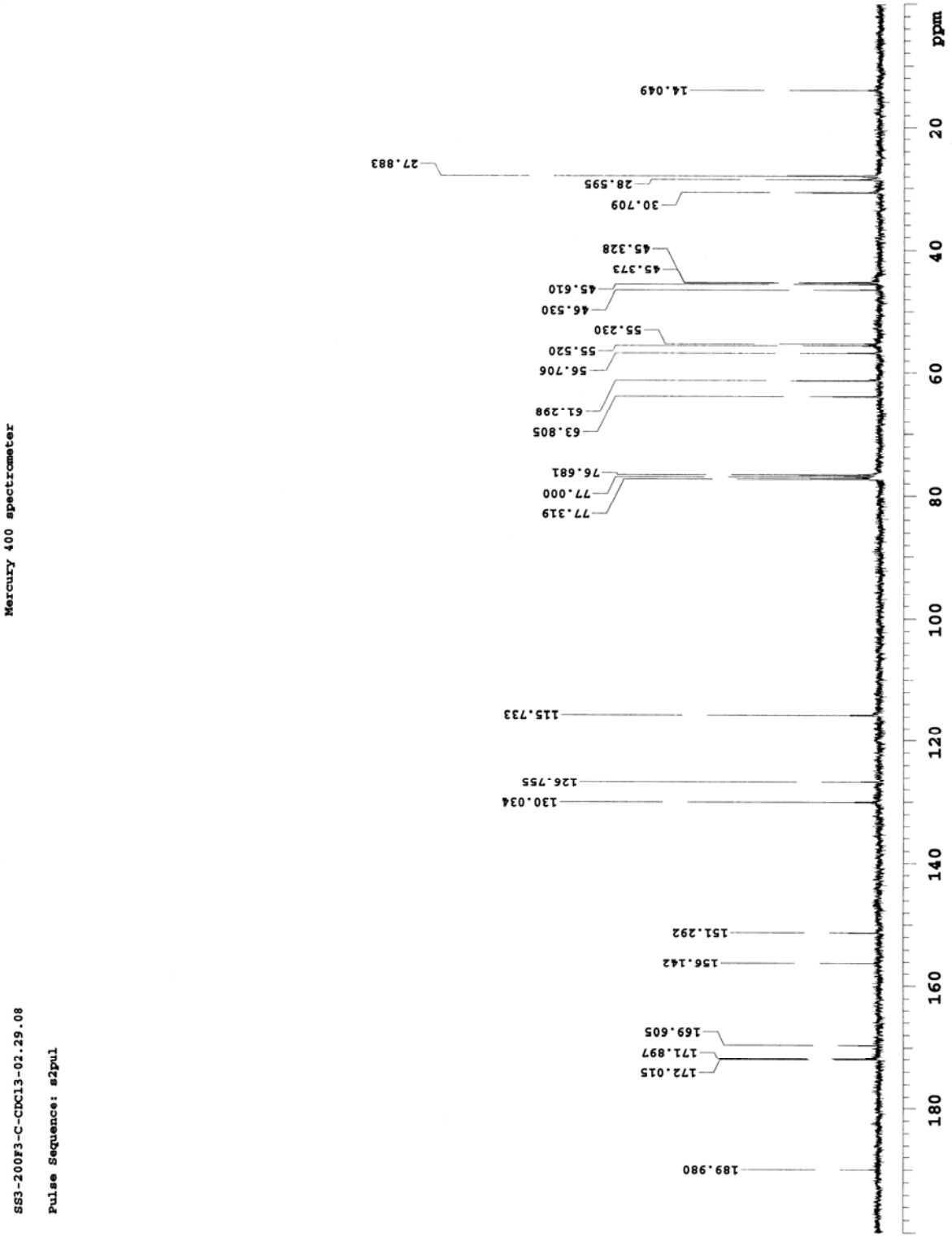
APPENDIX II

NMR Spectra of Chapter 3

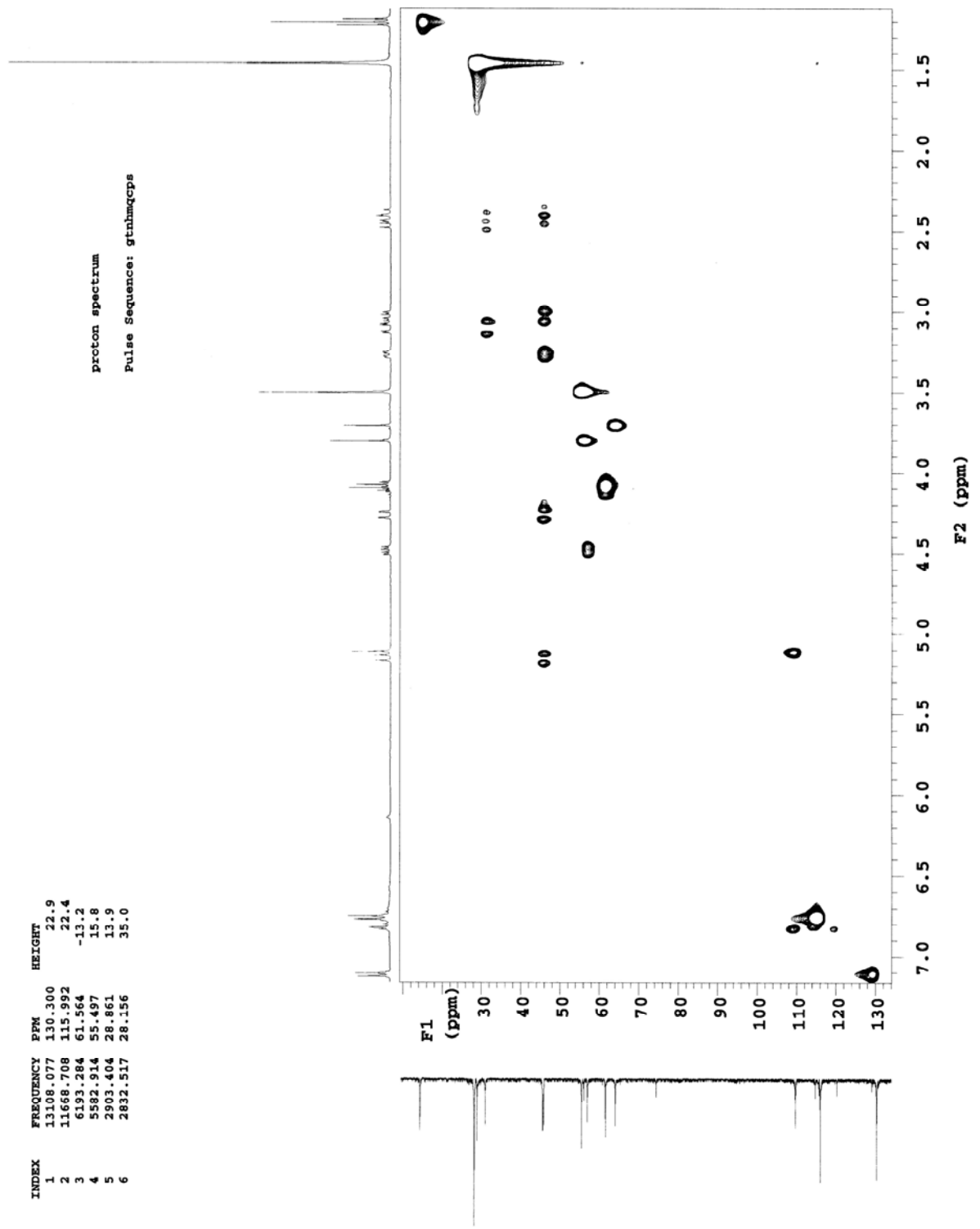
^{1}H NMR (Compound 215)



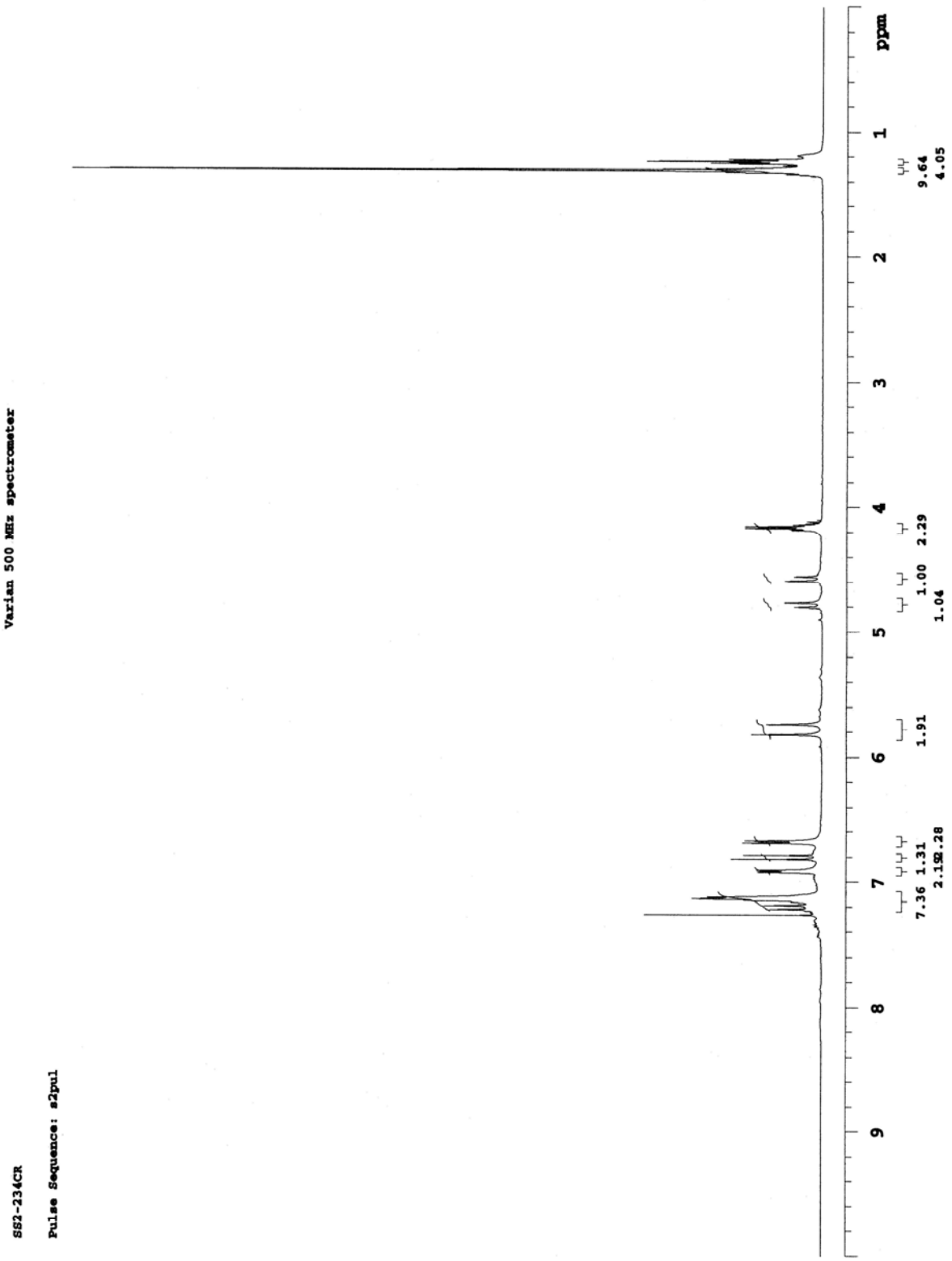
^{13}C NMR (Compound 215)



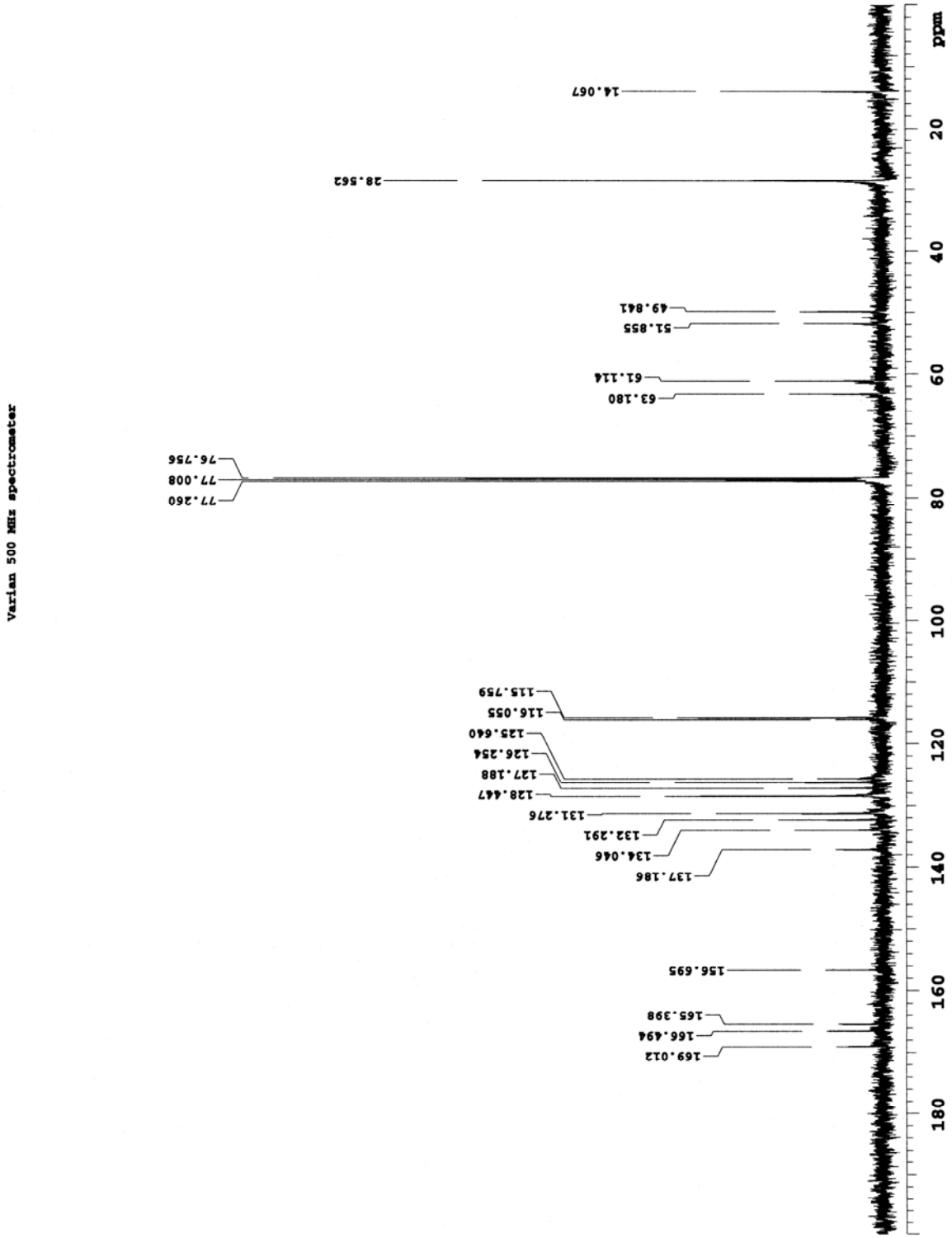
^{1}H-^{1}H GDQFCOSY NMR (Compound 215)



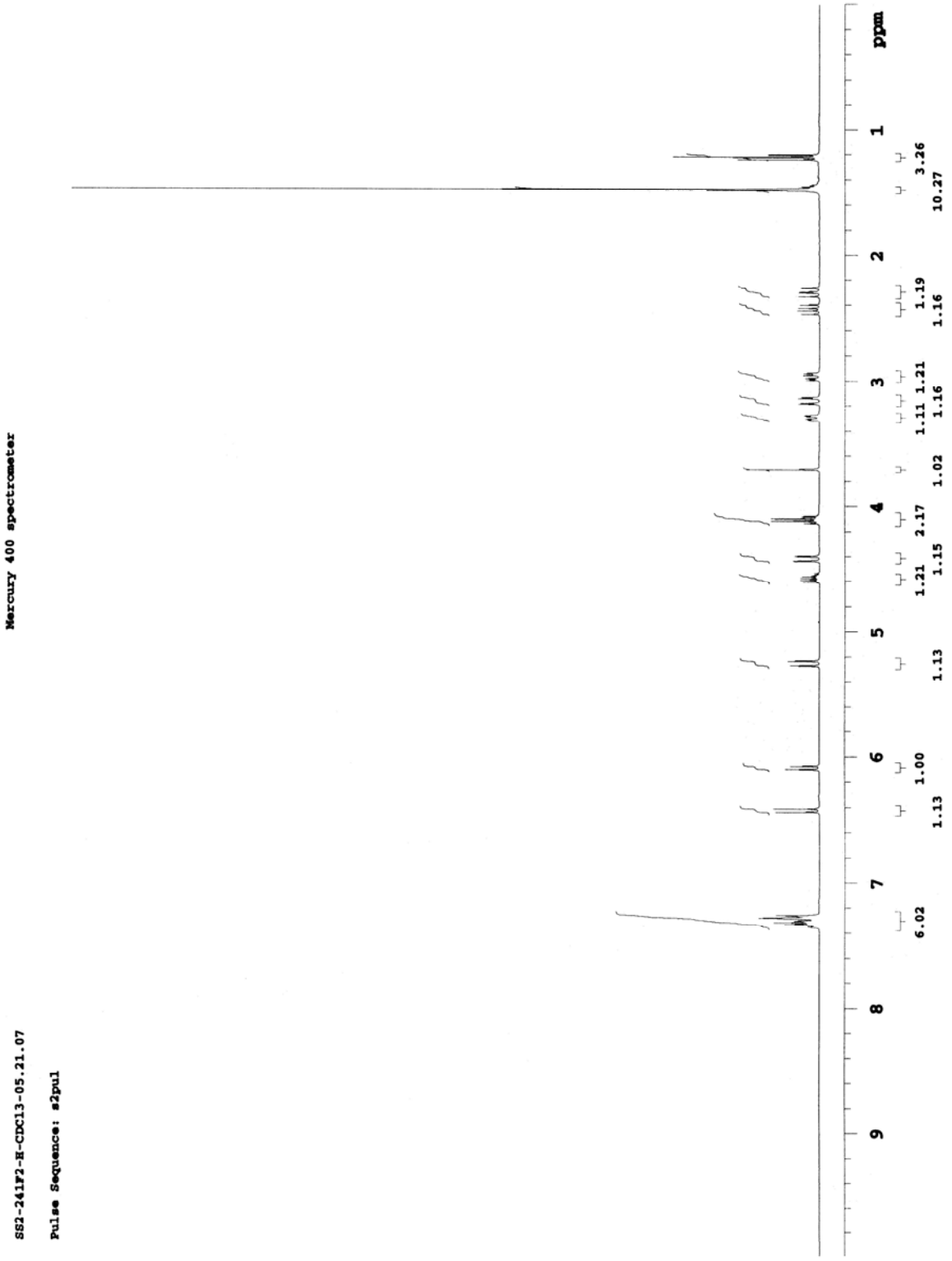
[1]H NMR (compound 219)



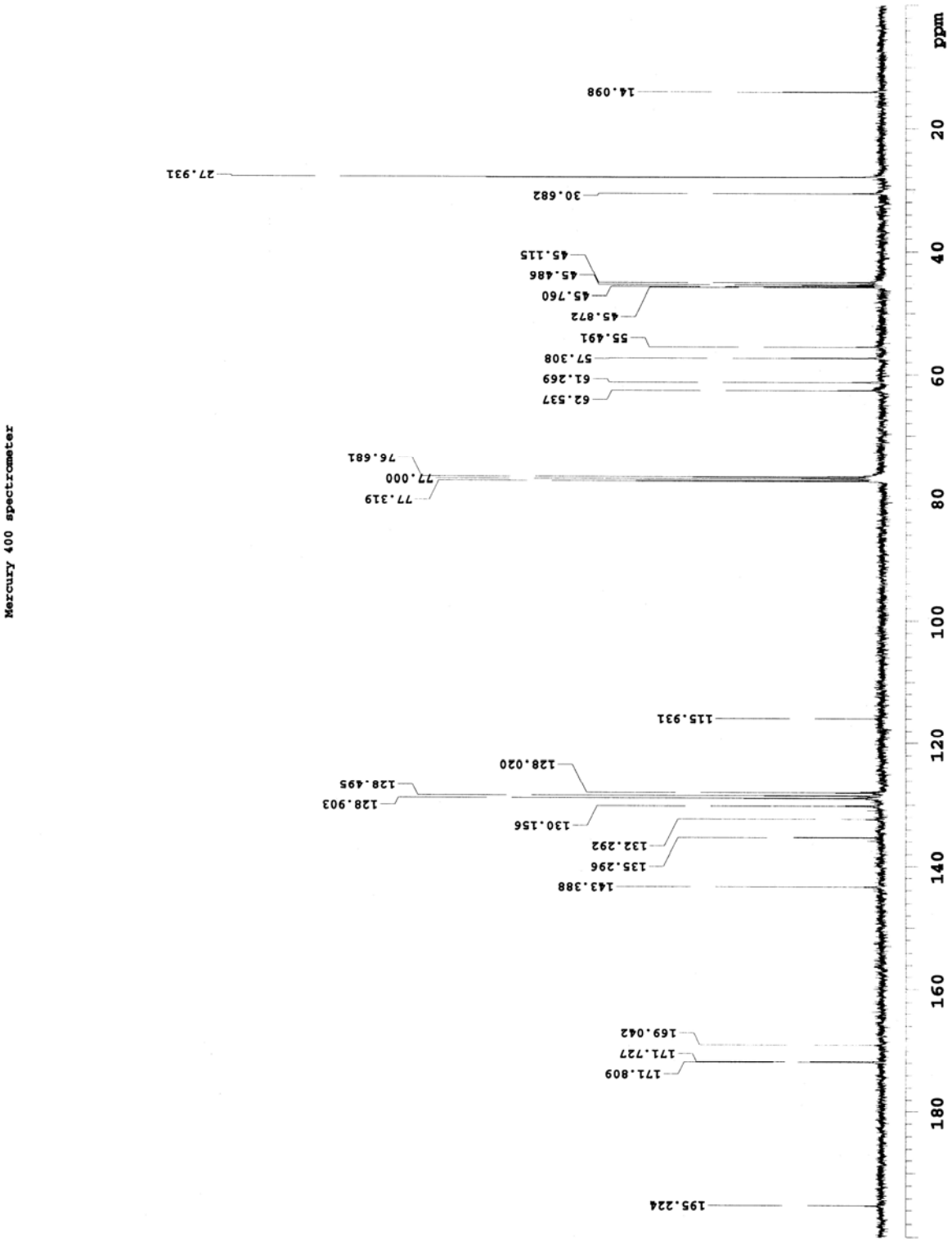
^{13}H NMR (compound 219)



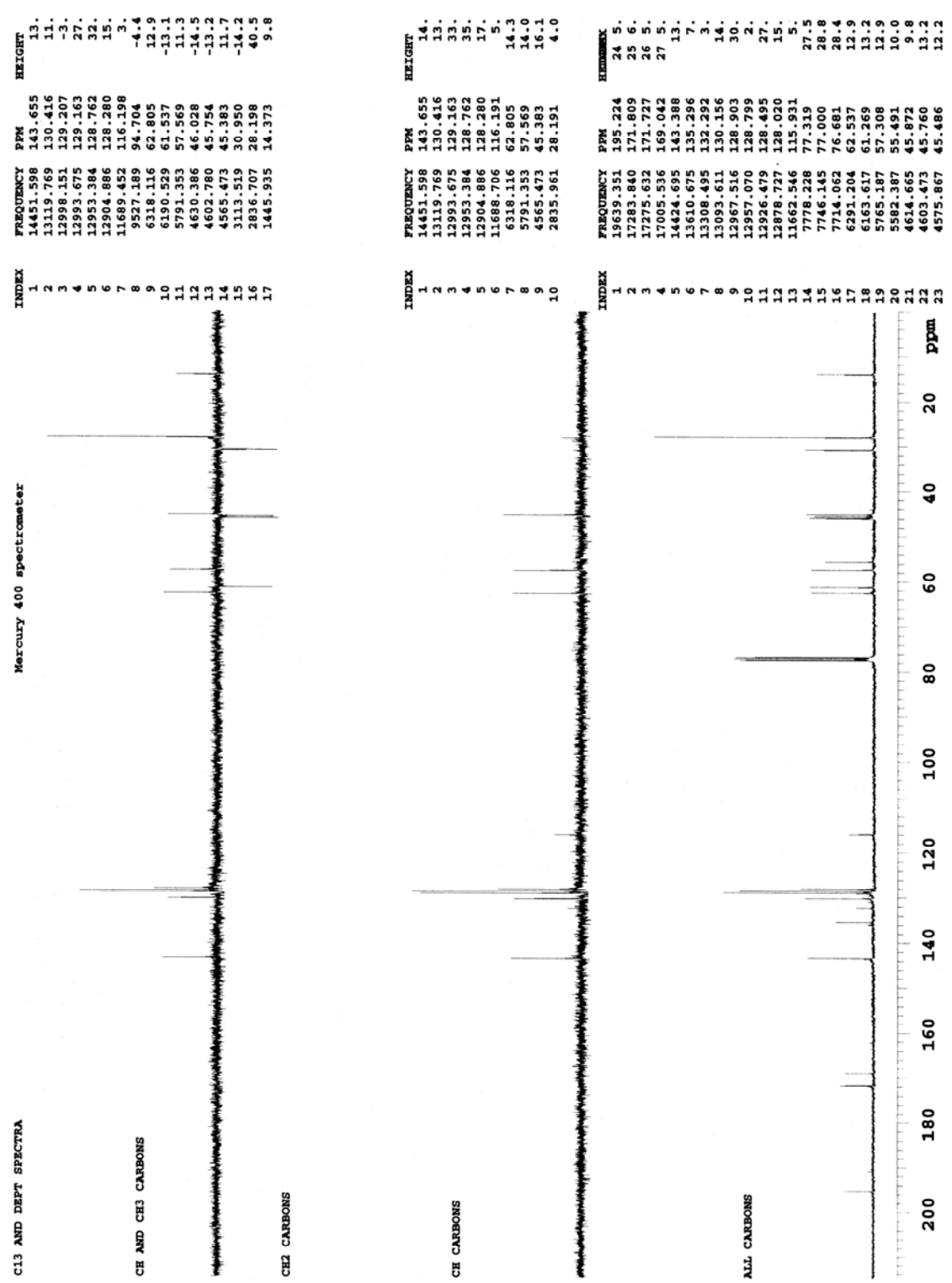
^{1}H NMR (Compound 220)



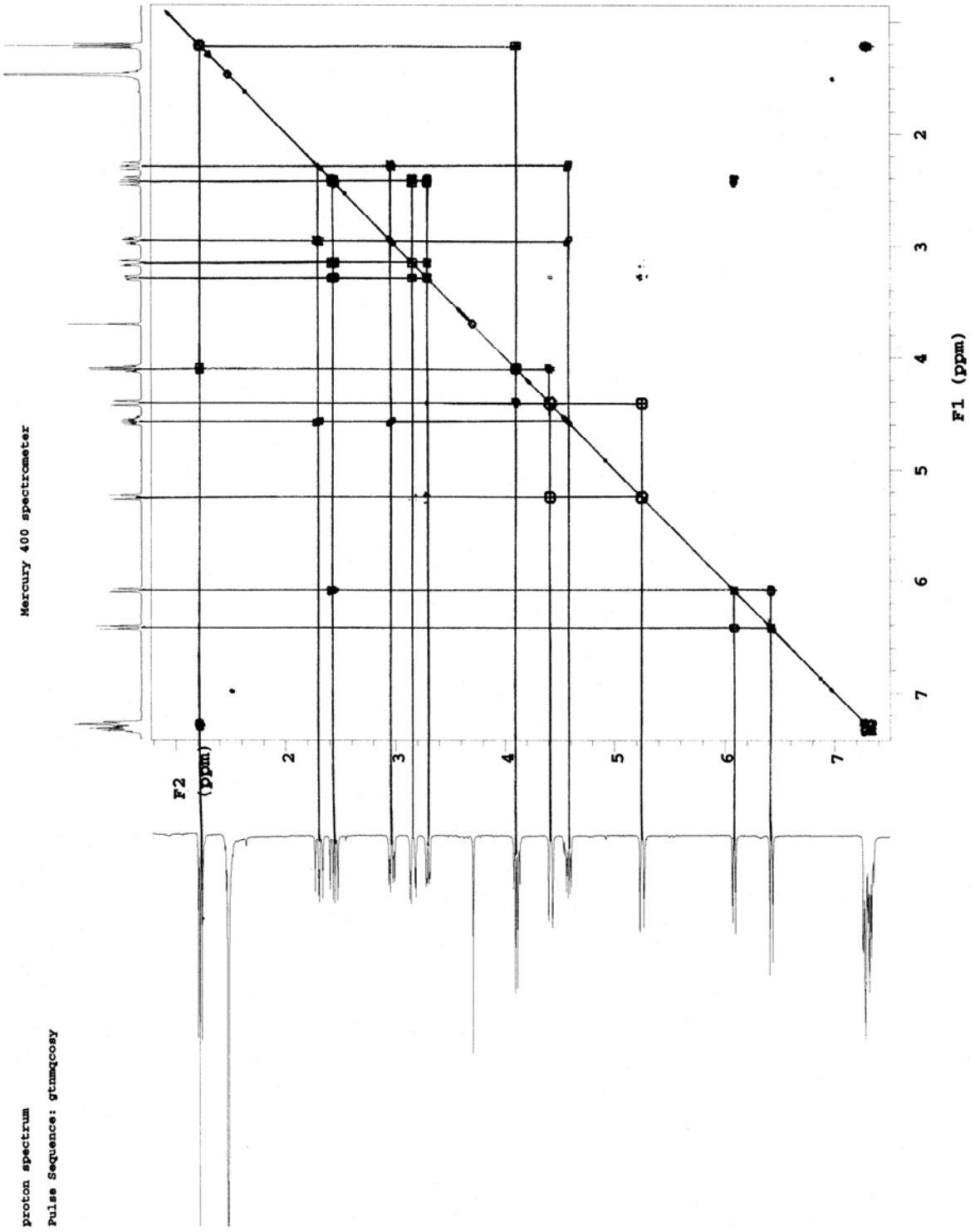
^{13}C NMR (Compound 220)



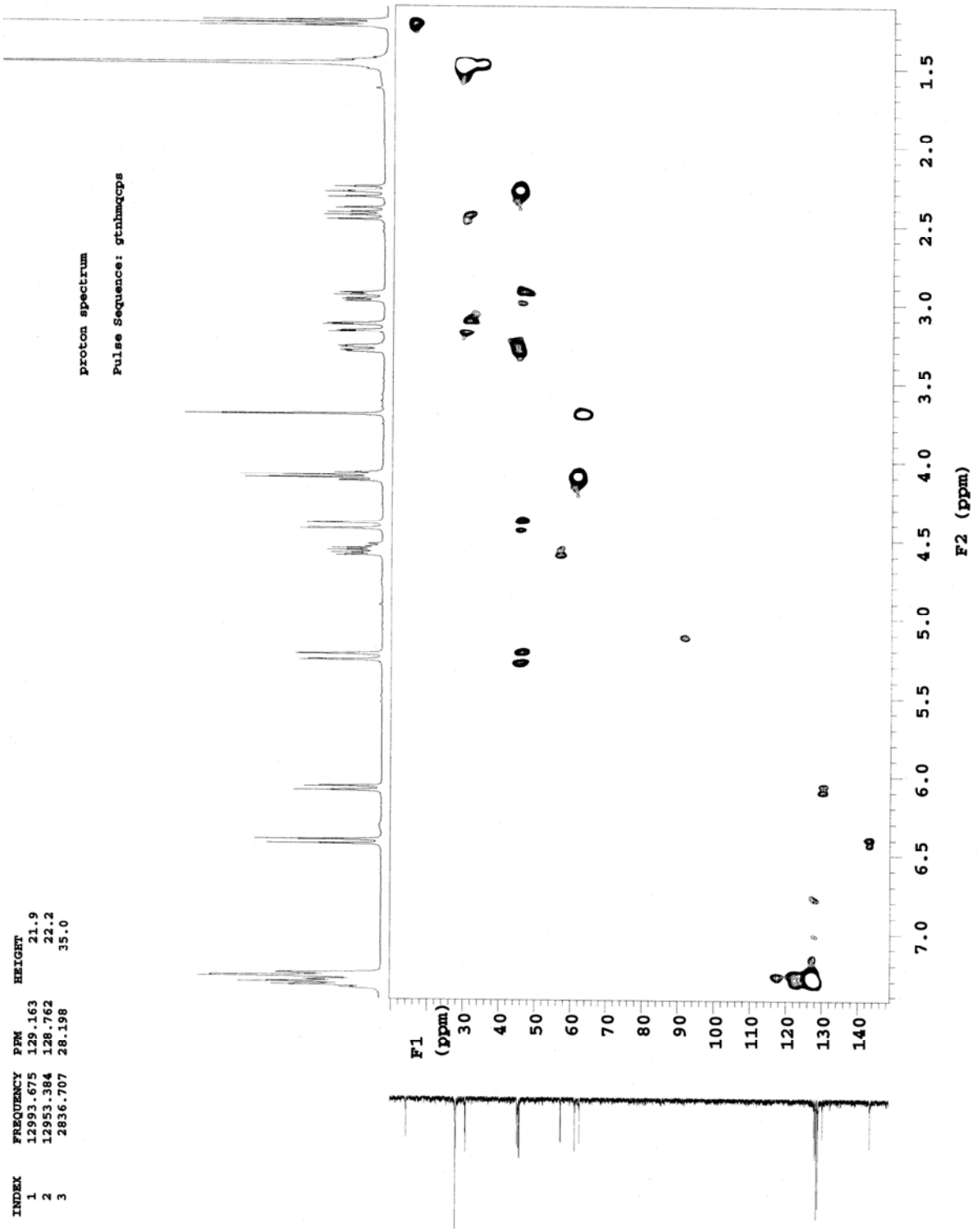
DEPT NMR (Compound 220)



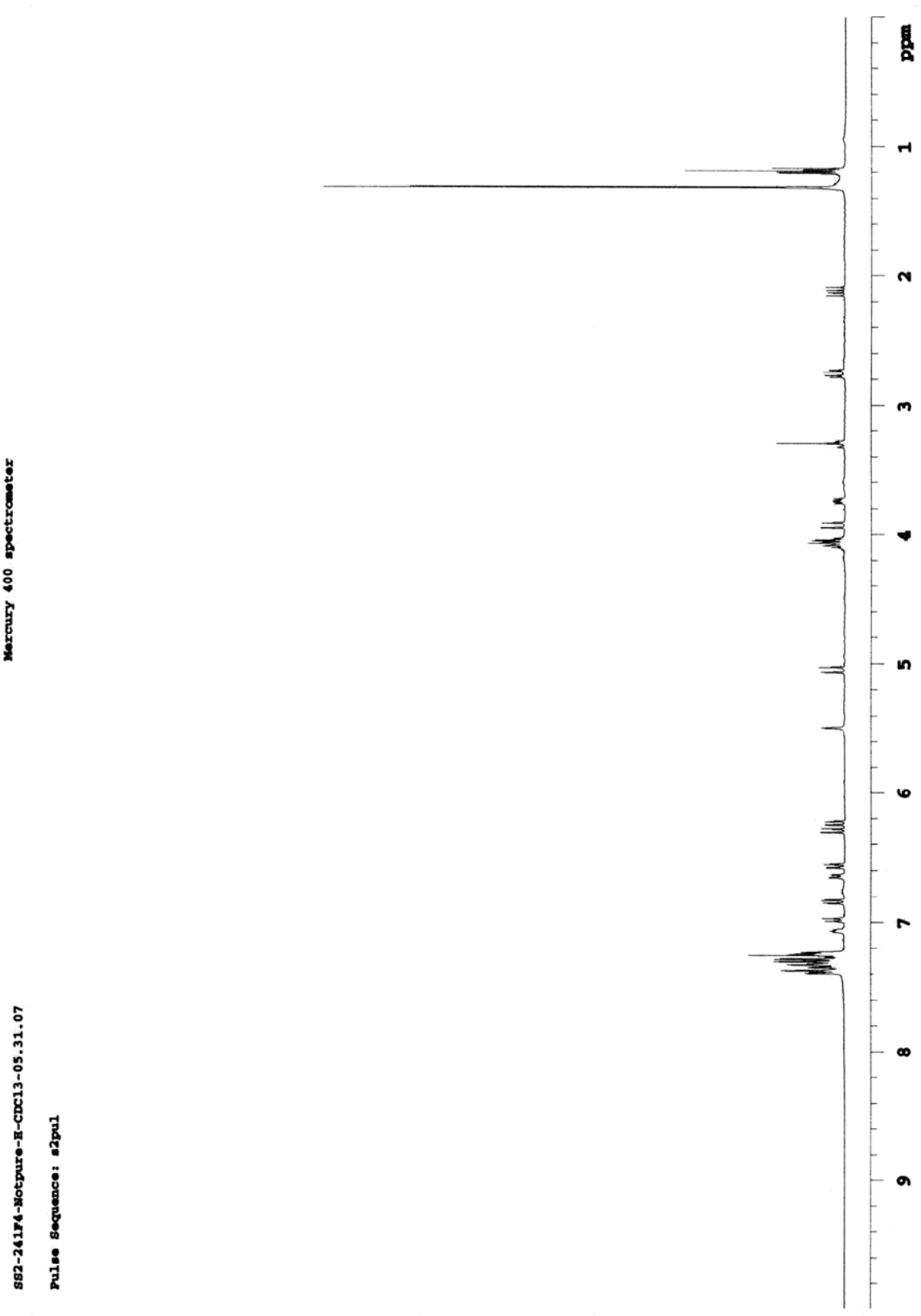
^{1}H-^{1}H GDQFCOSY (Compound 220)



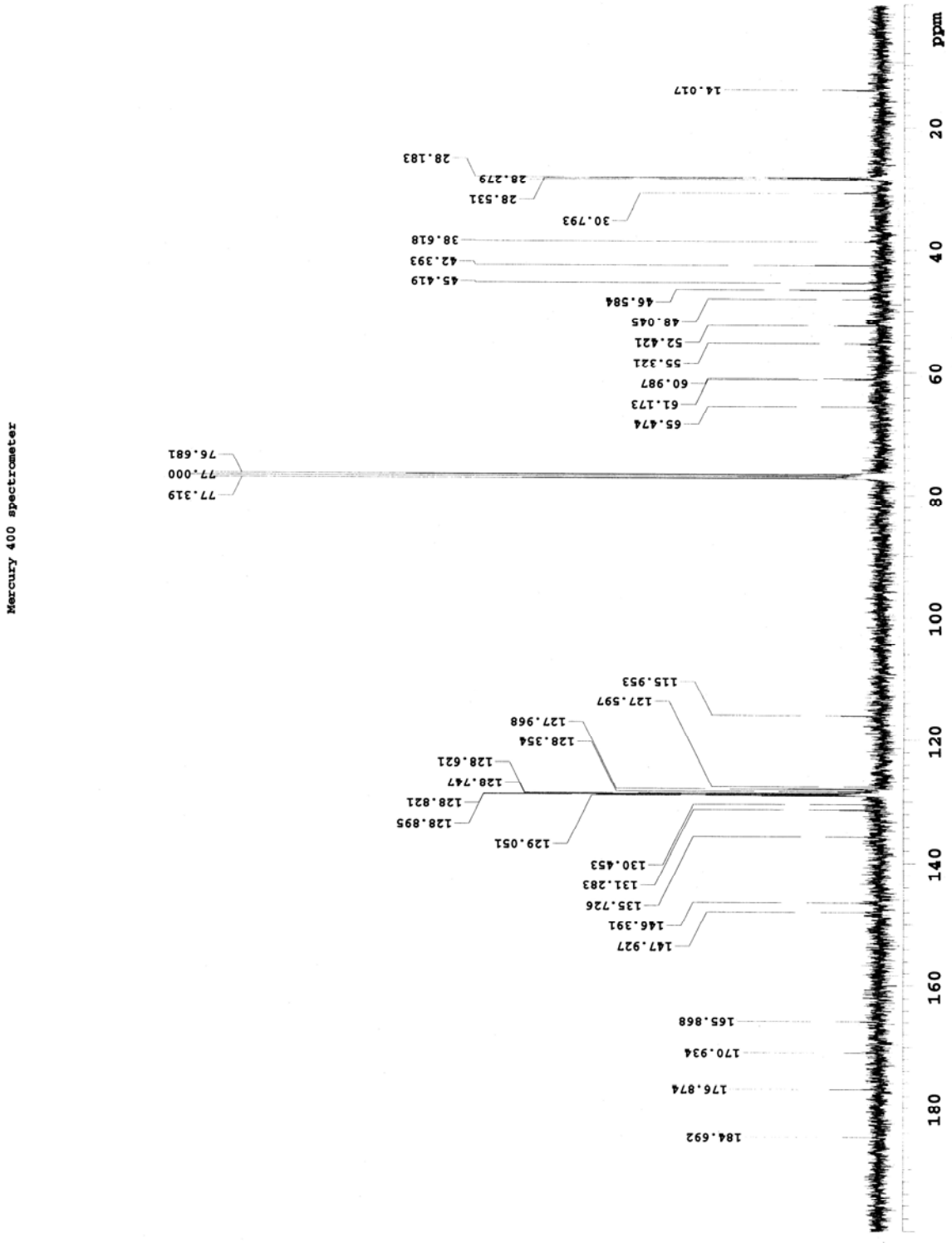
GHMQC NMR (Compound 220)



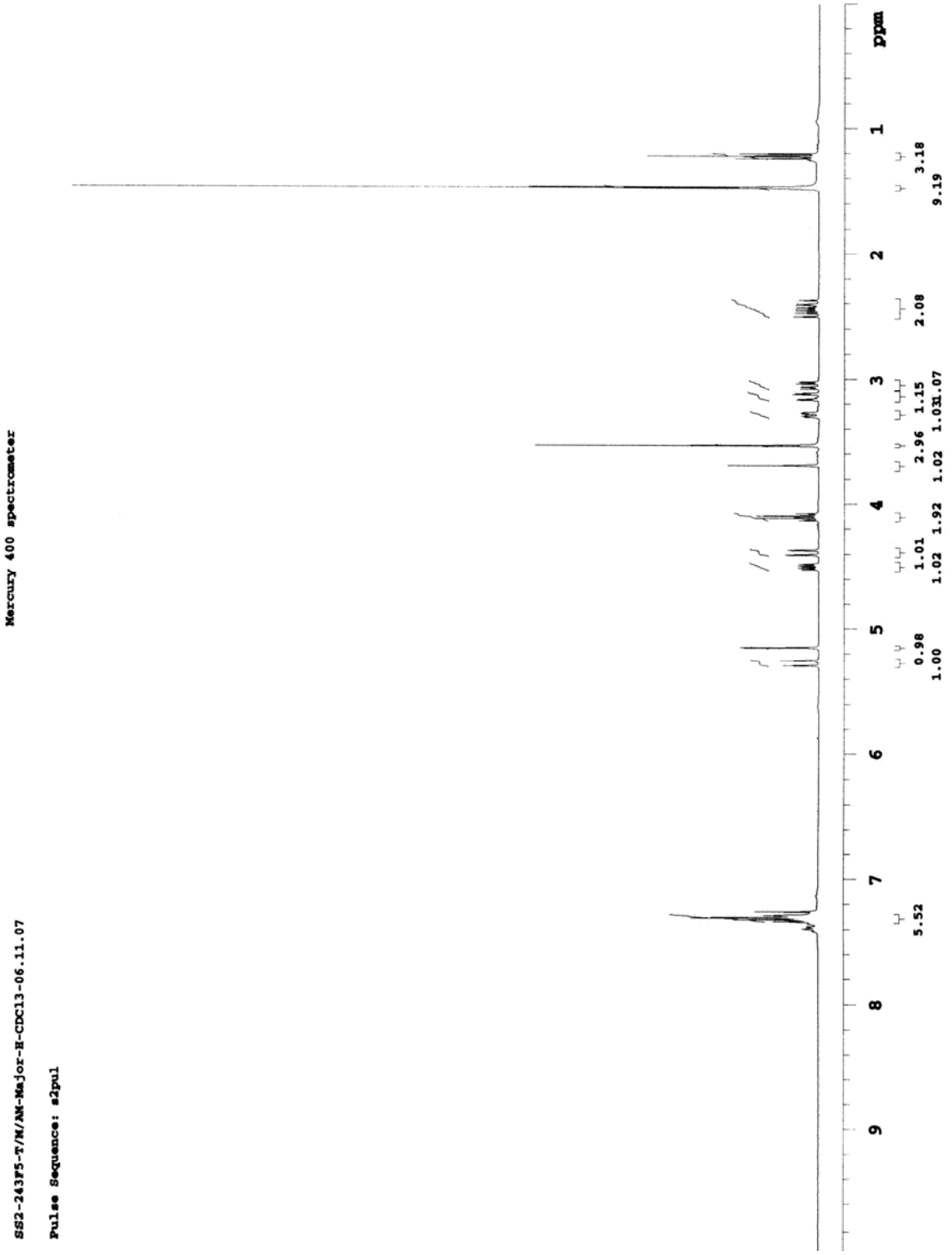
^{1}H NMR (Compound 221)



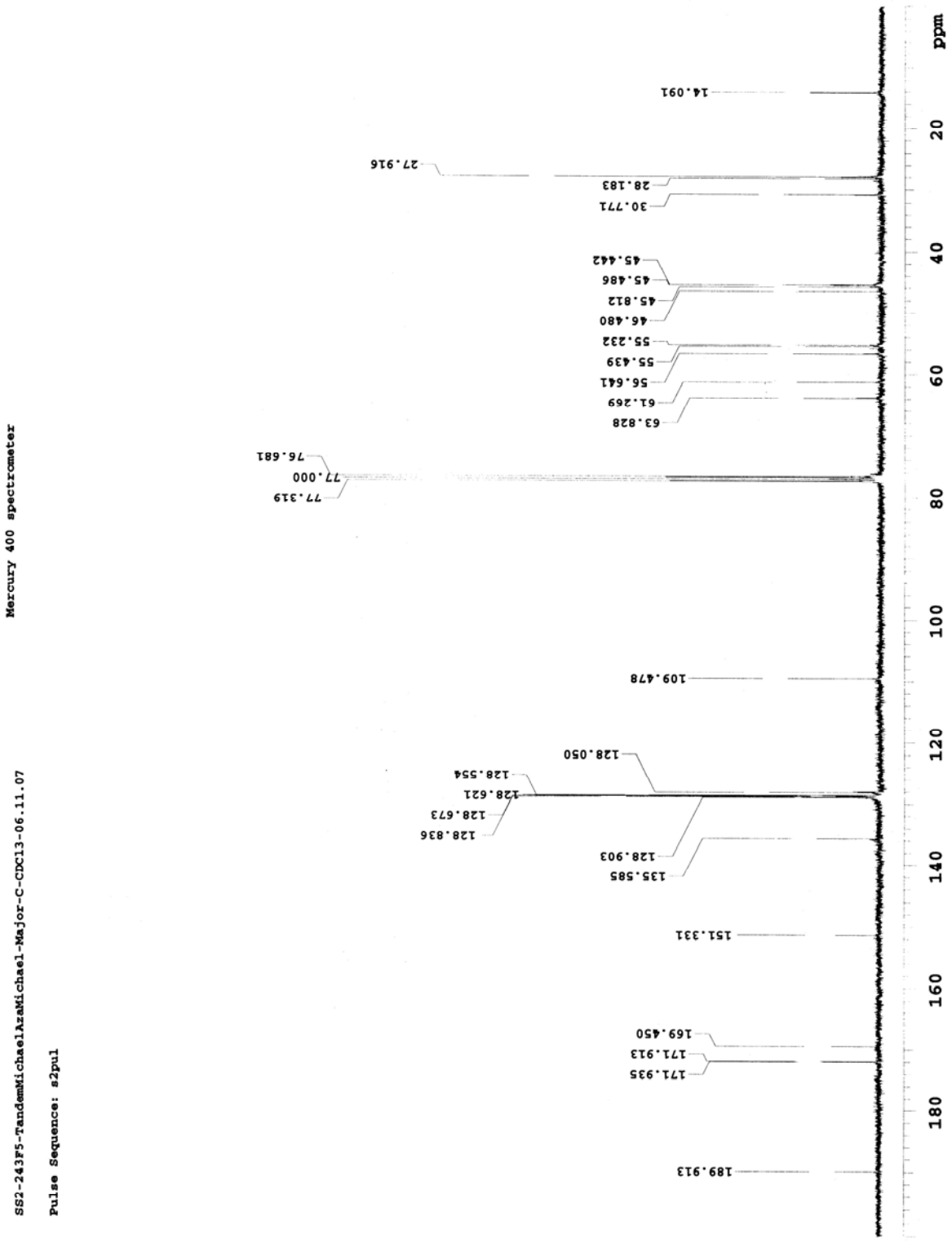
^{13}C NMR (Compound 221)



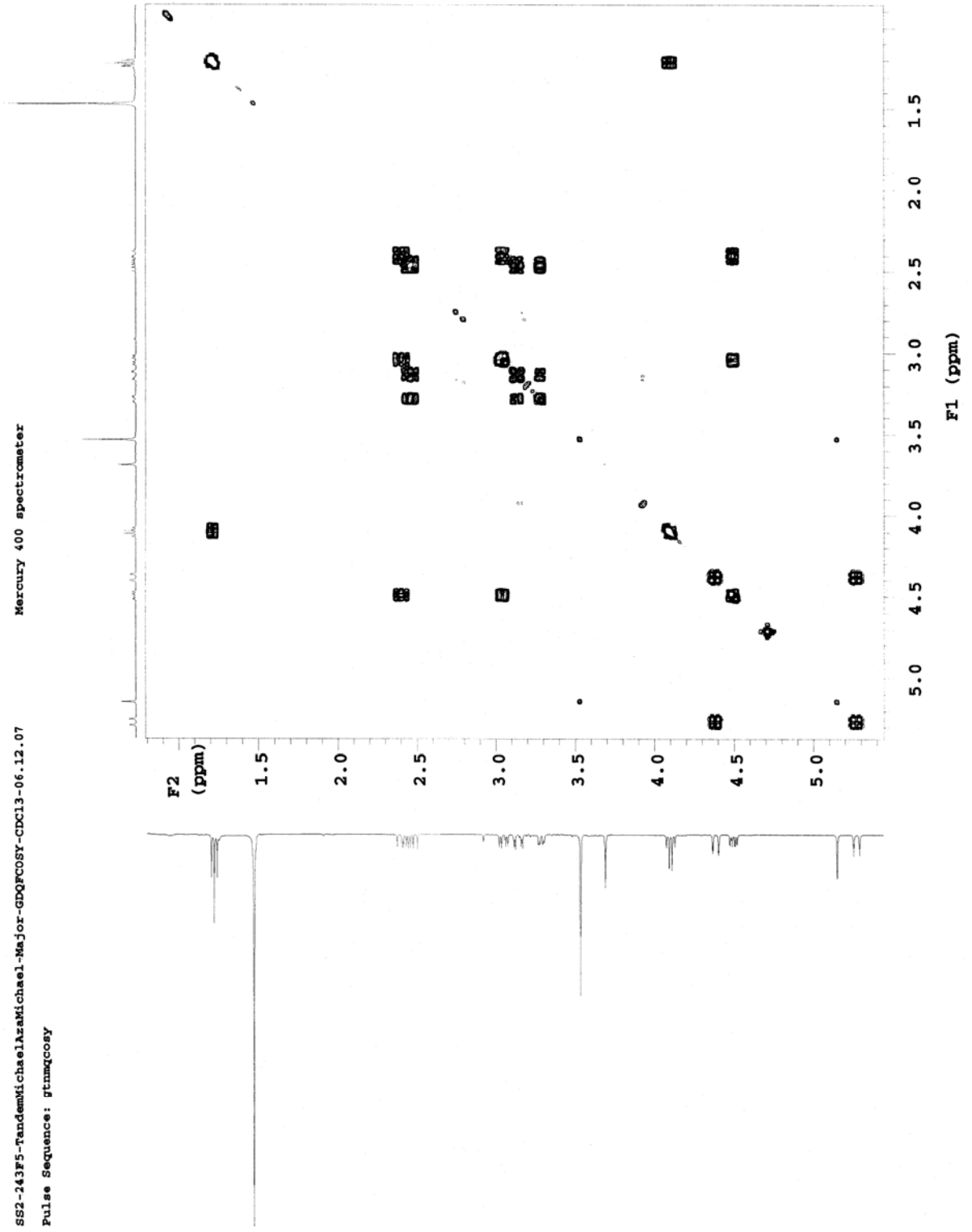
^{1}H NMR (Compound 222)



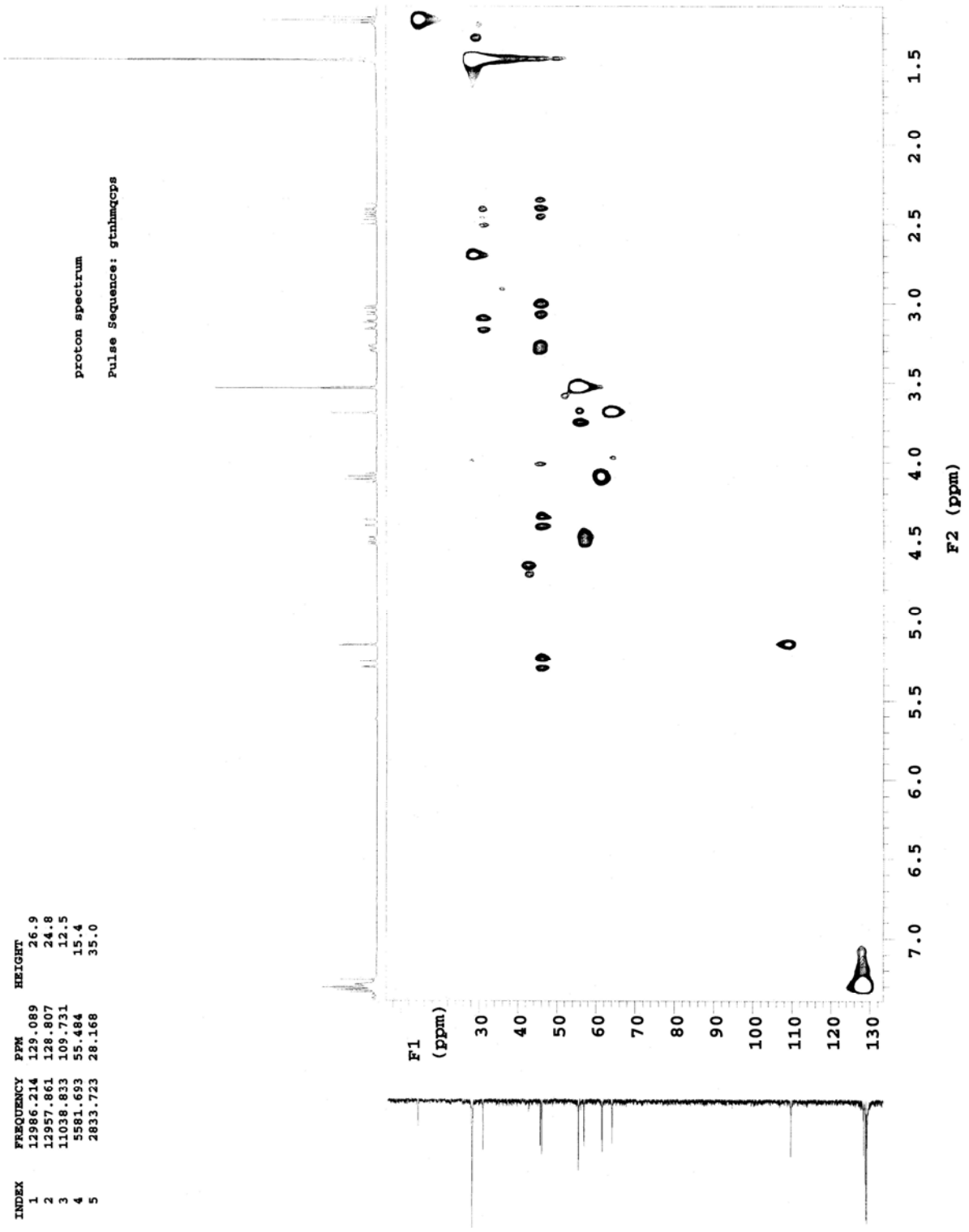
^{13}C NMR (Compound 222)



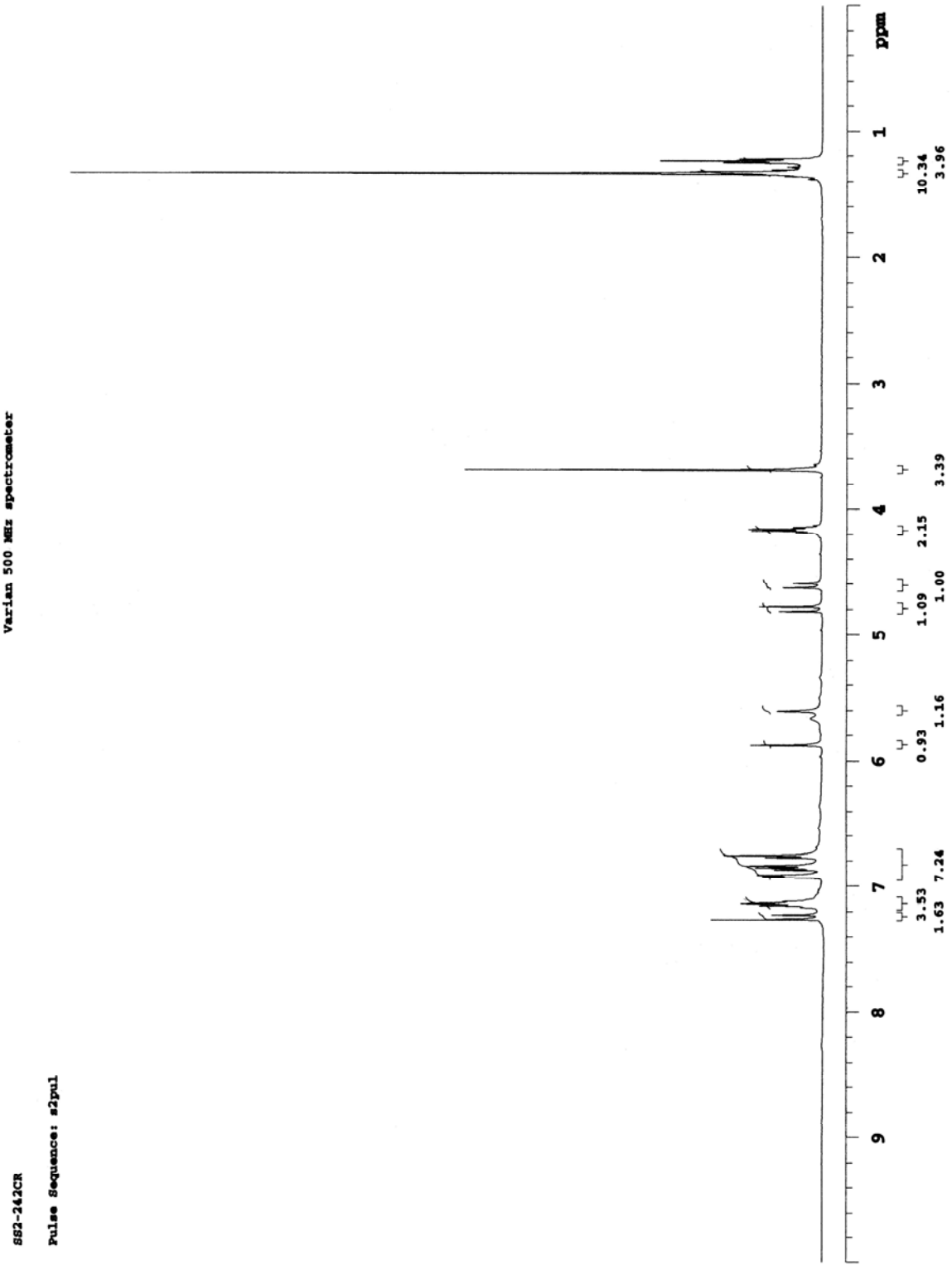
^{1}H-^{1}H GDQFCOSY (Compound 222)



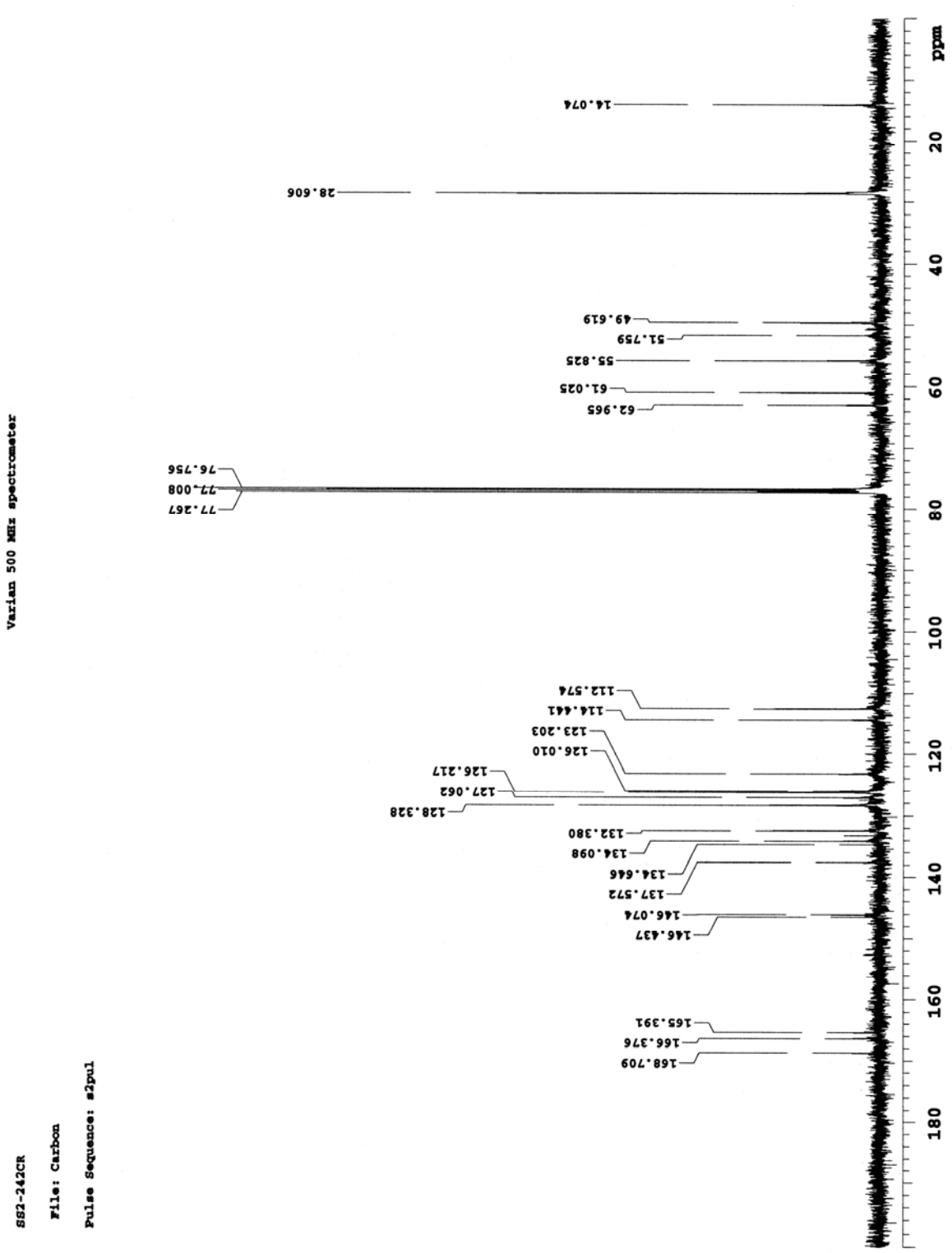
GHMQC NMR (Compound 222)



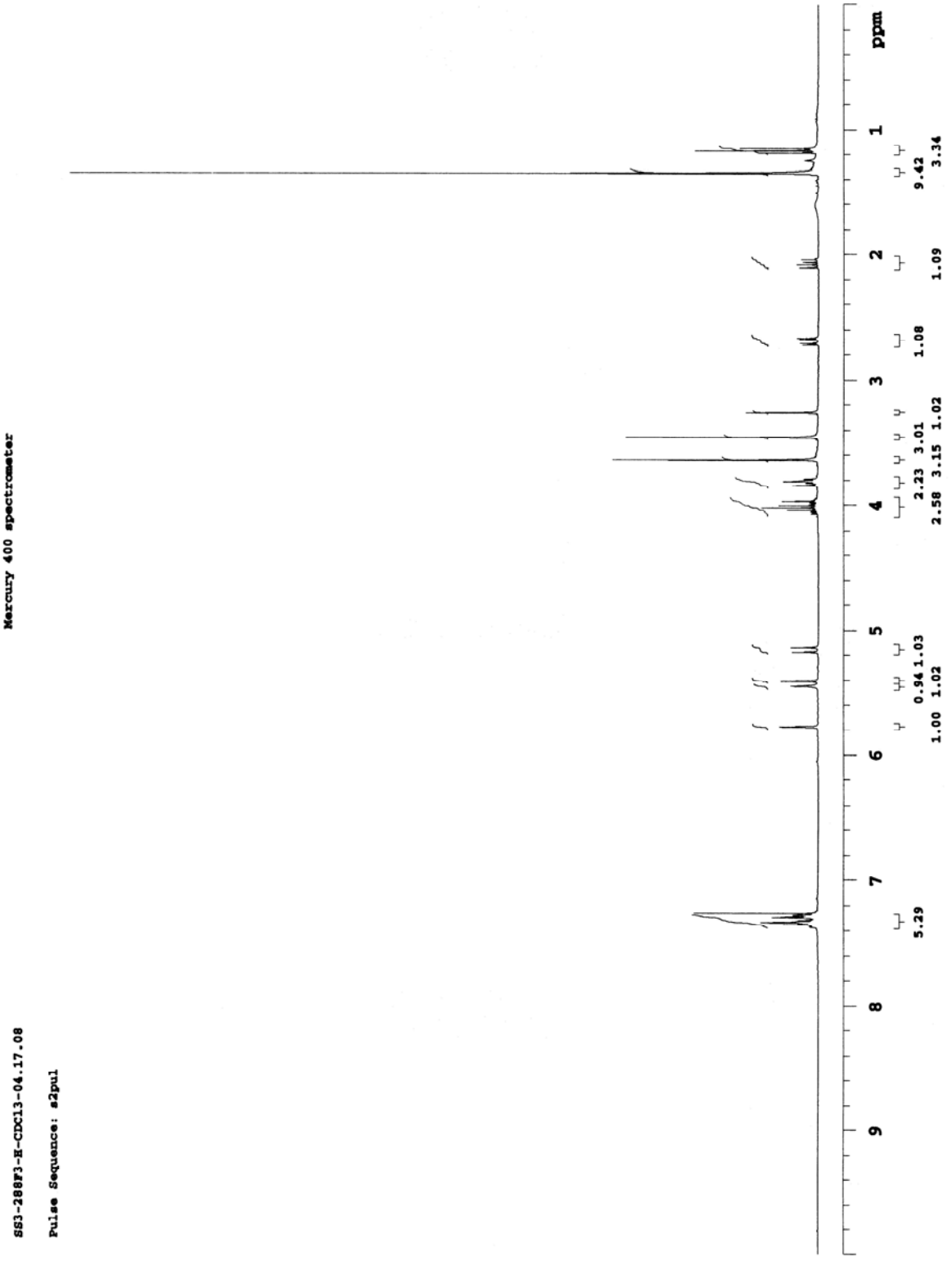
^{1}H NMR (Compound 224)



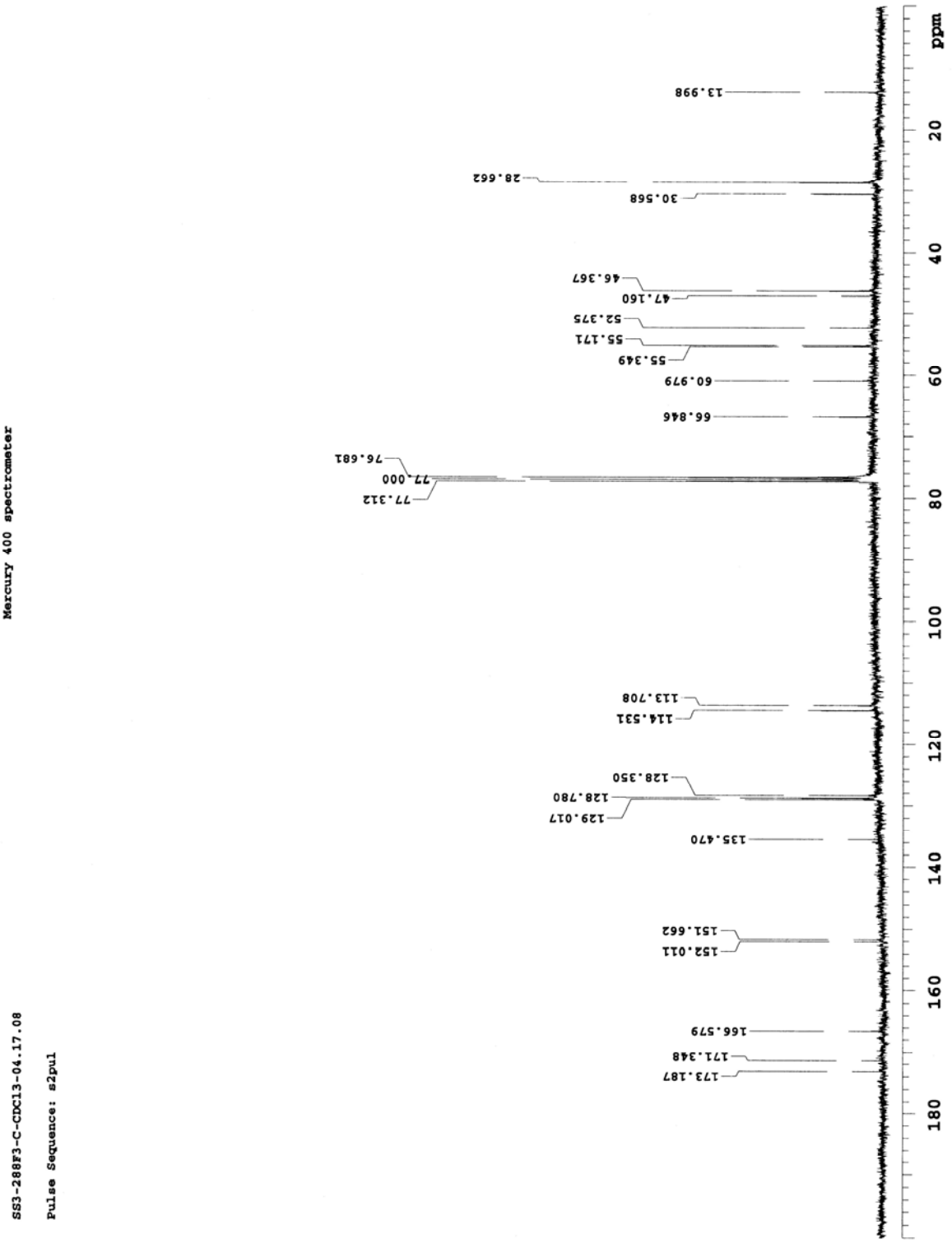
^{13}C NMR (Compound 224)



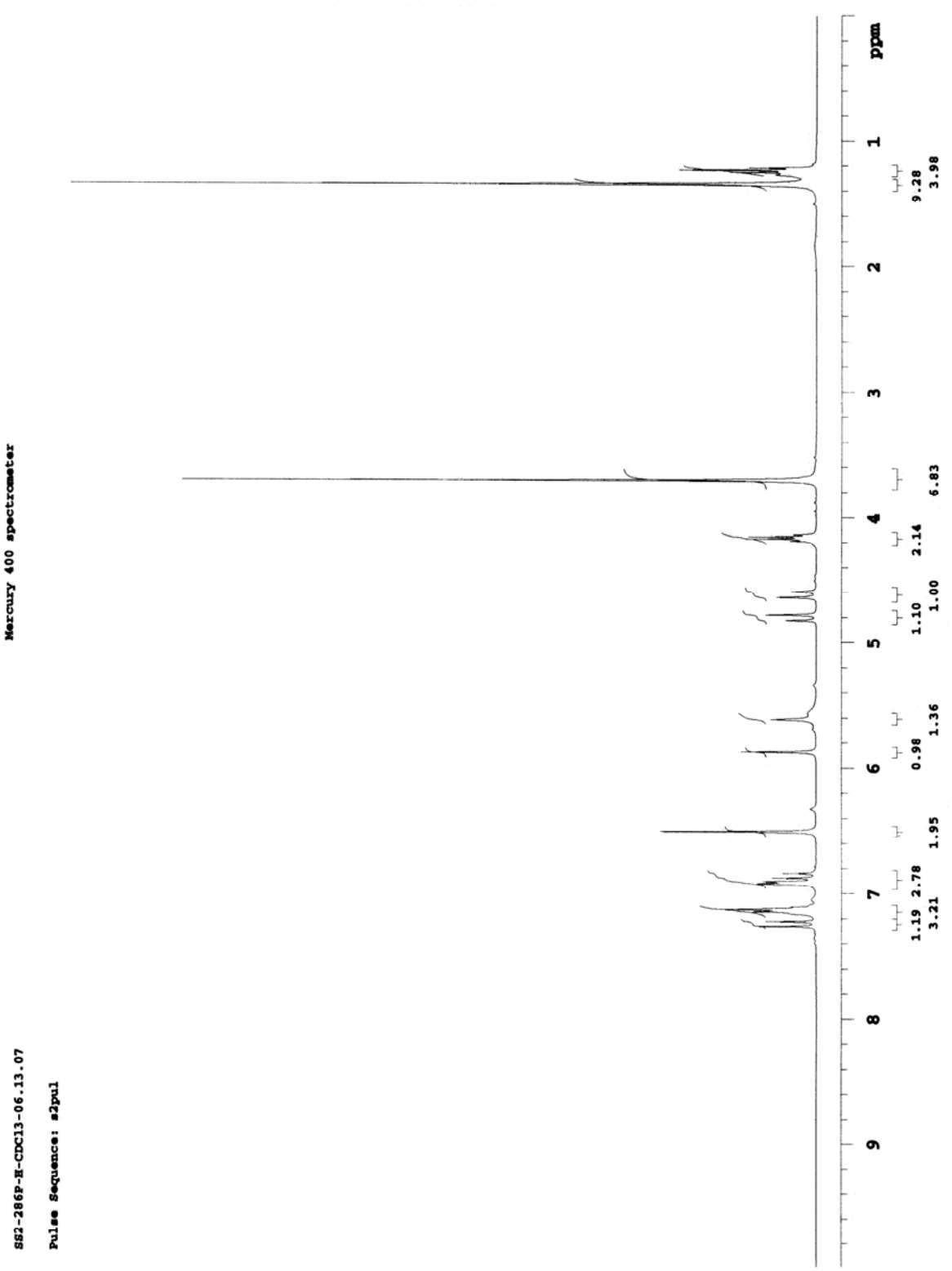
[1]H NMR (Compound 225)



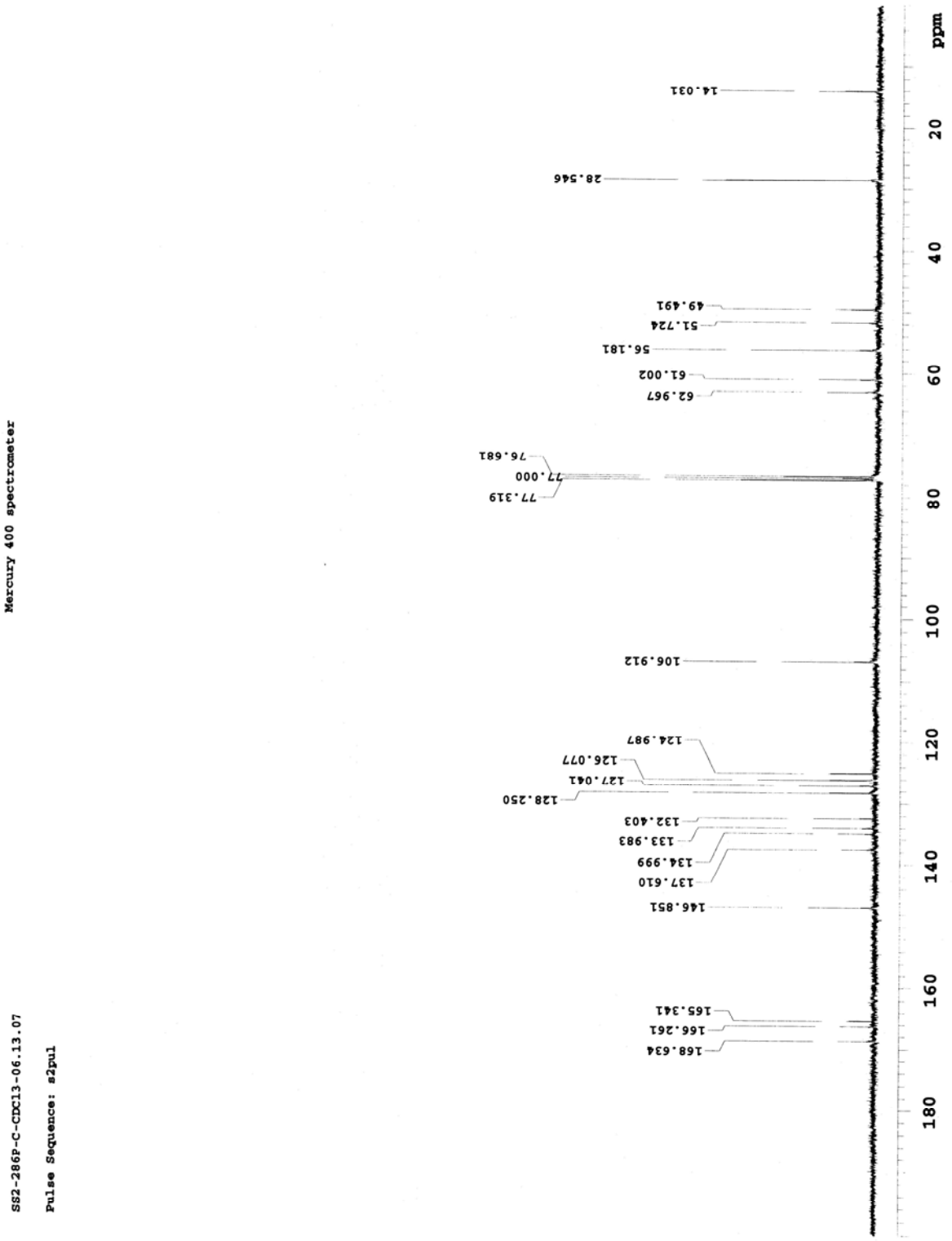
^{13}C NMR (Compound 225)



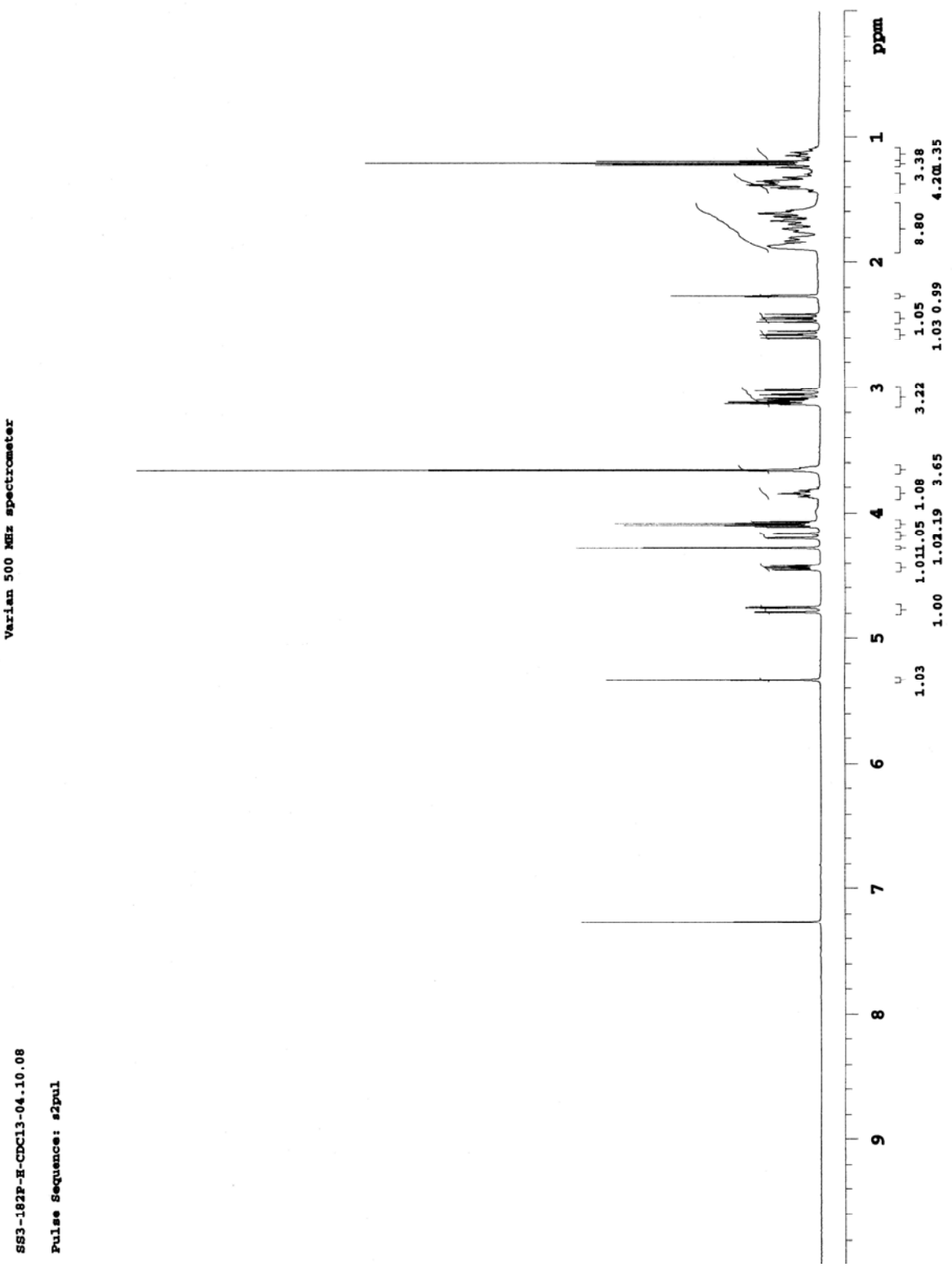
^{1}H NMR (Compound 227)



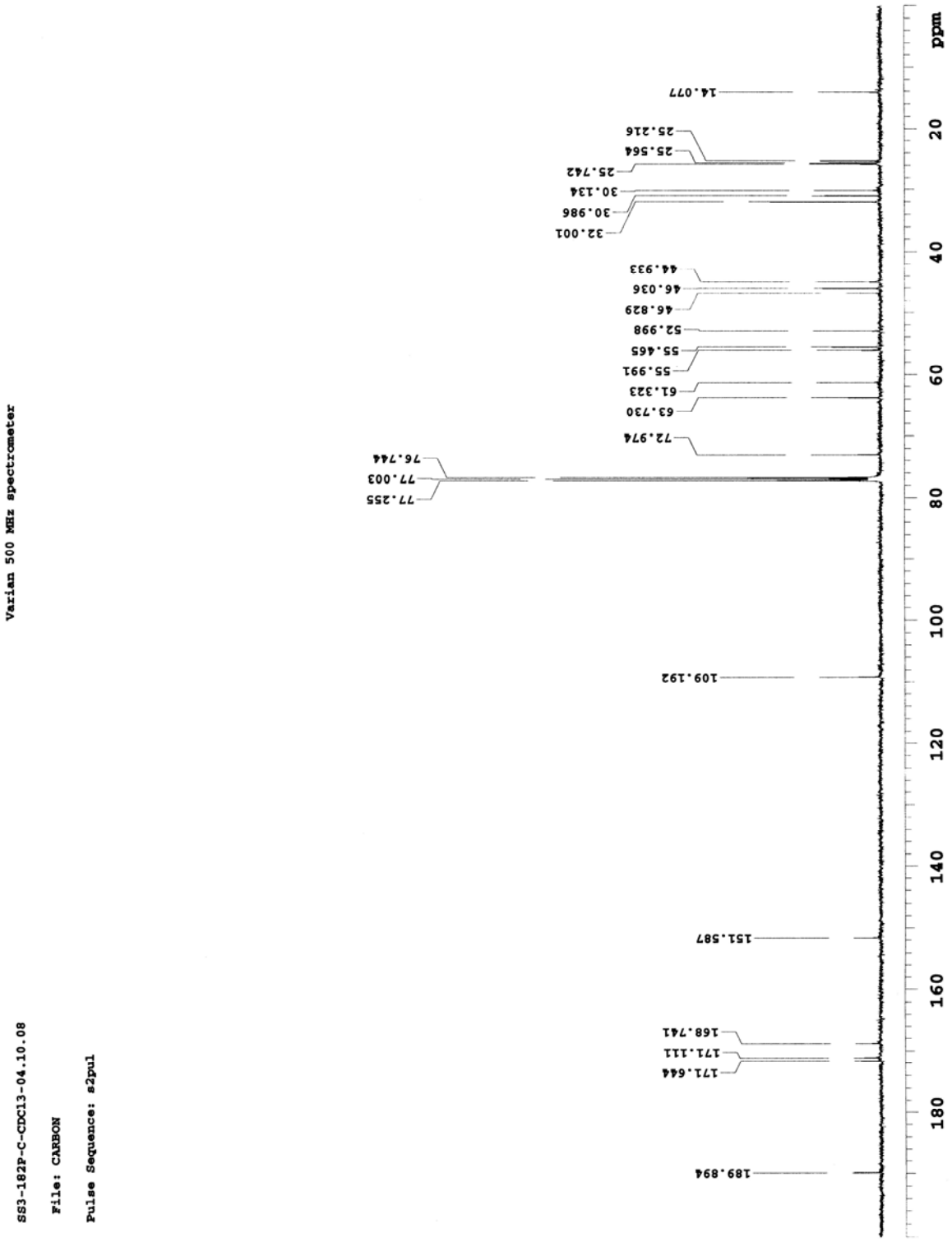
^{13}C NMR (Compound 227)



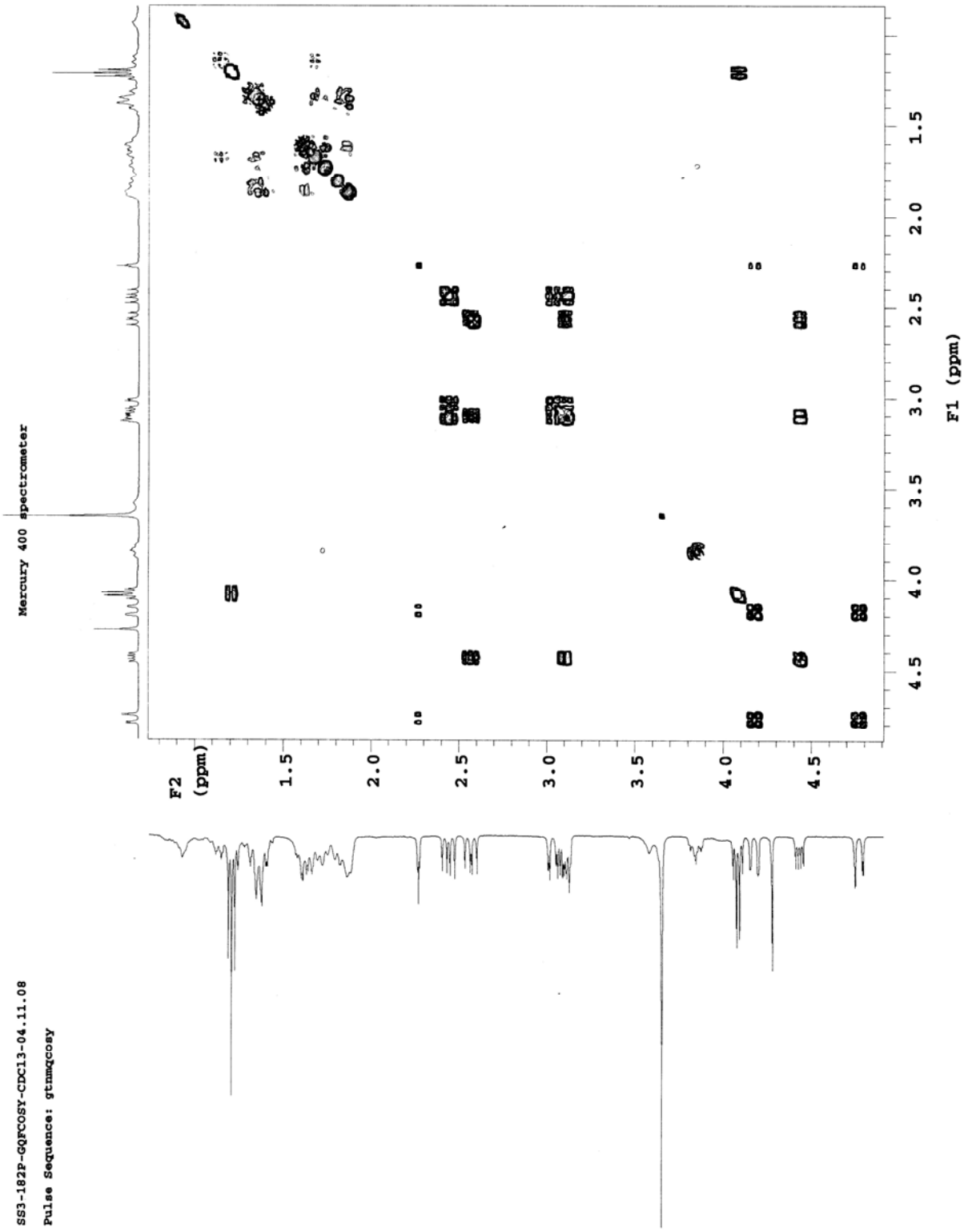
^{1}H NMR (Compound 228)



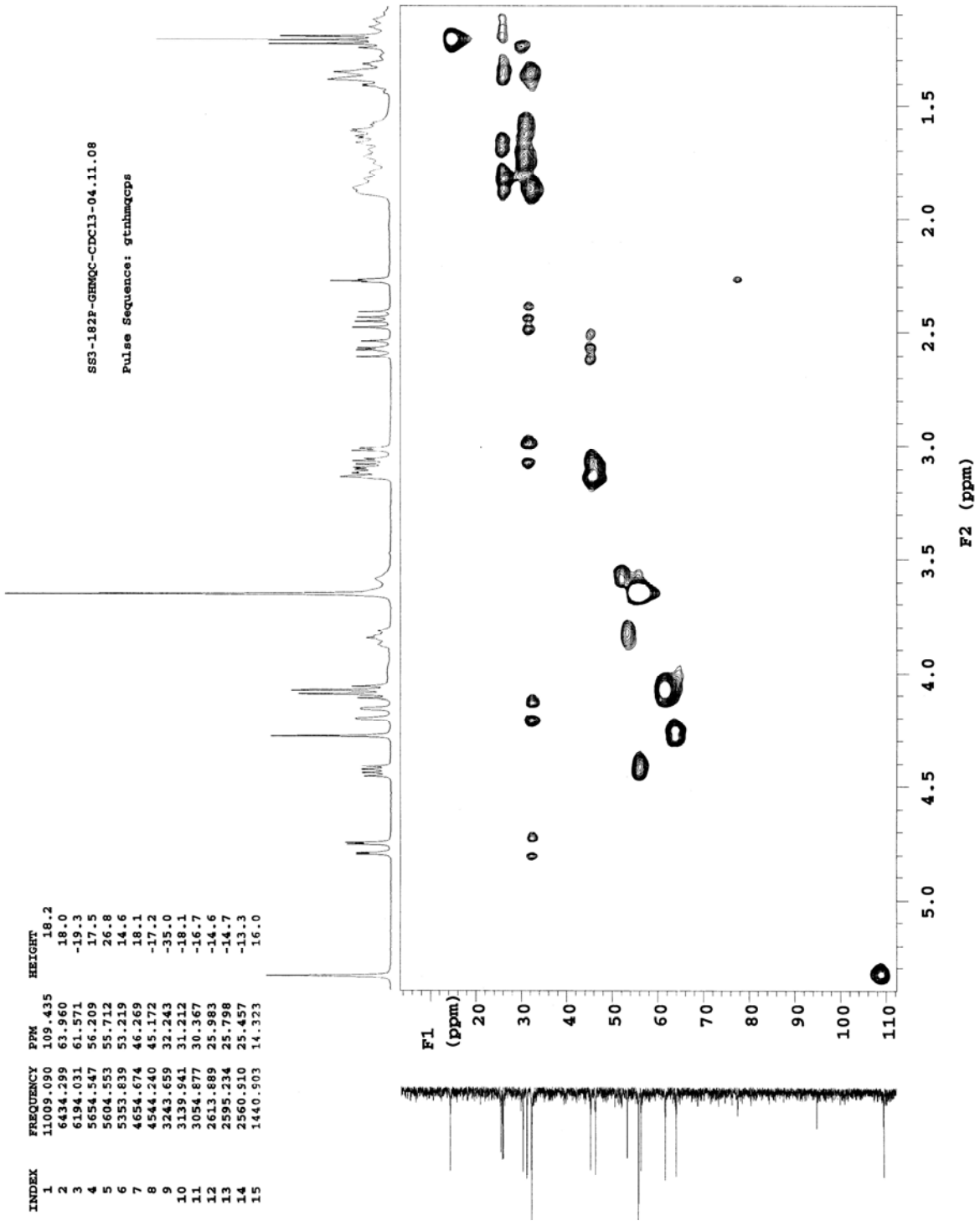
^{13}C NMR (Compound 228)



^{1}H-^{1}H GDQFCOSY NMR (Compound 228)

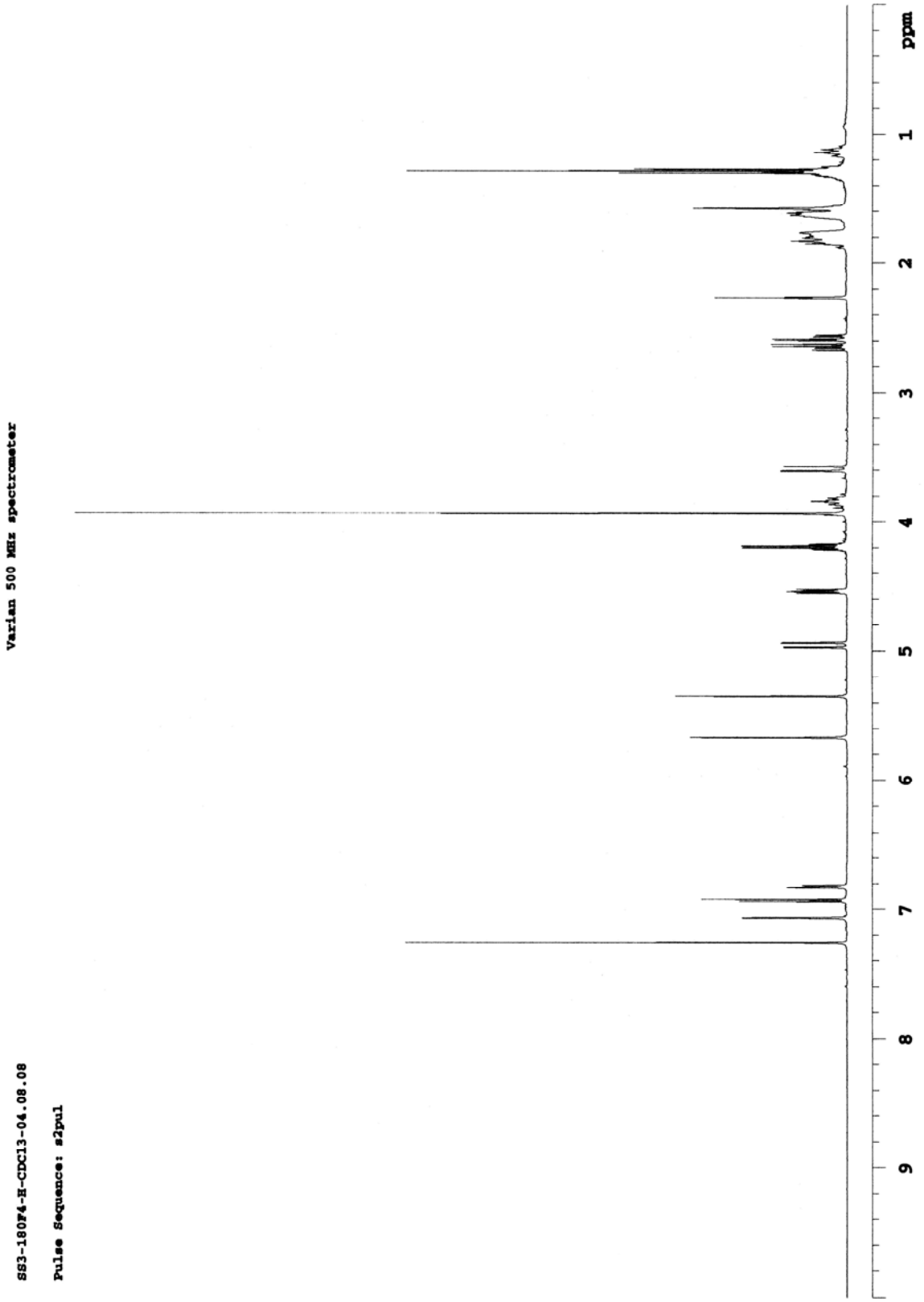


GHMQC NMR (Compound 228)

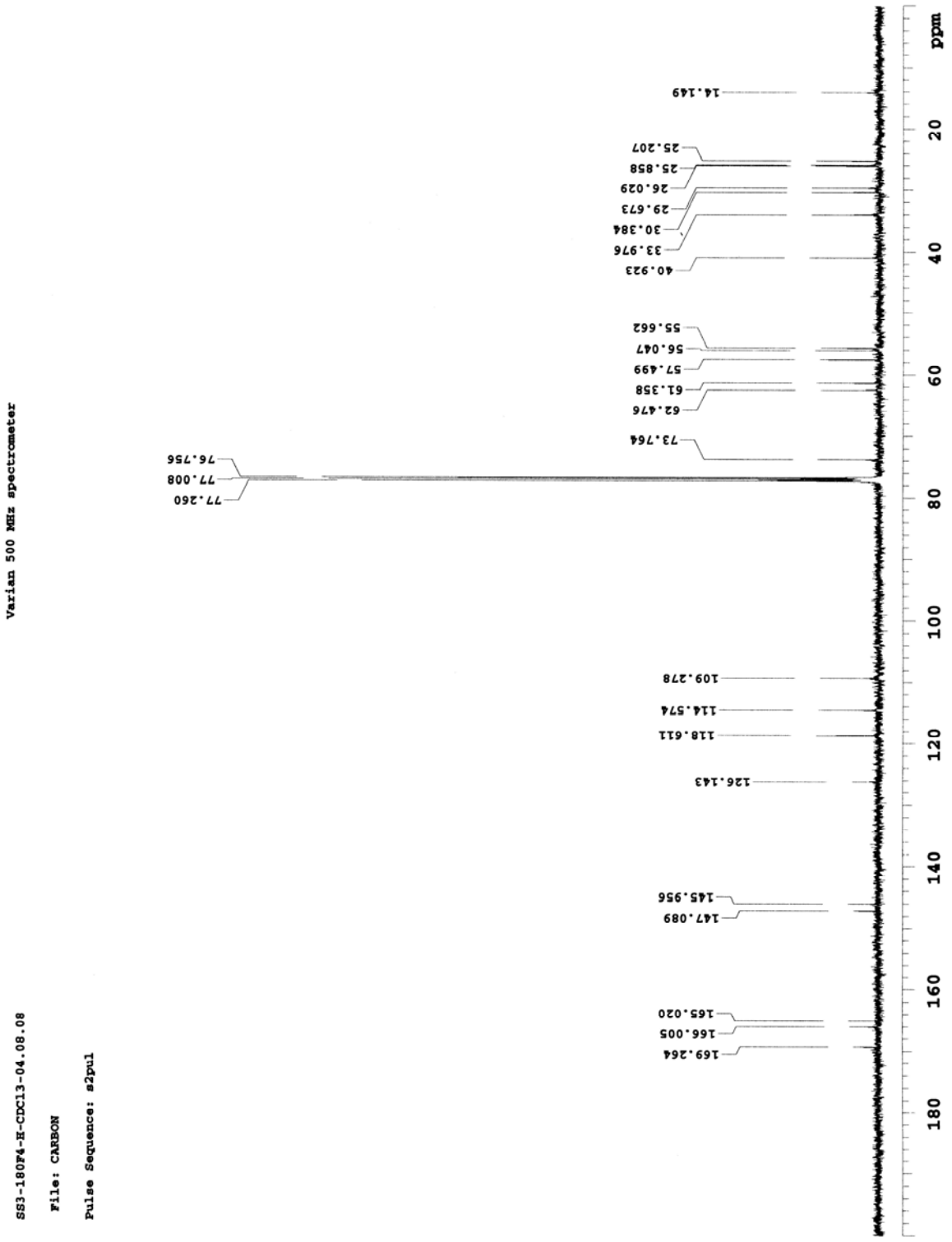


INDEX	FREQUENCY	PPM	HEIGHT
1	11009.090	109.435	18.2
2	6434.299	63.960	18.0
3	6194.031	61.571	-19.3
4	5654.547	56.209	17.5
5	5604.553	55.712	26.8
6	5353.839	53.219	14.6
7	4654.674	46.269	18.1
8	4544.240	45.172	-17.2
9	3243.659	32.243	-35.0
10	3139.941	31.212	-18.1
11	3054.877	30.367	-16.7
12	2613.889	25.983	-14.6
13	2595.234	25.798	-14.7
14	2560.910	25.457	-13.3
15	1440.903	14.323	16.0

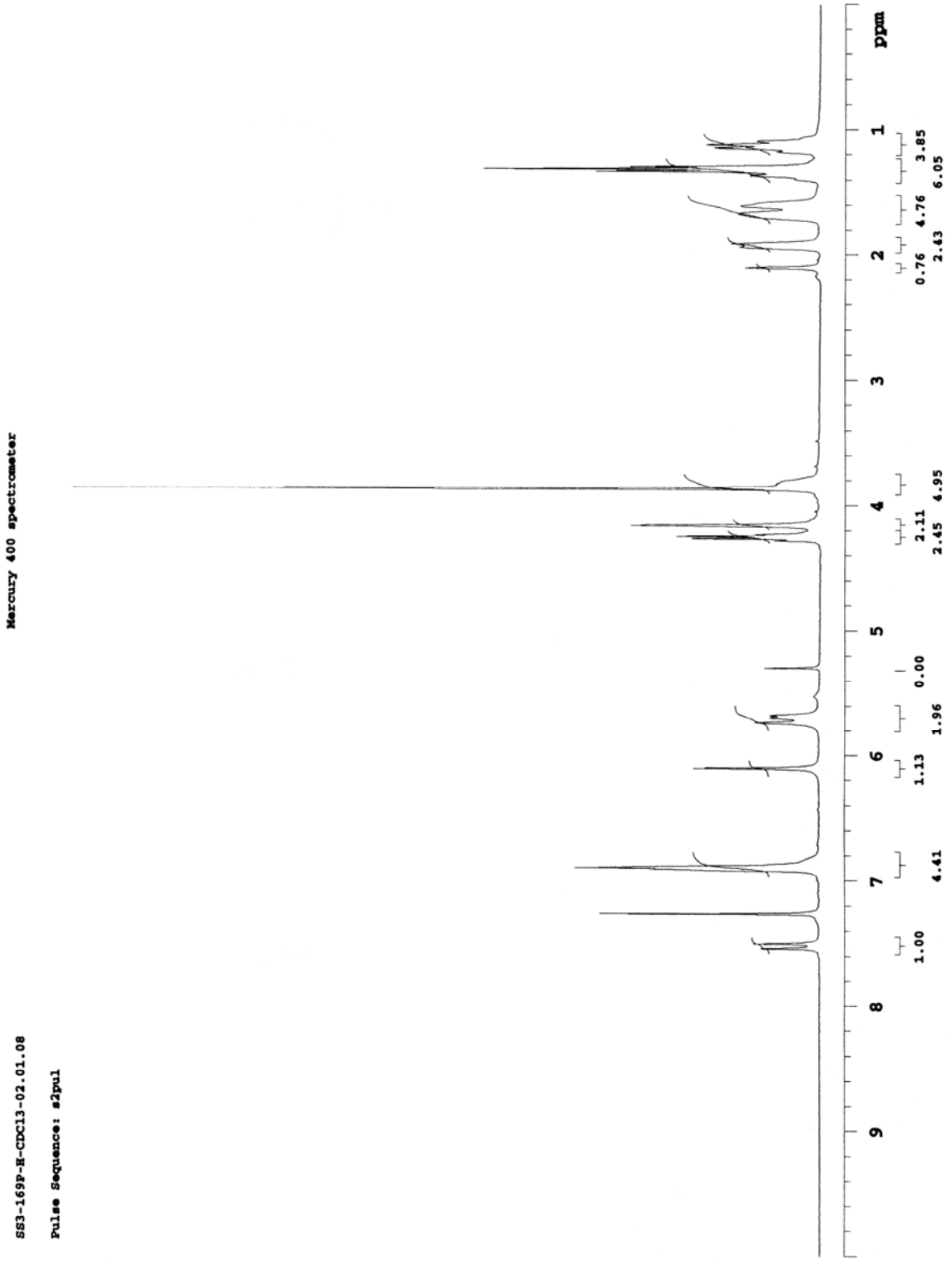
[1]H NMR (Compound 229)



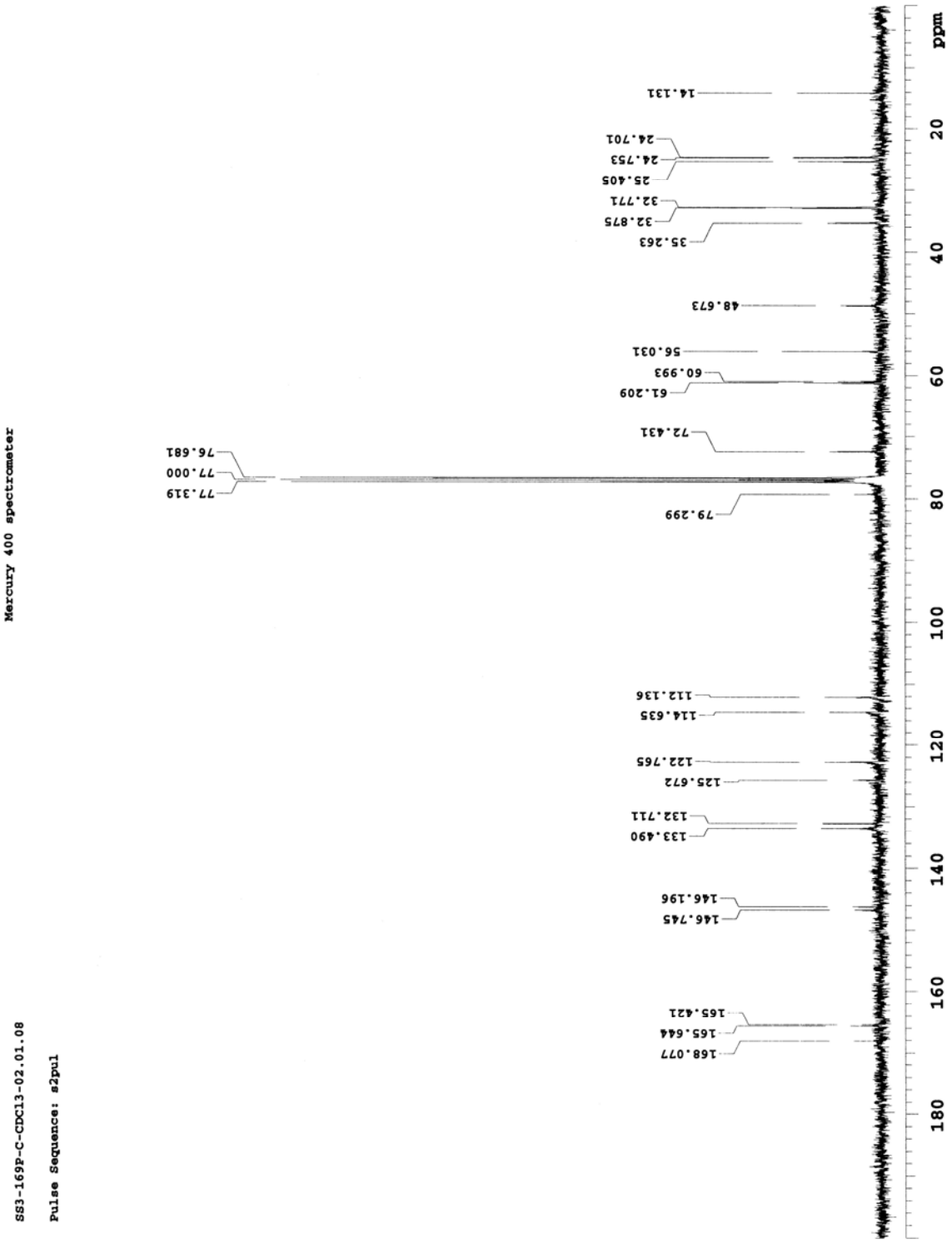
^{13}C NMR (Compound 229)



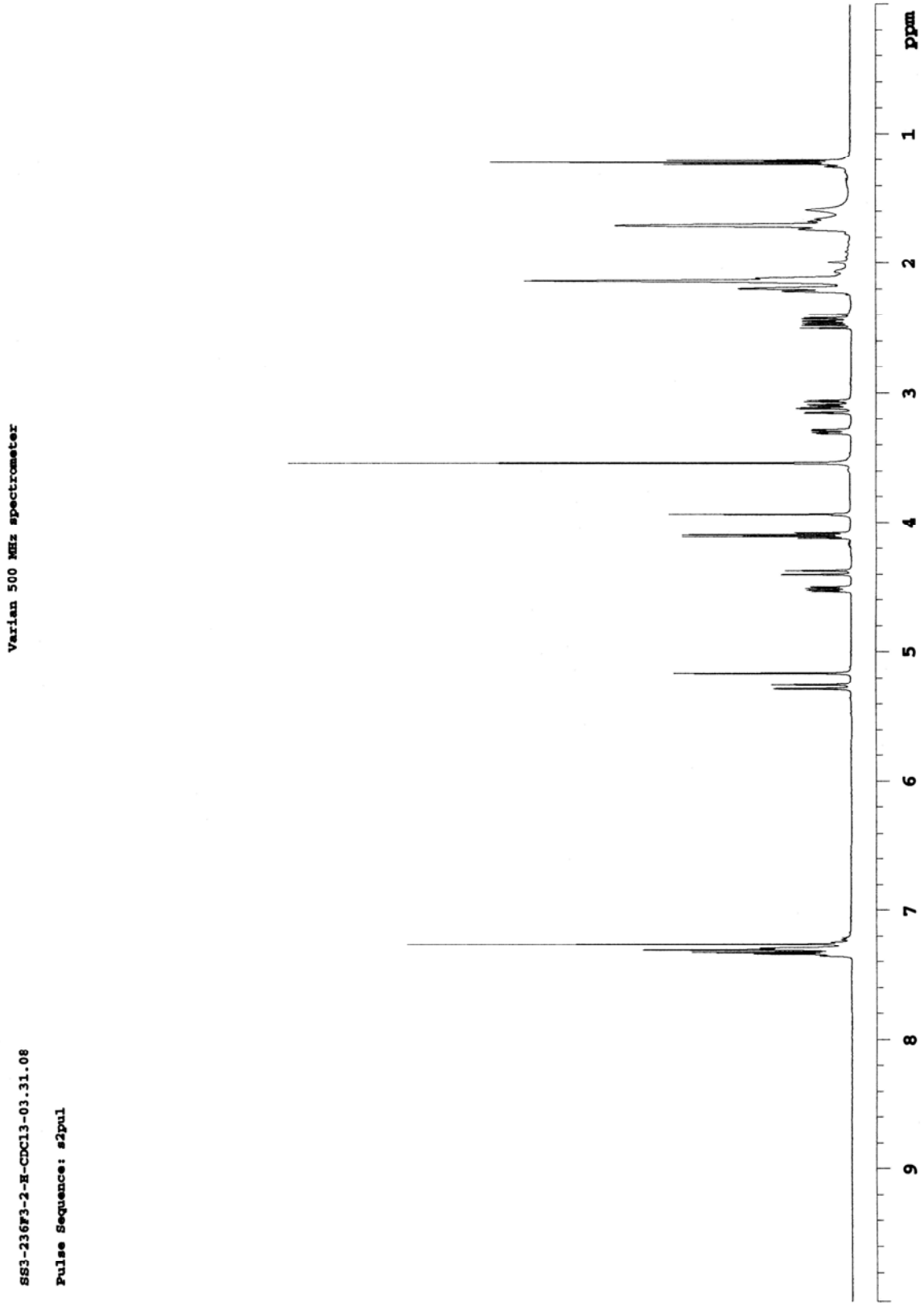
^{1}H NMR (Compound 229a)



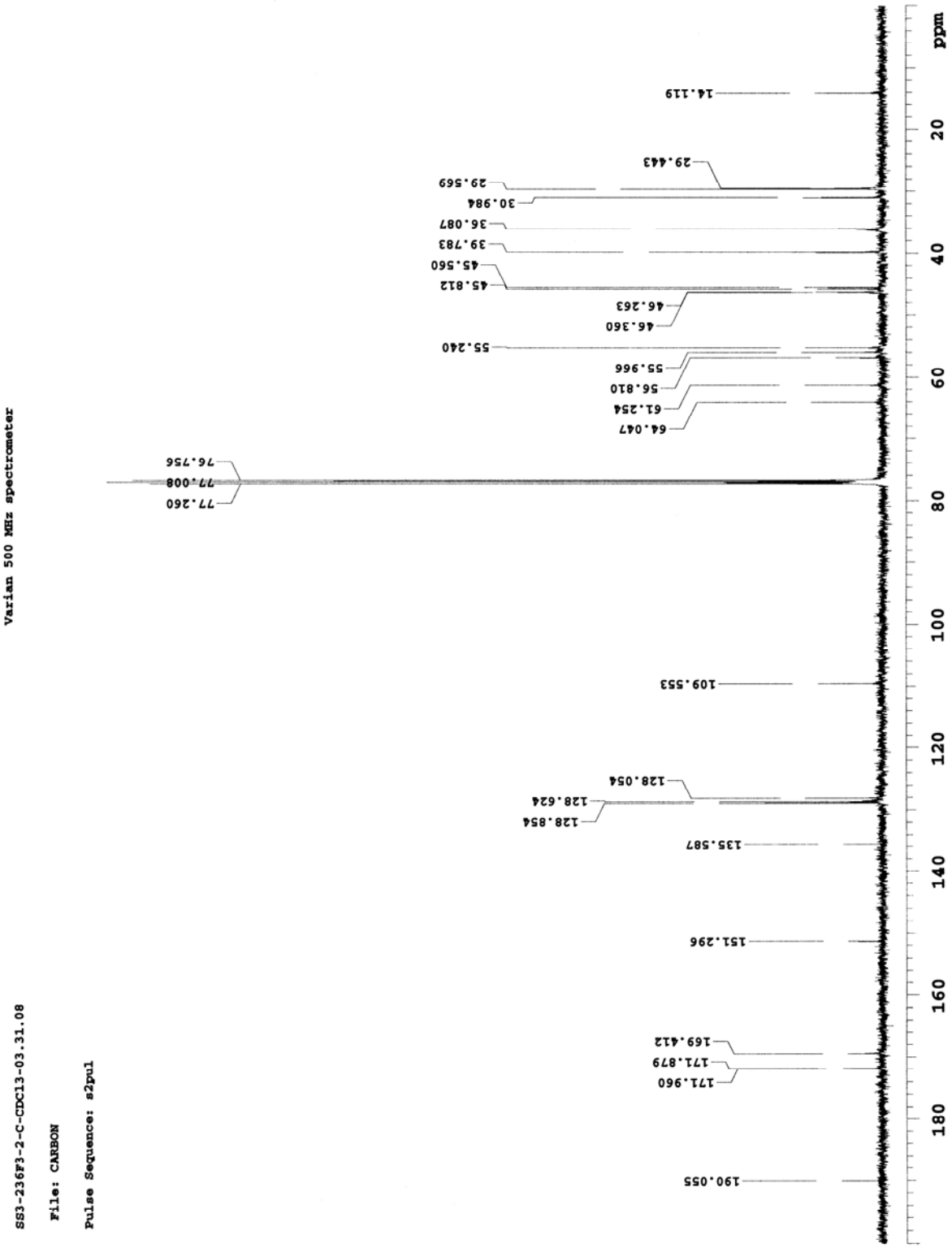
^{13}C NMR (Compound 230)



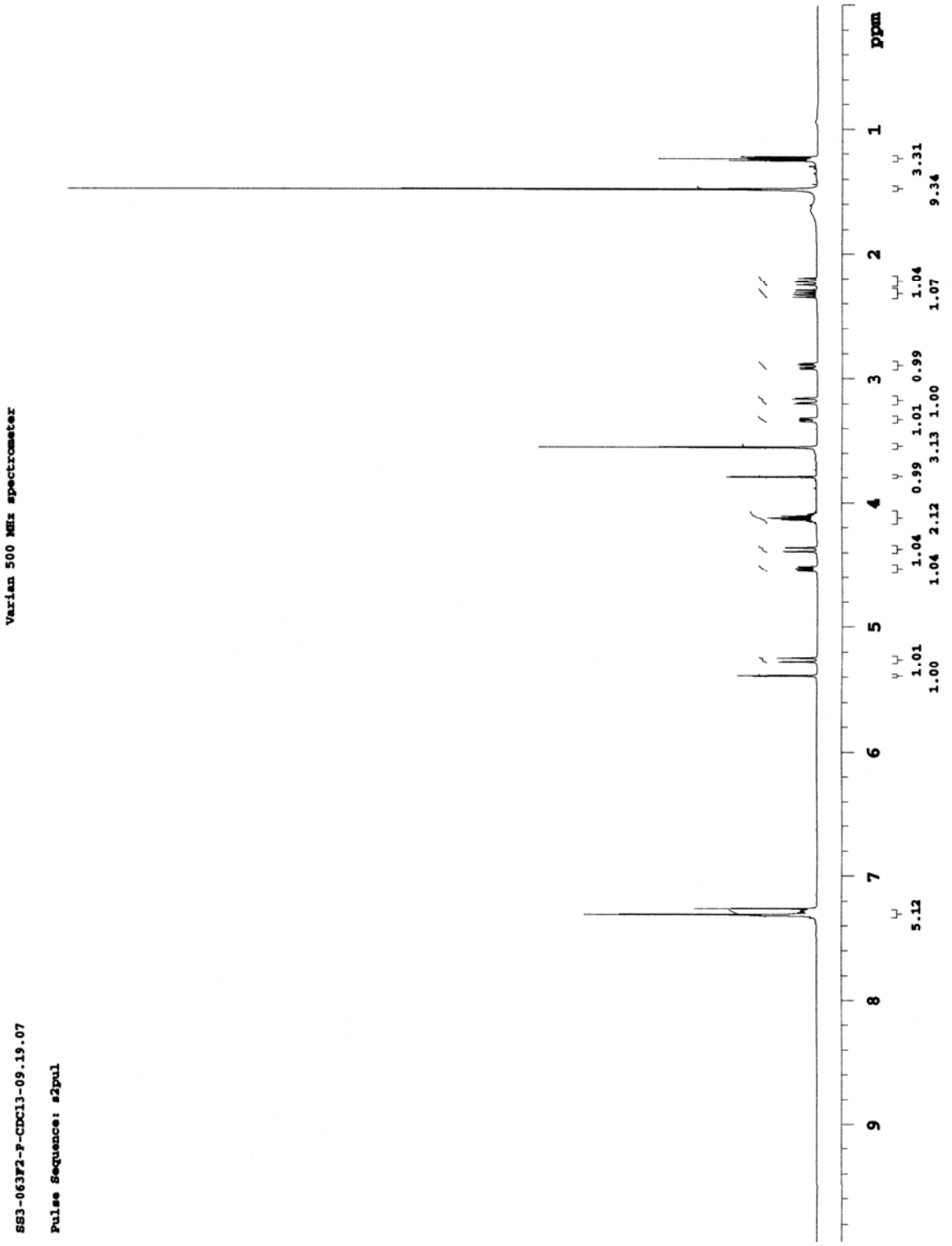
[1]H NMR (Compound 230)



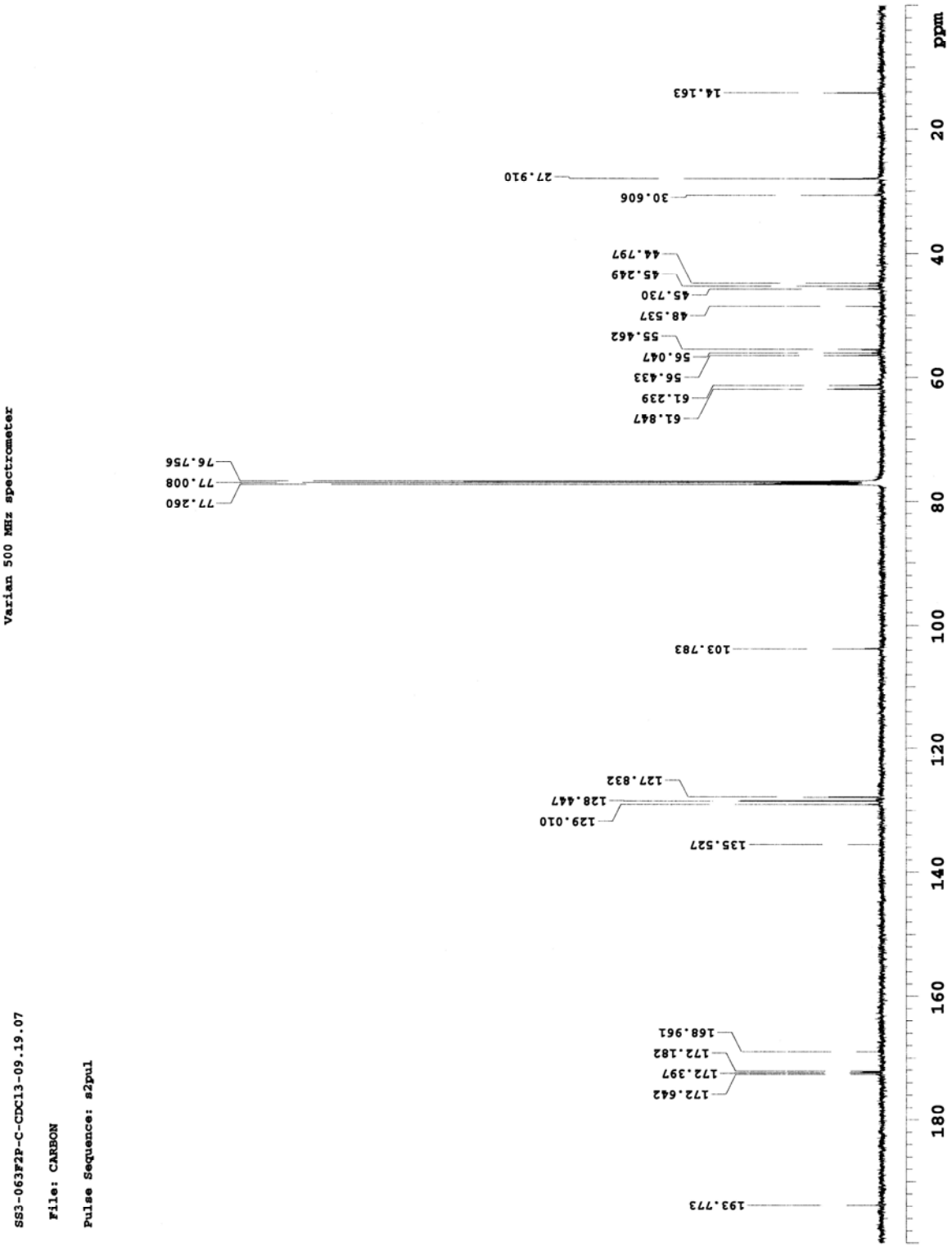
^{13}C NMR (Compound 230)



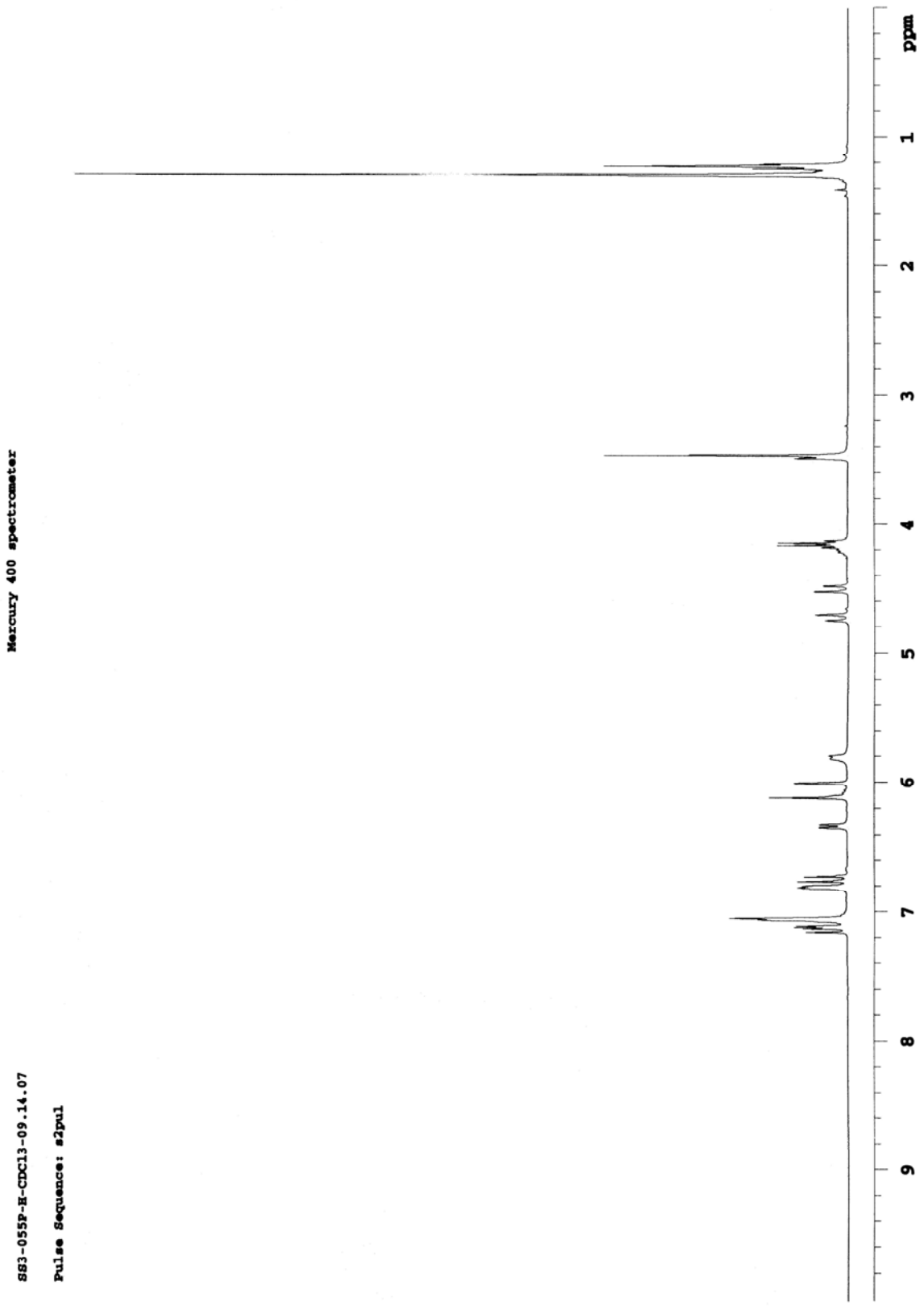
^{1}H NMR (Compound 233)



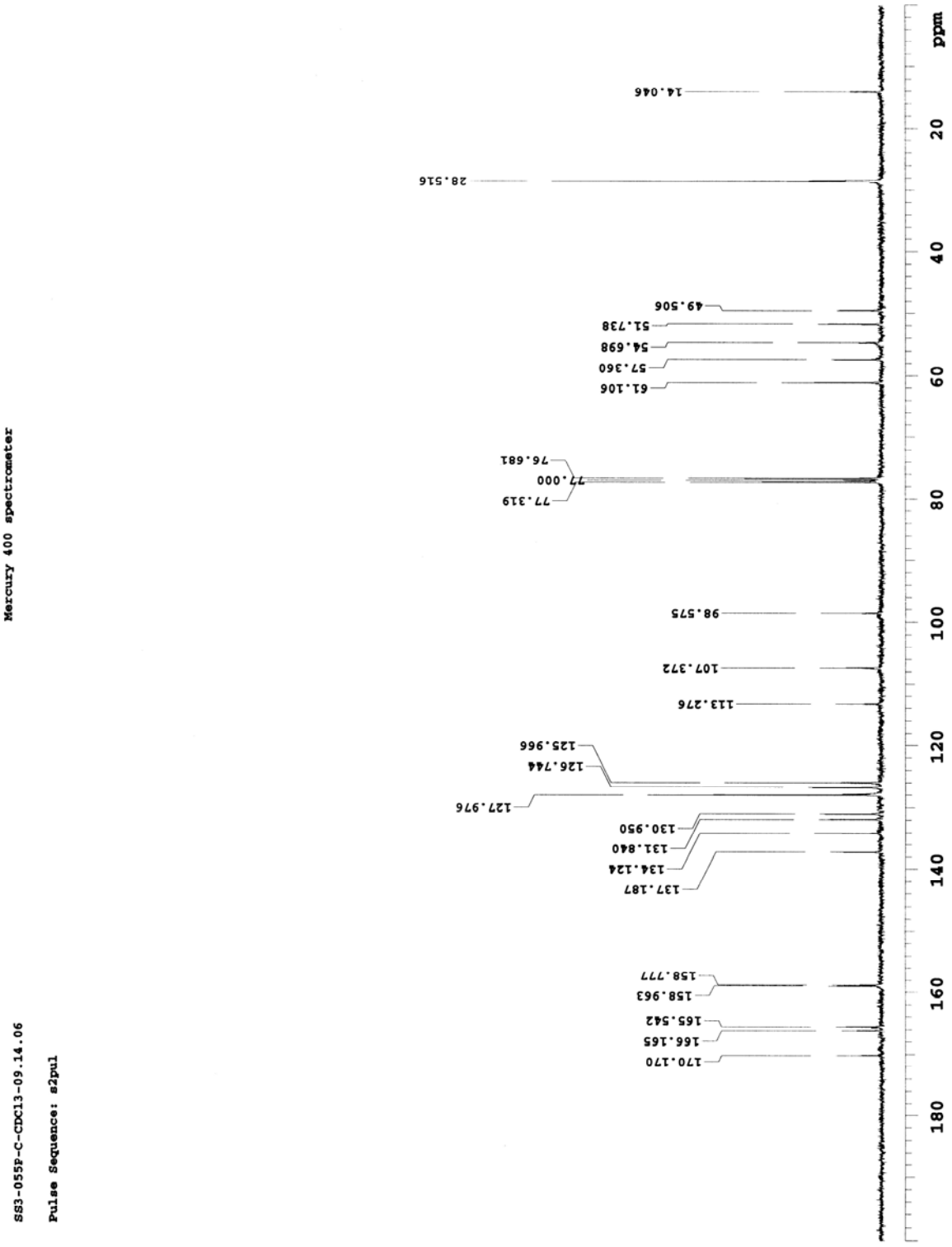
^{13}C NMR (Compound 233)



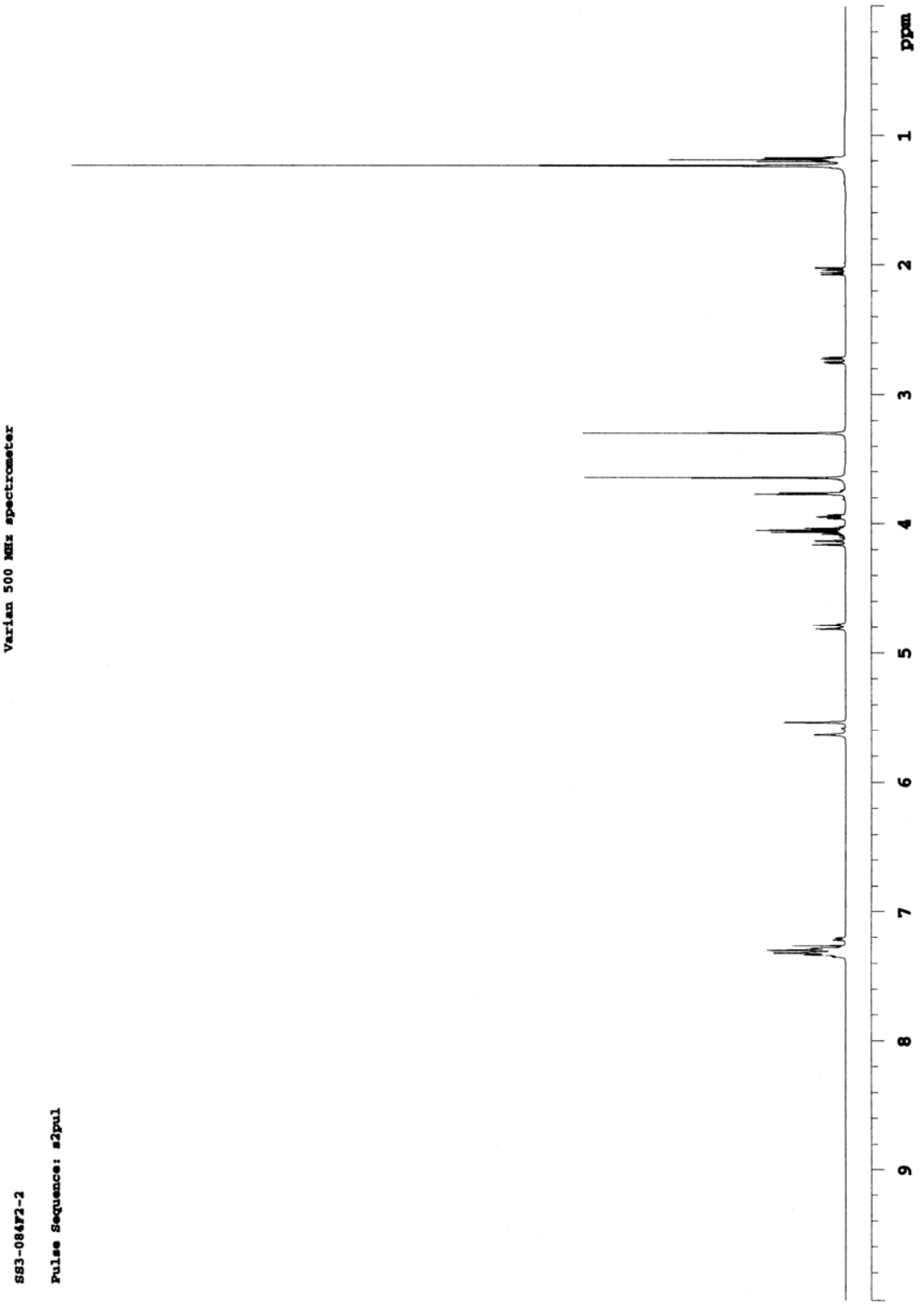
^{1}H NMR (Compound 235)



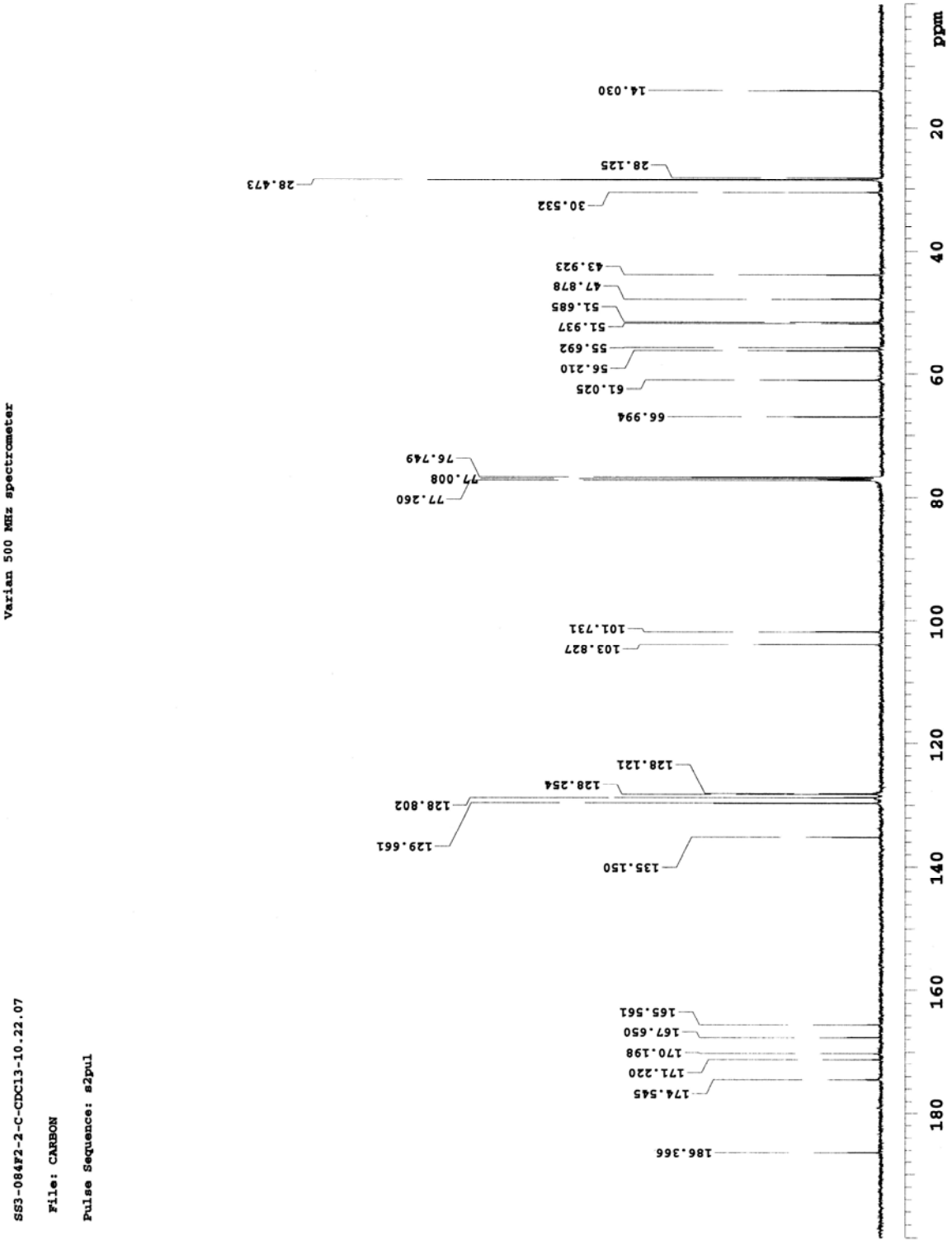
^{13}C NMR (Compound 235)



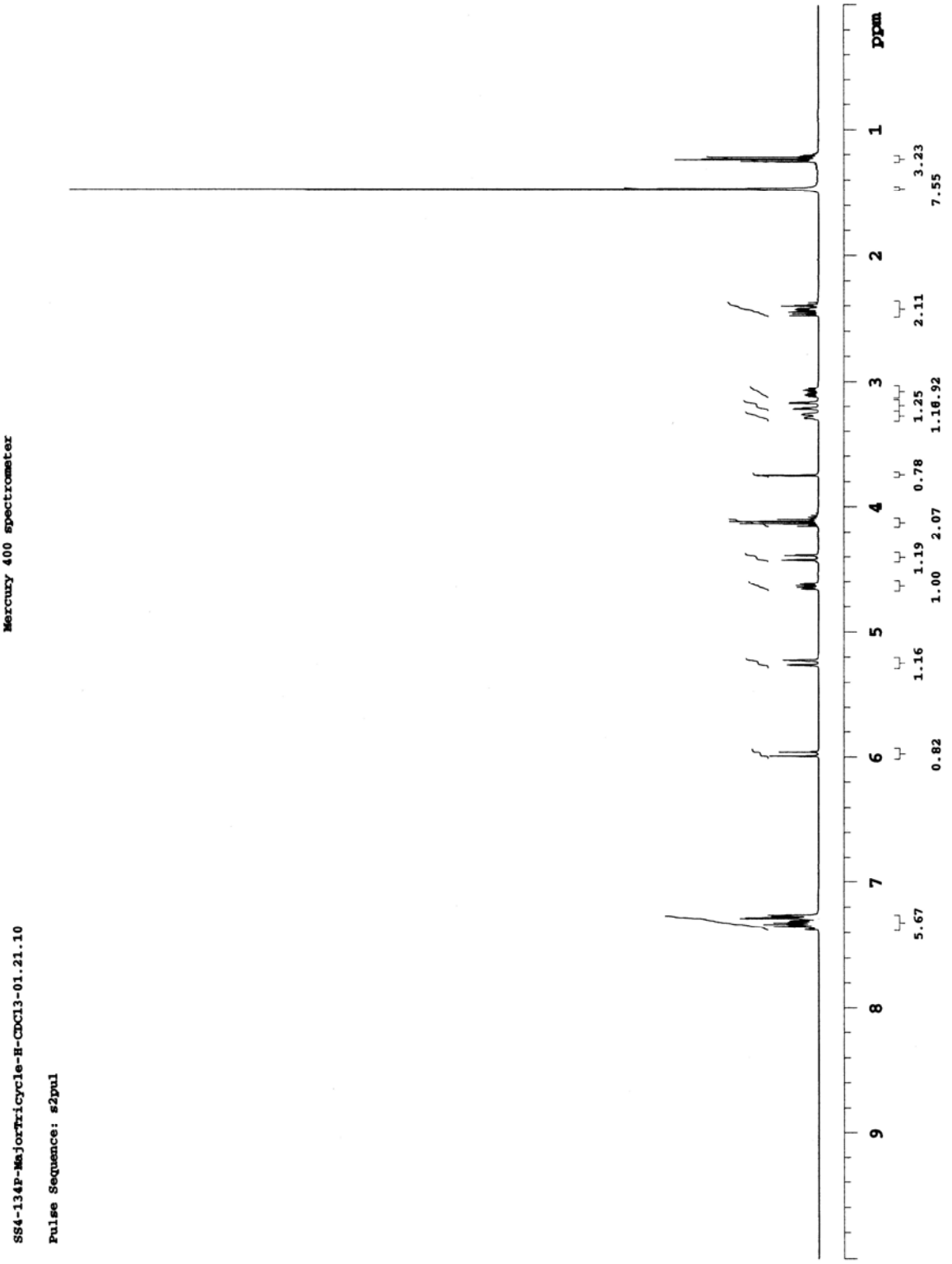
^{1}H NMR (Compound 236)



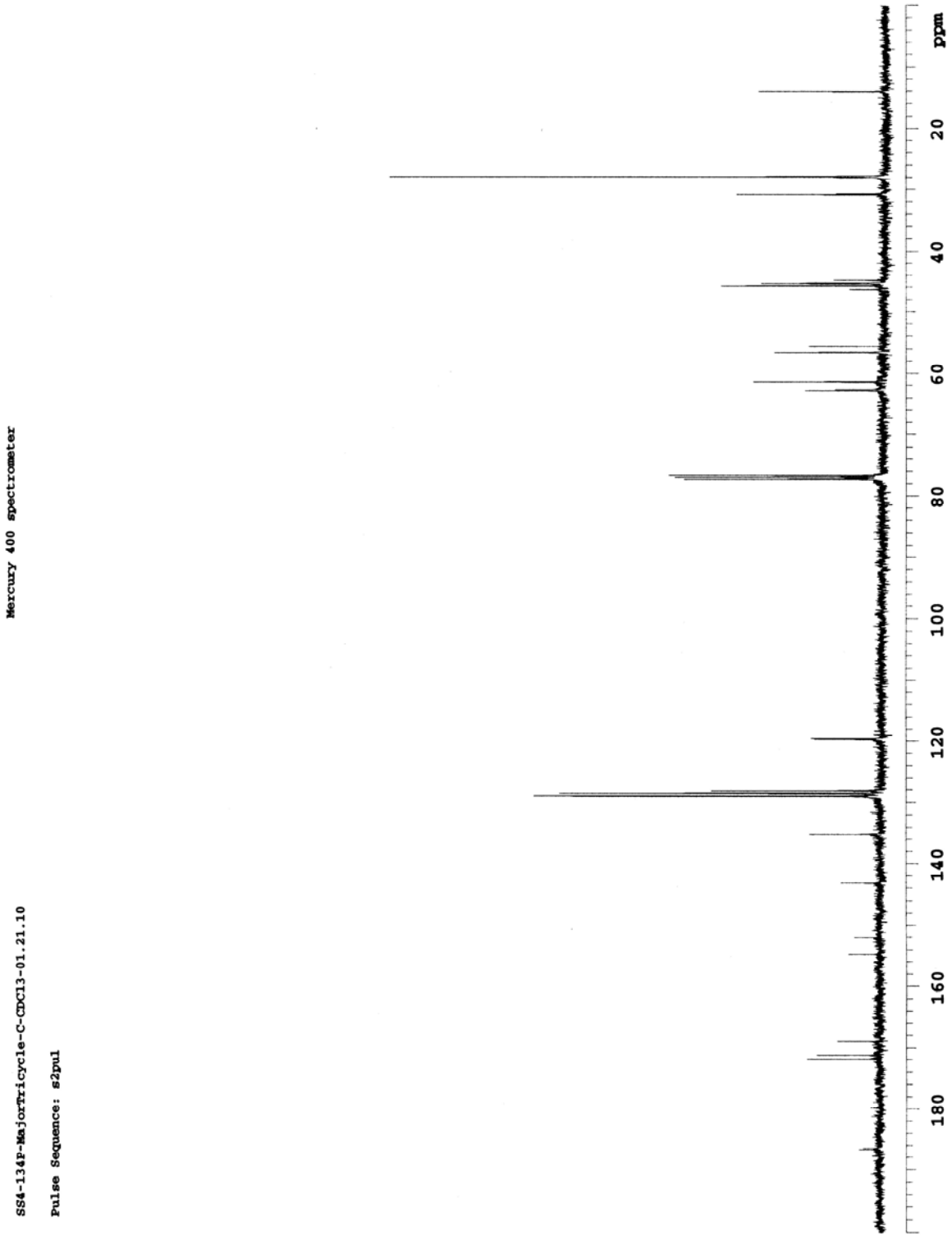
^{13}C NMR (Compound 236)



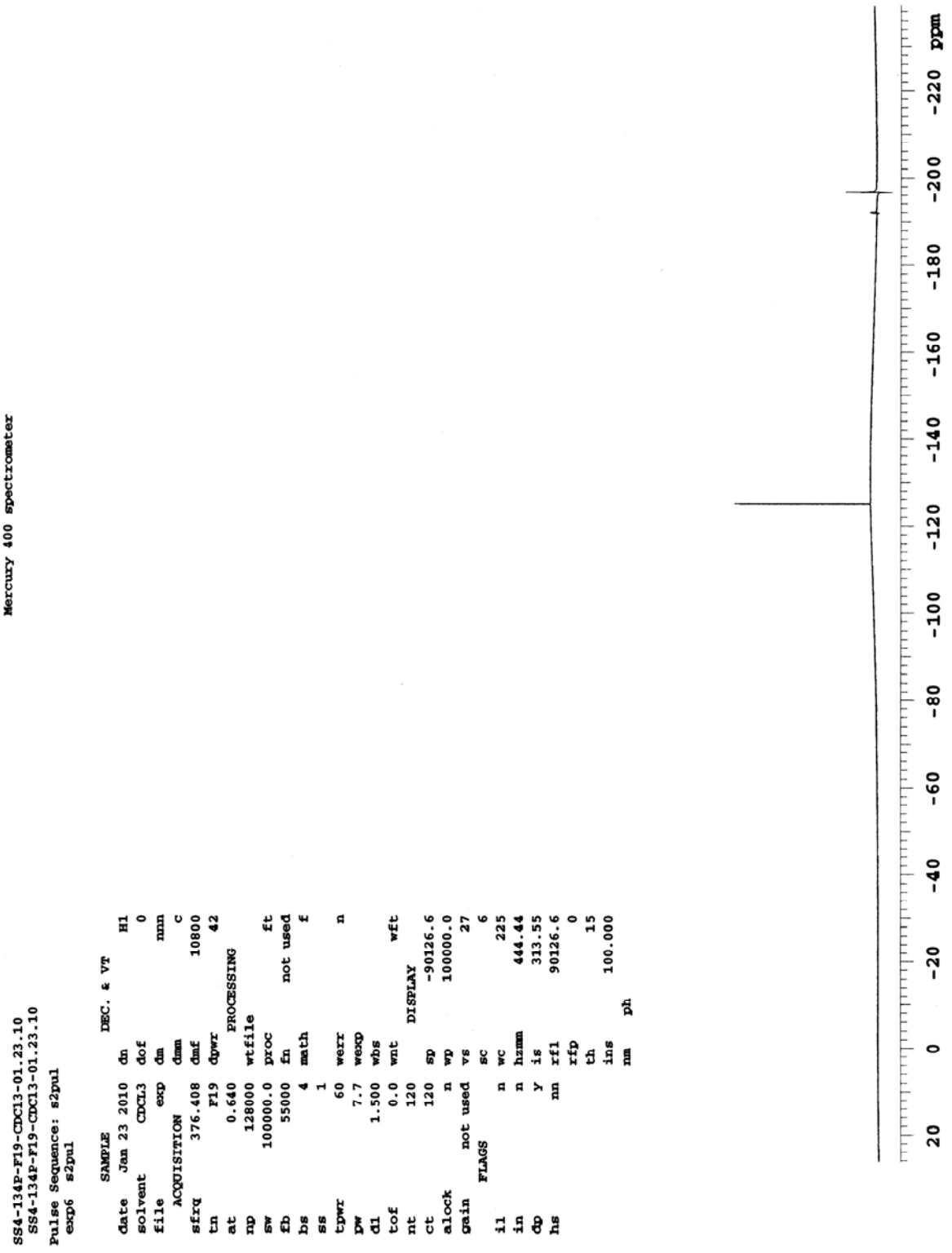
^{1}H NMR (Compound 238)



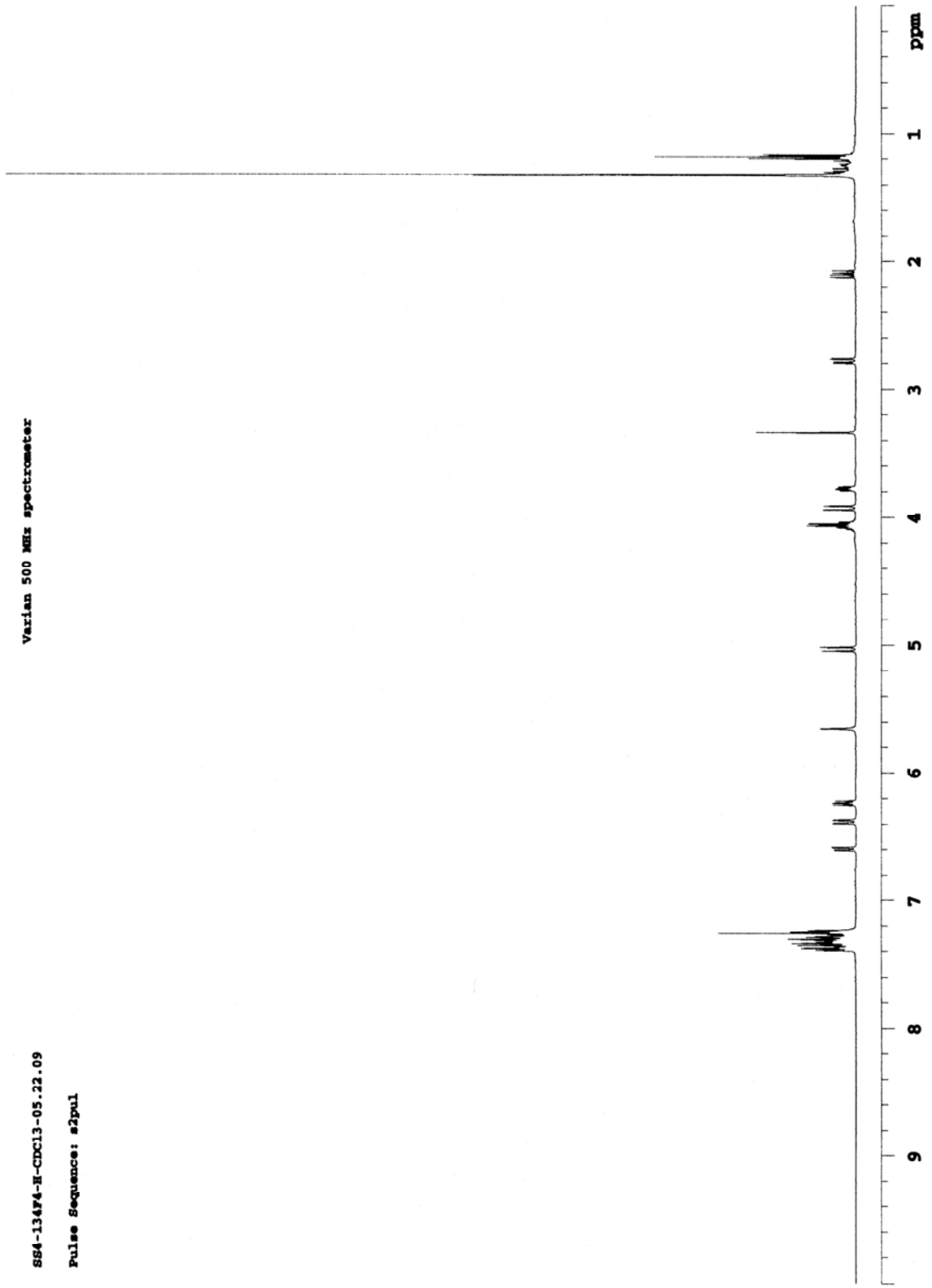
^{13}C NMR (Compound 238)



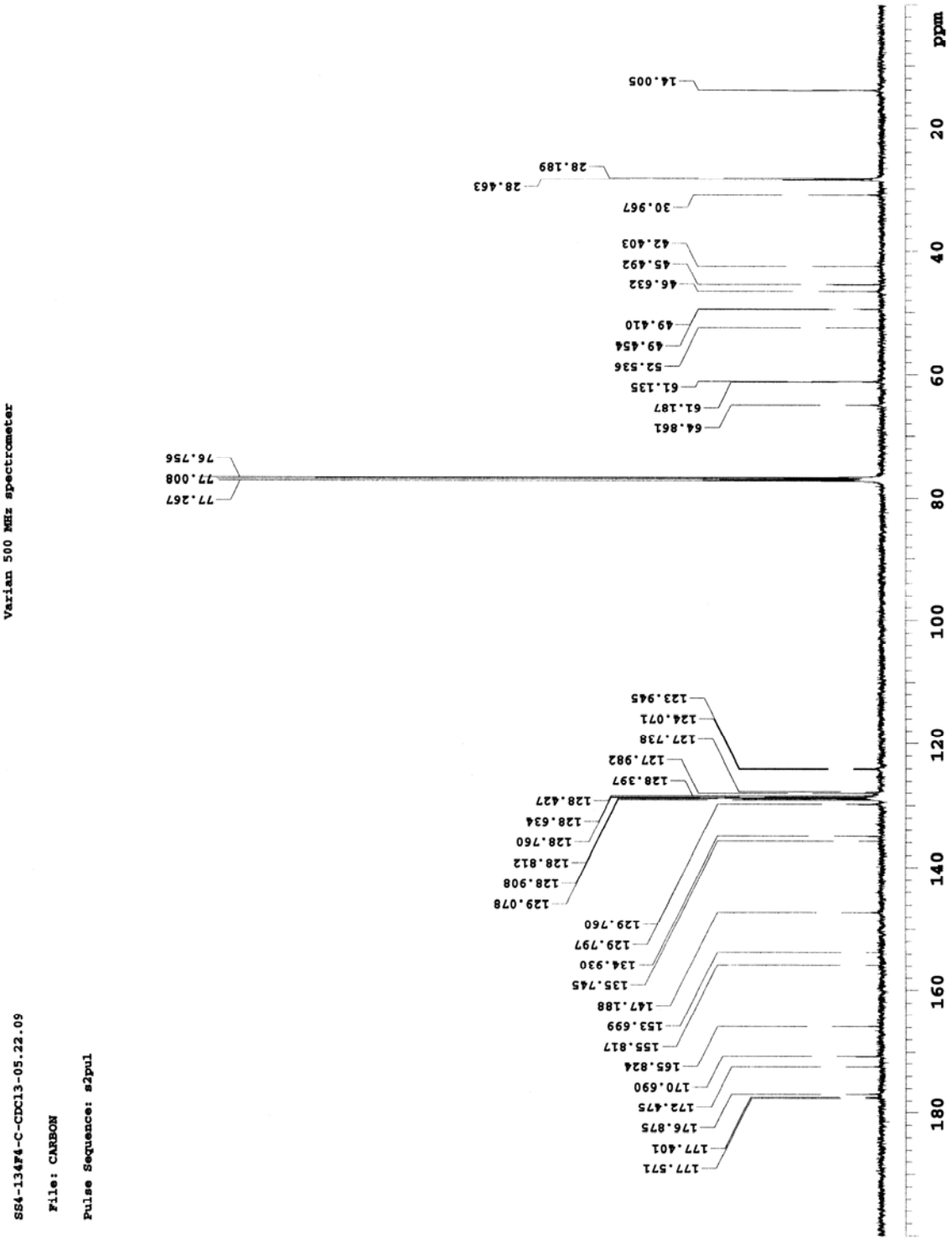
^{19}F NMR (Compound 238)



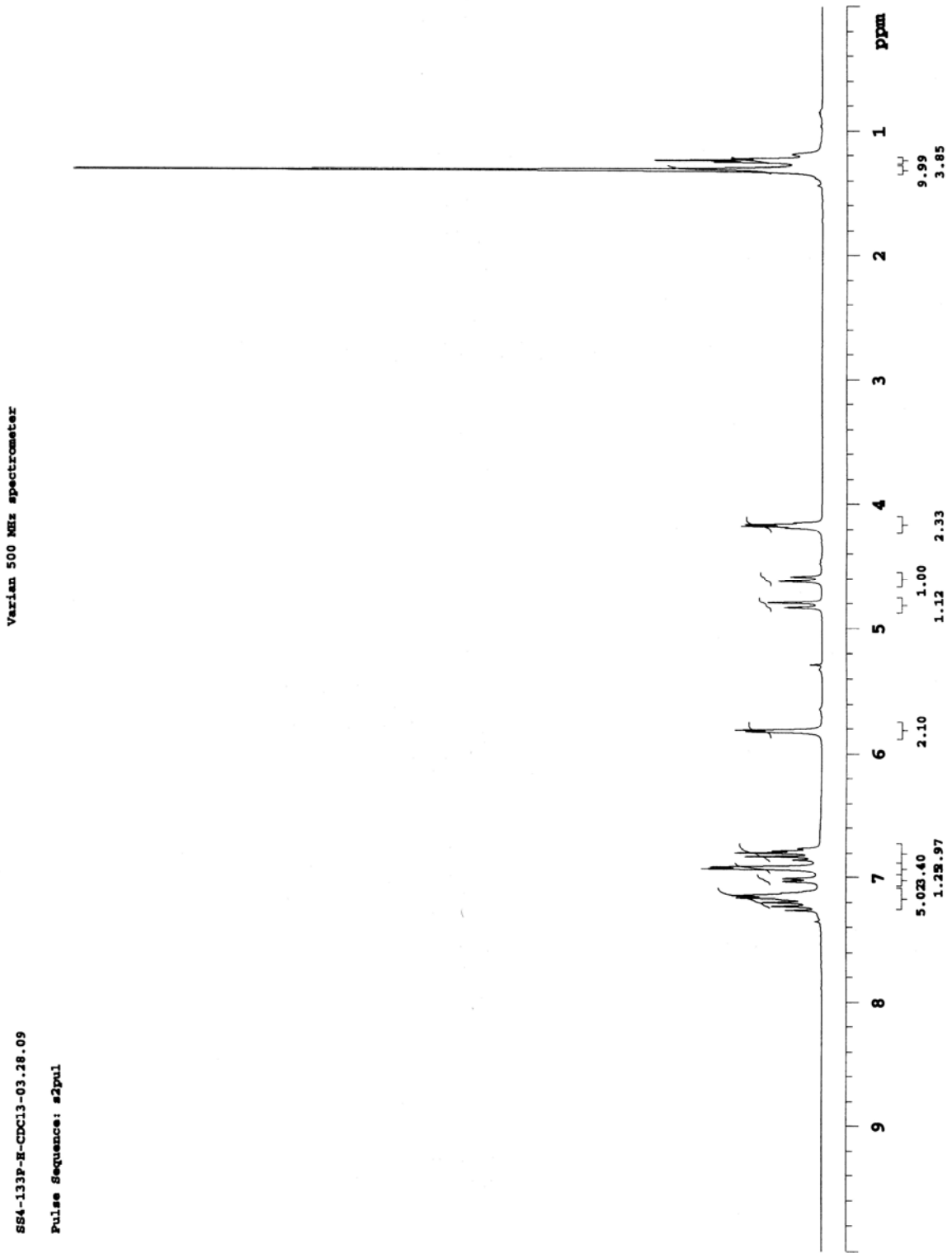
^{1}H NMR (Compound 238a)



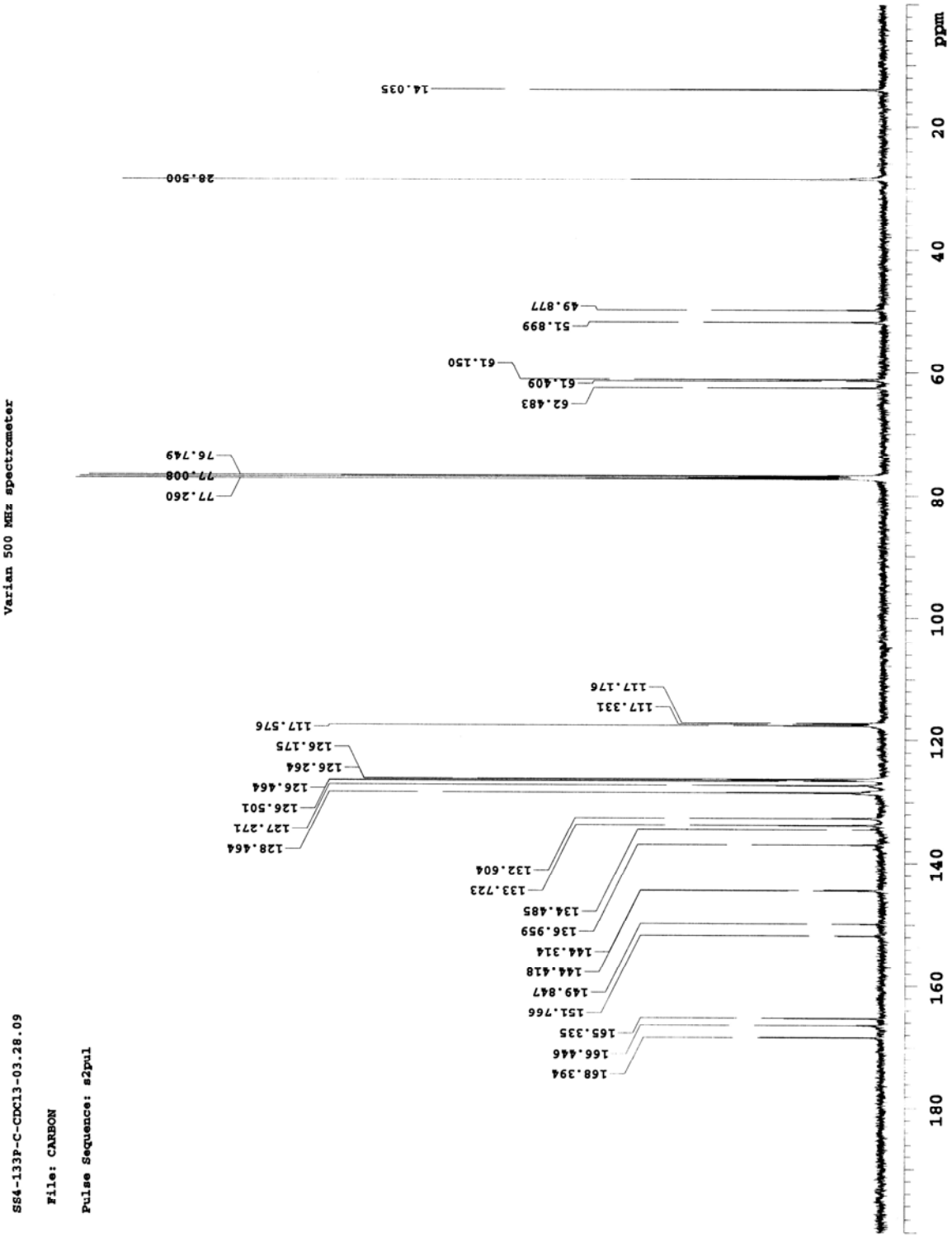
^{13}C NMR (Compound 238a)



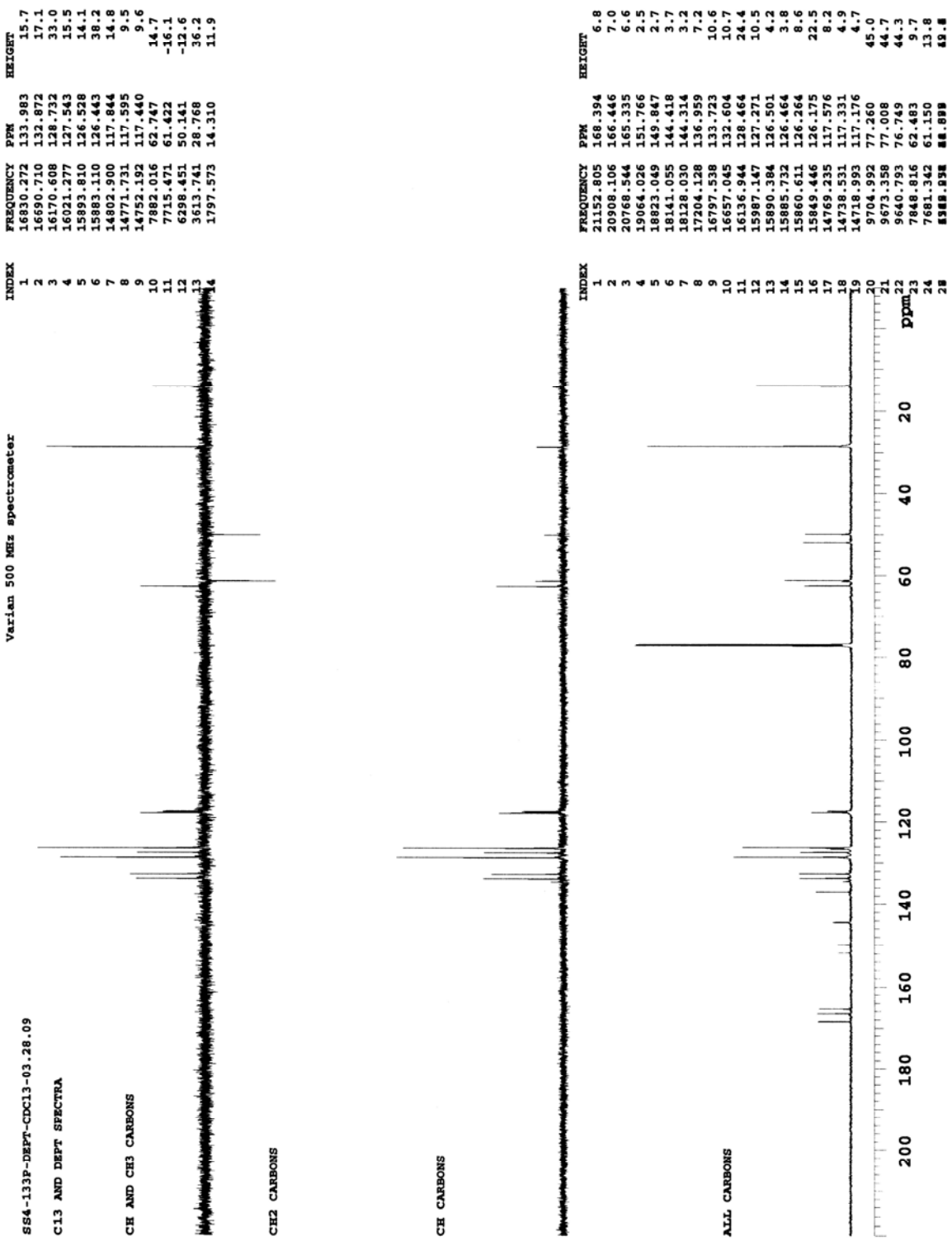
^{1}H NMR (Compound 239)



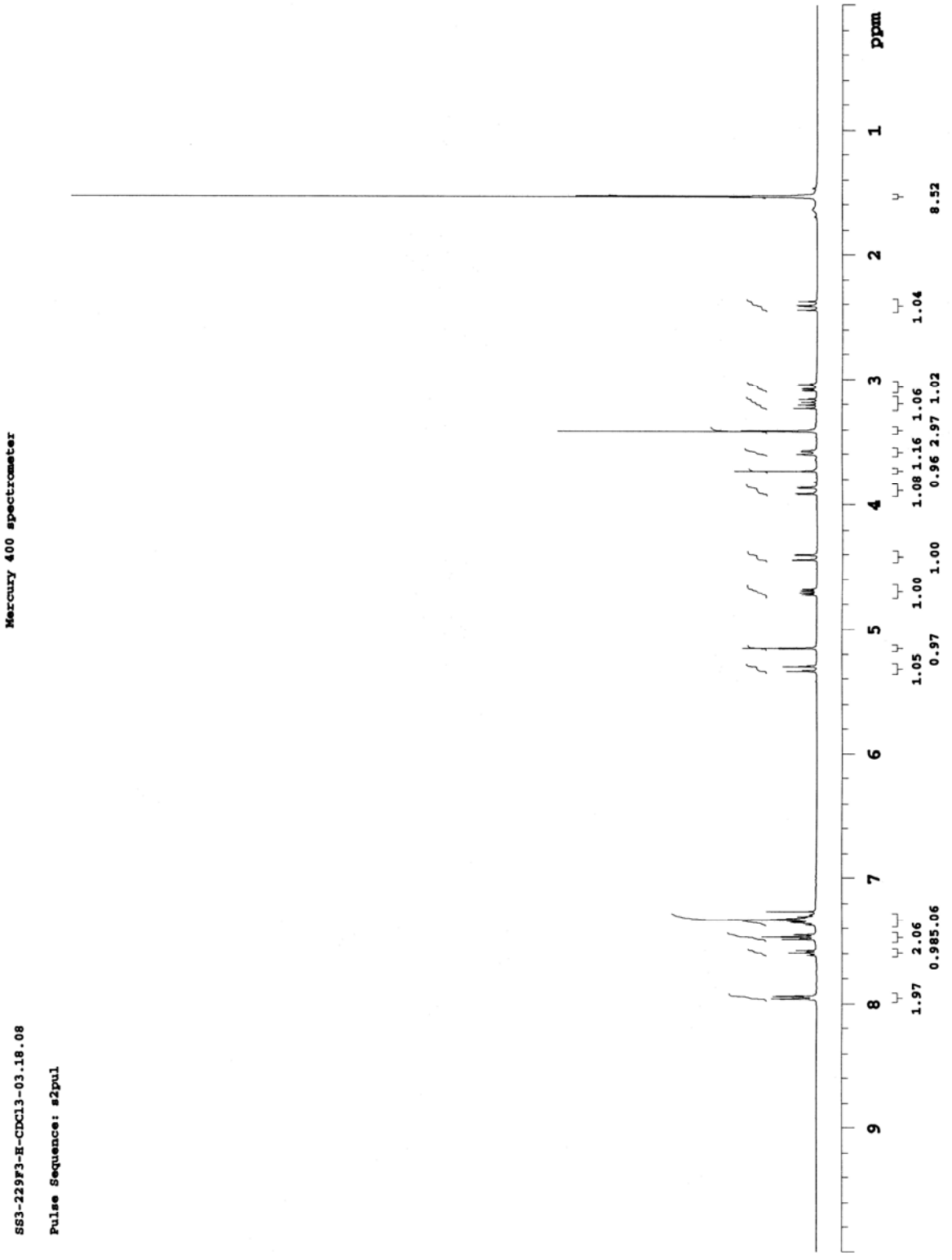
^{13}C NMR (Compound 239)



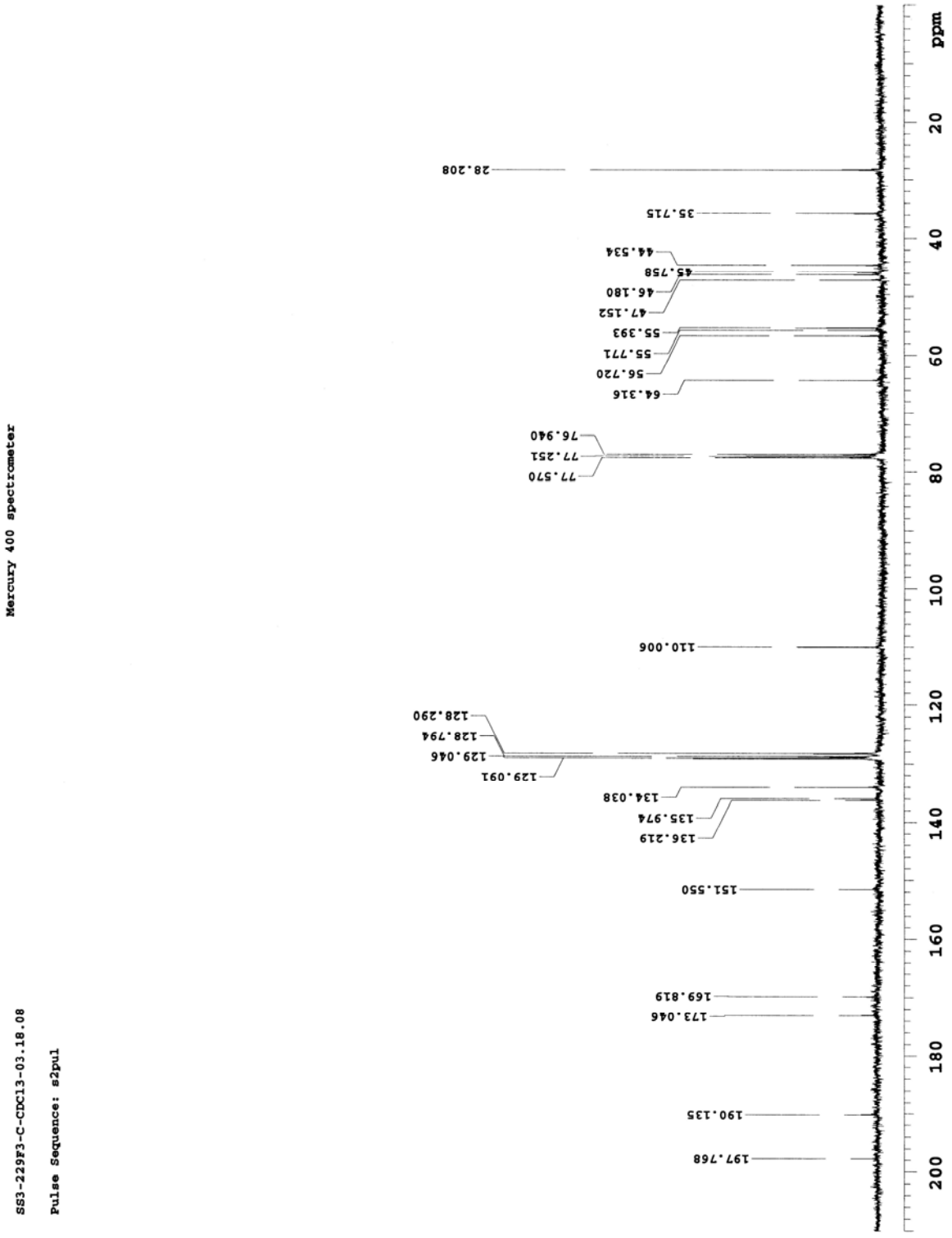
DEPT NMR (Compound 239)



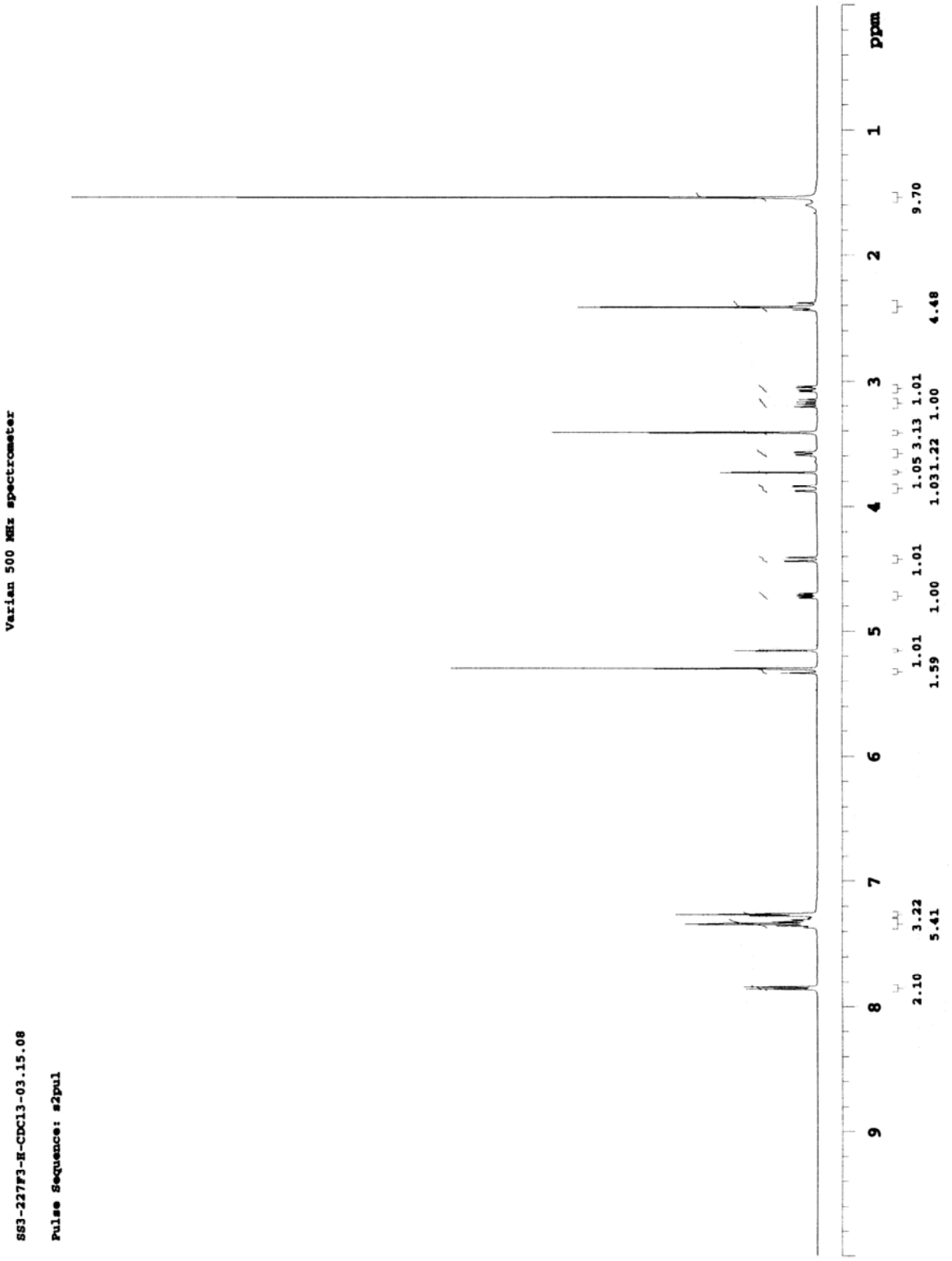
^{1}H NMR (Compound 240)



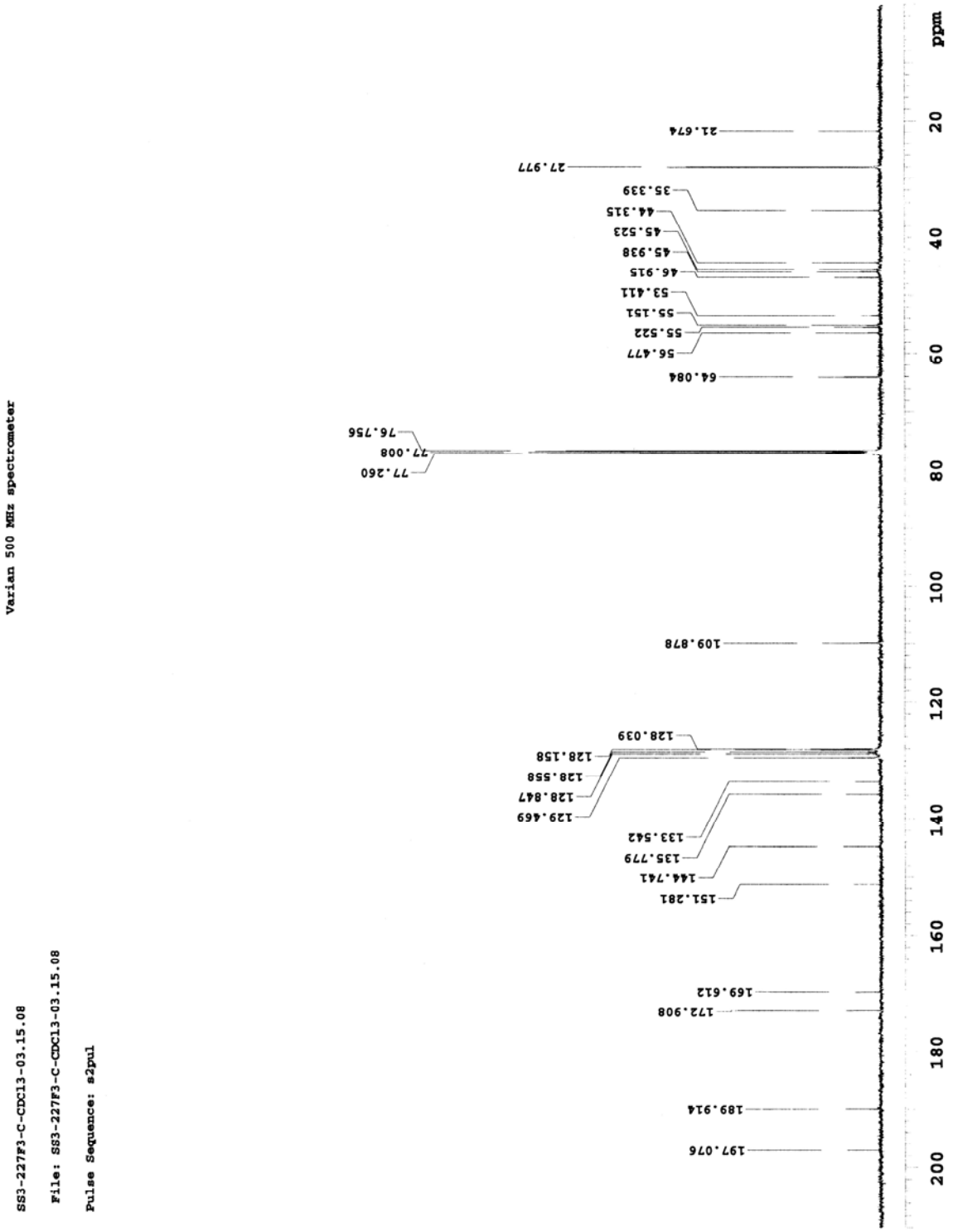
^{13}C NMR (Compound 240)



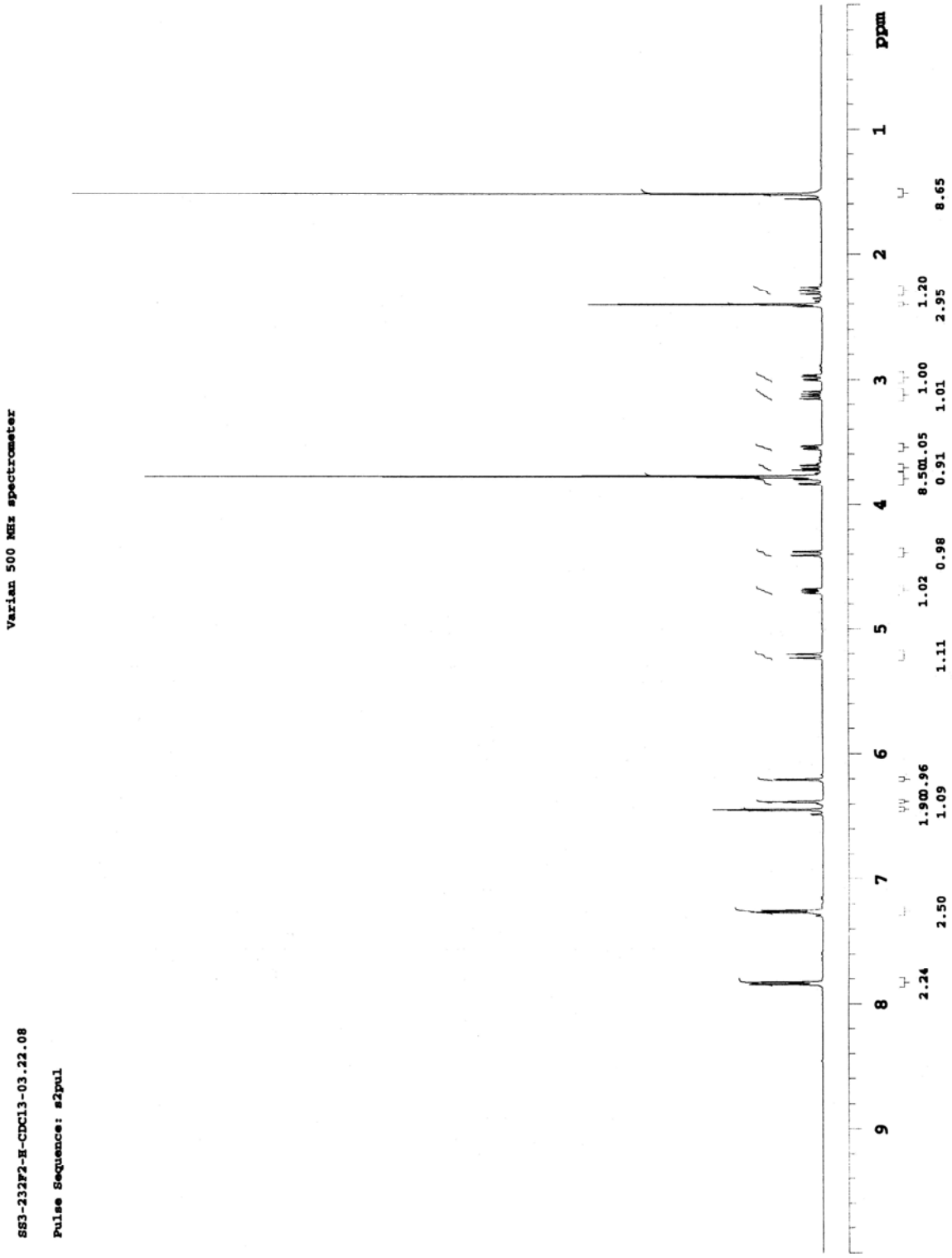
^{1}H NMR (Compound 243)



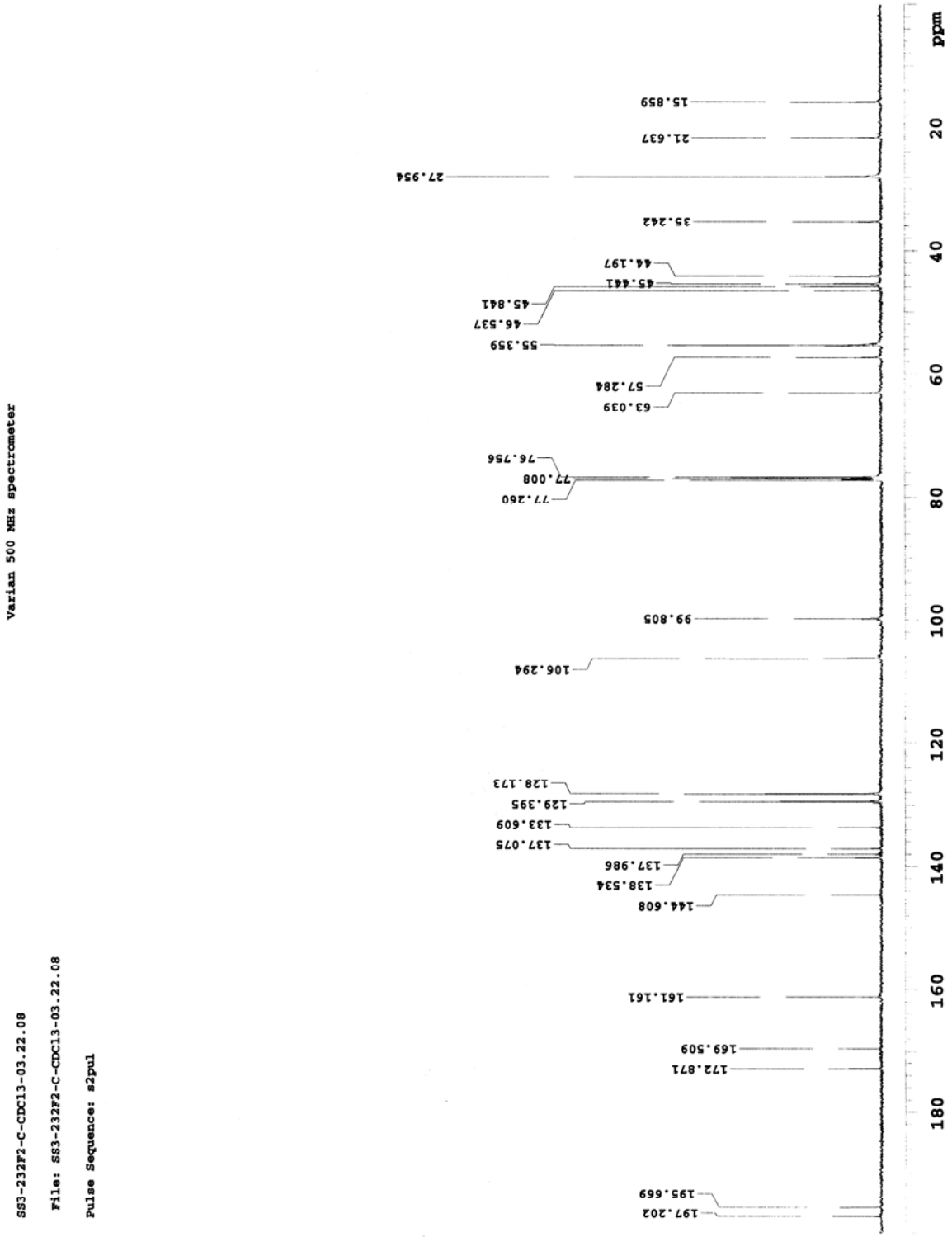
^{13}C NMR (Compound 243)



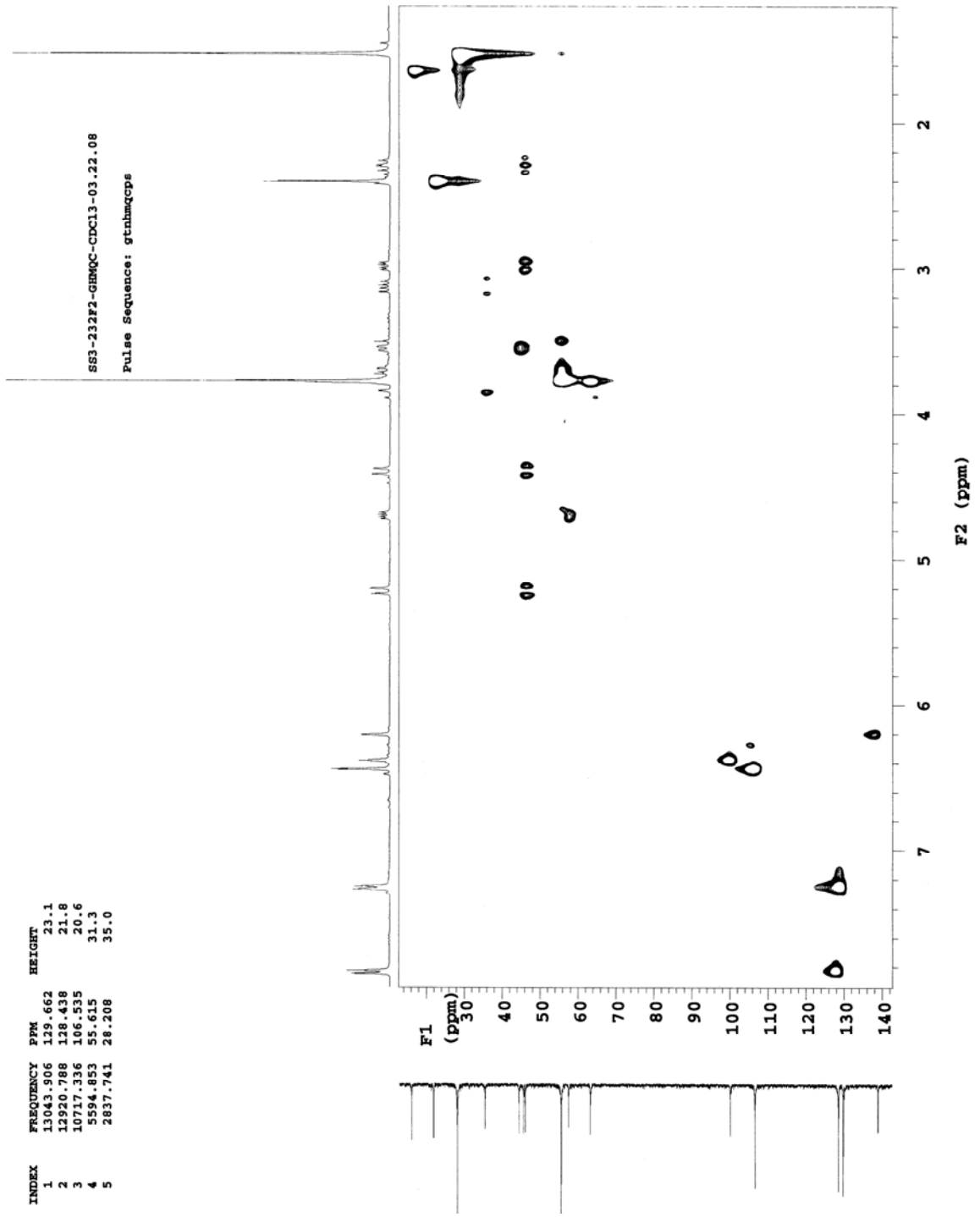
^{1}H NMR (Compound 246)



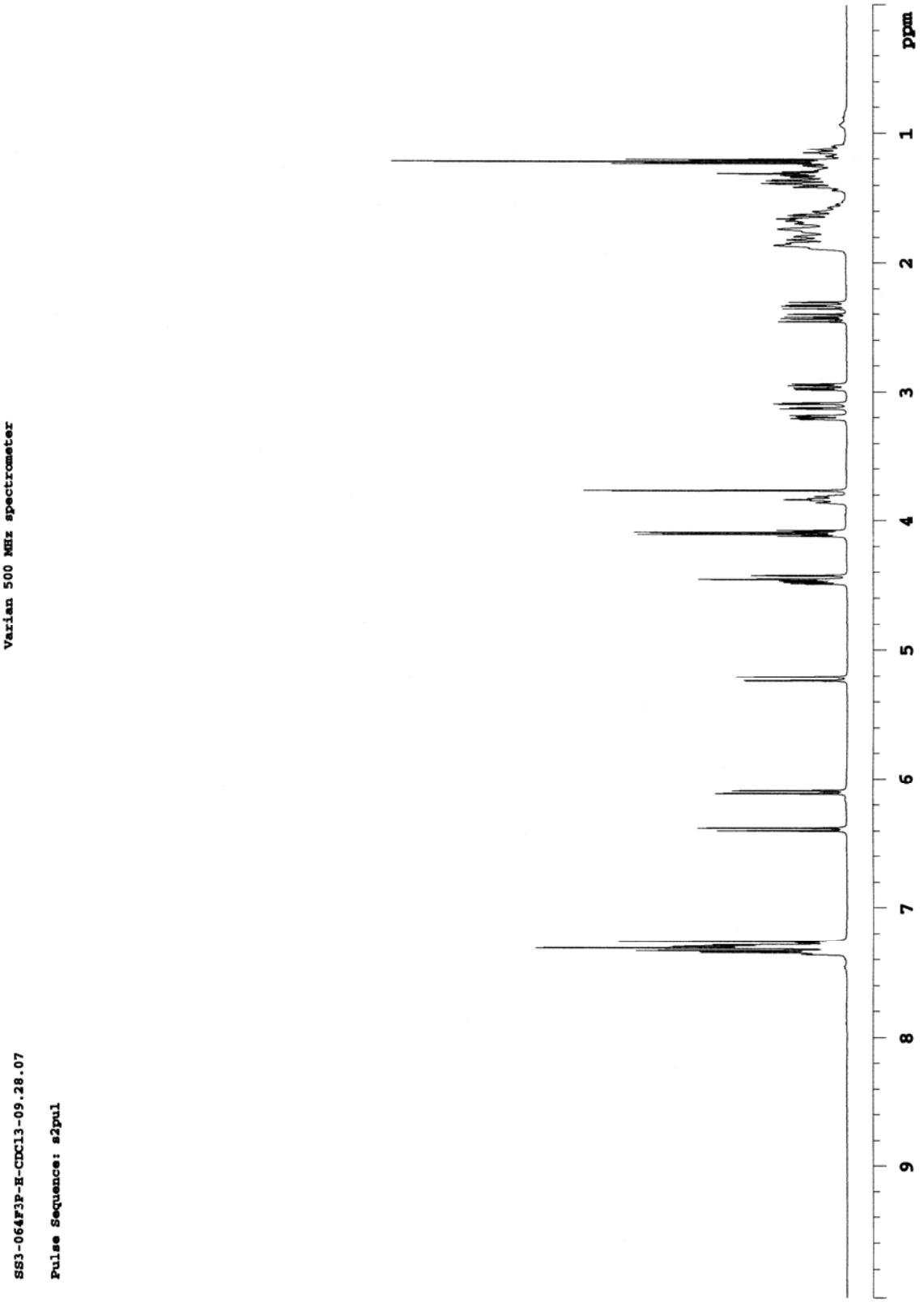
^{13}C NMR (Compound 246)



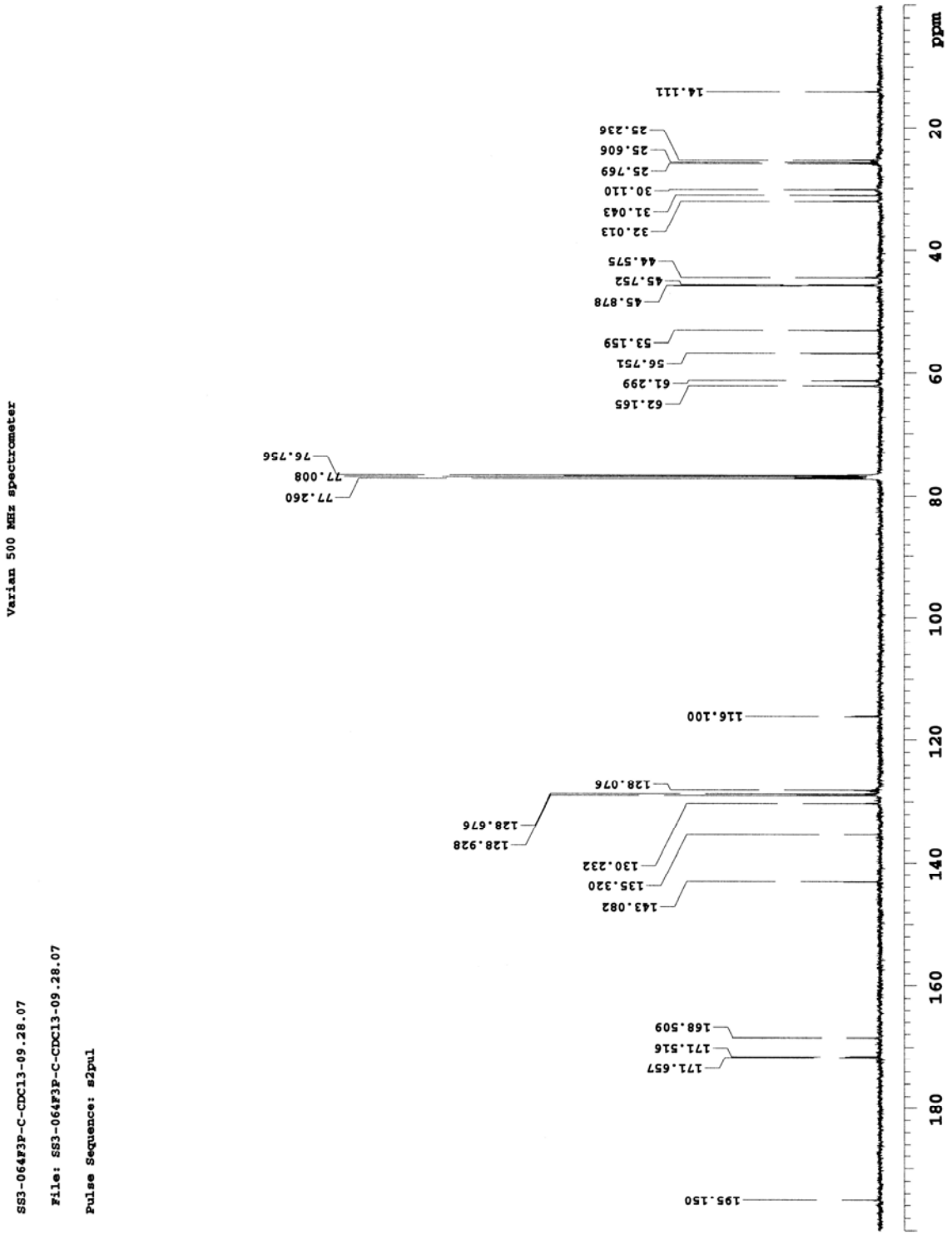
GHMQC NMR (Compound 246)



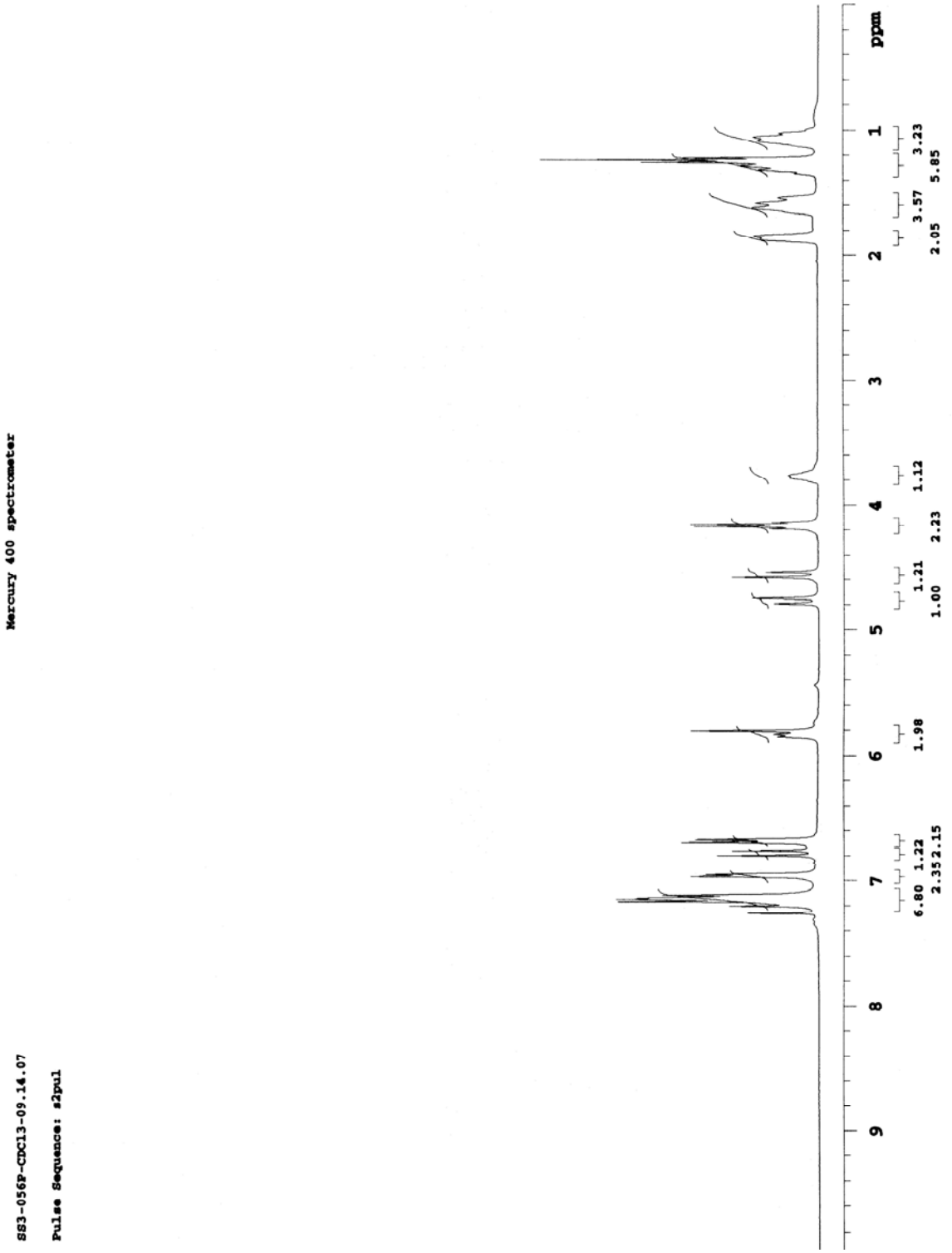
[1]H NMR (Compound 249)



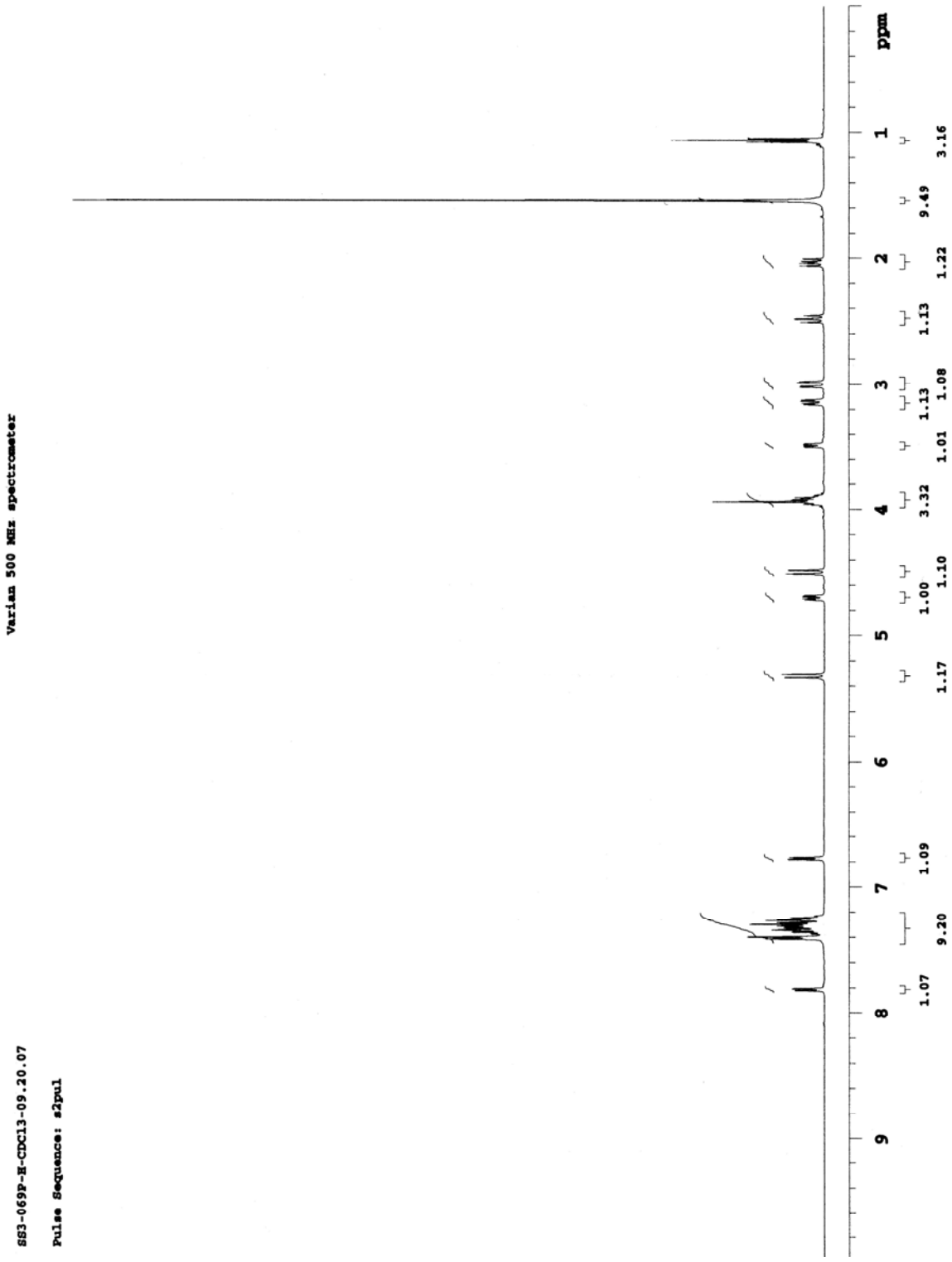
^{13}C NMR (Compound 249)



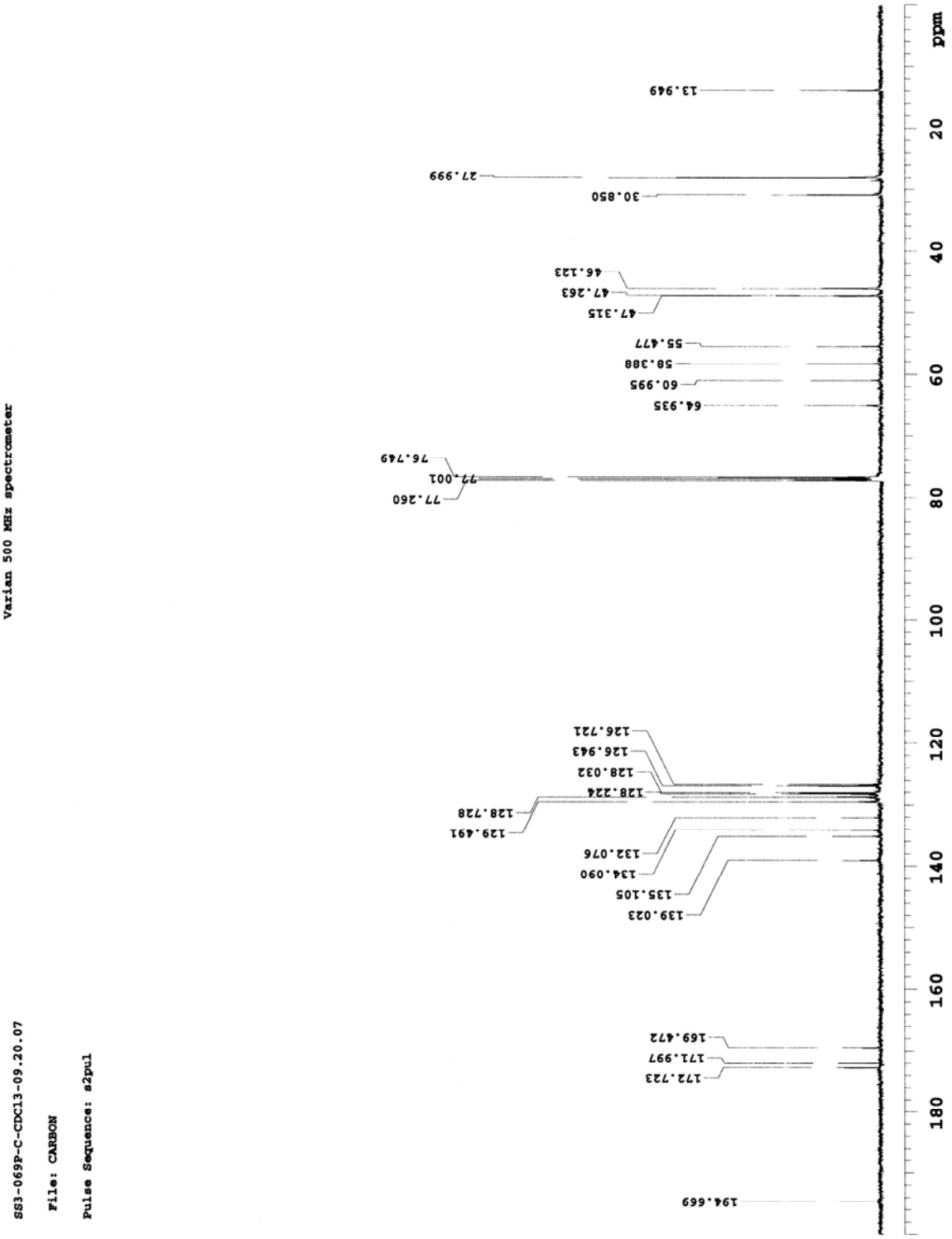
[1]H NMR (Compound 250a)



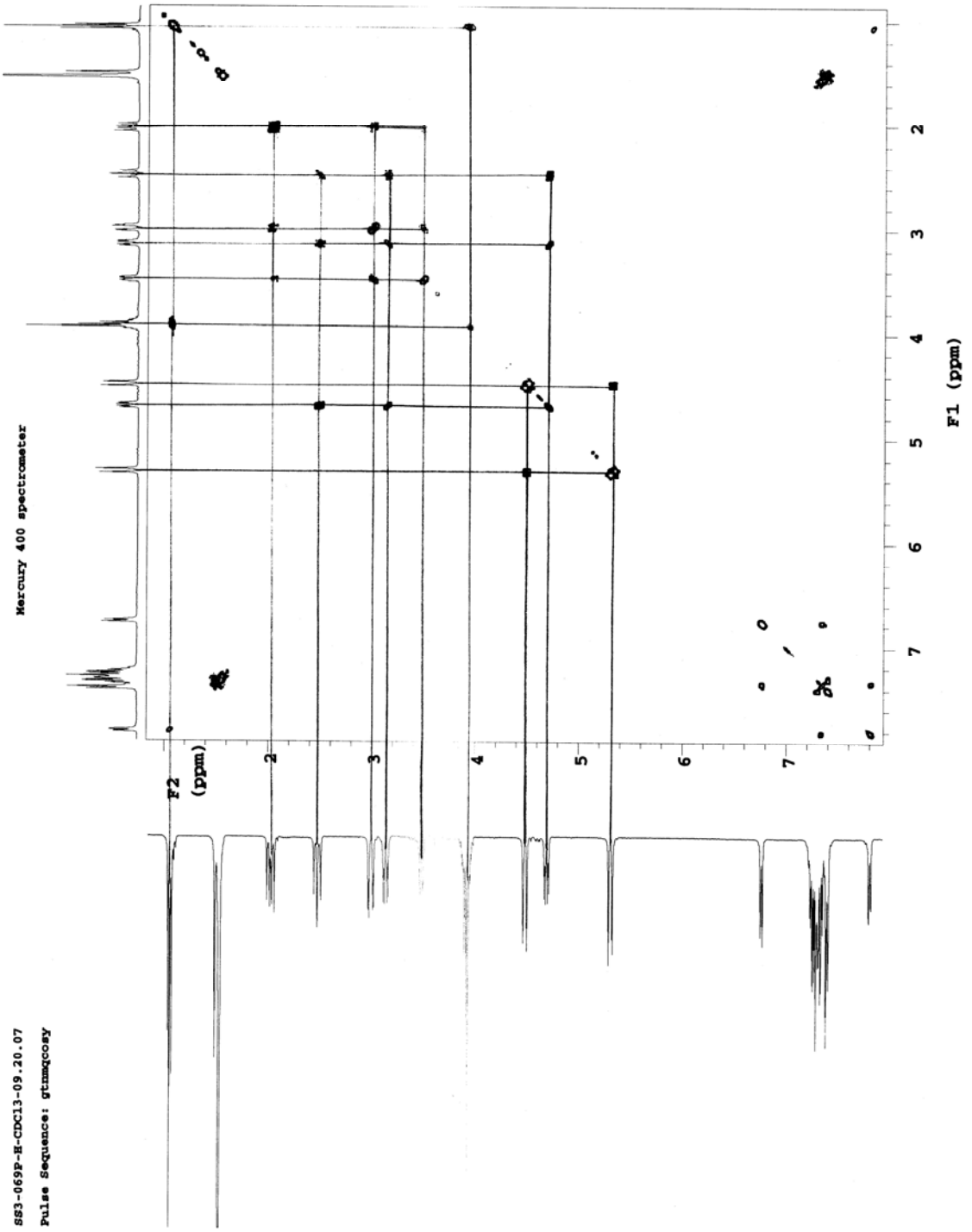
^{1}H NMR (Compound 251)



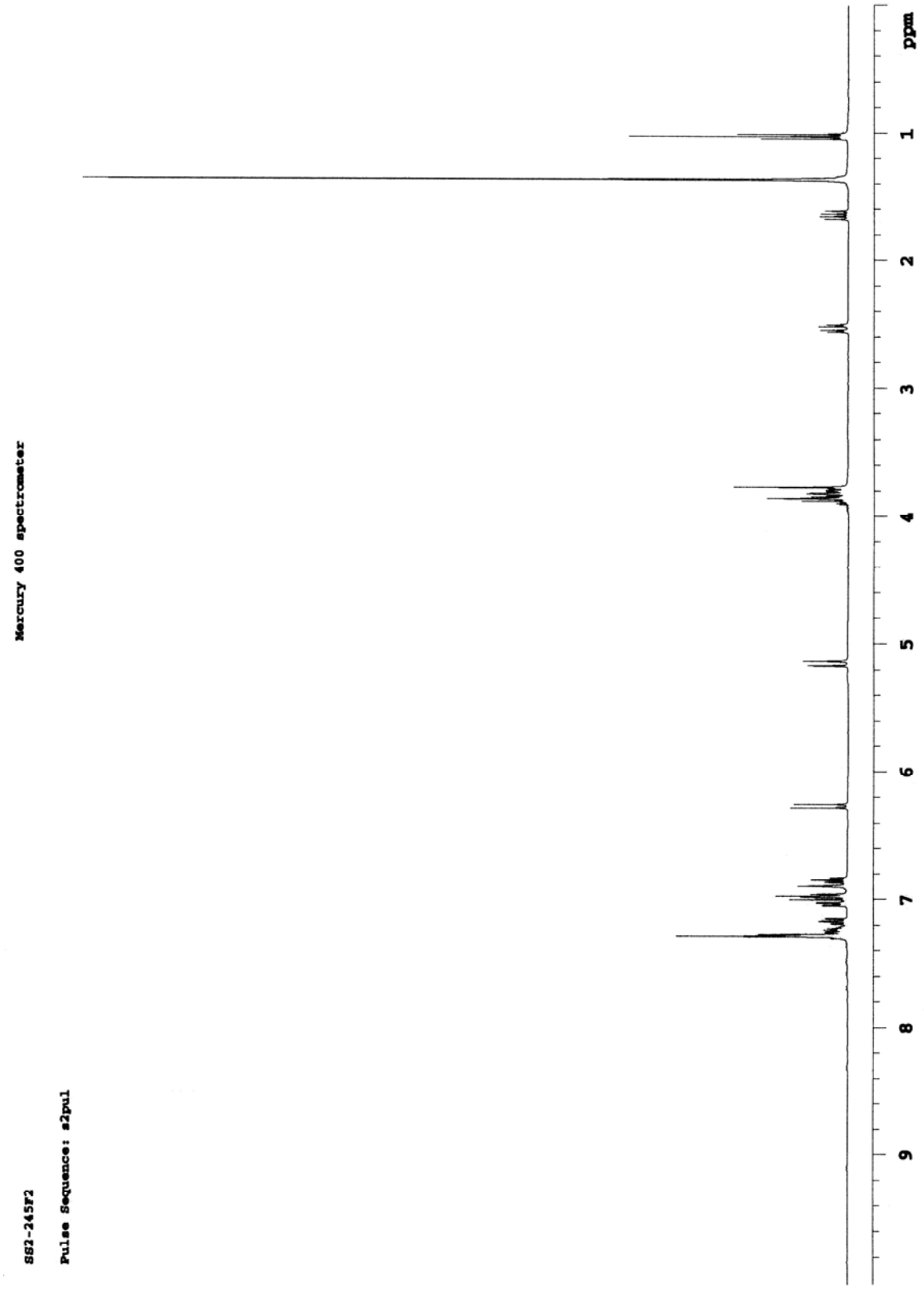
^{13}C NMR (Compound 251)



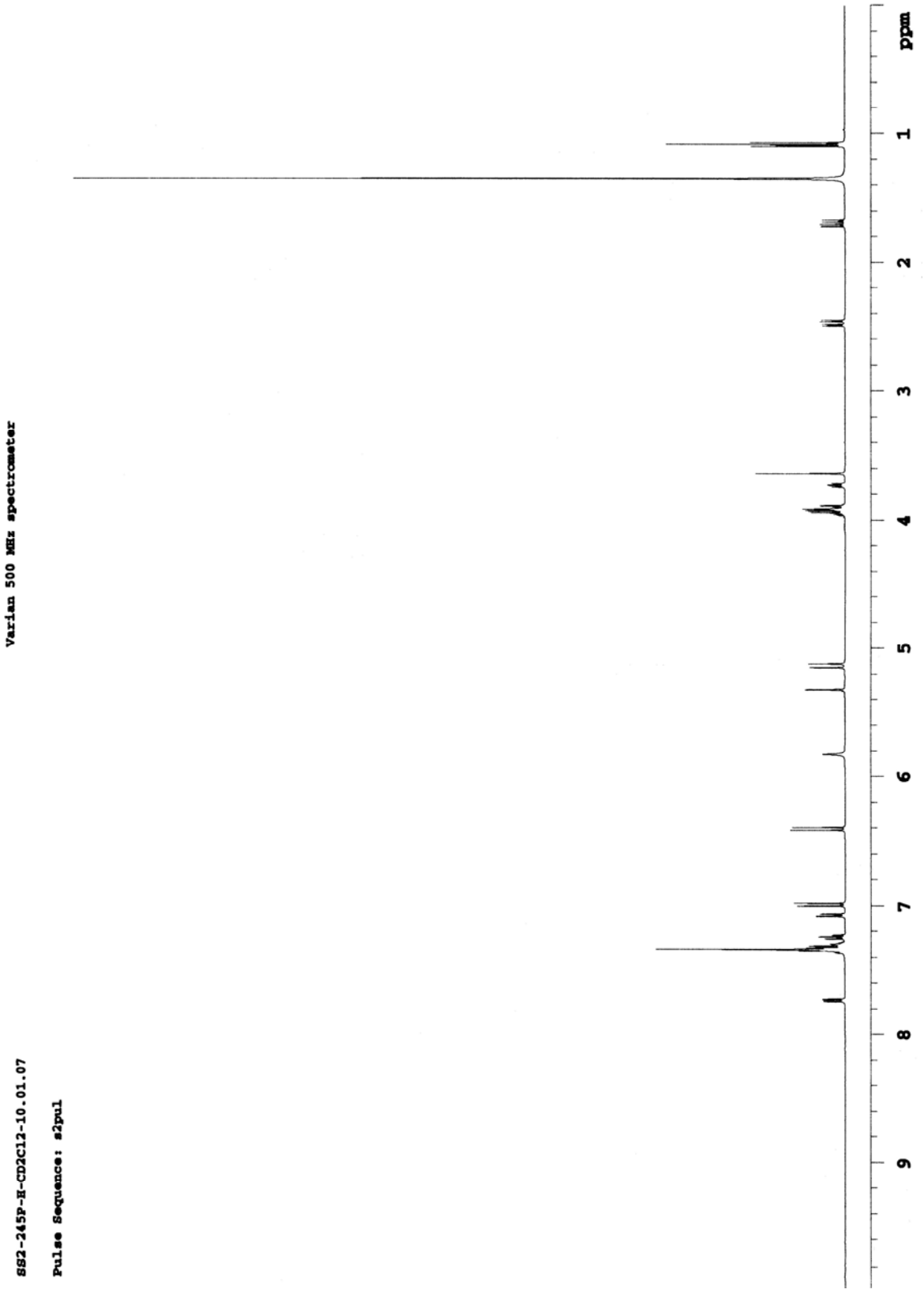
^{1}H-^{1}H GDQFCOSY (Compound 251)



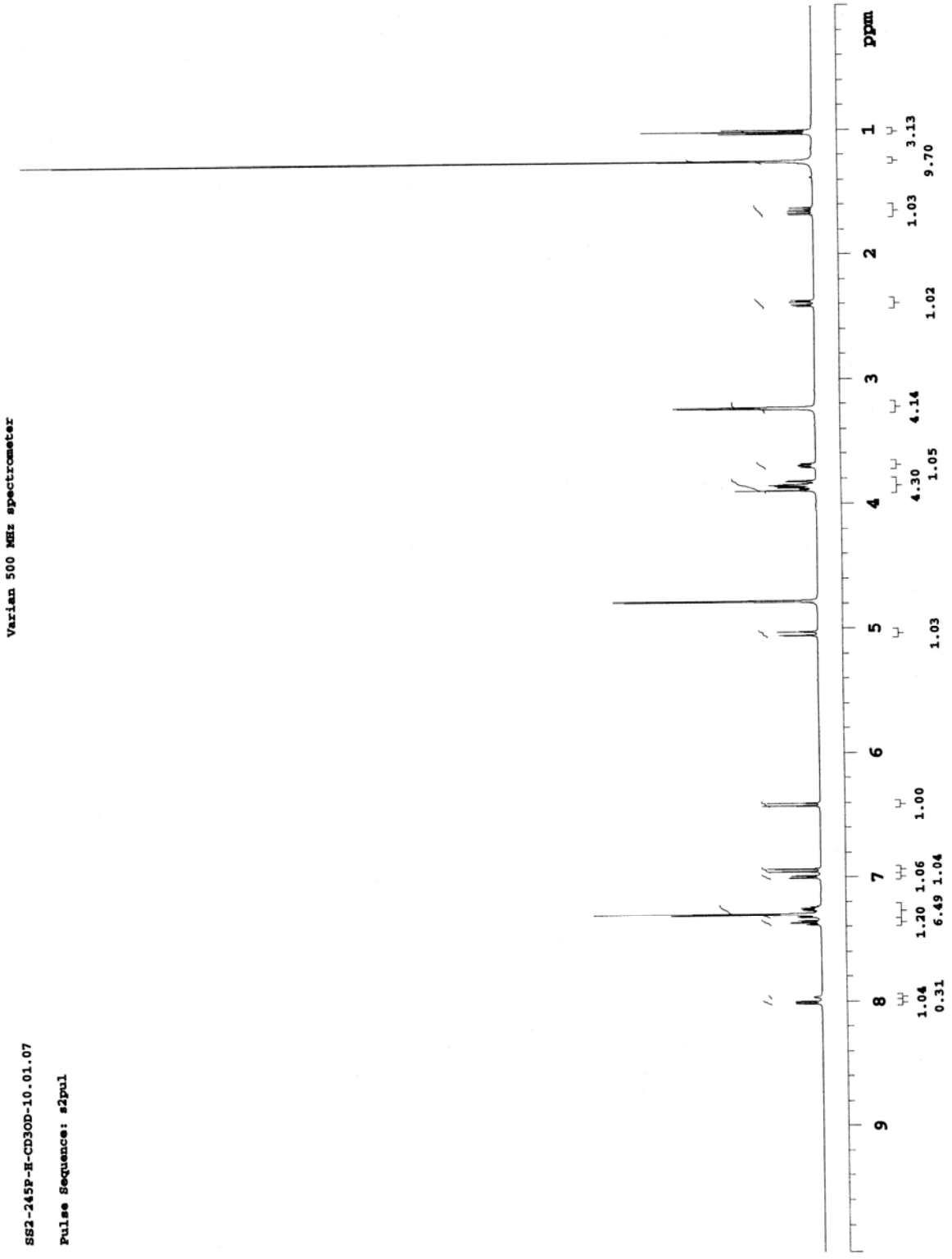
^{1}H NMR ($CDCl_3$, Compound 252)



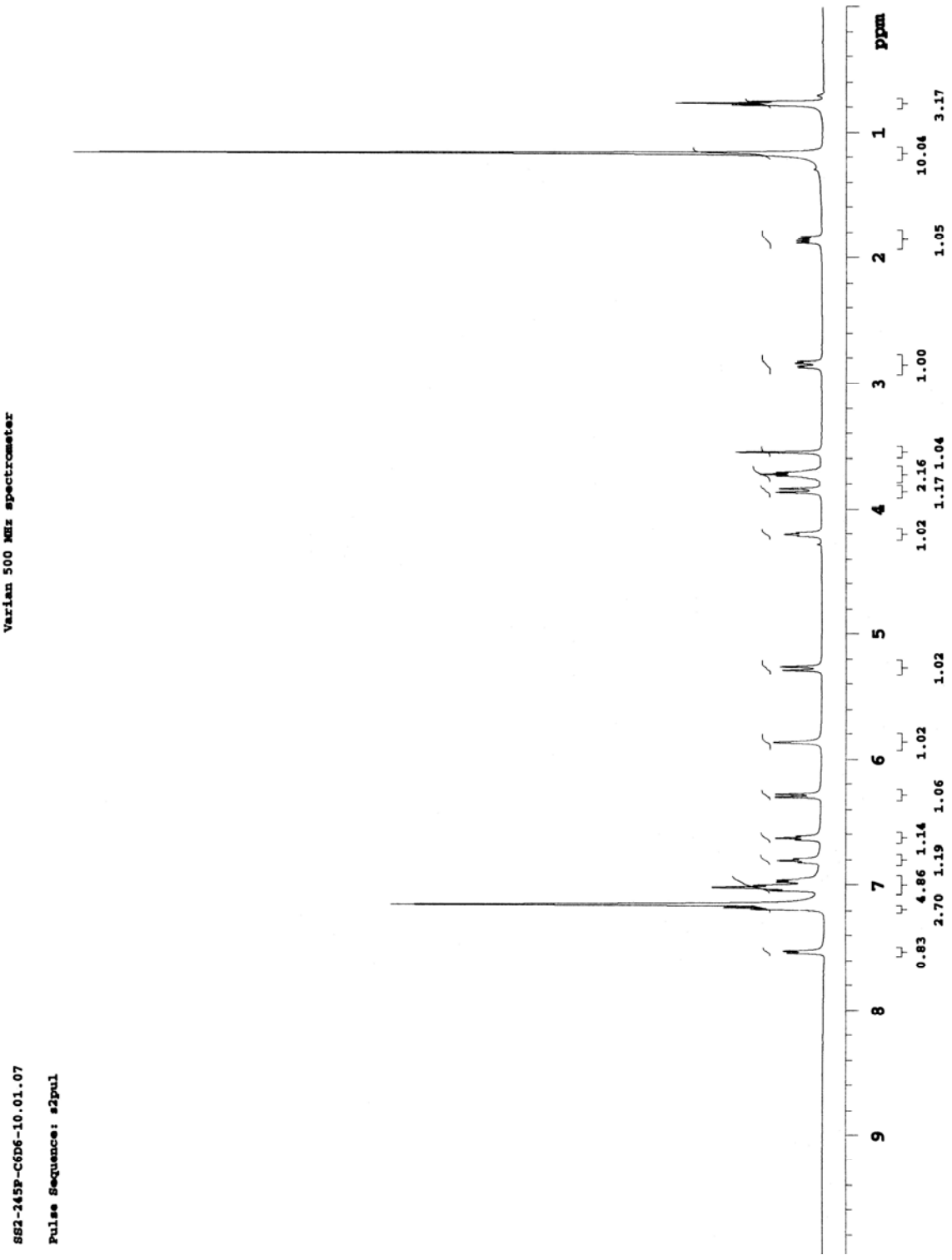
^{1}H NMR (CD_2Cl_2, Compound 252)



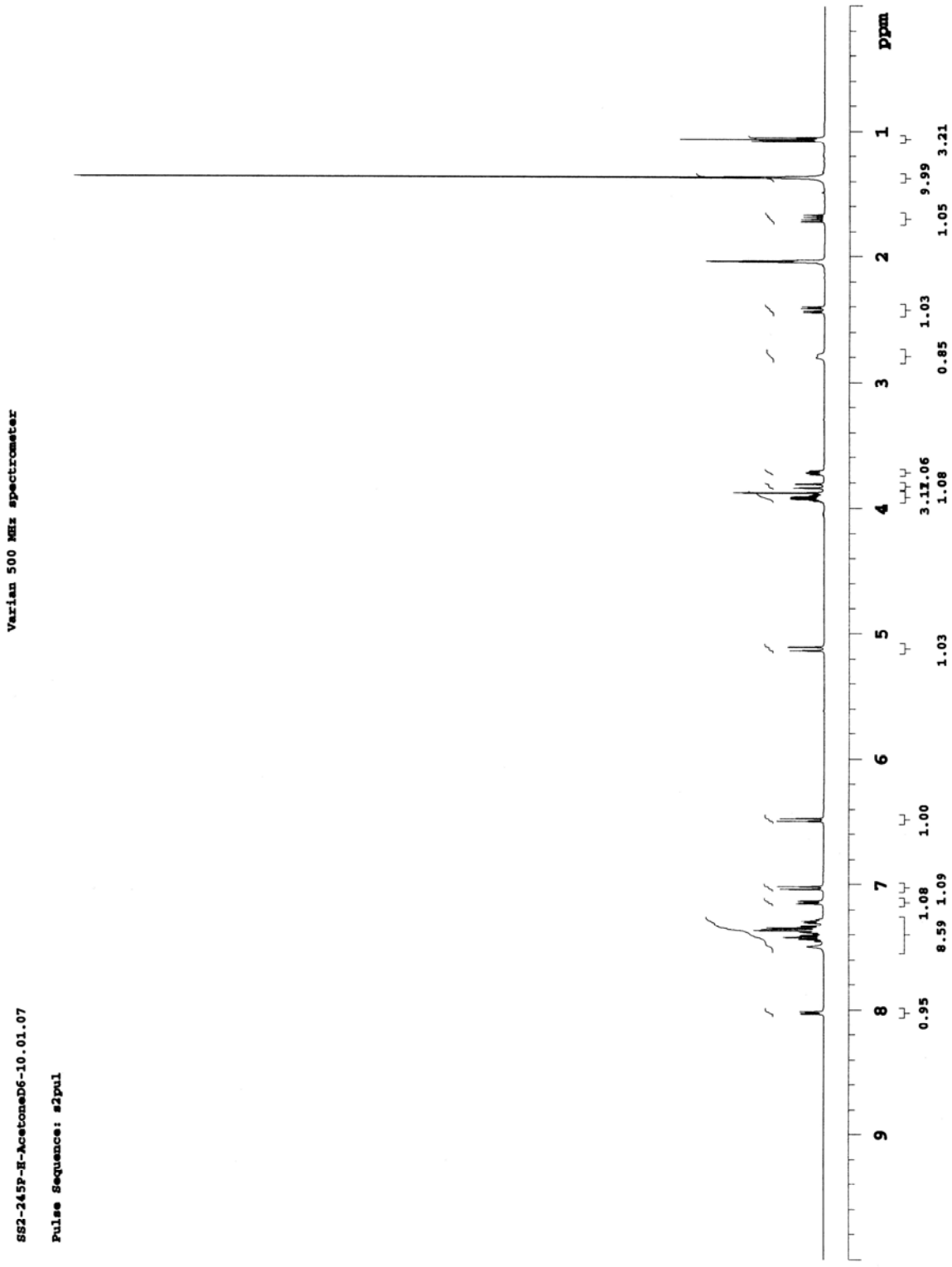
^{1}H NMR (CD_3OD, Compound 252)



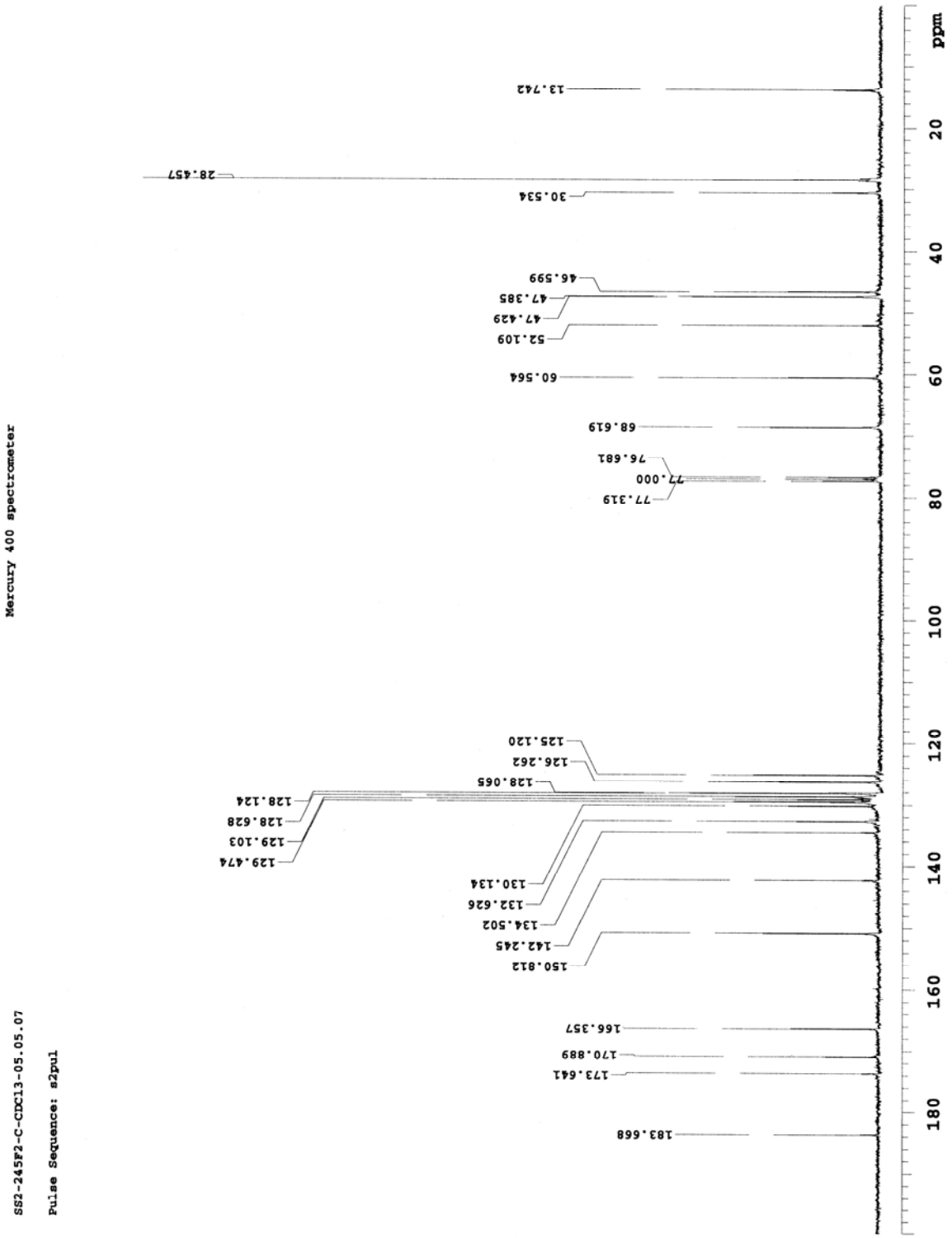
^{1}H NMR (C_6D_6, Compound 252)



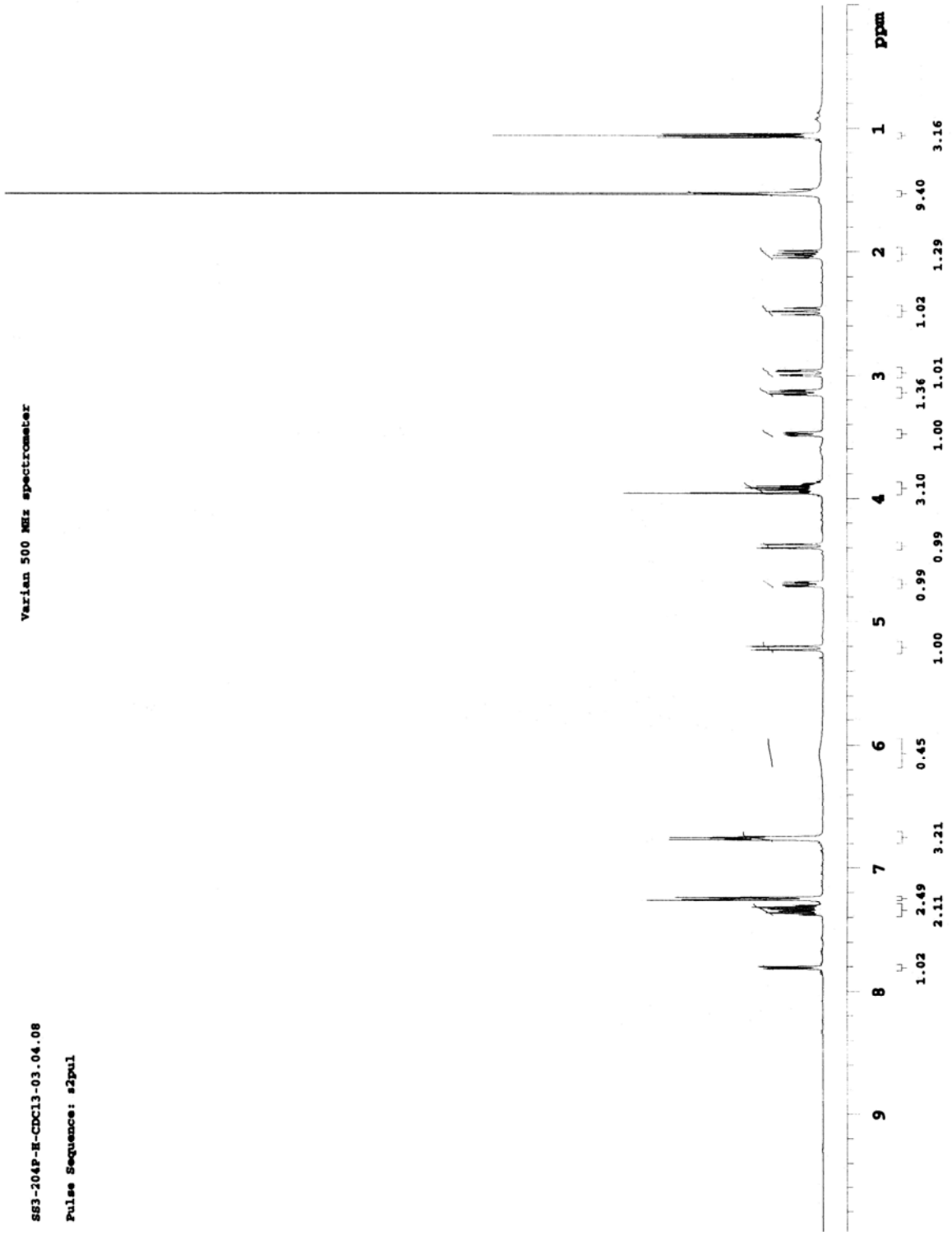
^{1}H NMR ($(CD_3)_2CO$), Compound 252)



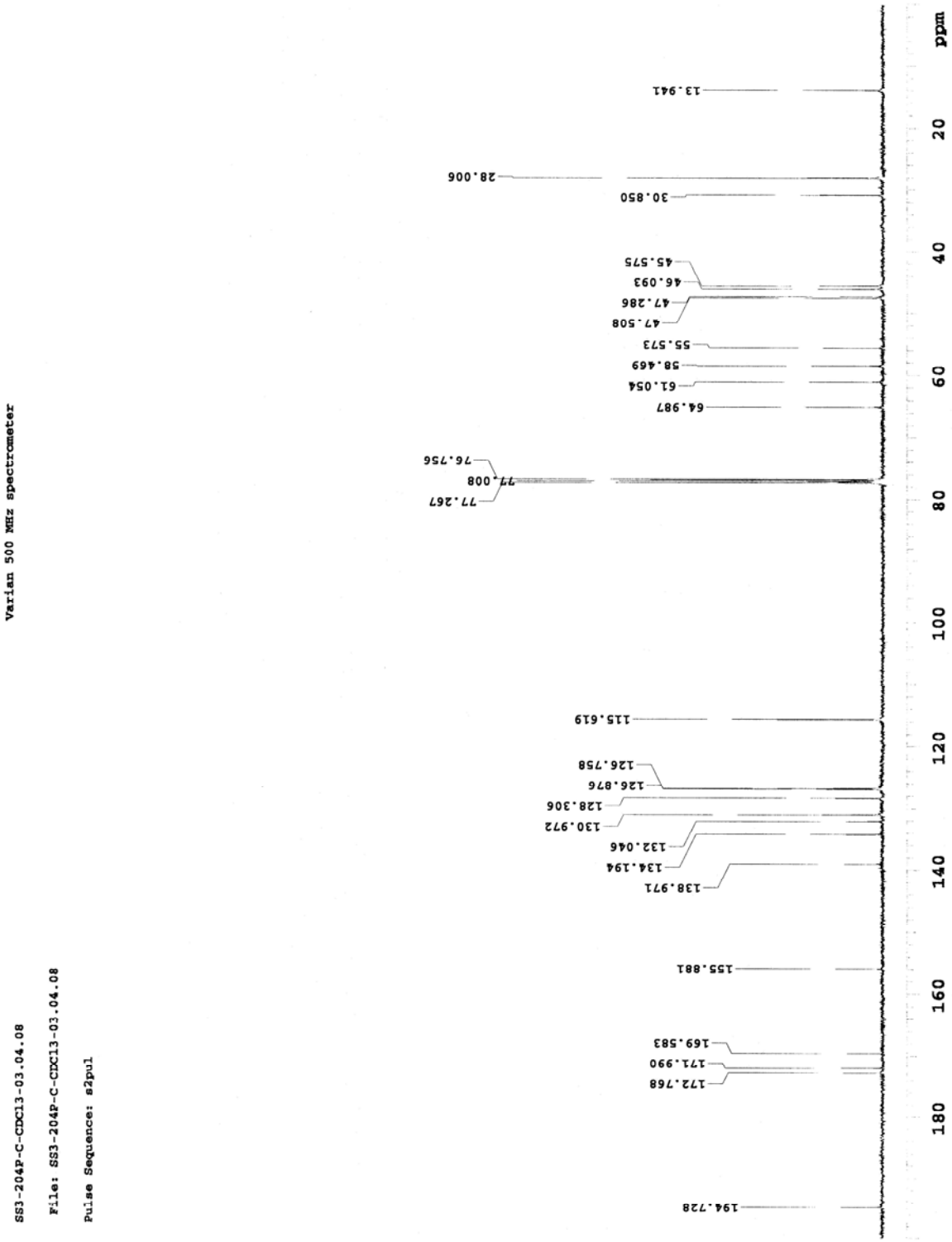
^{13}C NMR (Compound 252)



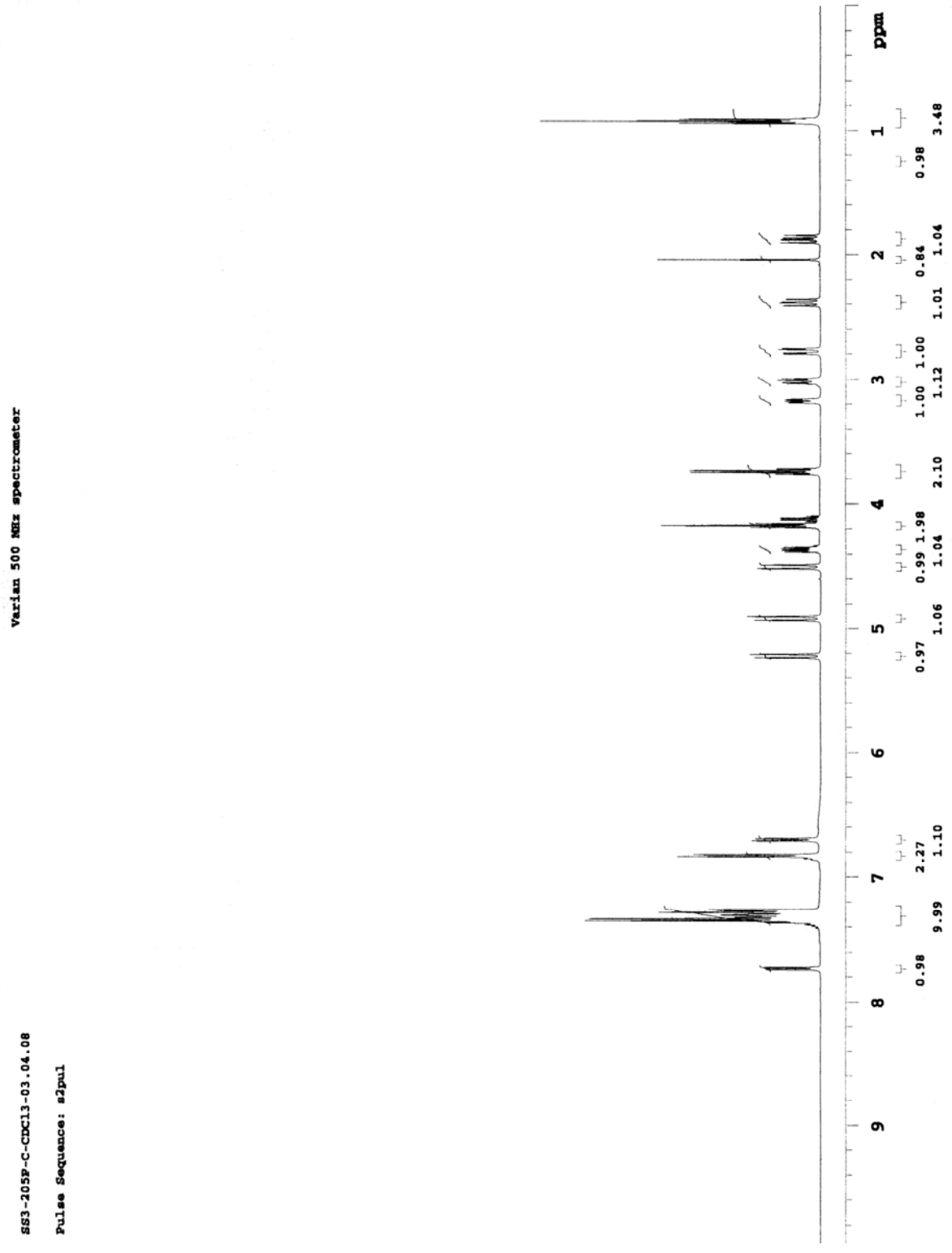
^{1}H NMR (Compound 253)



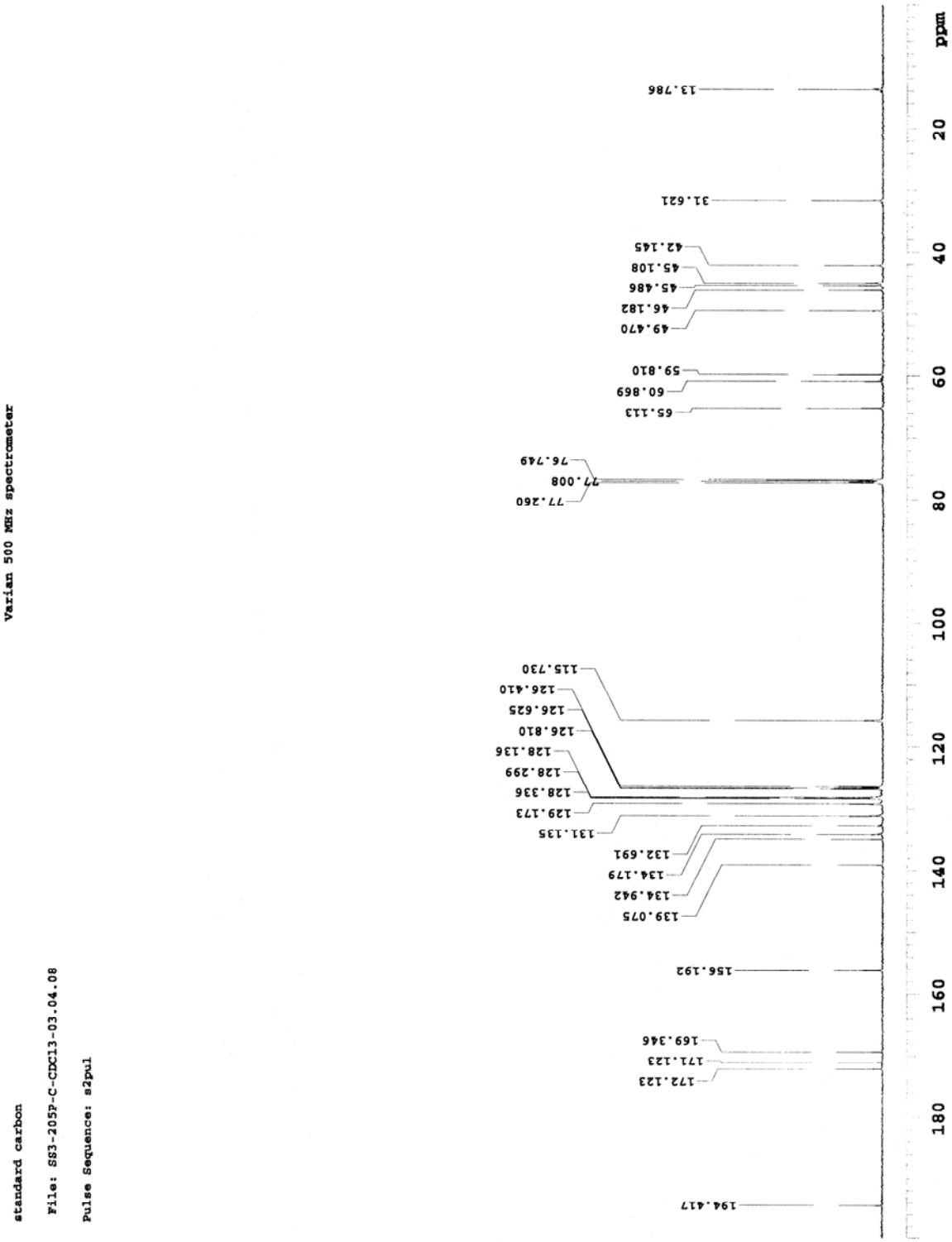
^{13}C NMR (Compound 253)



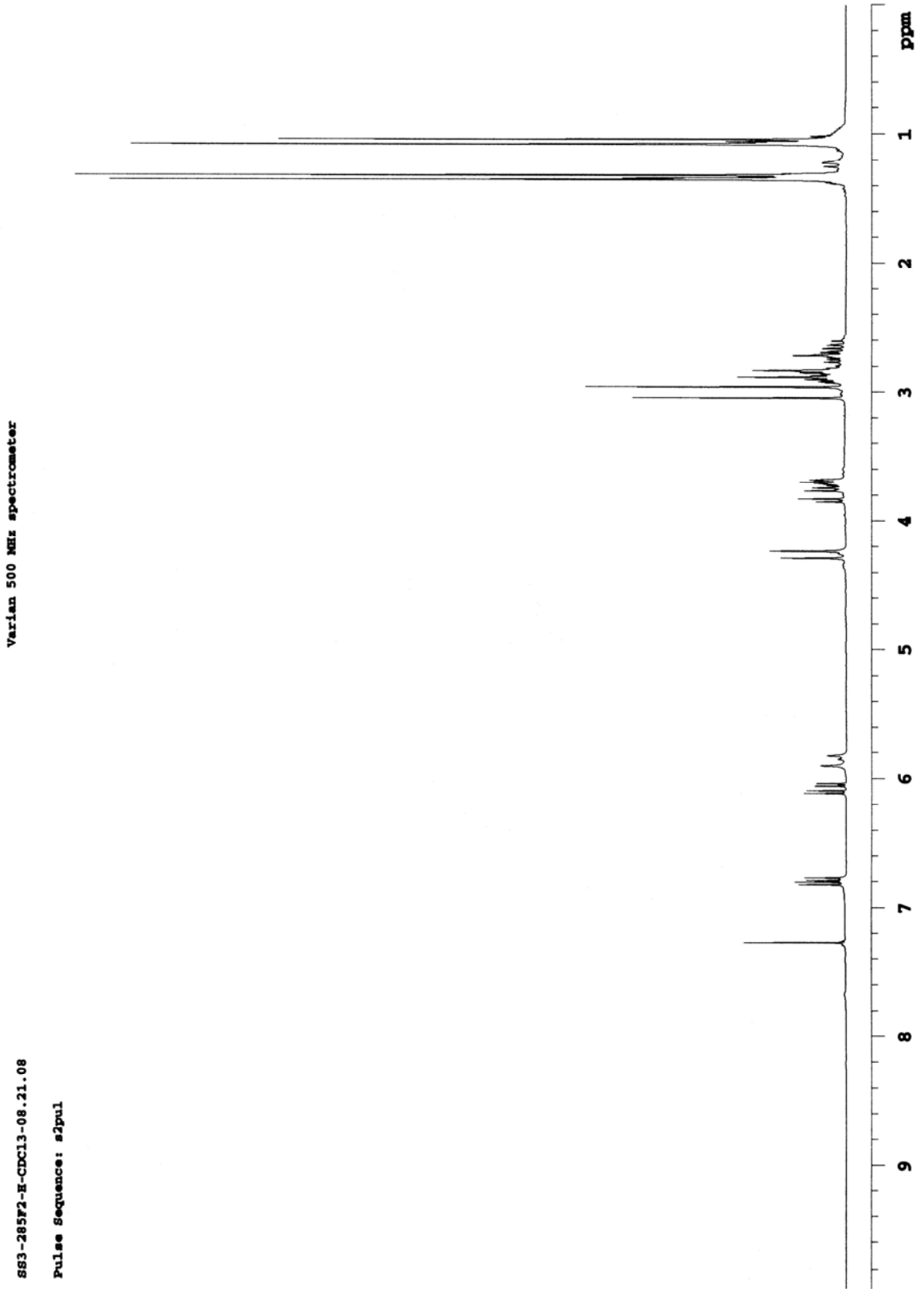
^{1}H NMR (Compound 255)



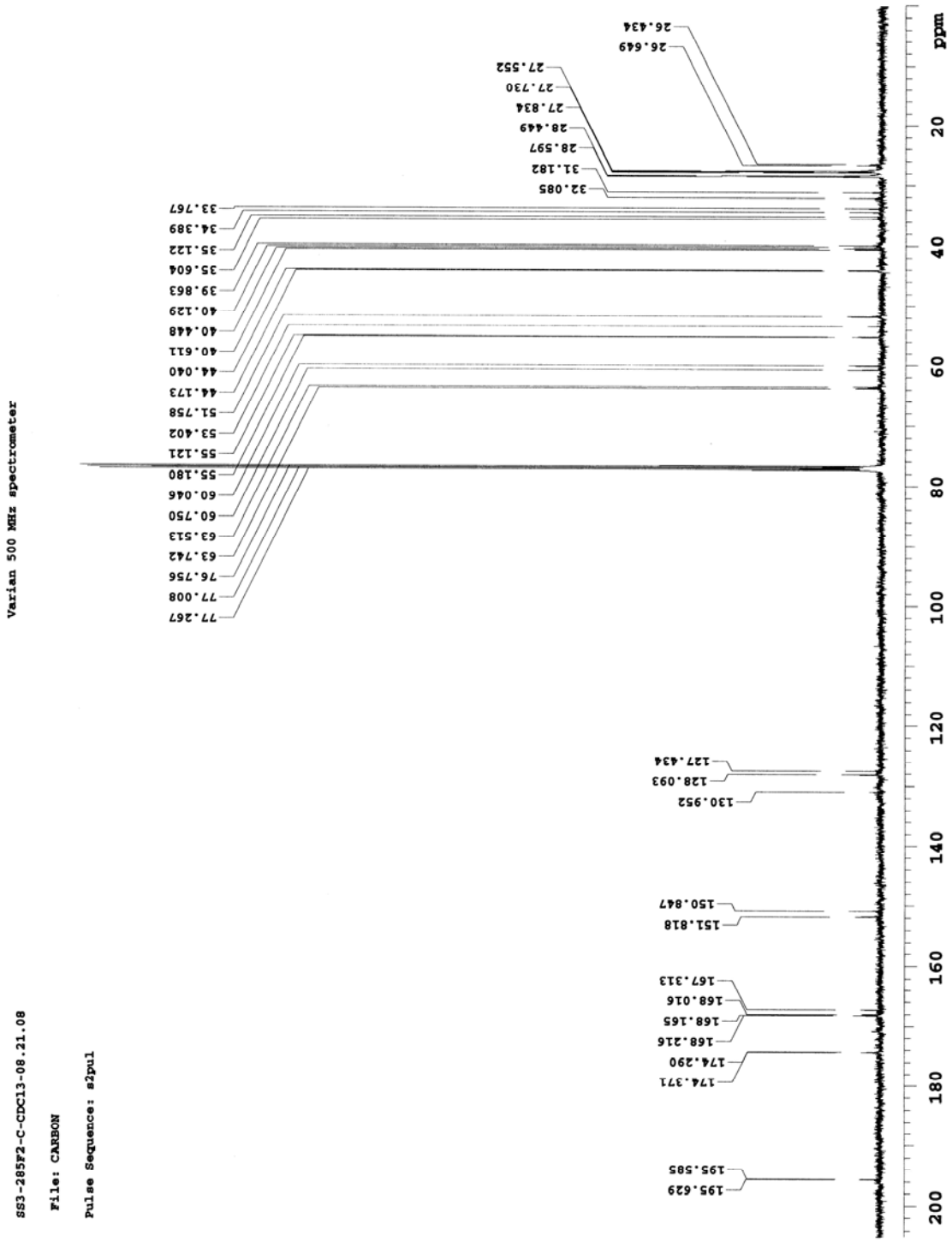
^{13}C NMR (Compound 255)



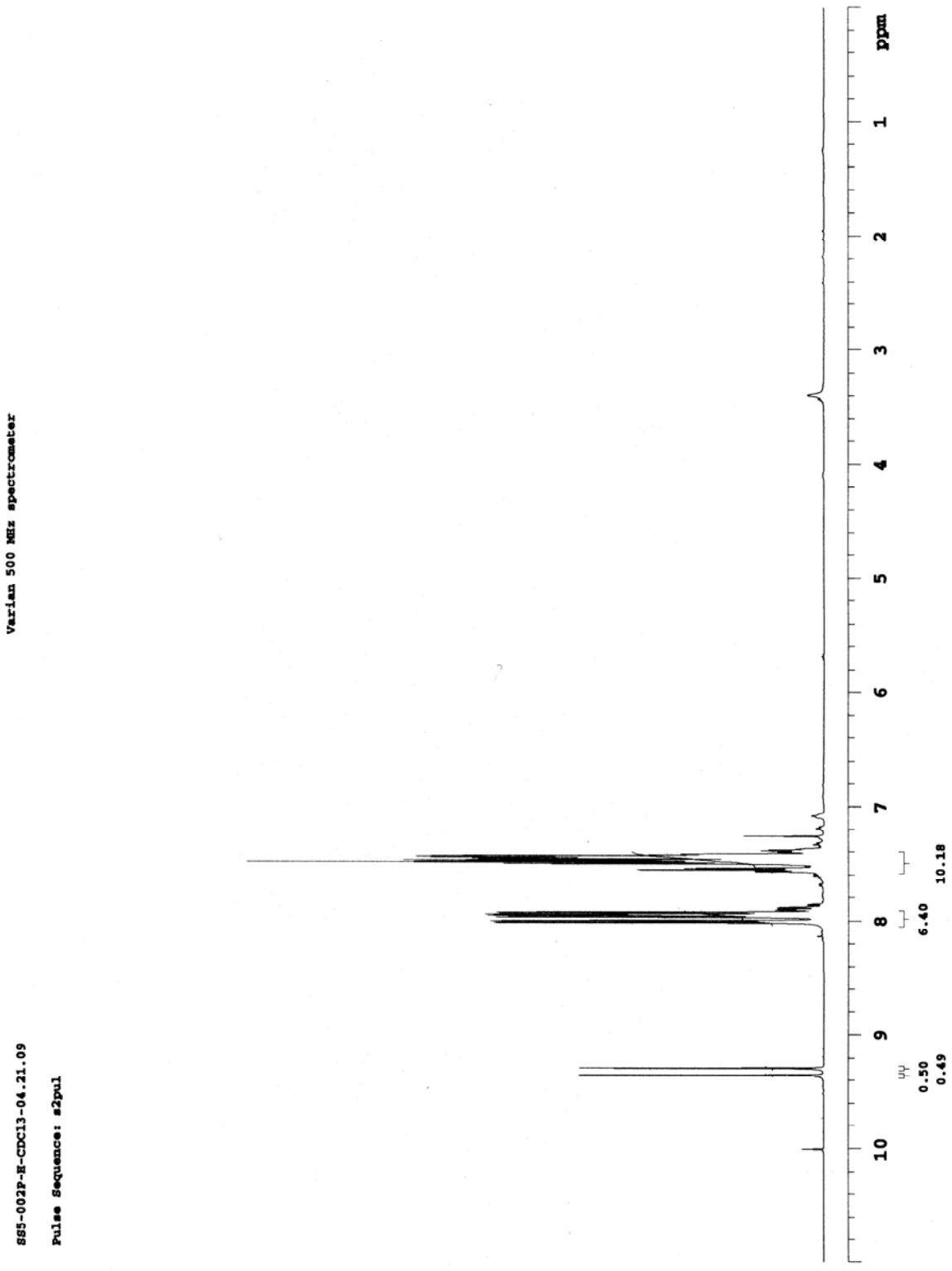
^{1}H NMR (Compound 261, Mixture of Diastereomers)



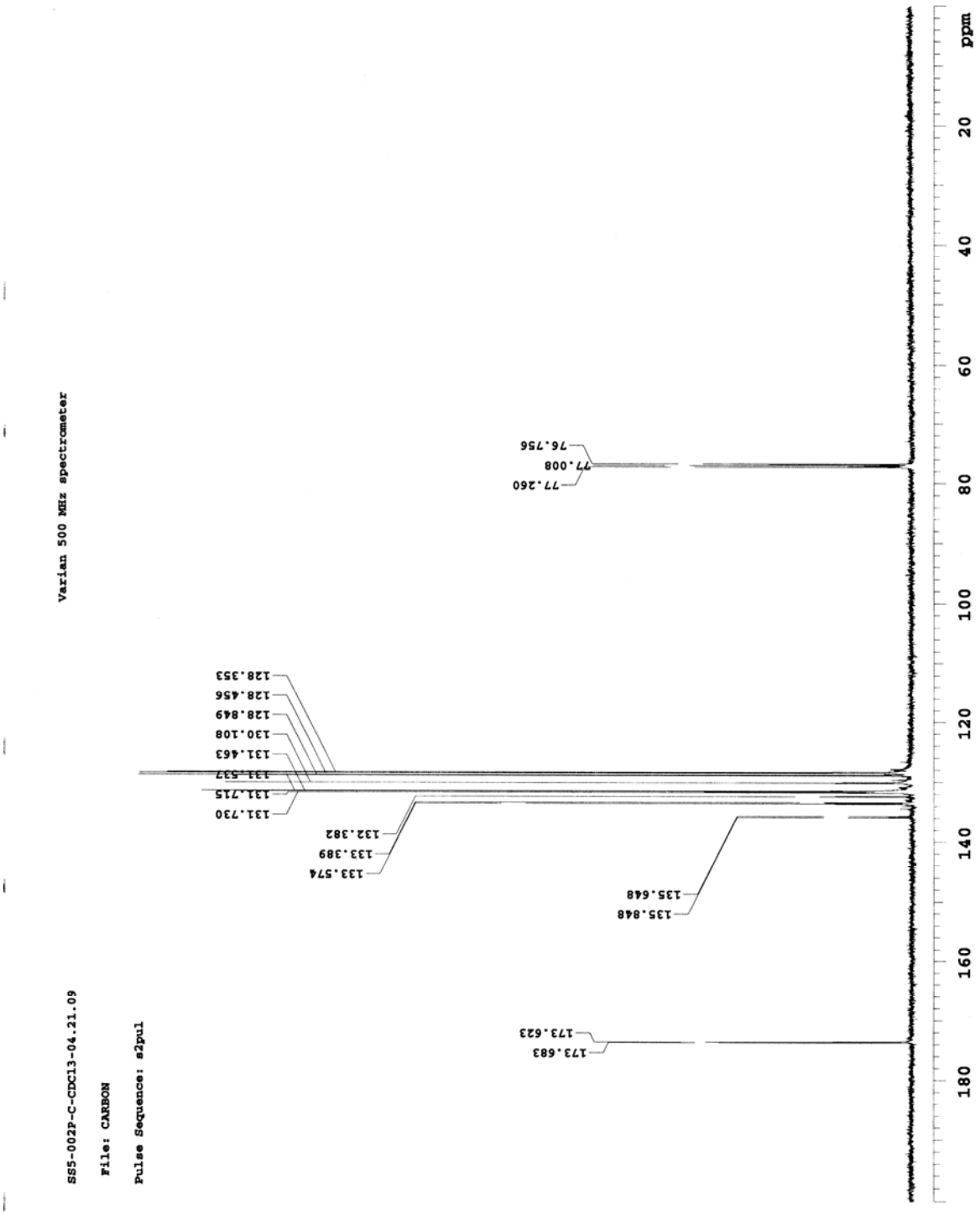
^{13}C NMR (Compound 261, Mixture of Diastereomers))



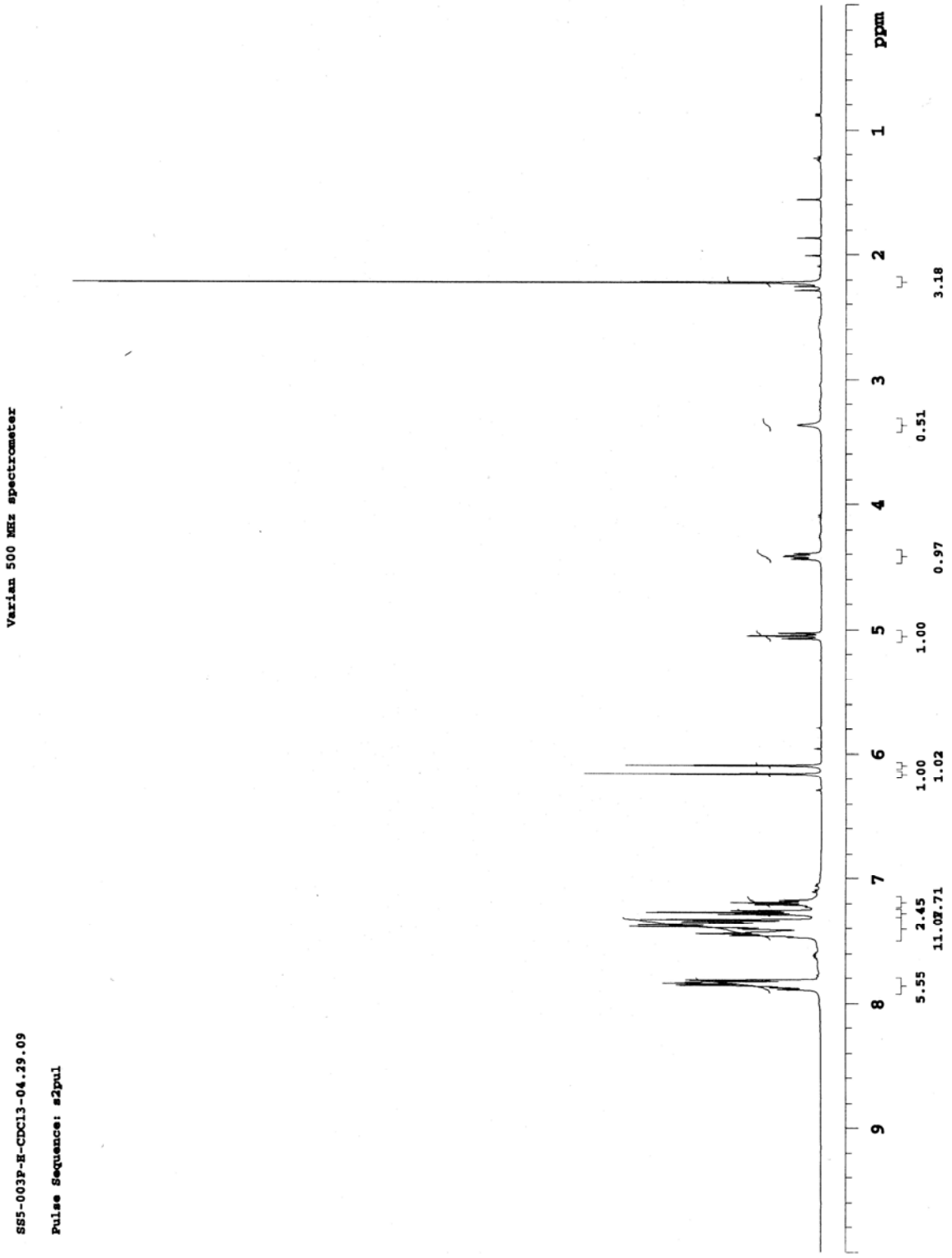
^{1}H NMR (Compound 289)



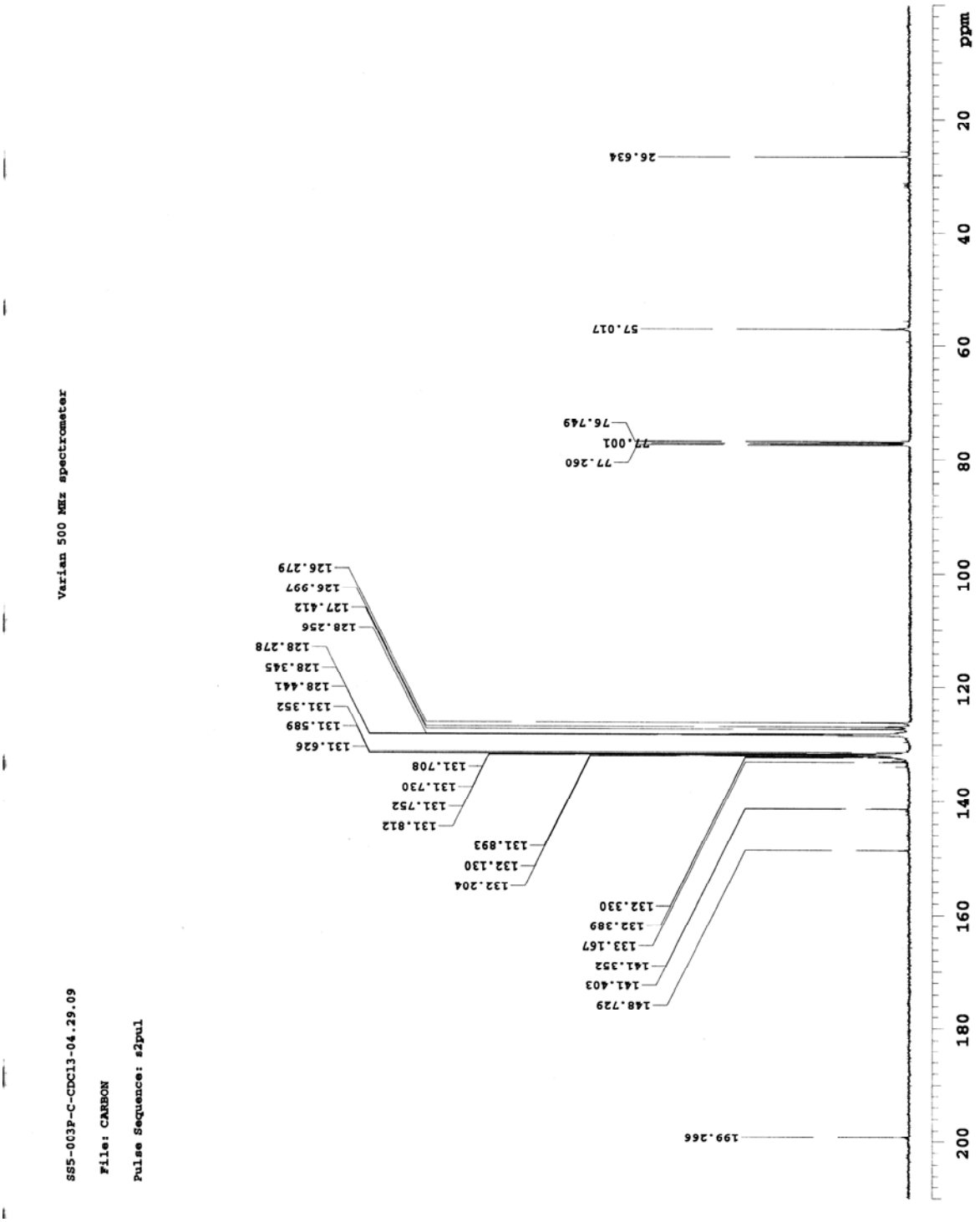
^{13}C NMR (Compound 289)



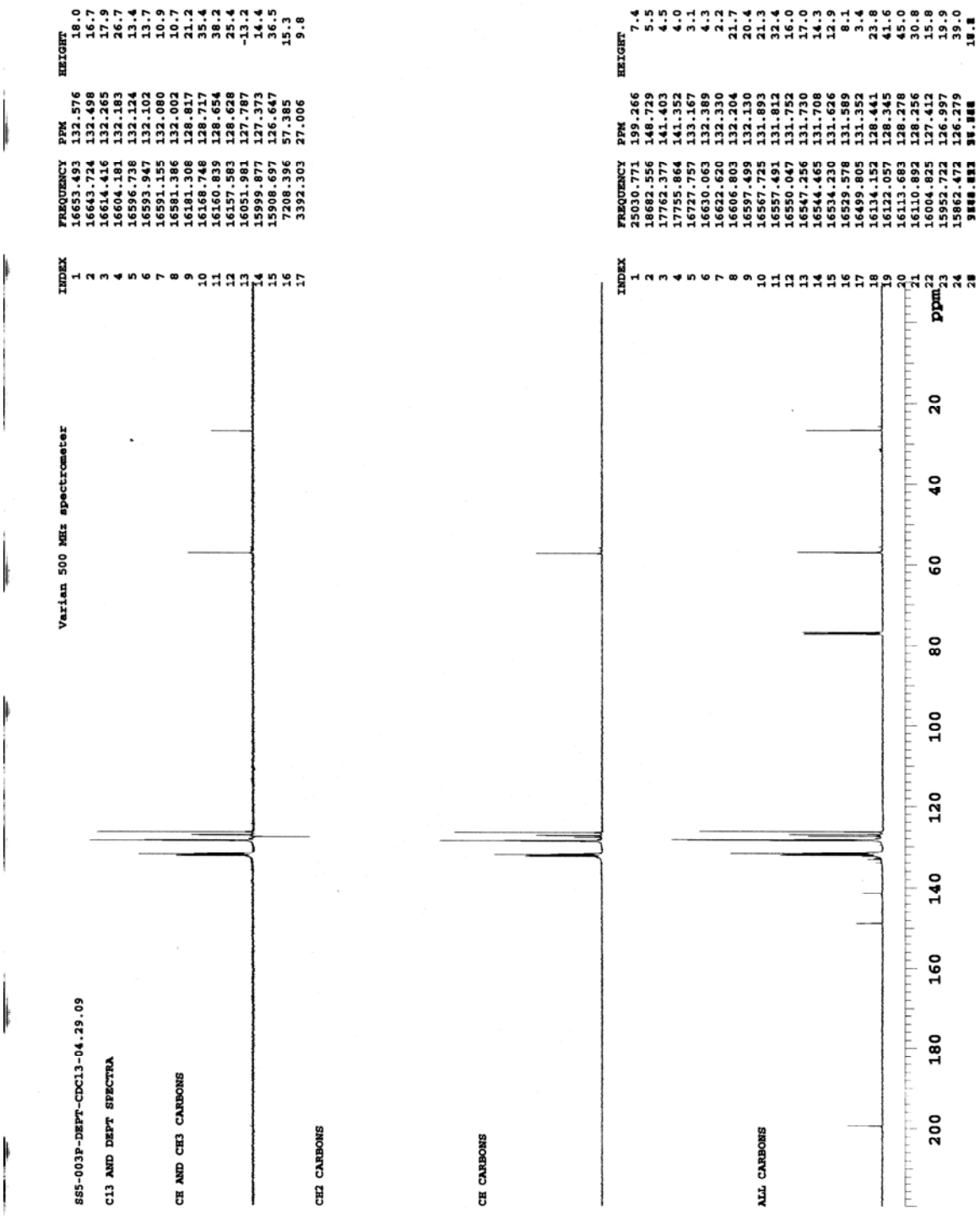
^{1}H NMR (Compound 291)



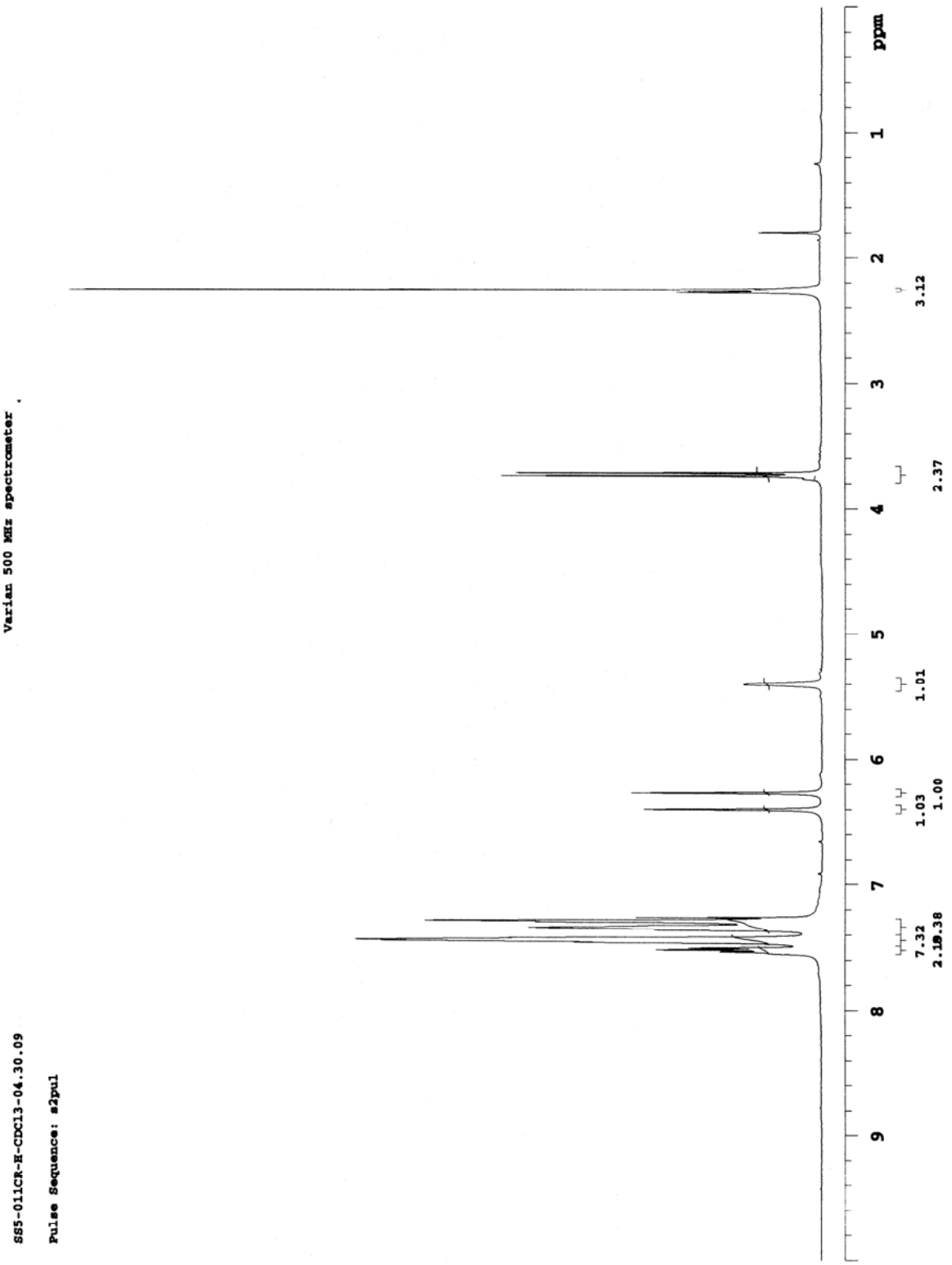
^{13}C NMR (Compound 291)



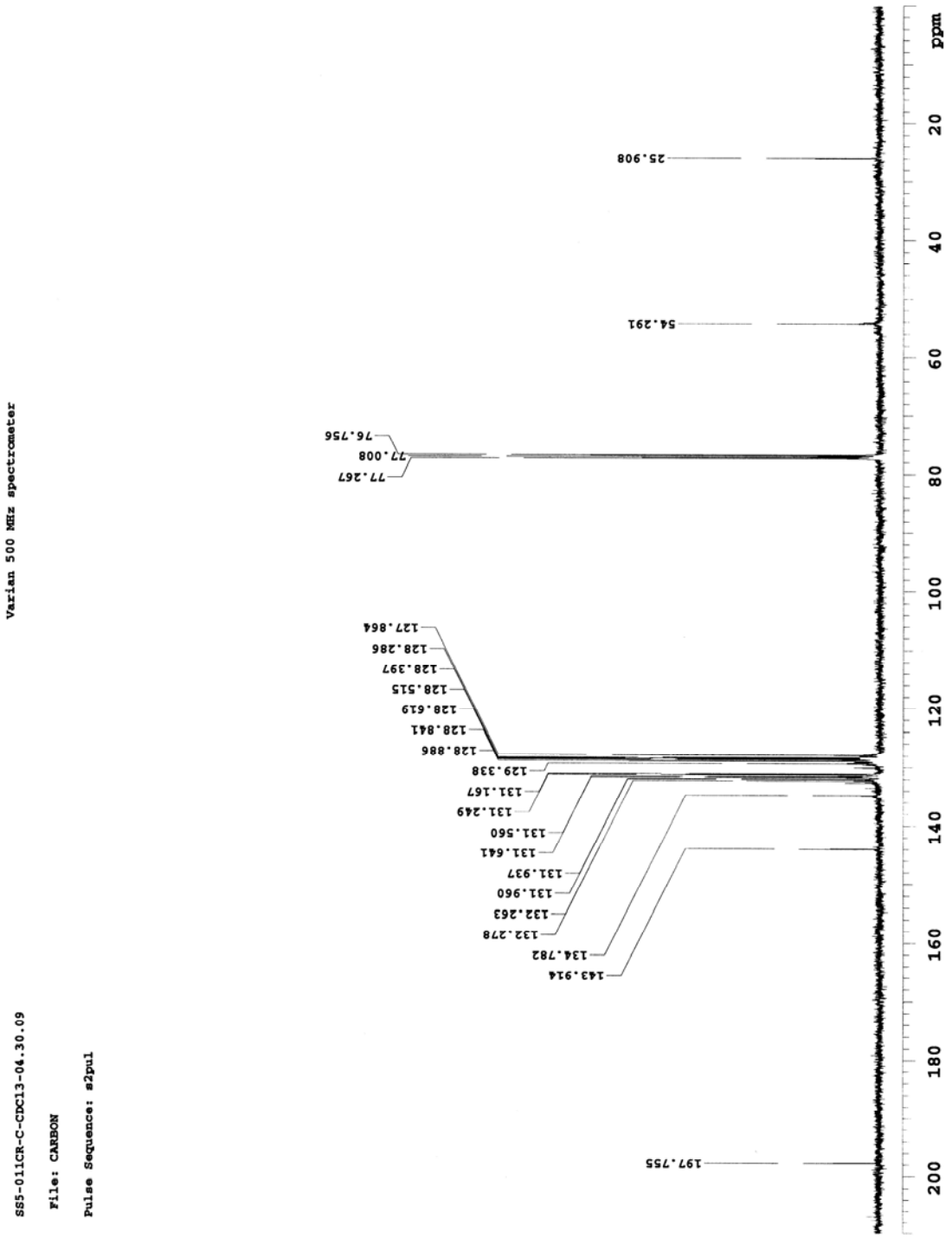
DEPT NMR (Compound 291)



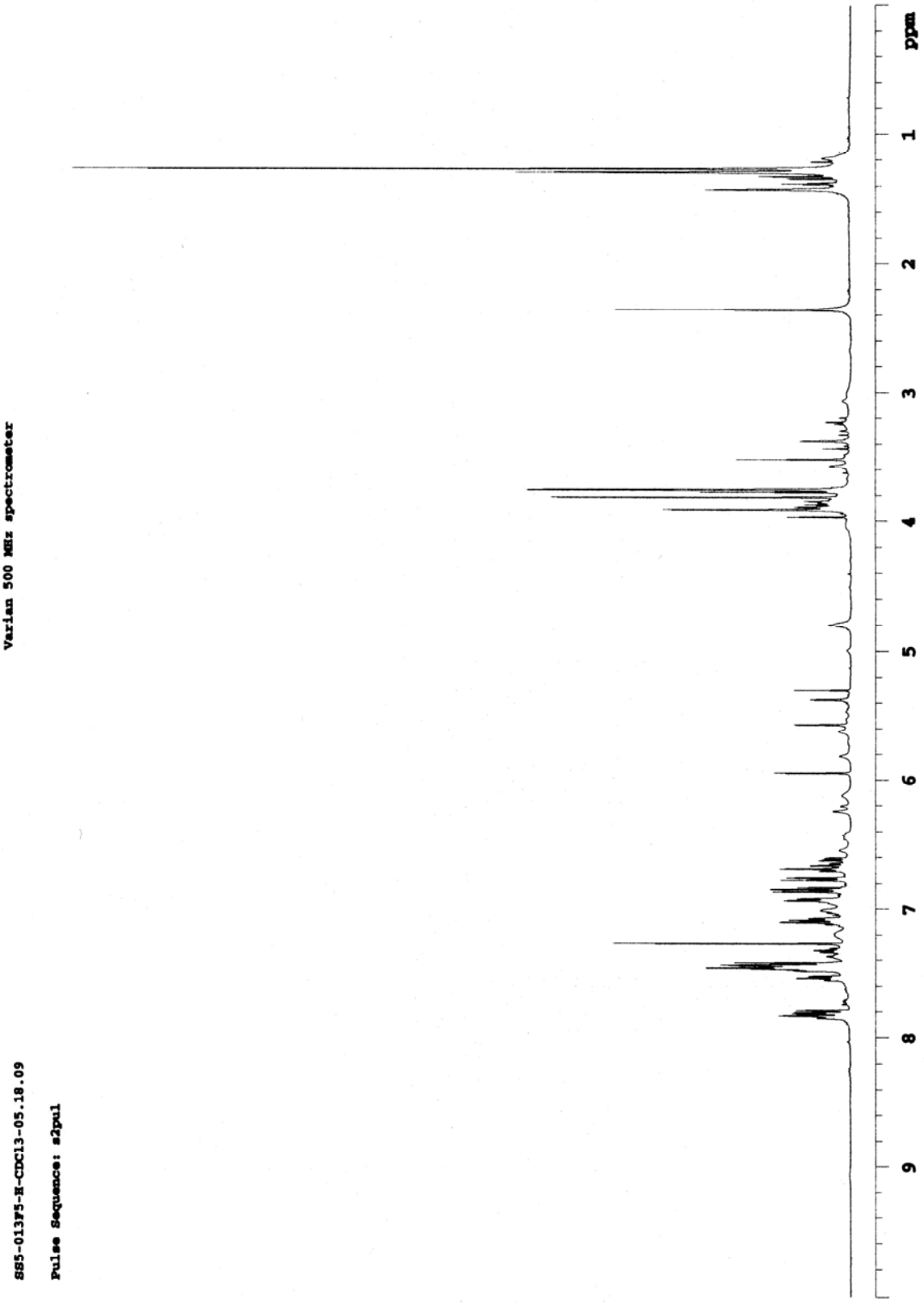
^{1}H NMR (Compound 1y)



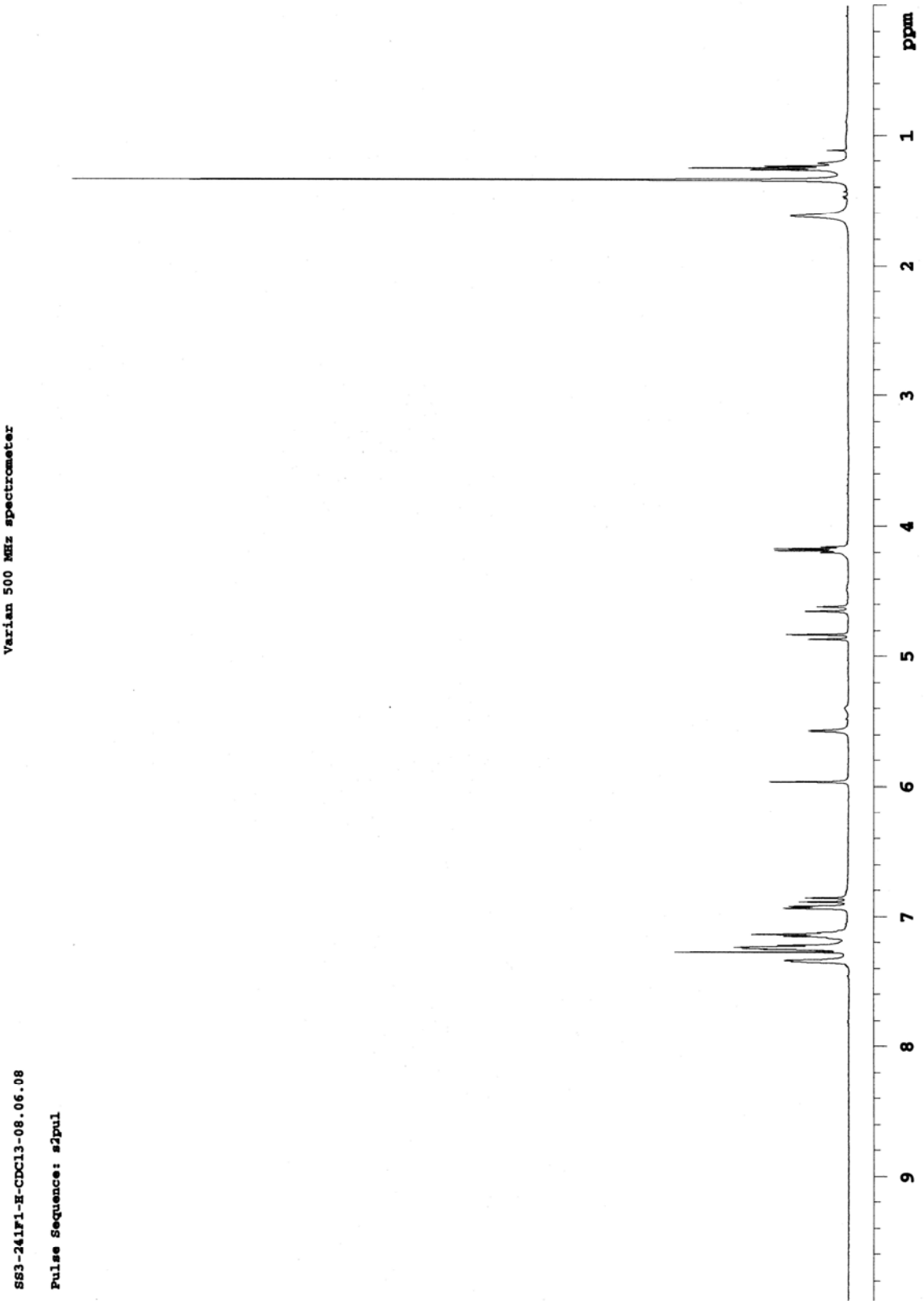
^{13}C NMR (Compound 1y)



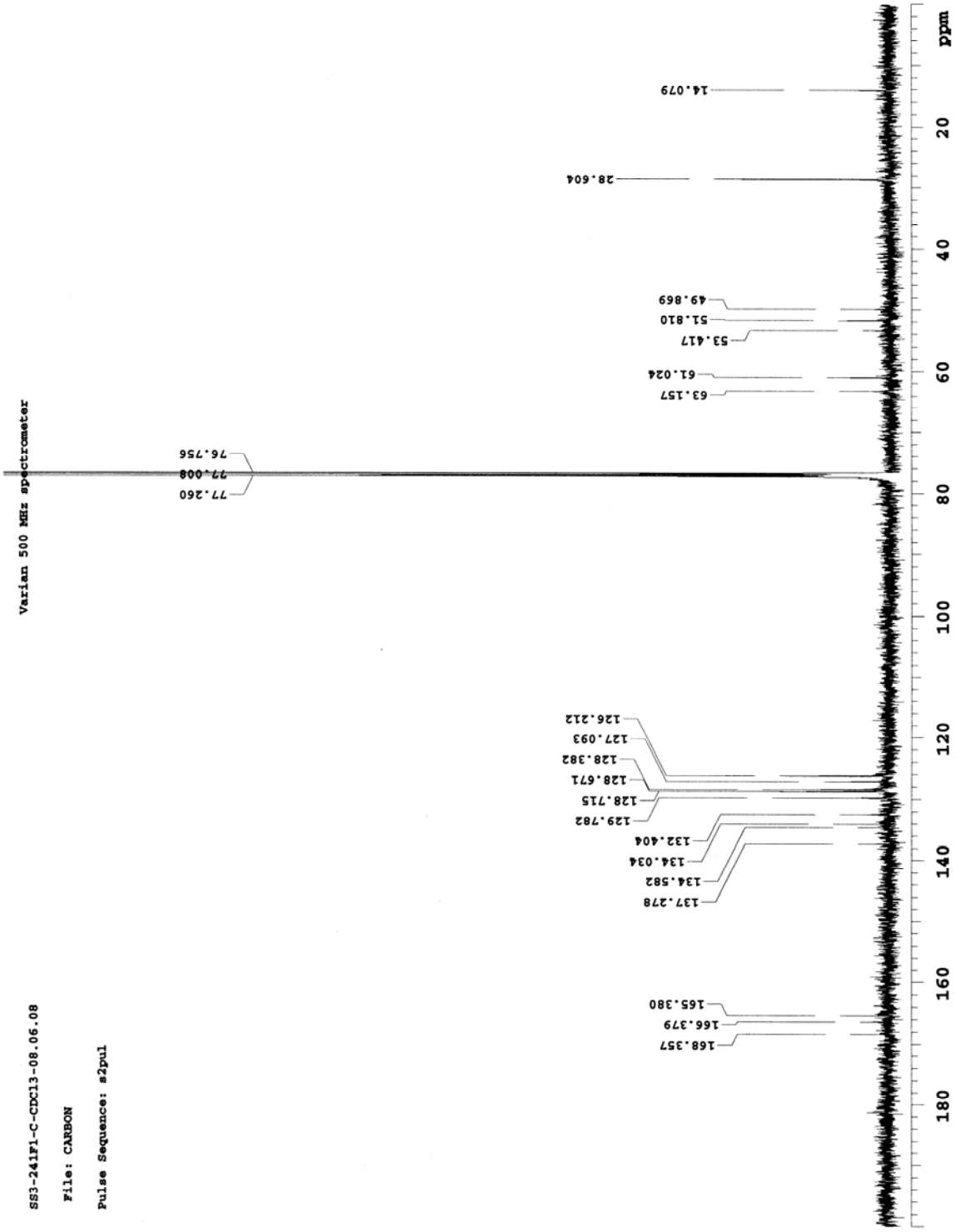
^{1}H NMR (Compound 292)



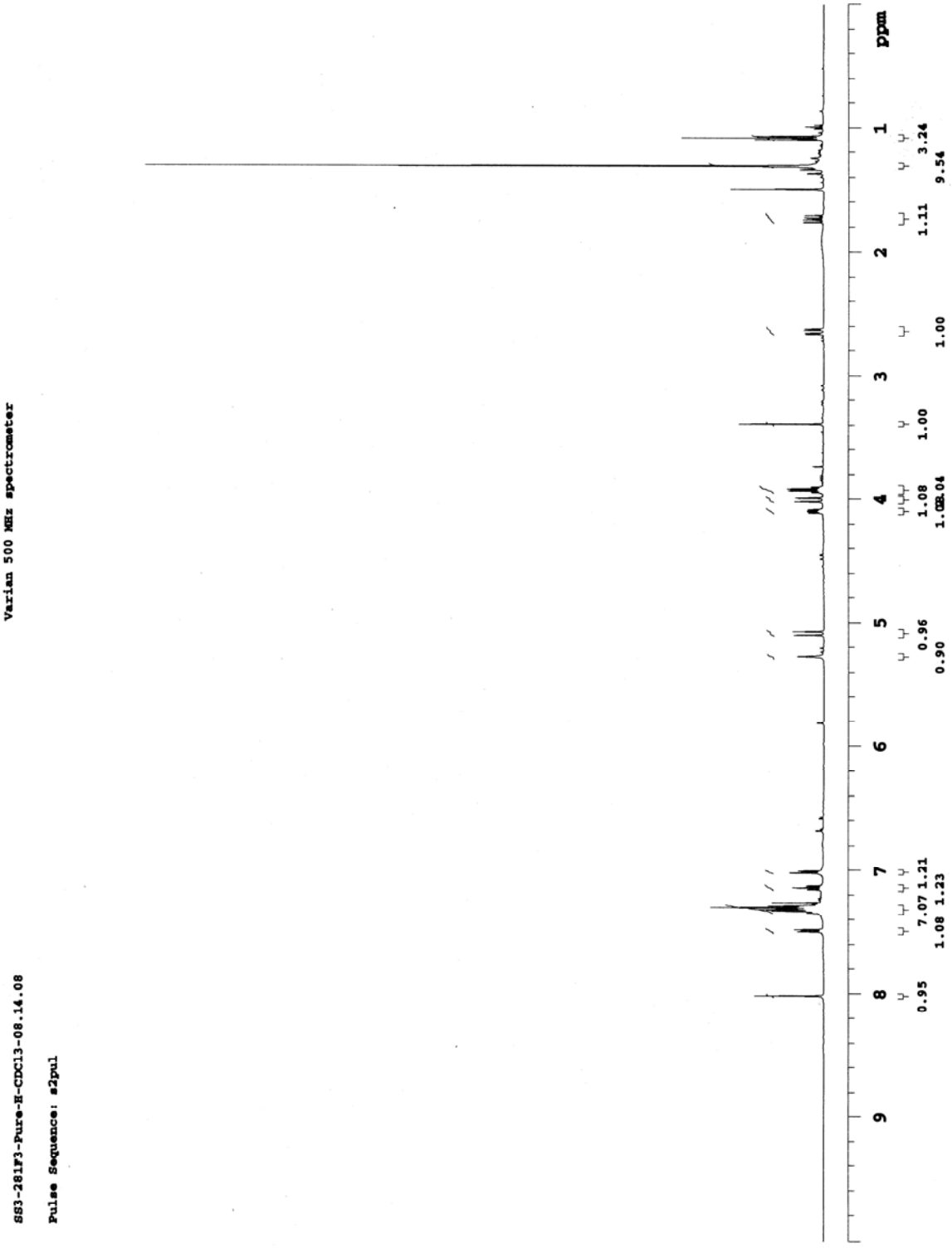
^{1}H NMR (Compound 338)



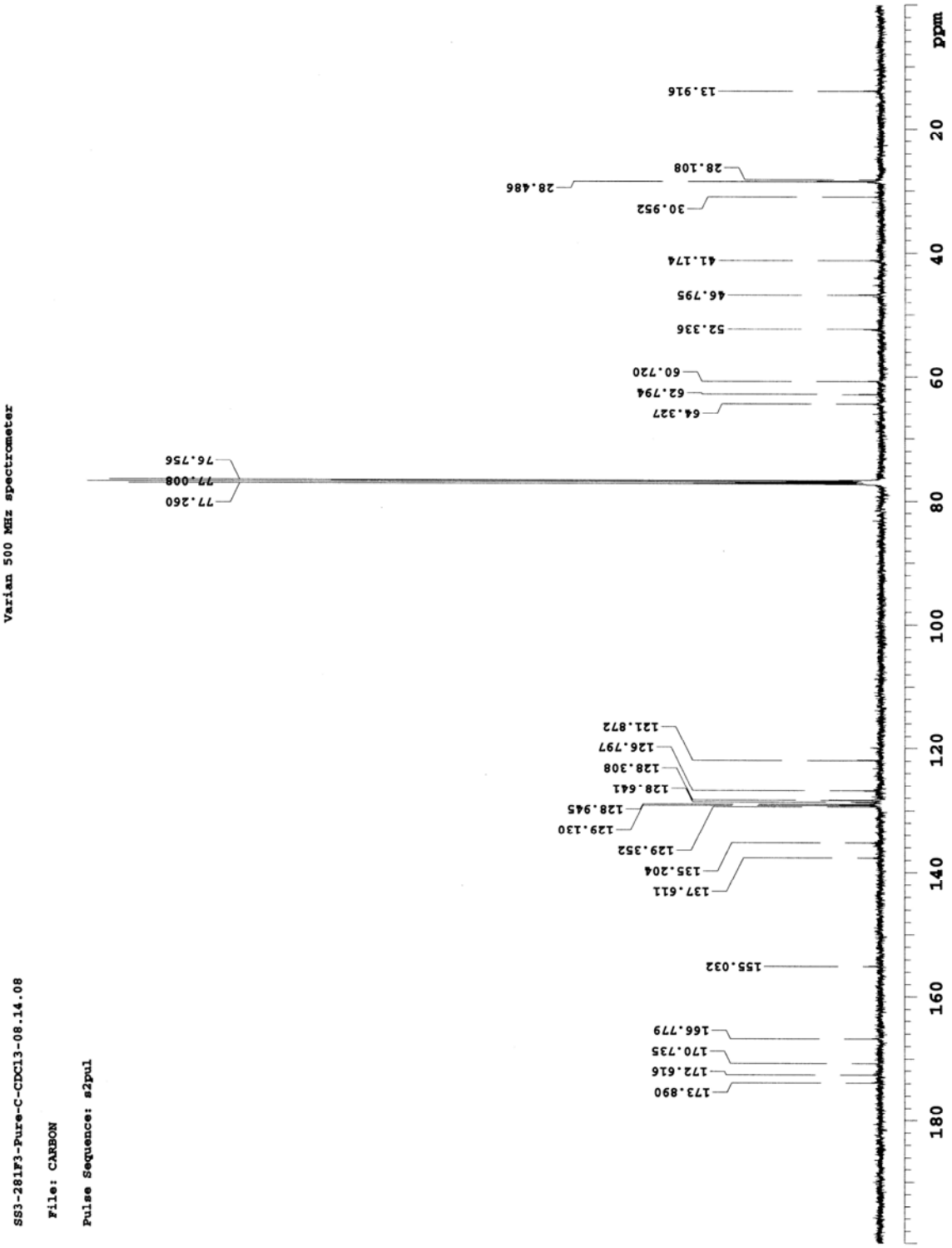
^{13}C NMR (Compound 338)



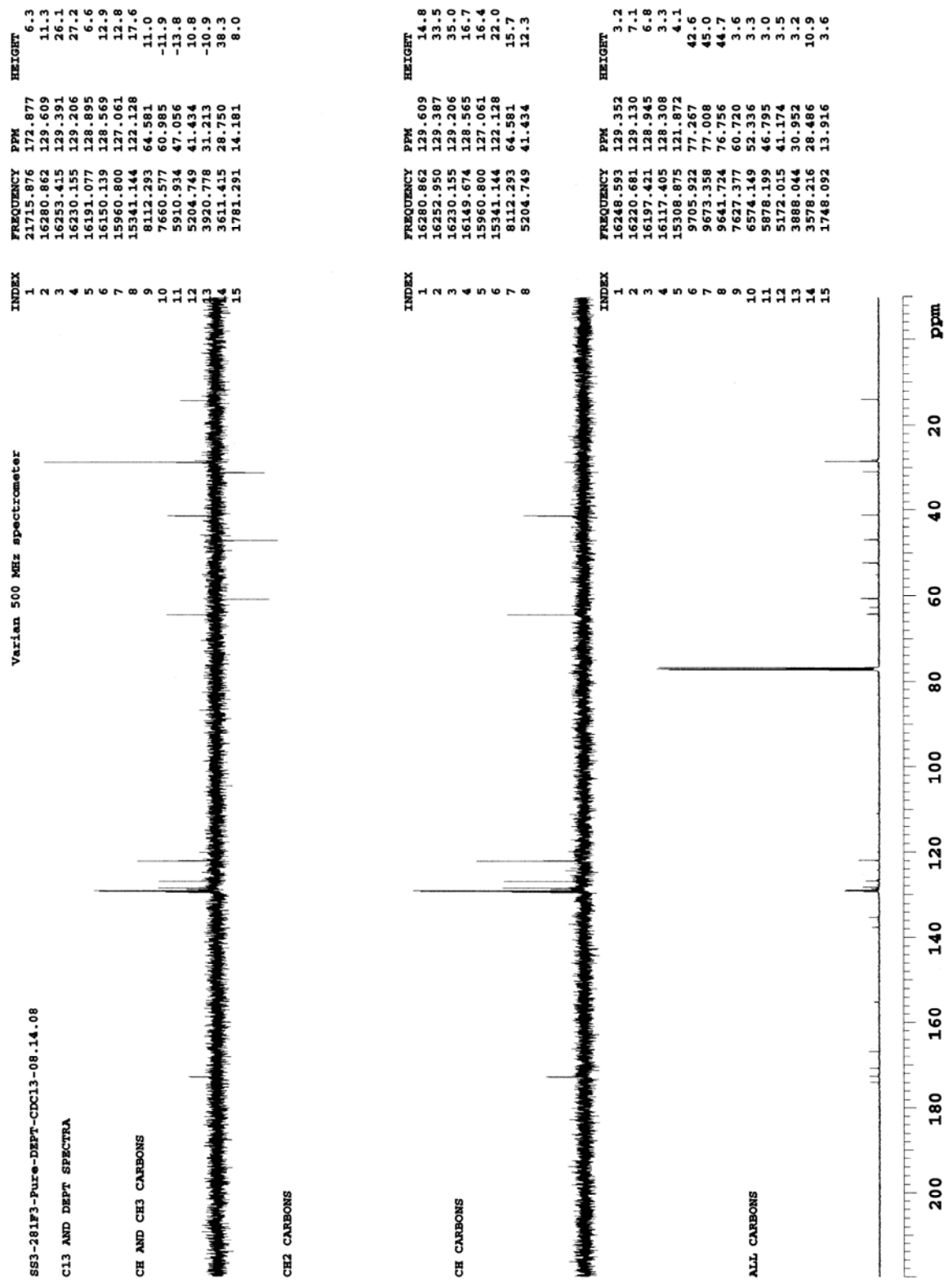
^{1}H NMR (Compound 339)



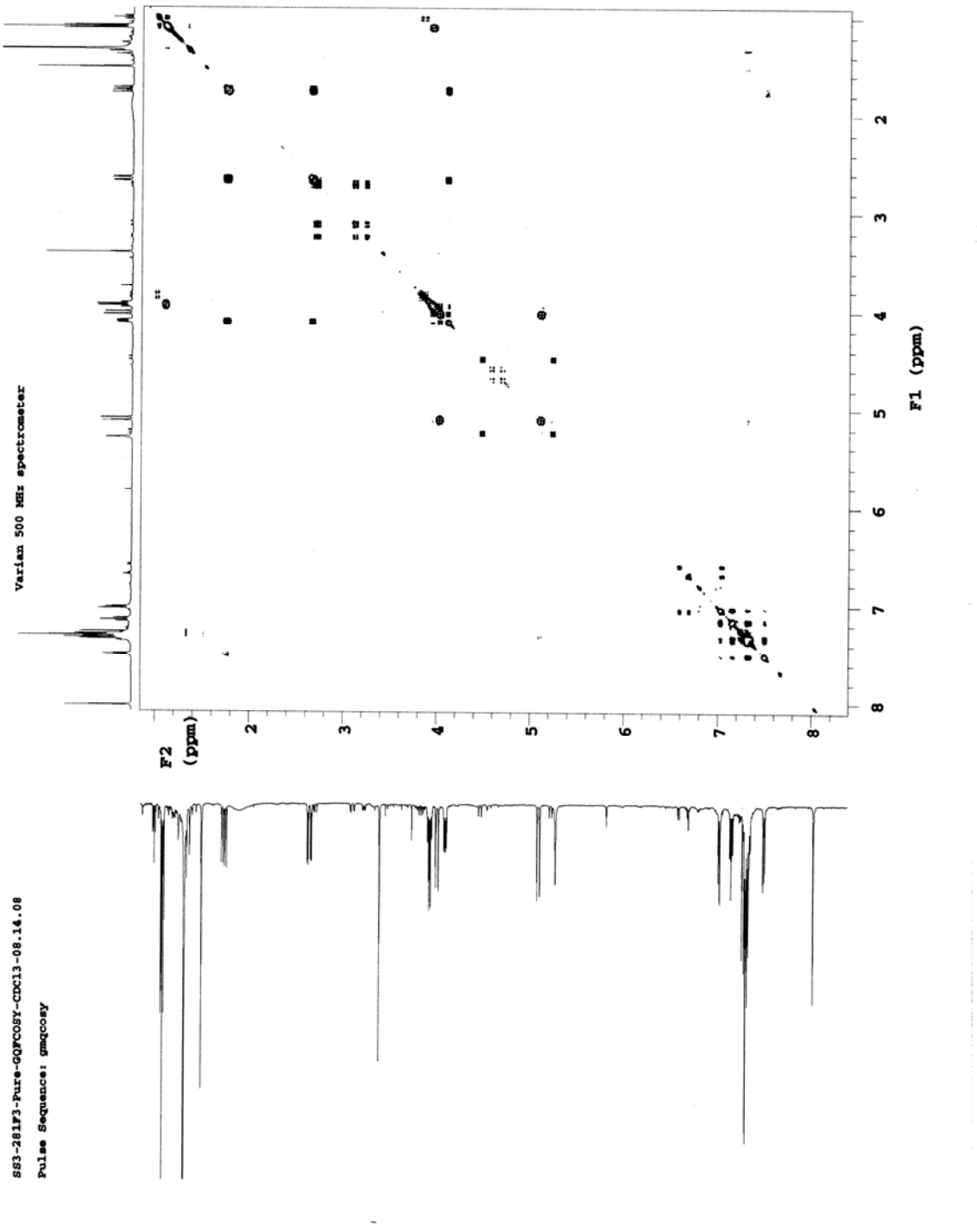
^{13}C NMR (Compound 339)



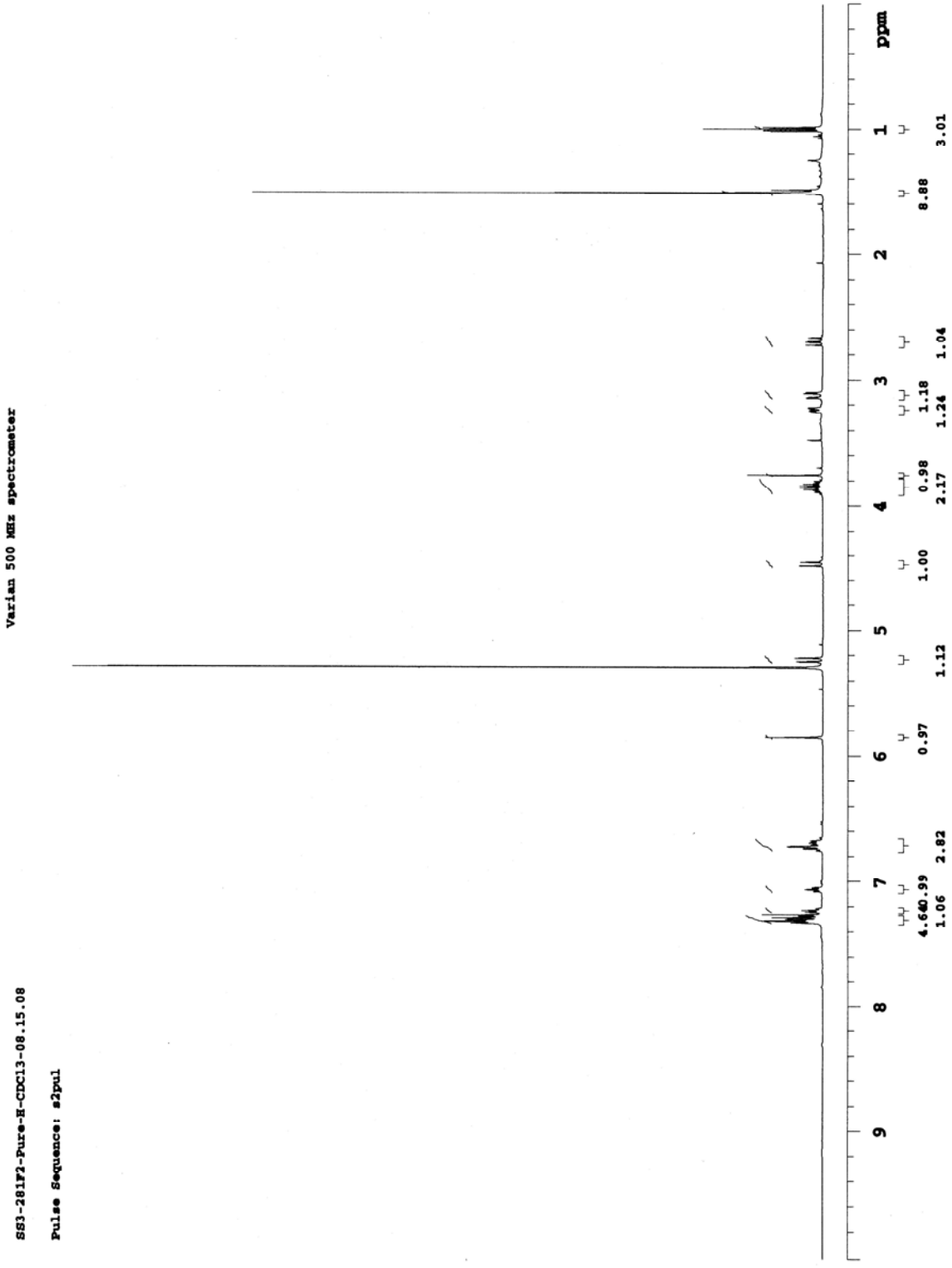
DEPT NMR (Compound 339)



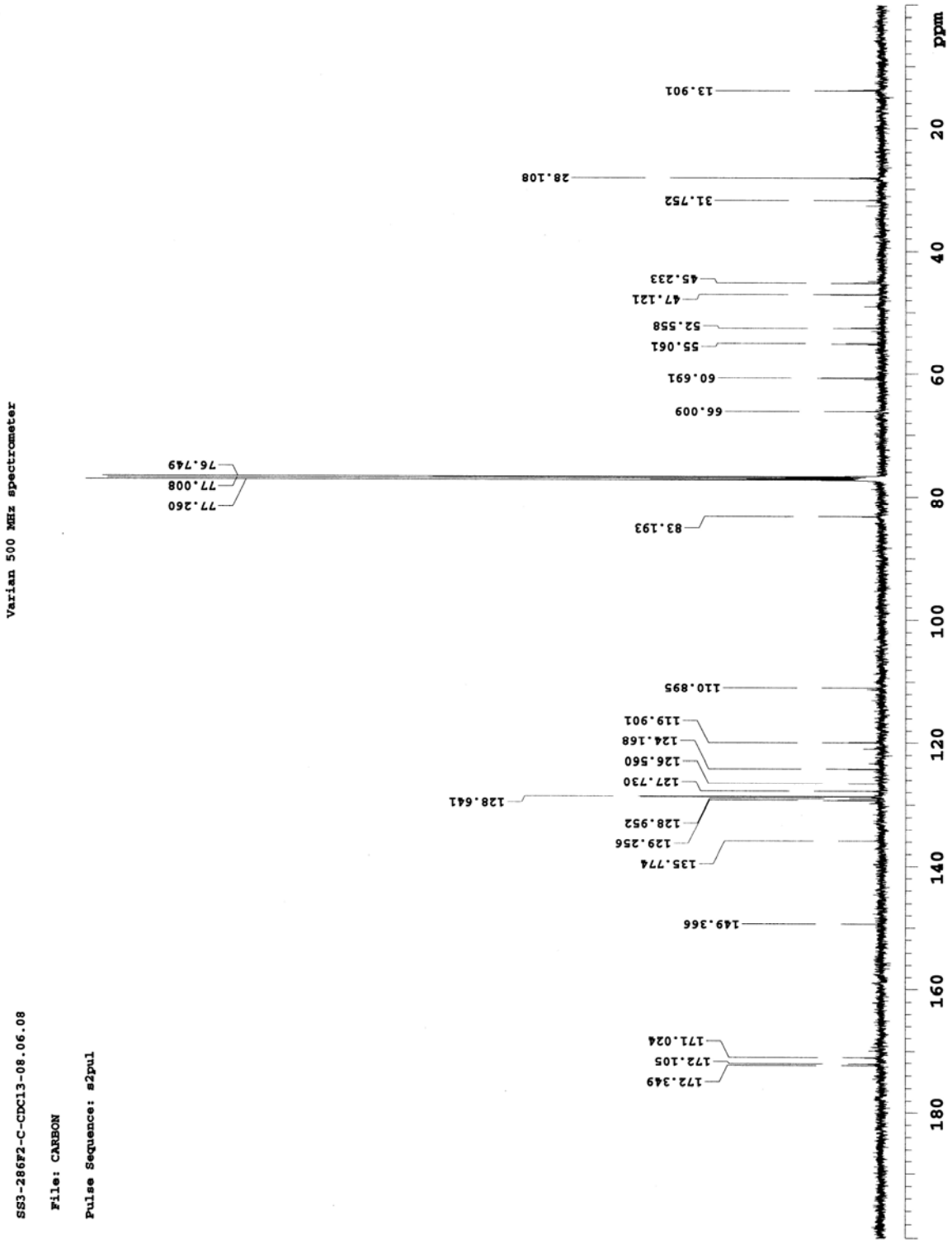
^{1}H-^{1}H GDQFCOSY NMR (Compound 339)



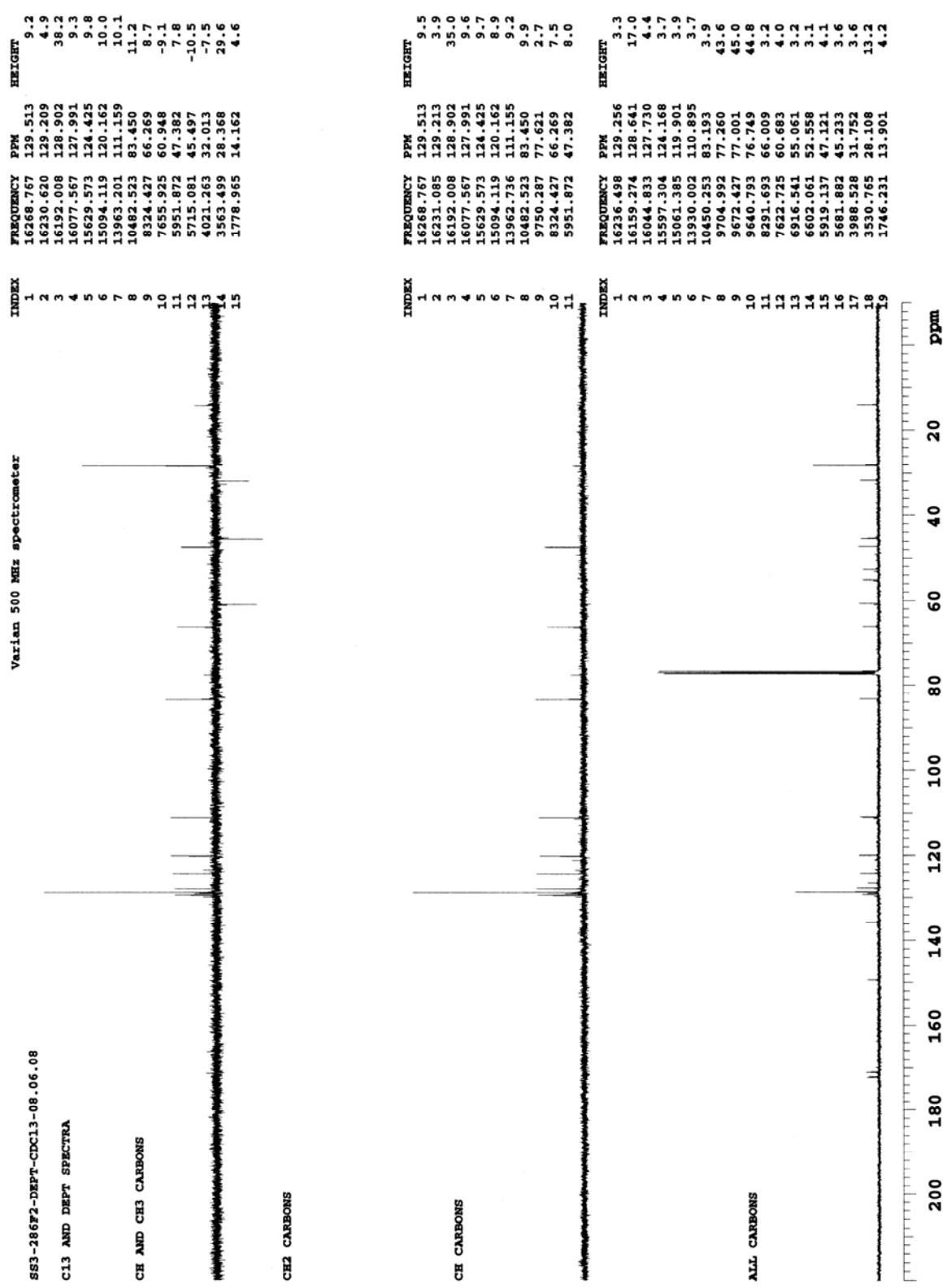
^{1}H NMR (Compound 340)



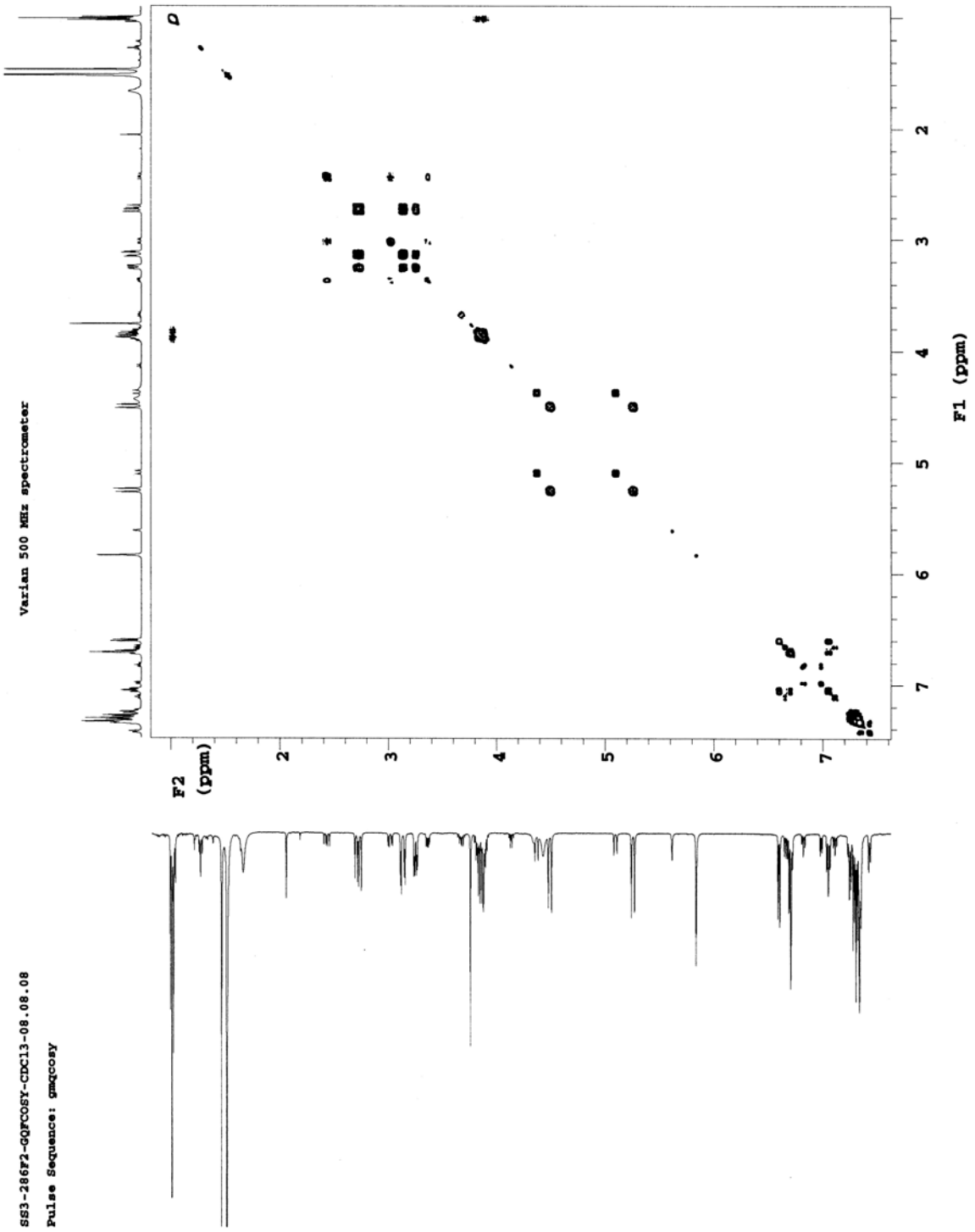
^{13}C NMR (Compound 340)



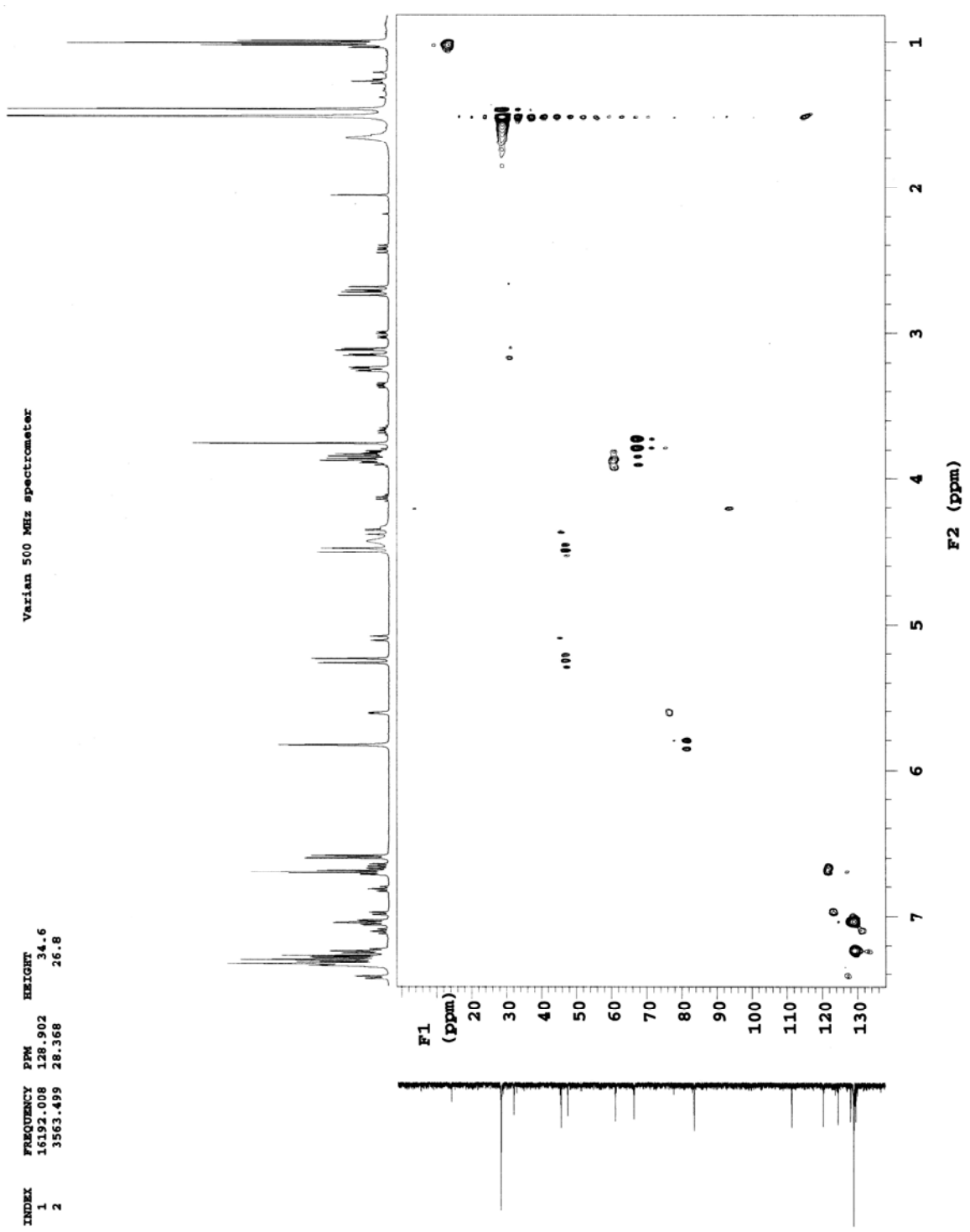
DEPT NMR (Compound 340)



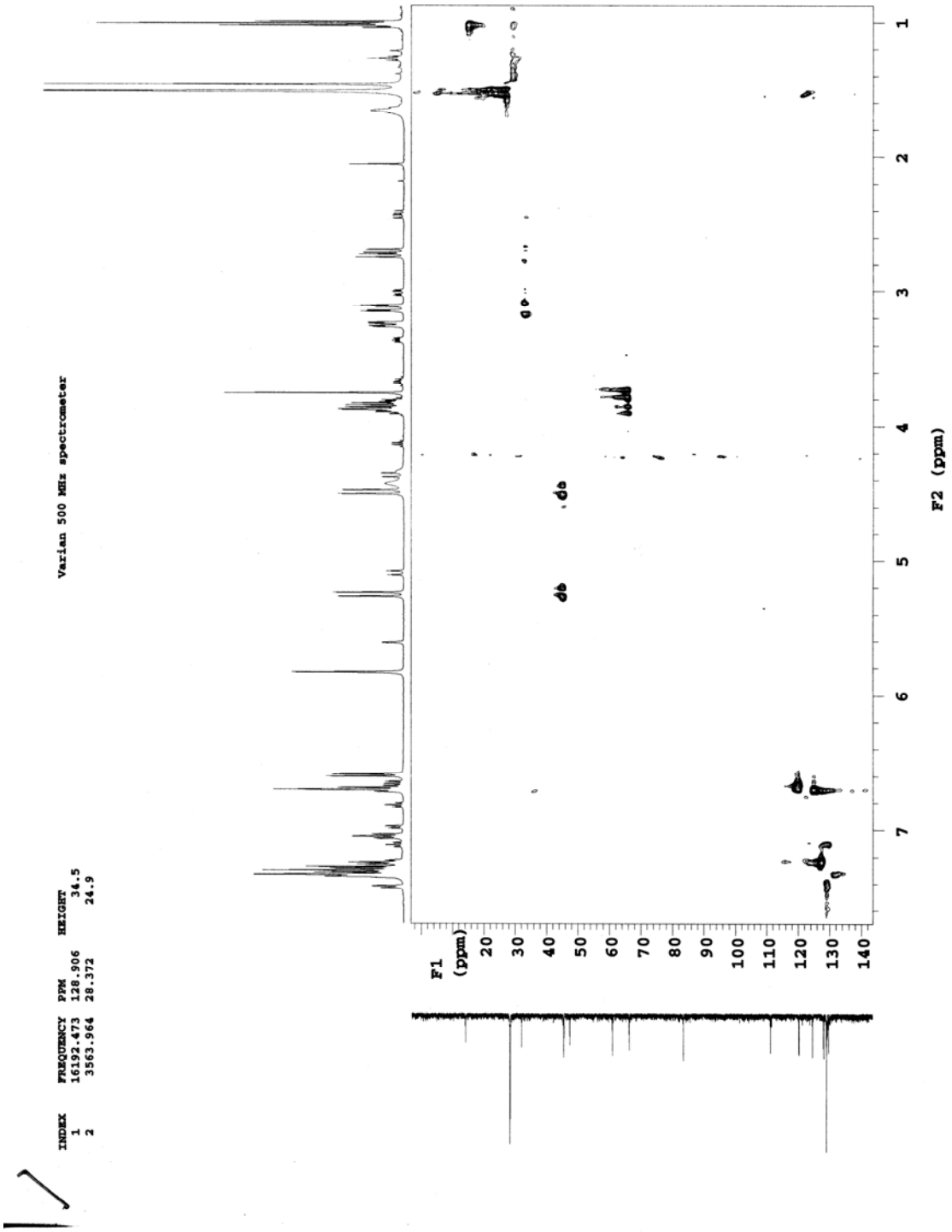
^{1}H-^{1}H GDQFCOSY NMR (Compound 340)



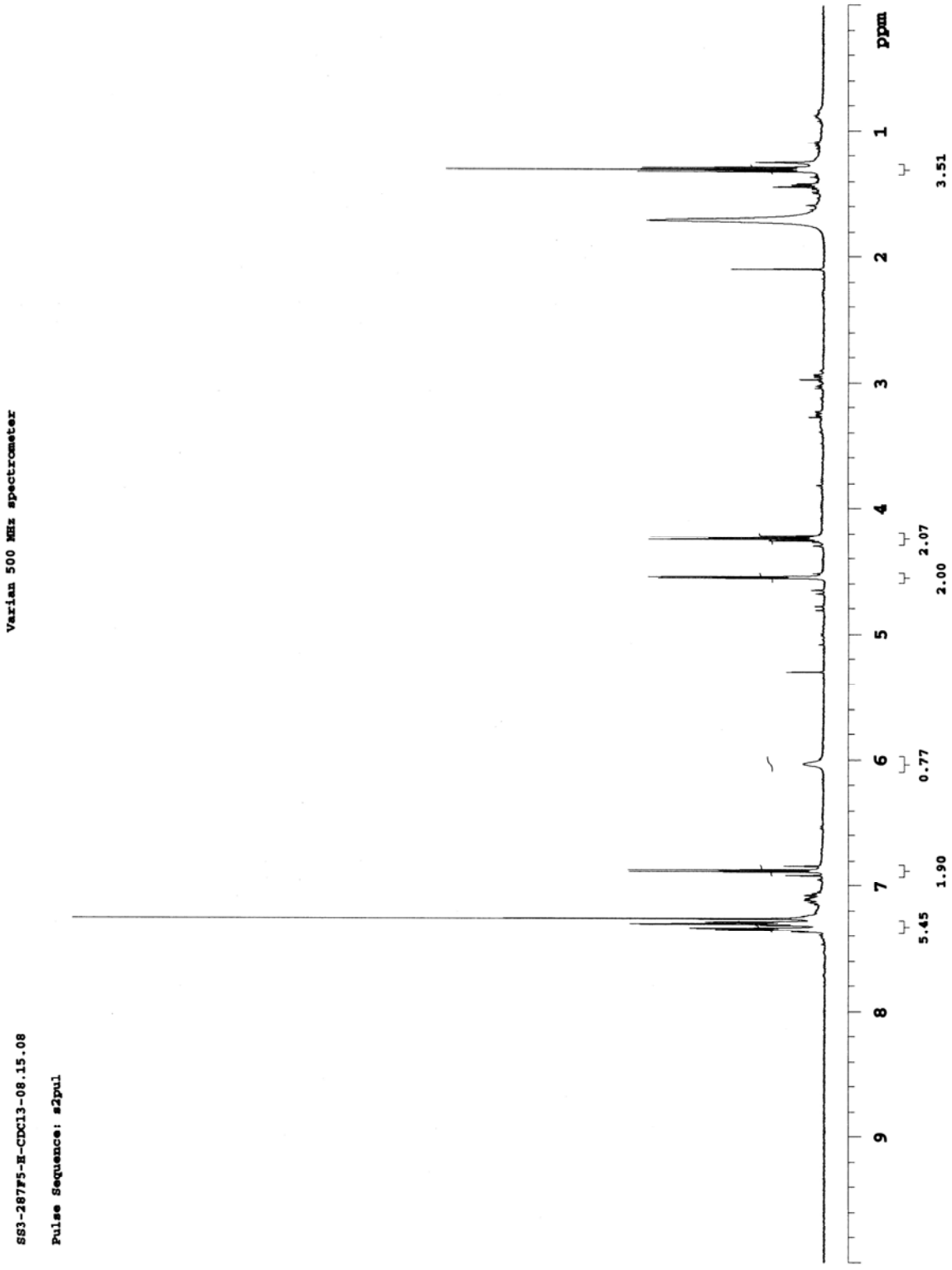
GHMQC-1 NMR (Compound 340)



GHMQC-2 NMR (Compound 340)



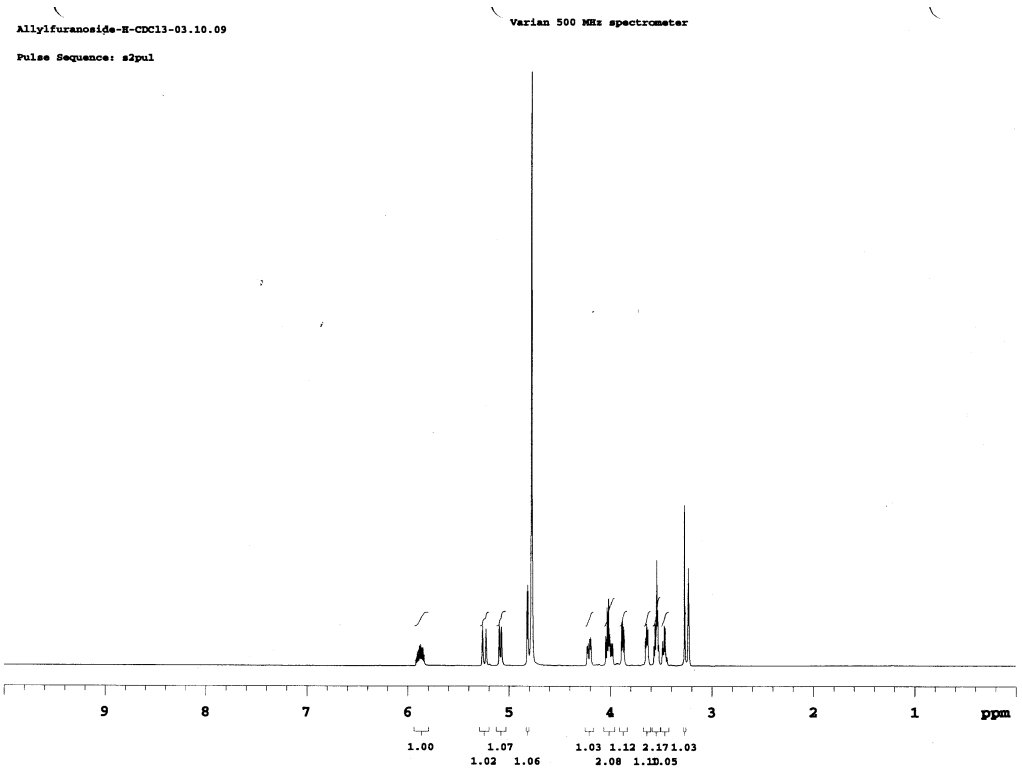
^{1}H NMR (Compound 347)



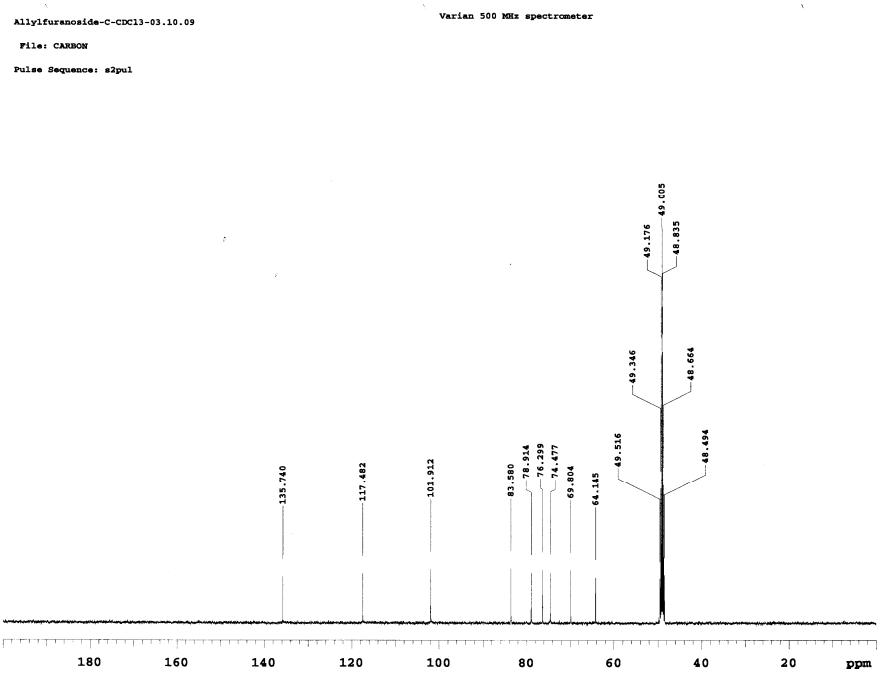
APPENDIX III

NMR Spectra of Chapter 4

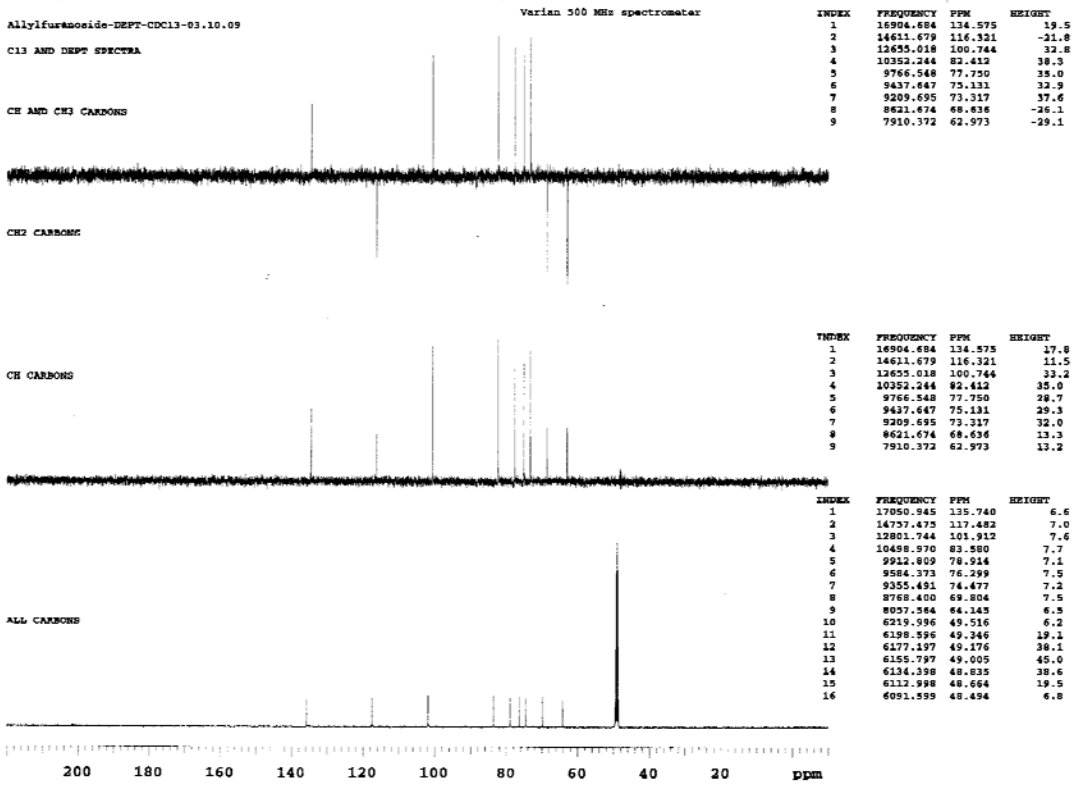
^{1}H NMR (Compound 370a)



^{13}C NMR (Compound 370a)



DEPT NMR (Compound 370a)

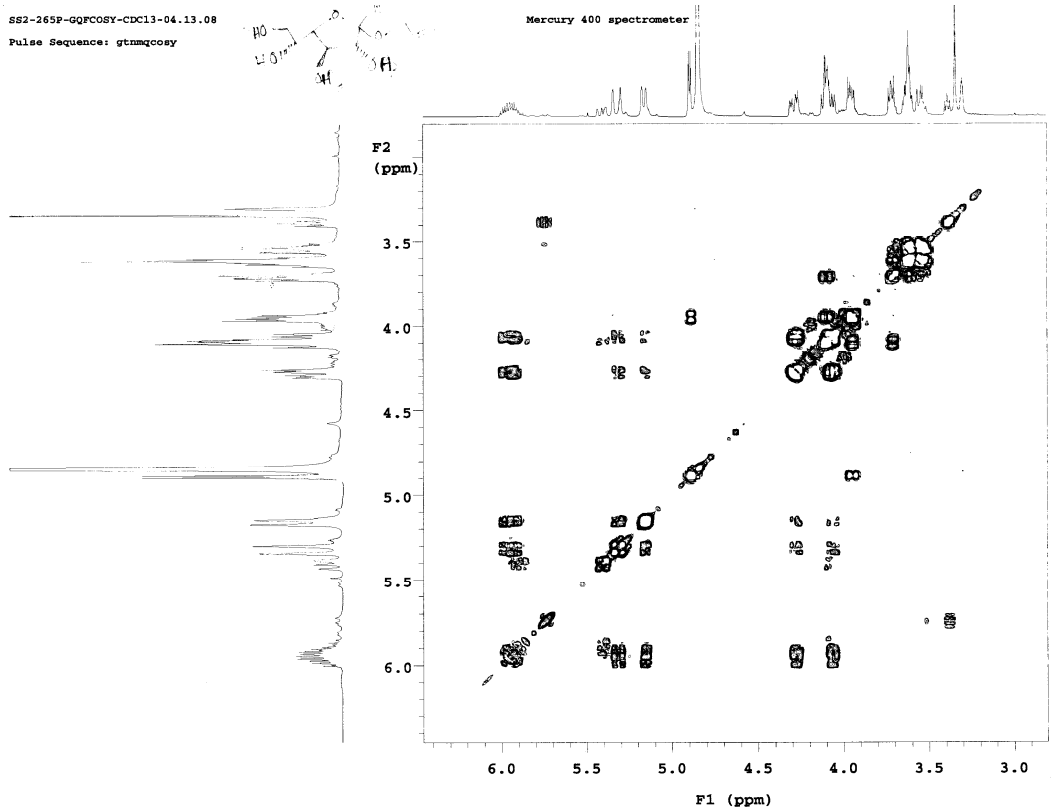


INDEX	FREQUENCY	PPM	HEIGHT
1	16904.684	134.575	19.5
2	14611.679	116.321	-21.8
3	12655.018	100.744	32.8
4	10352.244	82.412	38.3
5	9766.548	77.750	35.0
6	9437.647	75.131	32.9
7	9209.695	73.317	37.6
8	8621.674	68.636	-26.1
9	7910.372	62.973	-29.1

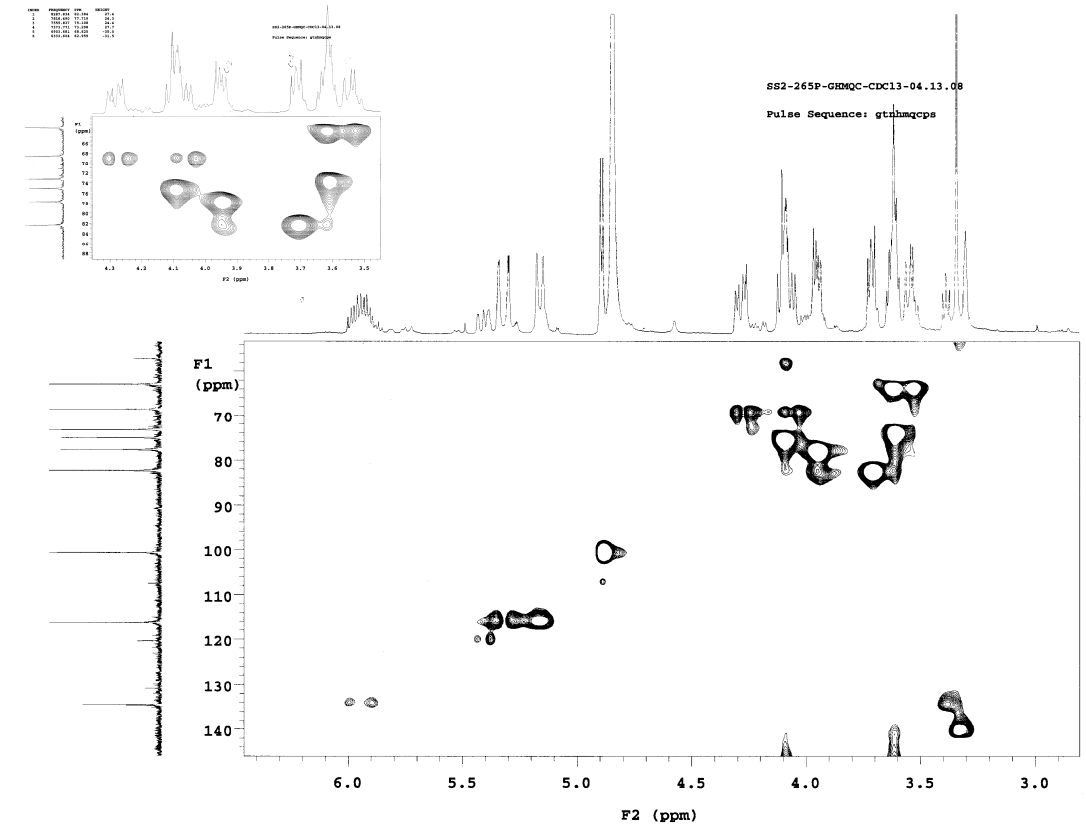
INDEX	FREQUENCY	PPM	HEIGHT
1	16904.684	134.575	17.8
2	14611.679	116.321	11.5
3	12655.018	100.744	33.2
4	10352.244	82.412	35.0
5	9766.548	77.750	28.7
6	9437.647	75.131	29.3
7	9209.695	73.317	32.0
8	8621.674	68.636	13.3
9	7910.372	62.973	13.2

INDEX	FREQUENCY	PPM	HEIGHT
1	17050.945	135.740	6.6
2	14757.475	117.482	7.0
3	12801.744	101.912	7.6
4	10498.970	83.580	7.7
5	9912.809	78.914	7.1
6	9584.373	76.299	7.5
7	9355.491	74.477	7.2
8	8768.400	69.804	7.5
9	8057.584	64.145	6.5
10	6219.996	49.516	6.2
11	6198.596	49.346	19.1
12	6177.197	49.176	38.1
13	6155.797	49.005	45.0
14	6134.398	48.835	38.6
15	6112.998	48.664	19.5
16	6091.599	48.494	6.8

GDQFCOSY NMR (Compound 370a)

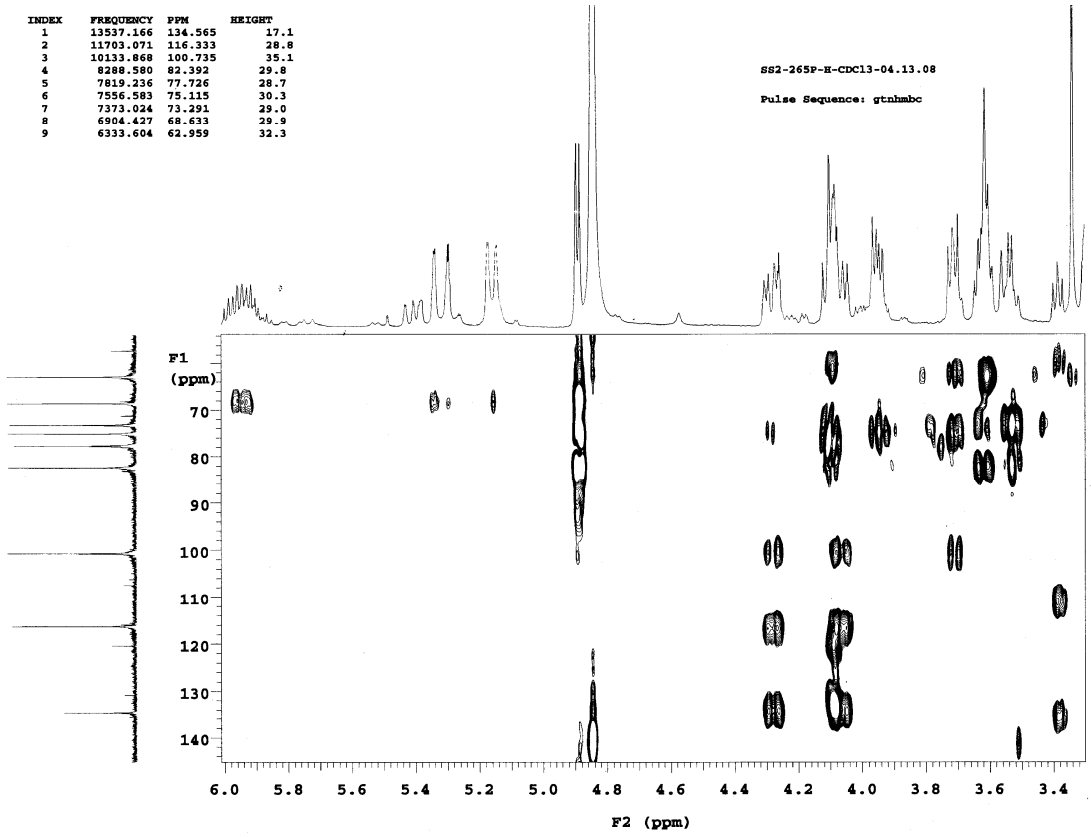


GHMQC NMR (Compound 370a)

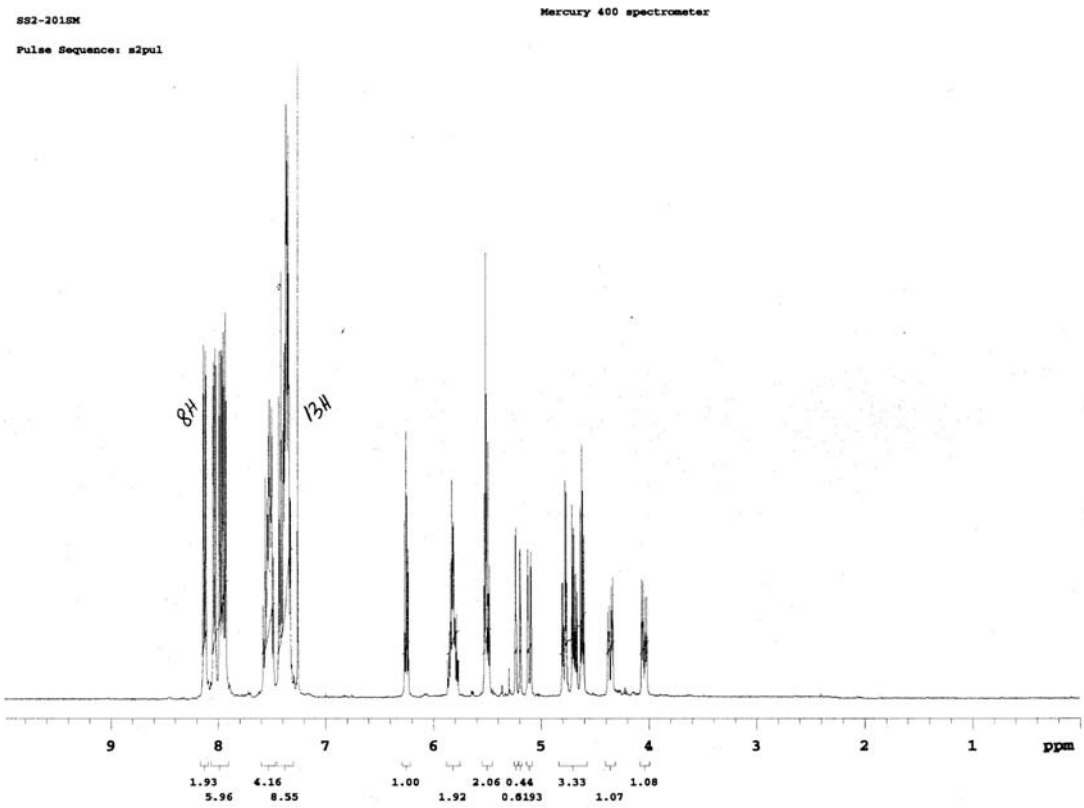


GHMBC NMR (Compound 370a)

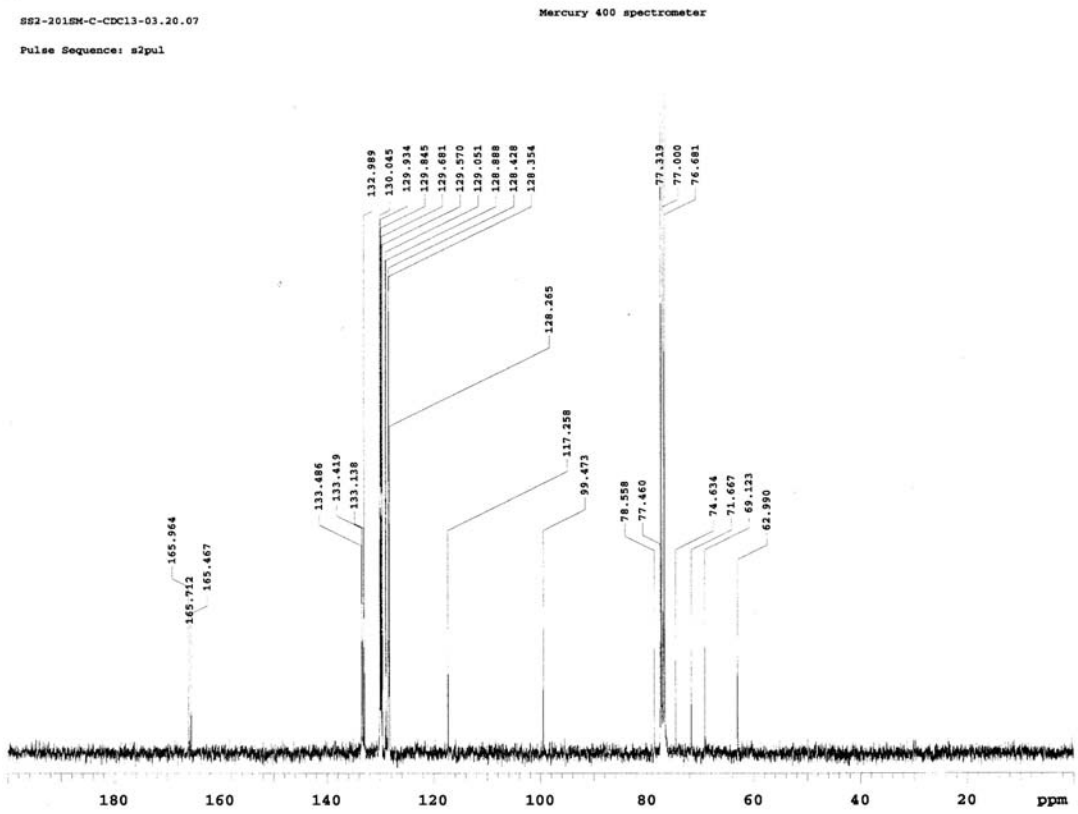
INDEX	FREQUENCY	PPM	HEIGHT
1	13537.166	134.565	17.1
2	11703.071	116.333	28.8
3	10133.868	100.735	35.1
4	8288.580	82.392	29.8
5	7819.236	77.726	28.7
6	7556.583	75.115	30.3
7	7373.024	73.291	29.0
8	6904.427	68.633	29.9
9	6333.604	62.959	32.3



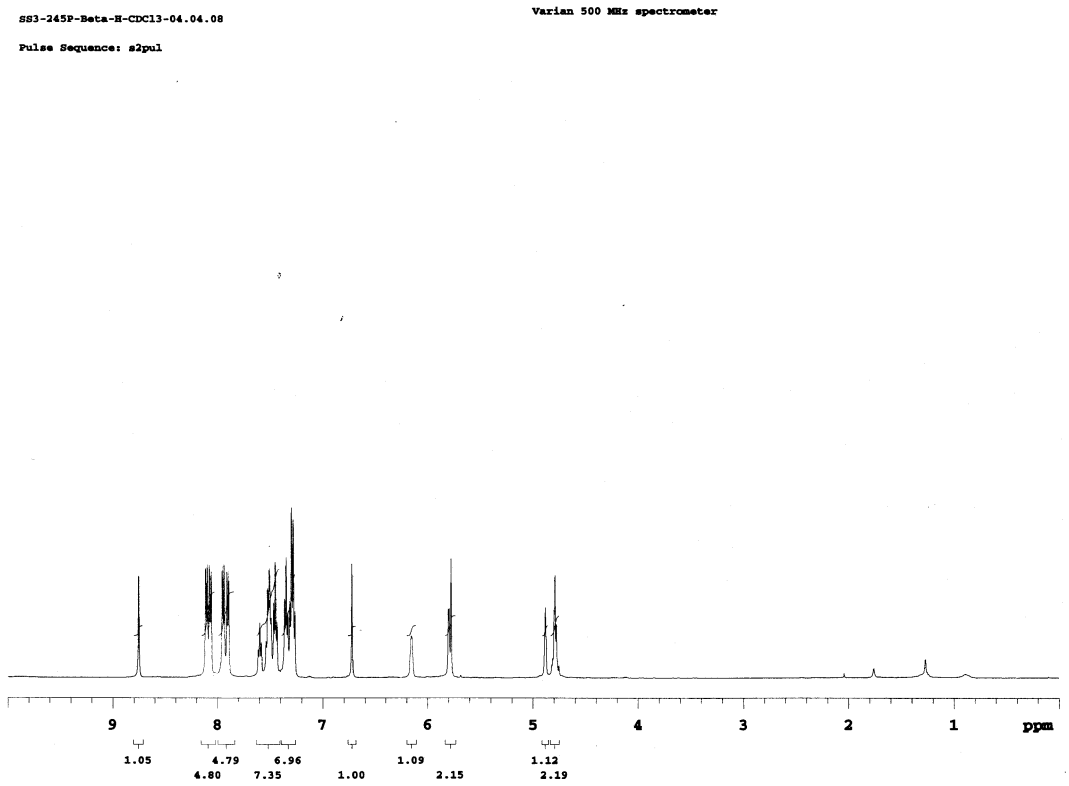
^{1}H NMR (Compound 377a)



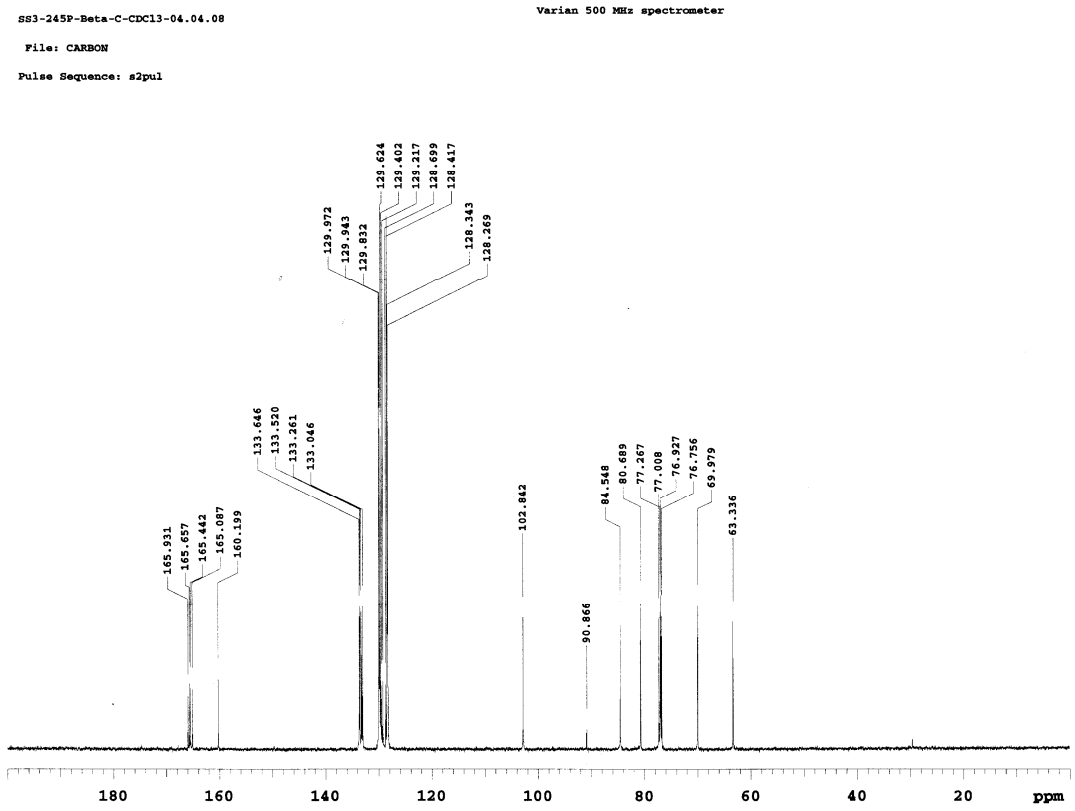
^{13}C NMR (Compound 377a)



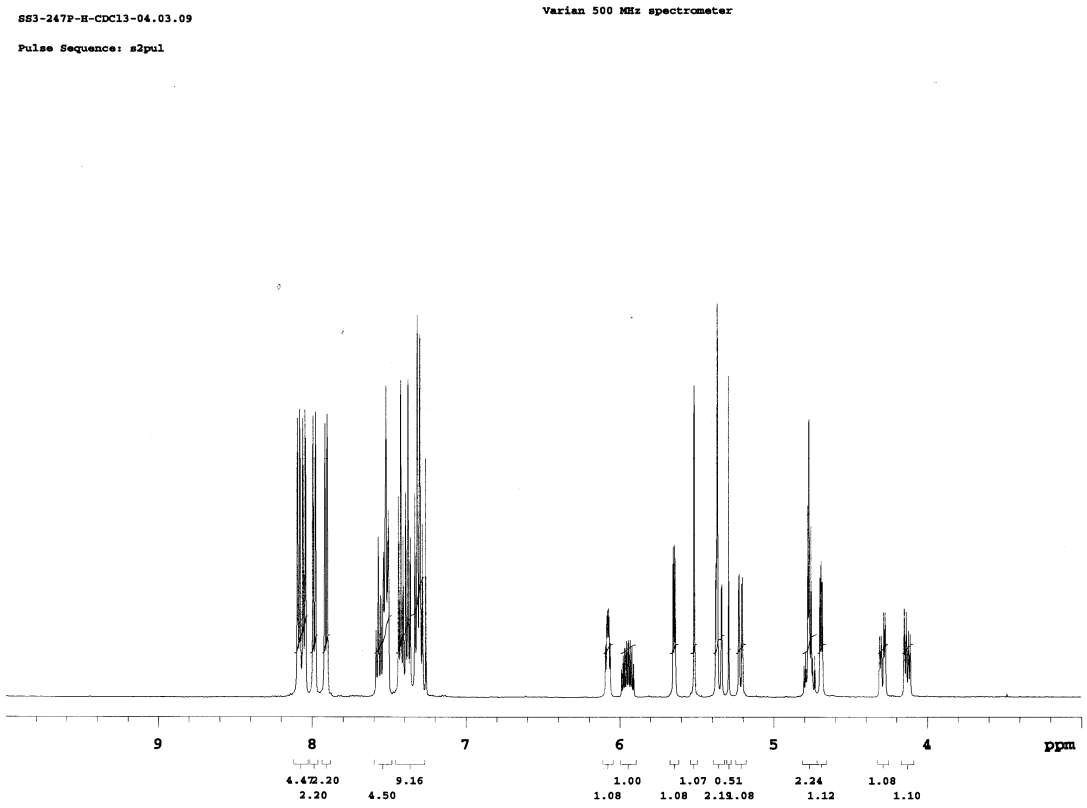
^{1}H NMR (Compound 376, β isomer)



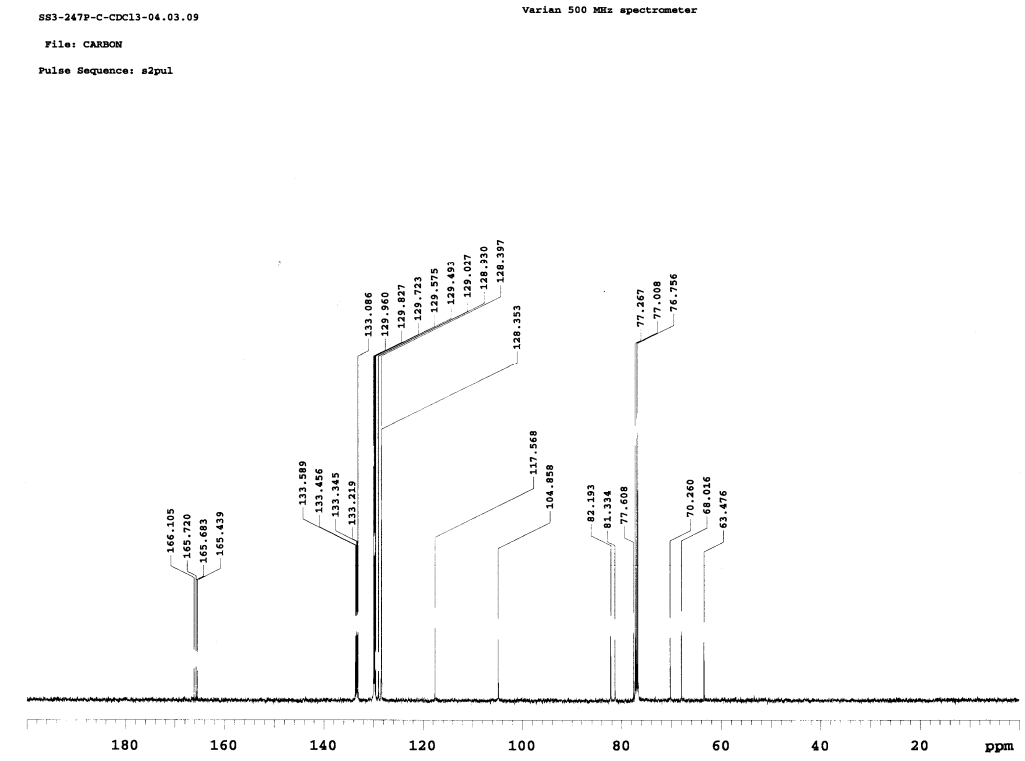
^{13}C NMR (Compound 376, β isomer)



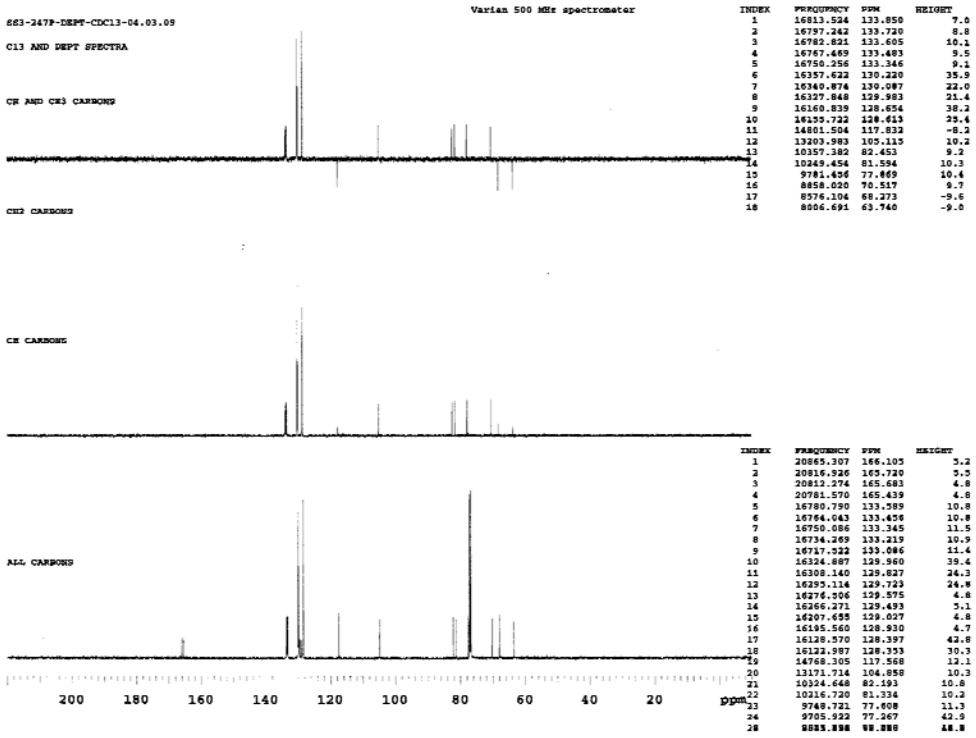
^{1}H NMR (Compound 377b)



^{13}C NMR (Compound 377b)



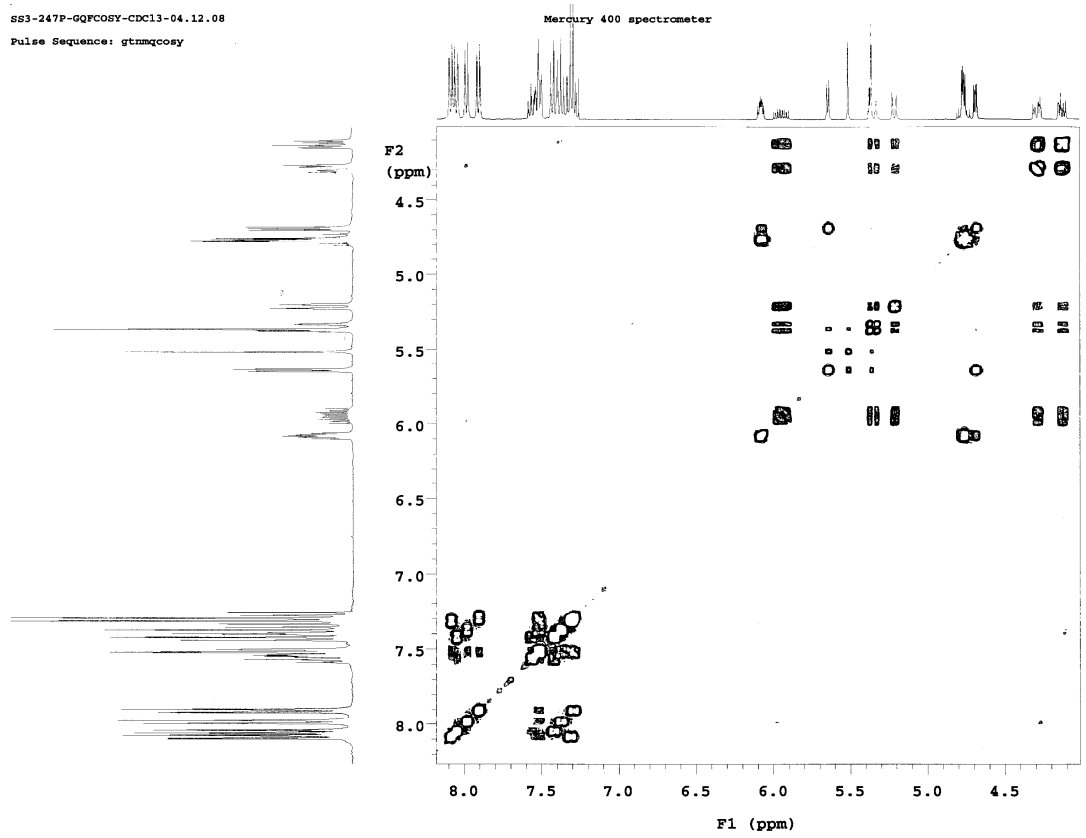
DEPT NMR (Compound 377b)



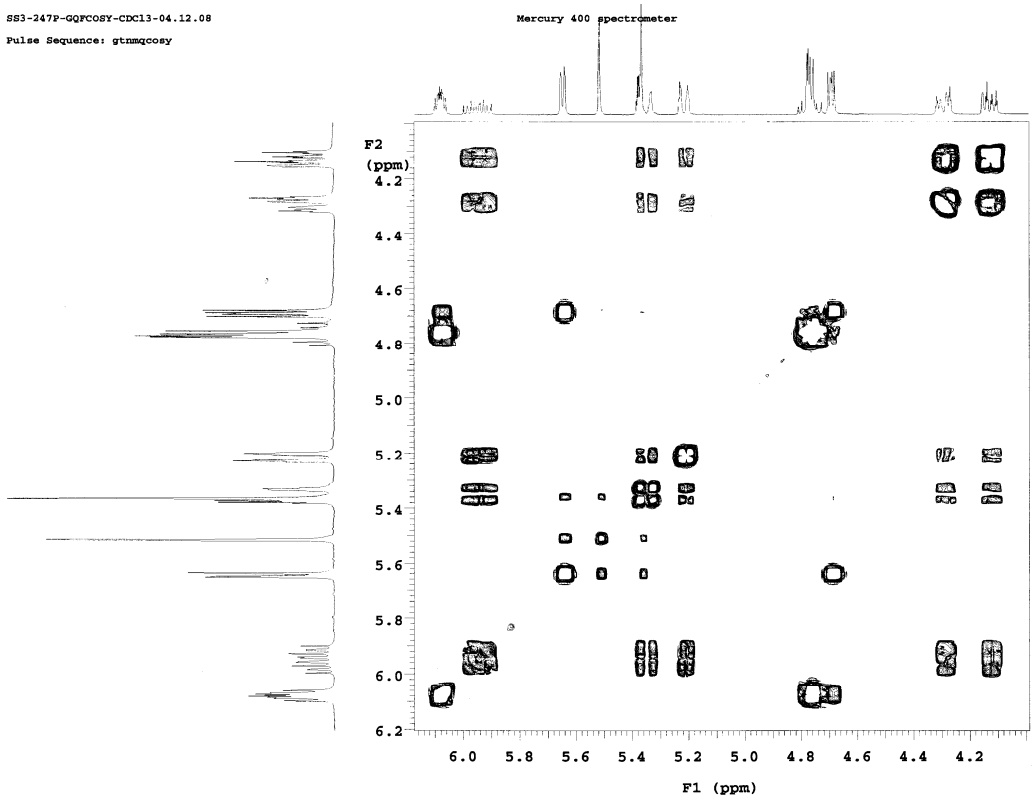
INDEX	FREQUENCY	PPM	HEIGHT
1	16813.524	133.850	7.0
2	16797.262	133.720	8.8
3	16782.821	133.605	10.1
4	16767.469	133.483	9.5
5	16750.256	133.346	9.1
6	16357.622	130.220	35.9
7	16340.874	130.087	22.0
8	16327.848	129.983	21.4
9	16160.839	128.654	38.2
10	16155.722	128.613	29.4
11	14801.504	117.832	-8.2
12	13203.983	105.115	10.2
13	10357.382	82.453	9.2
14	10249.454	81.594	10.3
15	9781.456	77.869	10.4
16	8858.020	70.517	9.7
17	8576.104	68.273	-9.6
18	8006.691	63.740	-9.0

INDEX	FREQUENCY	PPM	HEIGHT
1	20865.307	166.105	5.2
2	20816.926	165.720	5.5
3	20812.274	165.683	4.8
4	20781.570	165.439	4.8
5	16780.790	133.589	10.8
6	16764.043	133.456	10.8
7	16750.086	133.345	11.5
8	16734.269	133.219	10.9
9	16717.522	133.086	11.4
10	16324.887	129.960	39.4
11	16308.140	129.827	24.3
12	16295.114	129.723	24.8
13	16276.506	129.575	4.8
14	16266.271	129.493	5.1
15	16207.655	129.027	4.8
16	16195.560	128.930	4.7
17	16128.570	128.397	42.8
18	16122.987	128.353	30.3
19	14768.305	117.568	12.1
20	13171.714	104.858	10.3
21	10324.648	82.193	10.8
22	10216.720	81.334	10.2
23	9748.721	77.608	11.3
24	9705.922	77.267	42.9
25	9685.898	98.888	48.8

GDQFCOSY NMR (Compound 377b)

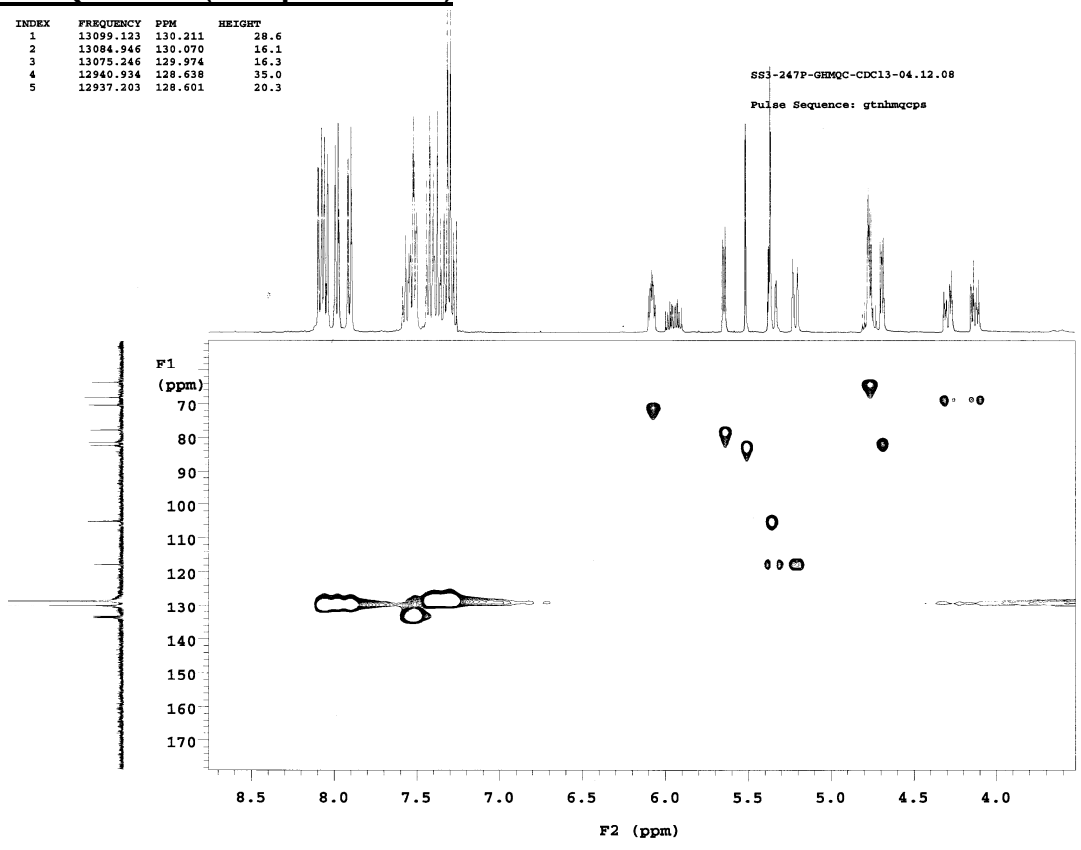


GDQFCOSY NMR (Compound 377b, Expansion)

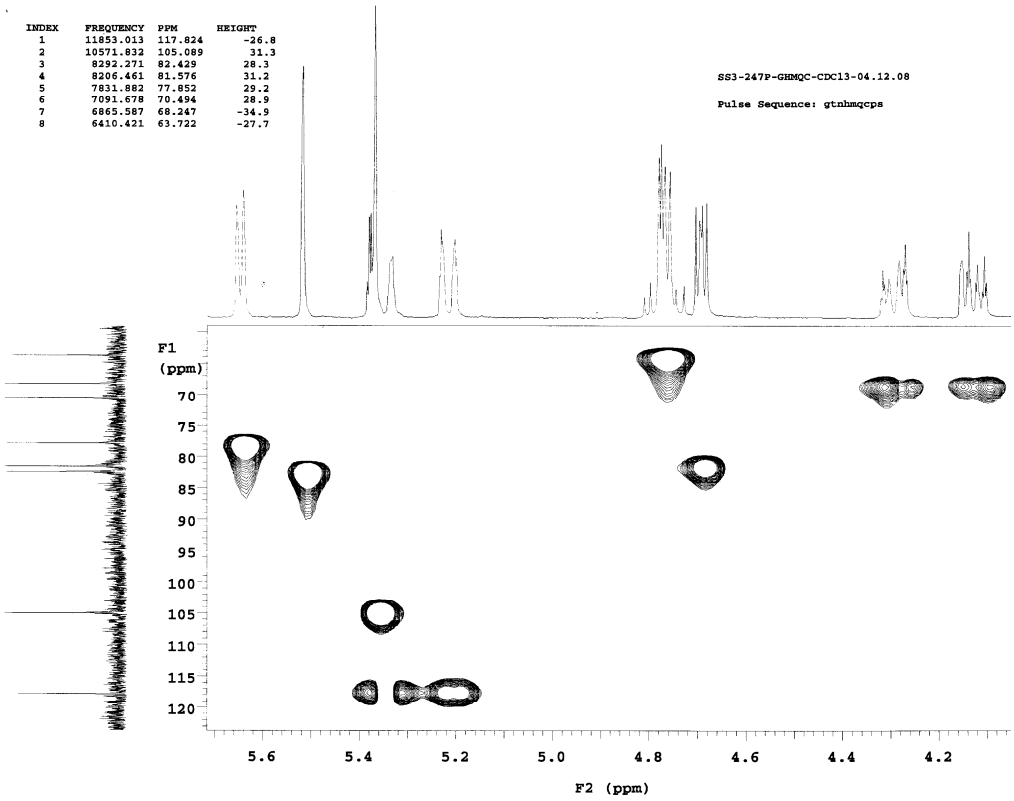


GHMQC NMR (Compound 377b)

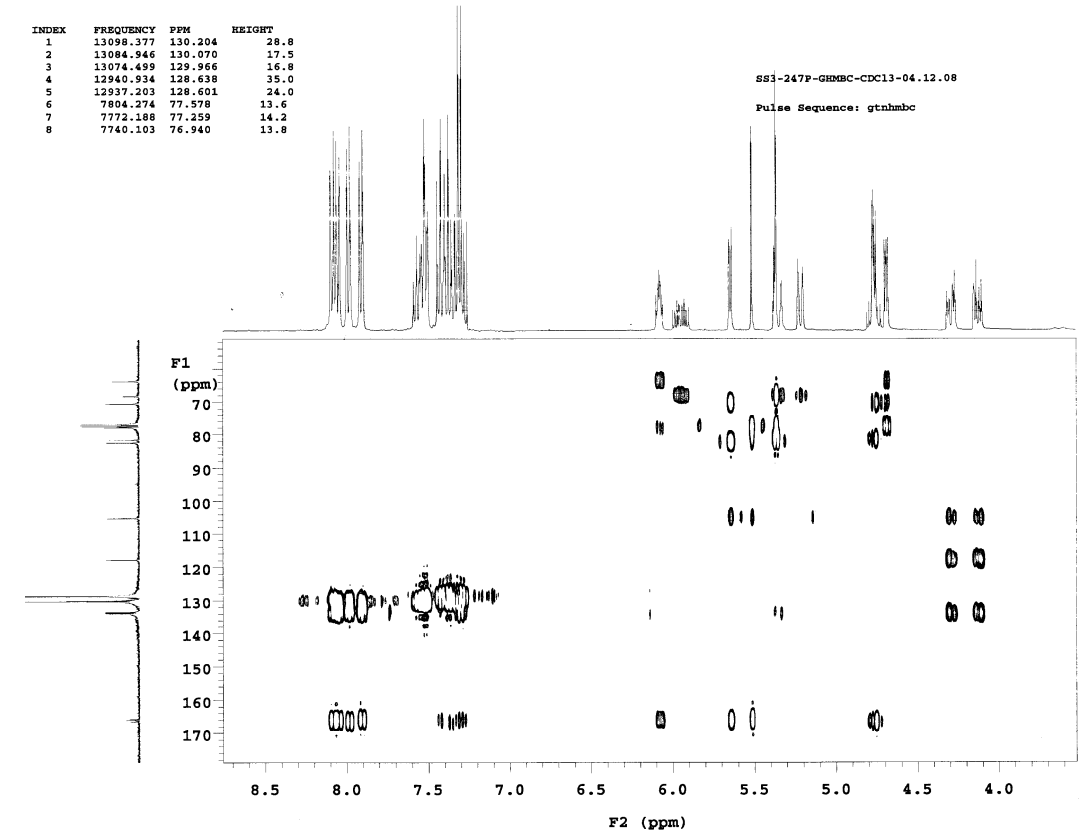
INDEX	FREQUENCY	PPM	HEIGHT
1	13099.123	130.211	28.6
2	13084.946	130.070	16.1
3	13075.246	129.974	16.3
4	12940.934	128.638	35.0
5	12937.203	128.601	20.3



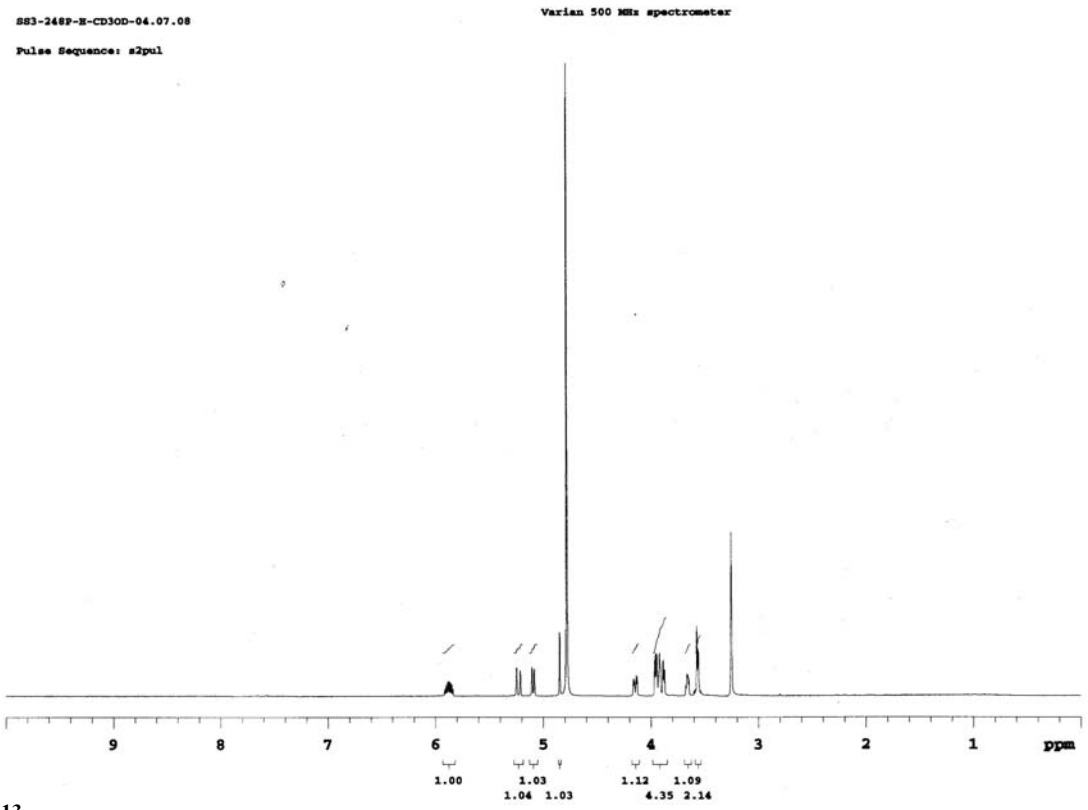
GHMQC NMR (Compound 377b, Expansion)



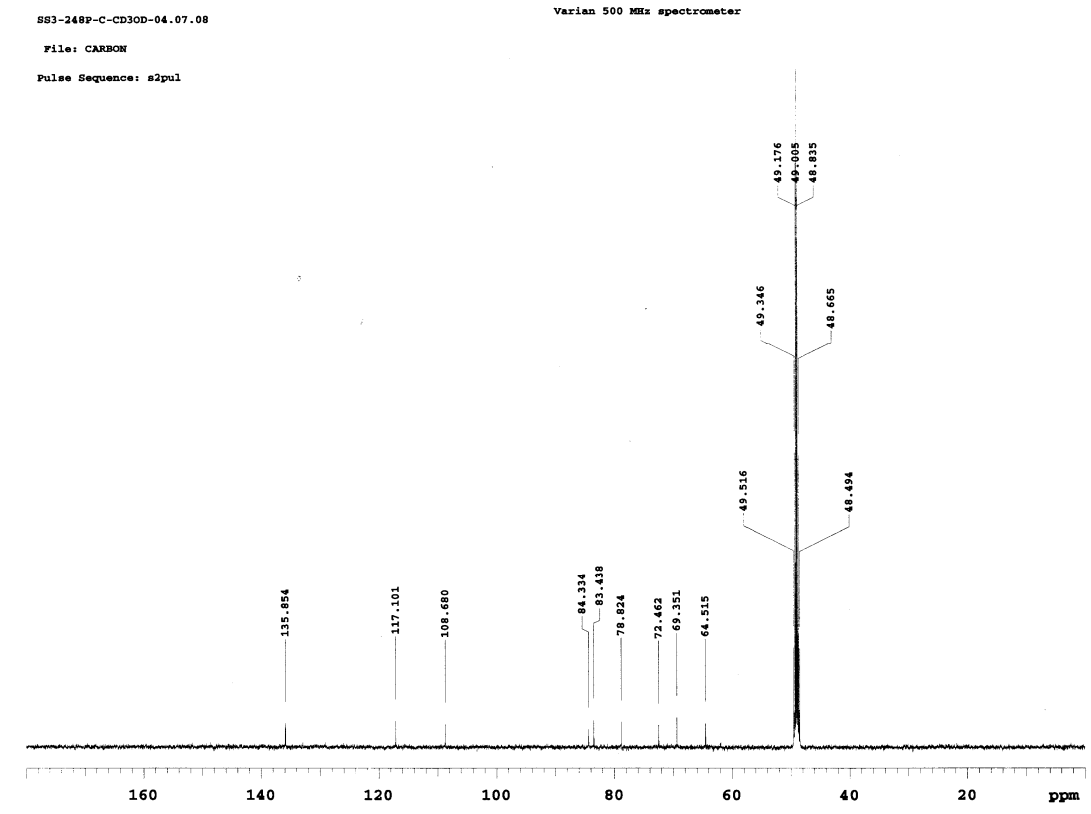
GHMBC NMR (Compound 377b)



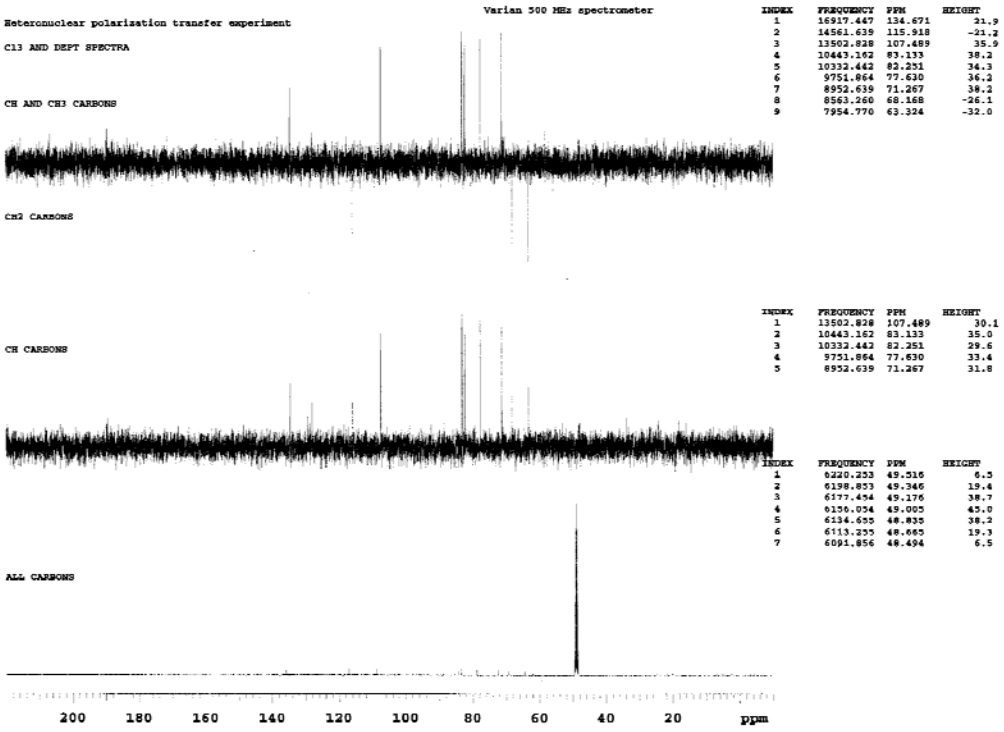
^{1}H NMR (Compound 370b)



^{13}C NMR (Compound 370b)



DEPT NMR (Compound 370b)

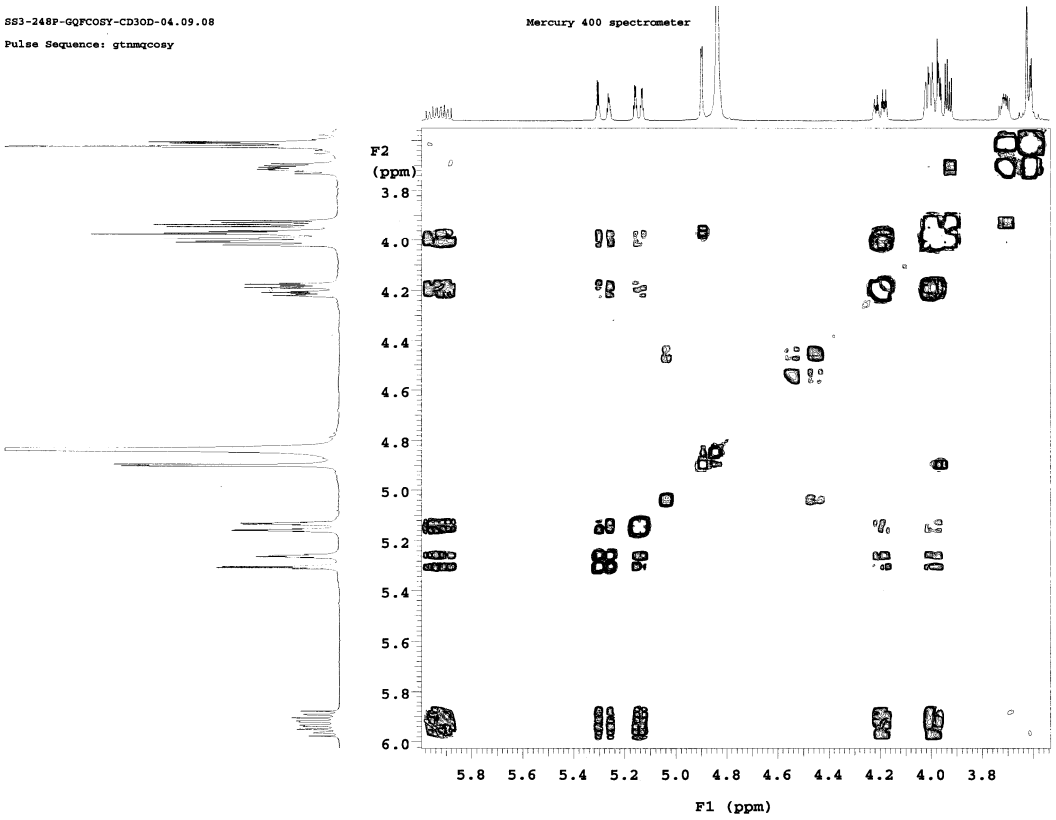


INDEX	FREQUENCY	PPM	HEIGHT
1	16917.447	134.671	31.9
2	14561.639	115.918	-21.2
3	13502.828	107.489	35.9
4	10443.162	83.133	38.2
5	10332.442	82.251	34.3
6	9751.864	77.630	36.2
7	8952.639	71.267	38.2
8	8563.260	68.168	-26.1
9	7954.770	63.324	-32.0

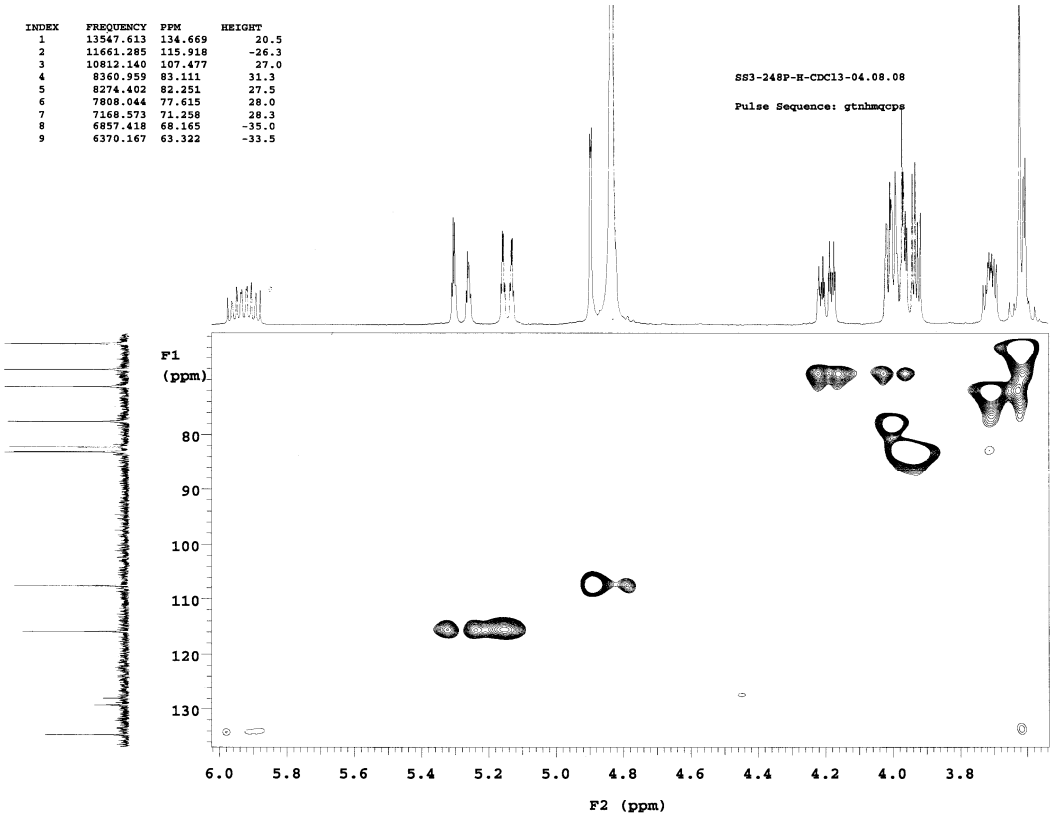
INDEX	FREQUENCY	PPM	HEIGHT
1	13502.828	107.489	30.1
2	10443.162	83.133	35.0
3	10332.442	82.251	29.6
4	9751.864	77.630	33.4
5	8952.639	71.267	31.8

INDEX	FREQUENCY	PPM	HEIGHT
1	6220.253	49.516	6.5
2	6198.853	49.346	19.4
3	6177.454	49.176	38.7
4	6156.054	49.005	45.0
5	6134.655	48.835	38.2
6	6113.255	48.665	19.3
7	6091.856	48.494	6.5

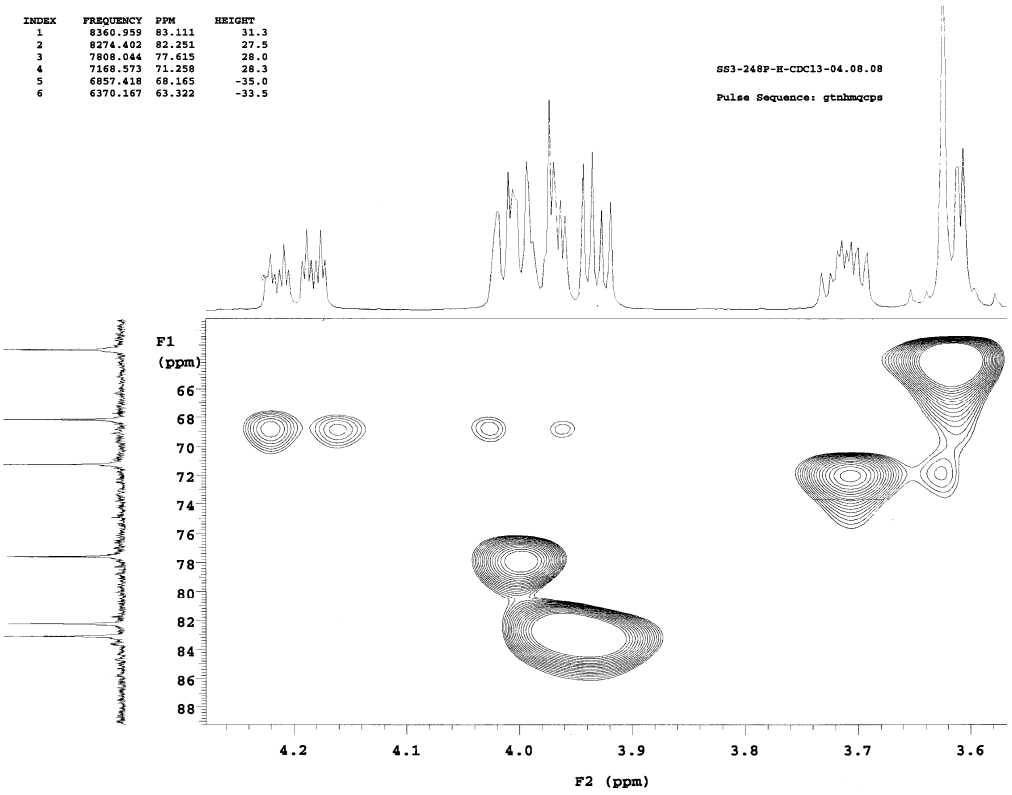
GDQFCOSY NMR (Compound 370b)



GHMQC NMR (Compound 370b)

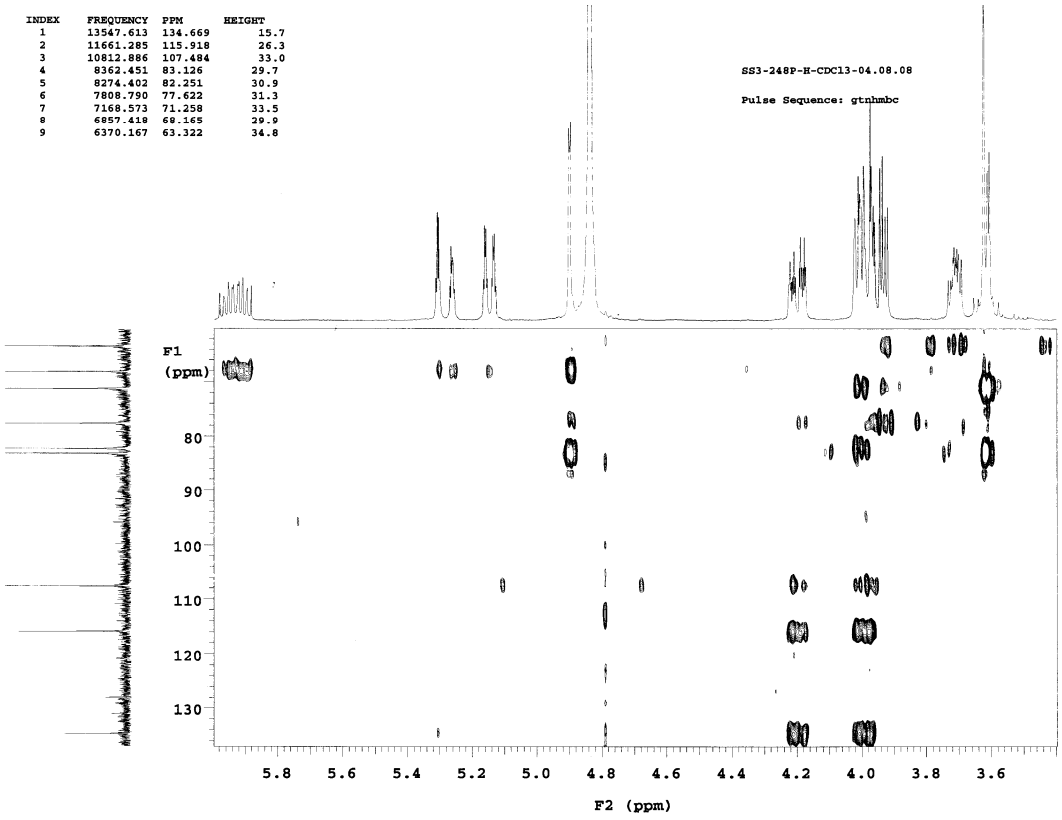


GHMQC NMR (Compound 370b)

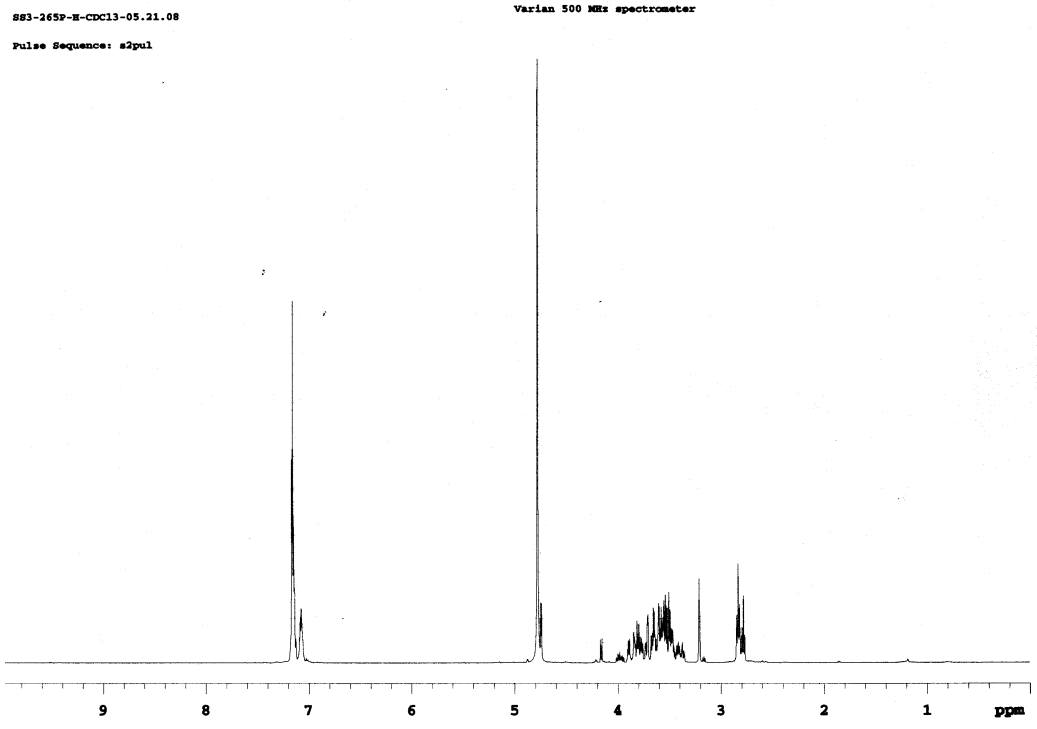


GHMBC NMR (Compound 370b)

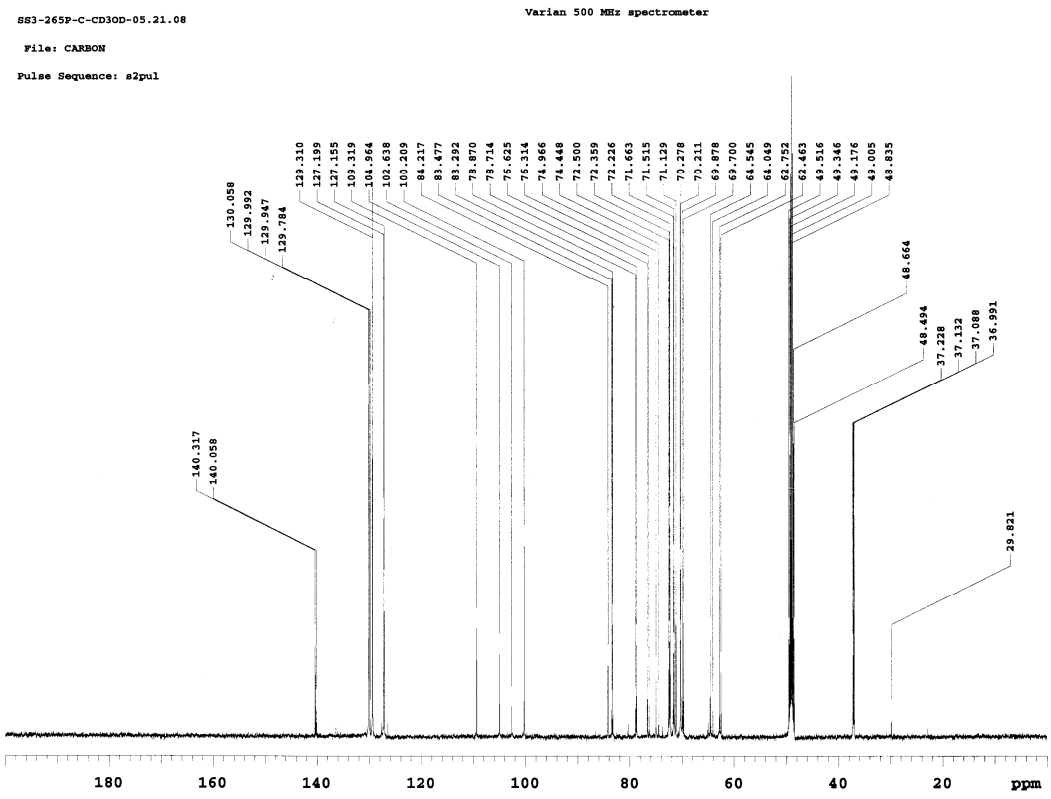
INDEX	FREQUENCY	PPM	HEIGHT
1	13547.613	134.669	15.7
2	11661.285	115.918	26.3
3	10812.886	107.484	33.0
4	8362.451	83.126	29.7
5	8274.402	82.251	30.9
6	7808.790	77.622	31.3
7	7168.573	71.258	33.5
8	6857.418	68.165	29.9
9	6370.167	63.322	34.8



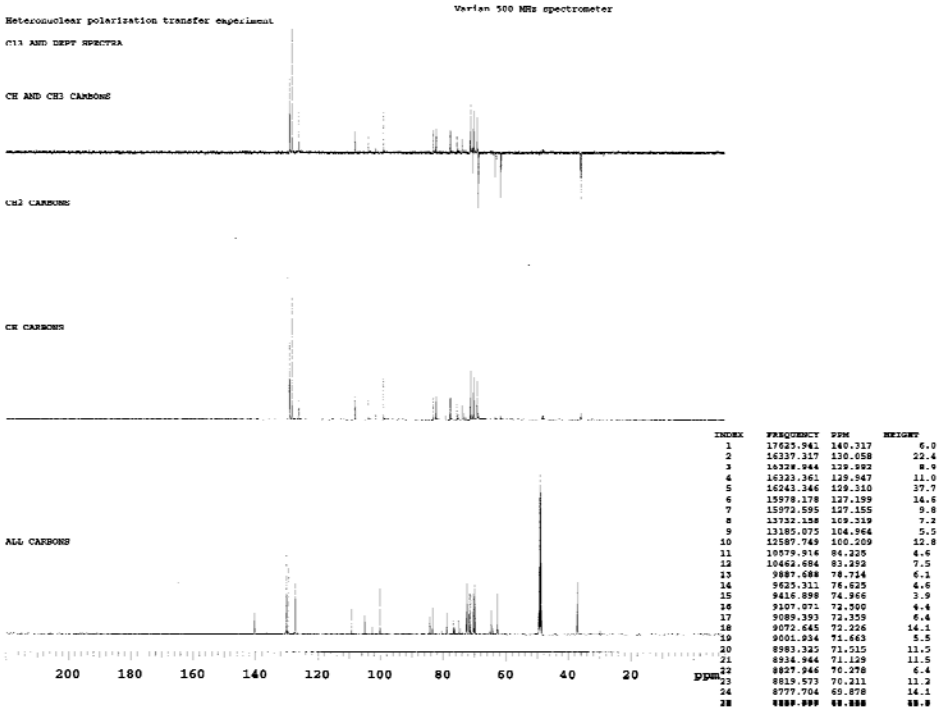
^{1}H NMR (mixture of compound 371 and 373 in CD_3OD)



^{13}C NMR (mixture of compound 371 and 373 in CD_3OD)

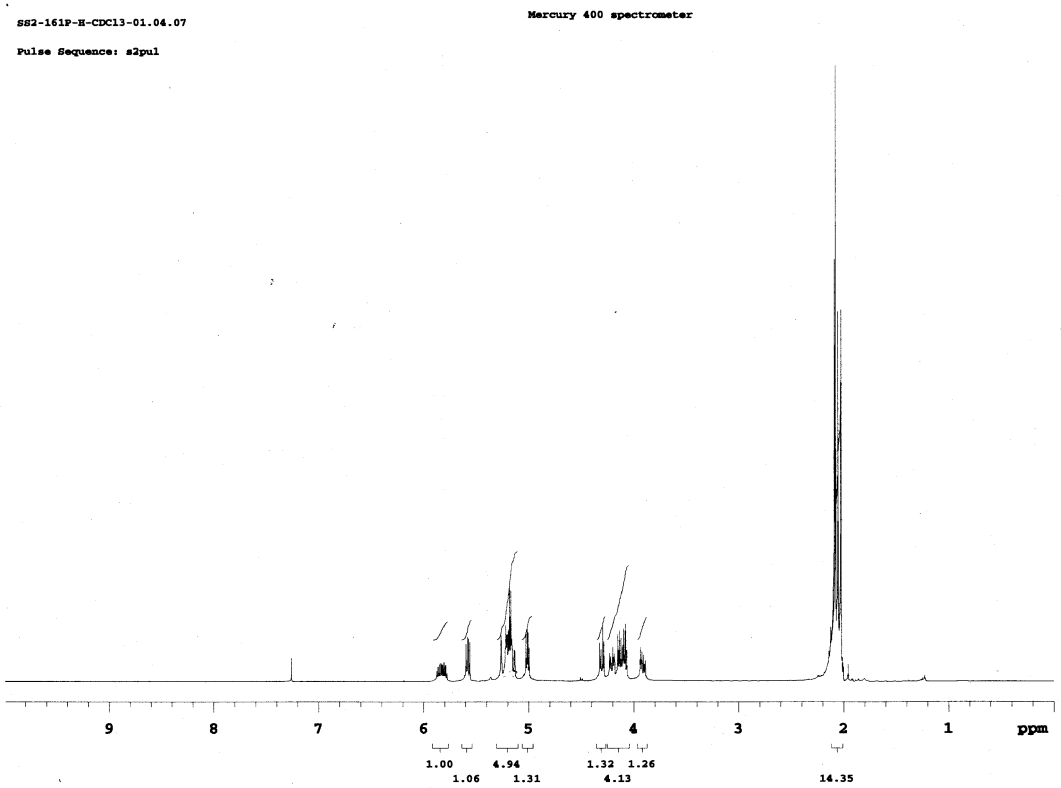


DEPT NMR ((mixture of compound 371 and 373 in CD_3OD)

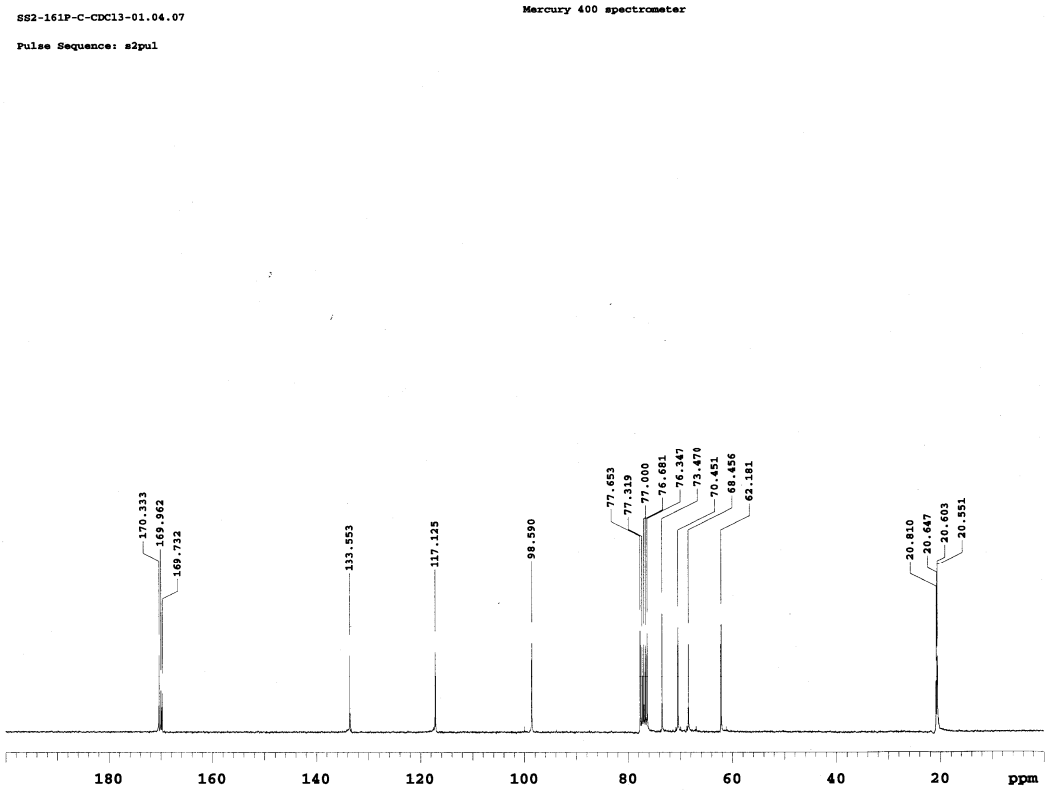


INDEX	FREQUENCY	PPM	HEIGHT
1	17625.941	140.317	6.0
2	16337.317	130.058	22.4
3	16328.944	129.992	8.9
4	16323.361	129.947	11.0
5	16243.346	129.310	37.7
6	15978.178	127.199	14.6
7	15972.595	127.155	9.8
8	13732.158	109.319	7.2
9	13185.075	104.964	5.5
10	12587.749	100.209	12.8
11	10579.916	84.225	4.6
12	10462.684	83.292	7.5
13	9887.688	78.714	6.1
14	9625.311	76.625	4.6
15	9416.898	74.966	3.9
16	9107.071	72.500	4.4
17	9089.393	72.359	6.4
18	9072.645	72.226	14.1
19	9001.834	71.663	5.5
20	8983.325	71.515	11.5
21	8934.944	71.129	11.5
22	8827.946	70.278	6.4
23	8819.573	70.211	11.2
24	8777.704	69.878	14.1
25	8888.888	88.888	88.8

^{1}H NMR (Compound 377c)



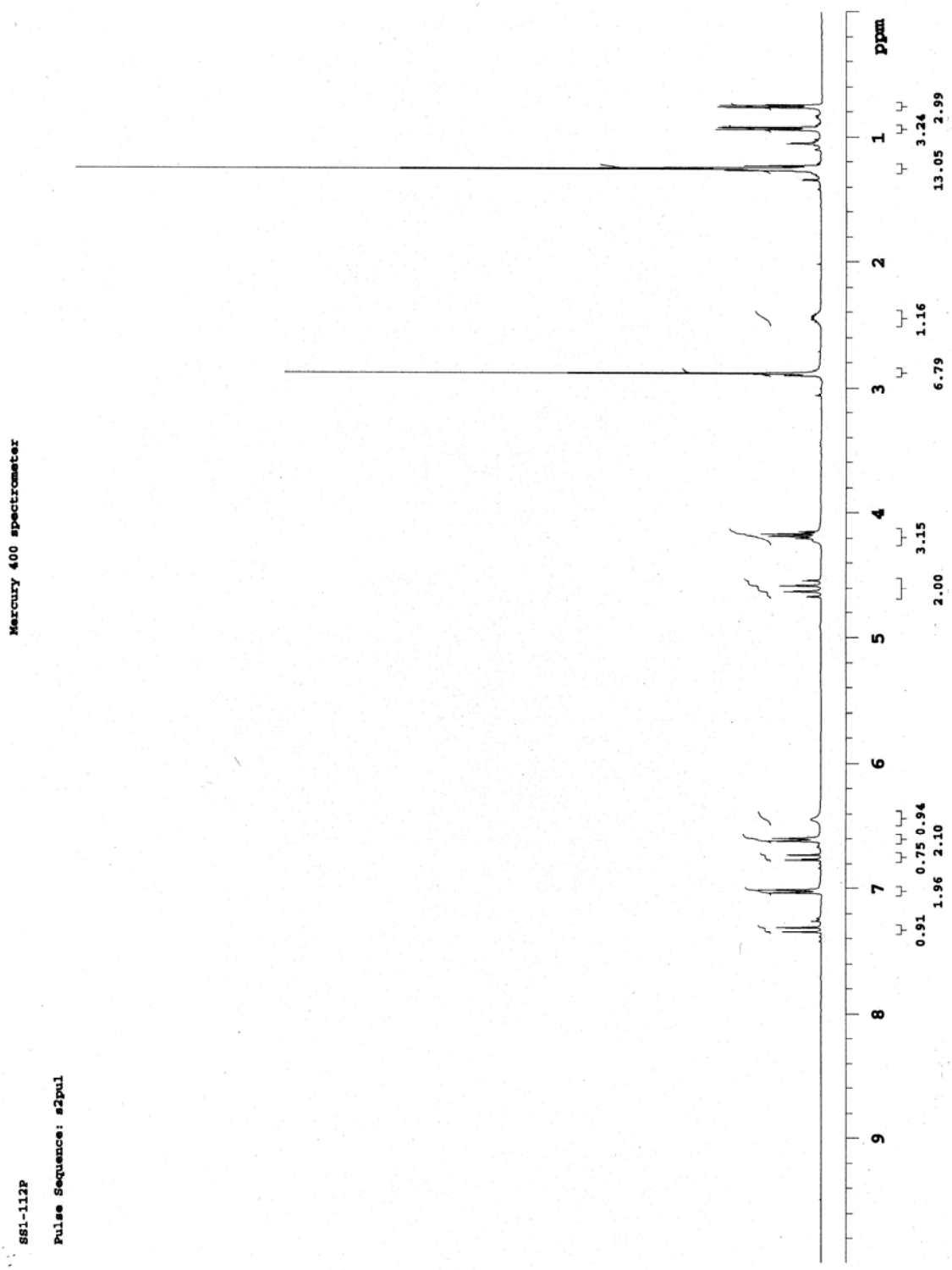
^{13}C NMR (Compound 377c)



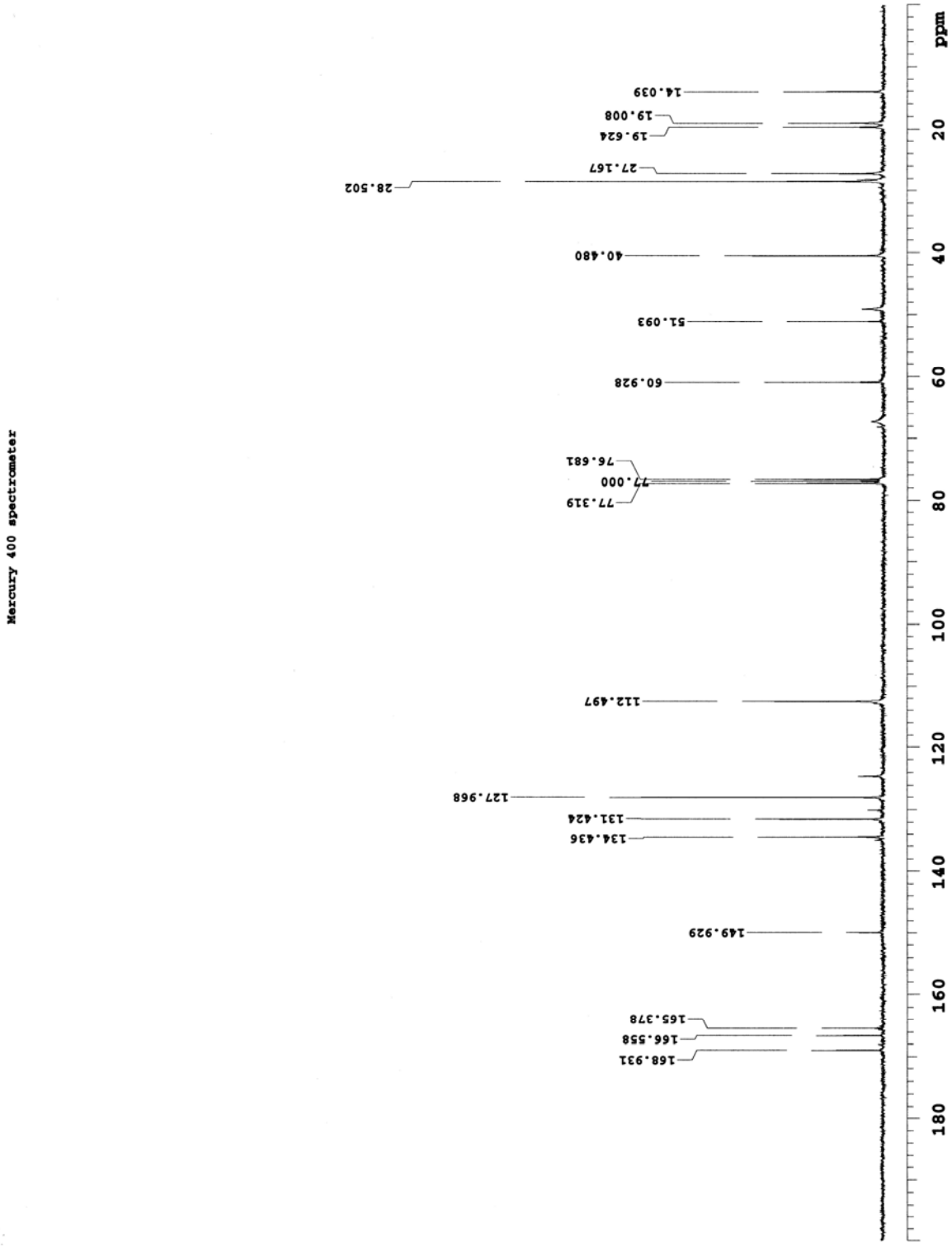
APPENDIX IV

NMR Spectra of Chapter 5

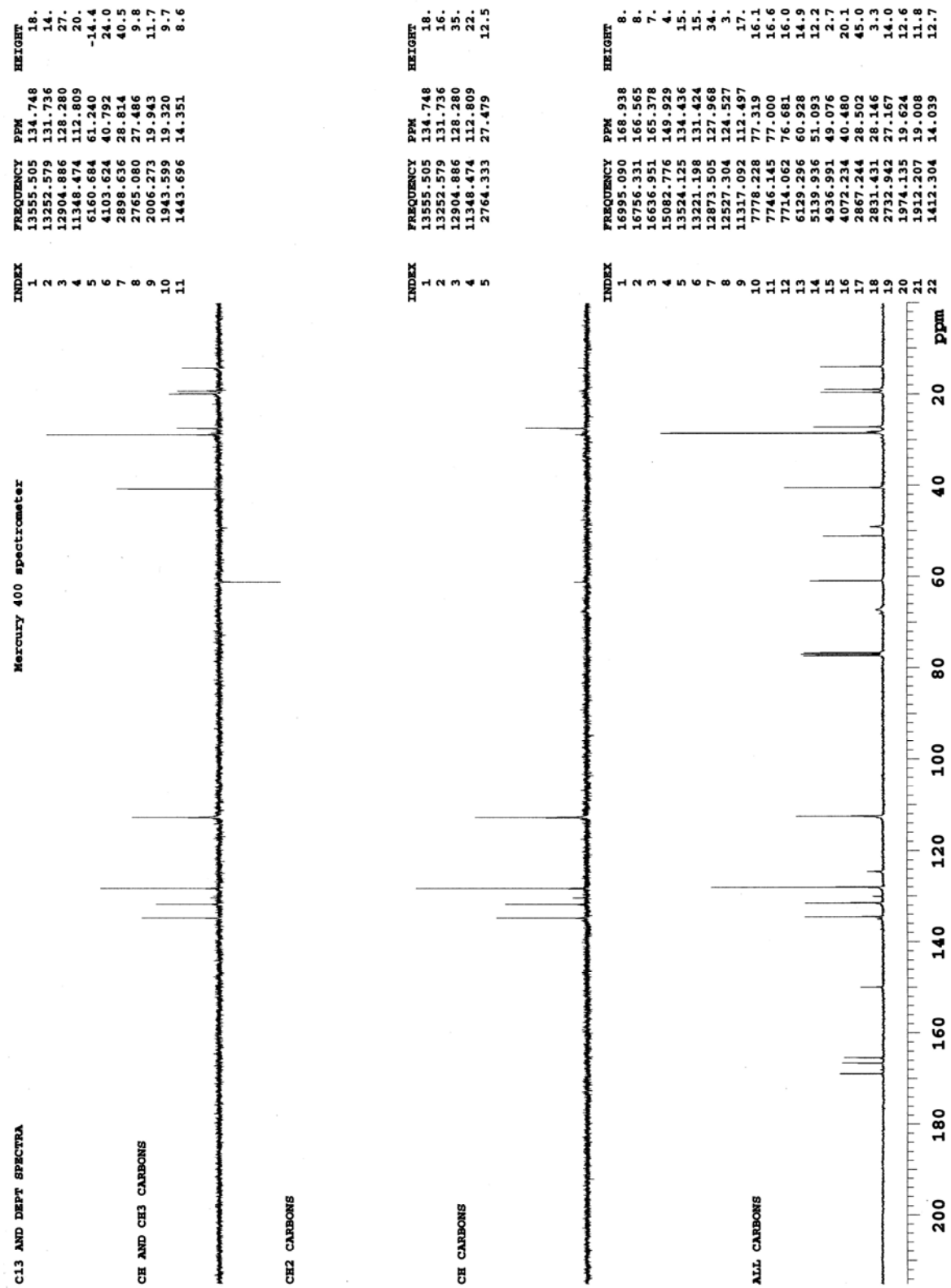
^{1}H NMR (Compound 415)



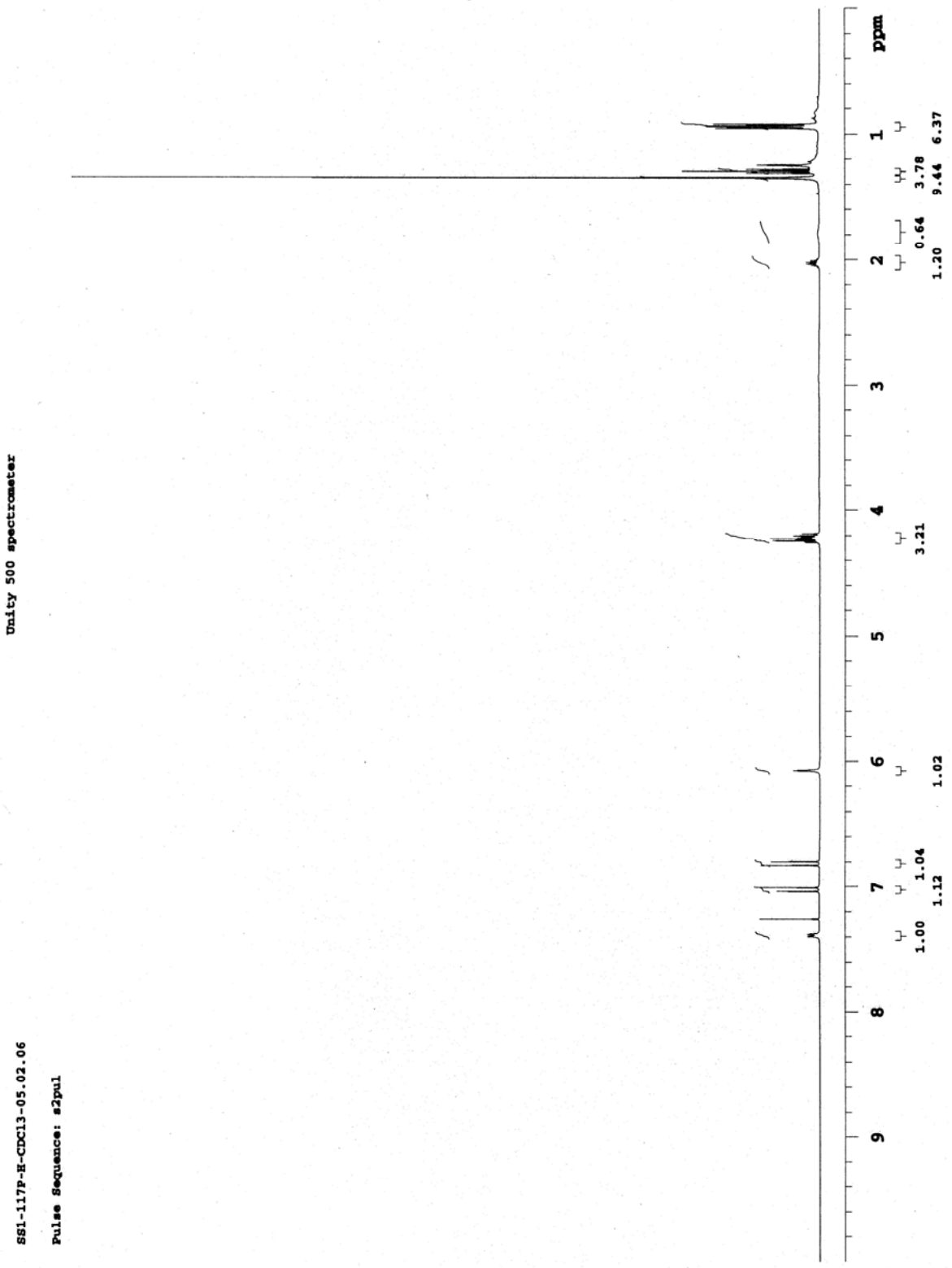
^{13}C NMR (Compound 415)



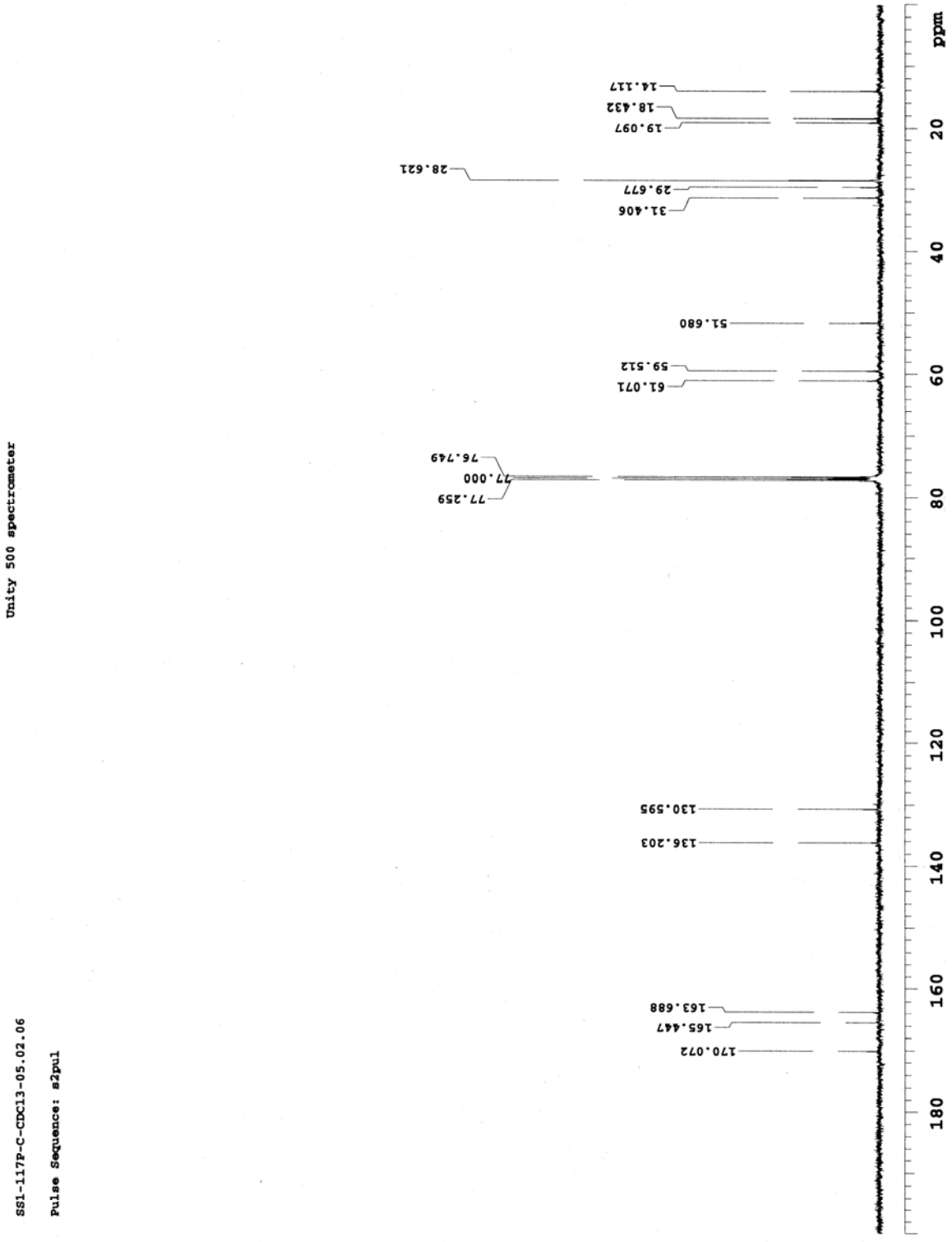
DEPT NMR (Compound 415)



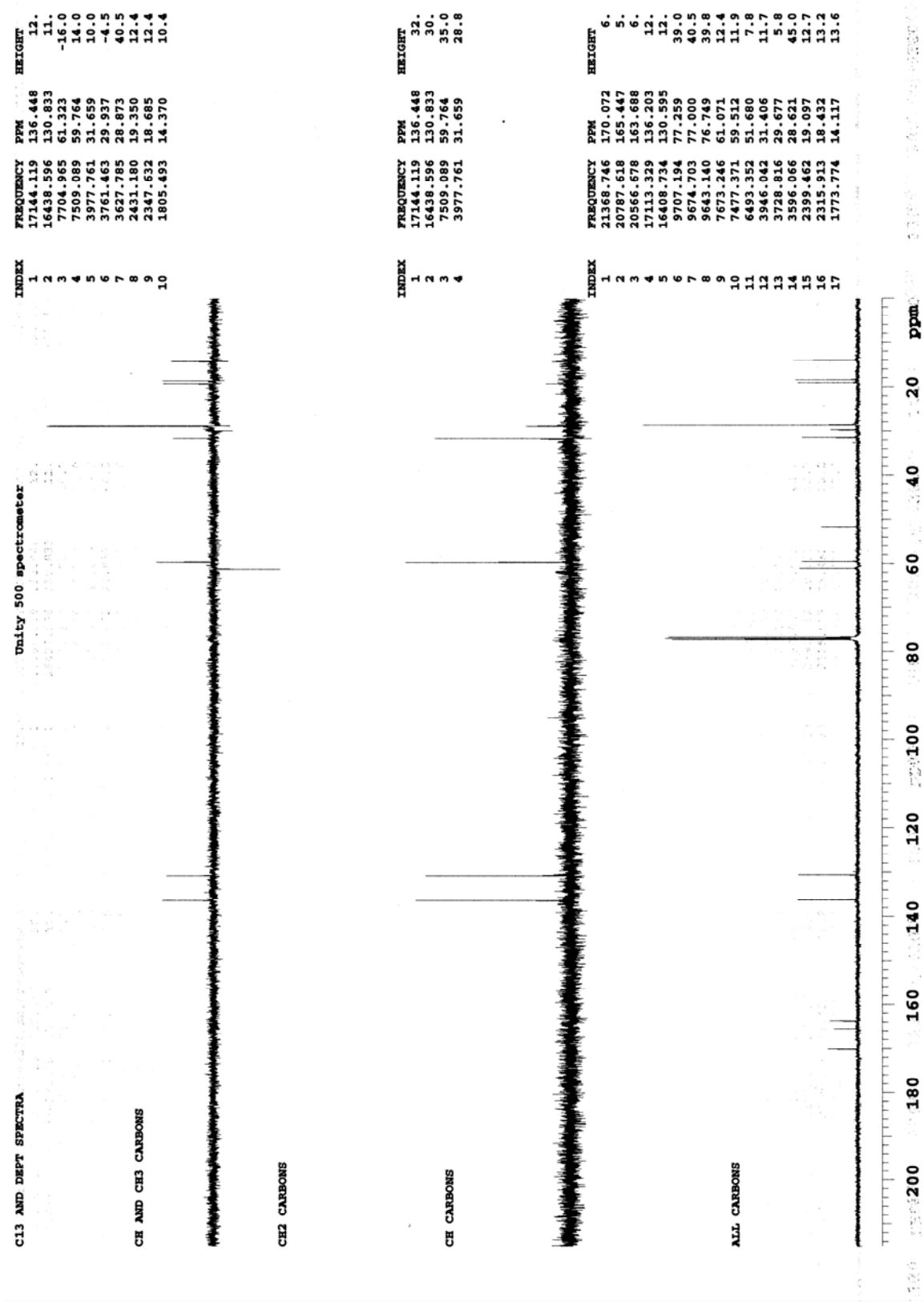
[1]H NMR (Compound 417)



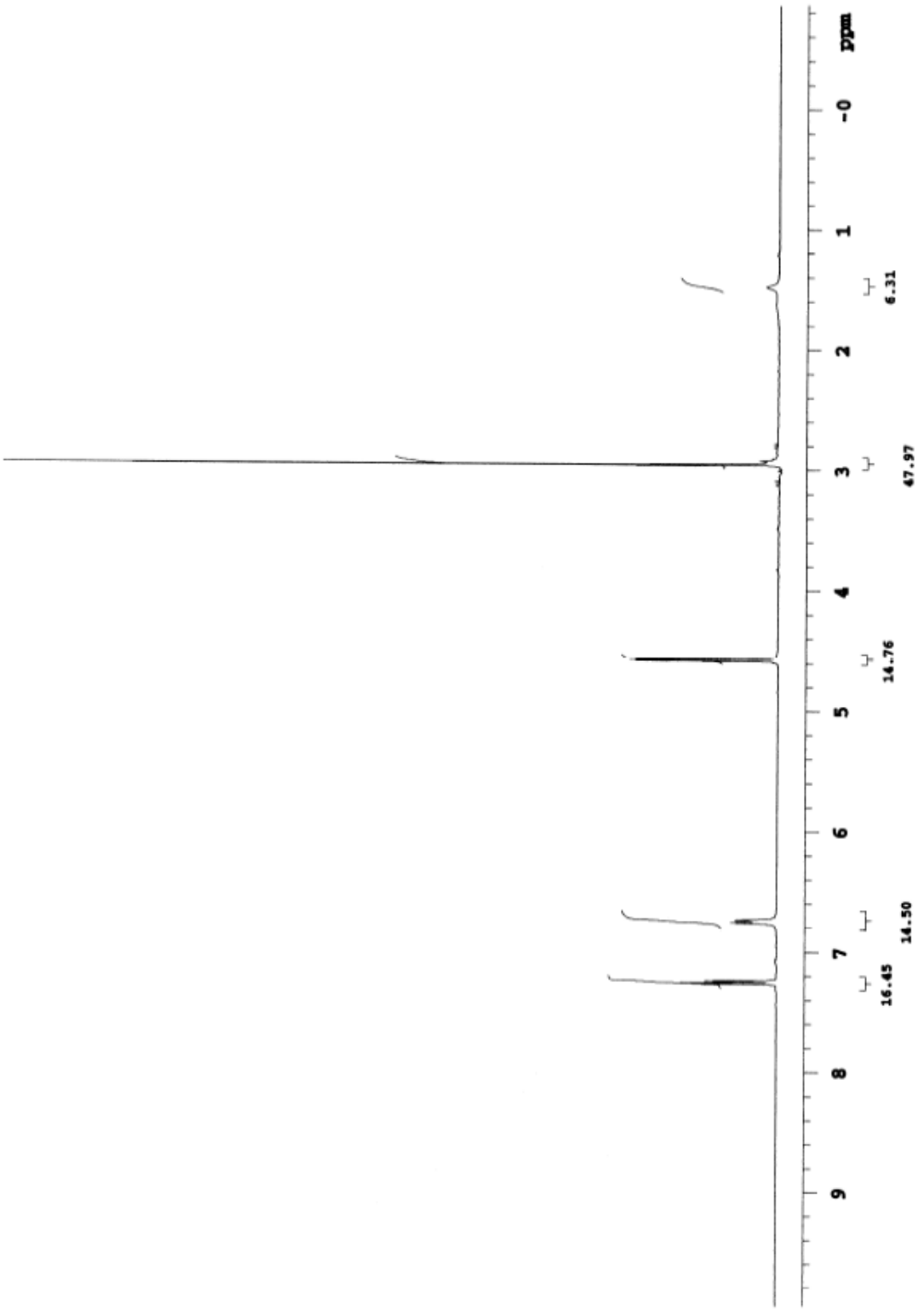
^{13}C NMR (Compound 417)



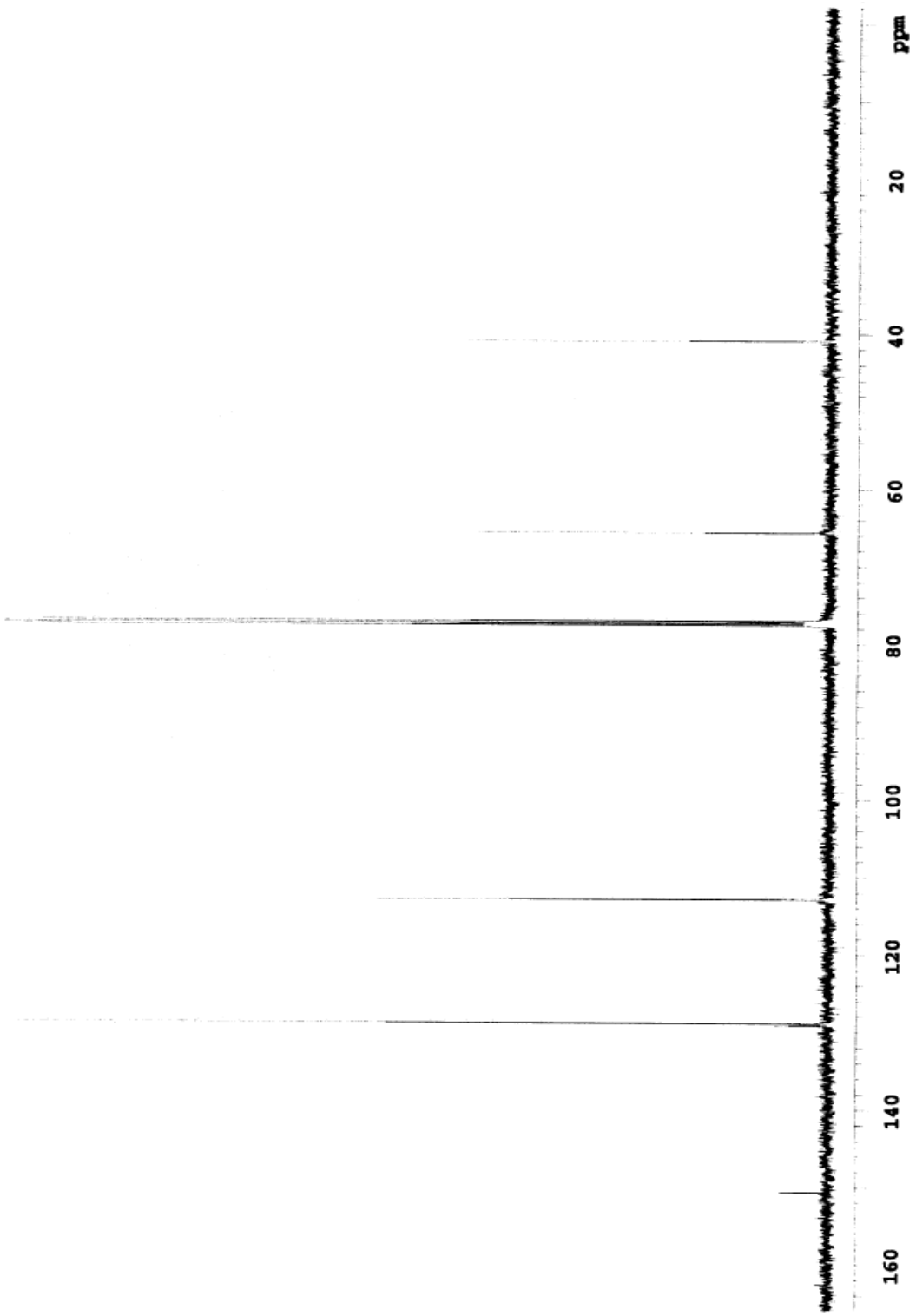
DEPT NMR (Compound 417)



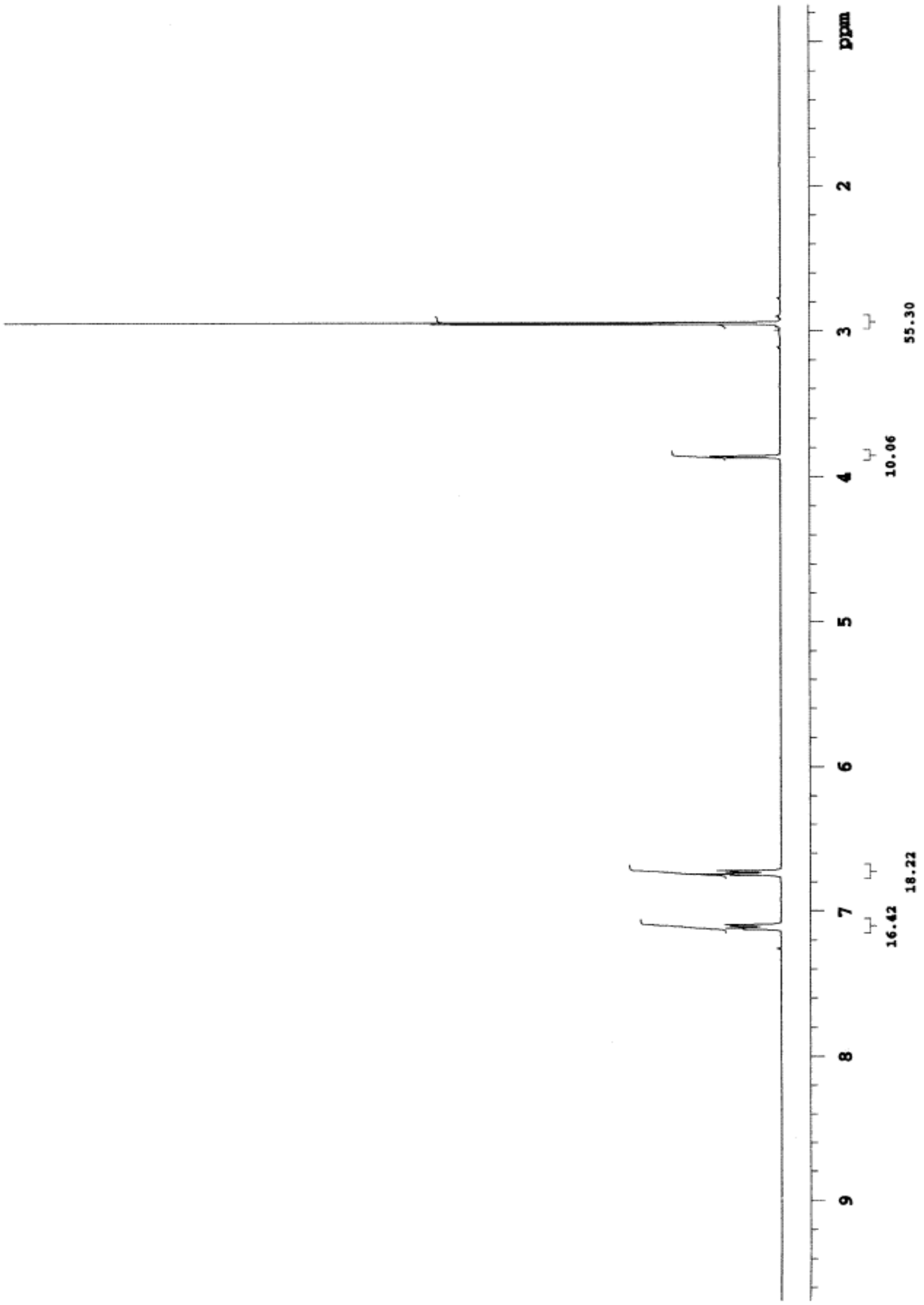
^{1}H NMR (Compound 424)



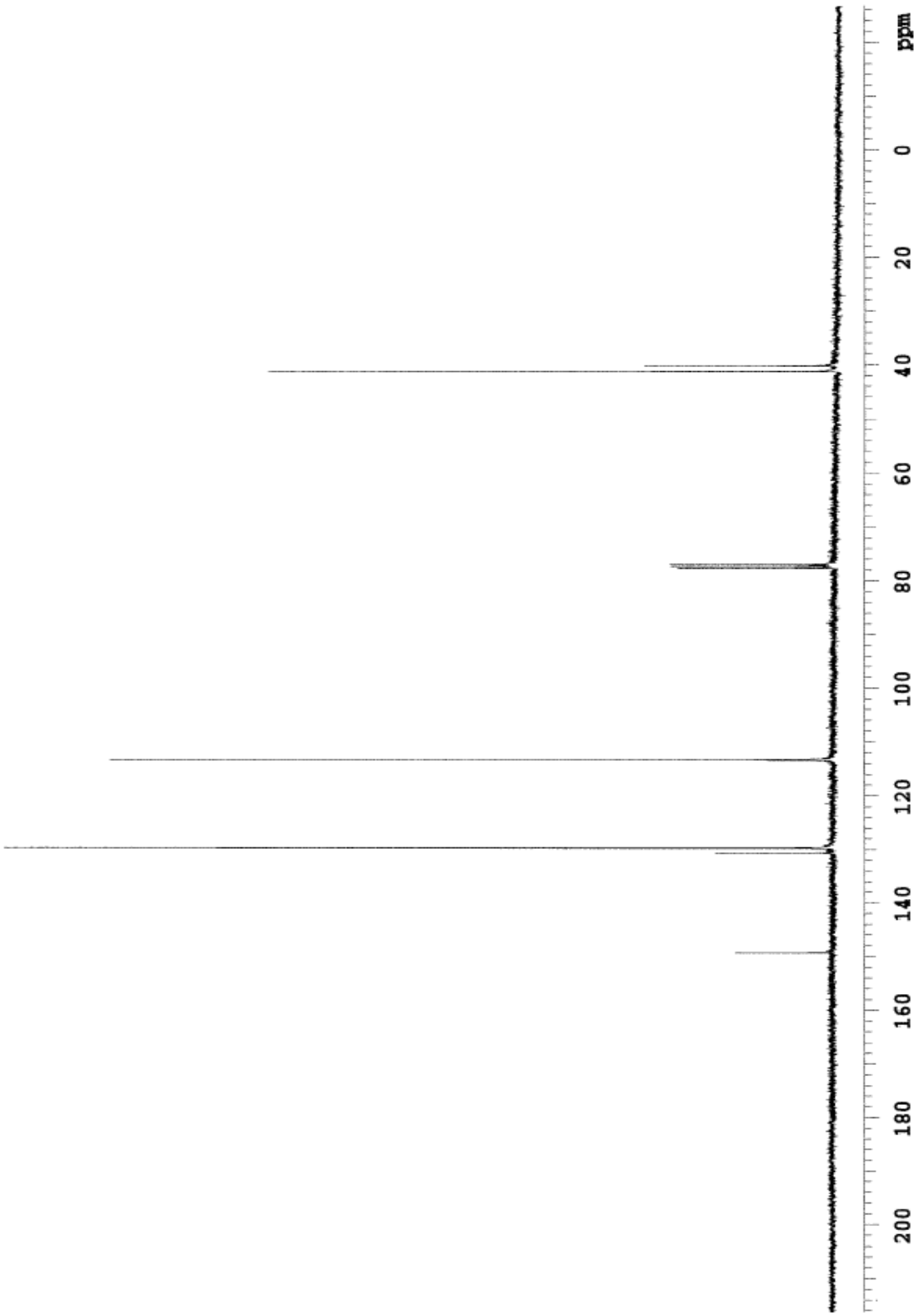
^{13}C NMR (Compound 424)



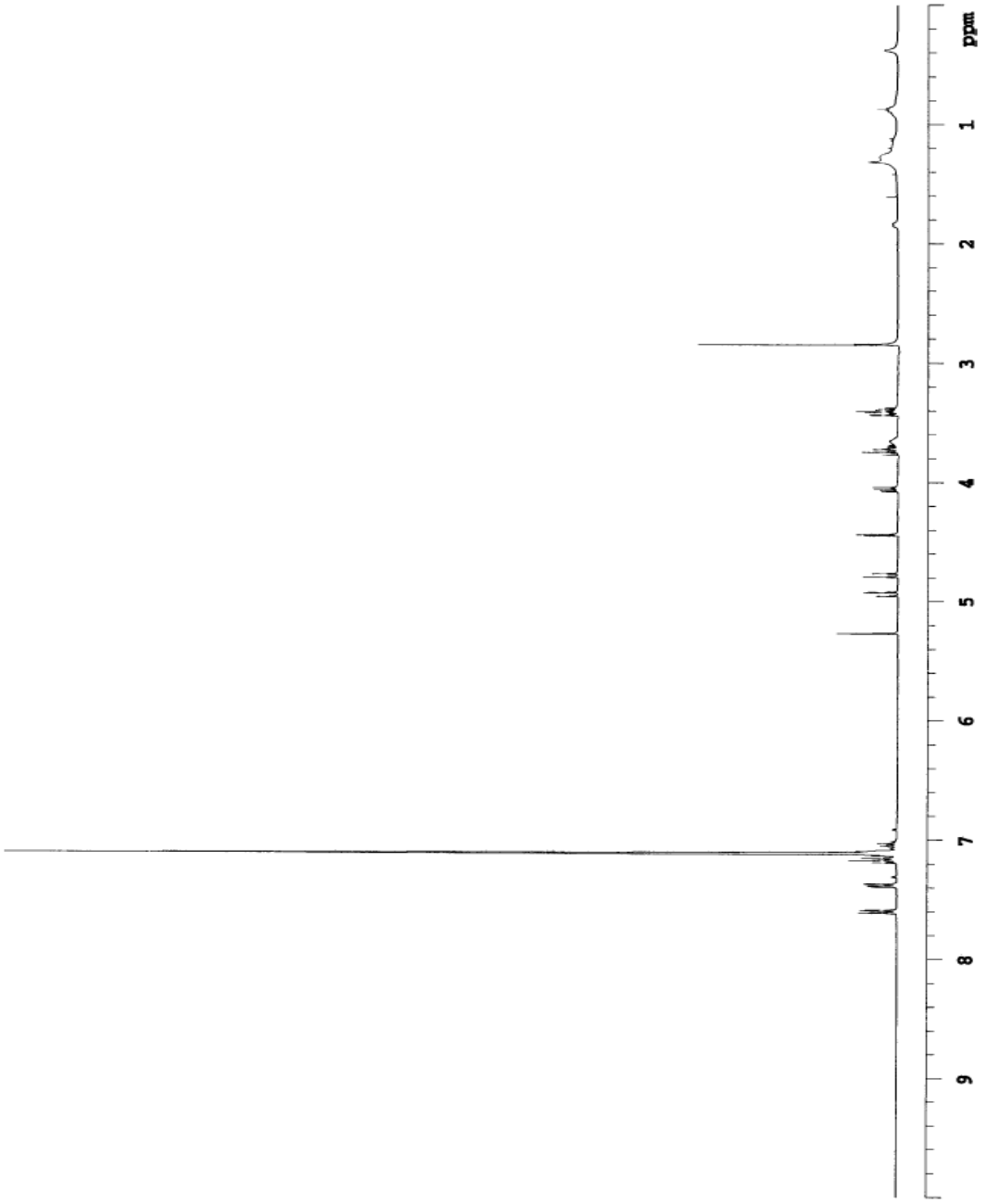
^{1}H NMR (Compound 427)



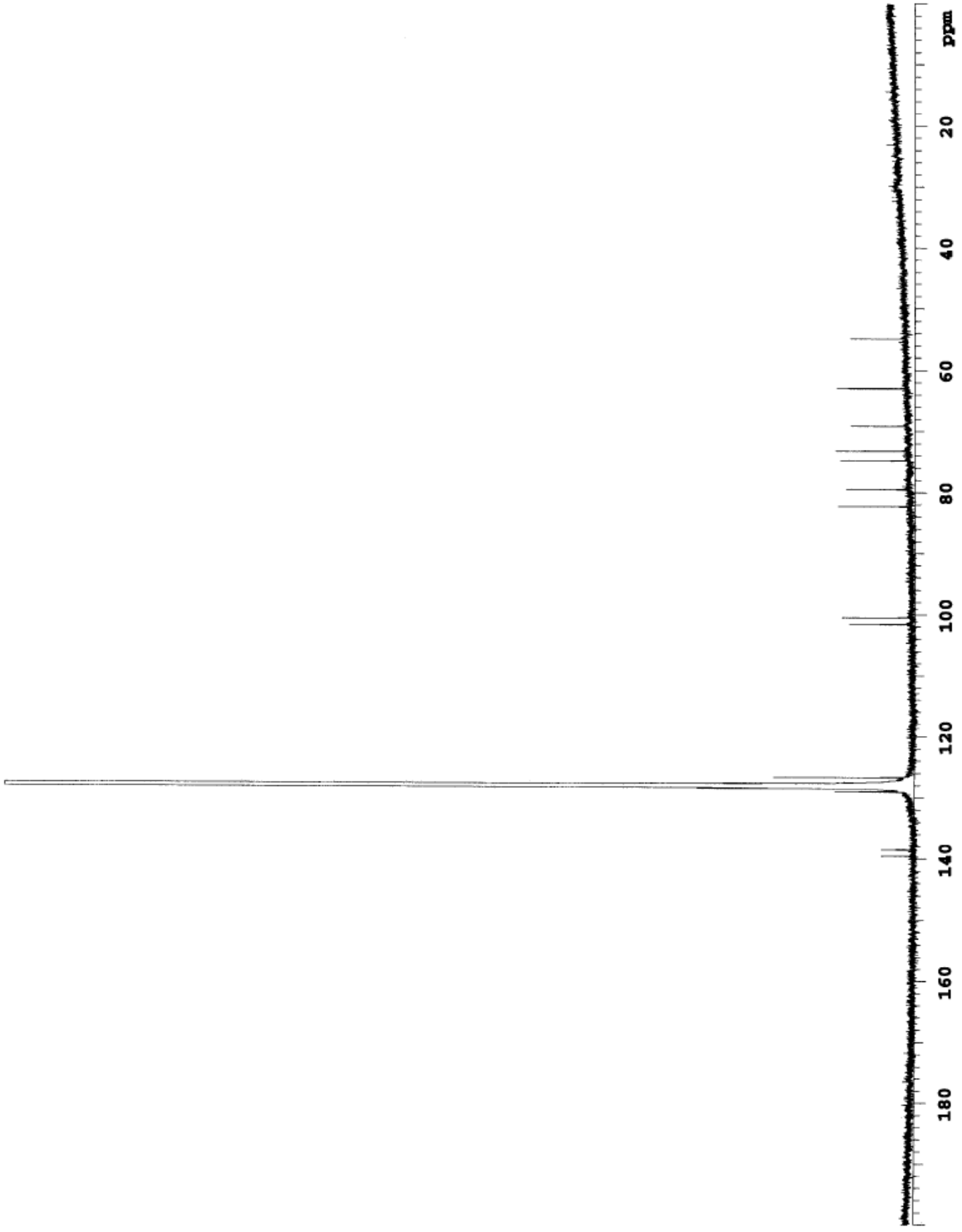
^{13}C NMR (Compound 427)



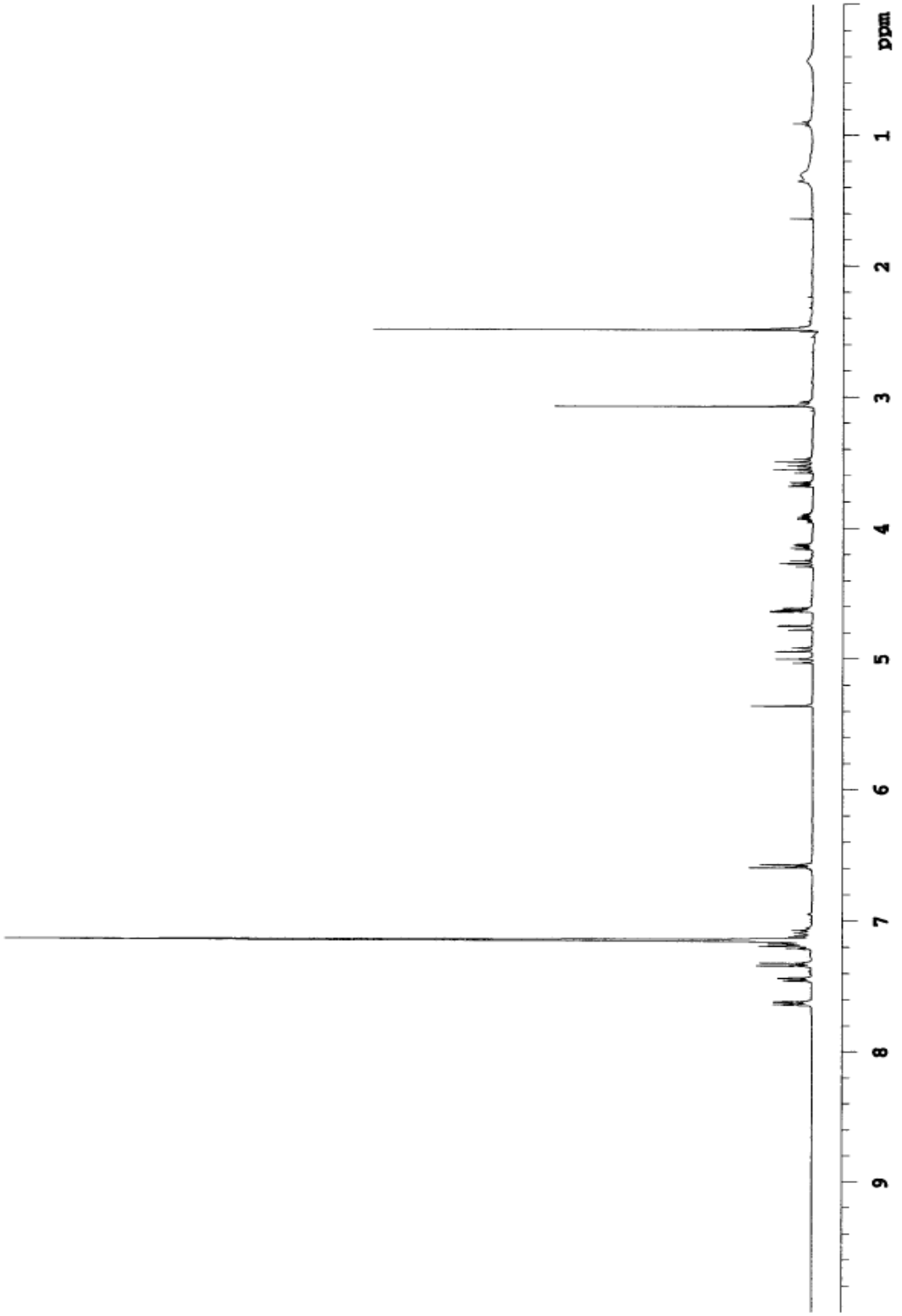
^{1}H NMR (Compound 430)



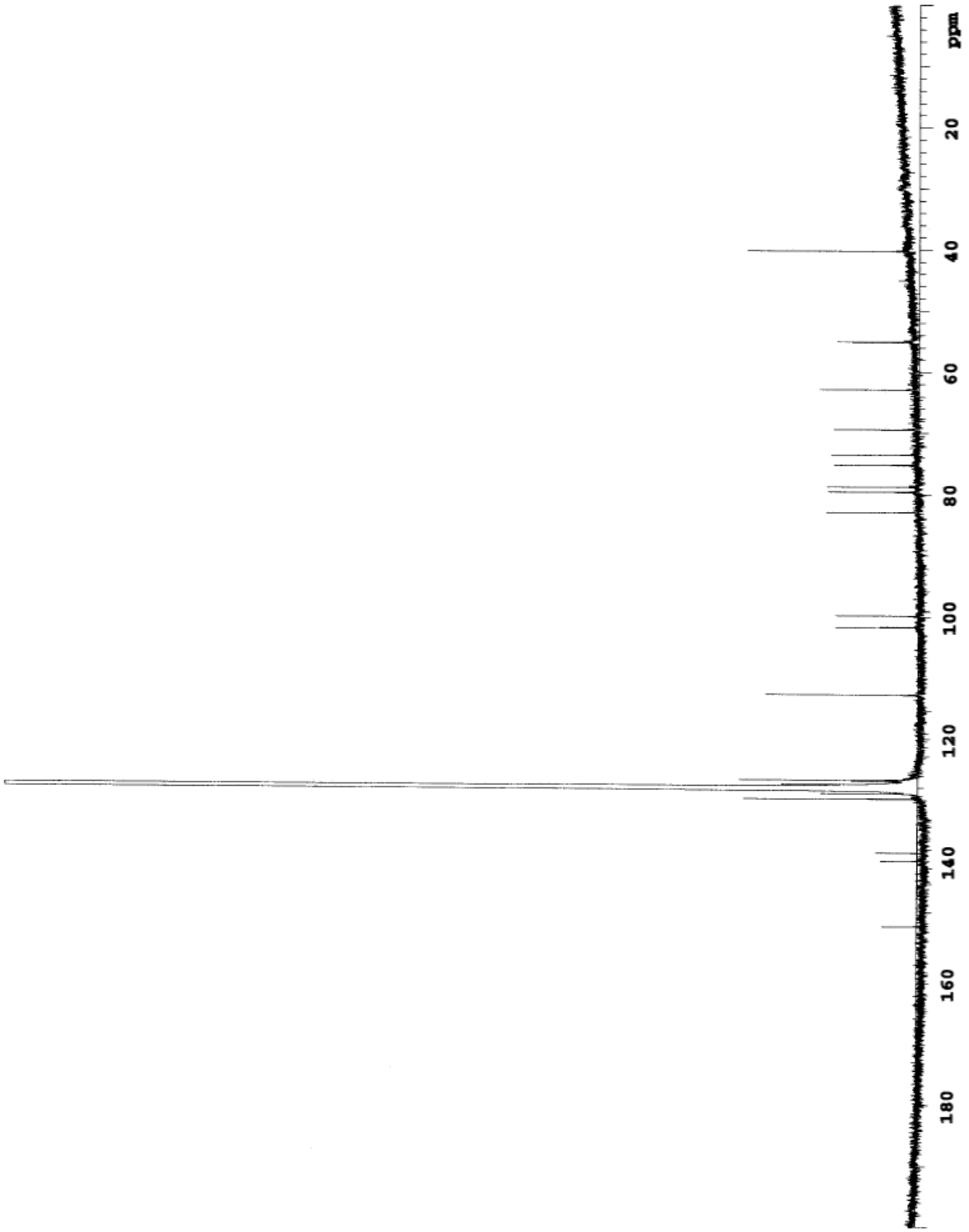
^{13}C NMR (Compound 430)



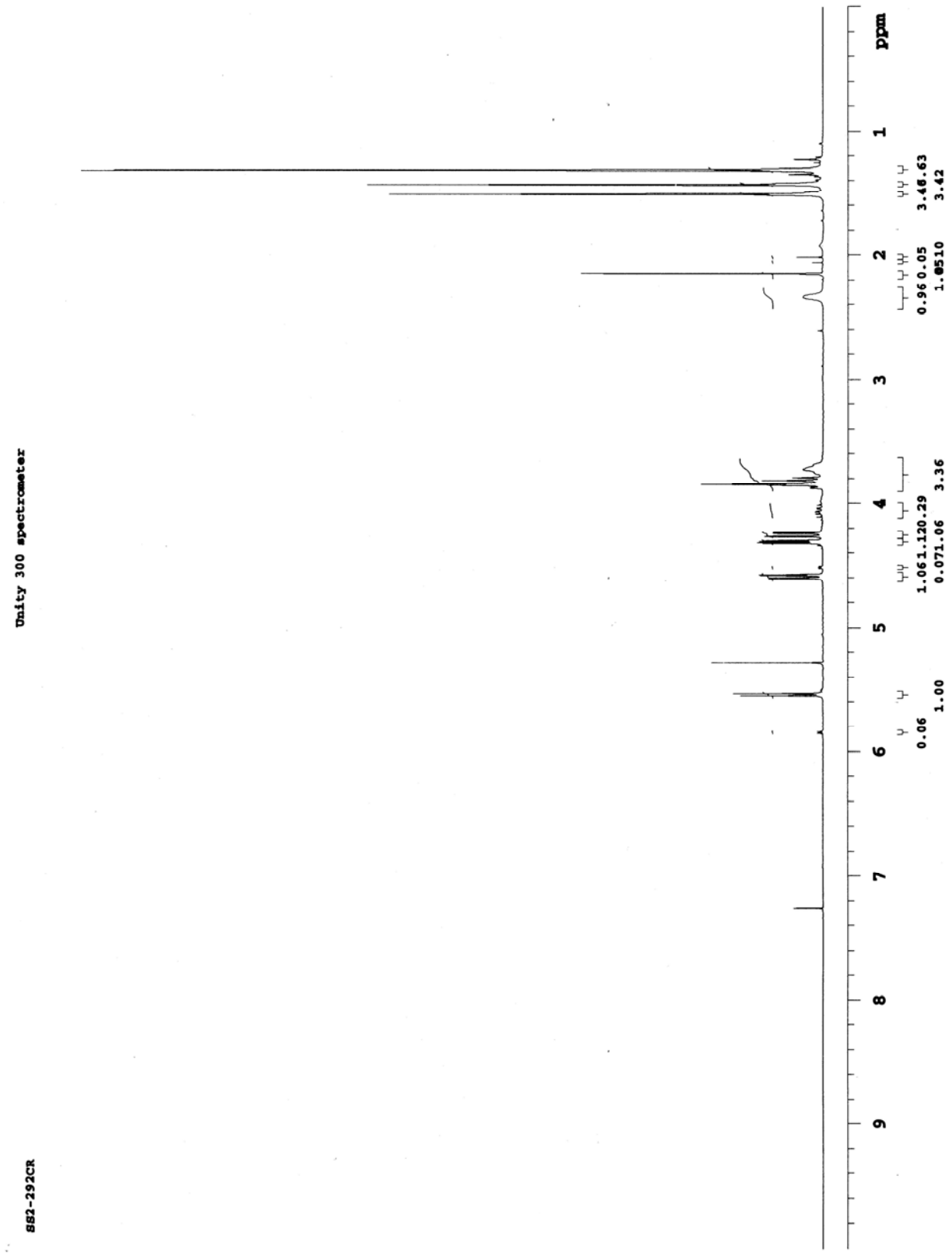
^{1}H NMR (Compound 431)



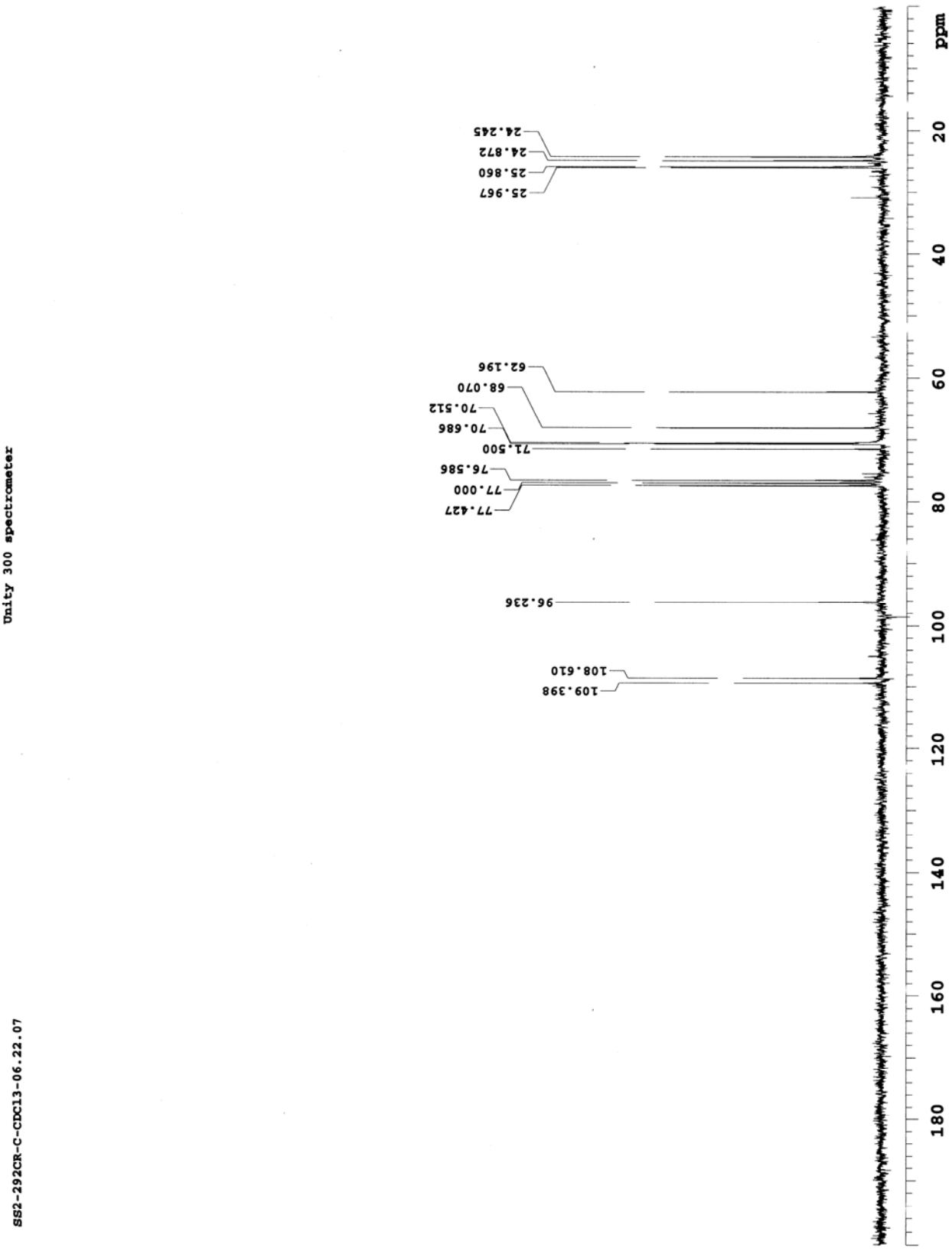
^{13}C NMR (Compound 431)



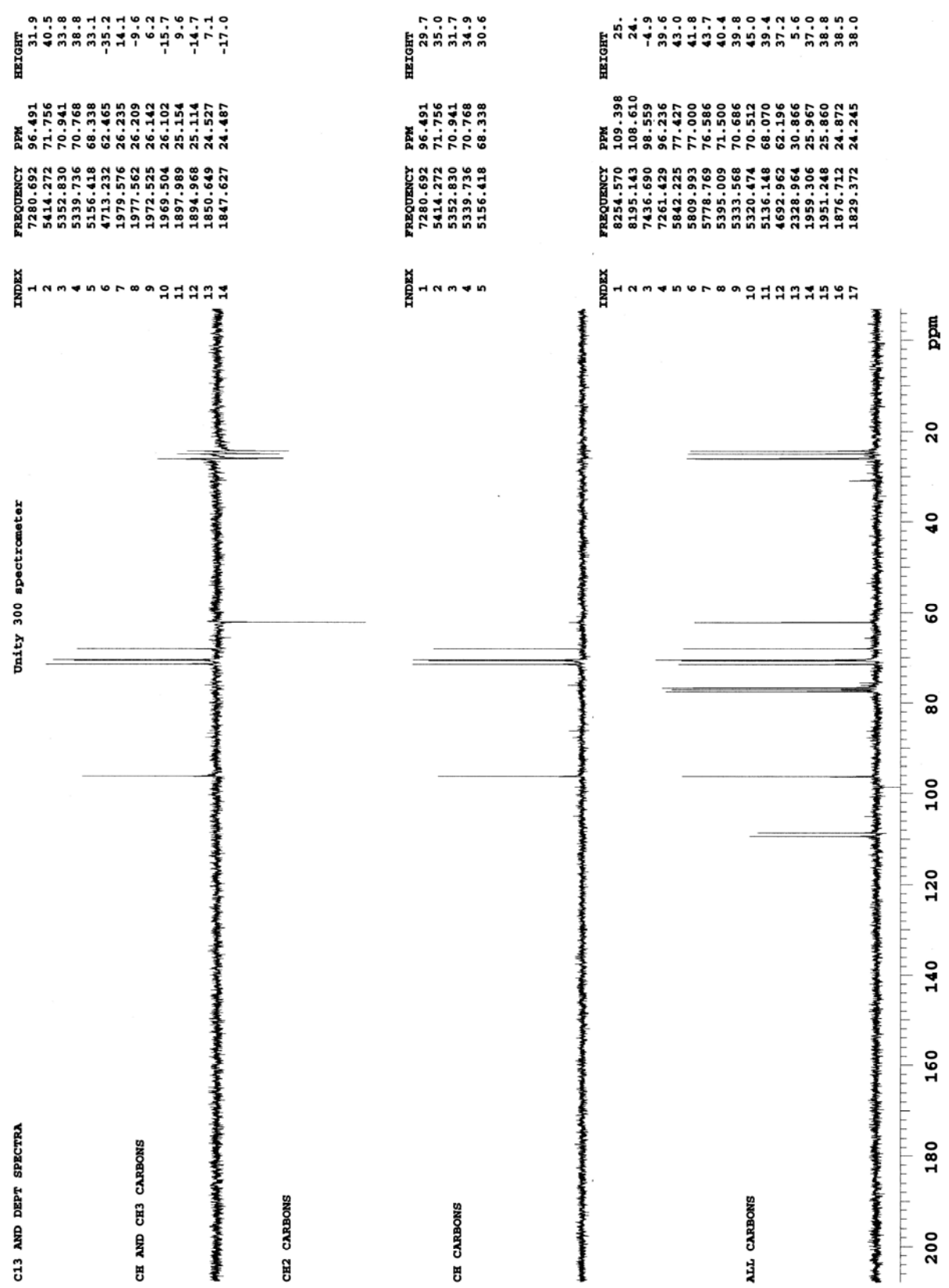
^{1}H NMR (Compound 448)



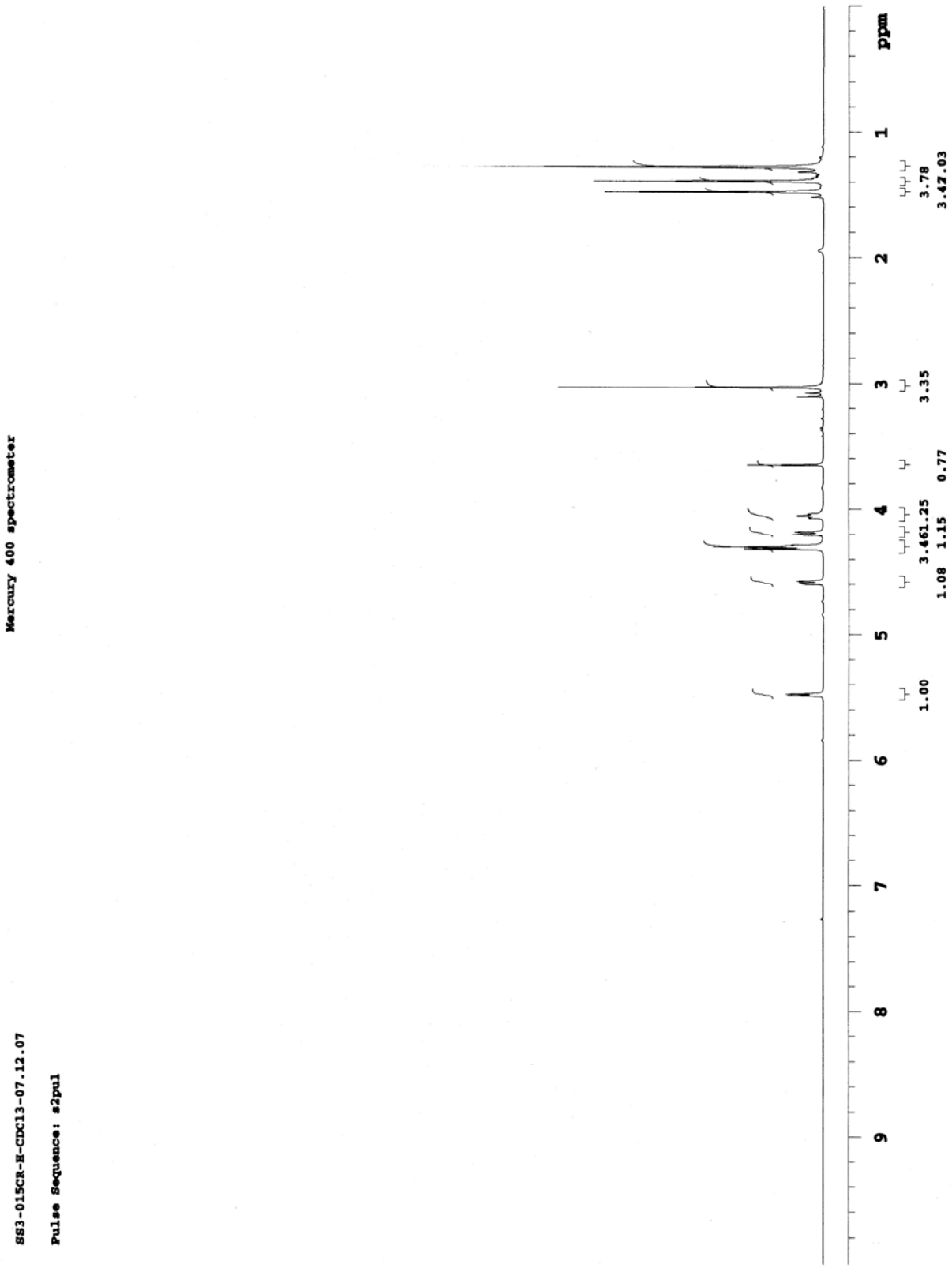
^{13}C NMR (Compound 448)



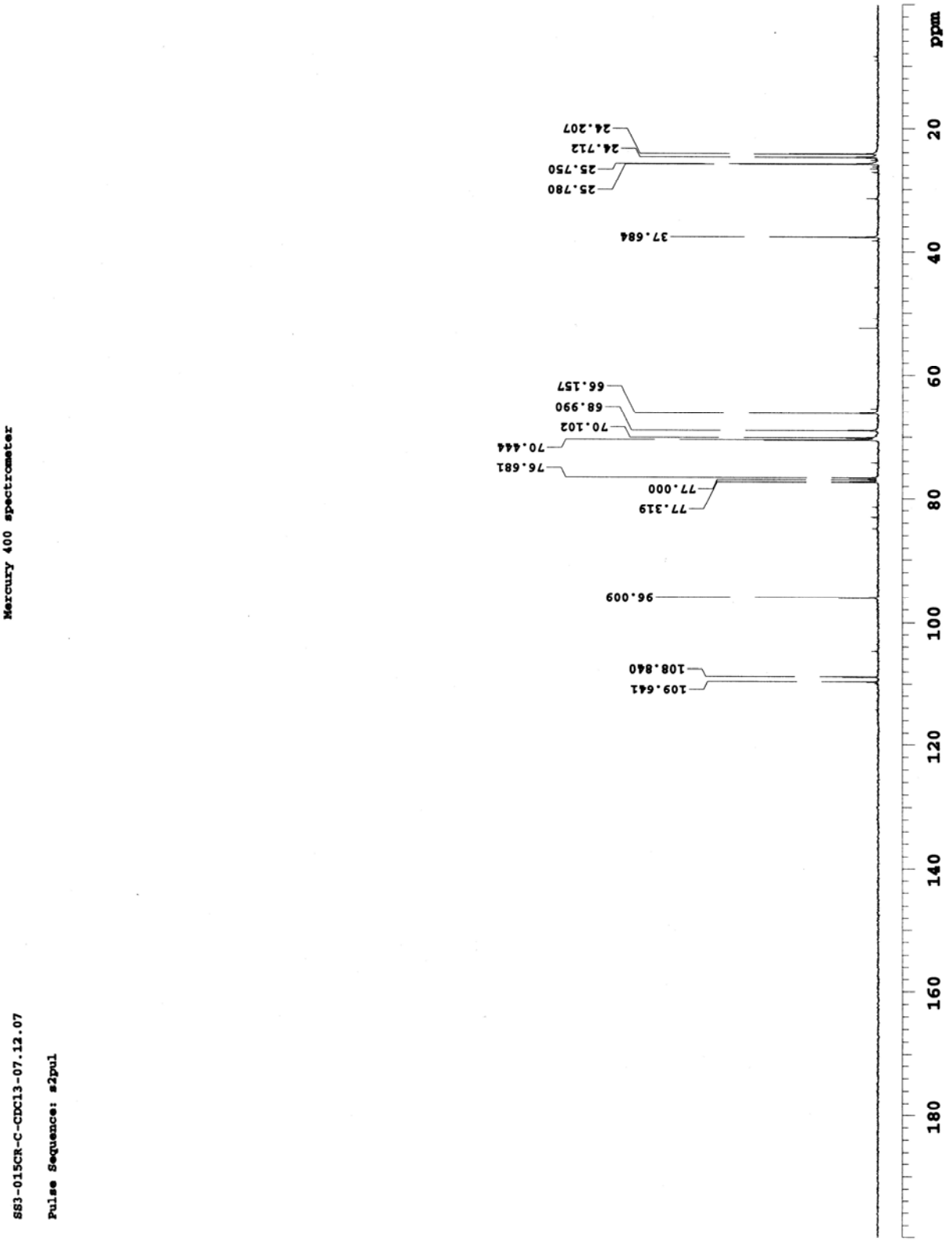
DEPT NMR (Compound 448)



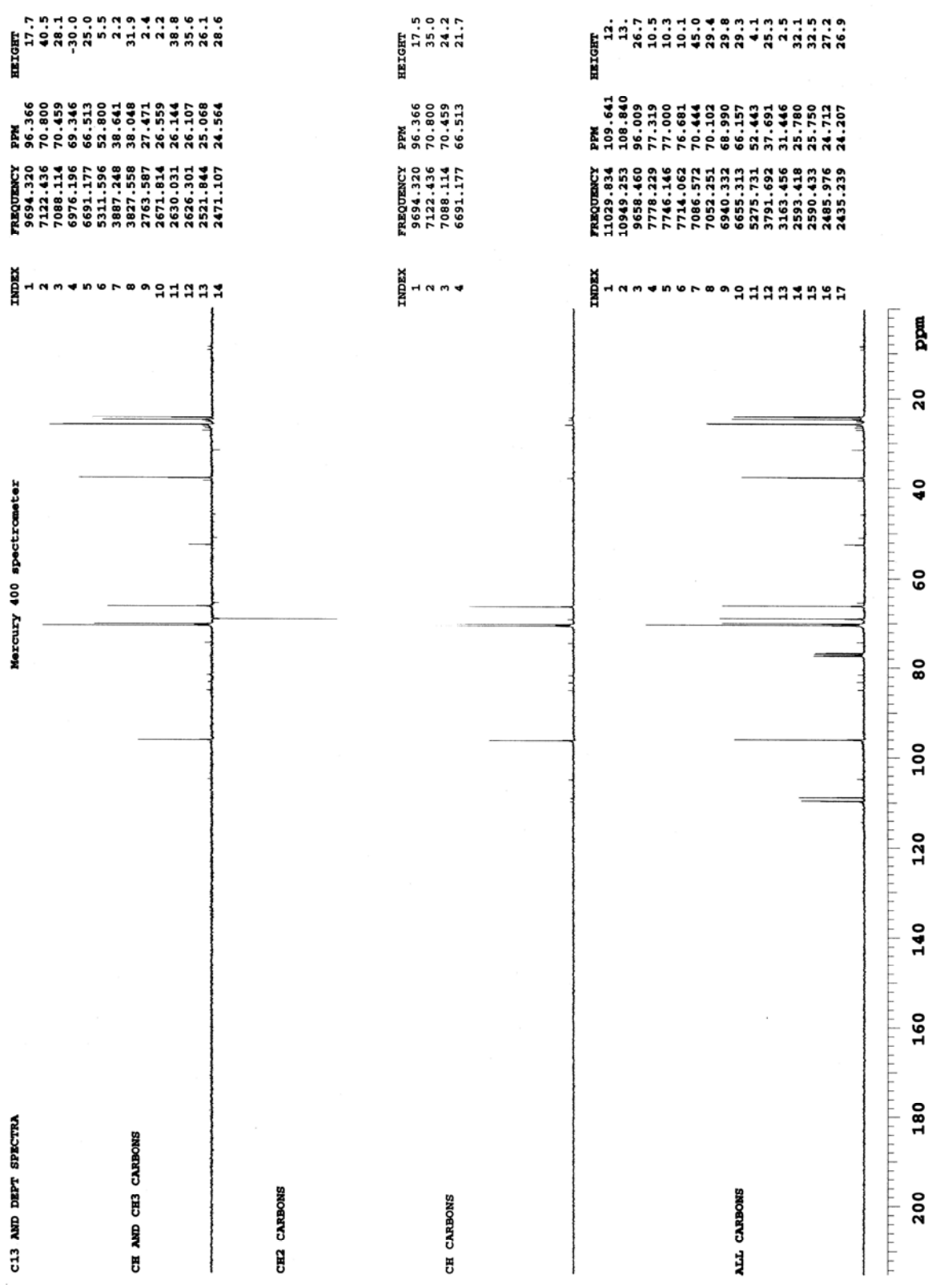
^{1}H NMR (Compound 449)



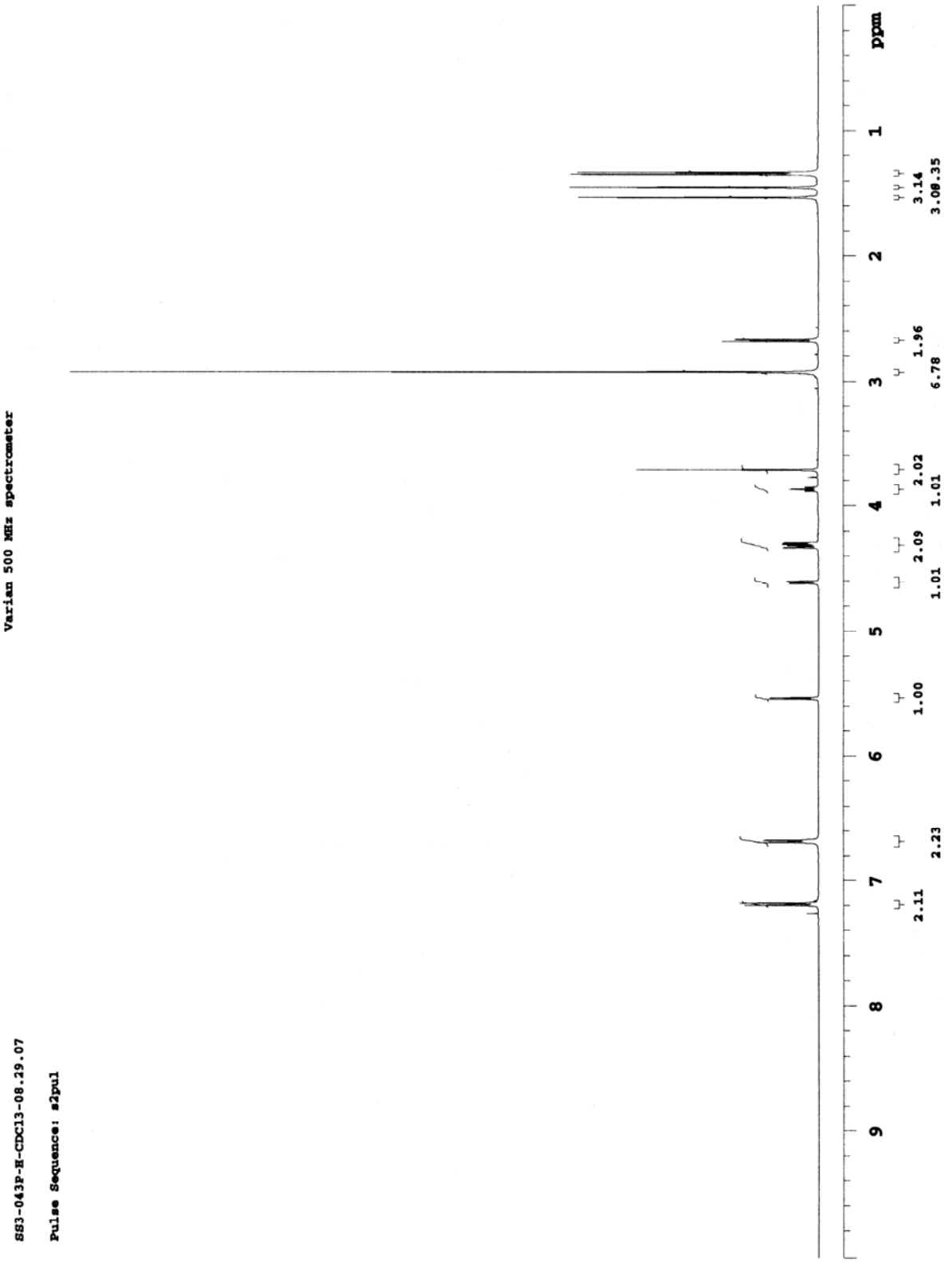
^{13}C NMR (Compound 449)



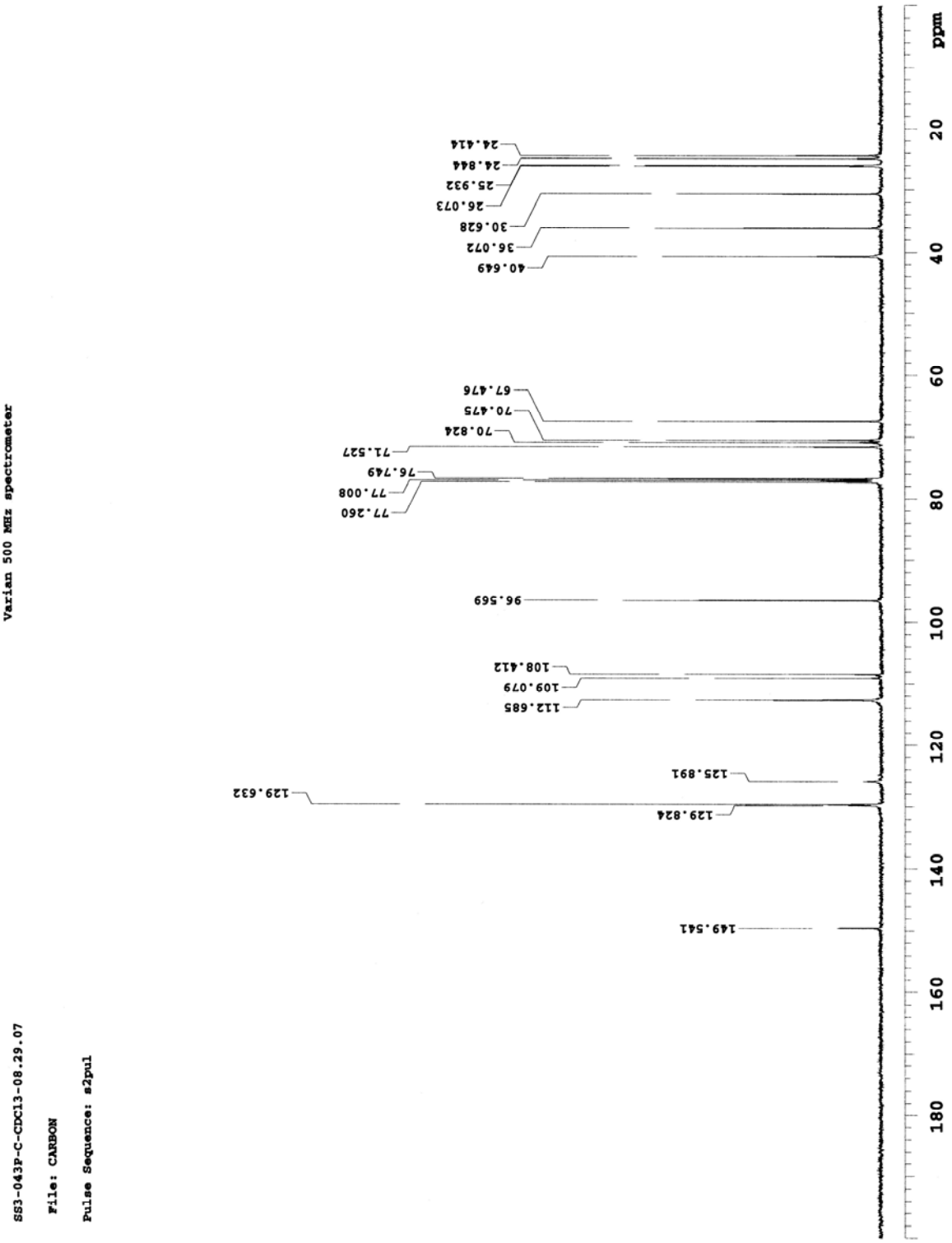
DEPT NMR (Compound 449)



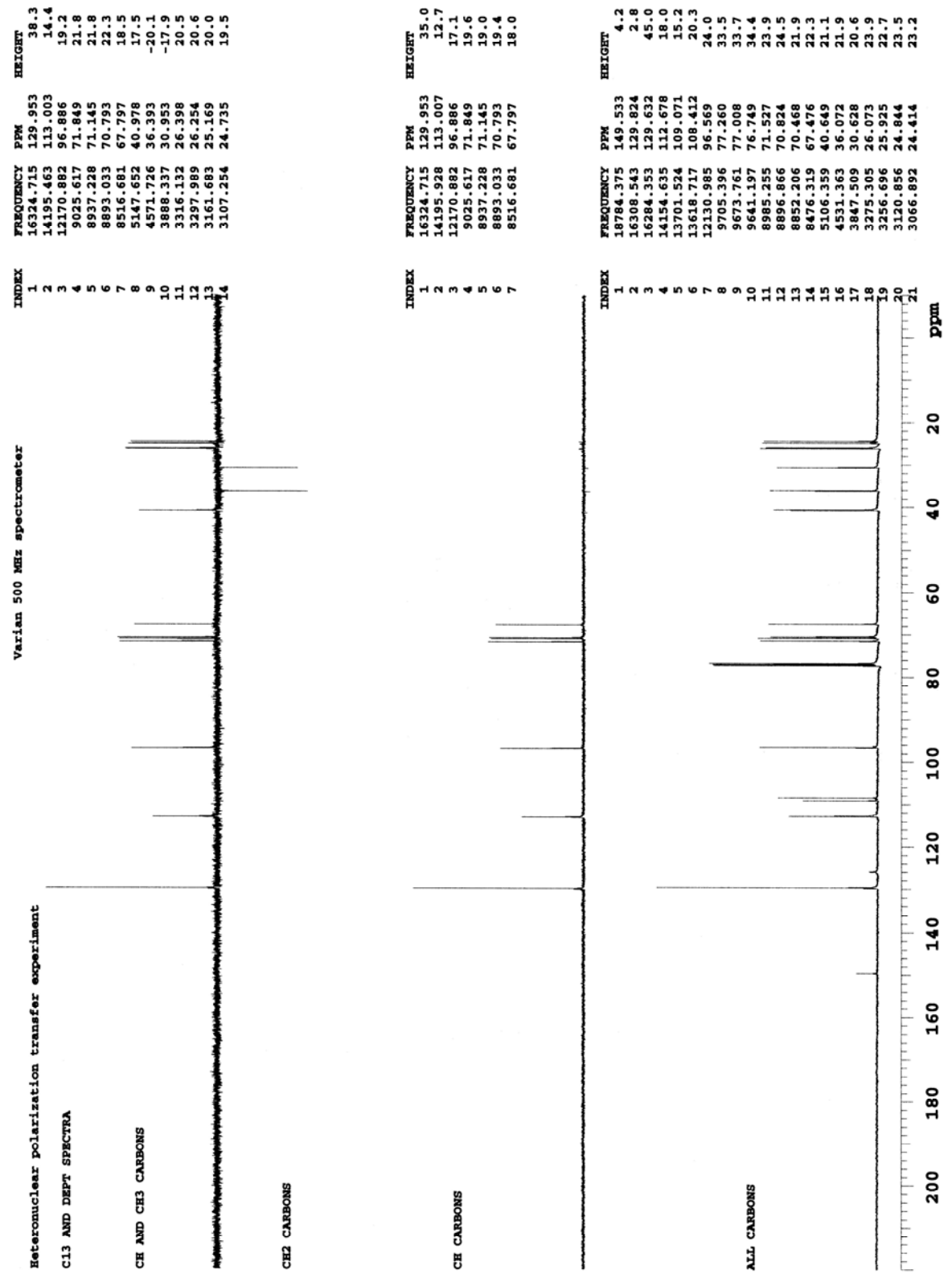
^{1}H NMR (Compound 450)



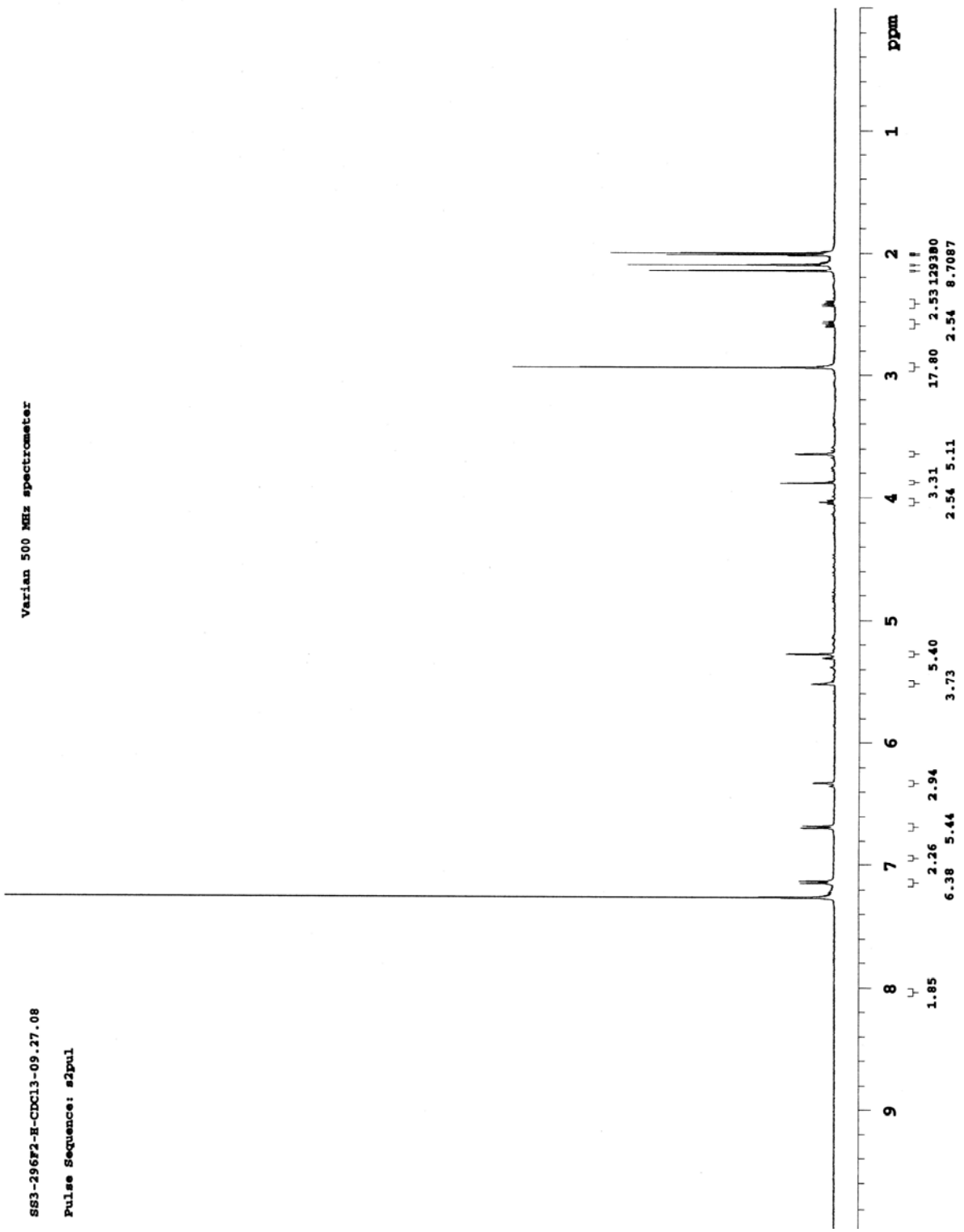
^{13}C NMR (Compound 450)



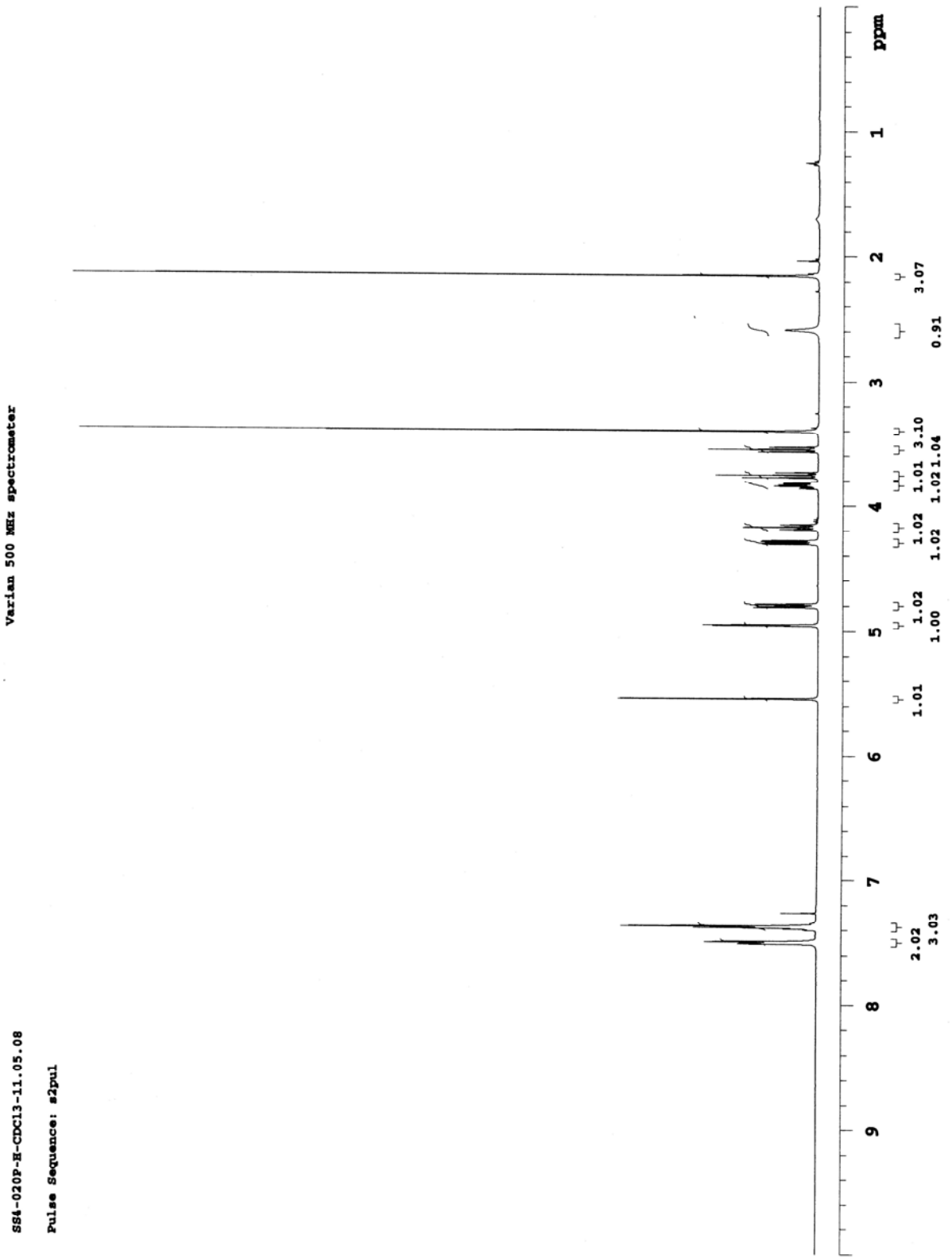
DEPT NMR (Compound 450)



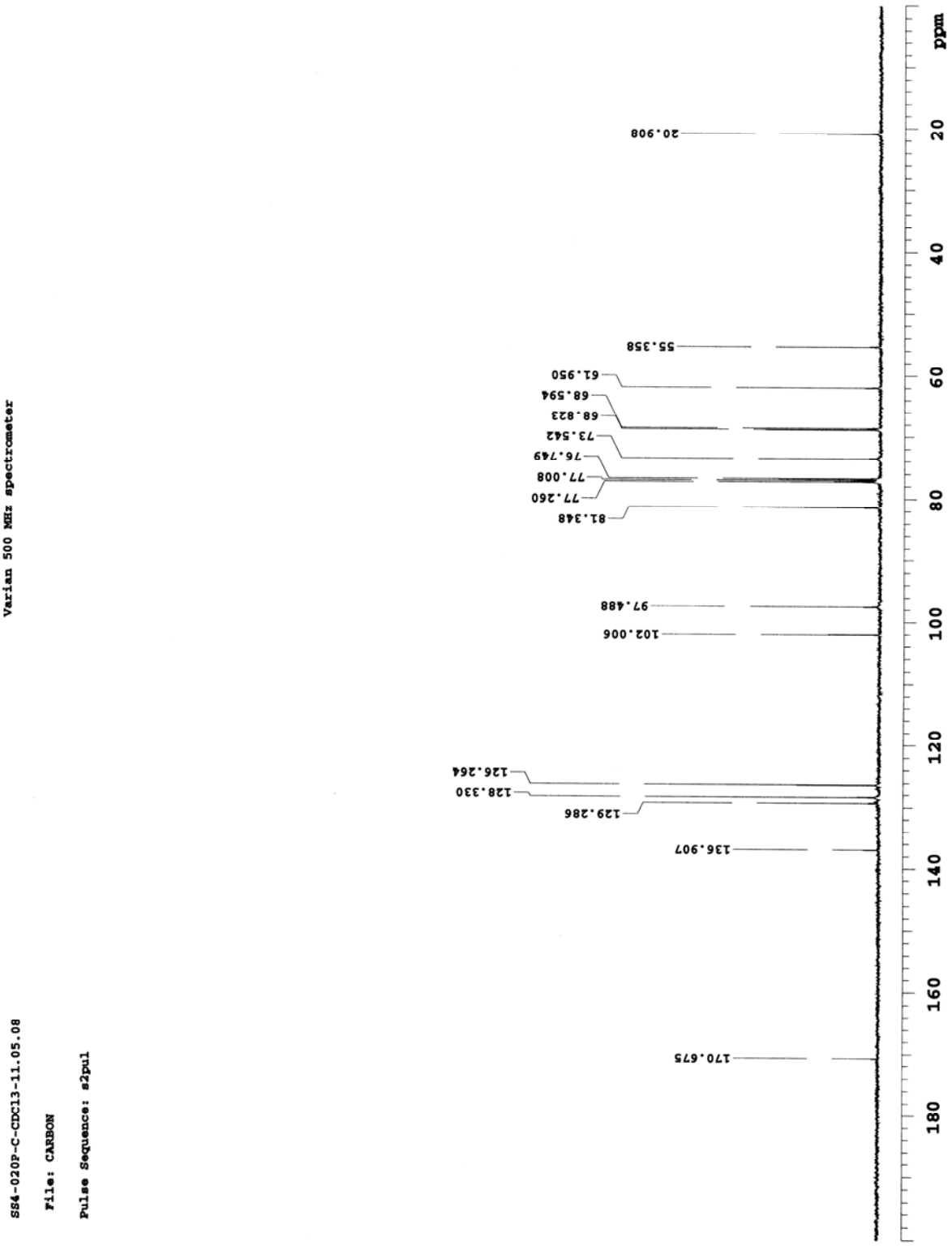
^{1}H NMR (Compound 453)



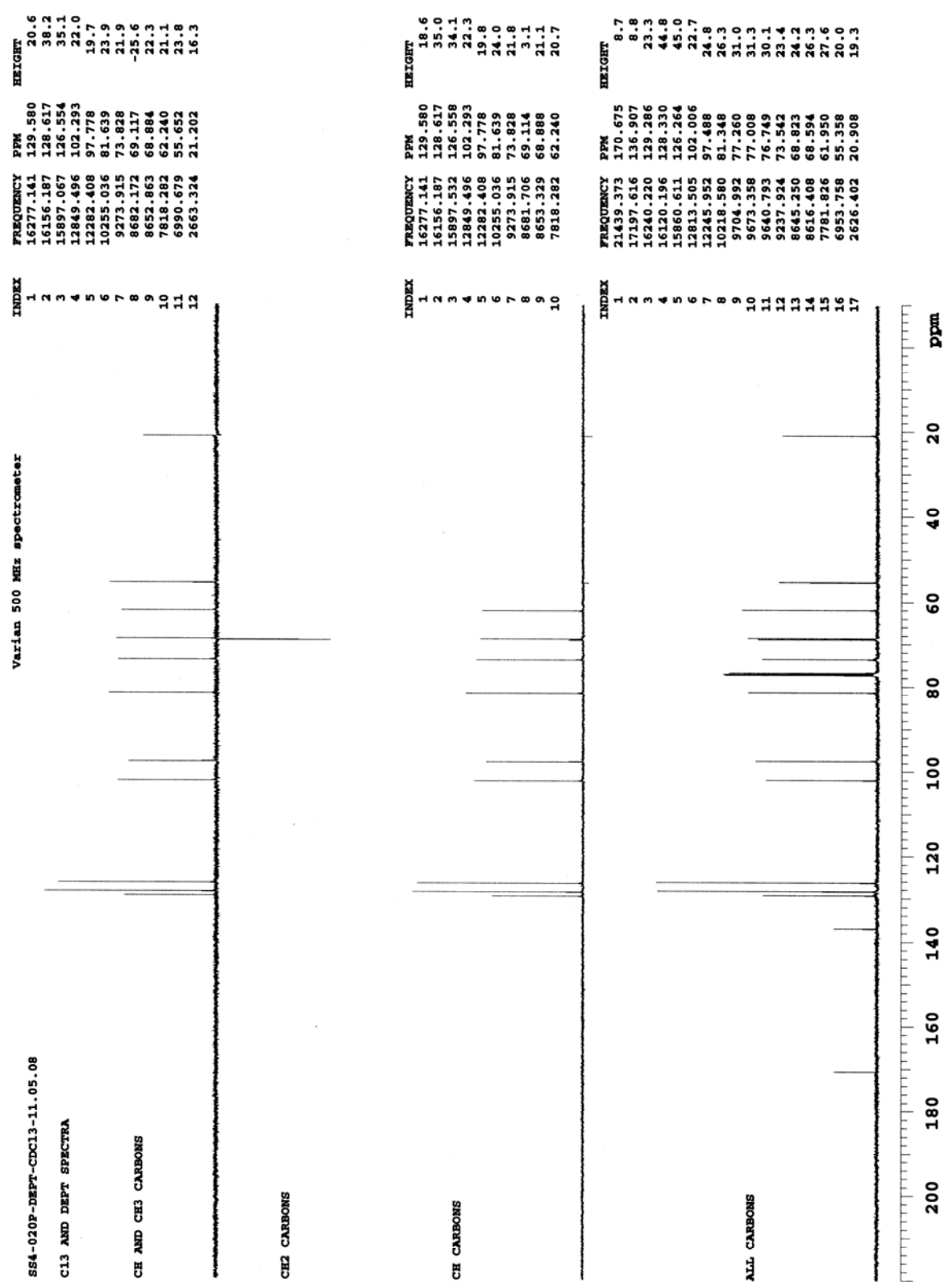
^{1}H NMR (Compound 455)



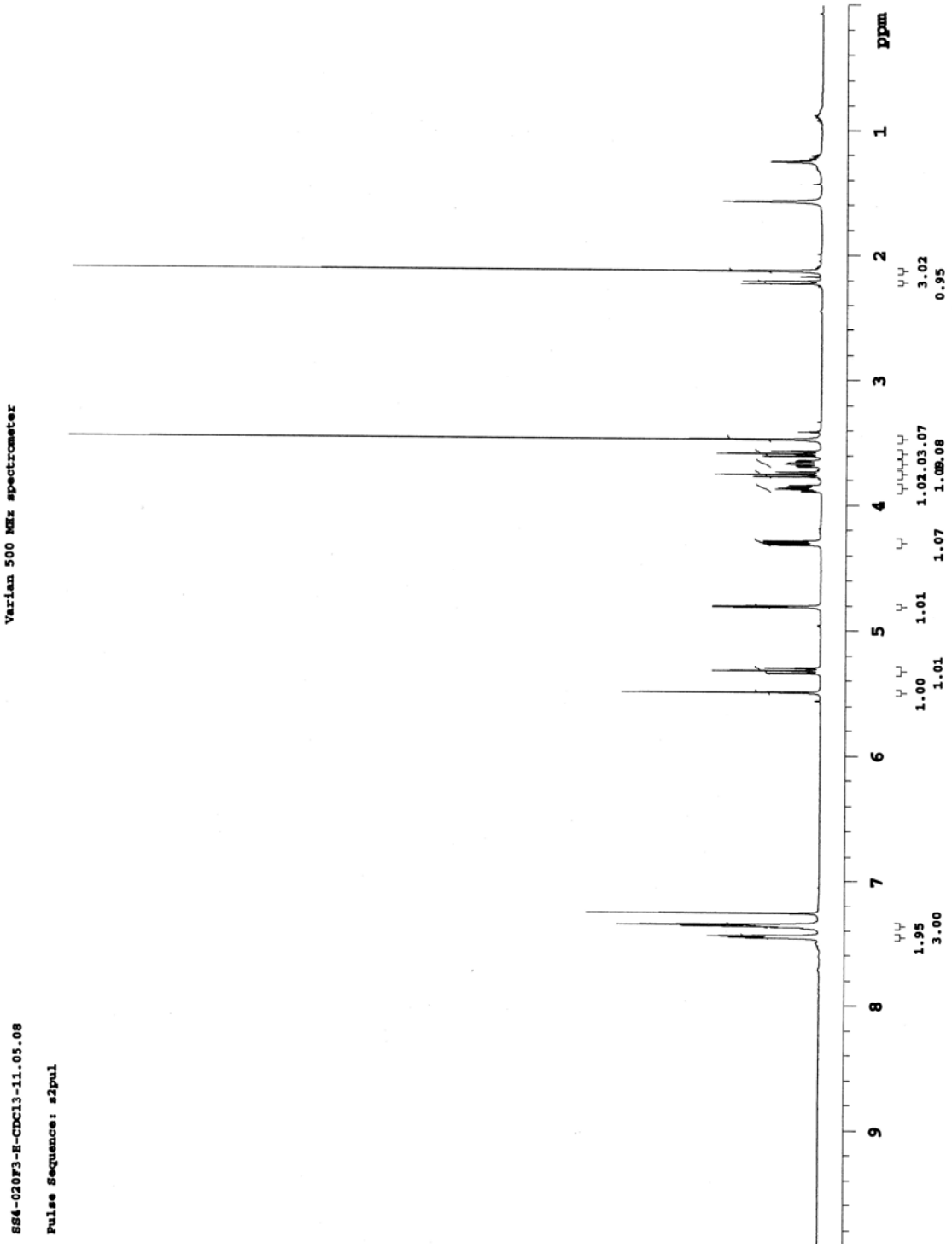
^{13}C NMR (Compound 455)



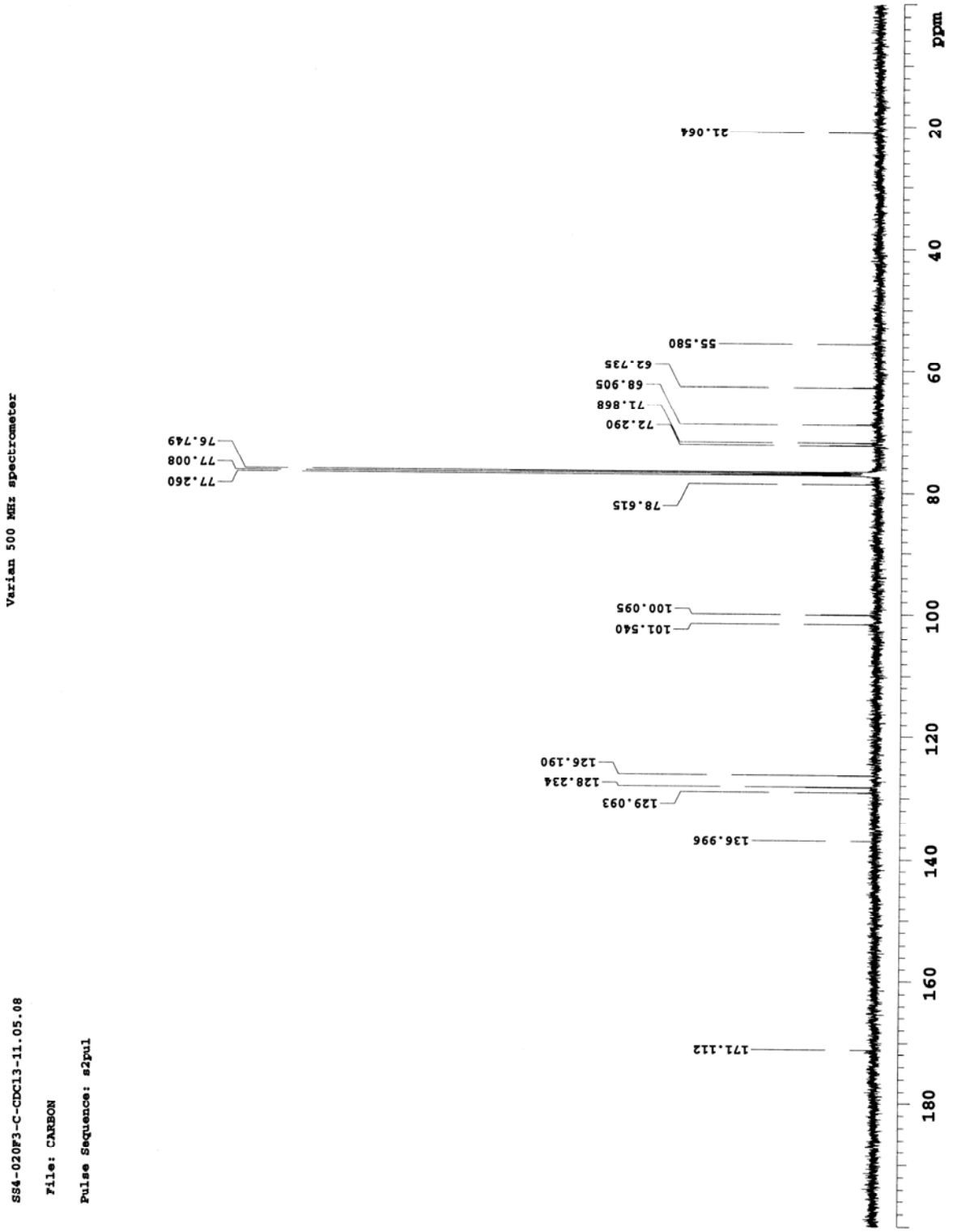
DEPT NMR (Compound 455)



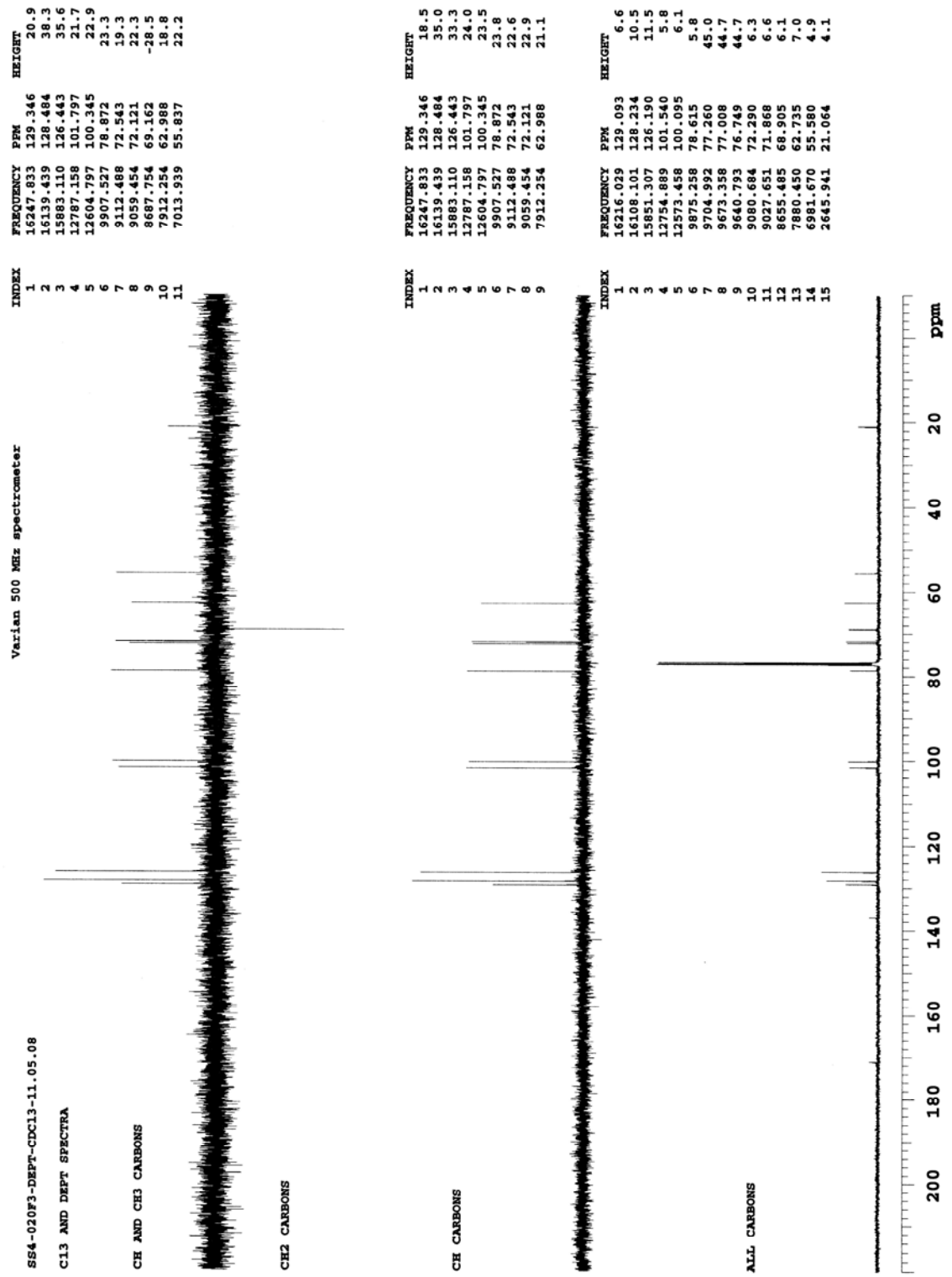
^{1}H NMR ((2R,4aR,6S,7R,8R,8aR)-7-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl acetate)



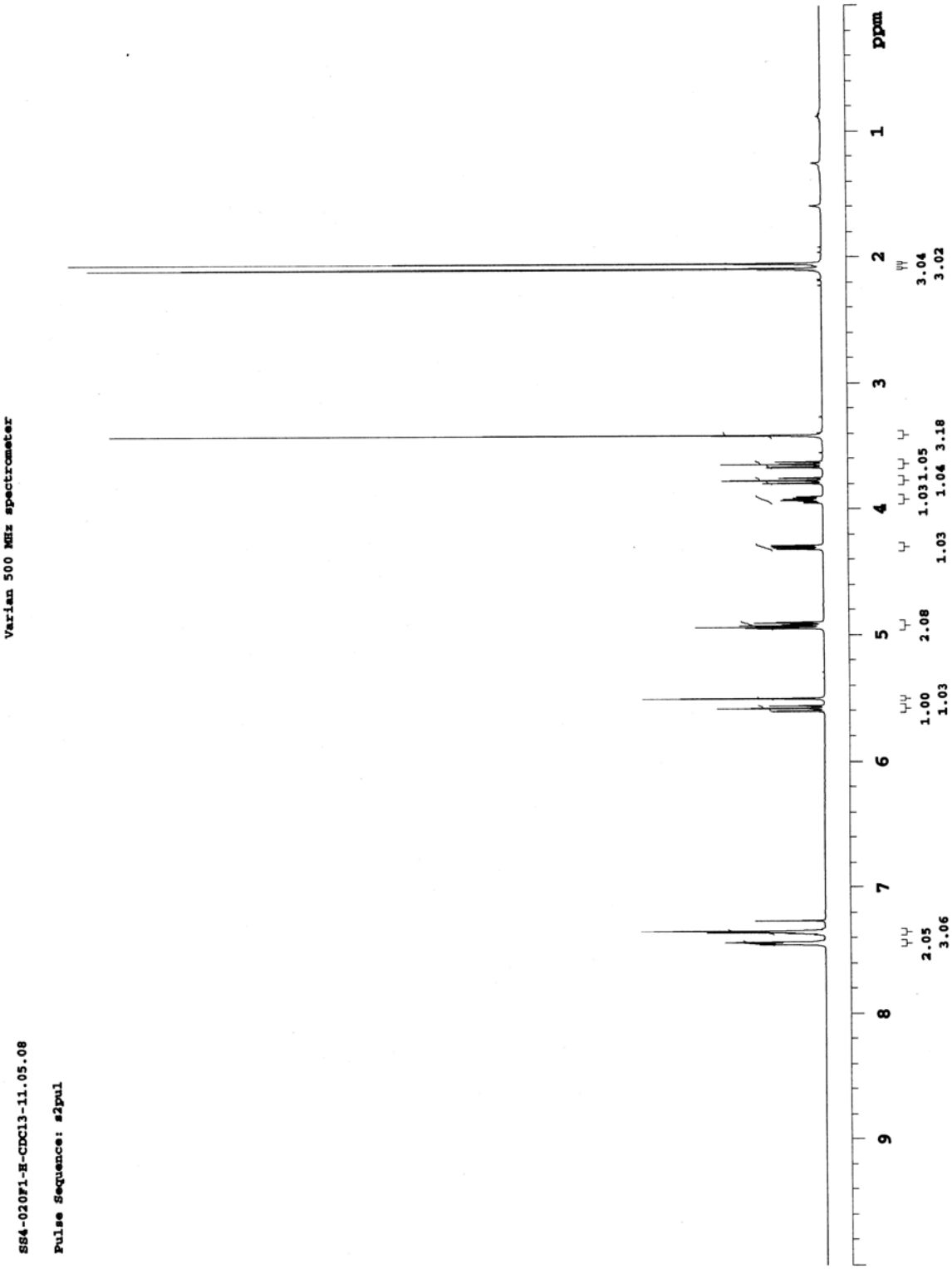
^{13}C NMR ((2R,4aR,6S,7R,8R,8aR)-7-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl acetate)



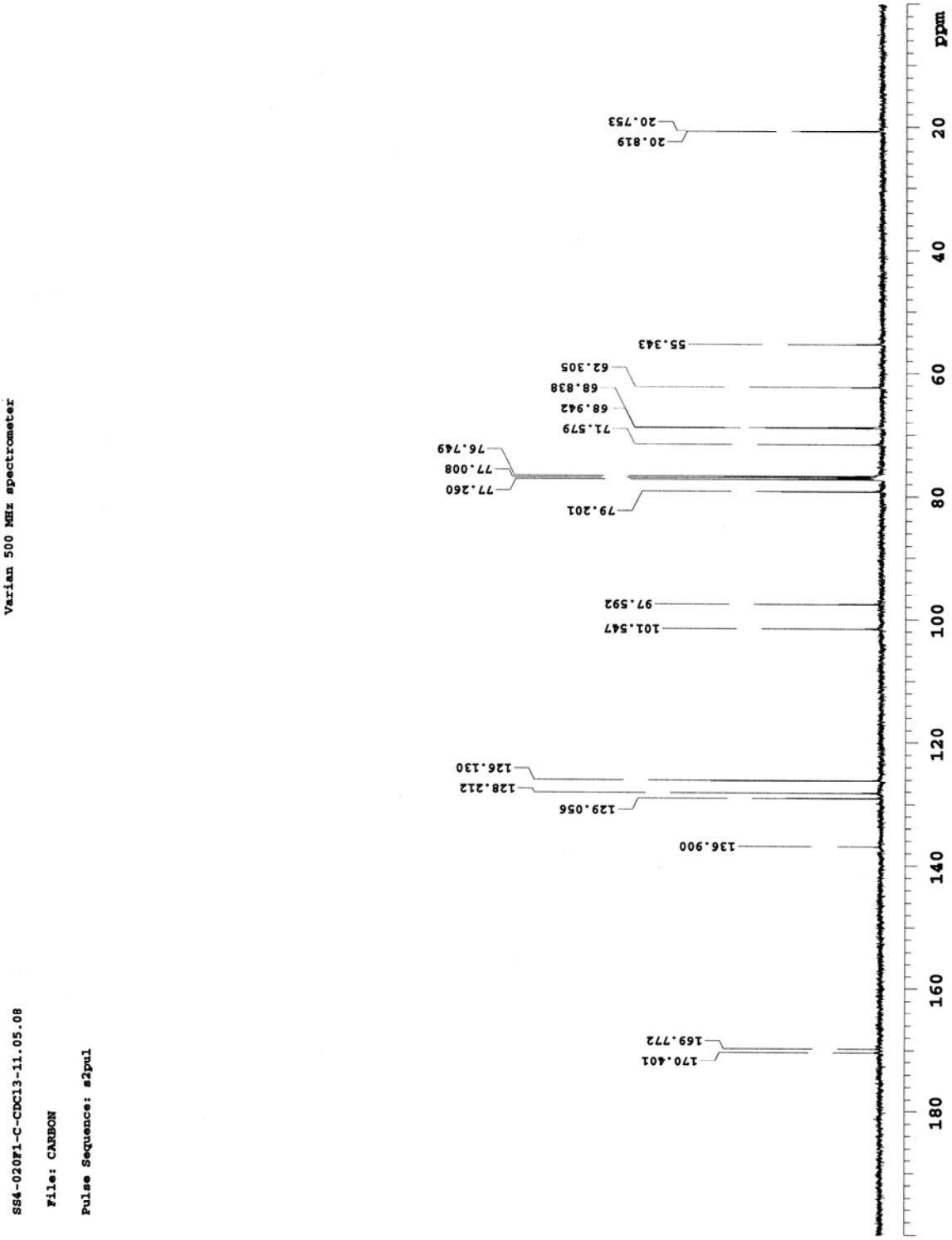
DEPT NMR ((2R,4aR,6S,7R,8R,8aR)-7-hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-yl acetate)



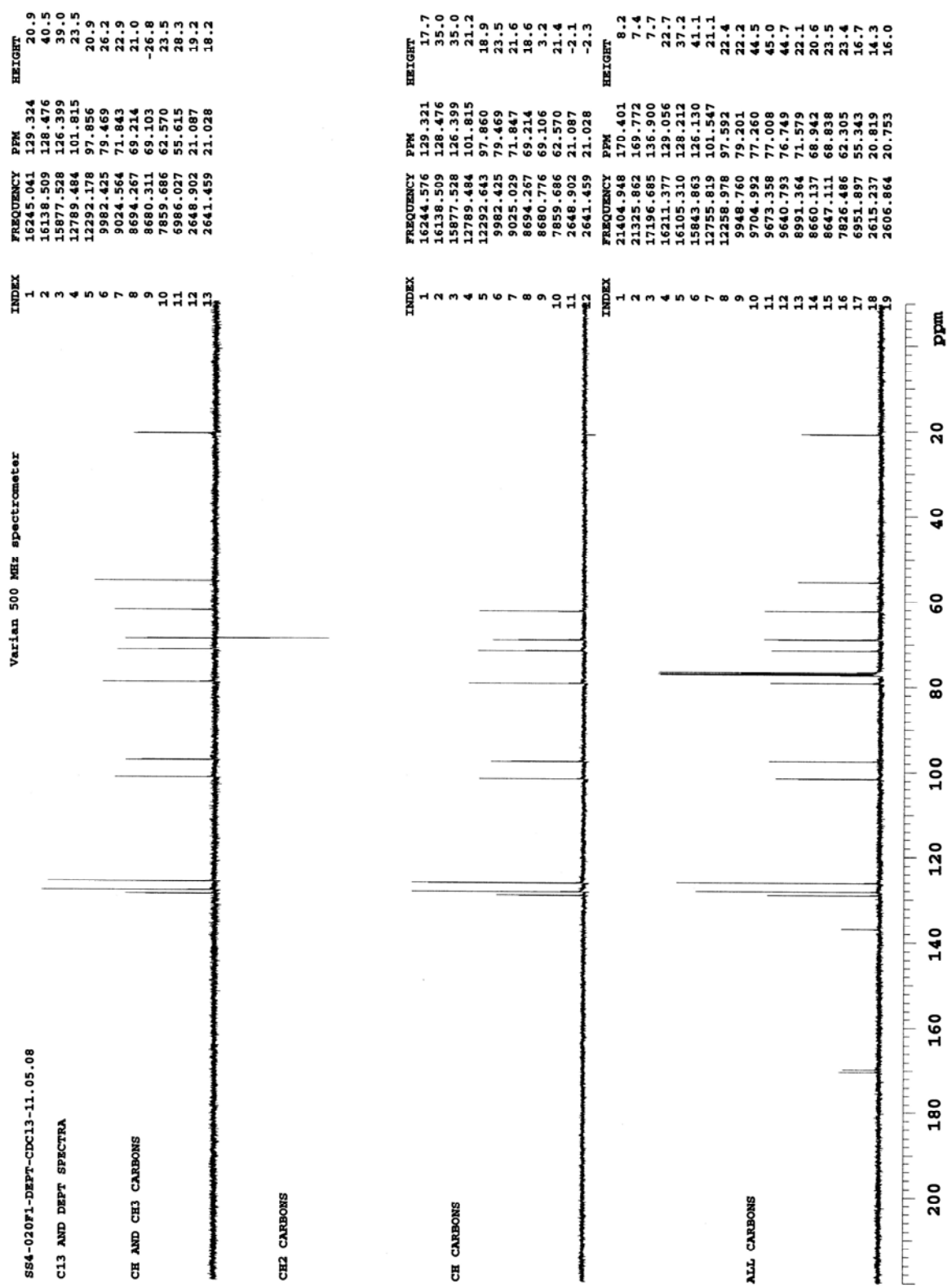
^{1}H NMR ((2R,4aR,6S,7R,8S,8aR)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl diacetate)



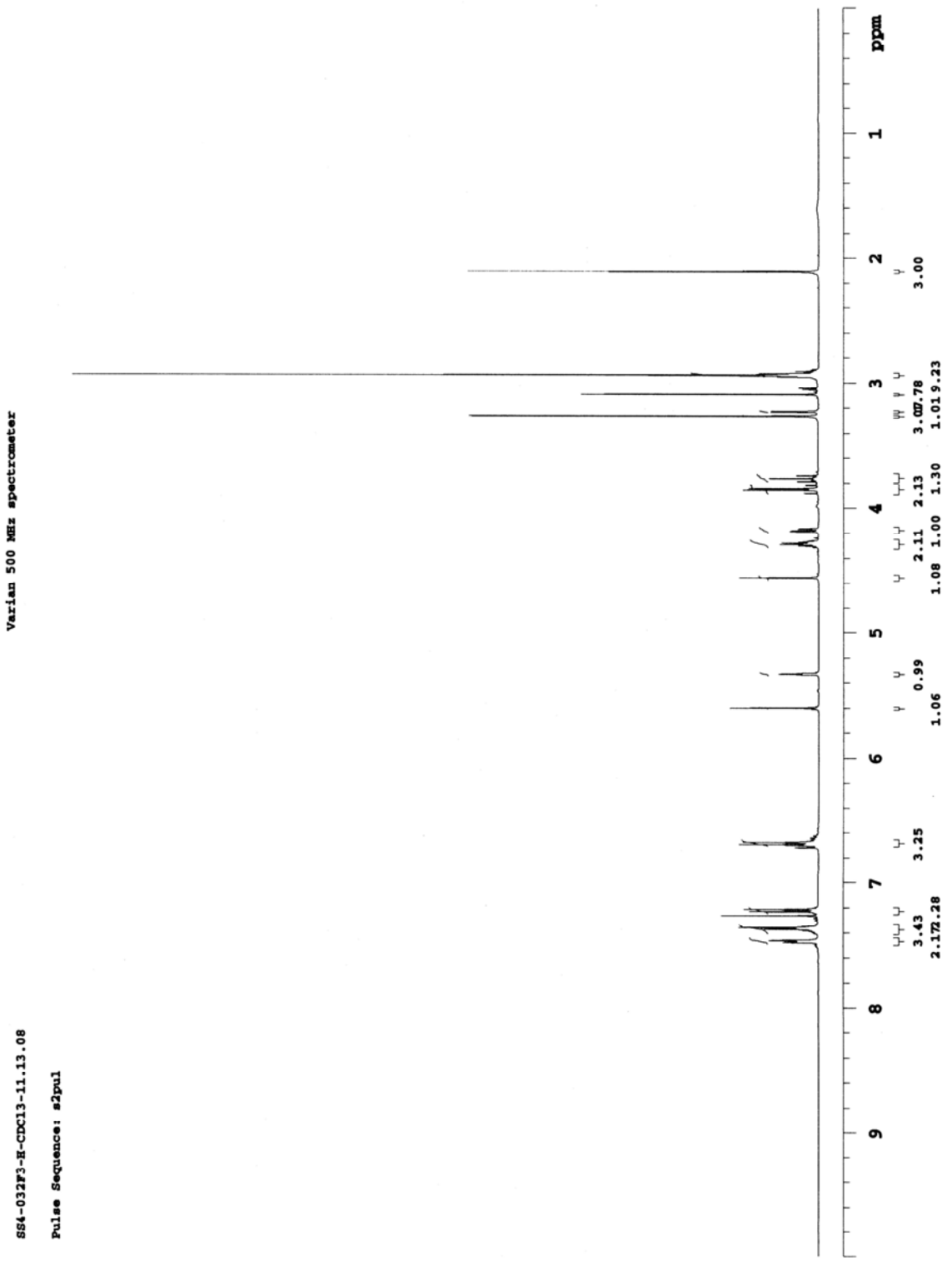
^{13}C NMR ((2R,4aR,6S,7R,8S,8aR)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl diacetate)



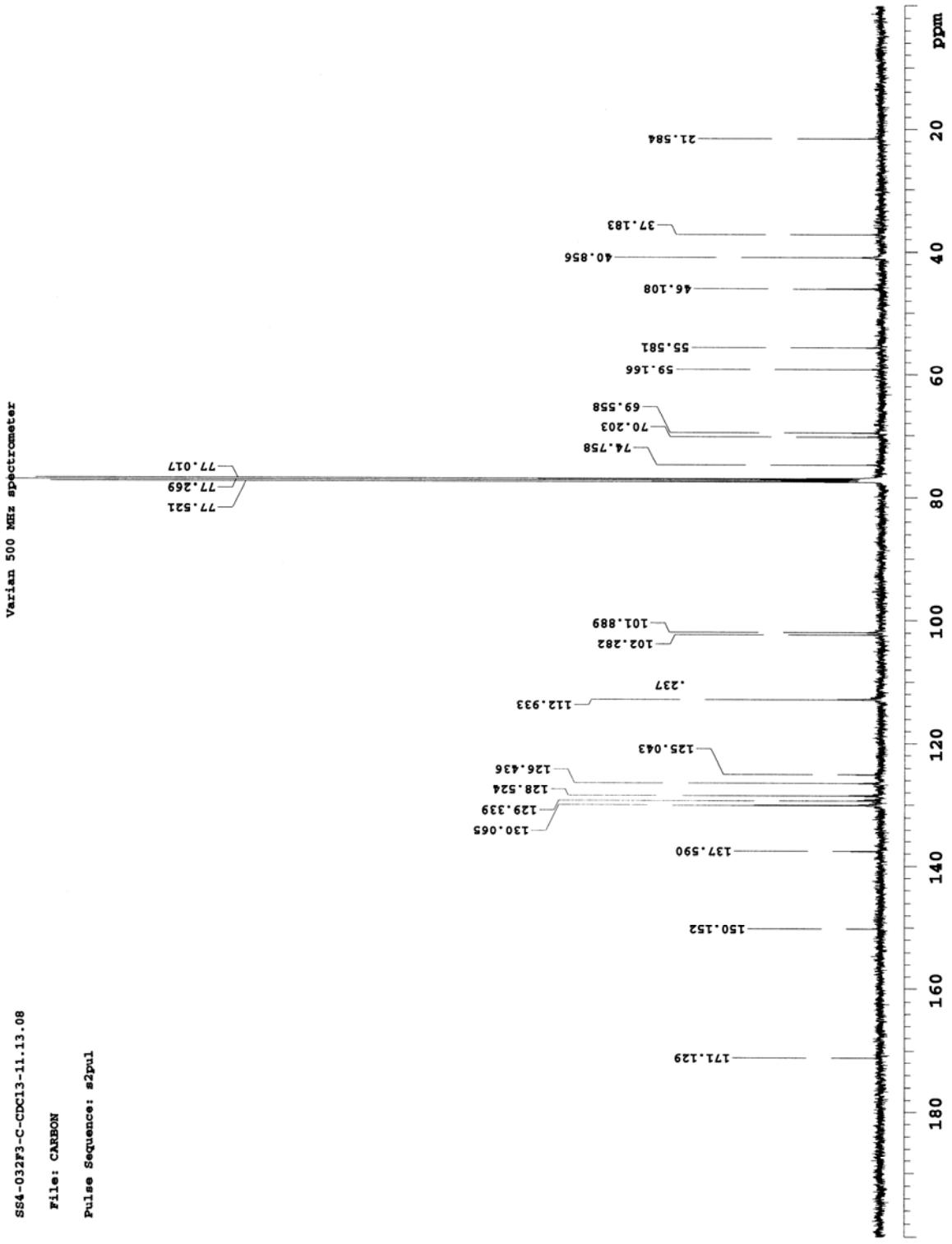
DEPT NMR ((2R,4aR,6S,7R,8S,8aR)-6-methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl diacetate)



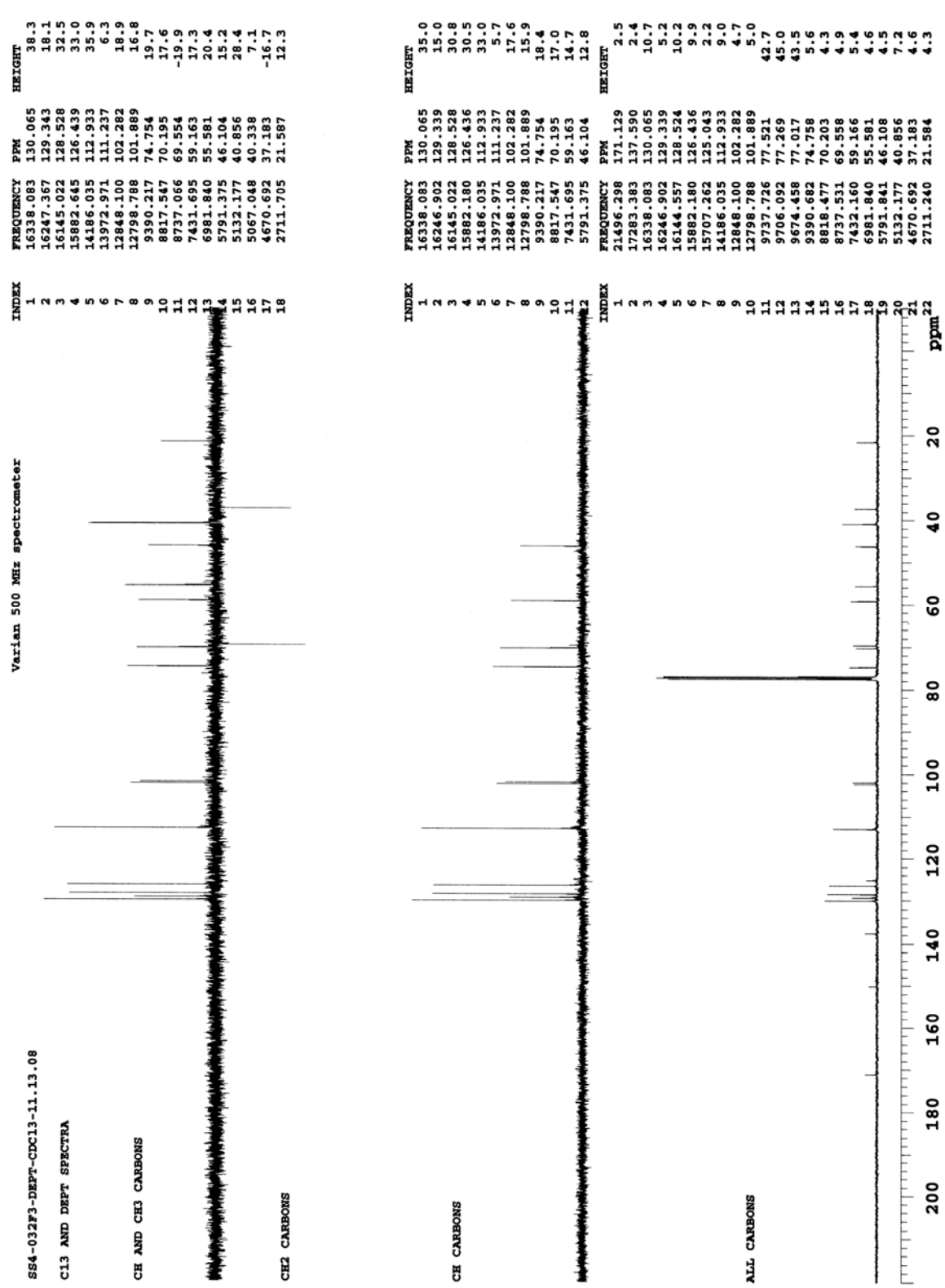
[1]H NMR (Compound 457)



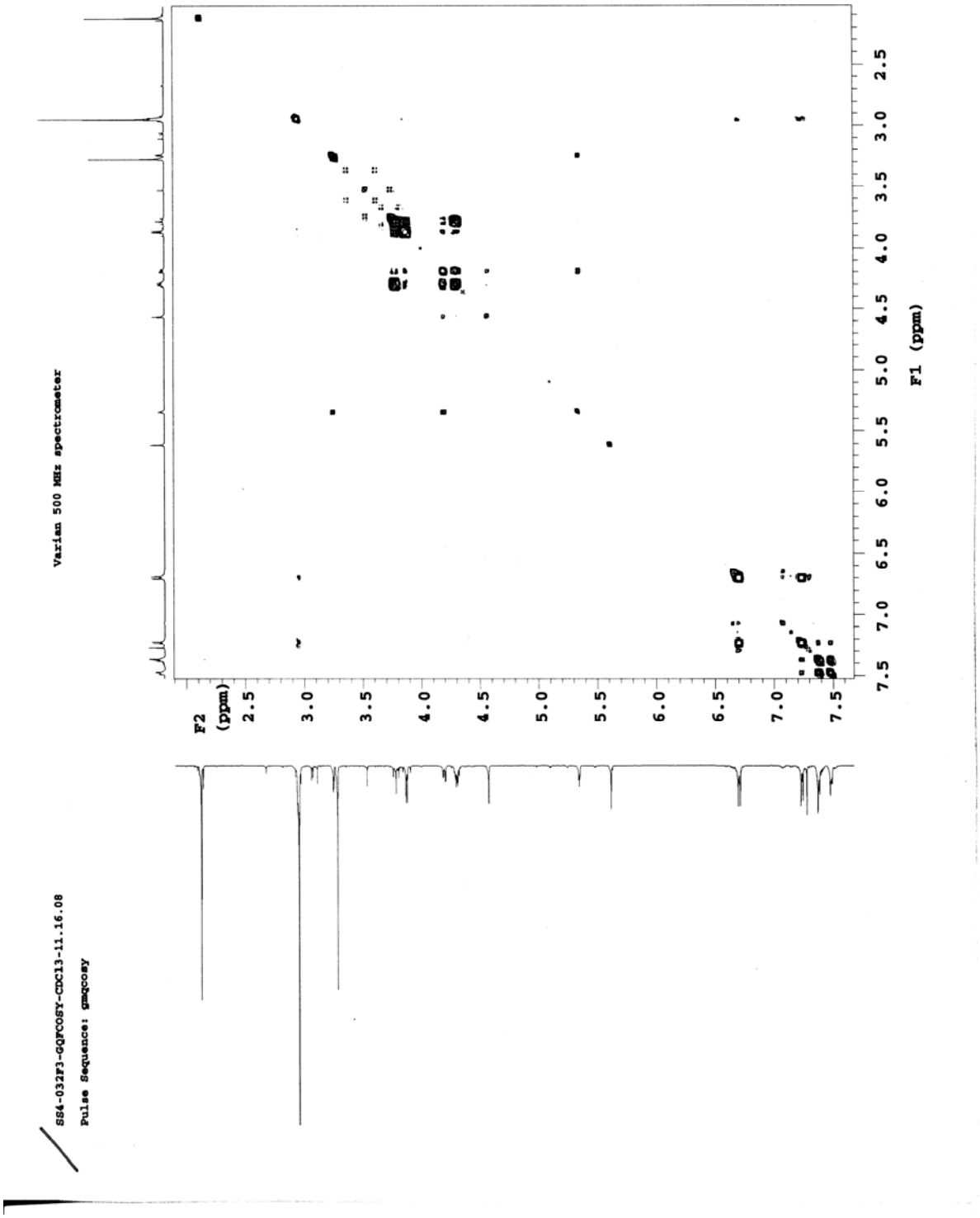
^{13}C NMR (Compound 457)



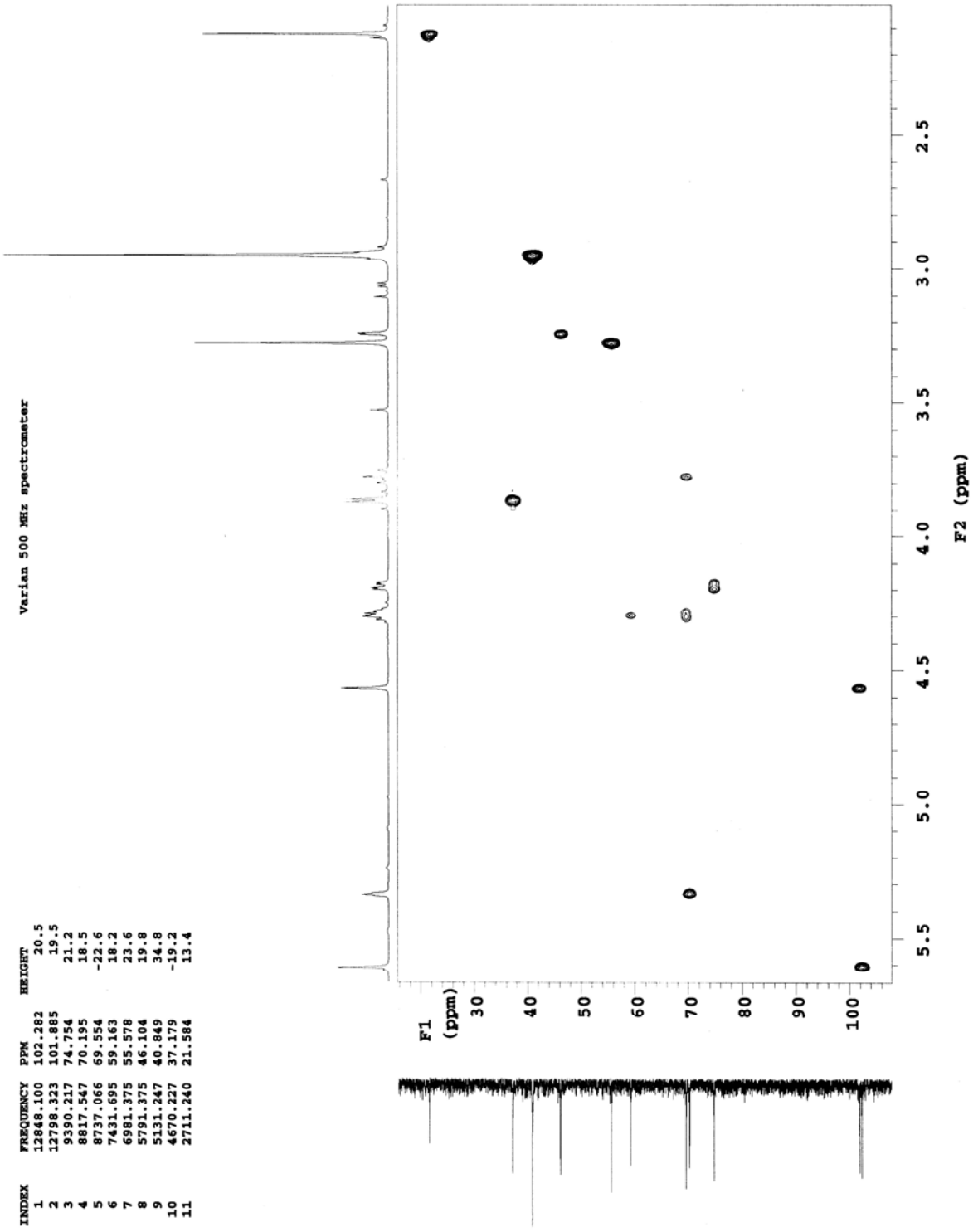
DEPT NMR (Compound 457)



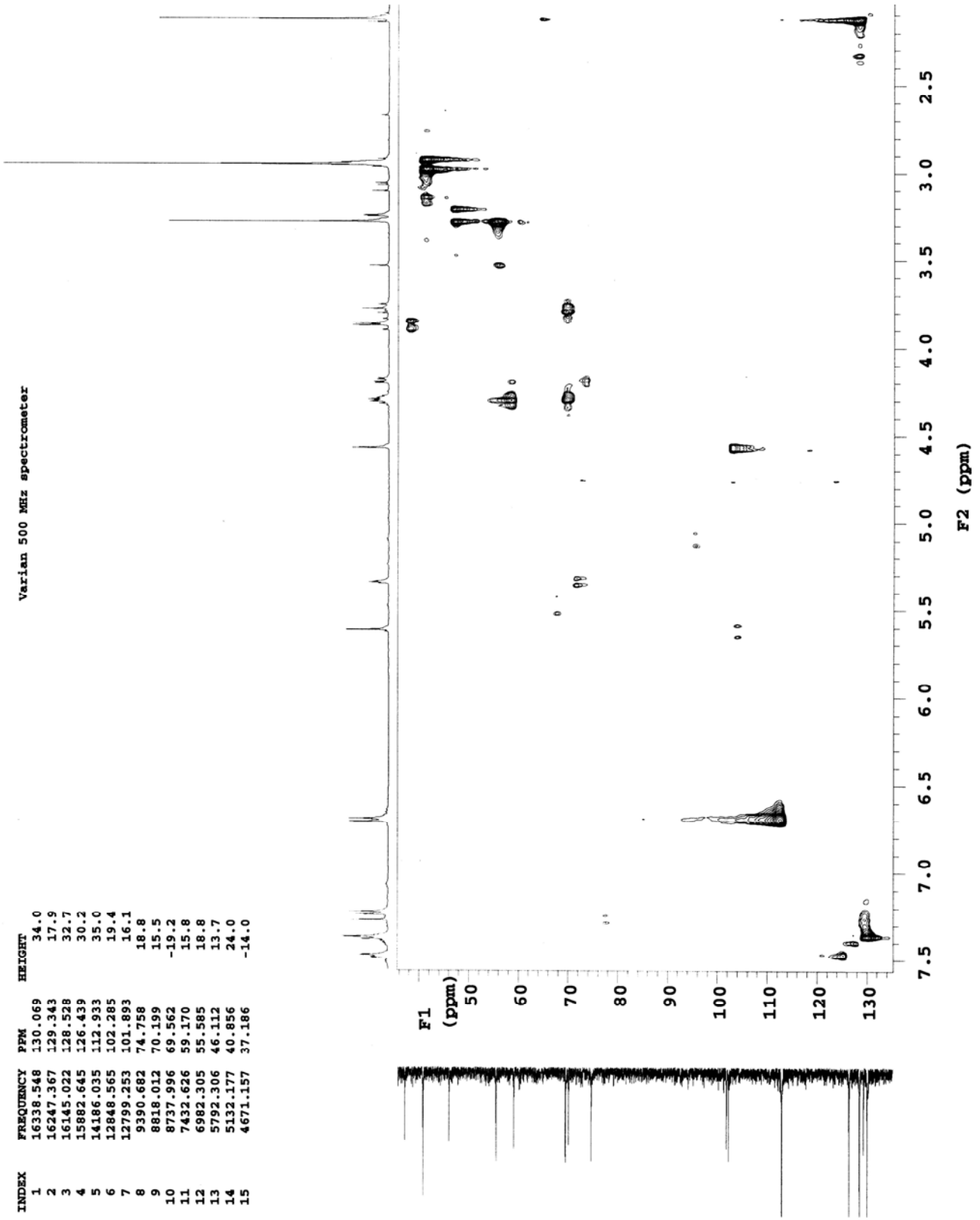
^{1}H-^{1}H GDQFCOSY NMR (Compound 457)



GHMQC-1 NMR (Compound 457)

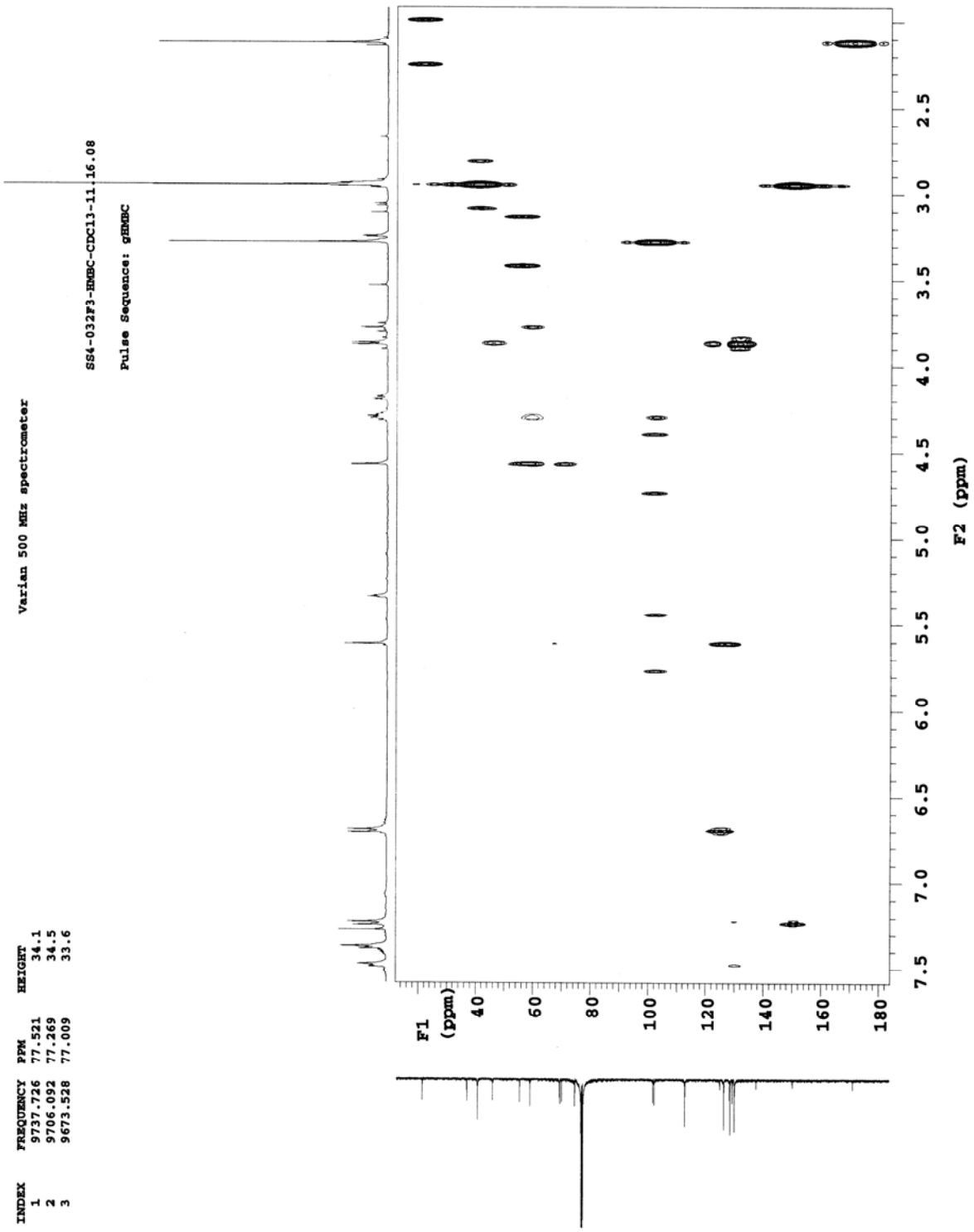


GHMQC-2 NMR (Compound 457)



INDEX	FREQUENCY	PPM	HEIGHT
1	16338.548	130.069	34.0
2	16247.367	129.343	17.9
3	16145.022	128.528	32.7
4	15882.645	126.439	30.2
5	14186.035	112.933	35.0
6	12848.565	102.285	19.4
7	12799.253	101.893	16.1
8	9390.682	74.758	18.8
9	8818.012	70.199	15.5
10	8737.996	69.562	-19.2
11	7432.626	59.170	15.8
12	6982.305	55.585	18.8
13	5792.306	46.112	13.7
14	5132.177	40.856	24.0
15	4671.157	37.186	-14.0

GHMBC NMR (Compound 457)



Elemental Composition Report

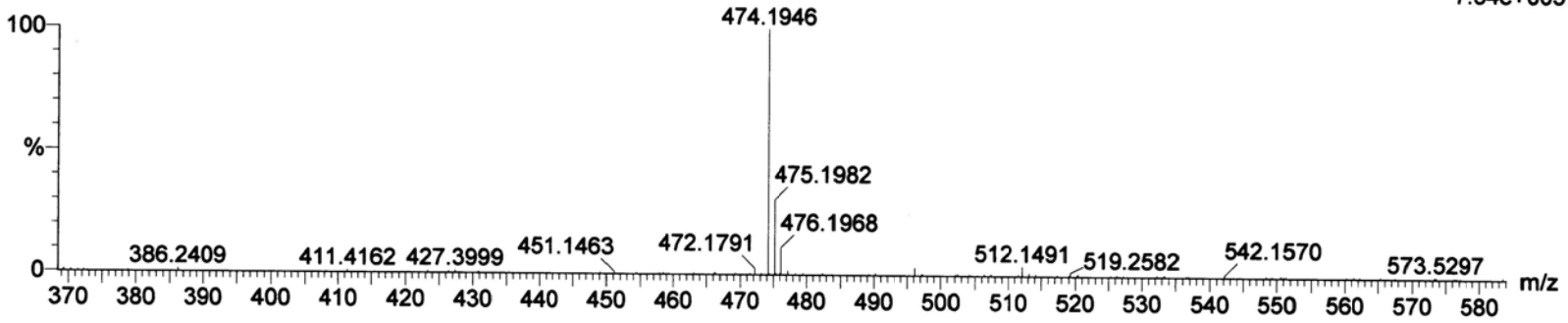
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
965 formula(e) evaluated with 3 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-4 O: 0-8 23Na: 0-1 S: 0-1

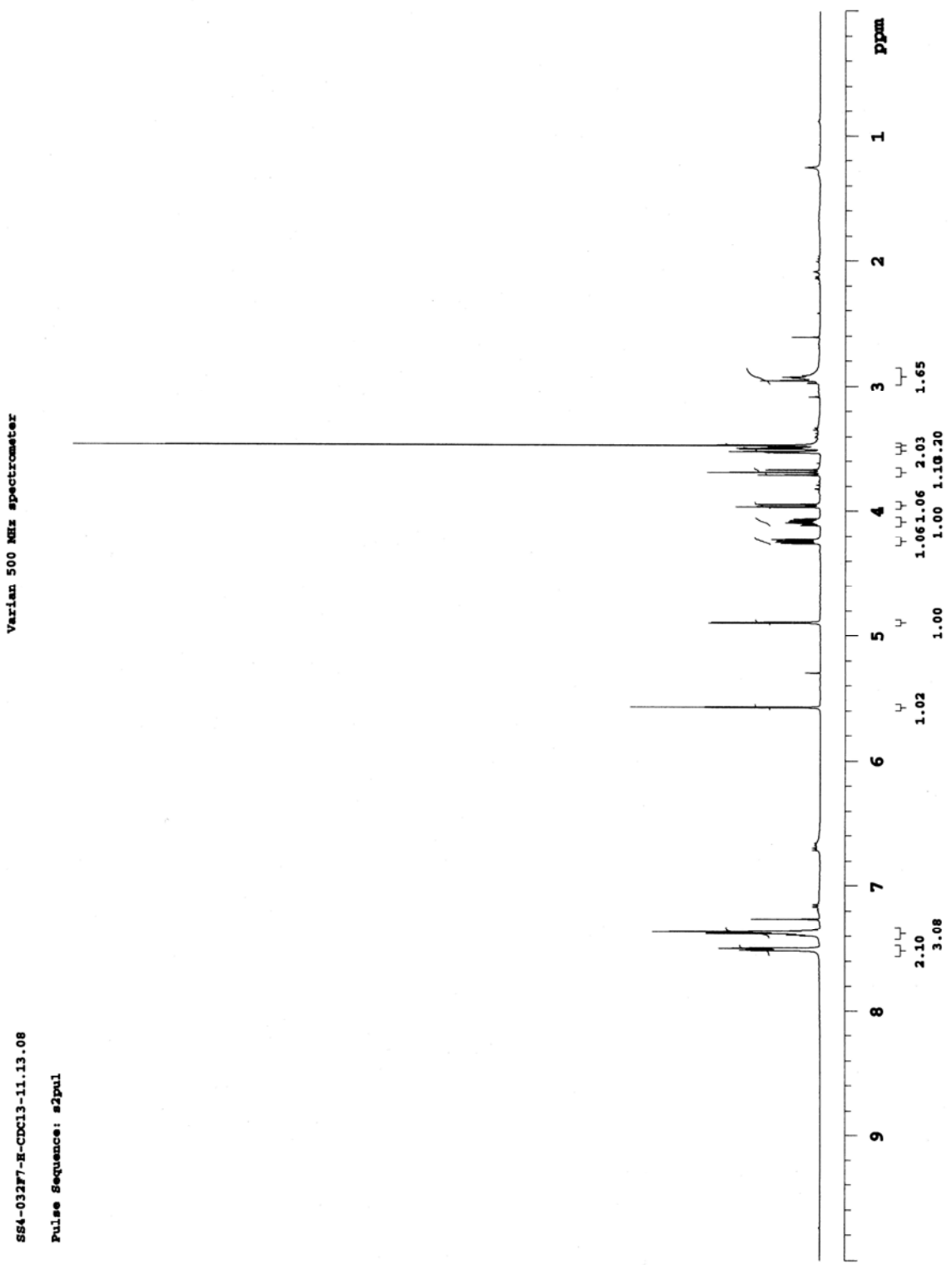
Andreana- Soumave Santra LCT0225 SS4-032f3 mw473 1uL meoh
Shay 2008-07b.pro
2008_1125_0225_05 20 (0.440) Cm (18:21-(1:5+28:32)x3.000)

LCT Premier 25-Nov-2008 09:58:53
1: TOF MS ES+
7.54e+003

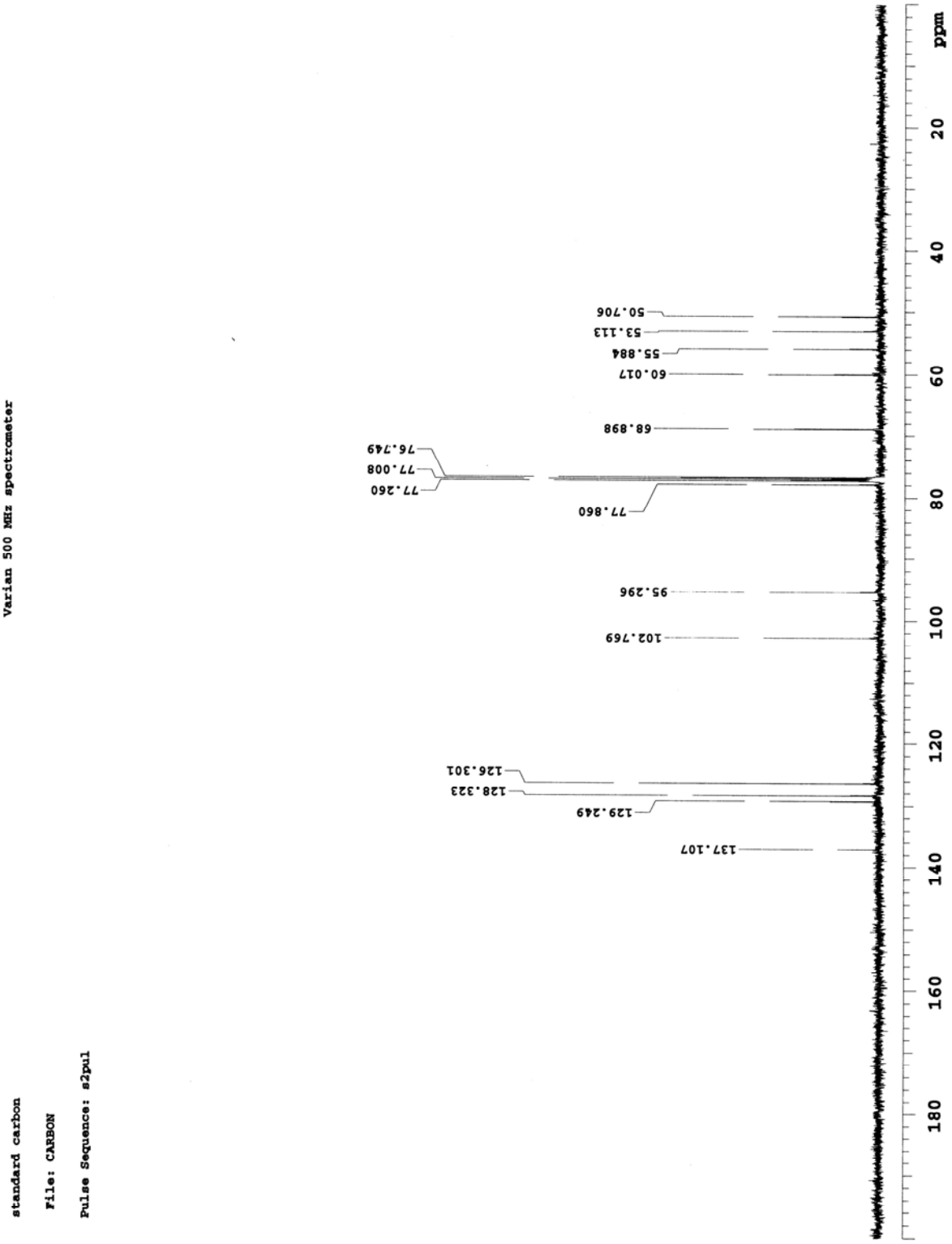


Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
474.1946	474.1950	-0.4	-0.8	10.5	32.2	0.0	C25 H32 N O6 S
	474.1926	2.0	4.2	7.5	38.1	6.0	C23 H33 N O6 23Na S
	474.1946	0.0	0.0	21.5	44.3	12.1	C32 H25 N3 23Na

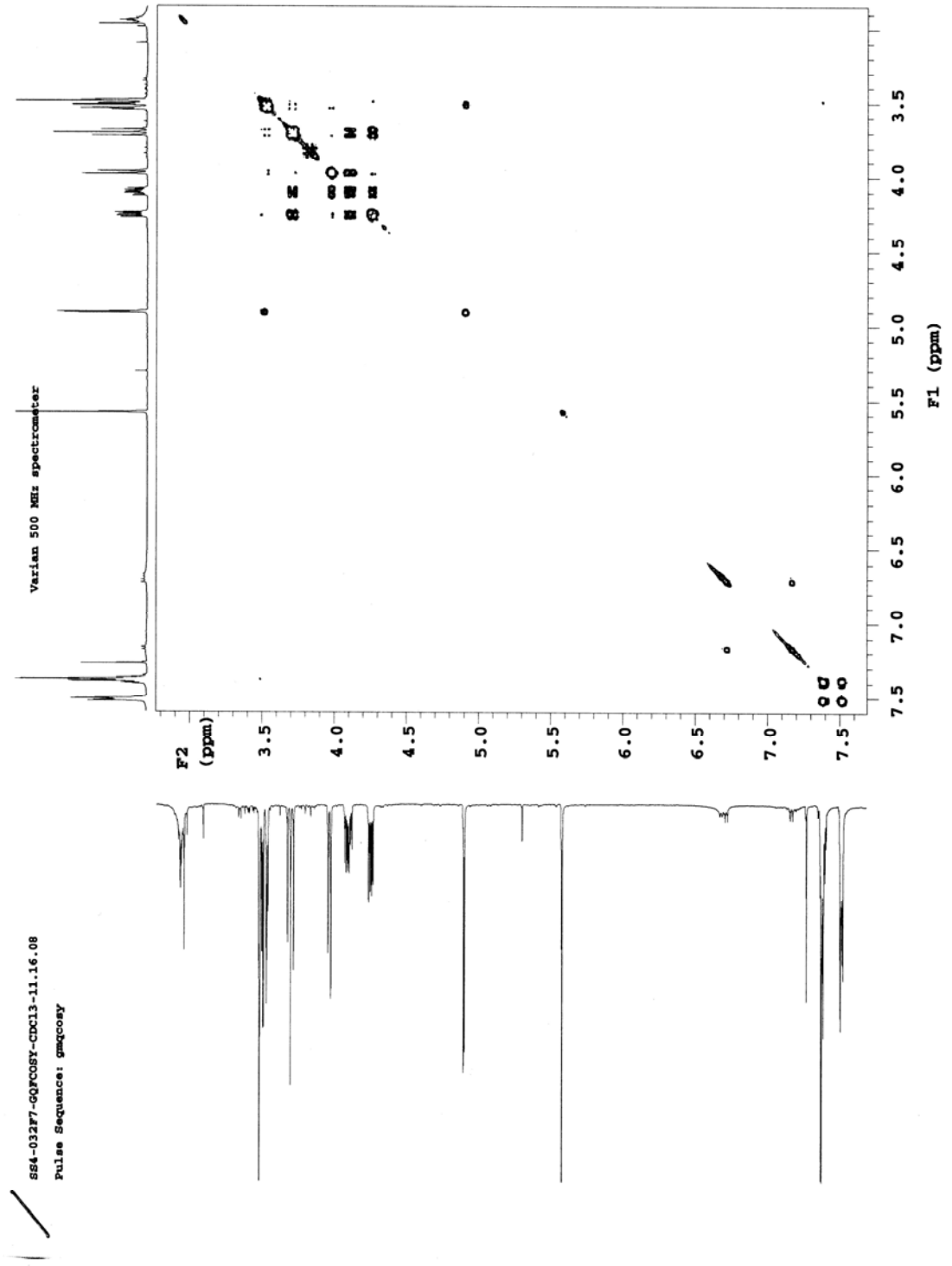
^{1}H NMR (Compound 458)



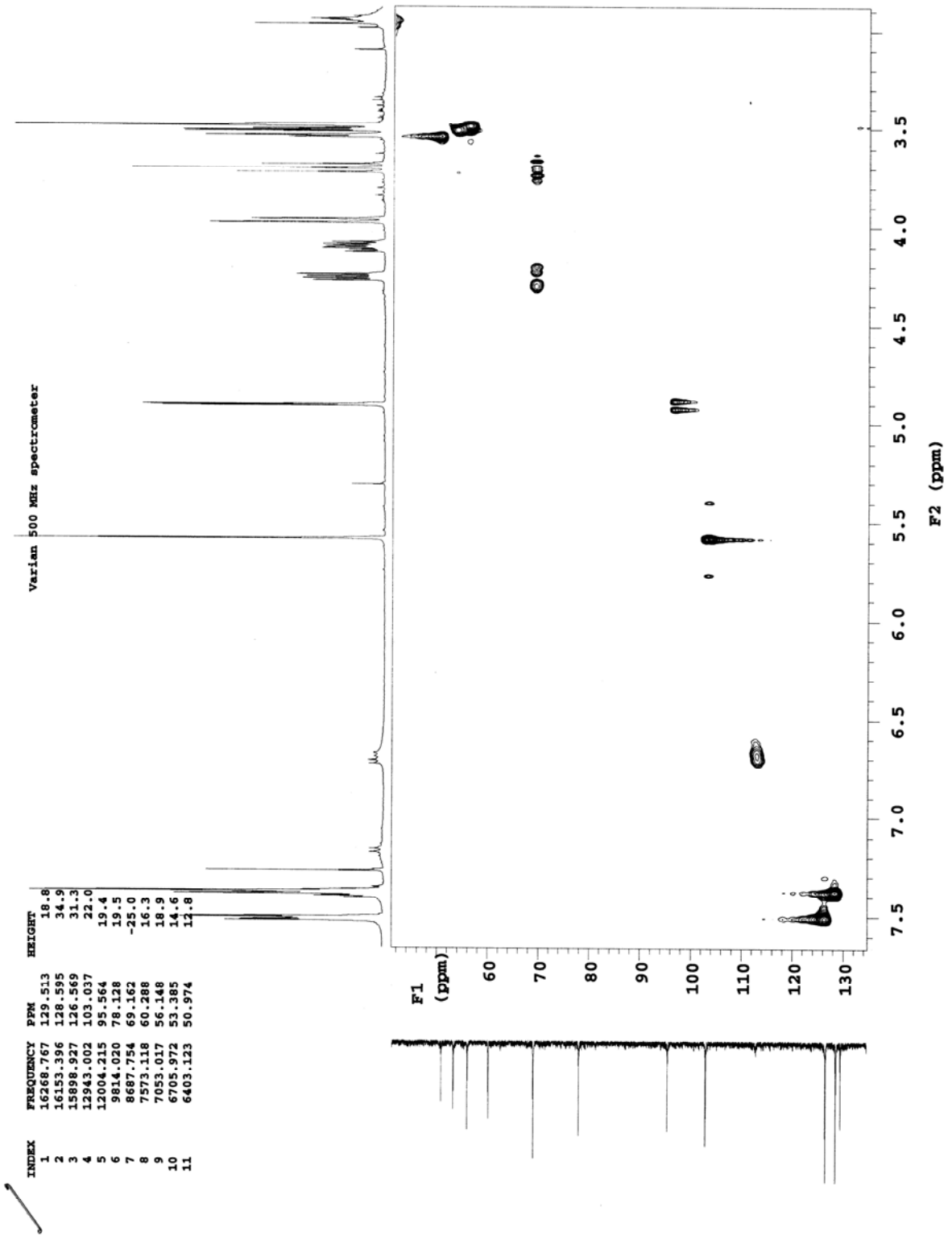
^{13}C NMR (Compound 458)



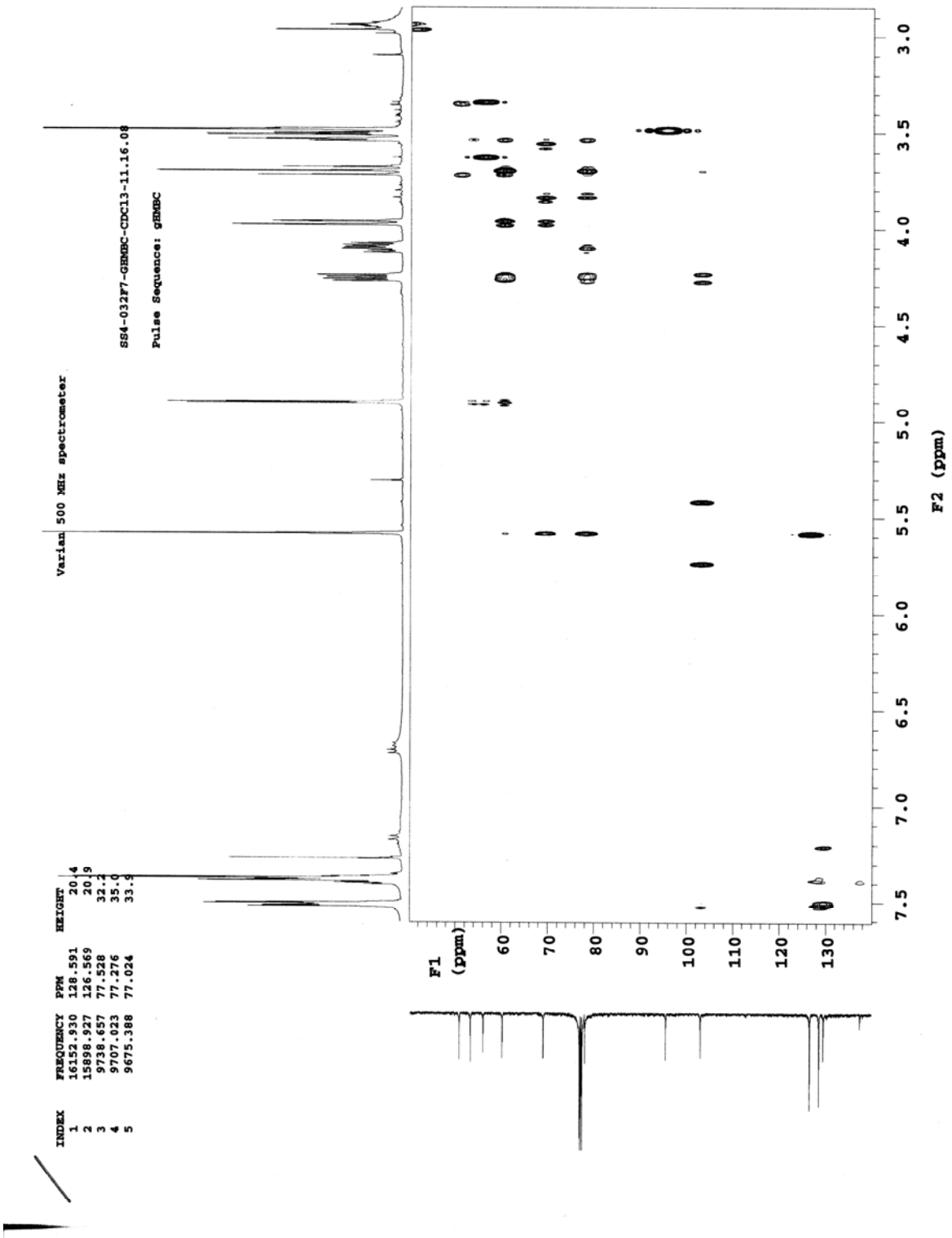
^{1}H-^{1}H GDQFCOSY NMR (Compound 458)



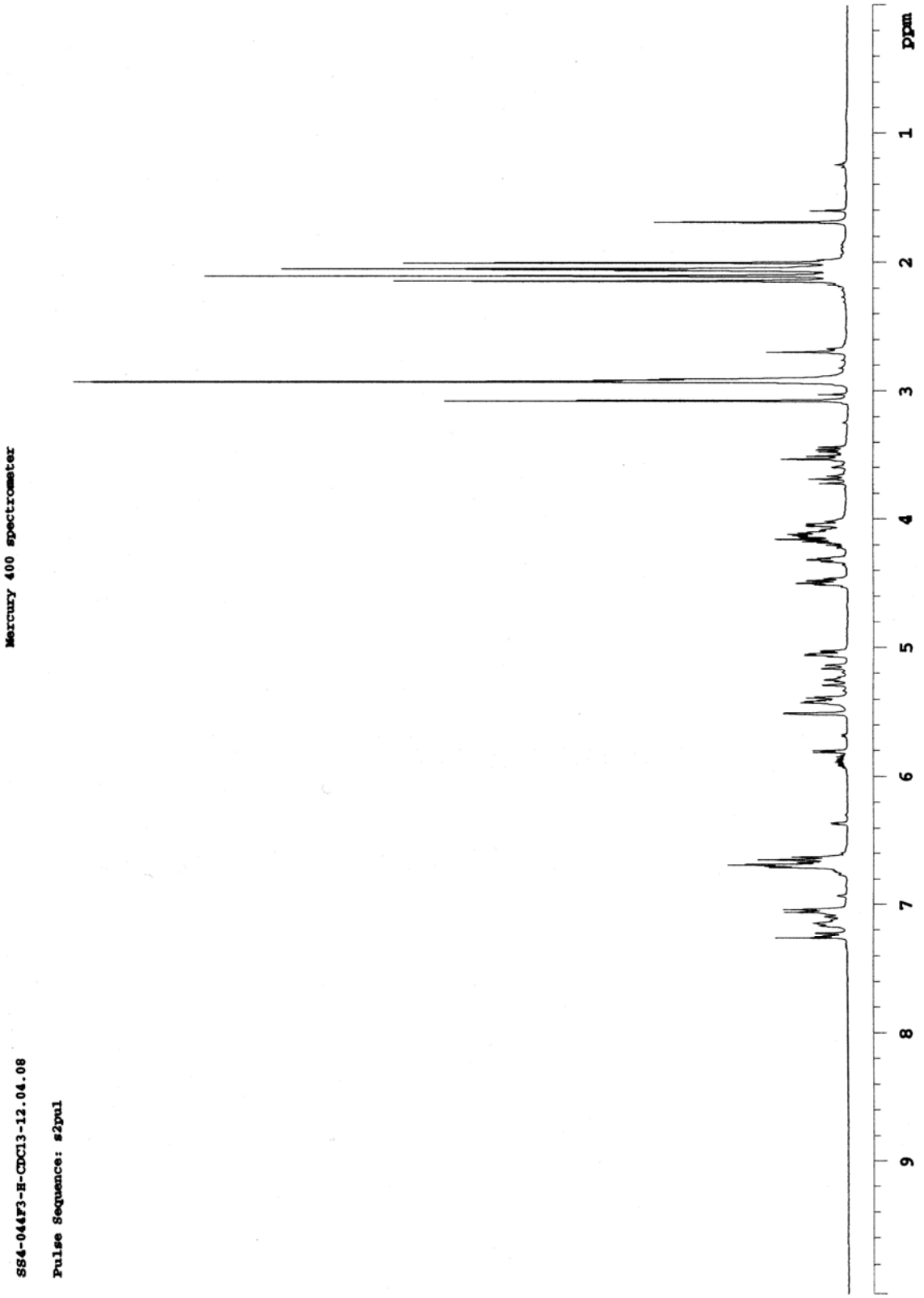
GHMQC NMR (Compound 458)



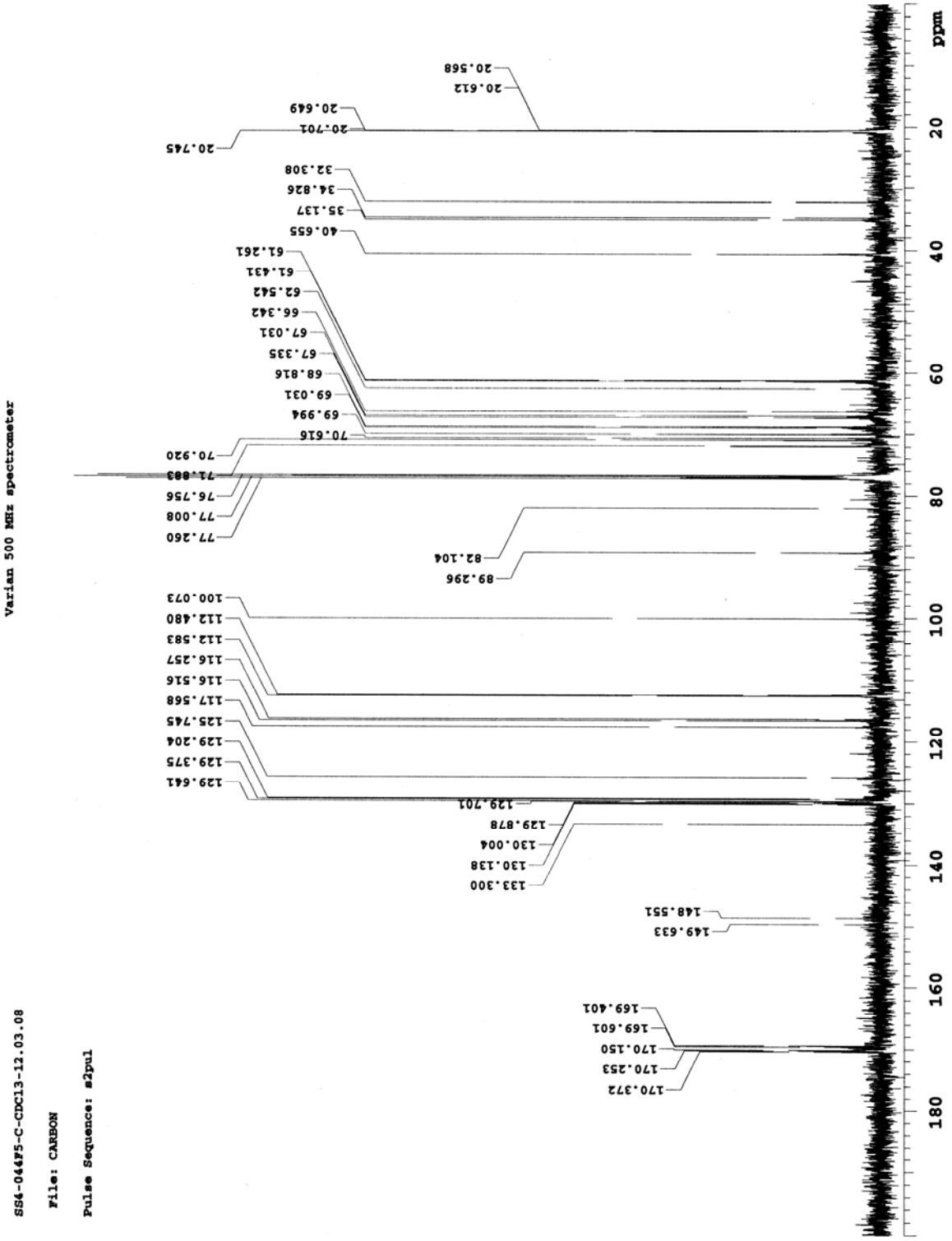
GHMBC NMR (Compound 458)



[1]H NMR (Compound 462)



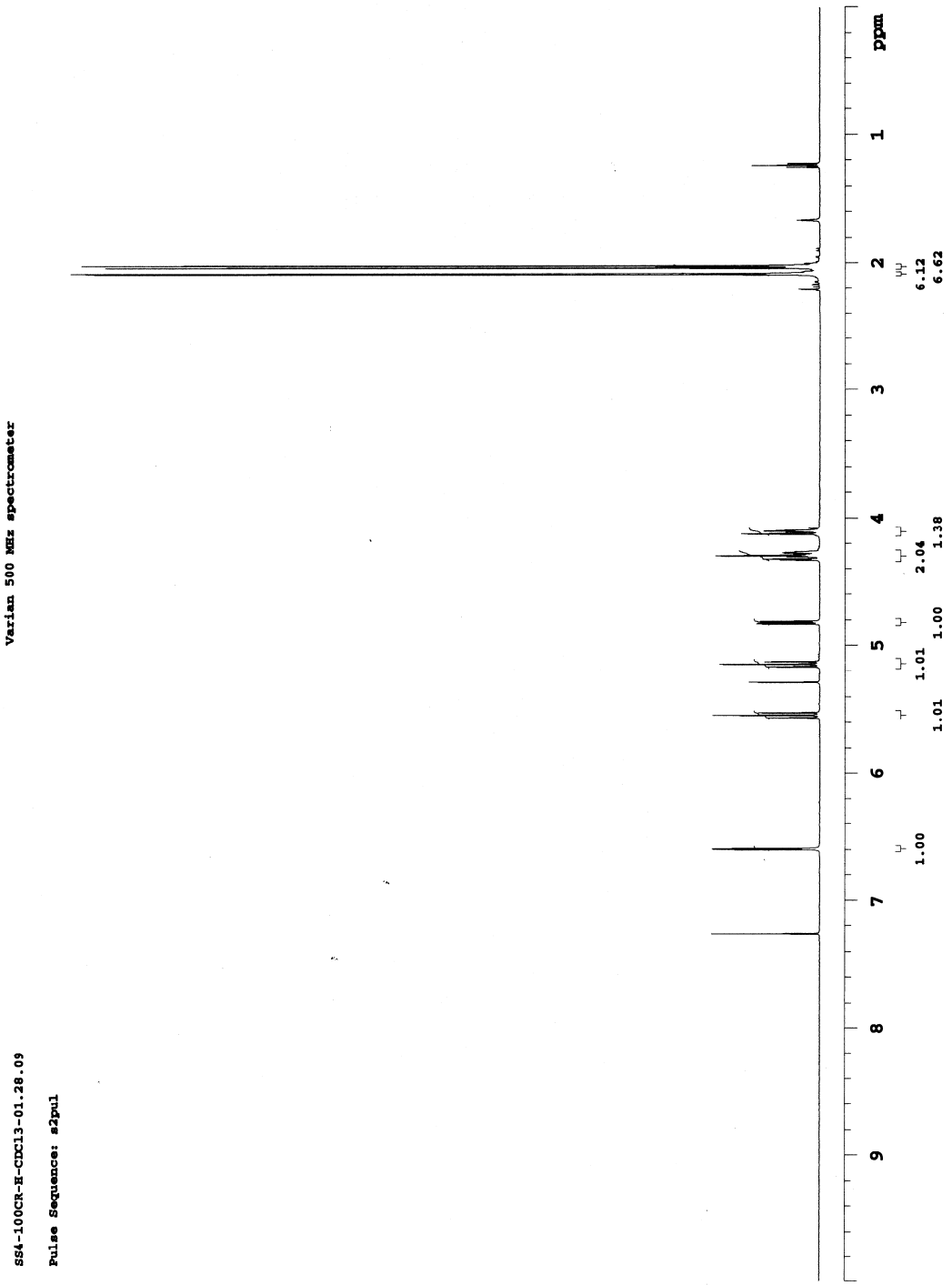
^{13}C NMR (Compound 462)



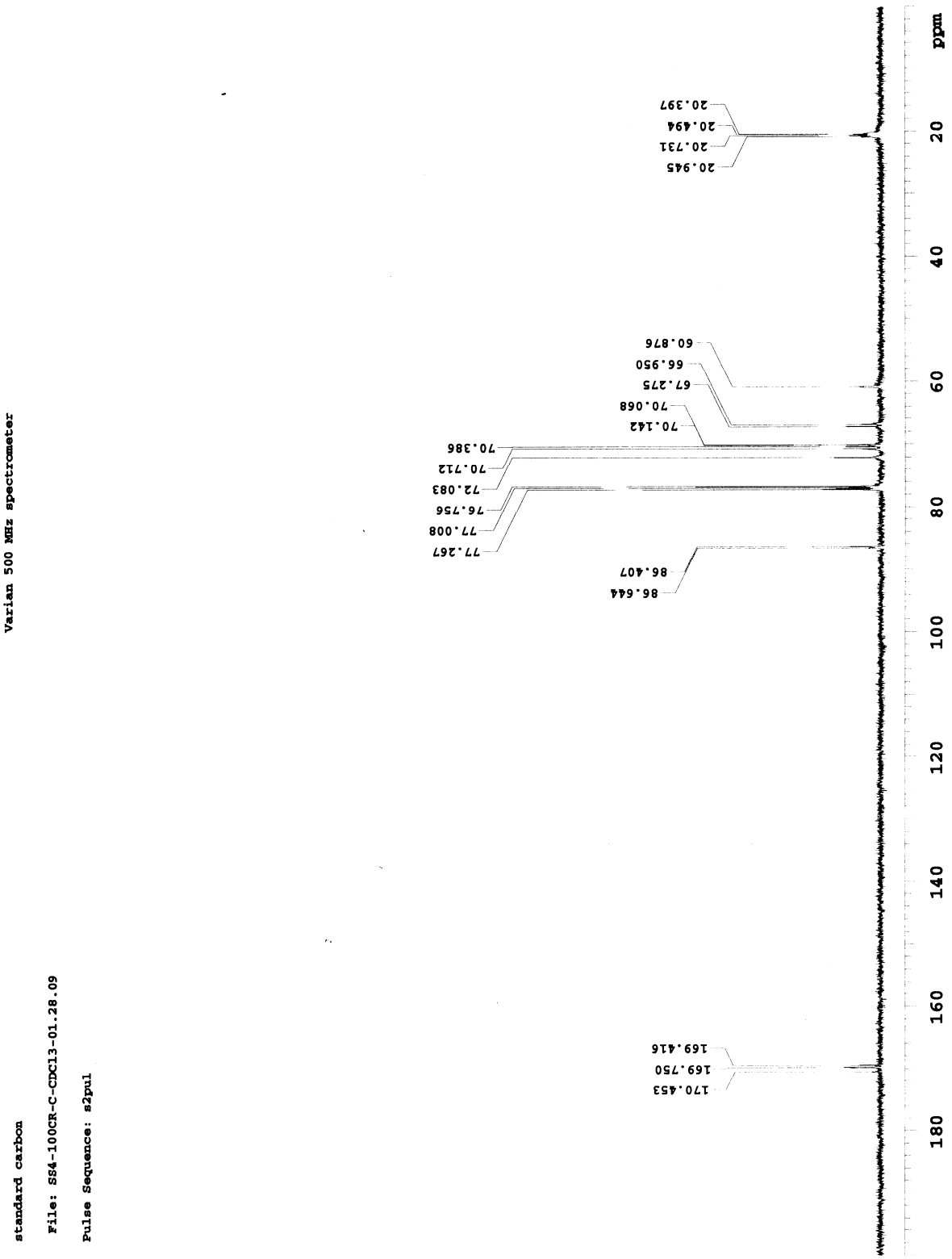
APPENDIX V

NMR Spectra of Chapter 6

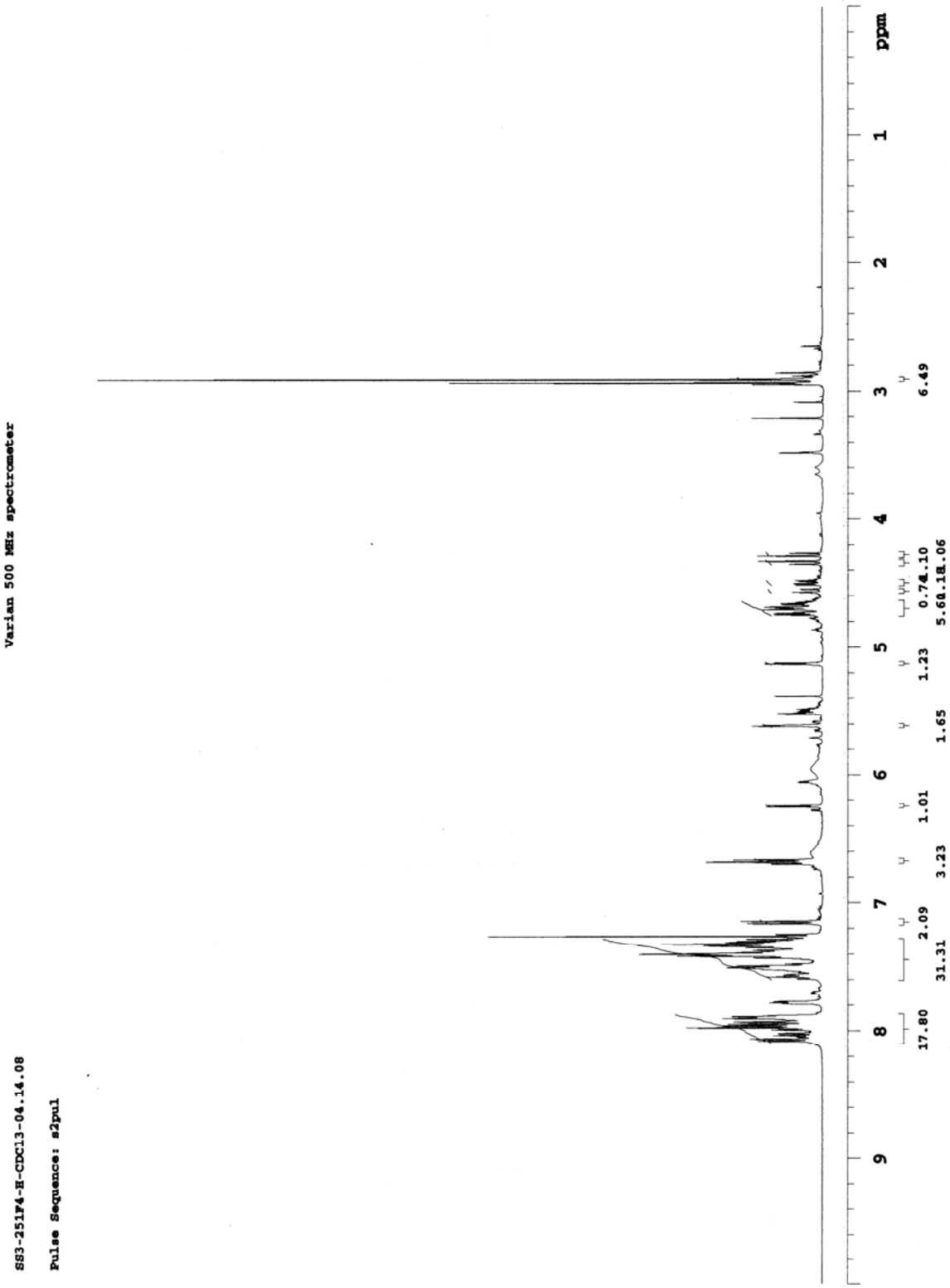
^{1}H NMR (Compound 461)



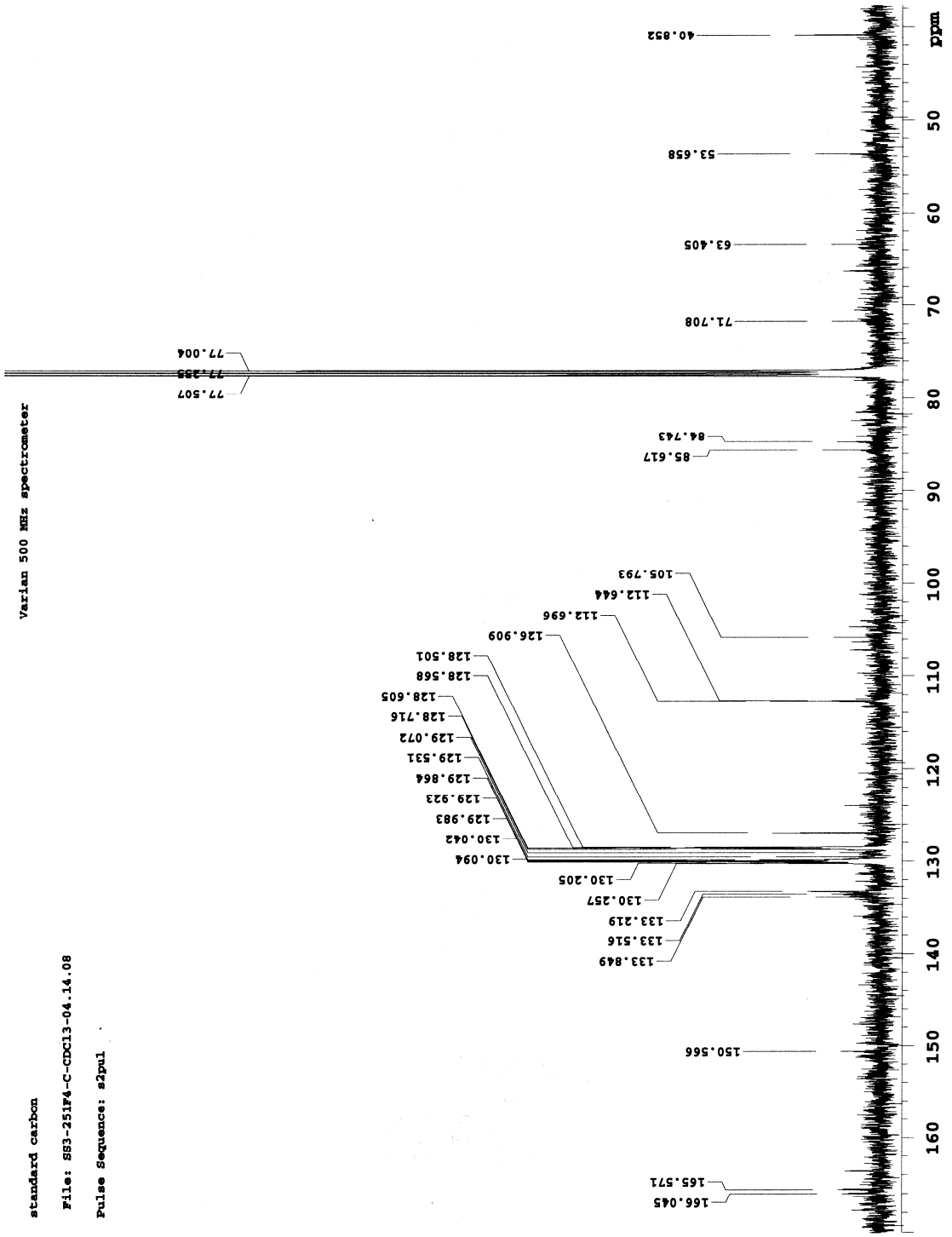
^{13}C NMR (Compound 461)



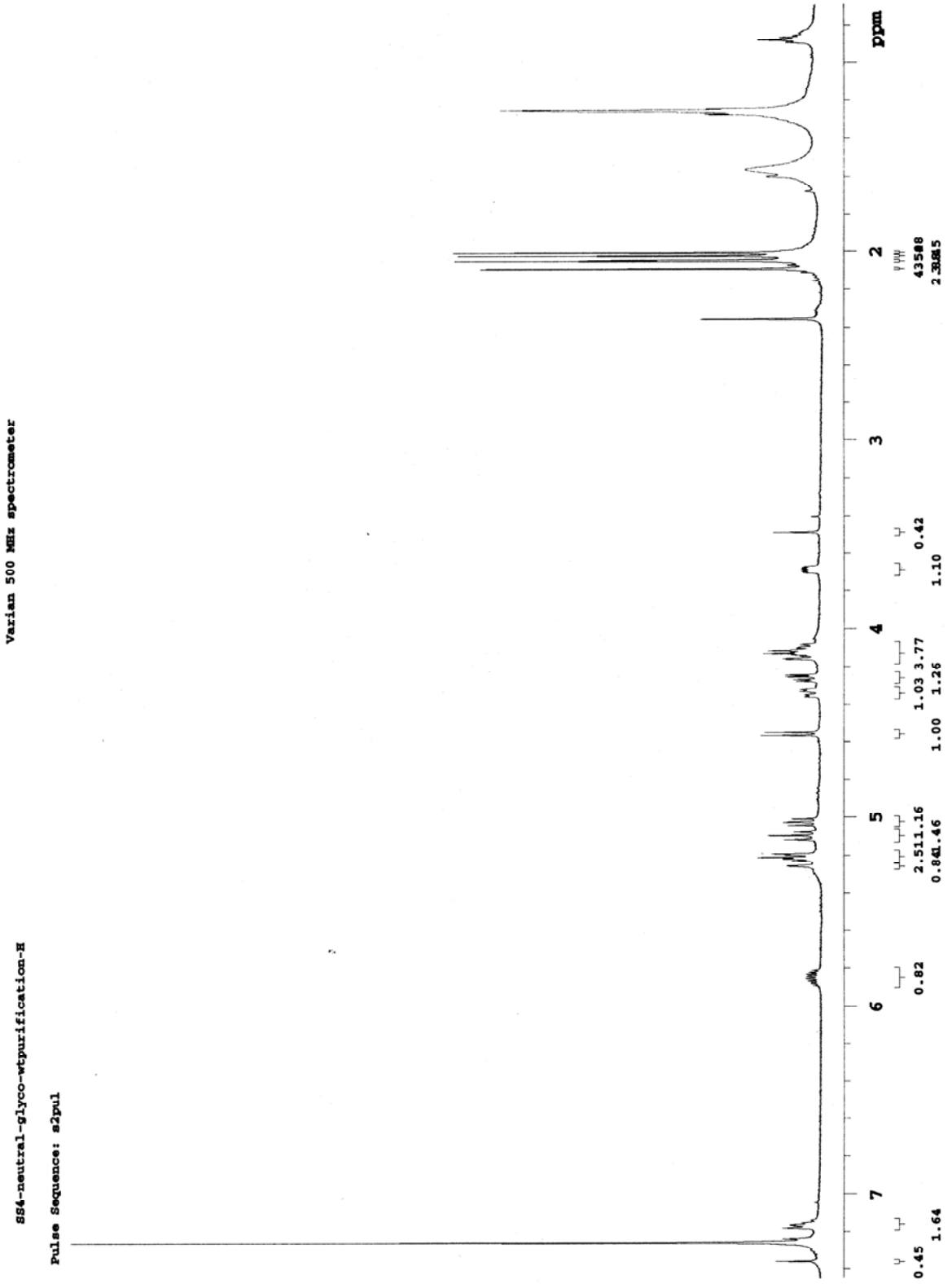
[1]H NMR (Compound 475)



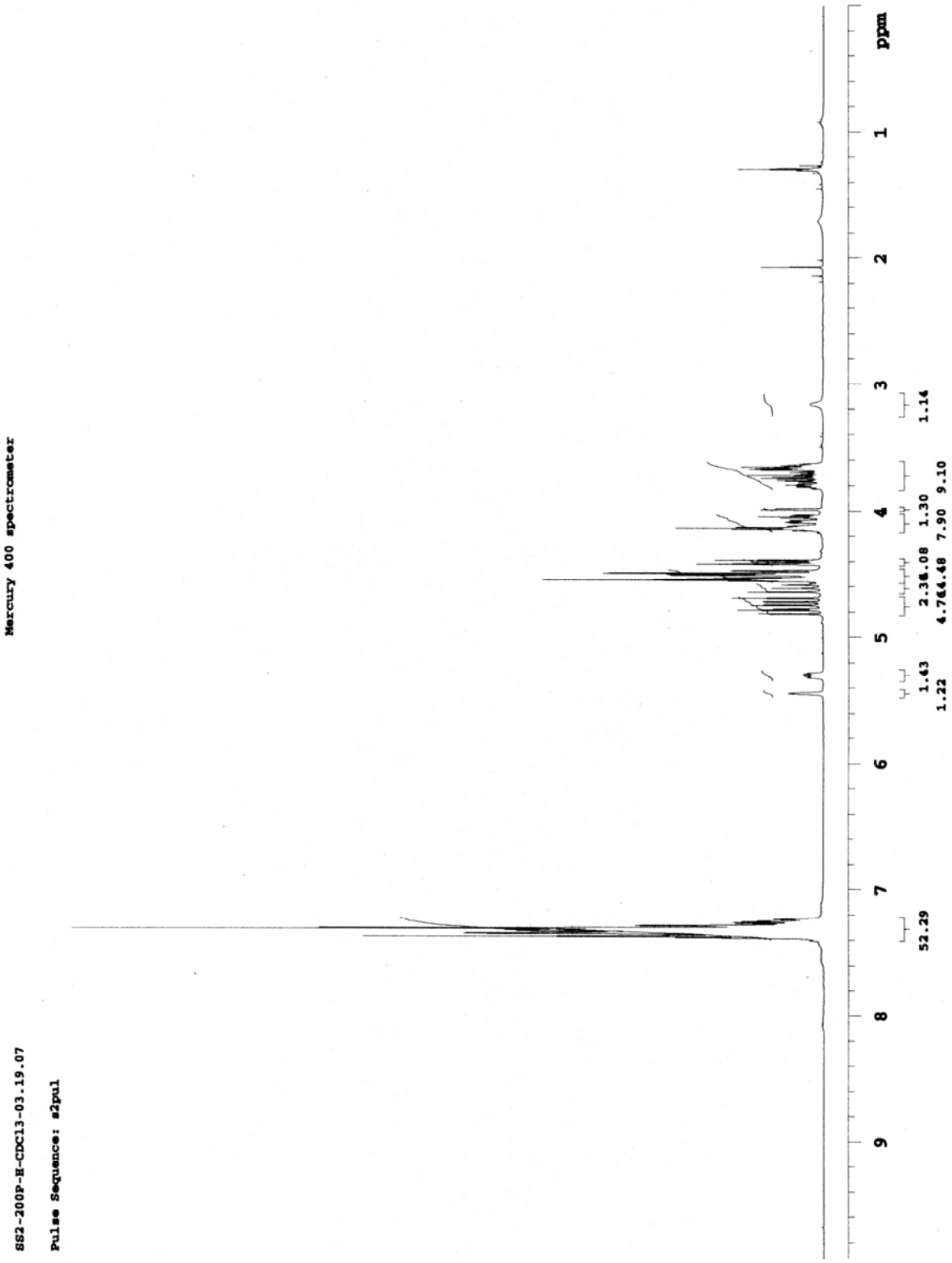
^{13}C NMR (Compound 475)



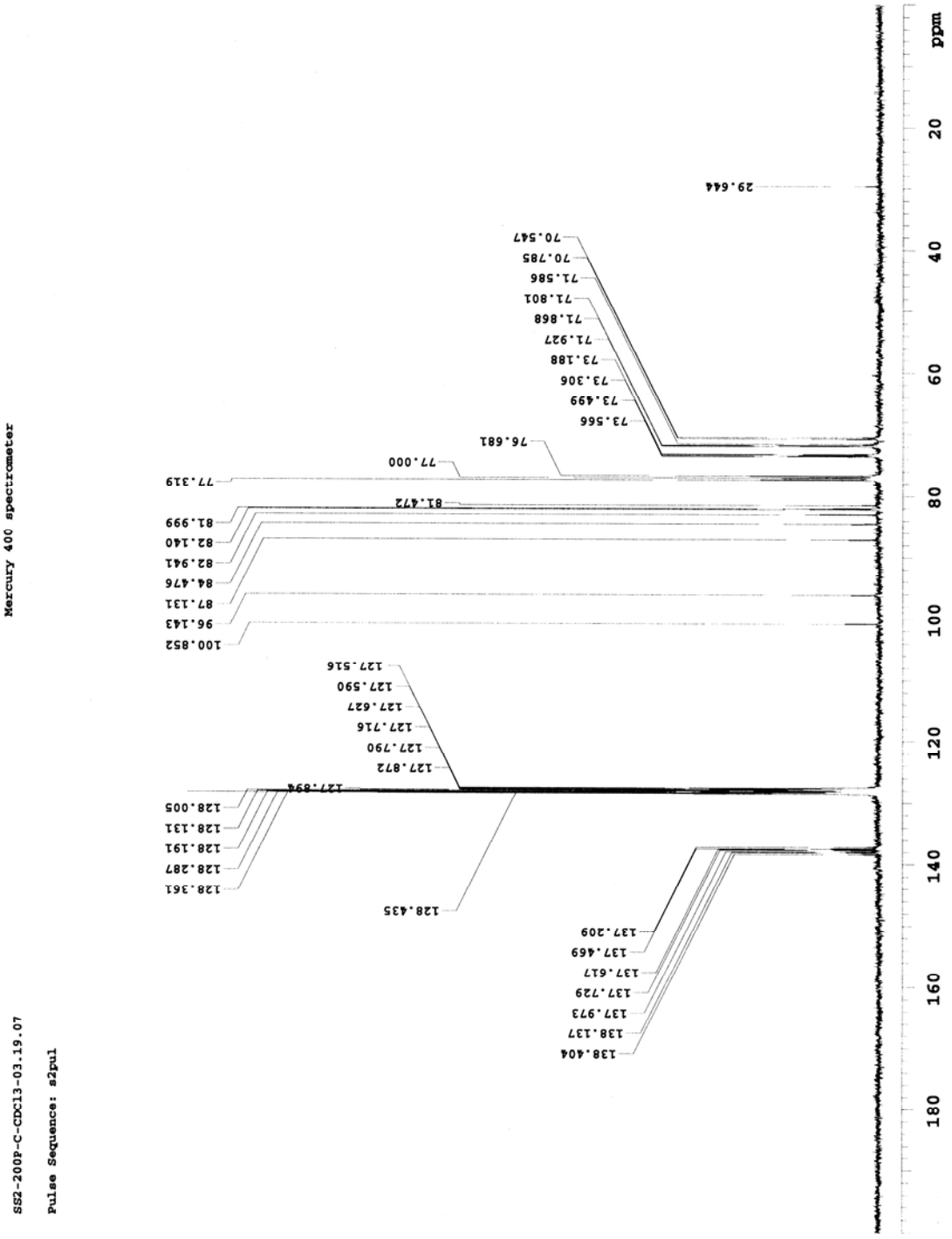
[1]H NMR (Compound 476)



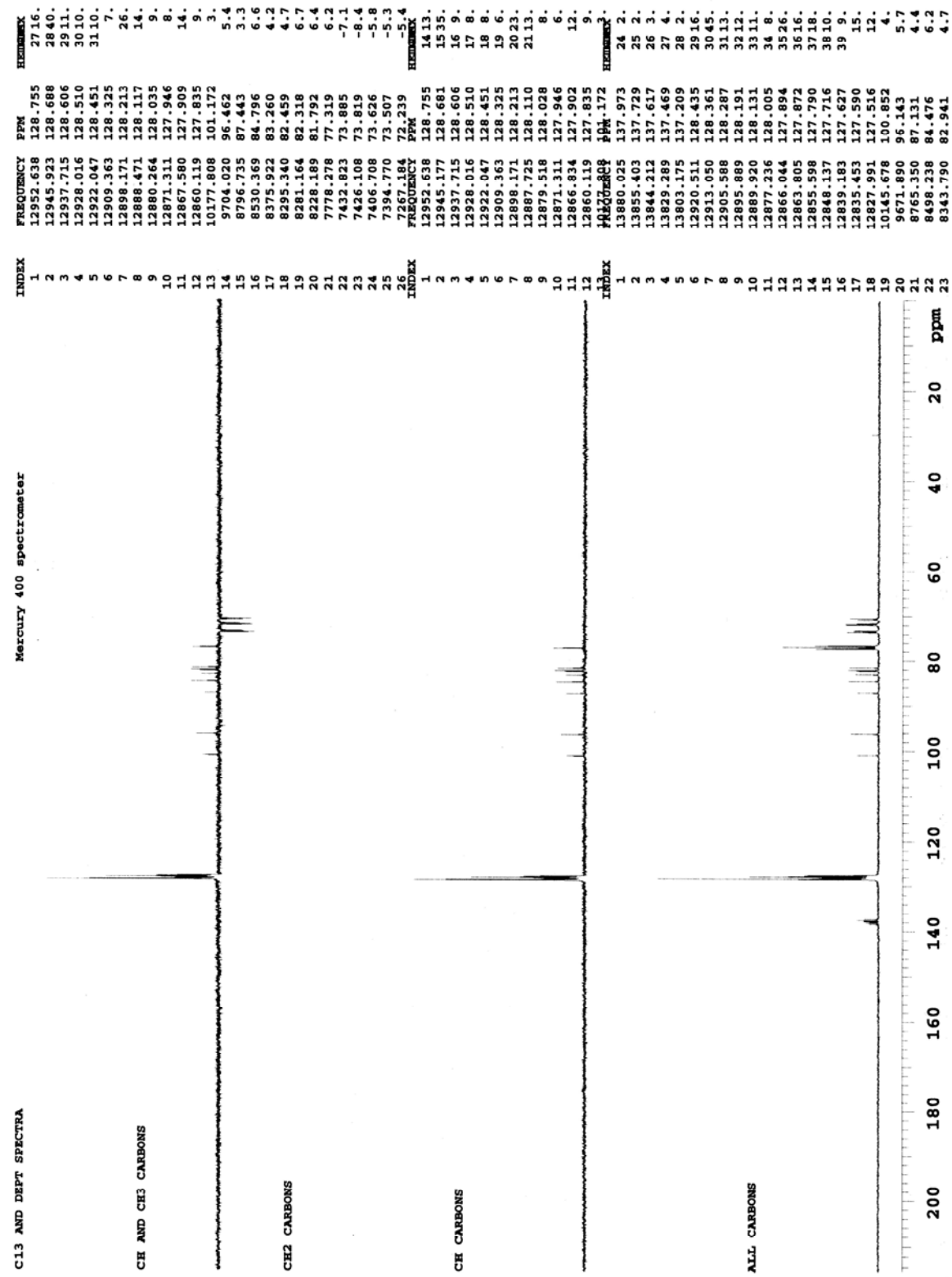
^{1}H NMR (Compound 494)



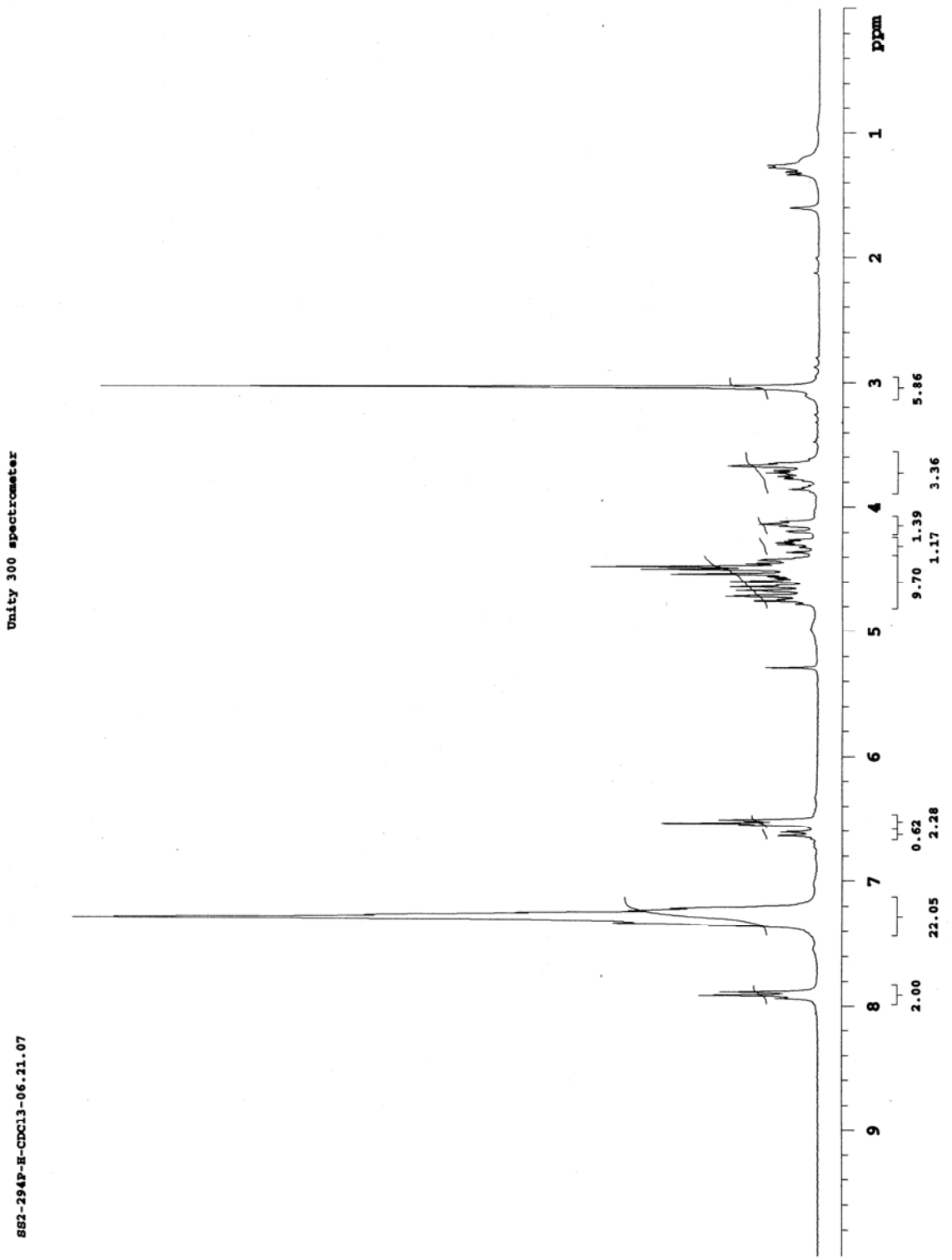
^{13}C NMR (Compound 494)



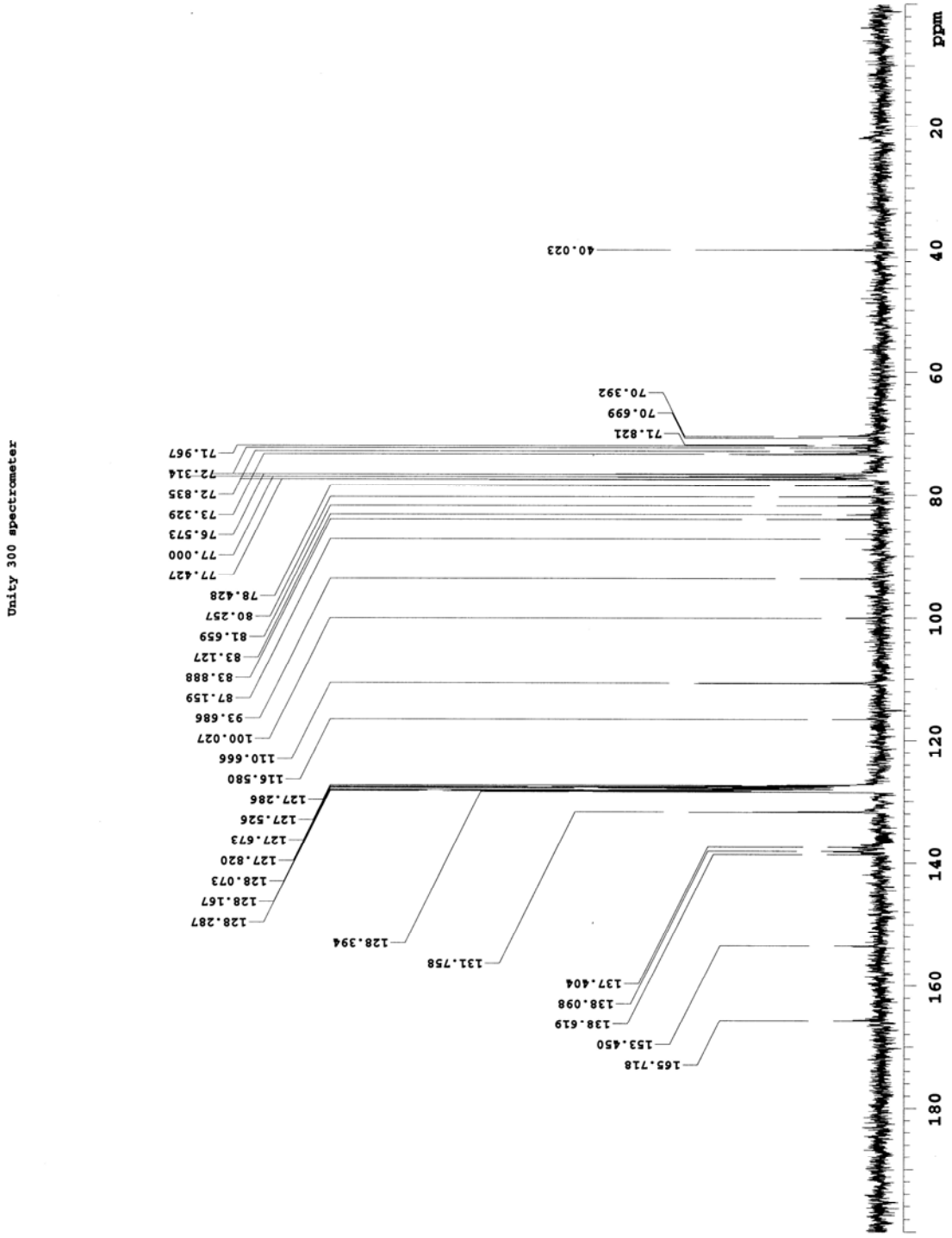
DEPT NMR (Compound 494)



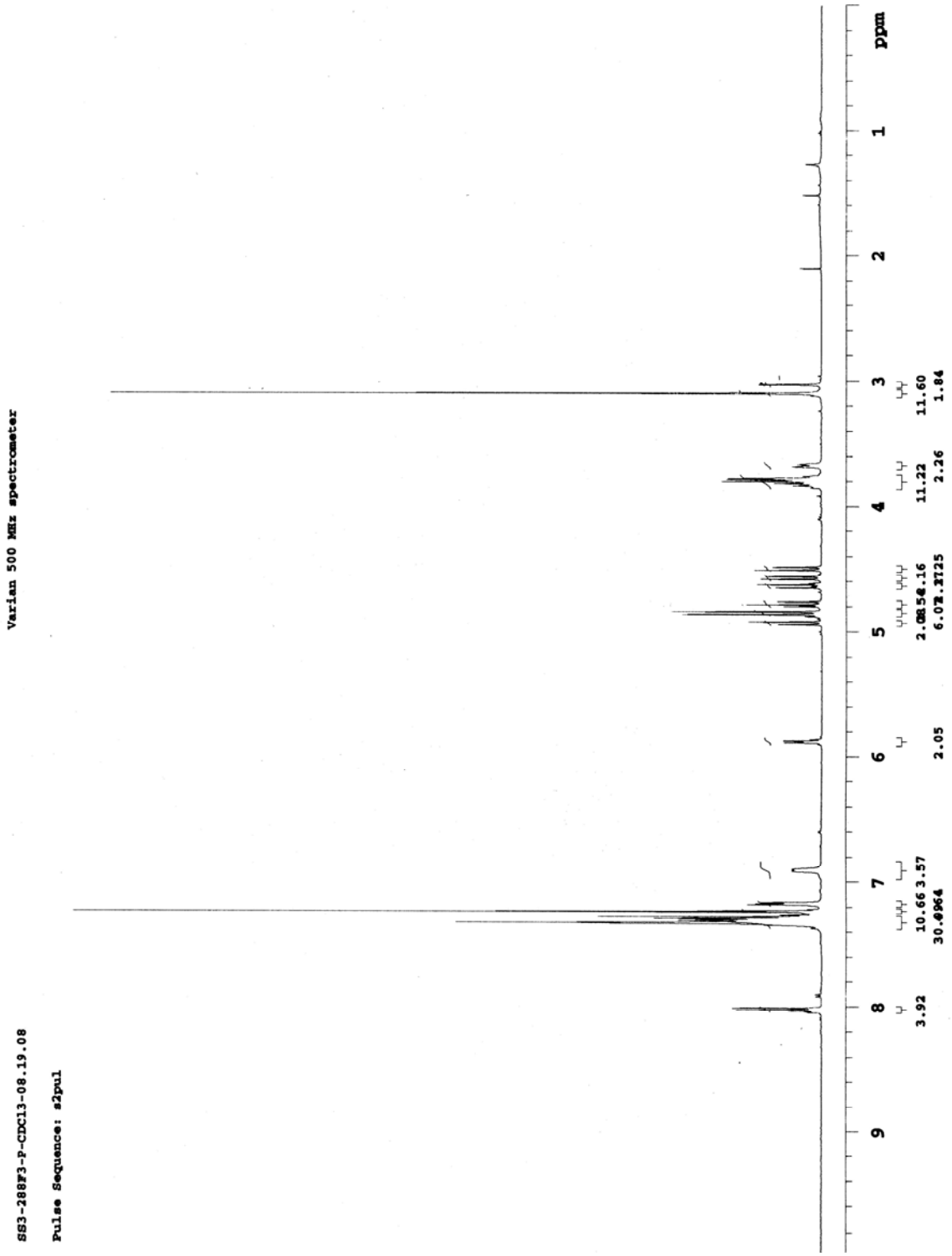
[1]H NMR (Compound 496)



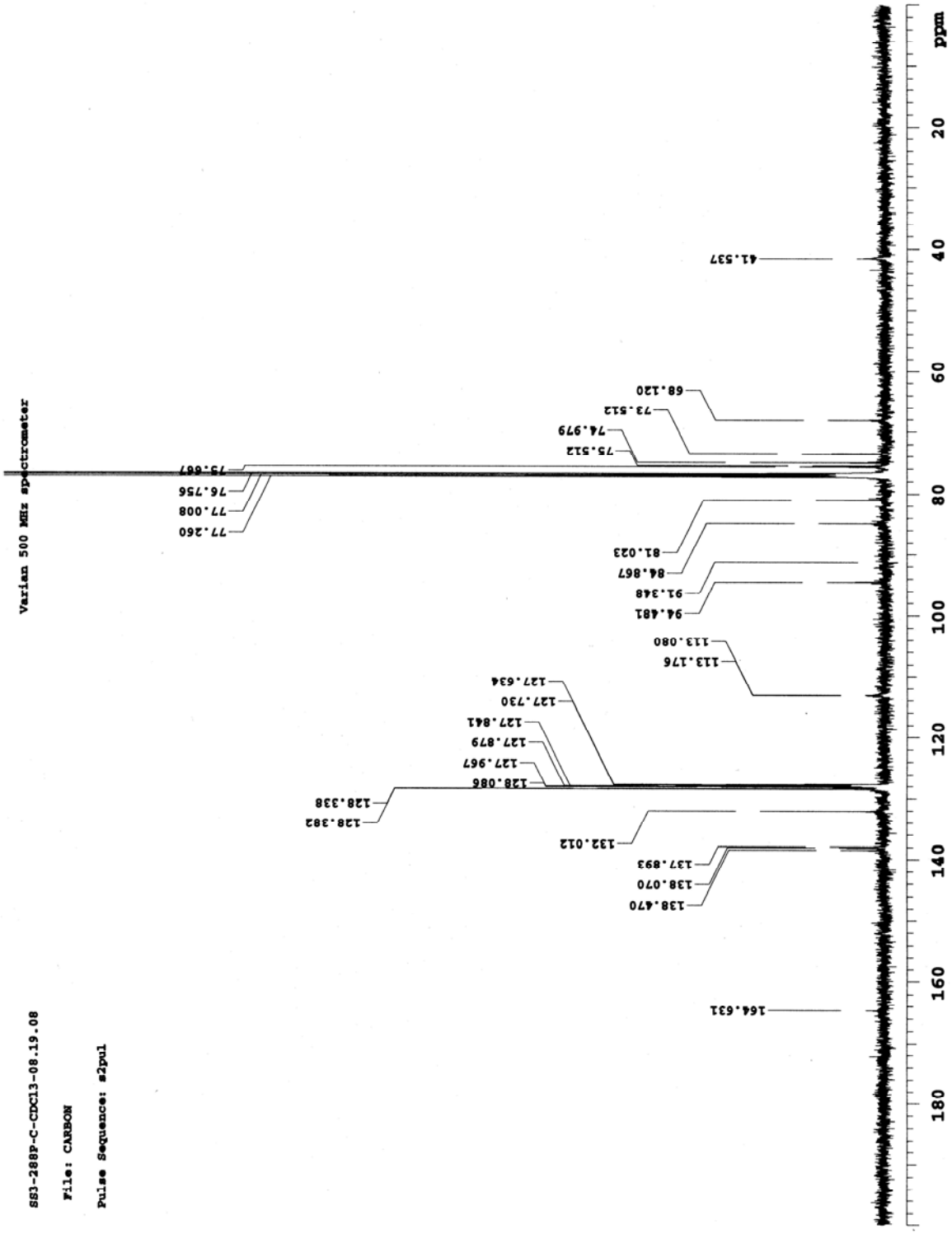
^{13}C NMR (Compound 496)



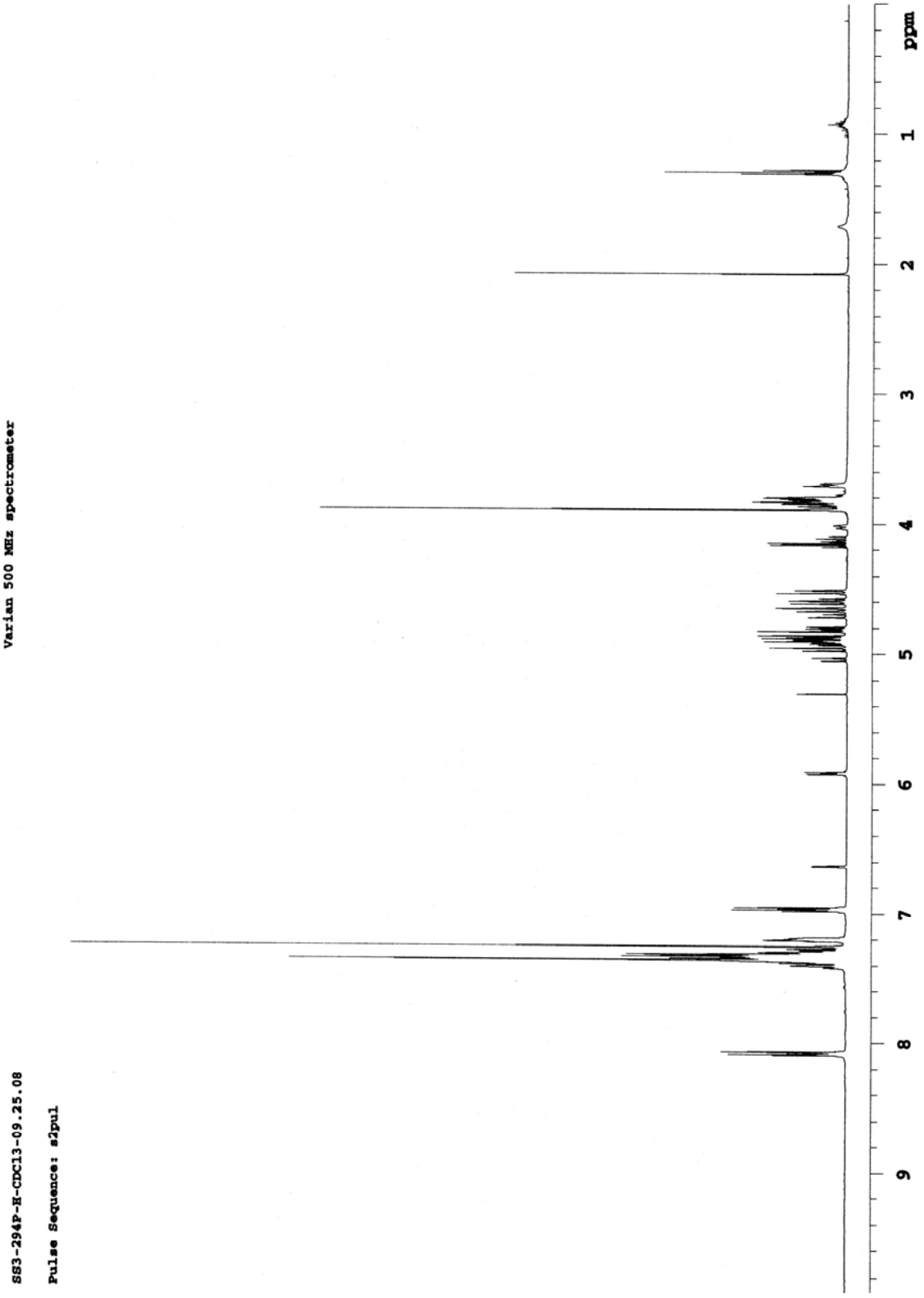
^{1}H NMR (Compound 501)



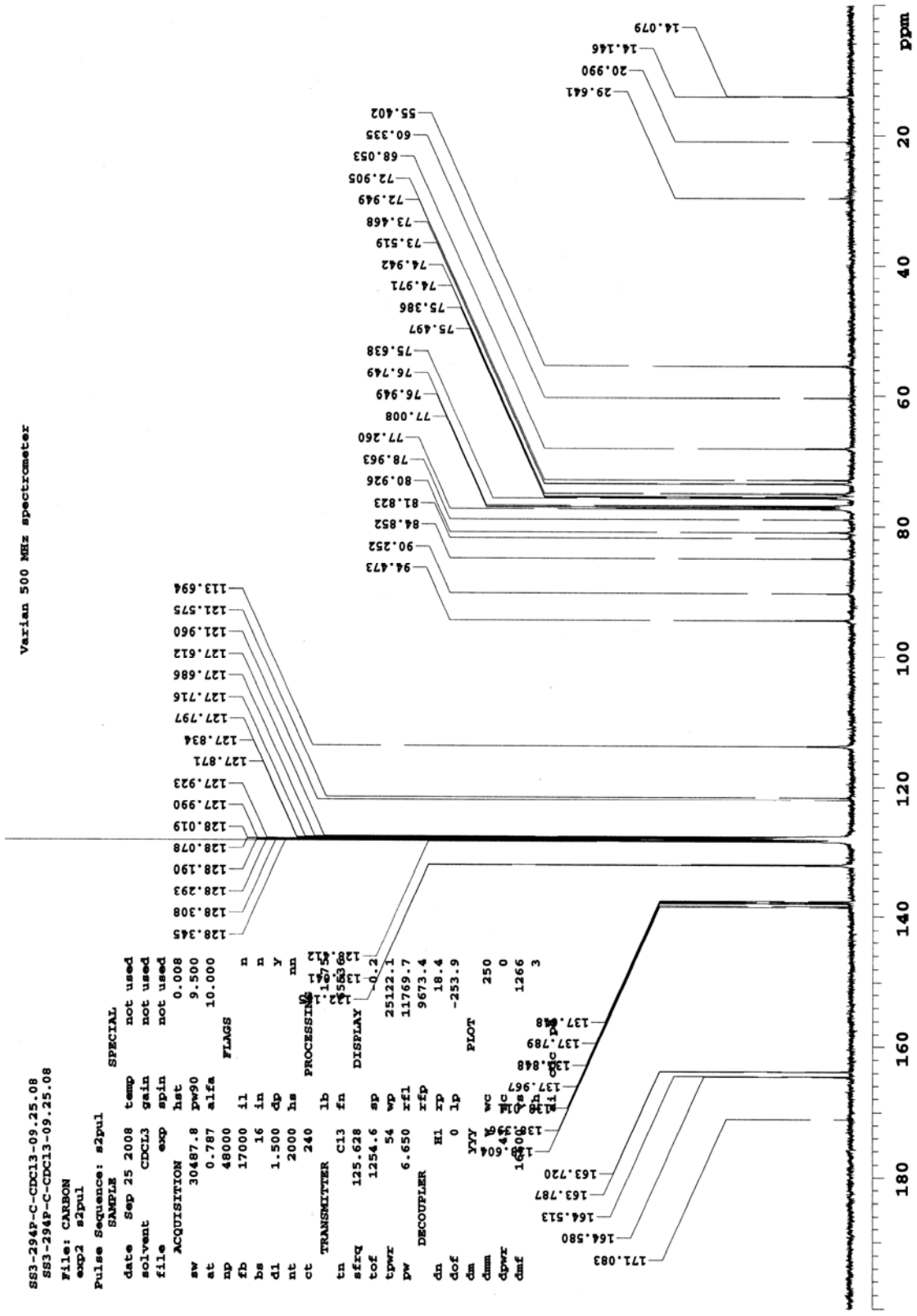
^{13}C NMR (Compound 501)



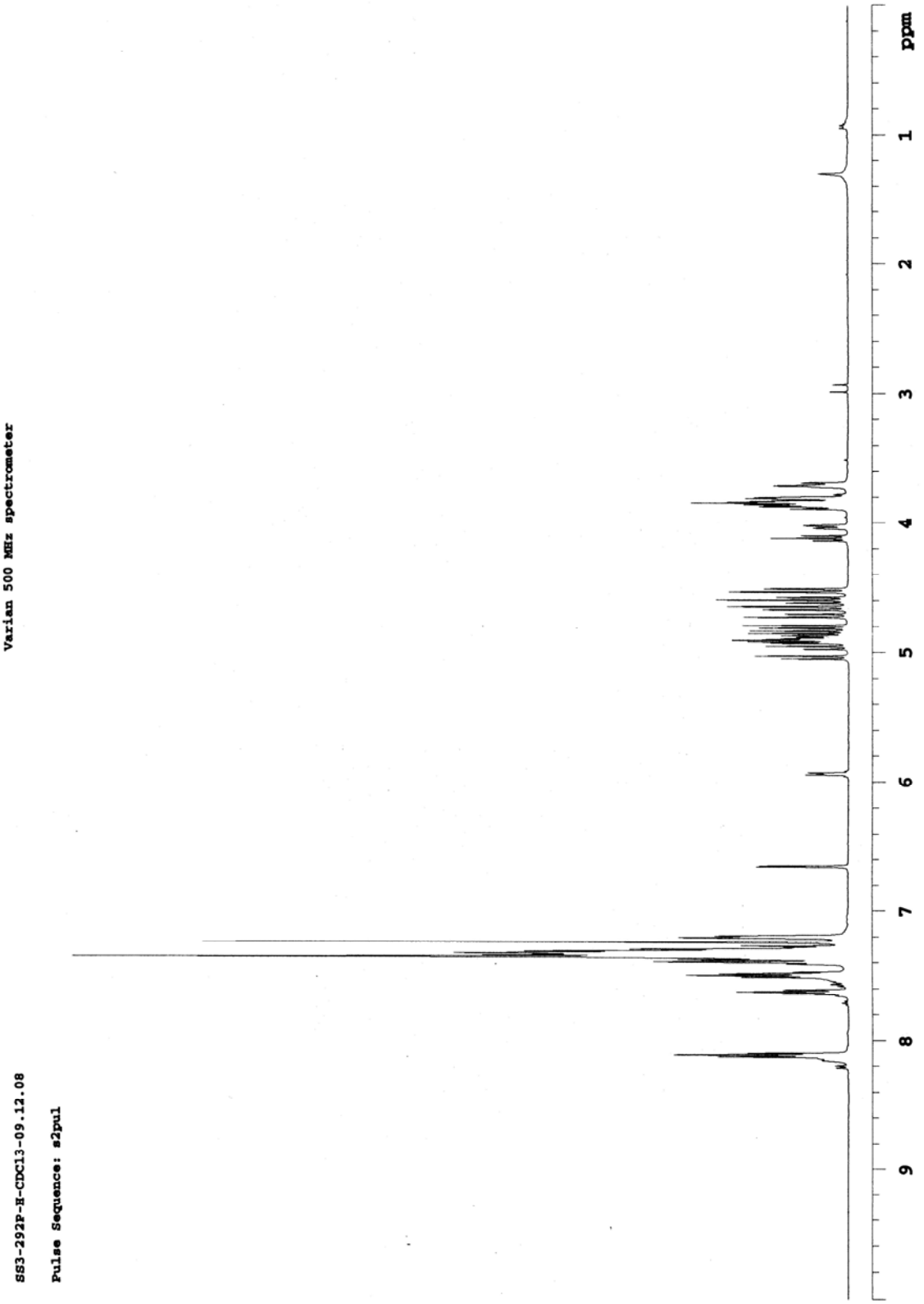
^{1}H NMR (Compound 505)



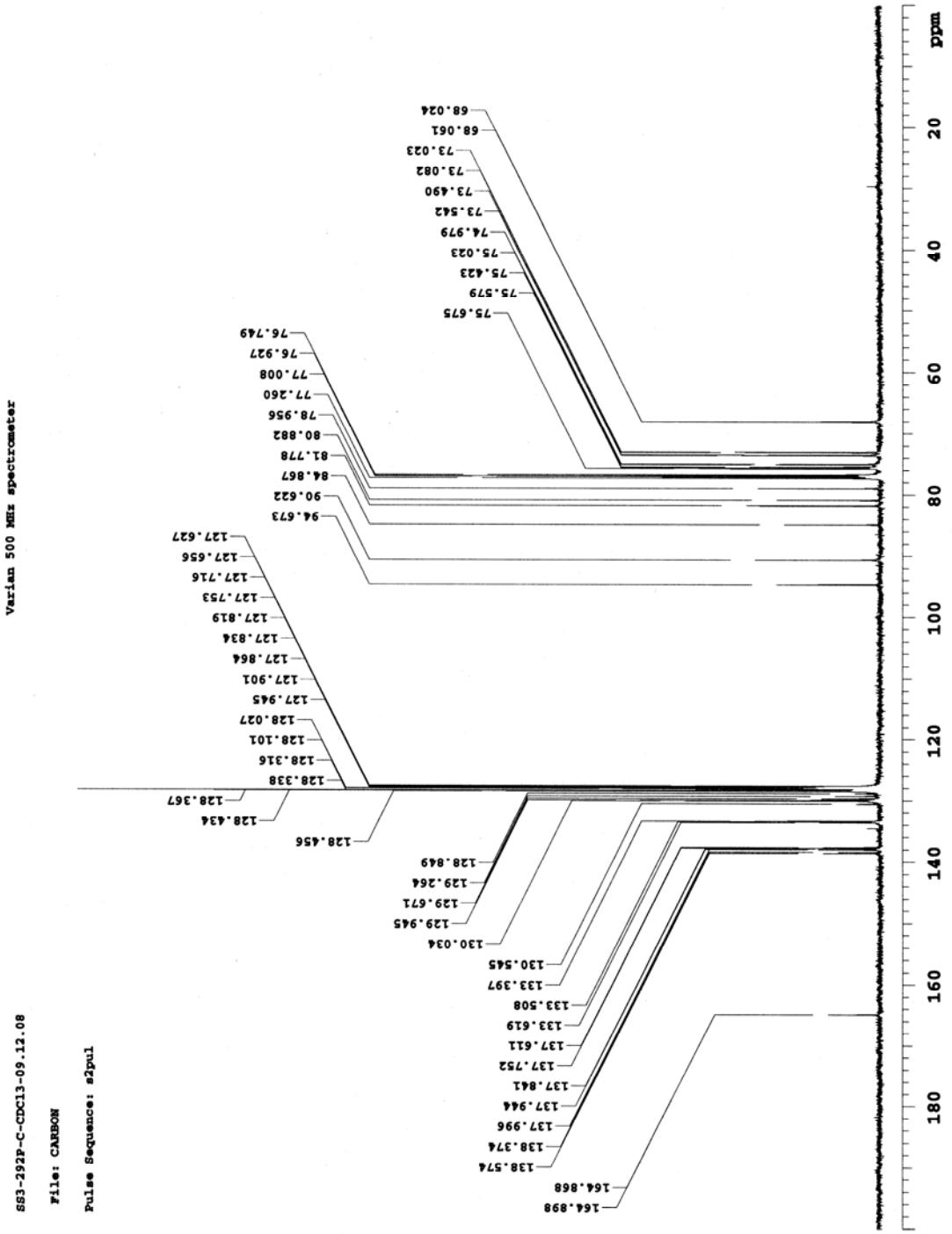
^{13}C NMR (Compound 505)



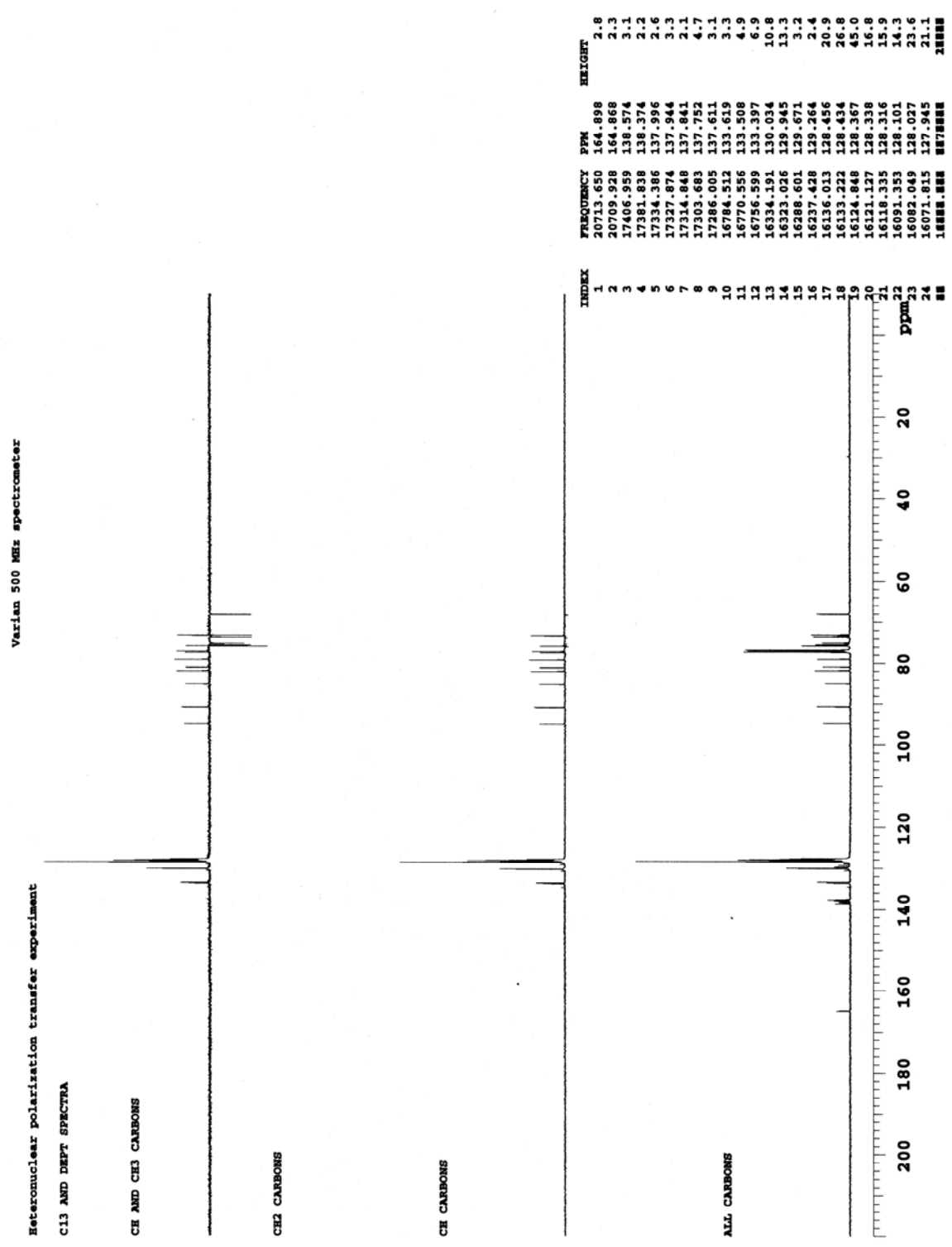
^{1}H NMR (Compound 509)



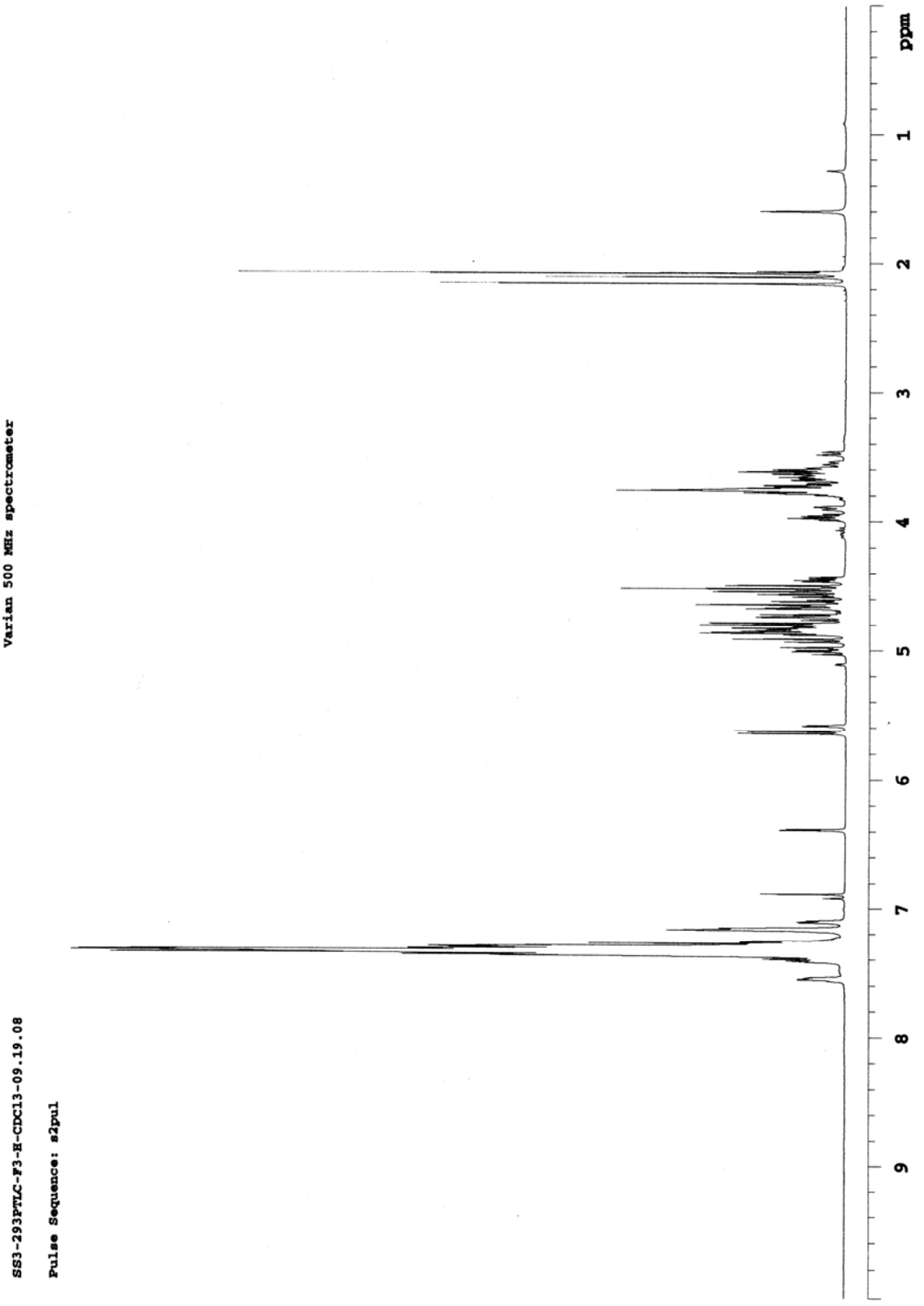
^{13}C NMR (Compound 509)



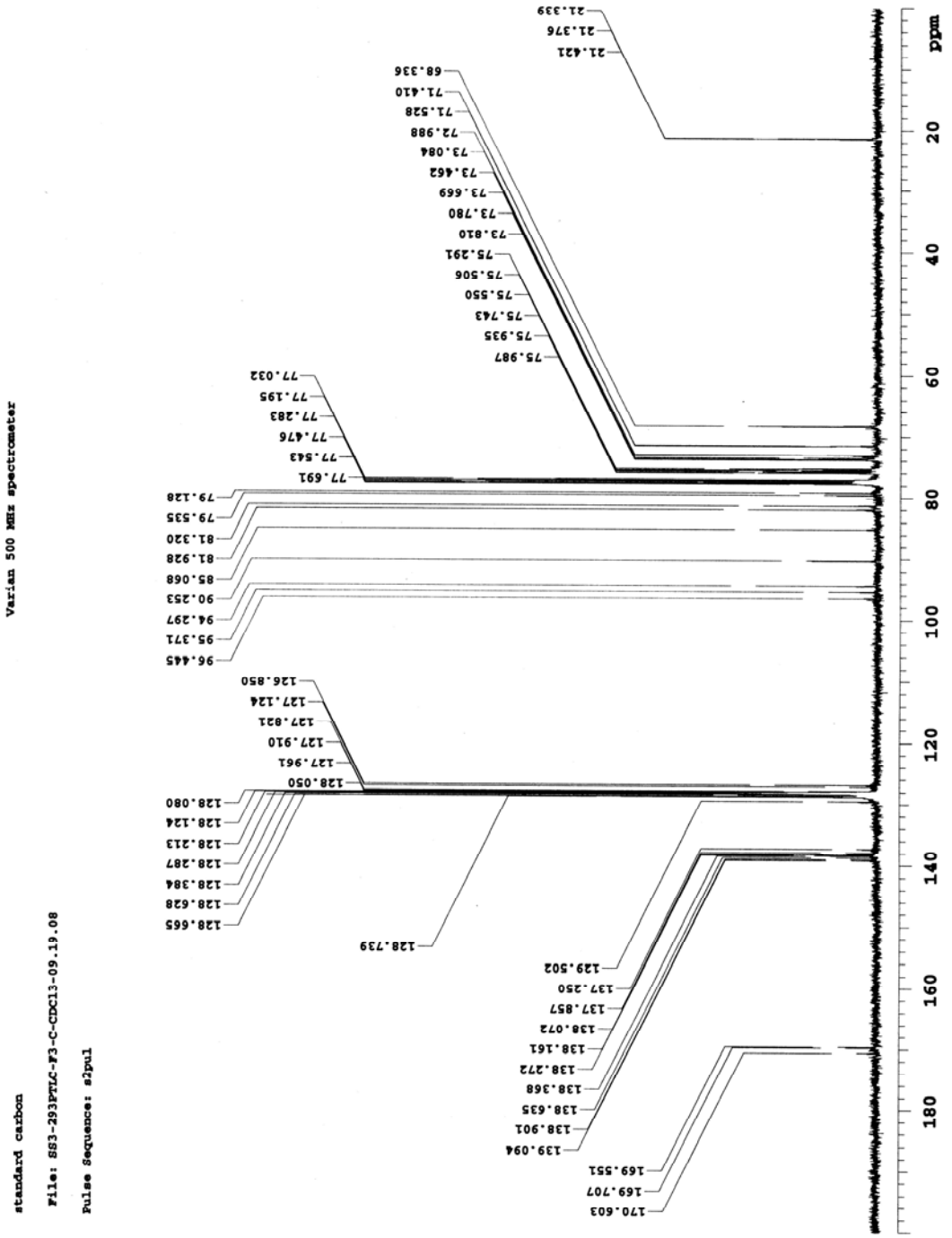
DEPT NMR (Compound 509)



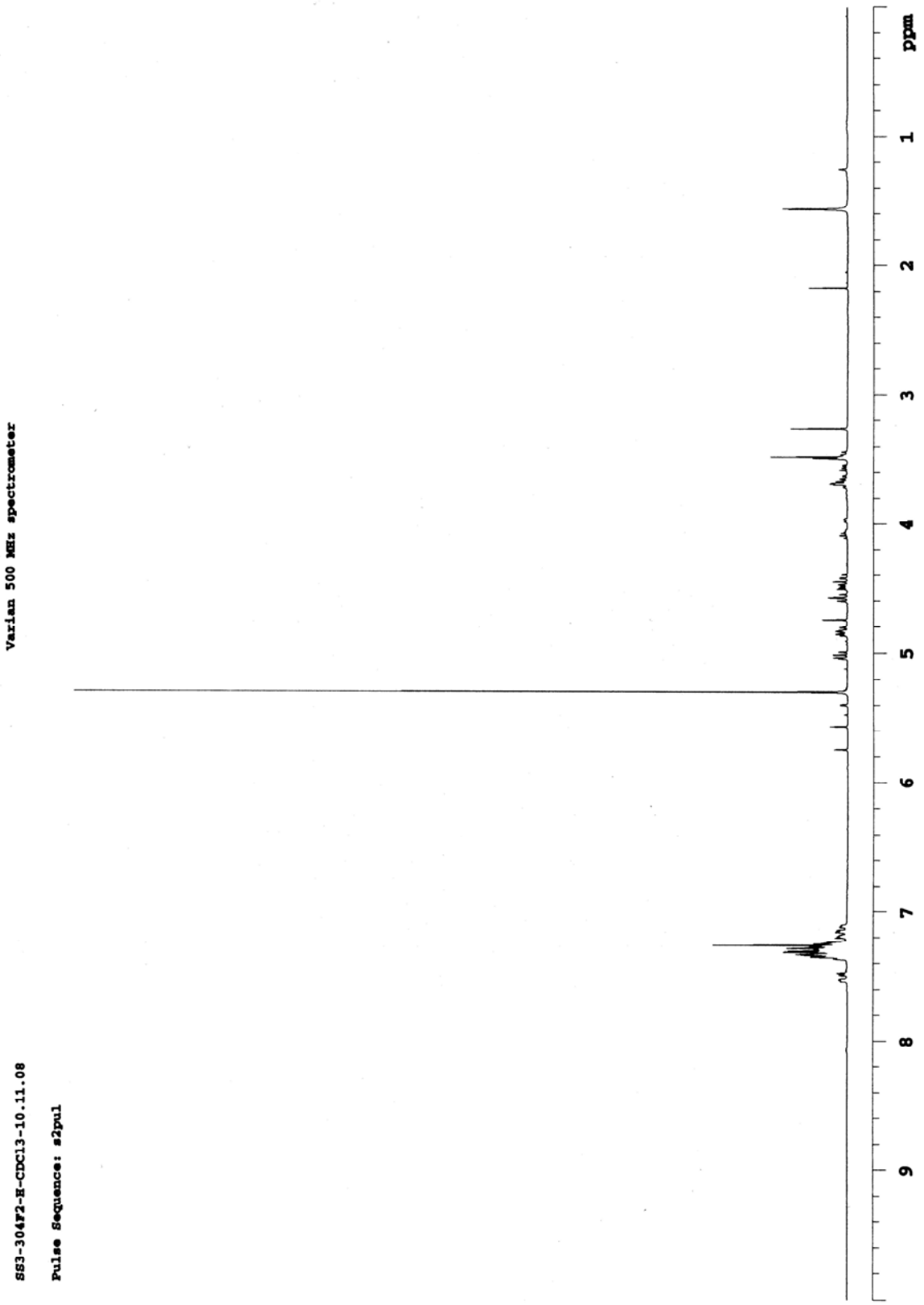
^{1}H NMR (Compound 510)



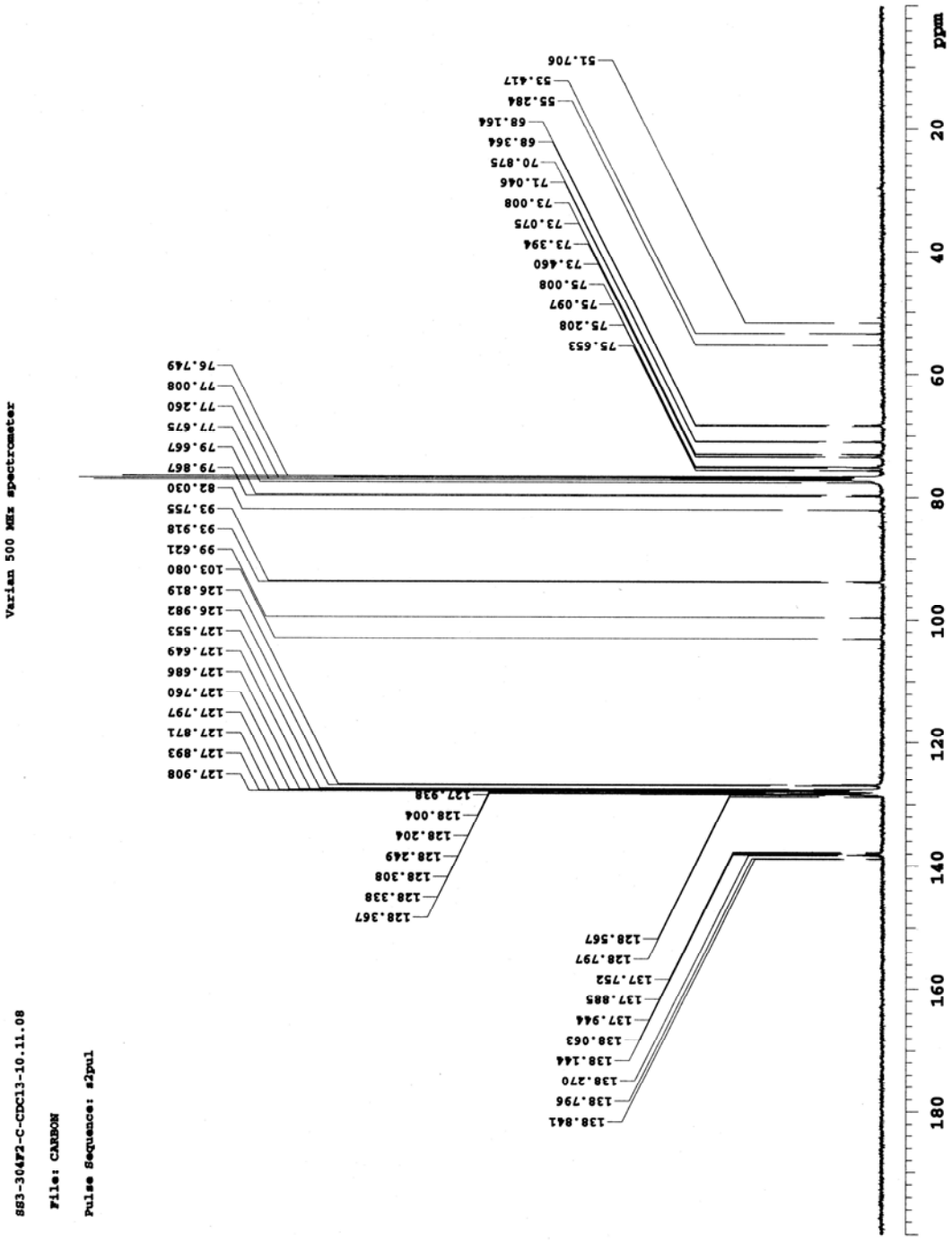
^{13}C NMR (Compound 510)



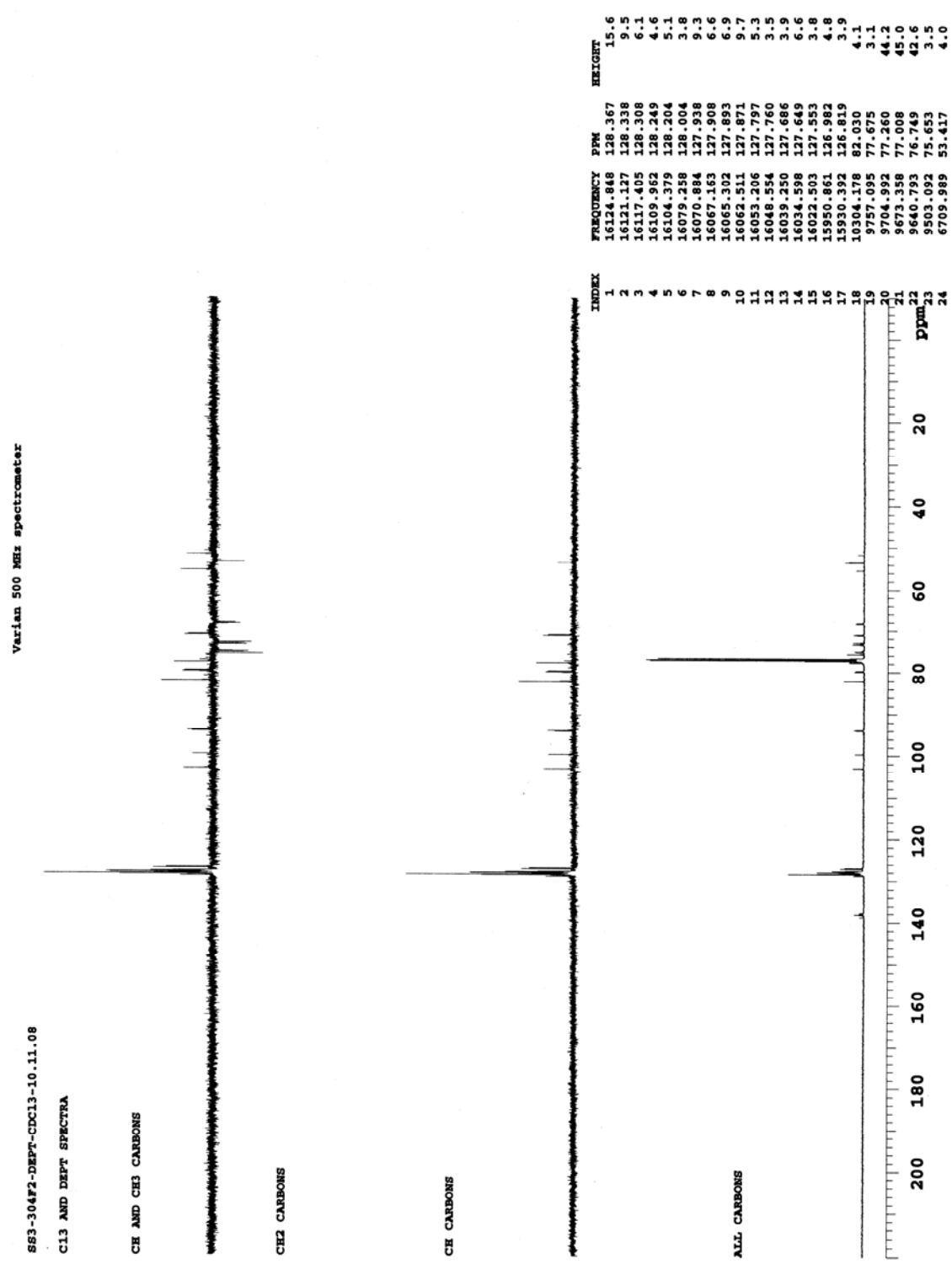
[1]H NMR (Compound 512)



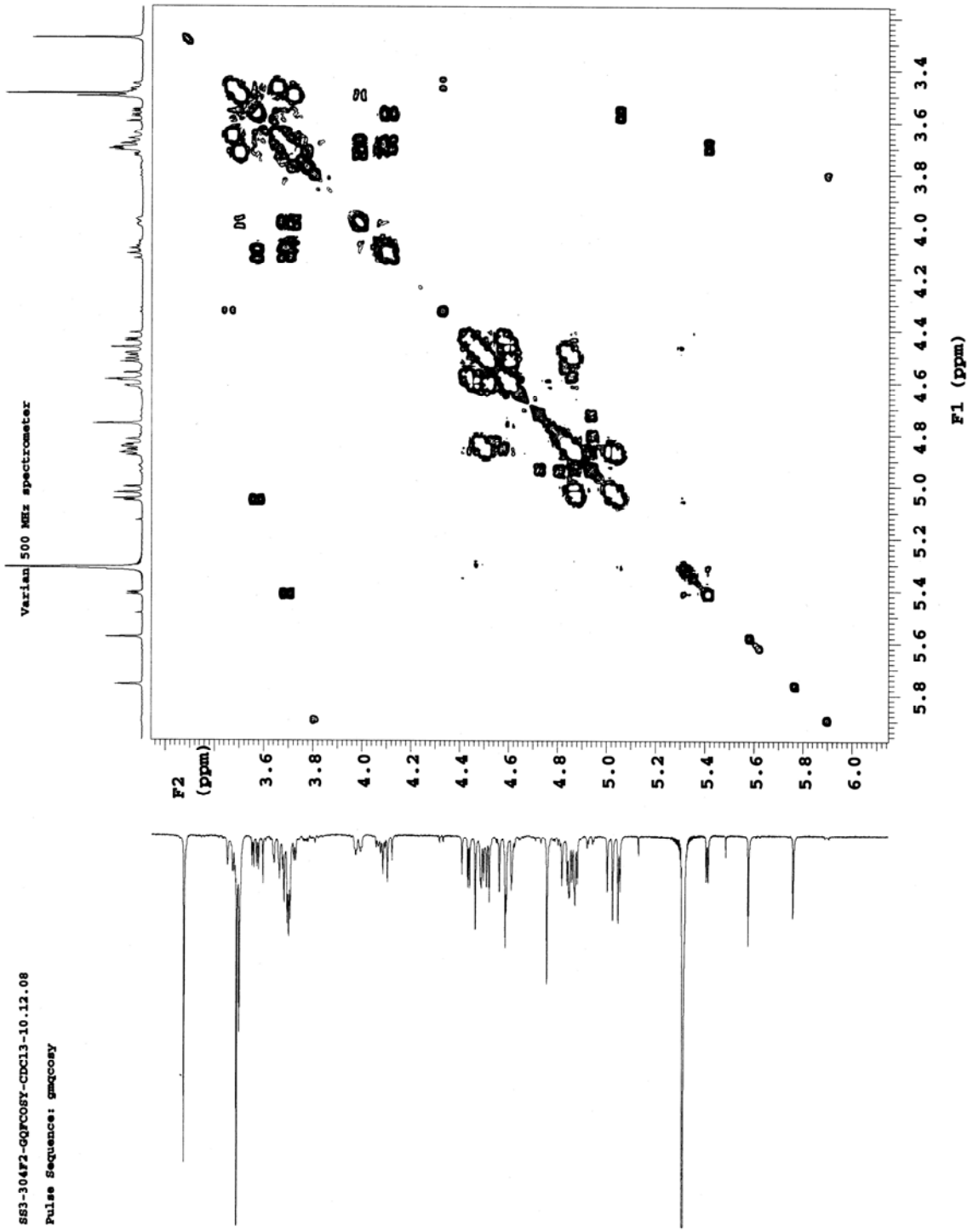
^{13}C NMR (Compound 512)



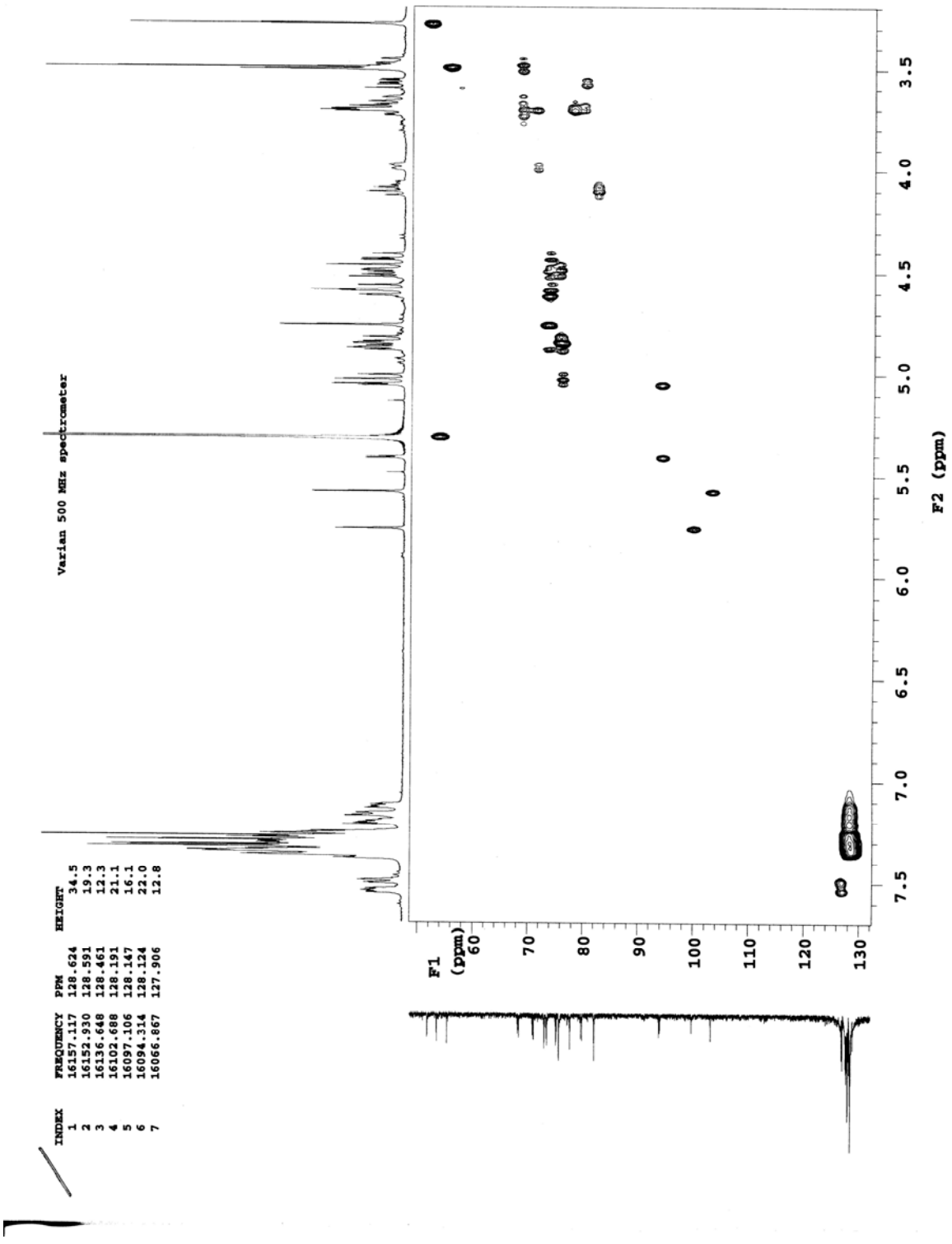
DEPT NMR (Compound 512)



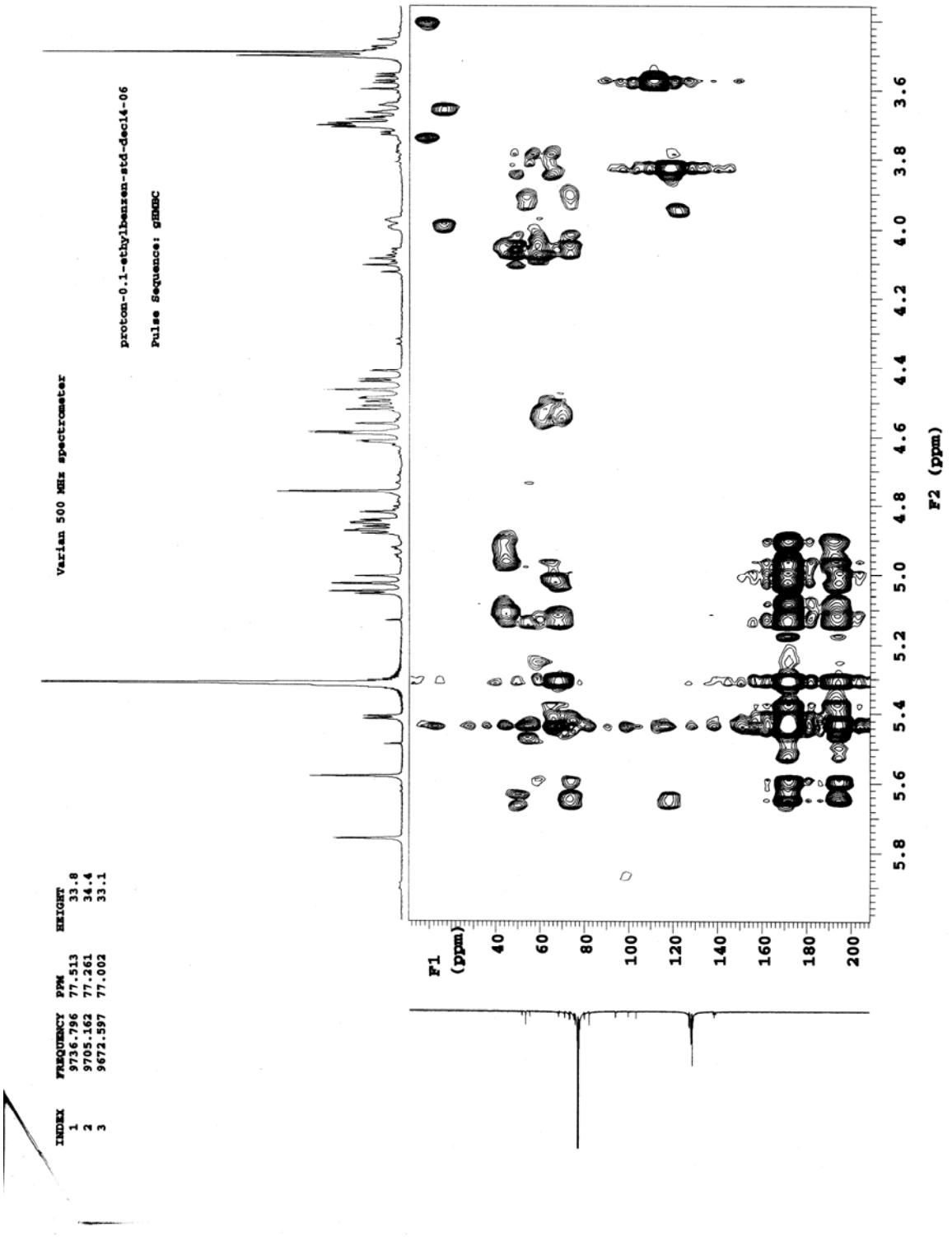
^{1}H-^{1}H GDQFCOSY NMR (Compound 512)



GHMQC NMR (Compound 512)



GHMBC NMR (Compound 512)



Elemental Composition Report

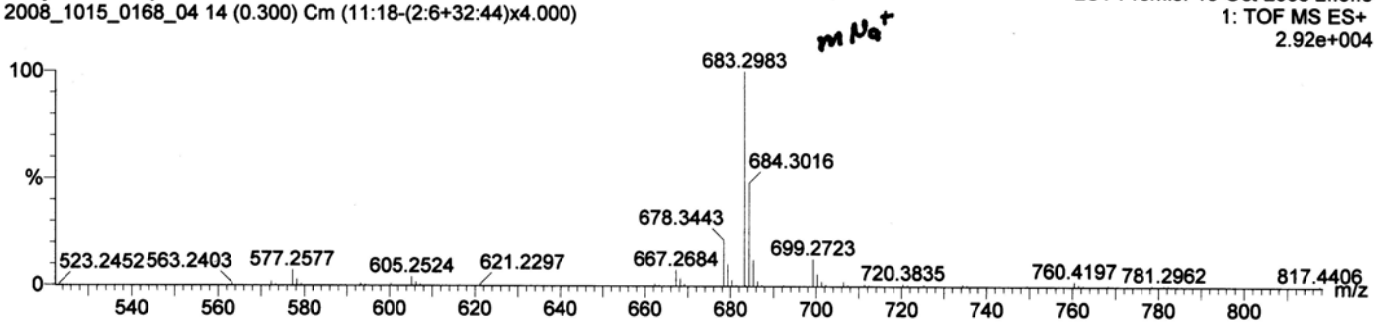
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

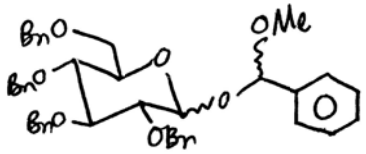
Monoisotopic Mass, Even Electron Ions
134 formula(e) evaluated with 3 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-7 23Na: 0-1

Andreana- Soumave Santra SS3-304F2 mw180 LCT0168 1uL meoh dif cal
Shay 2008-07b.pro
2008_1015_0168_04 14 (0.300) Cm (11:18-(2:6+32:44)x4.000)

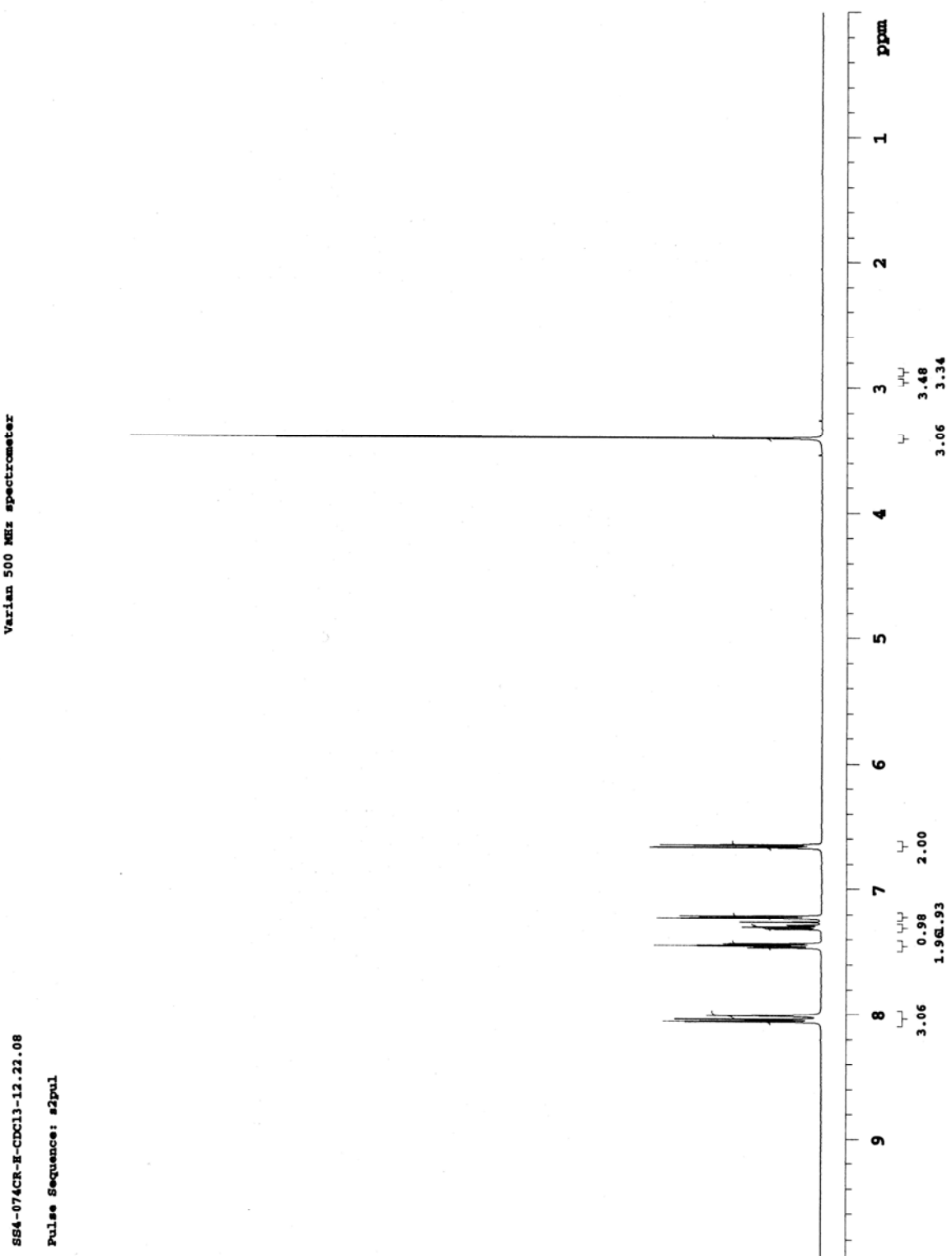
LCT Premier 15-Oct-2008 2::3::5
1: TOF MS ES+
2.92e+004



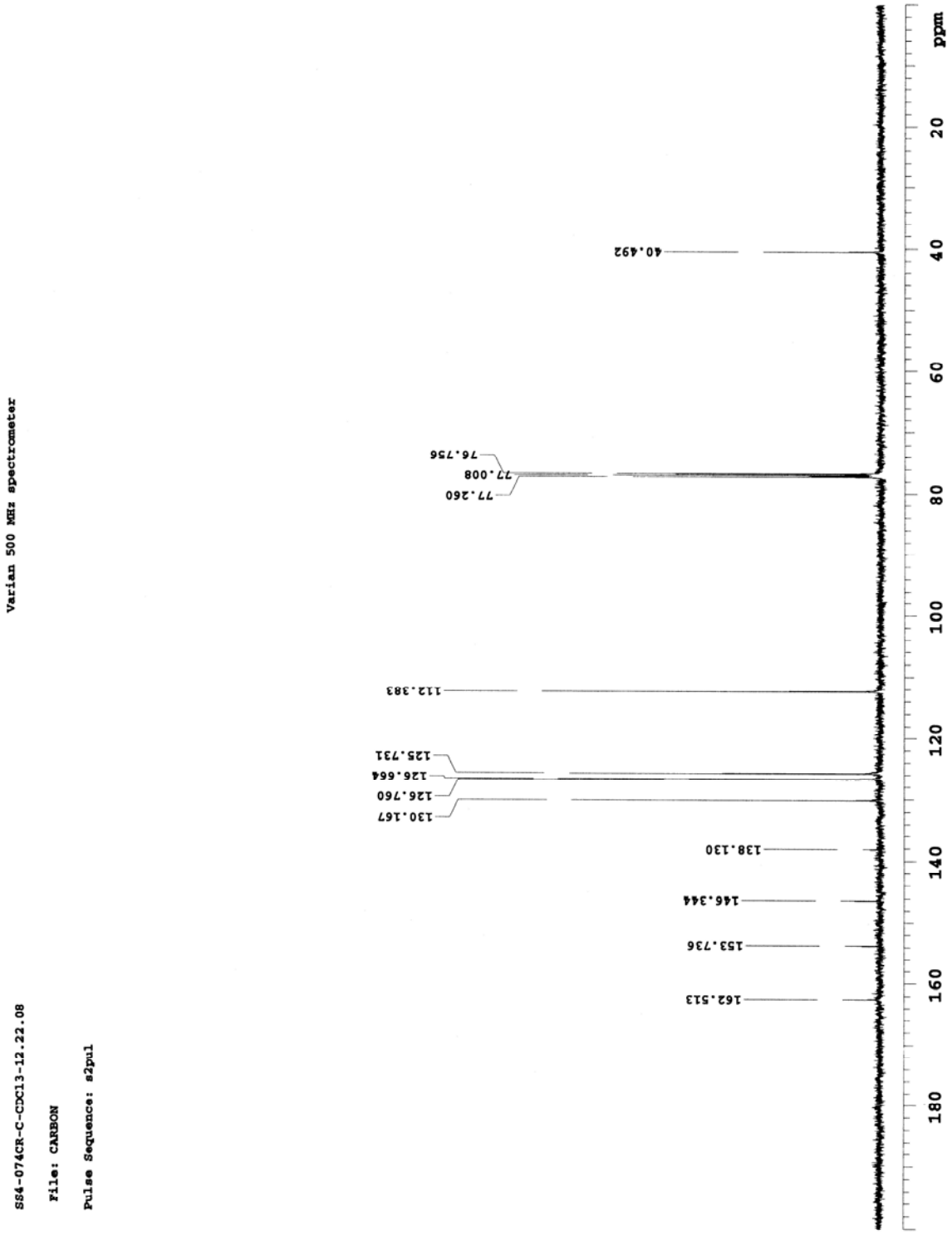
Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
683.2983	683.2985	-0.2	-0.3	20.5	18.0	0.0	C42 H44 O7 23Na
	683.3009	-2.6	-3.8	23.5	24.5	6.6	C44 H43 O7
	683.2950	3.3	4.8	32.5	30.2	12.2	C51 H39 O2



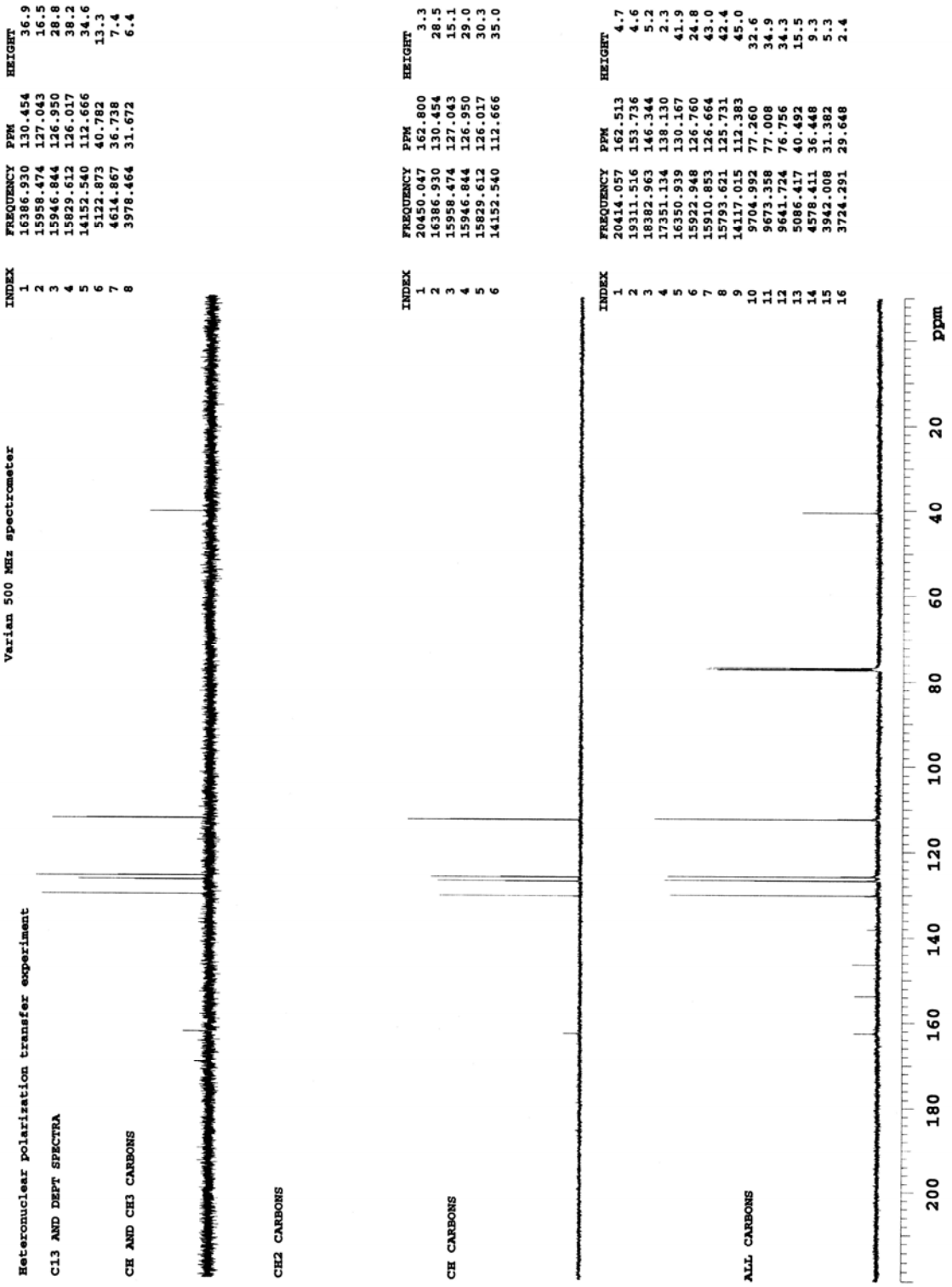
^{1}H NMR (Compound 523)



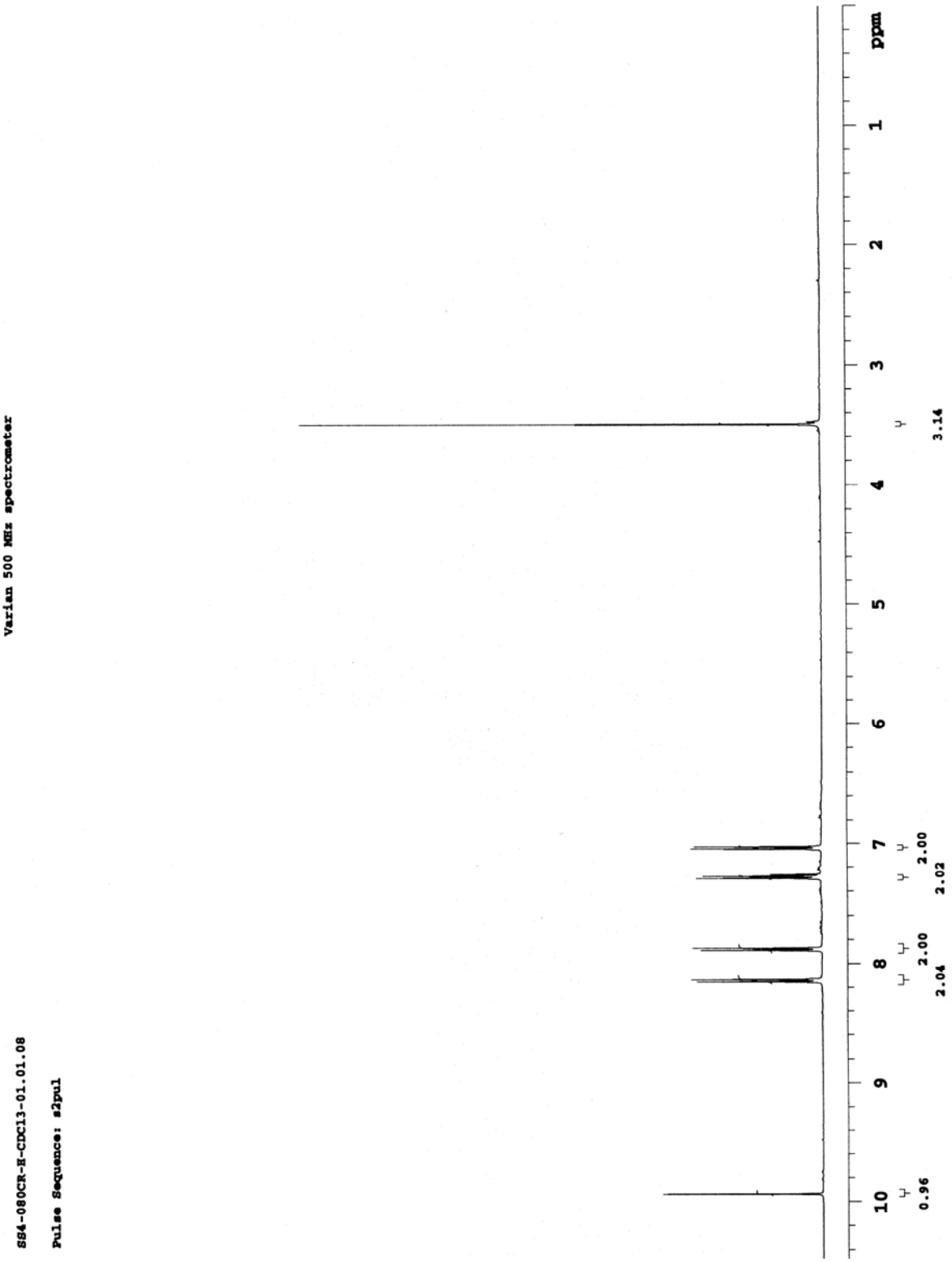
^{1}H NMR (Compound 523)



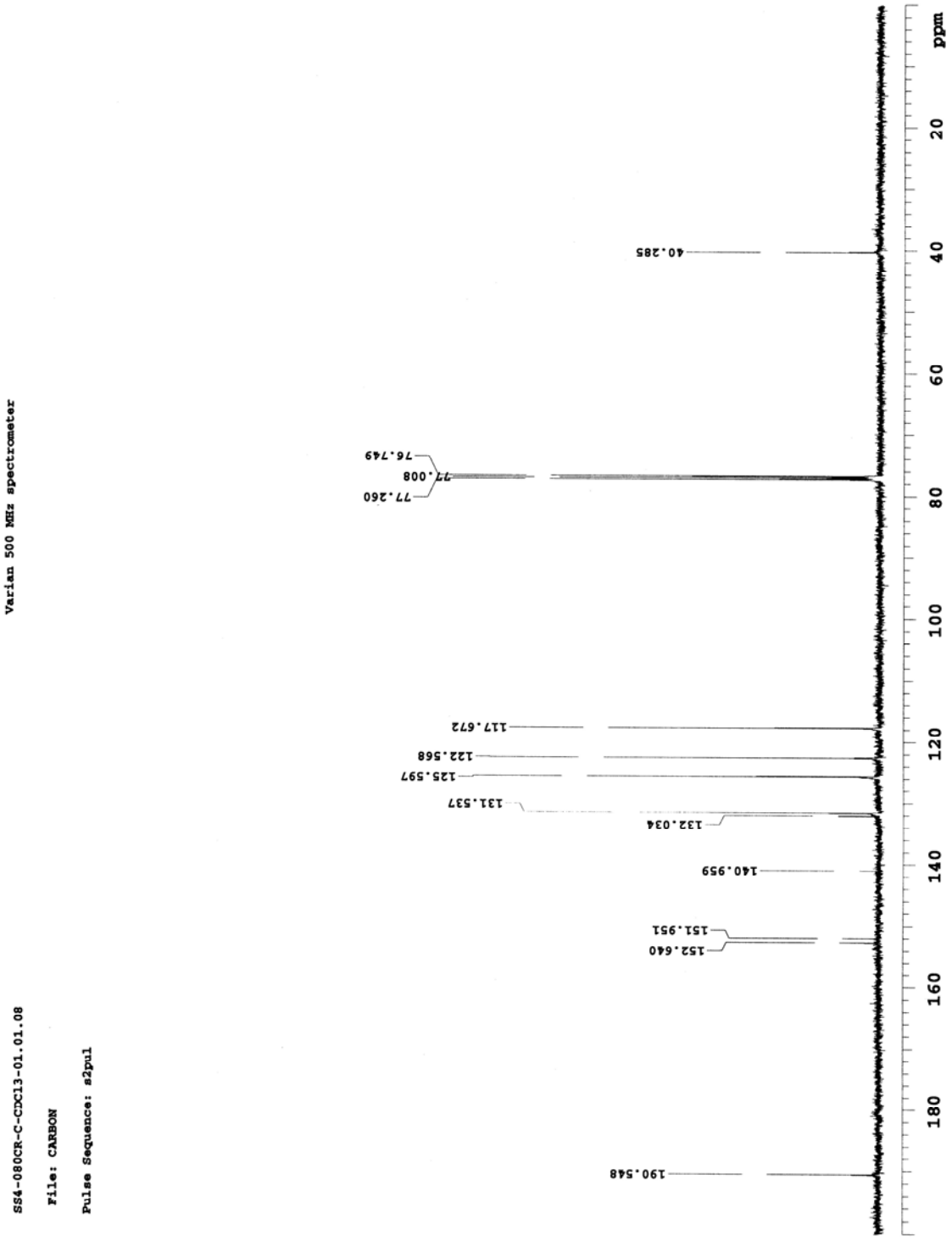
DEPT NMR (Compound 523)



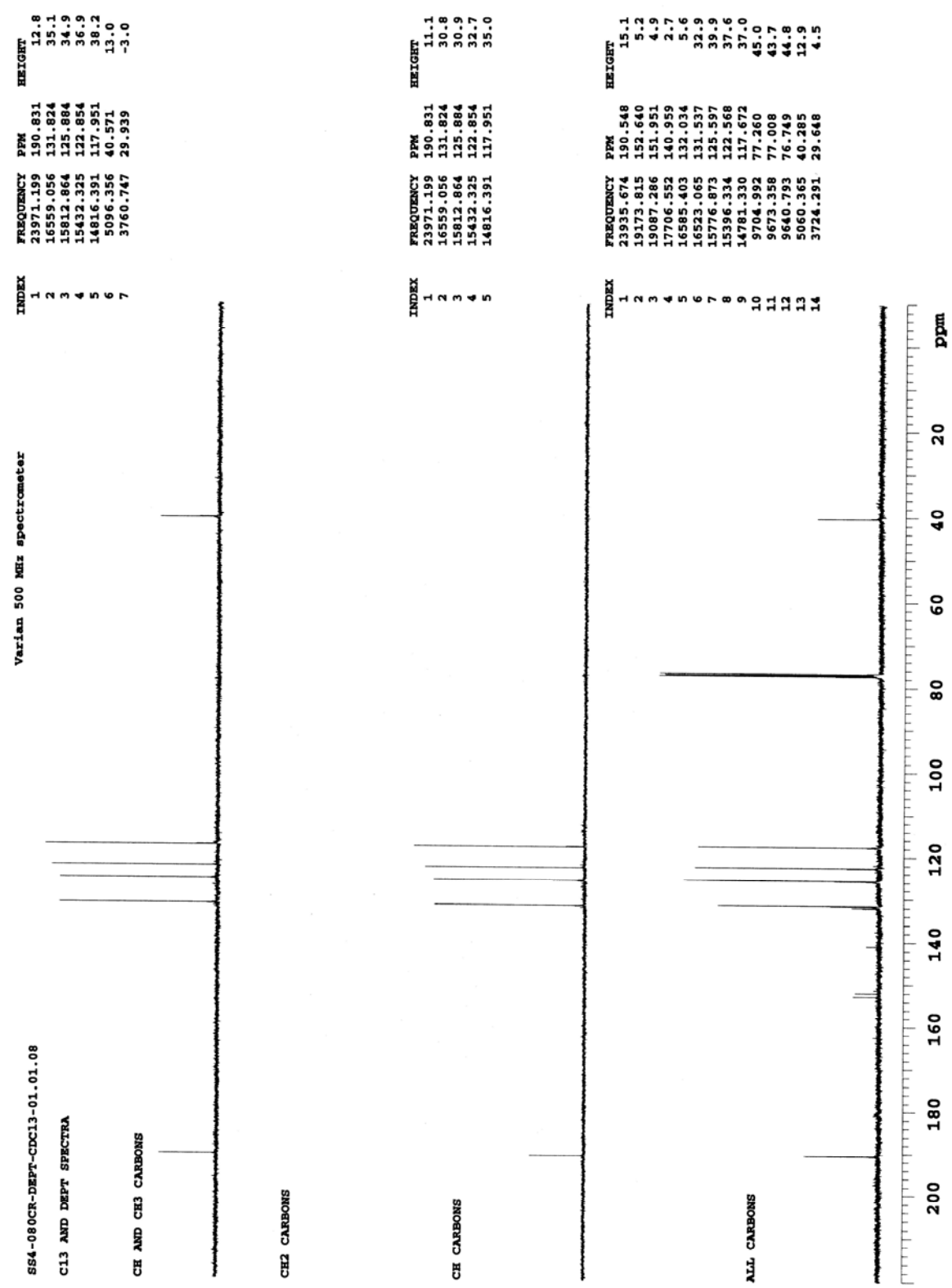
[1]H NMR (Compound 524)



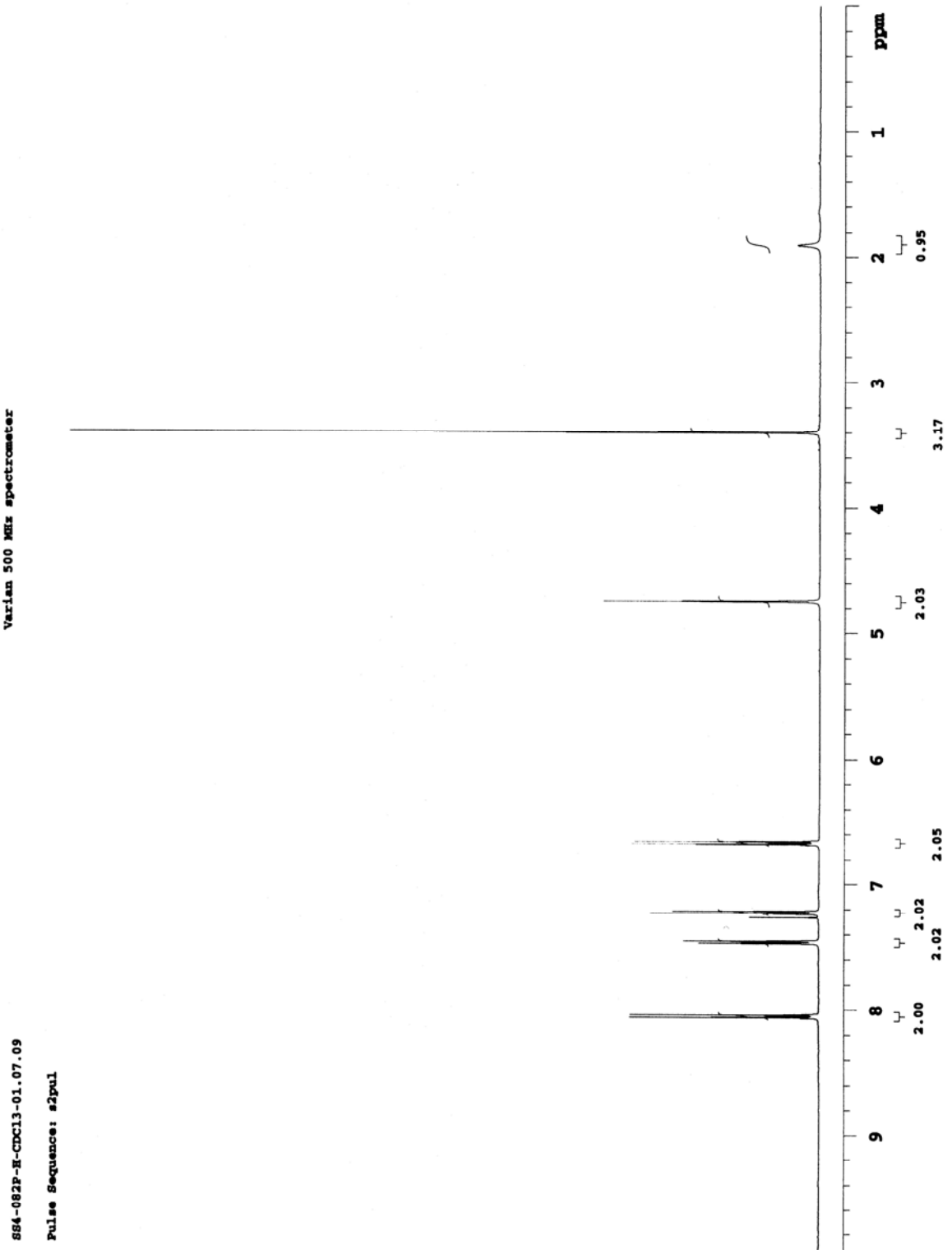
^{13}C NMR (Compound 524)



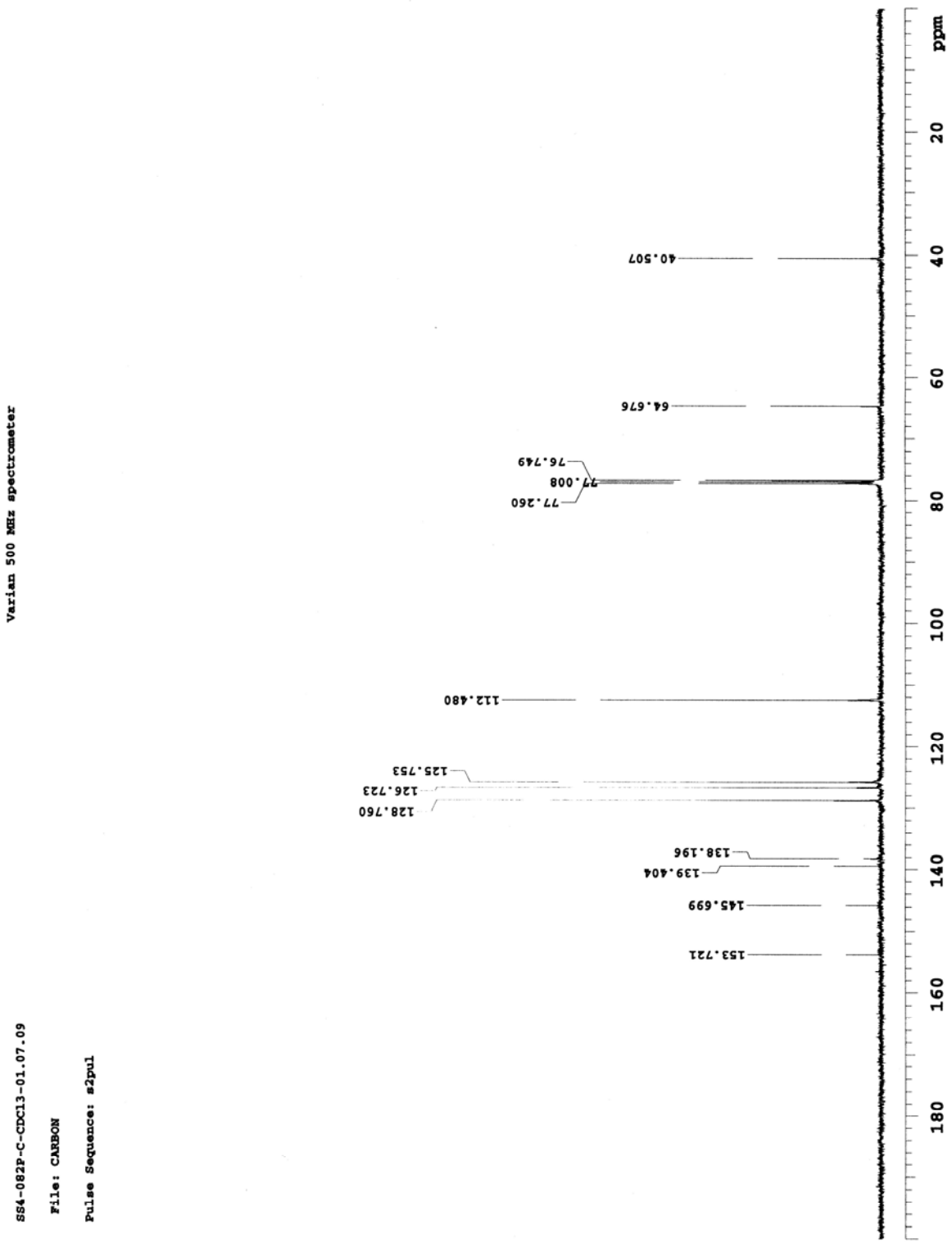
DEPT NMR (Compound 524)



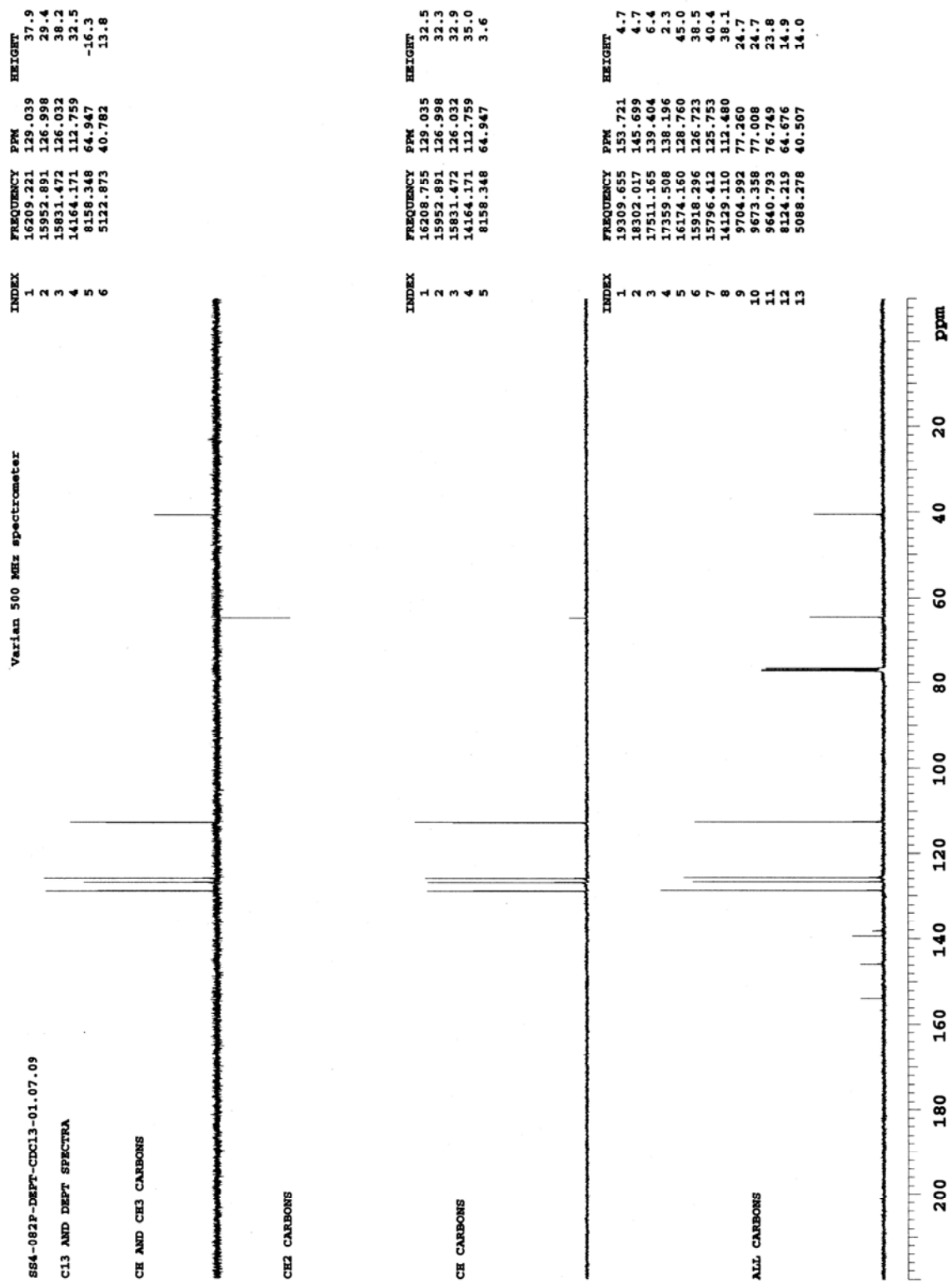
^{1}H NMR (Compound 525)



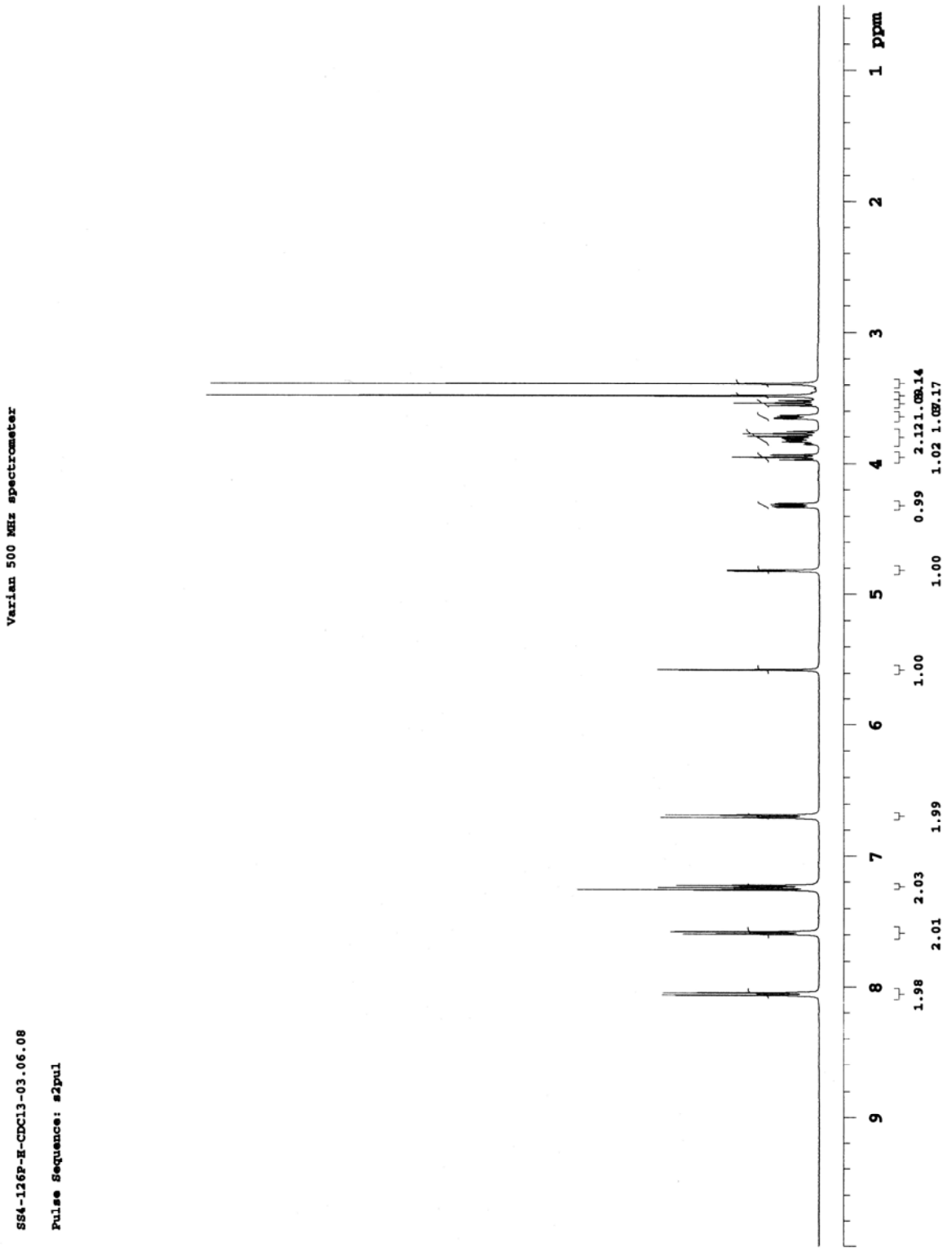
^{13}C NMR (Compound 525)



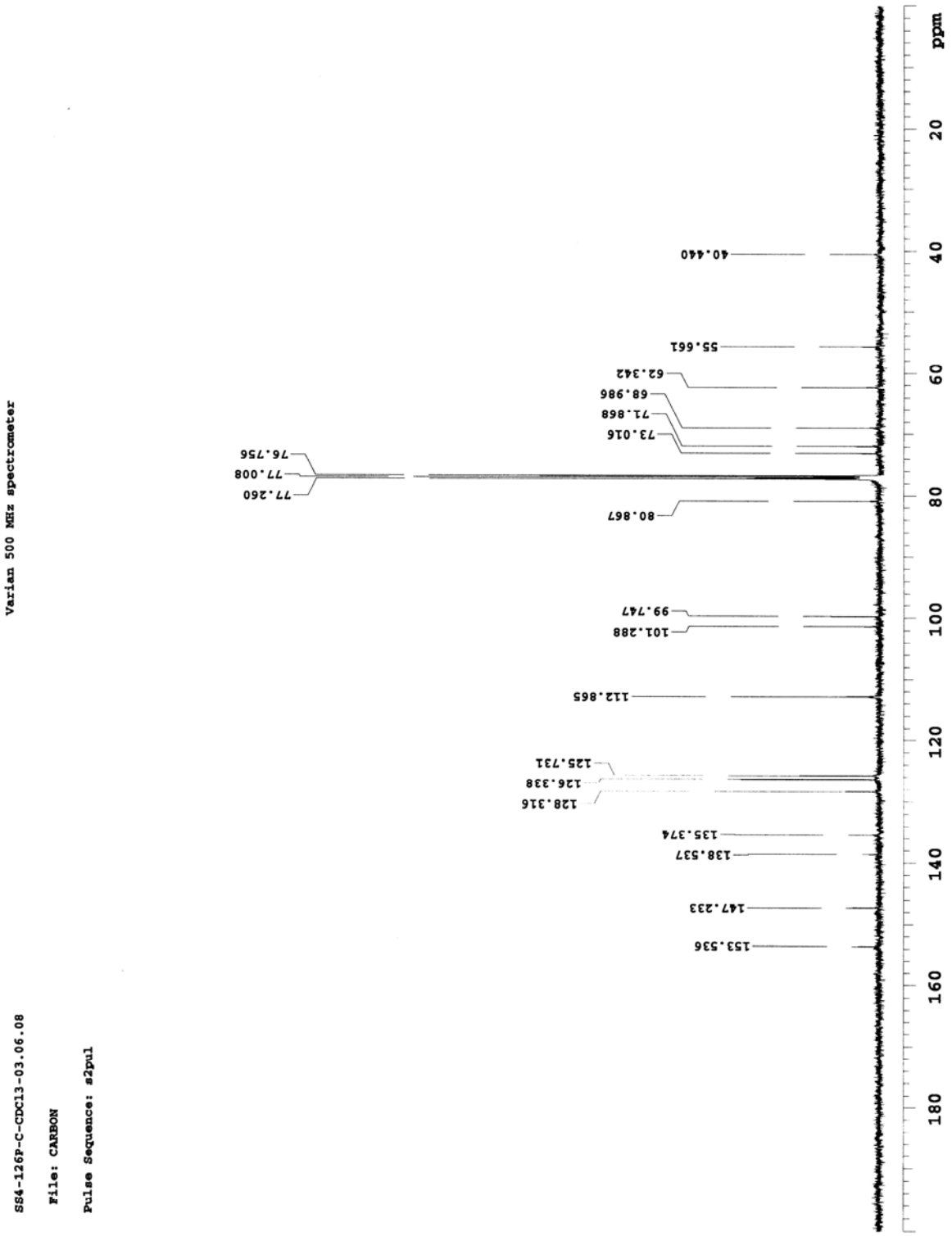
DEPT NMR (Compound 525)



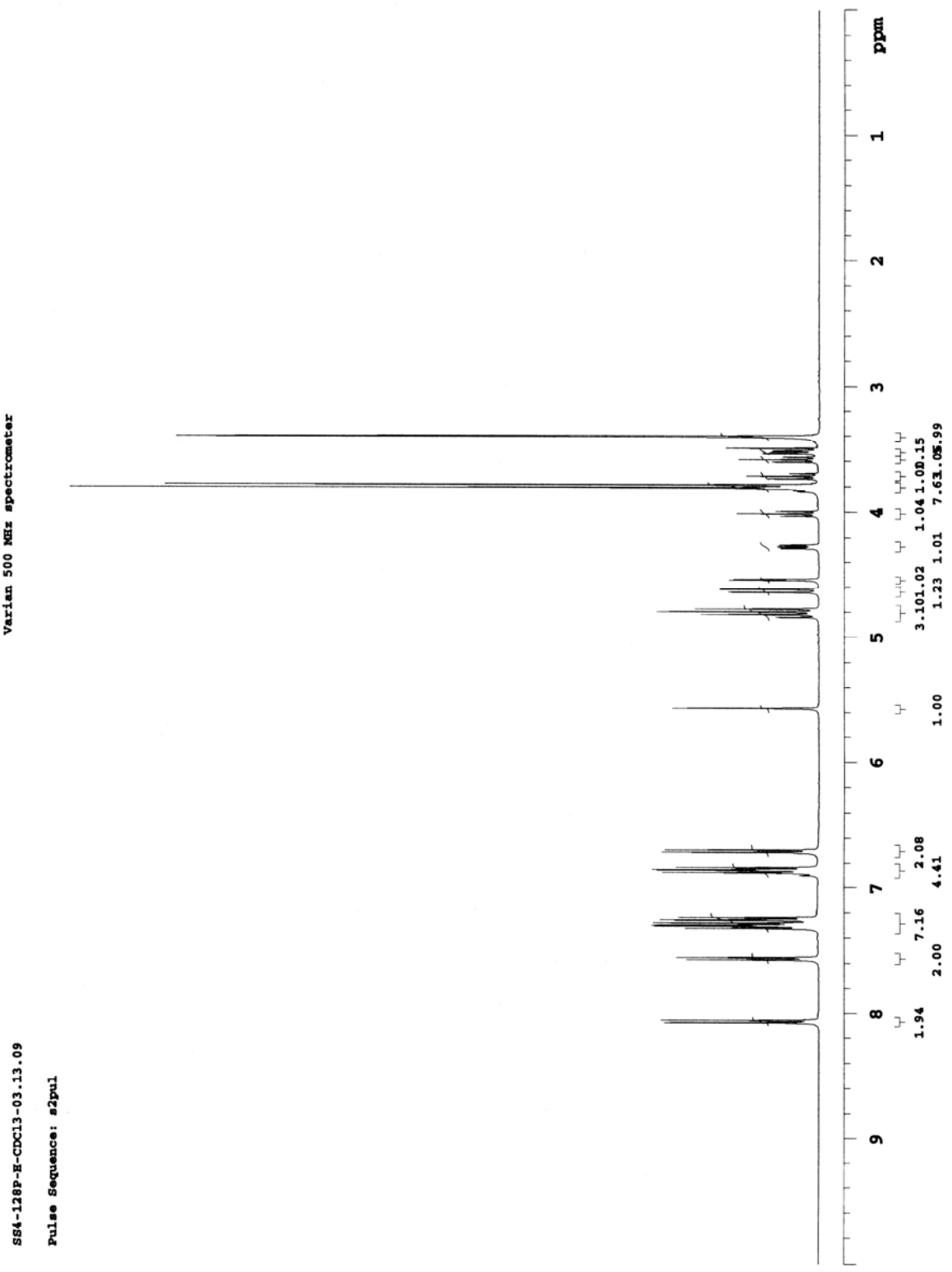
^{1}H NMR (Compound 527)



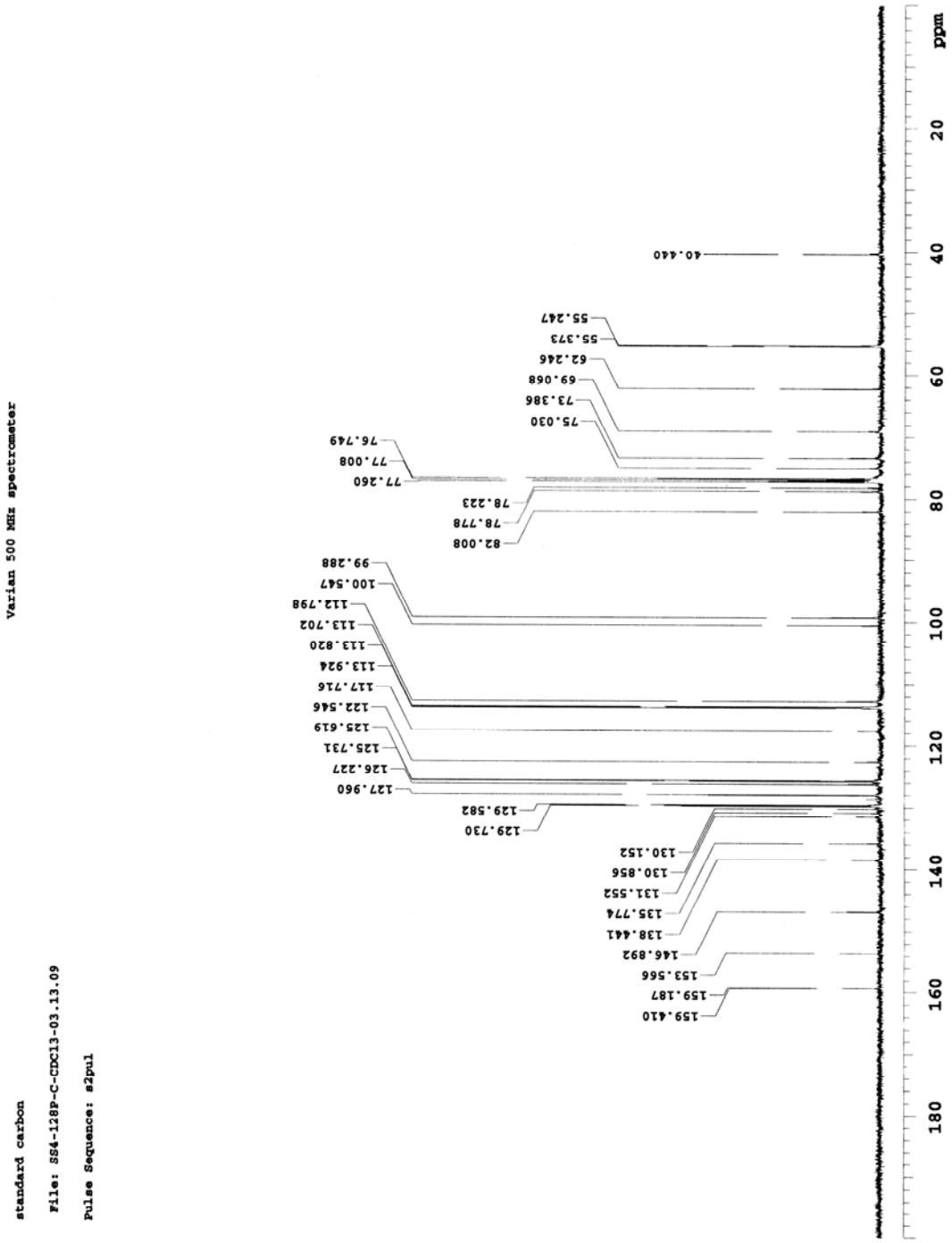
^{13}C NMR (Compound 527)



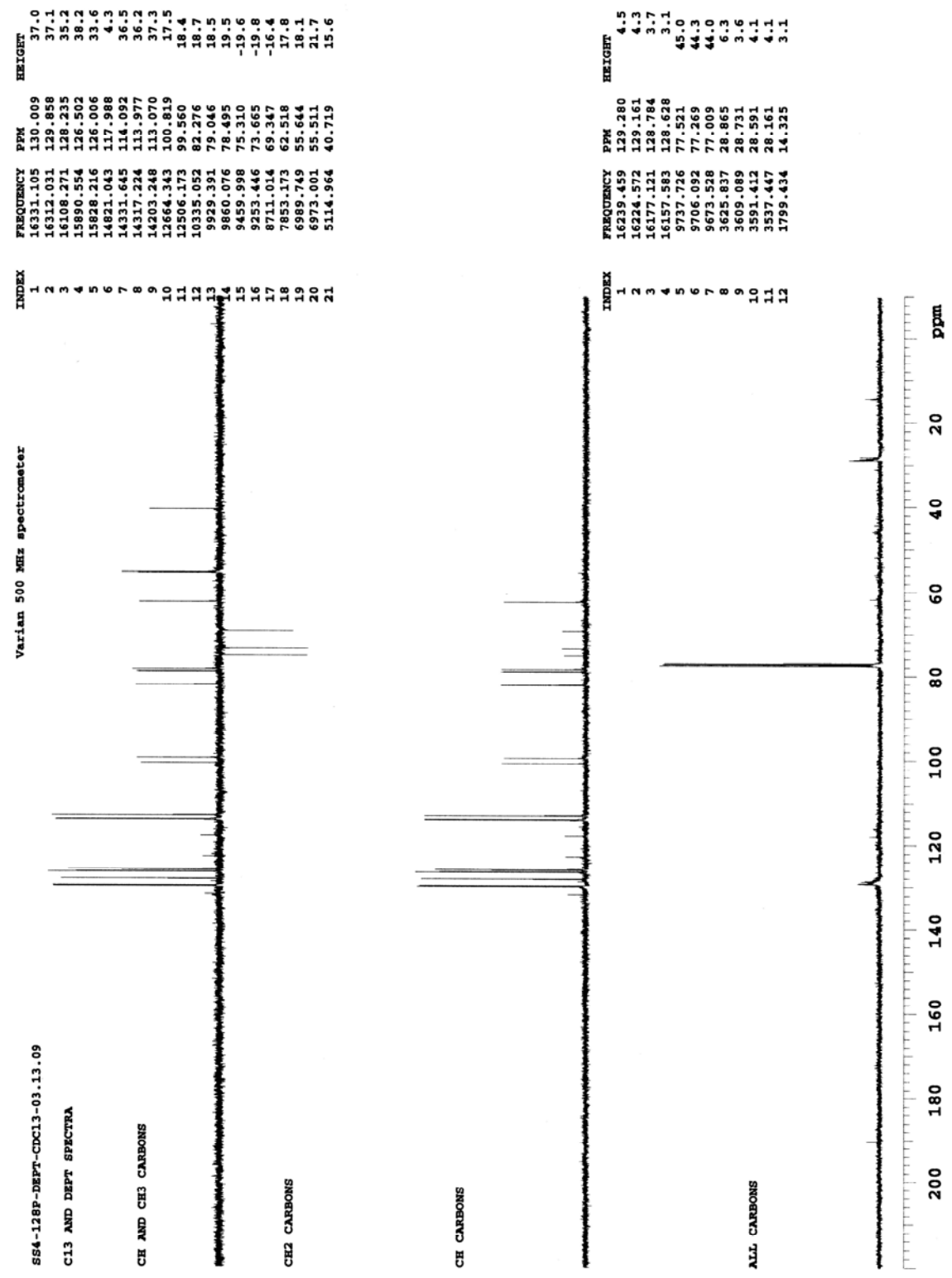
^{1}H NMR (Compound 528)



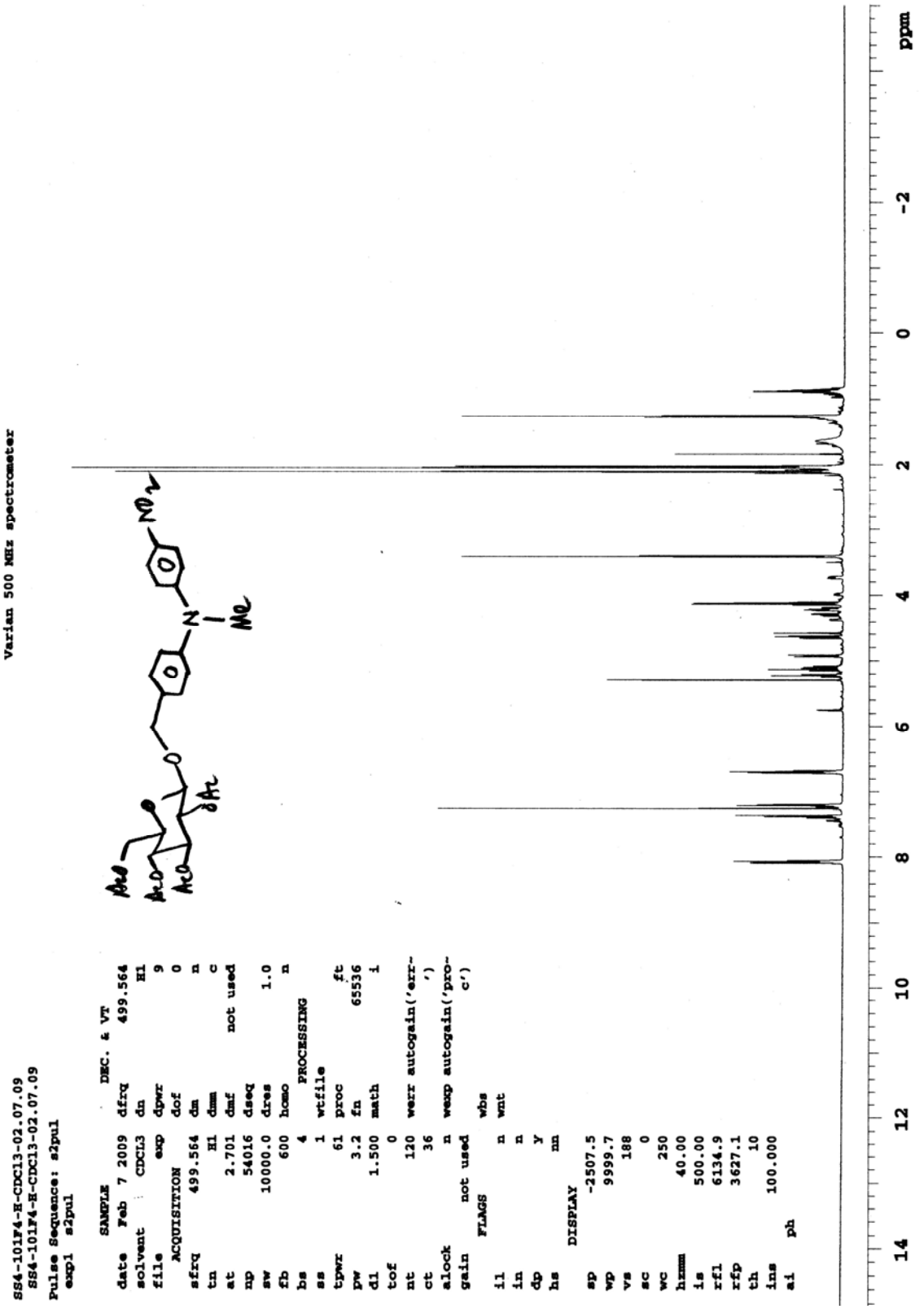
^{13}C NMR (Compound 528)



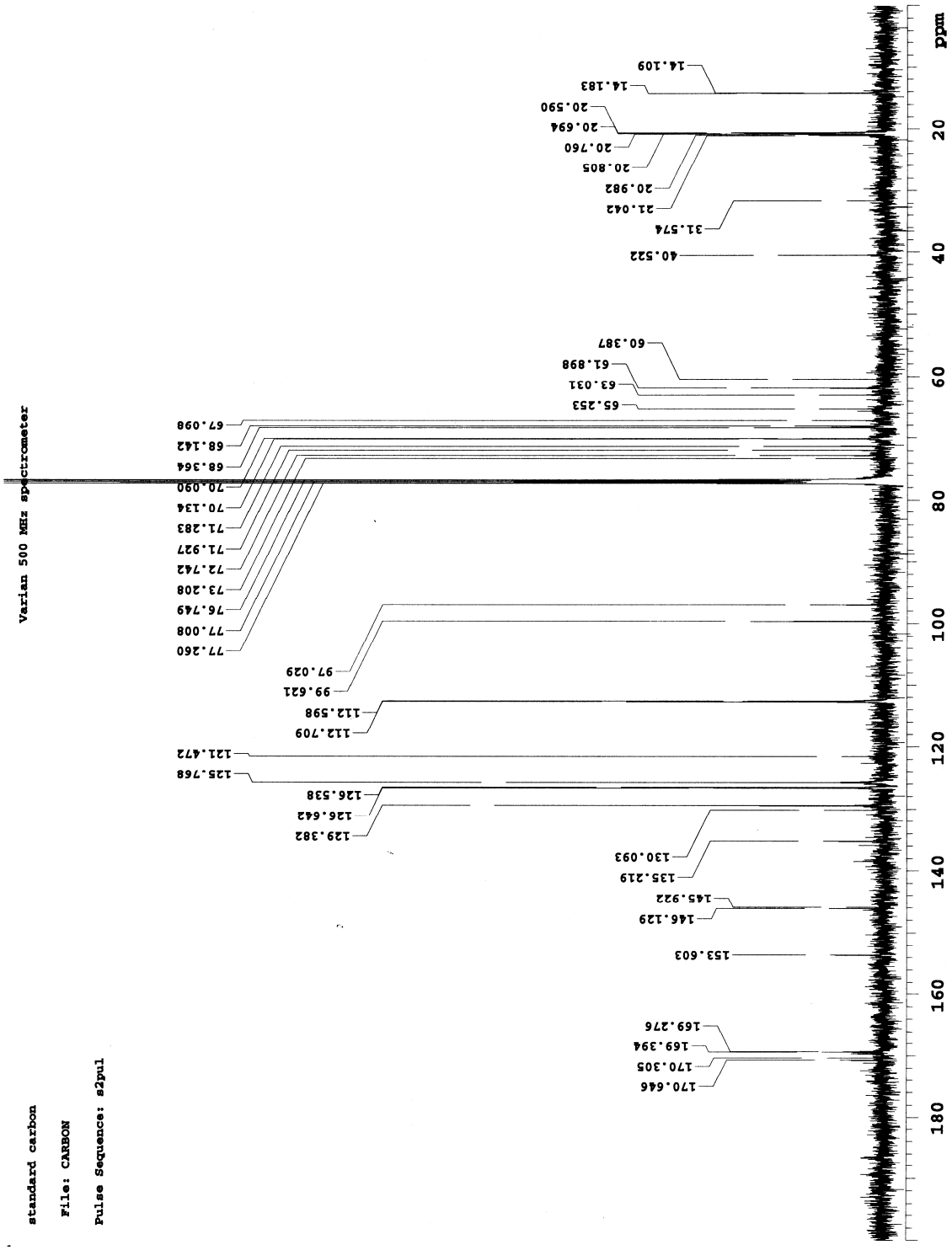
DEPT NMR (Compound 528)



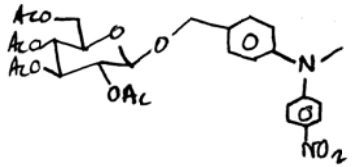
[1]H NMR (Compound 529)



^{13}C NMR (Compound 529)



Elemental Composition Report



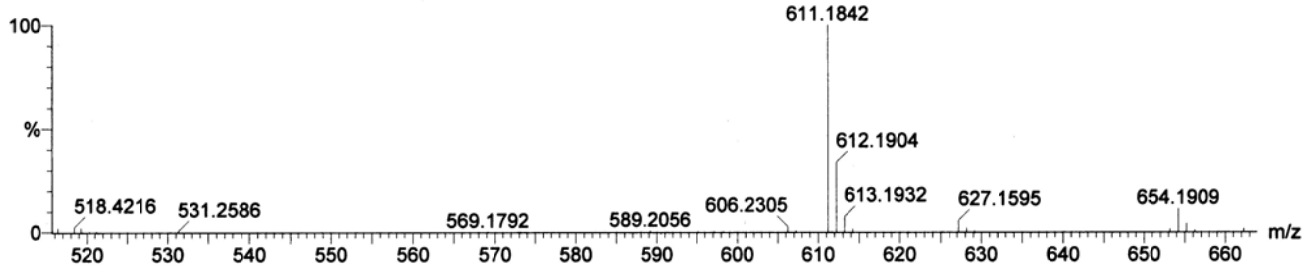
Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 500.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1596 formula(e) evaluated with 10 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-5 O: 0-22 23Na: 0-1

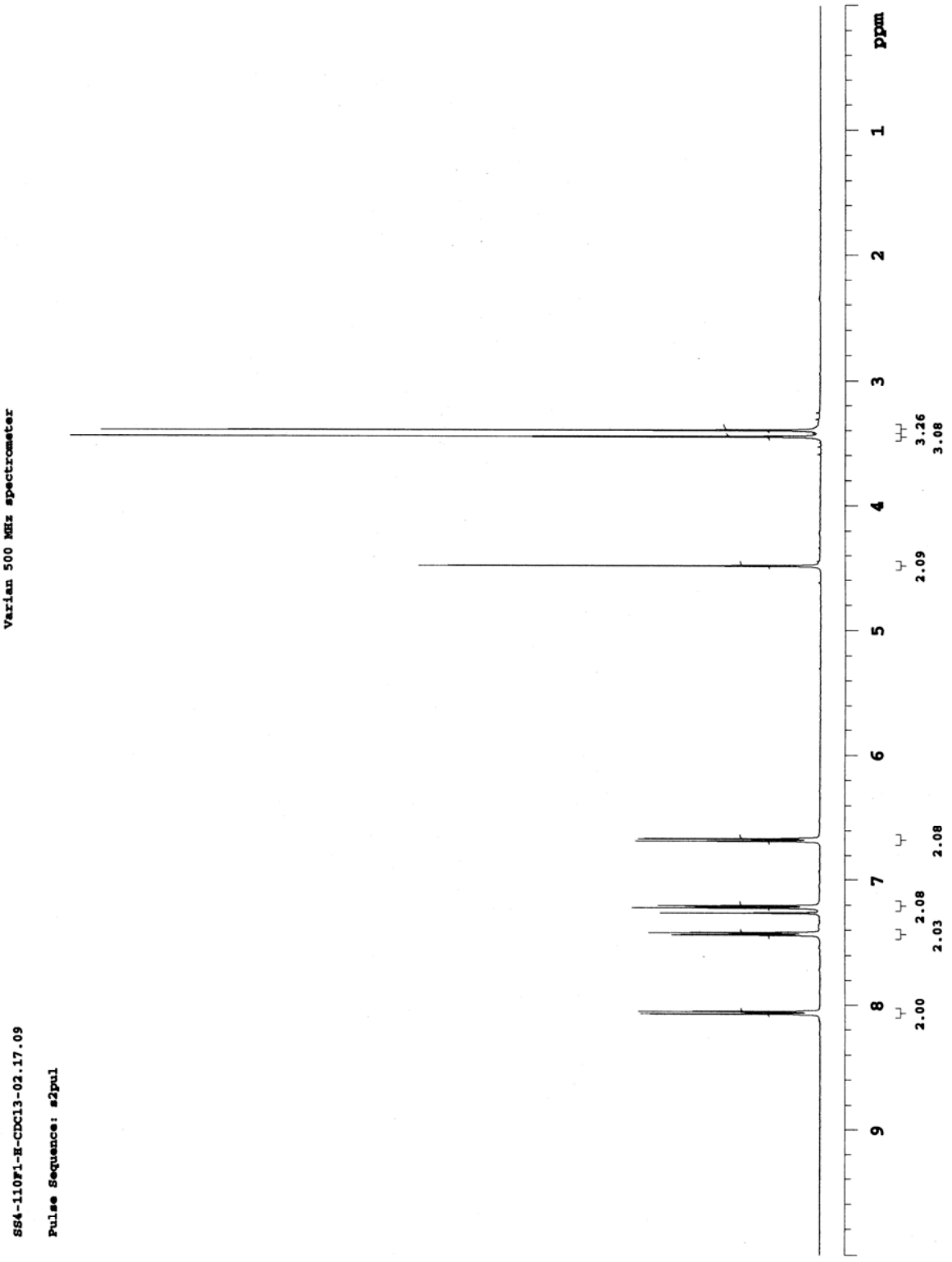
Soumava Santra SS4-101 F4
Lew 2008-07b.pro
2009_0212_0305c 15 (0.318) Cm (12:19-(2:5+27:32)x20.000)

LCT Premier 12-Feb-2009 11:11:09
1: TOF MS ES+
1.05e+005

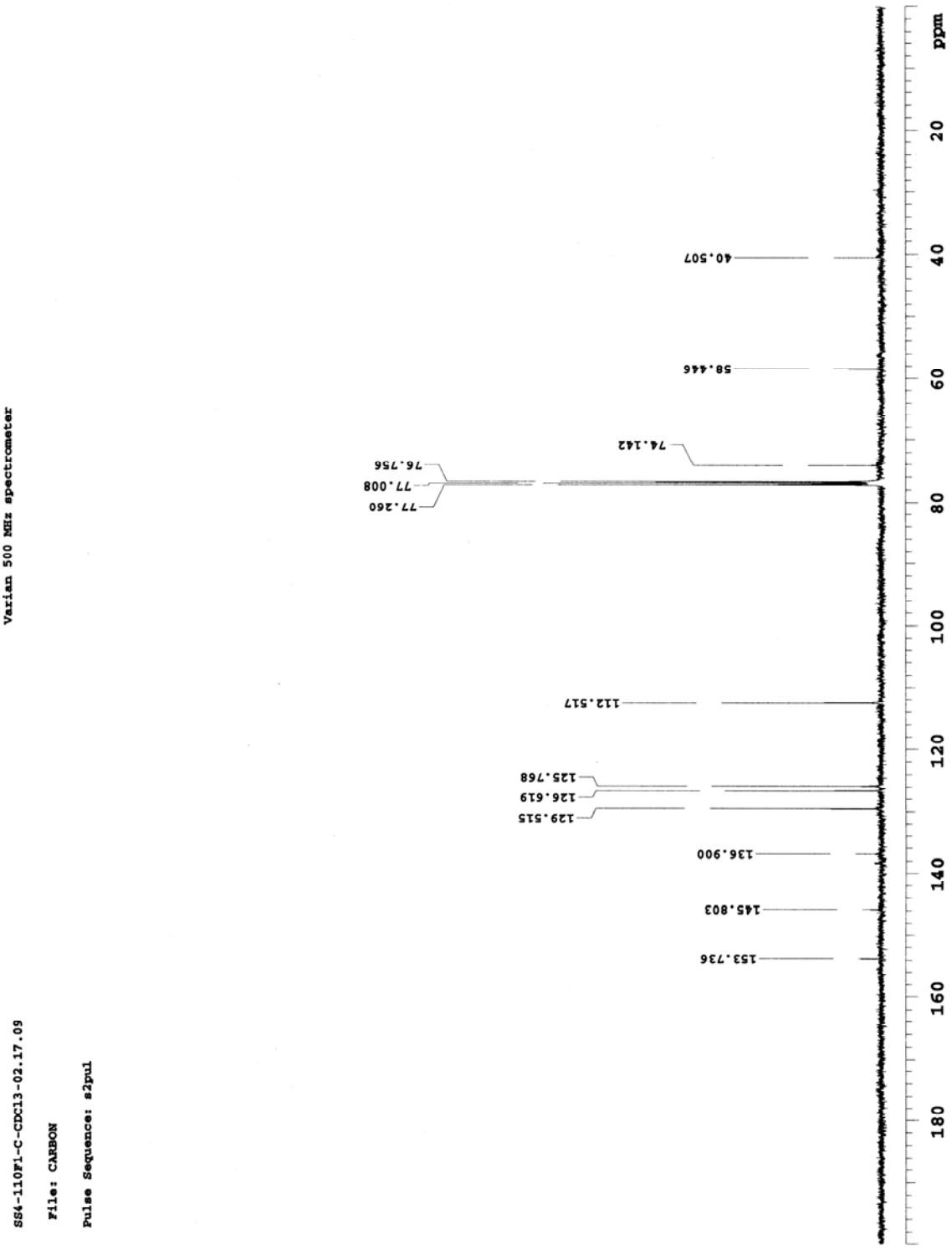


Minimum:				-1.5				
Maximum:		5.0	5.0	500.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula	
611.1842	611.1853	-1.1	-1.8	13.5	37.4	0.0	C28 H32 N2 O12 23Na	← RMM
	611.1837	0.5	0.8	12.5	42.6	5.1	C25 H31 N4 O14	
	611.1823	1.9	3.1	7.5	45.0	7.6	C24 H35 O18	
	611.1813	2.9	4.7	9.5	45.7	8.2	C23 H32 N4 O14 23Na	
	611.1834	0.8	1.3	26.5	47.0	9.6	C40 H28 O5 23Na	
	611.1818	2.4	3.9	25.5	47.0	9.6	C37 H27 N2 O7	
	611.1858	-1.6	-2.6	29.5	47.2	9.7	C42 H27 O5	
	611.1848	-0.6	-1.0	31.5	47.3	9.9	C41 H24 N4 O 23Na	
	611.1872	-3.0	-4.9	34.5	48.0	10.6	C43 H23 N4 O	
	611.1871	-2.9	-4.7	0.5	48.4	11.0	C16 H36 N4 O19 23Na	

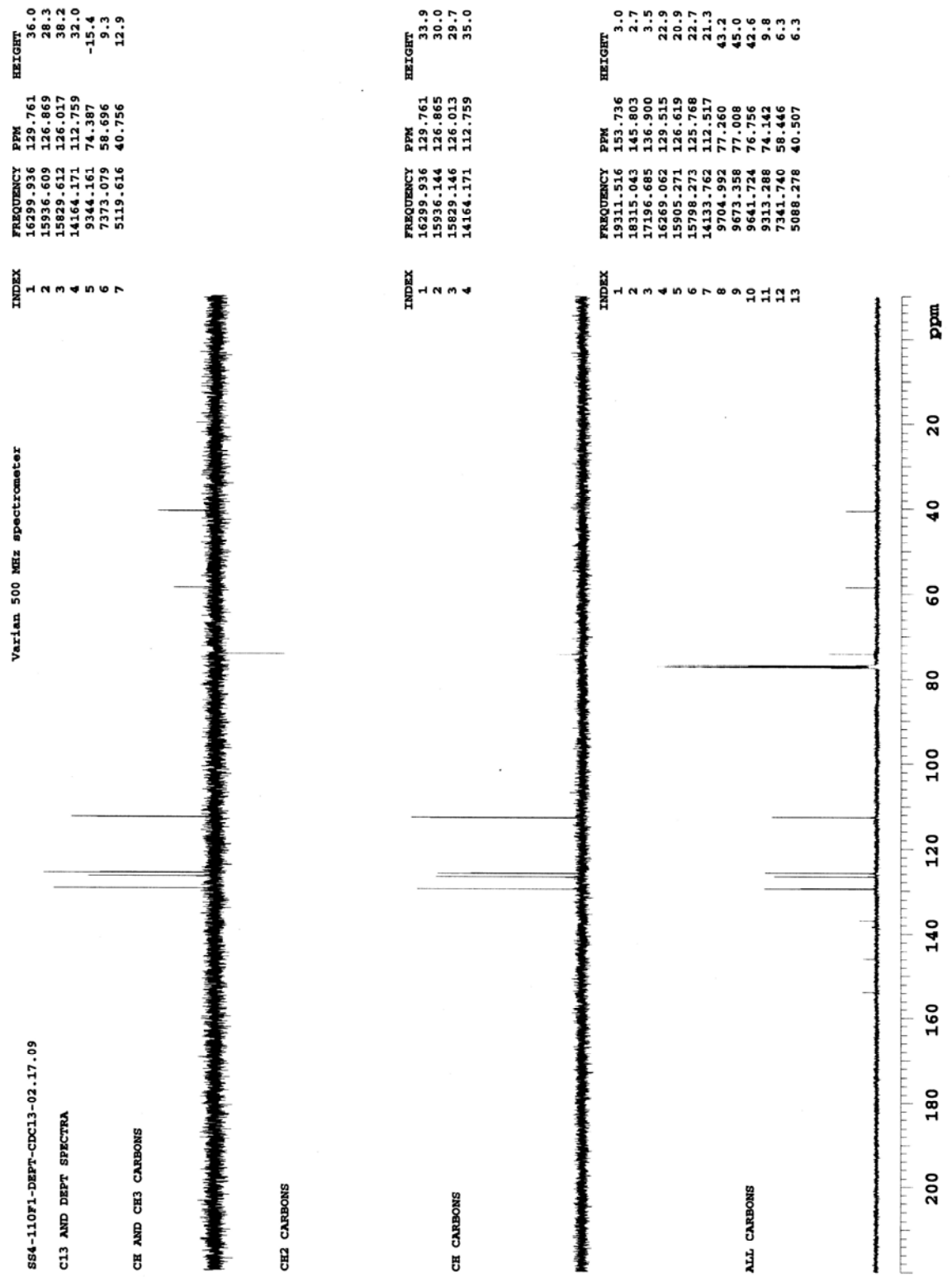
^{1}H NMR (Compound 531)



^{13}C NMR (Compound 531)



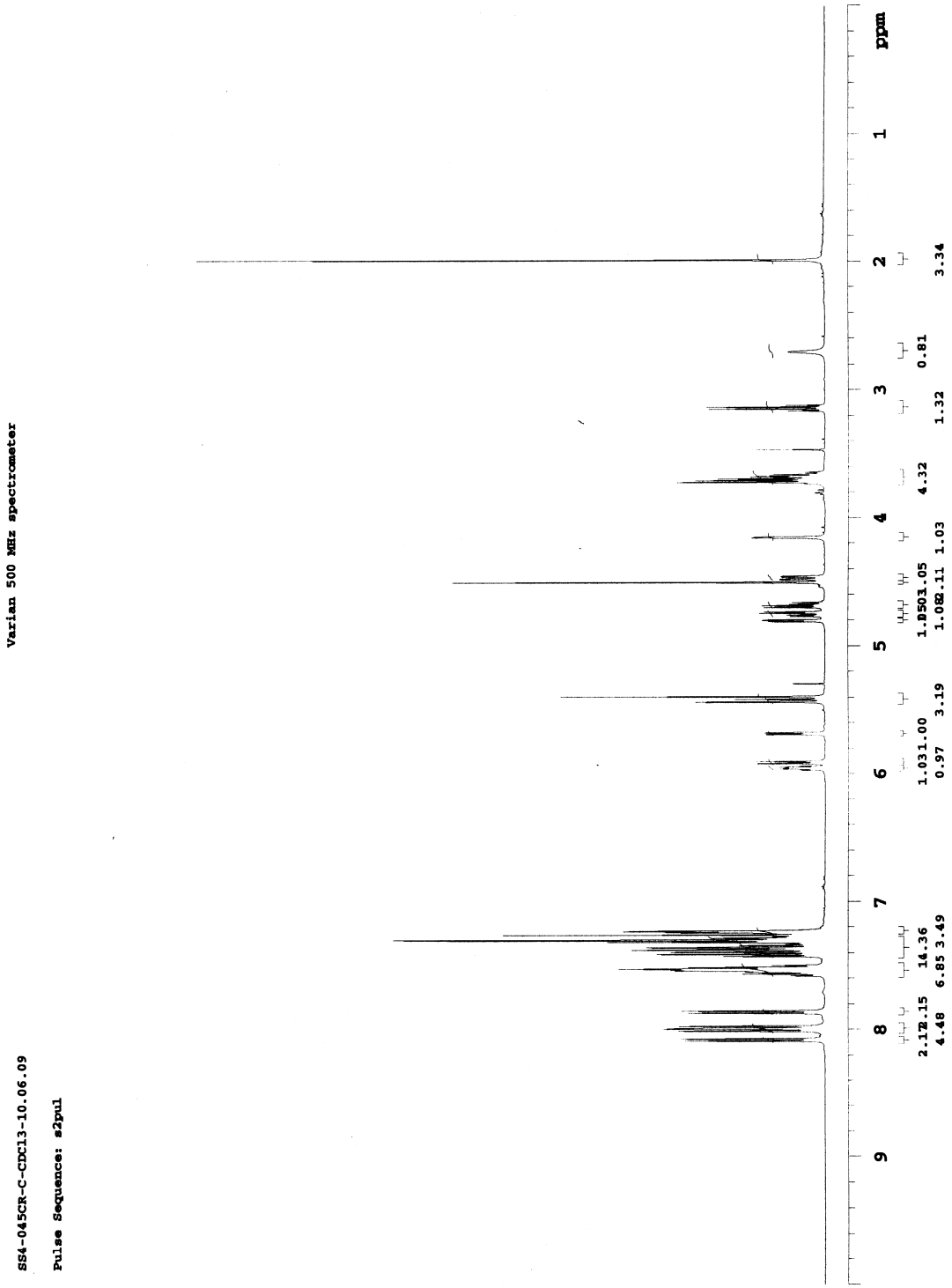
DEPT NMR (Compound 531)



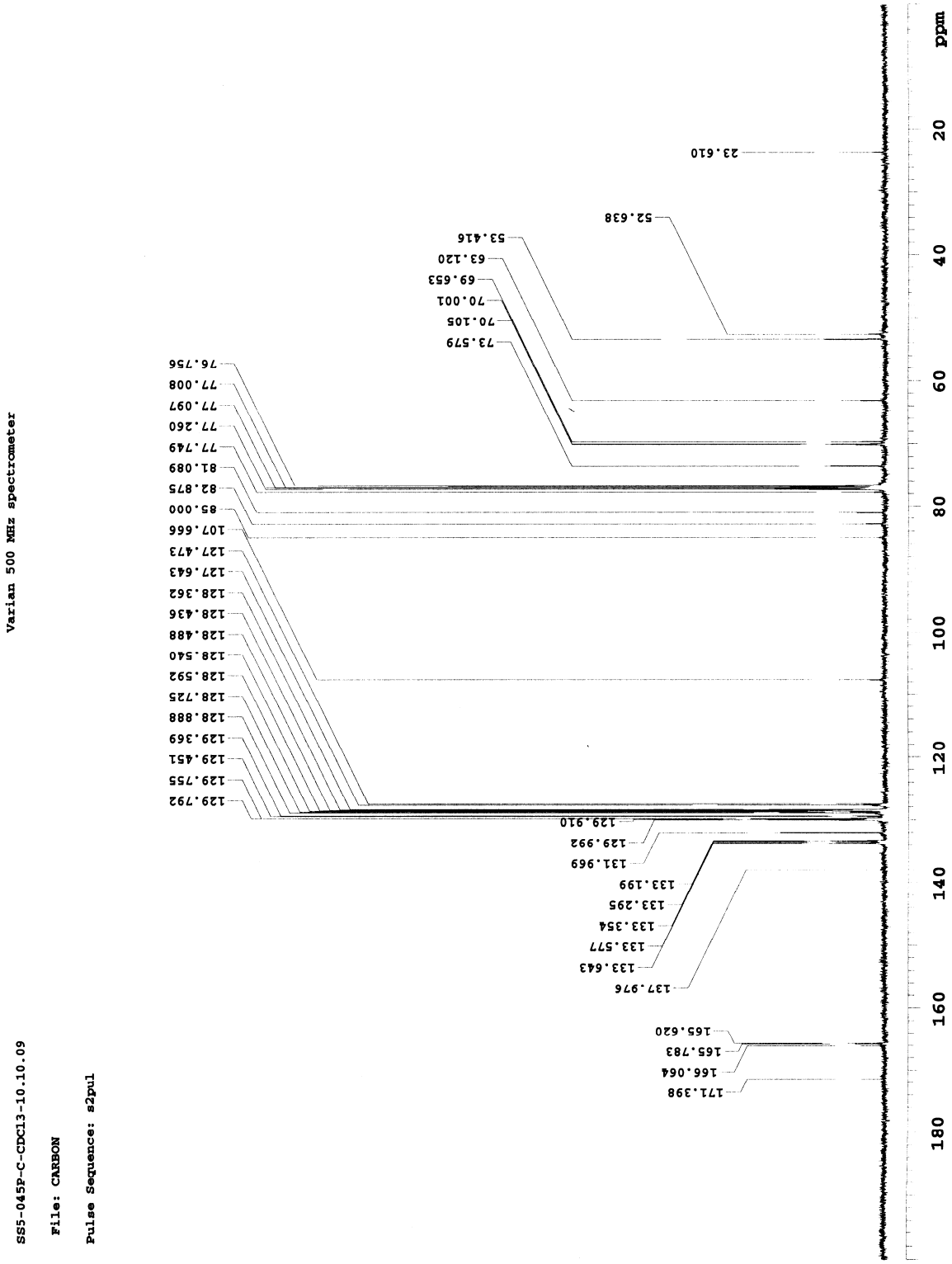
APPENDIX VI

NMR Spectra of Chapter 7

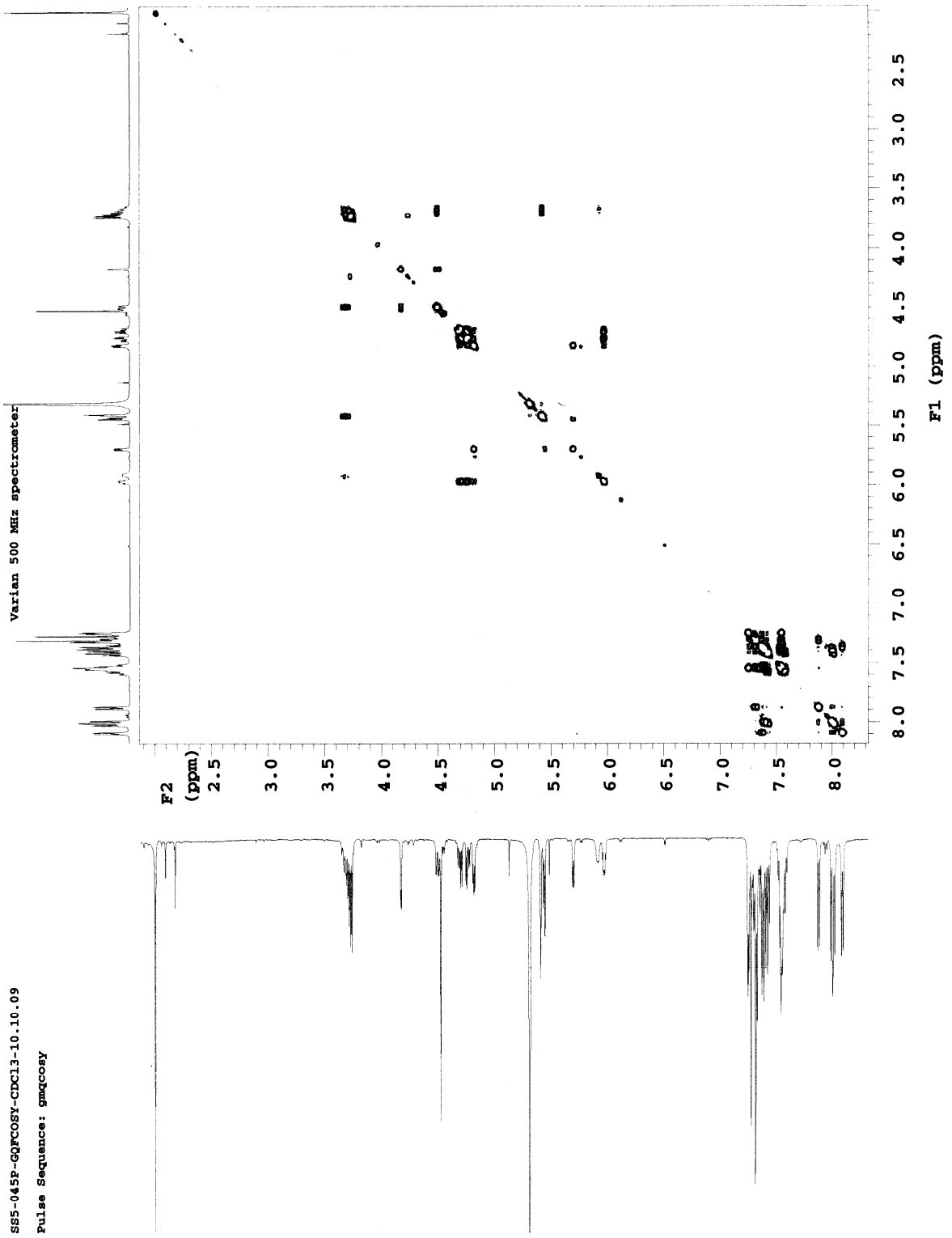
^{1}H NMR (Compound 557)



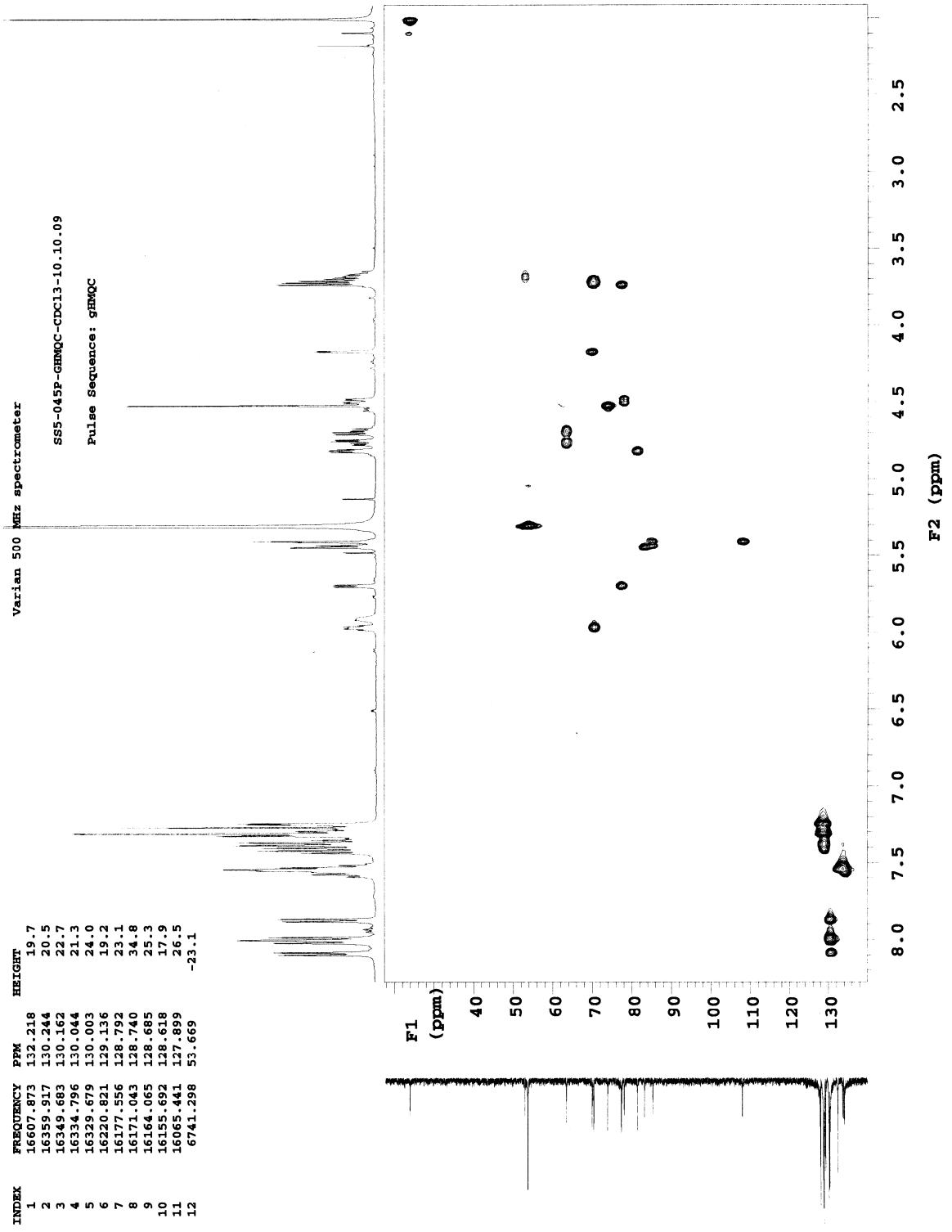
^{13}C NMR (Compound 557)



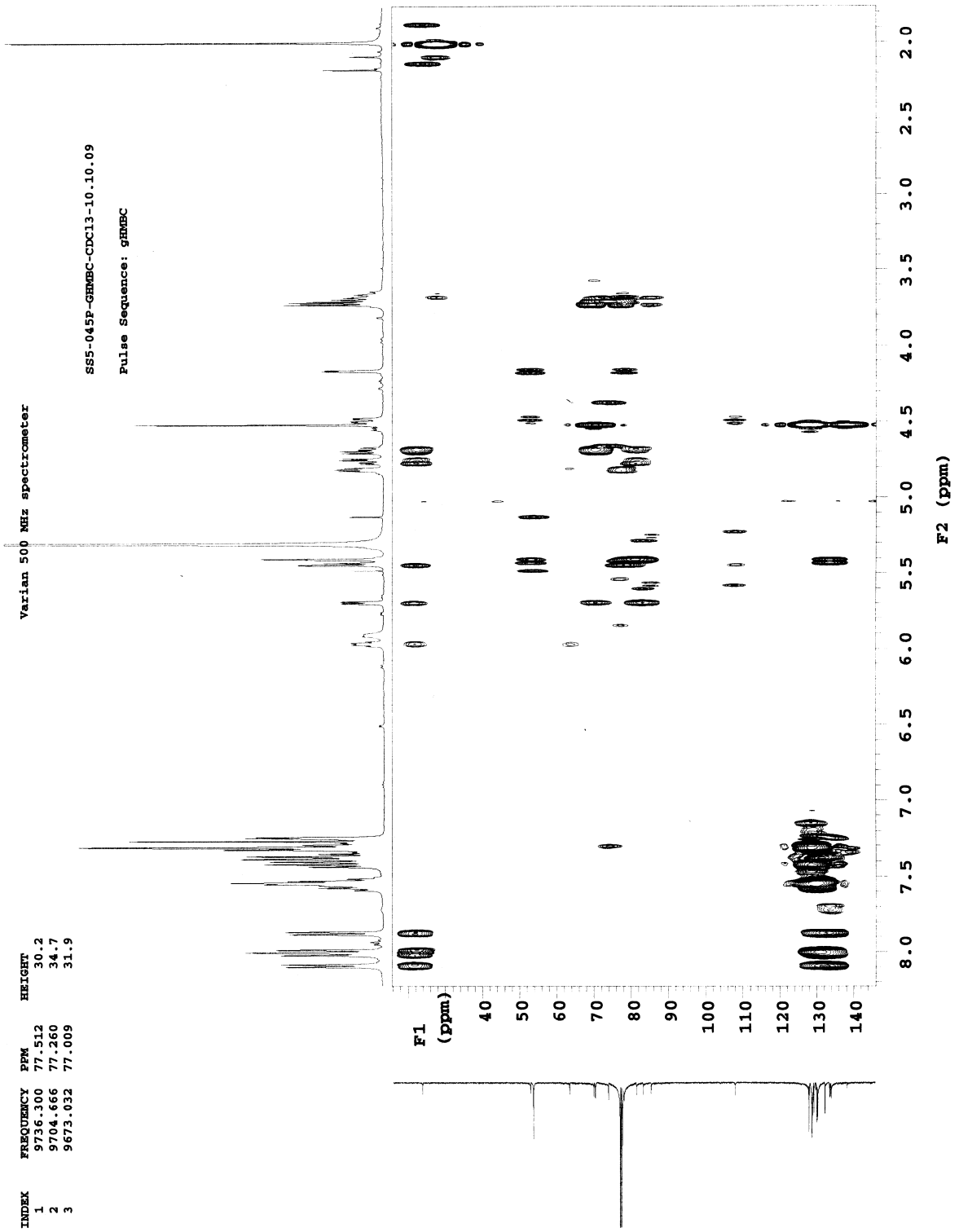
^{1}H-^{1}H GDQFCOSY NMR (Compound 557)



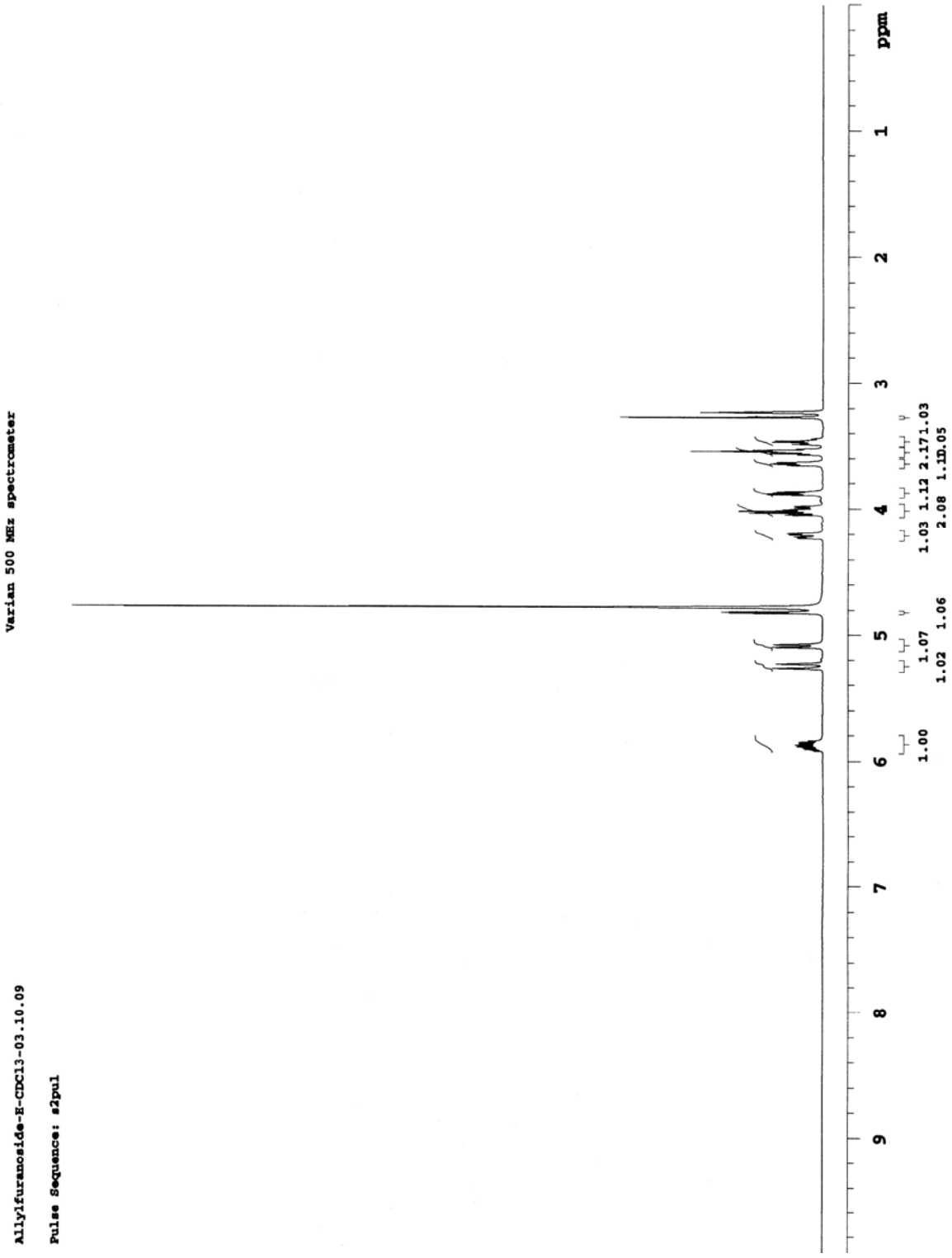
GHMQC NMR (Compound 557)



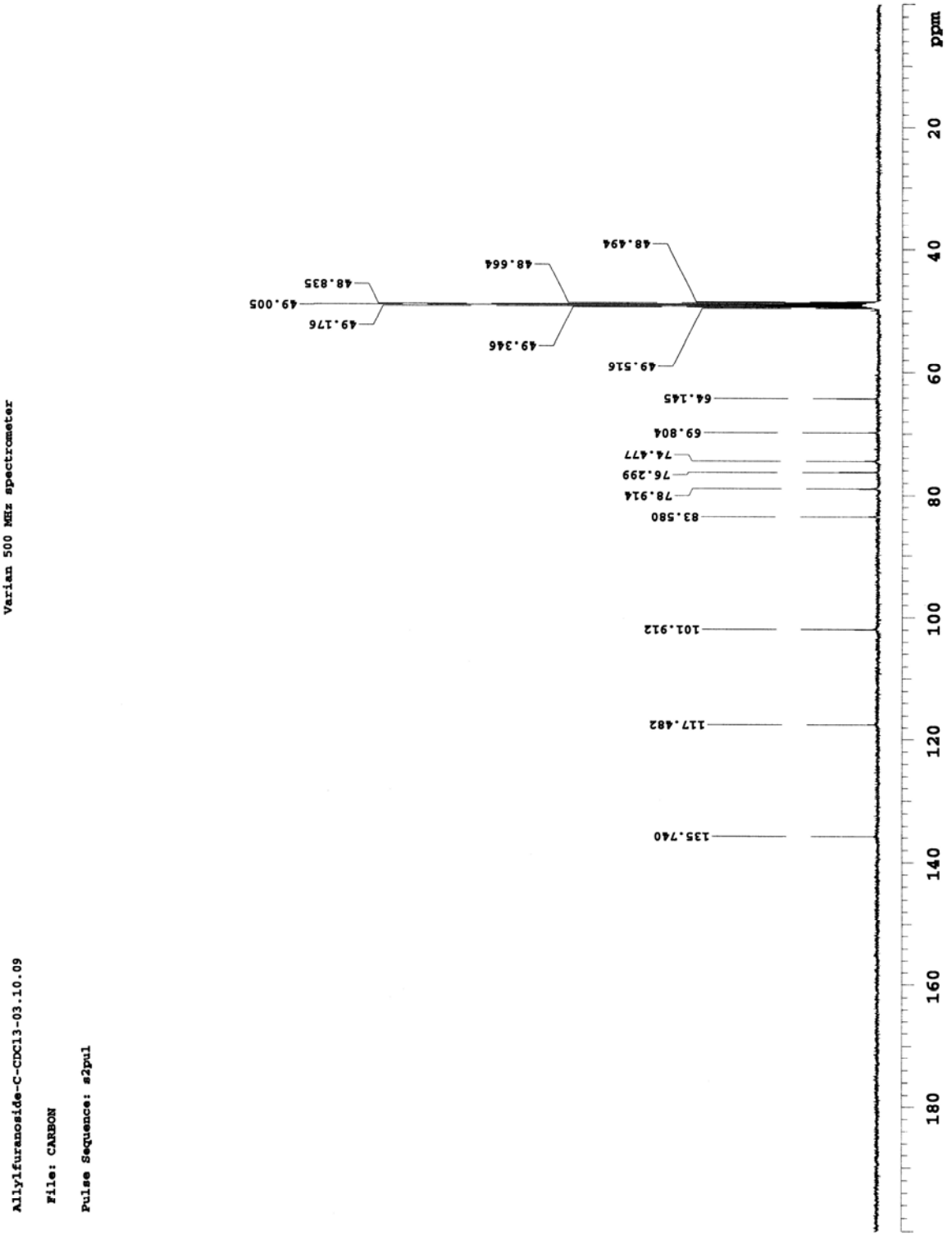
GHMBC NMR (Compound 557)



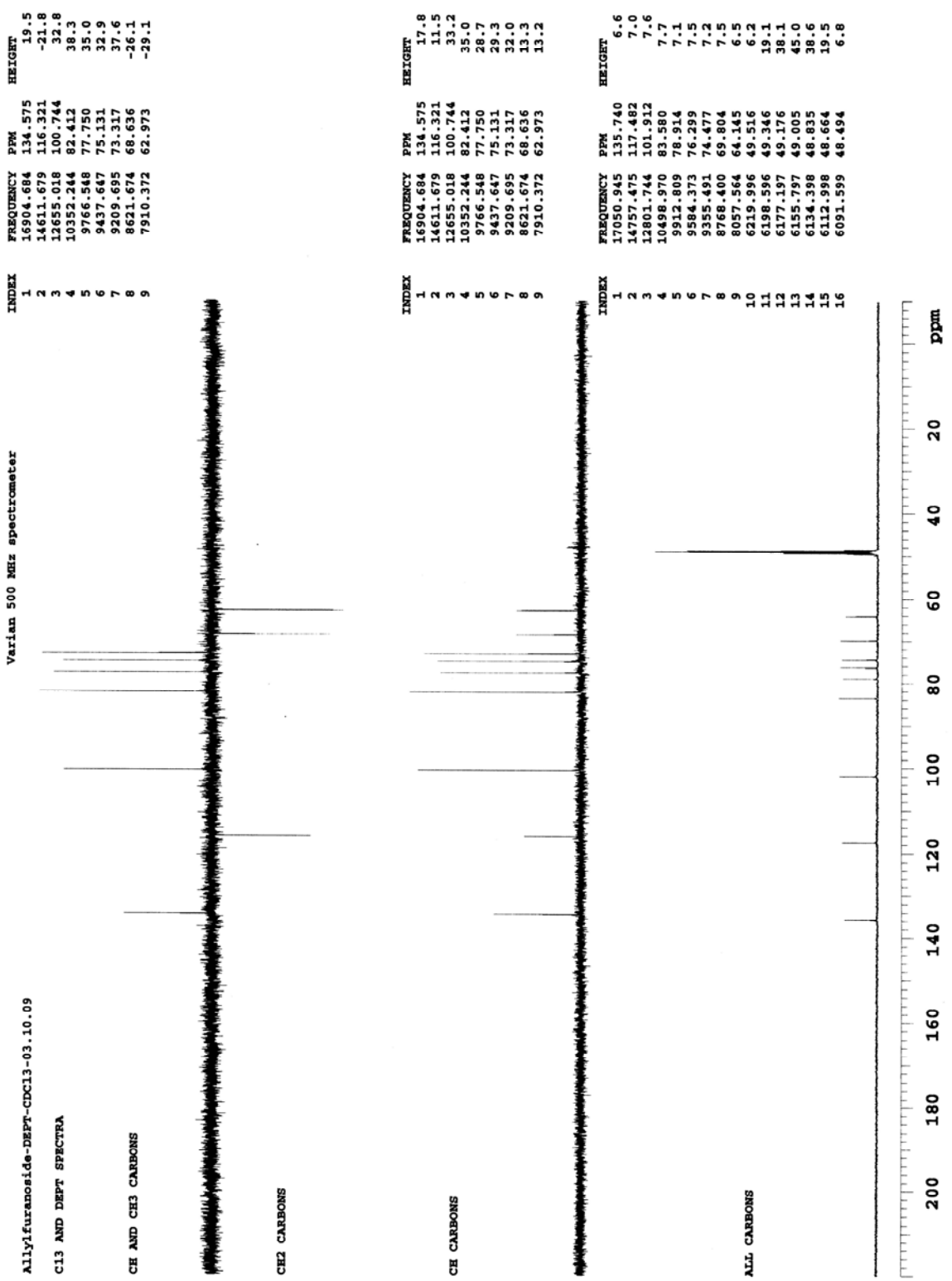
^{1}H NMR (Compound 568)



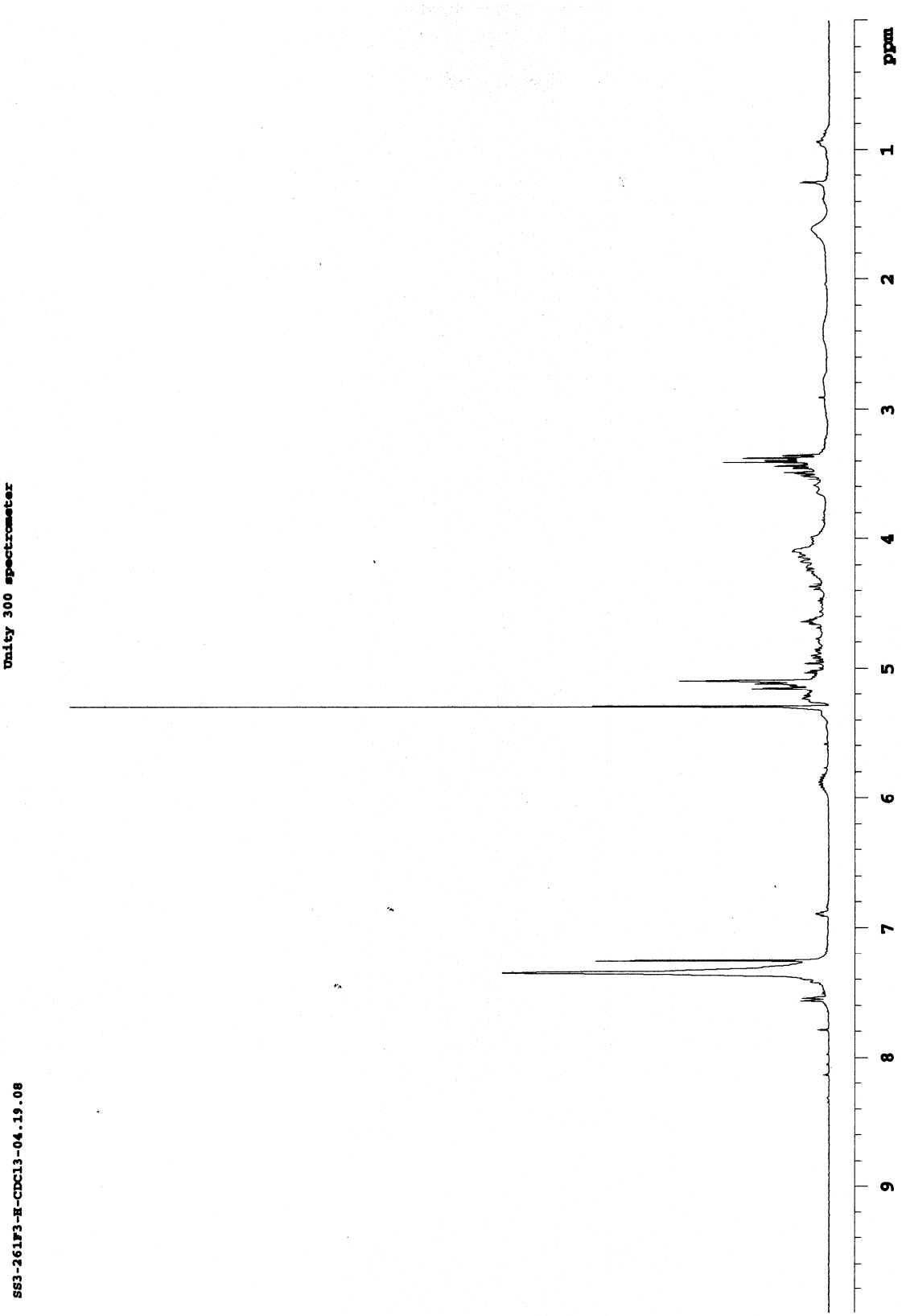
^{13}C NMR (Compound 568)



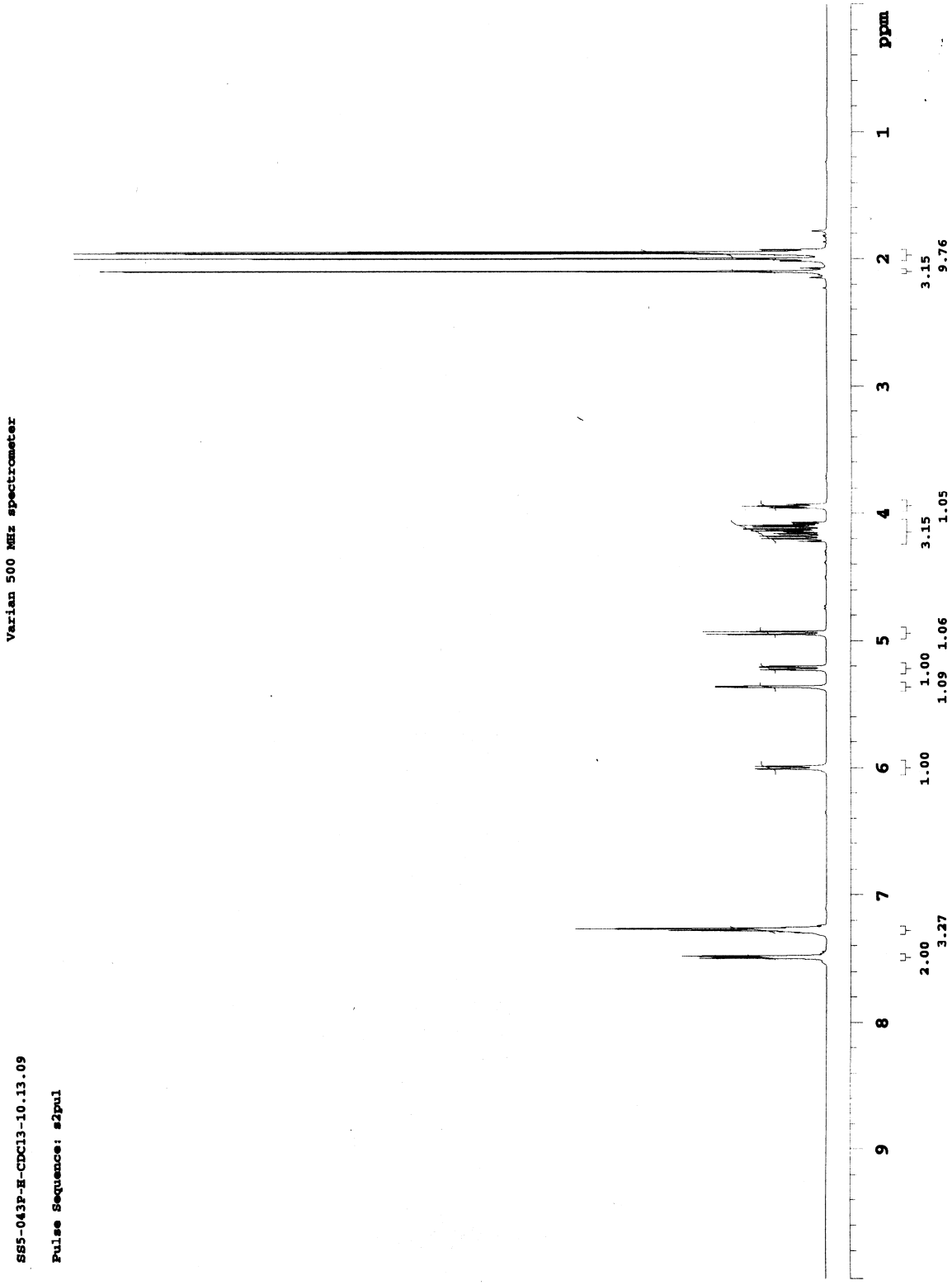
DEPT NMR (Compound 568)



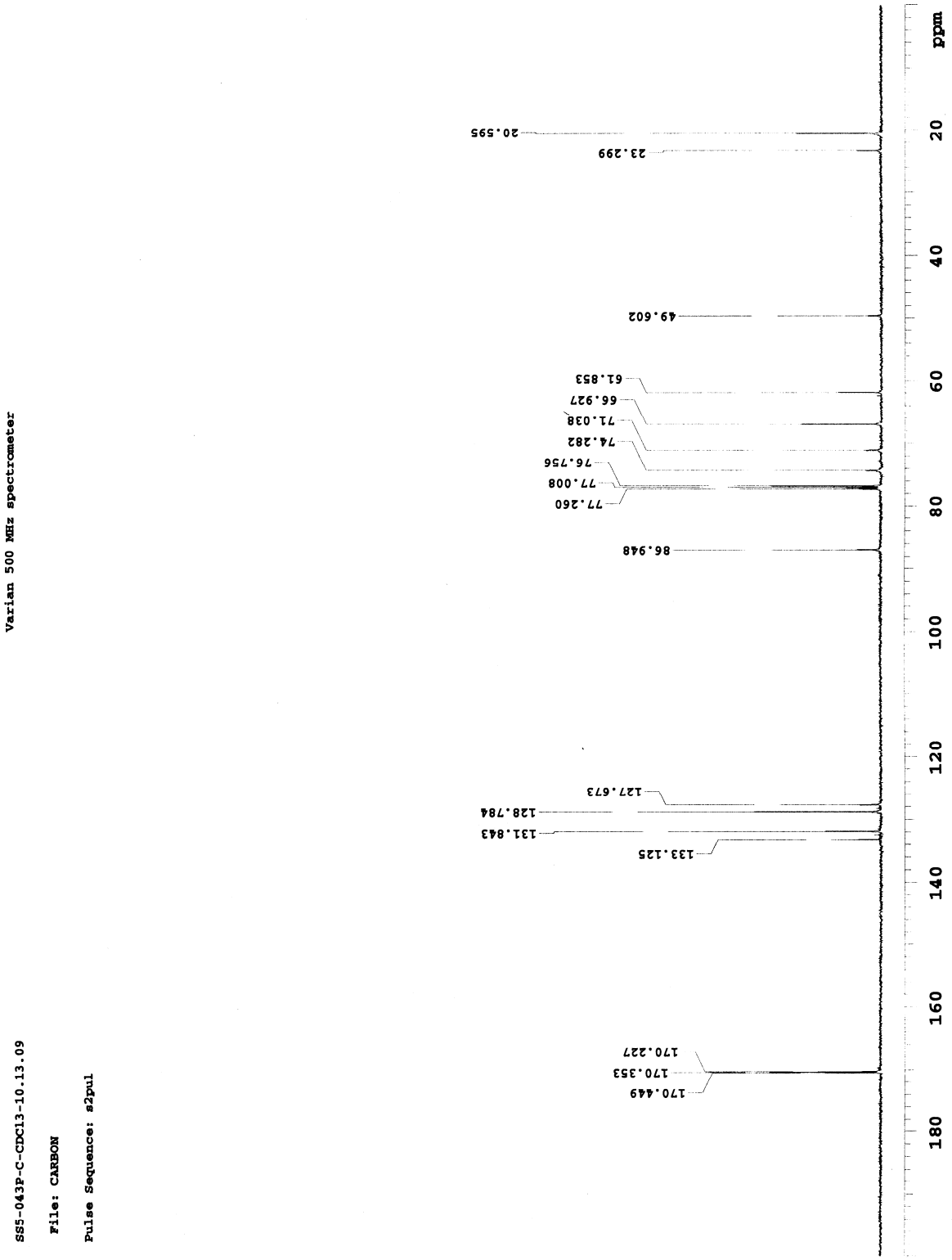
^{1}H NMR (Compound 572)



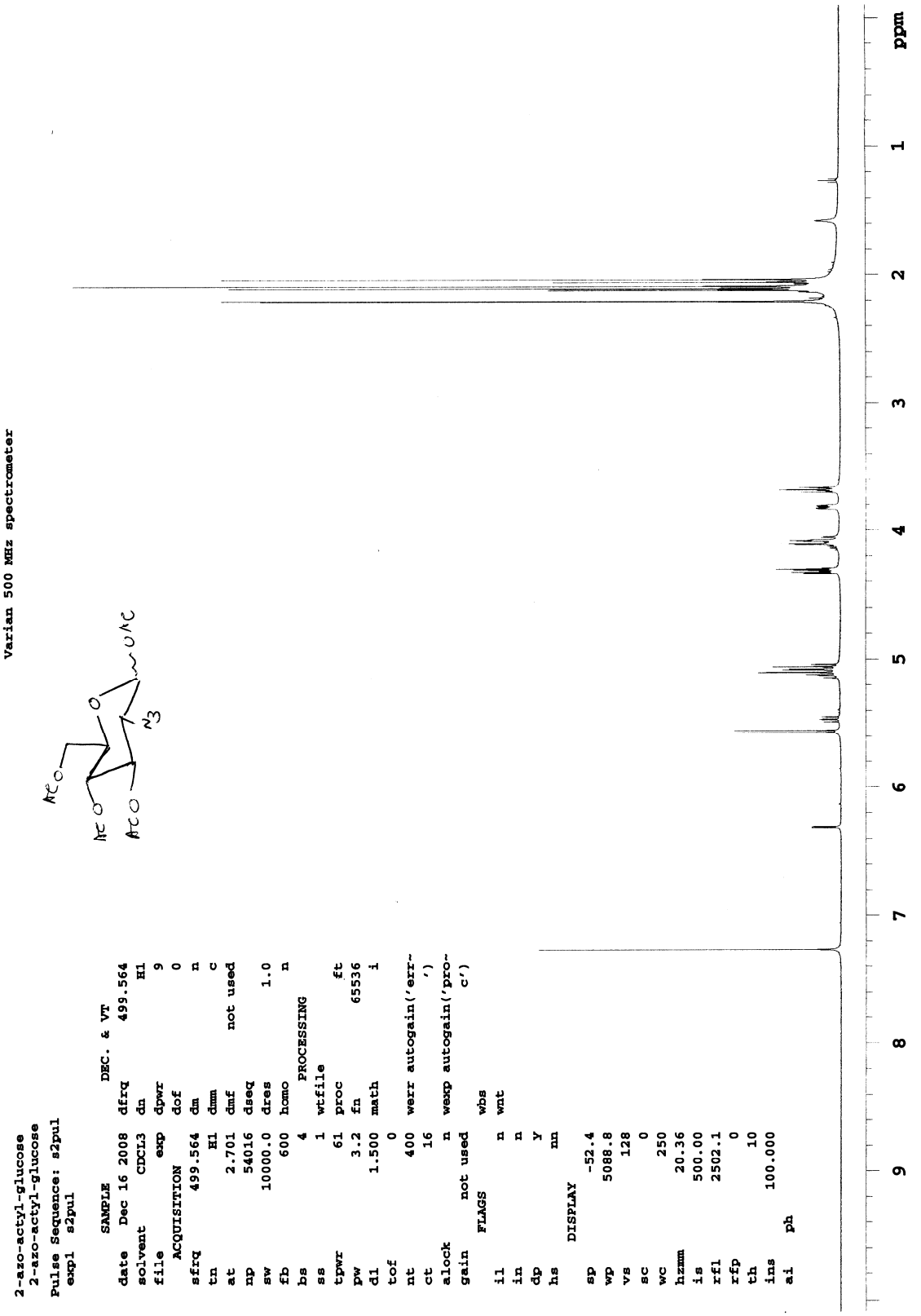
^{1}H NMR (Compound 575)



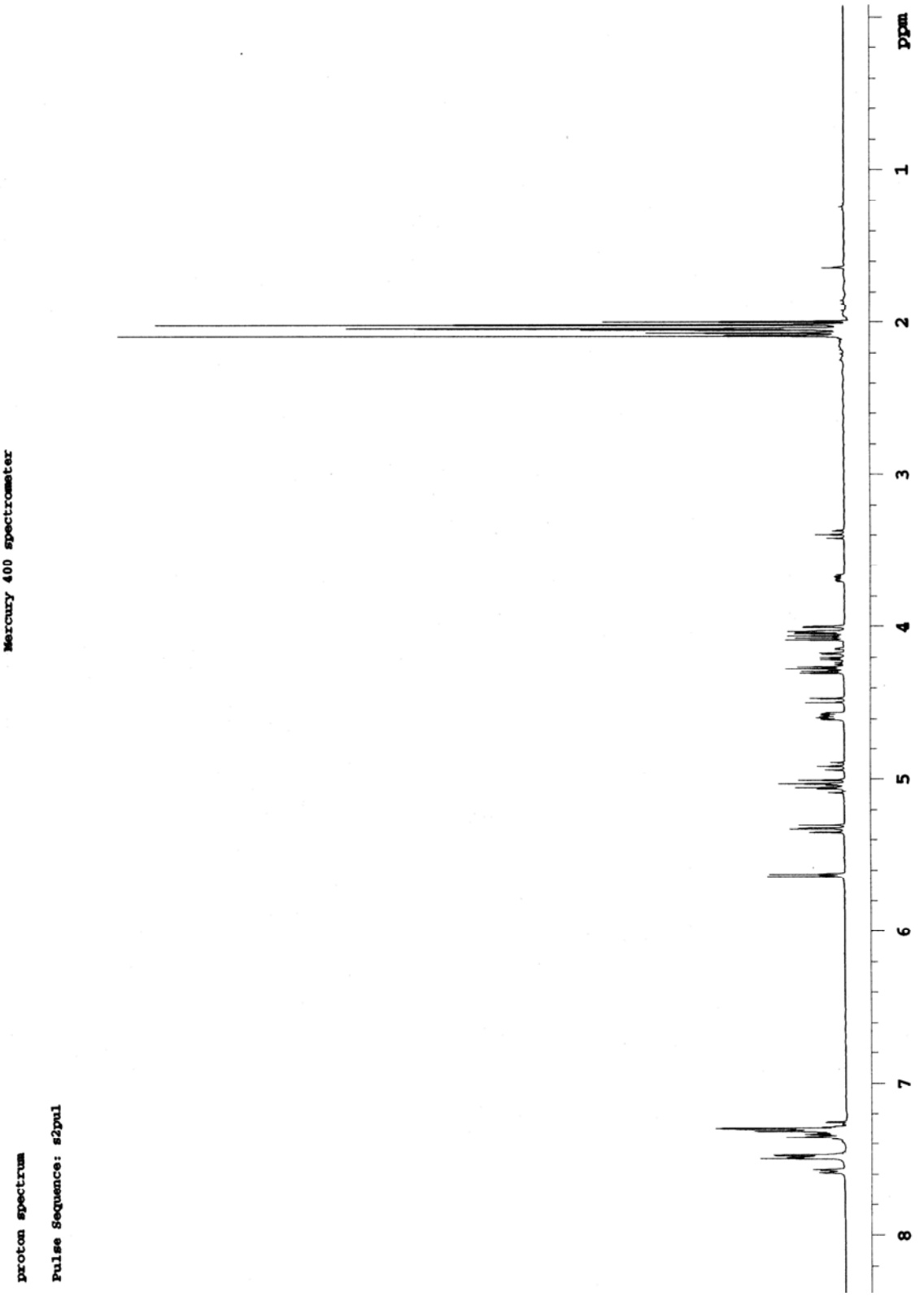
^{13}C NMR (Compound 575)



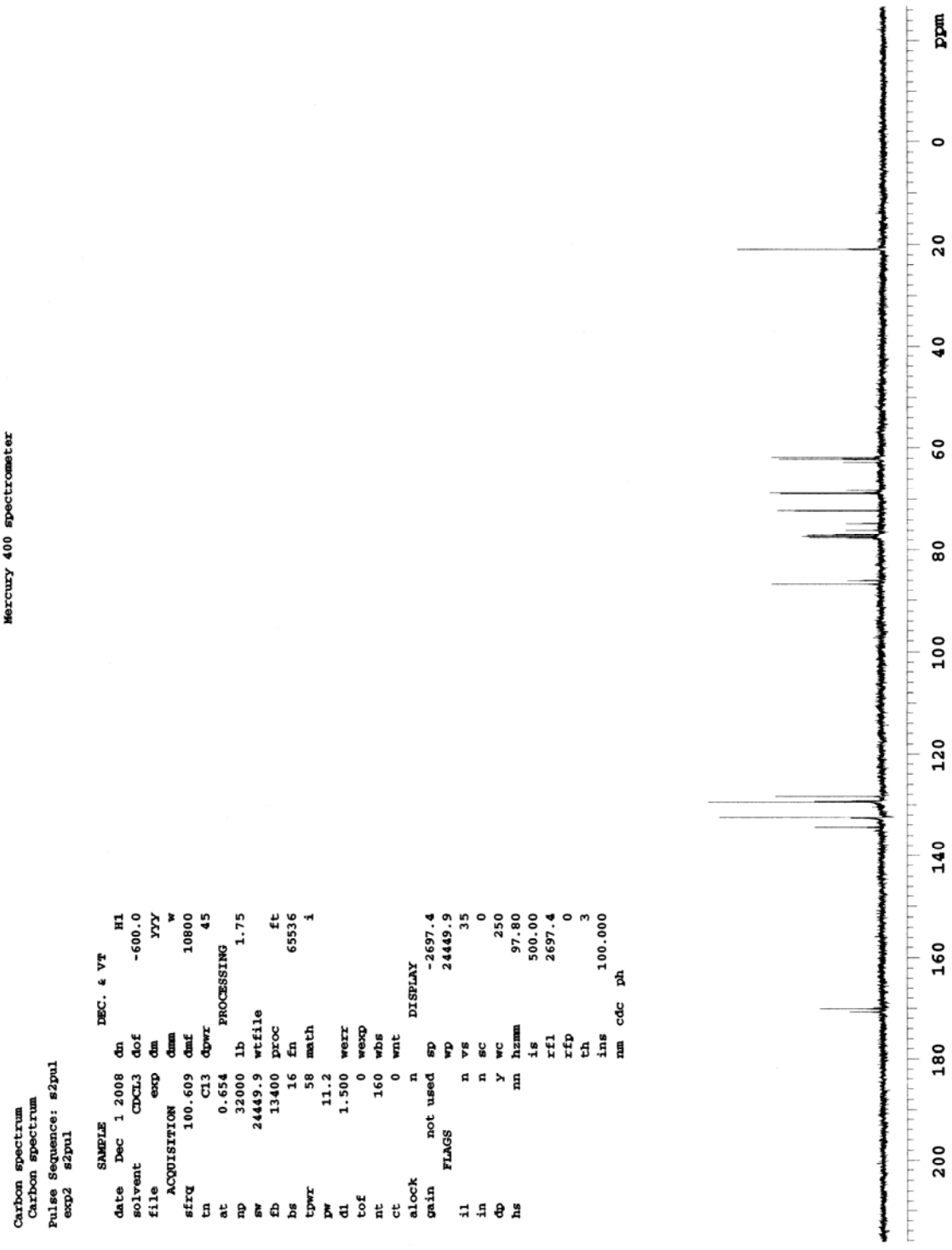
^{1}H NMR (Compound 576)



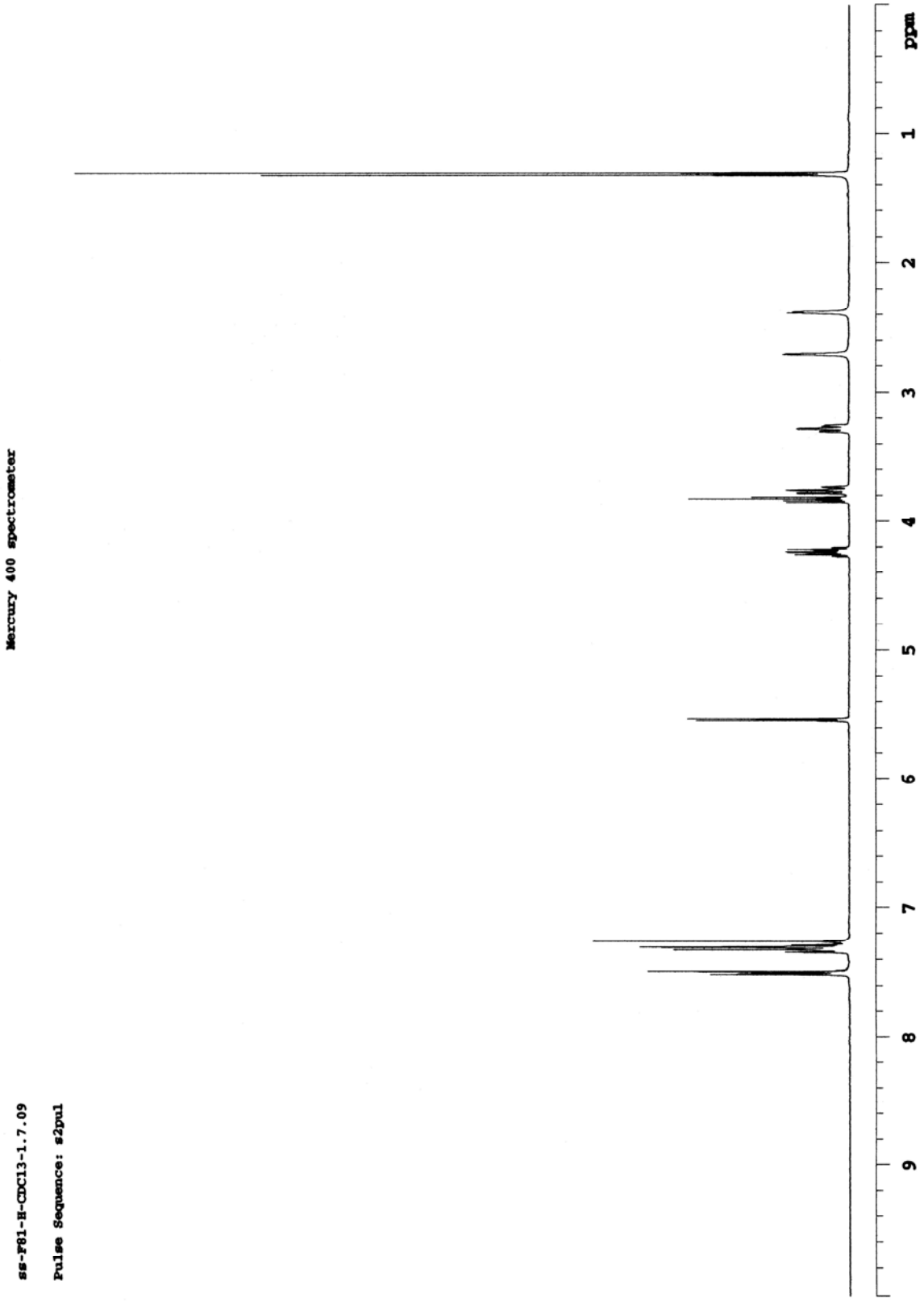
[1]H NMR (Compound 579)



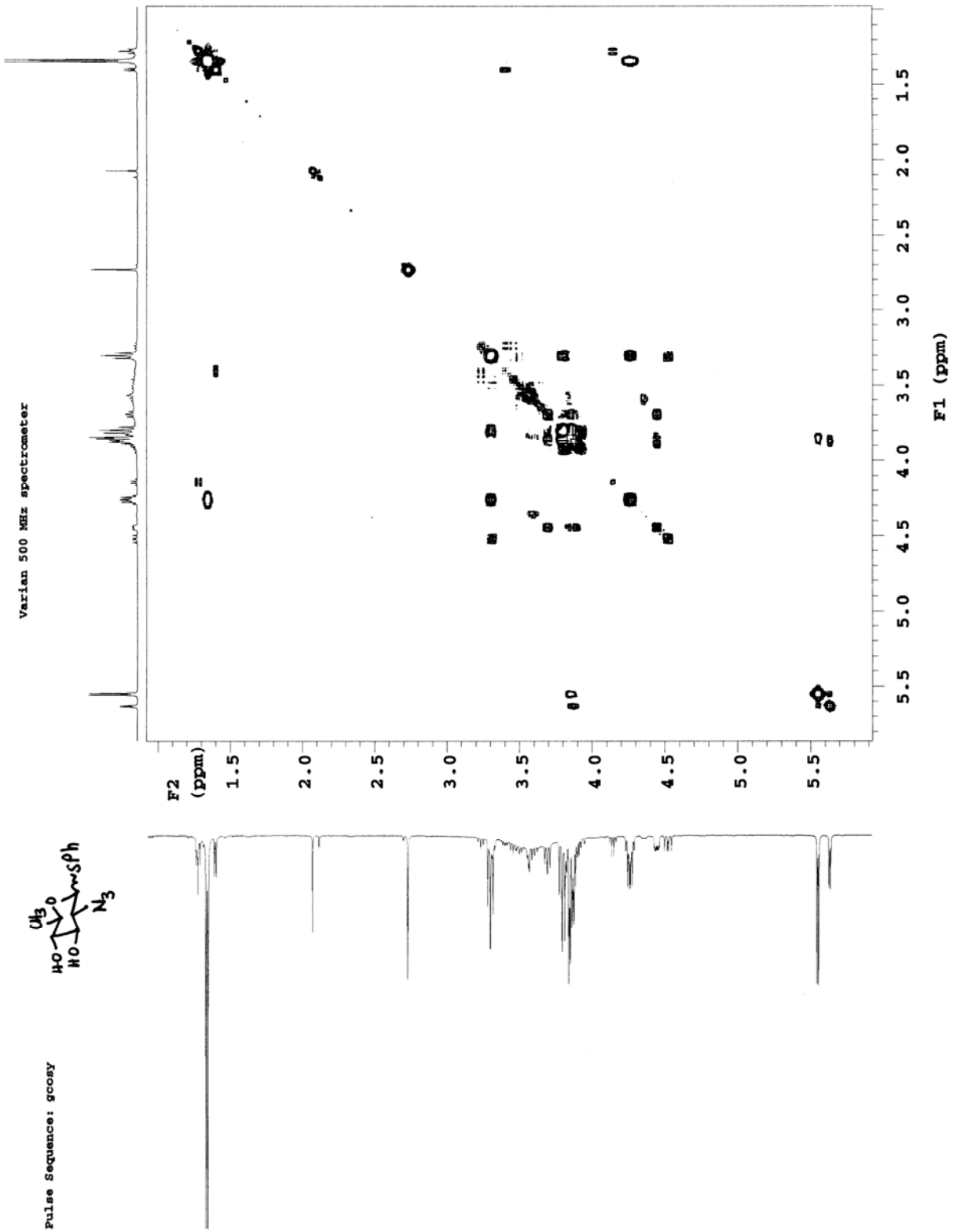
^{13}C NMR (Compound 579)



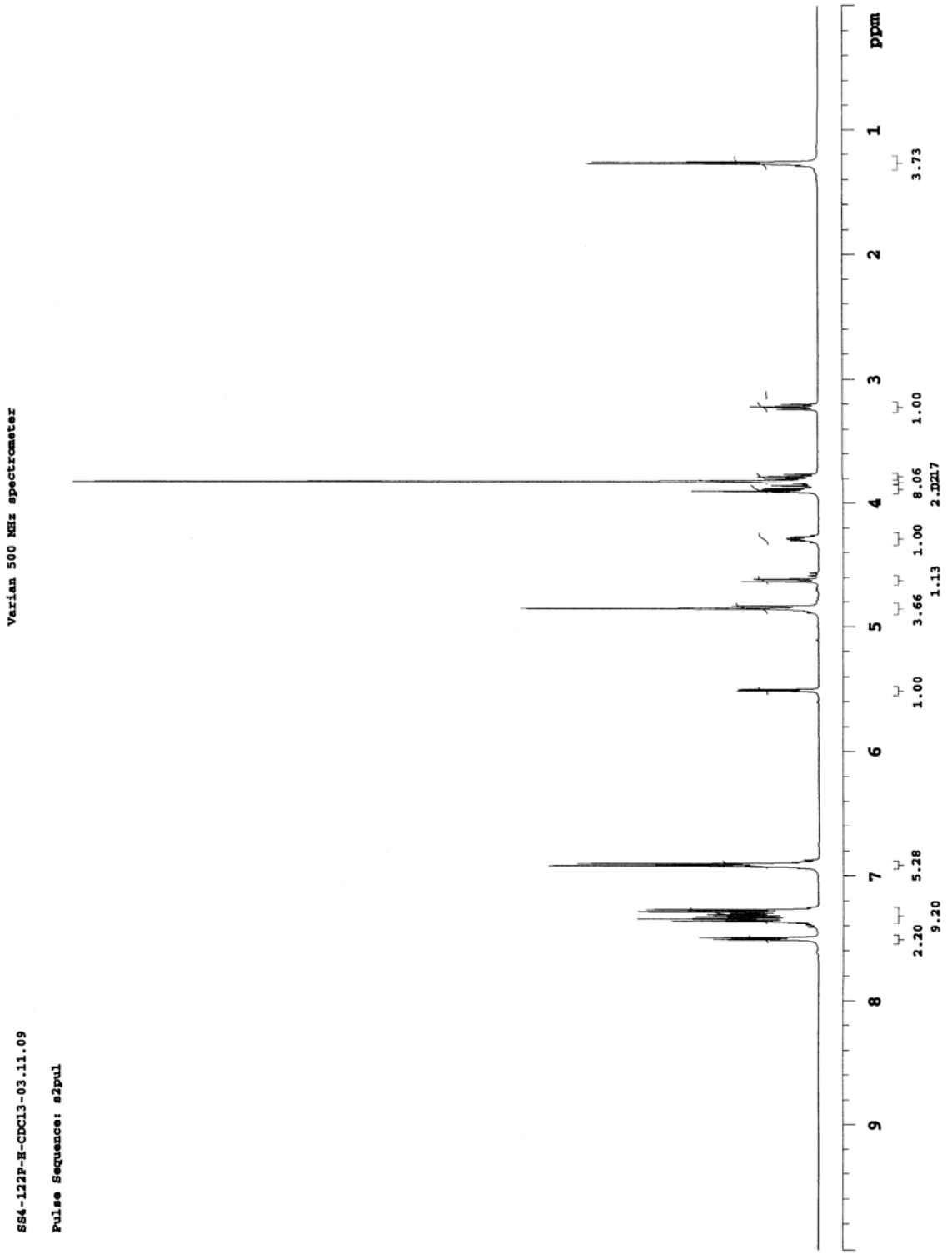
^{1}H NMR (Compound 581)



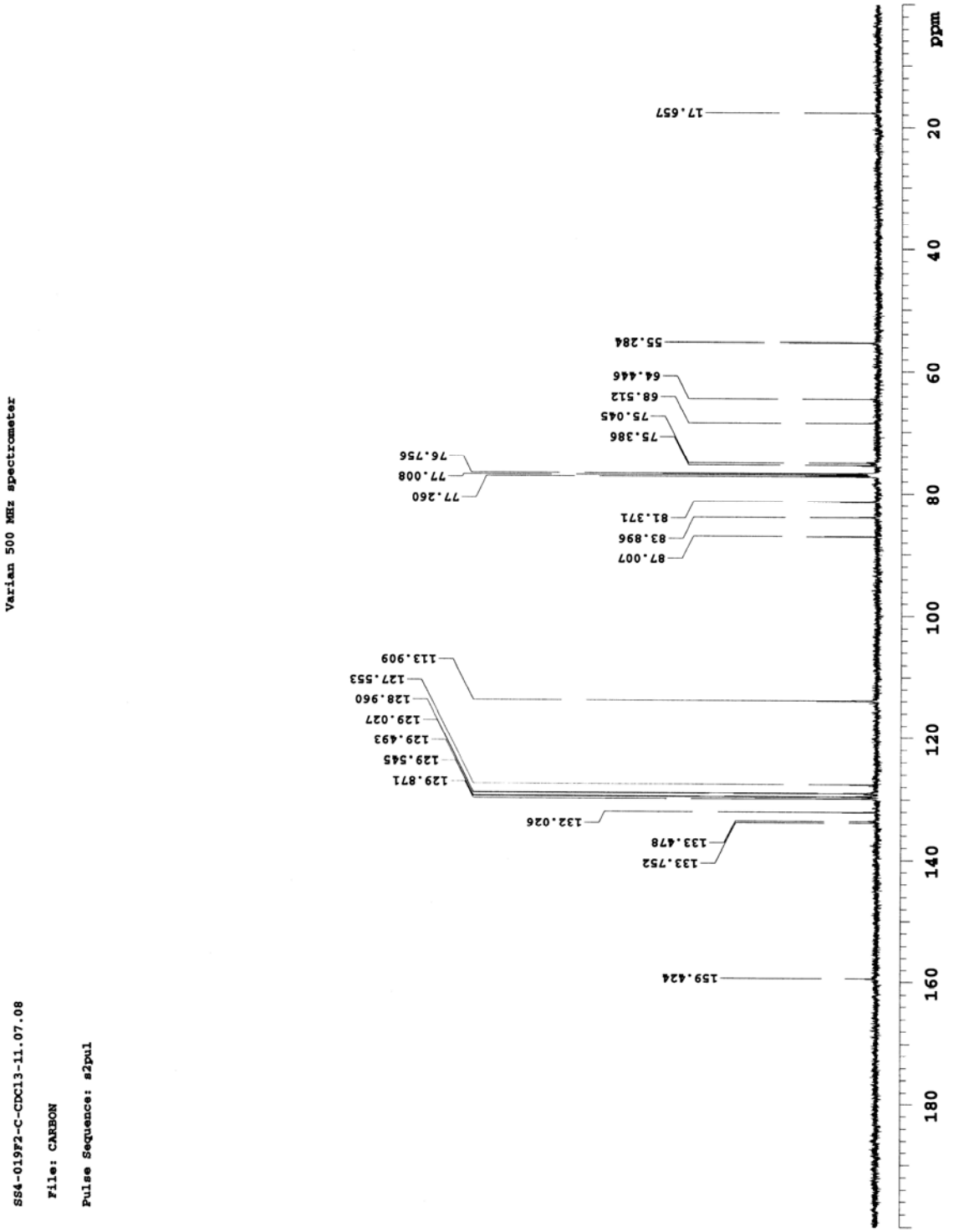
^{1}H-^{1}H GDQFCOSY NMR (Compound 581)



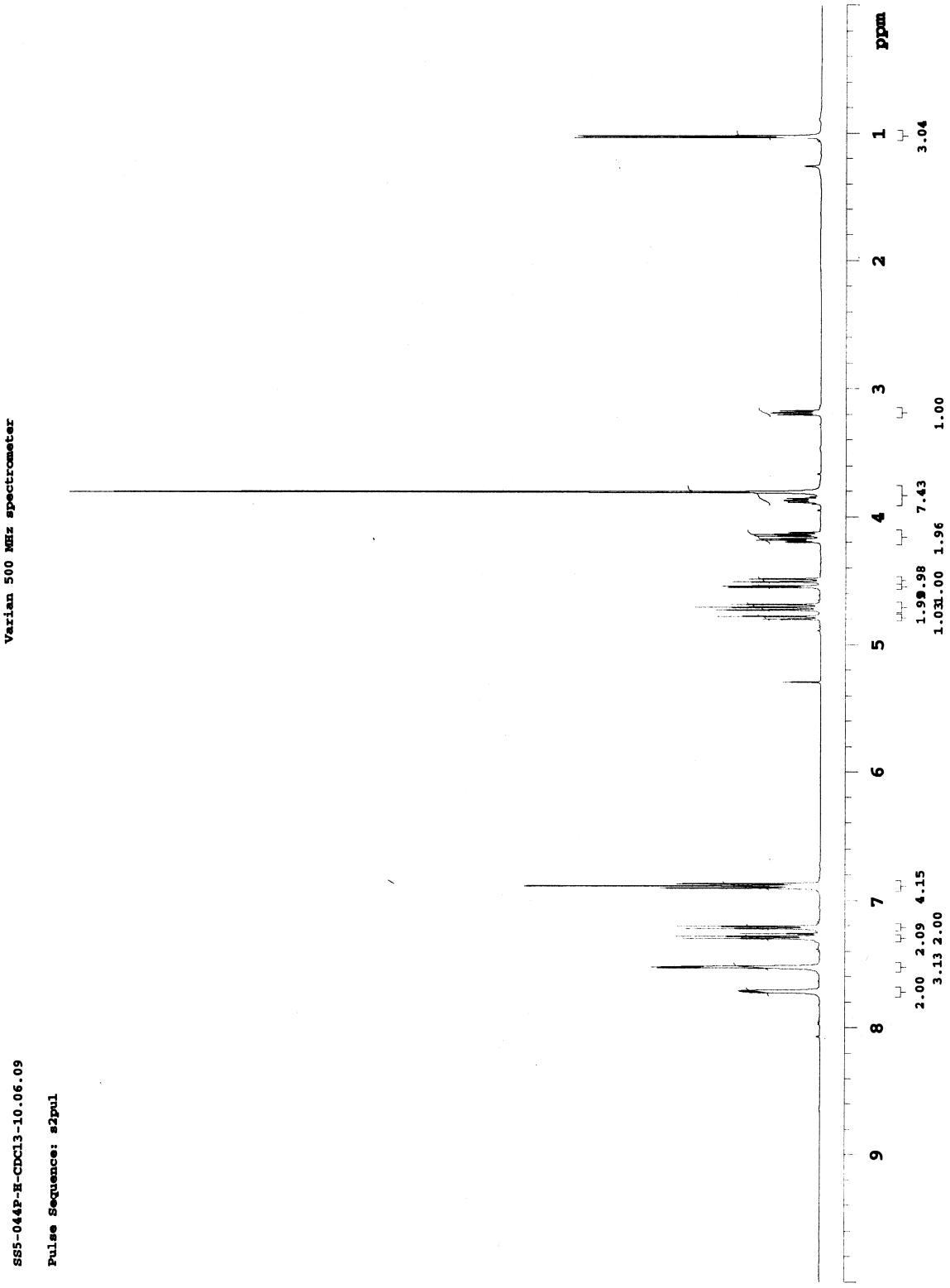
^{1}H NMR ((3R,4R,5R,6R)-3-azido-4,5-bis((4-methoxybenzyl)oxy)-6-methyl-2-(phenylthio)tetrahydro-2H-pyran)



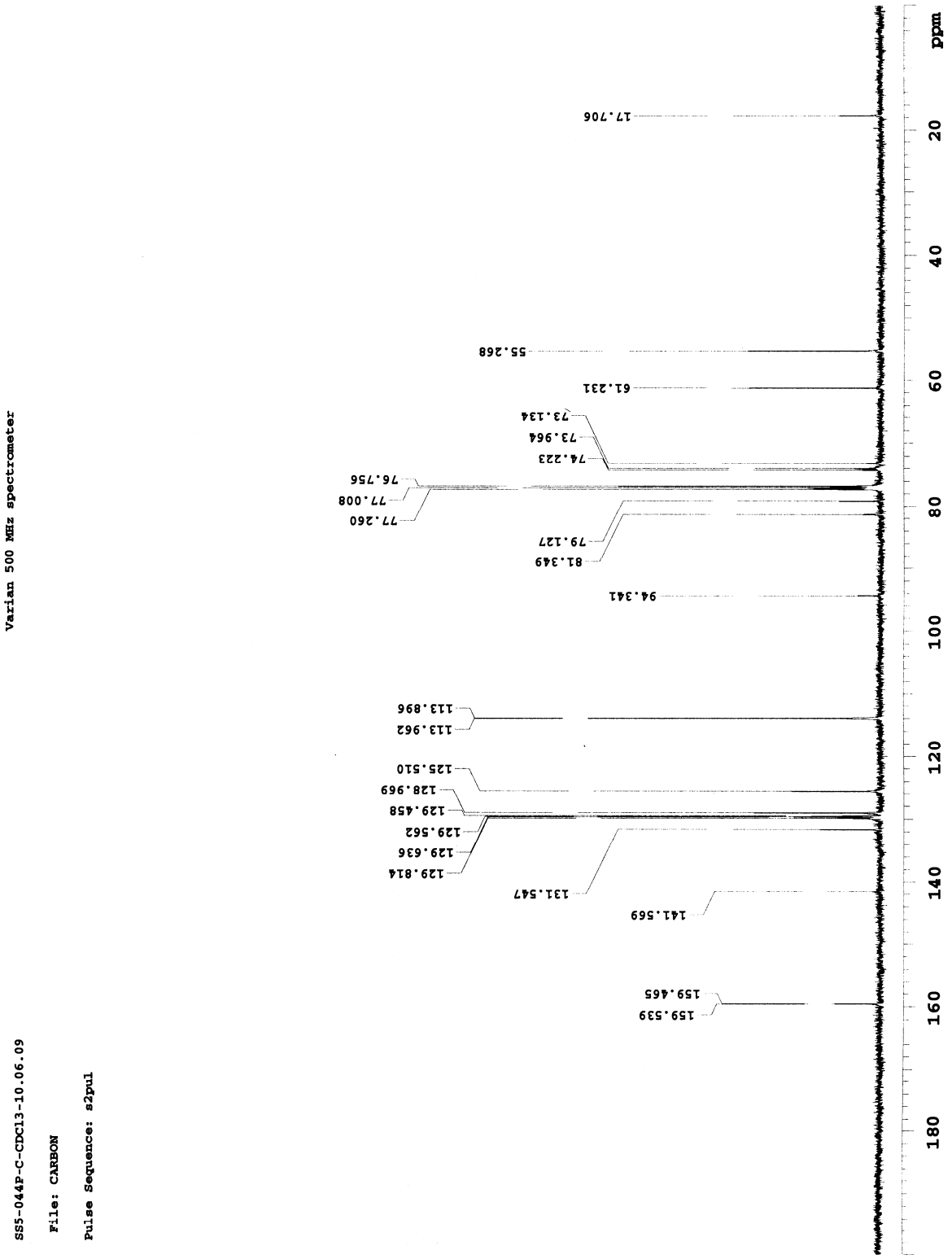
^{1}H NMR ((3R,4R,5R,6R)-3-azido-4,5-bis((4-methoxybenzyl)oxy)-6-methyl-2-(phenylthio)tetrahydro-2H-pyran)



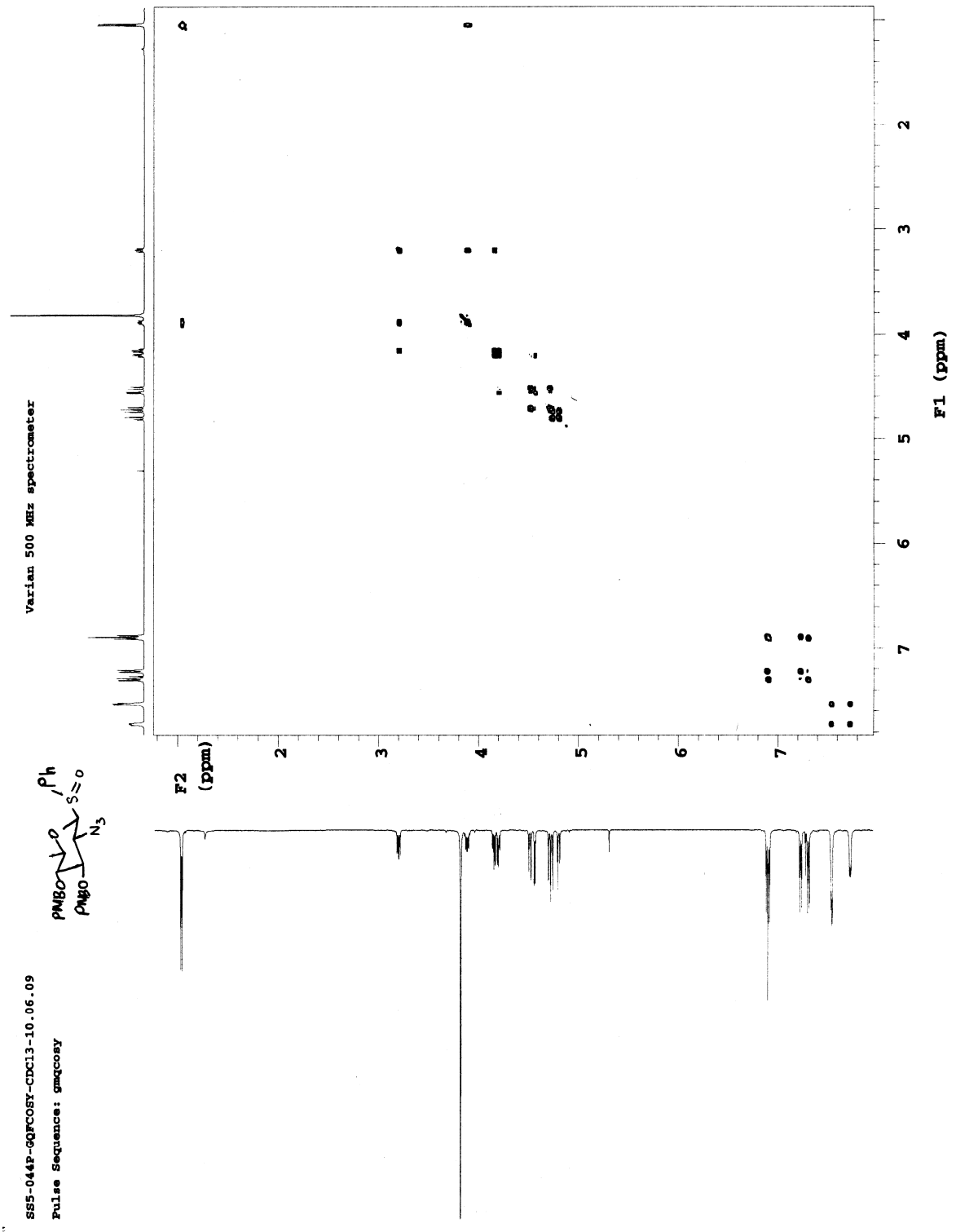
^{1}H NMR (Compound 582)



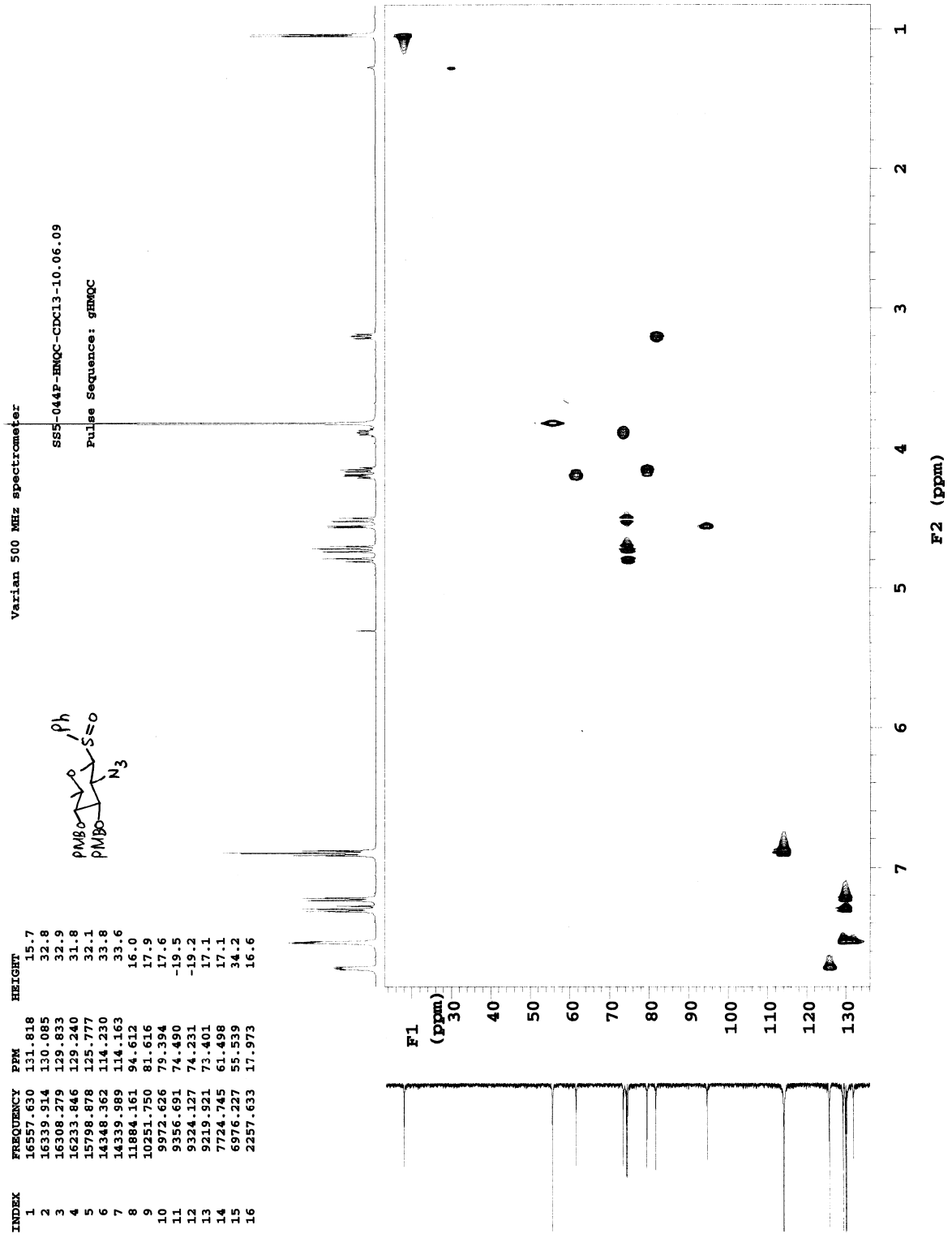
^{13}C NMR (Compound 582)



^{1}H-^{1}H GDQFCOSY NMR (Compound 582)

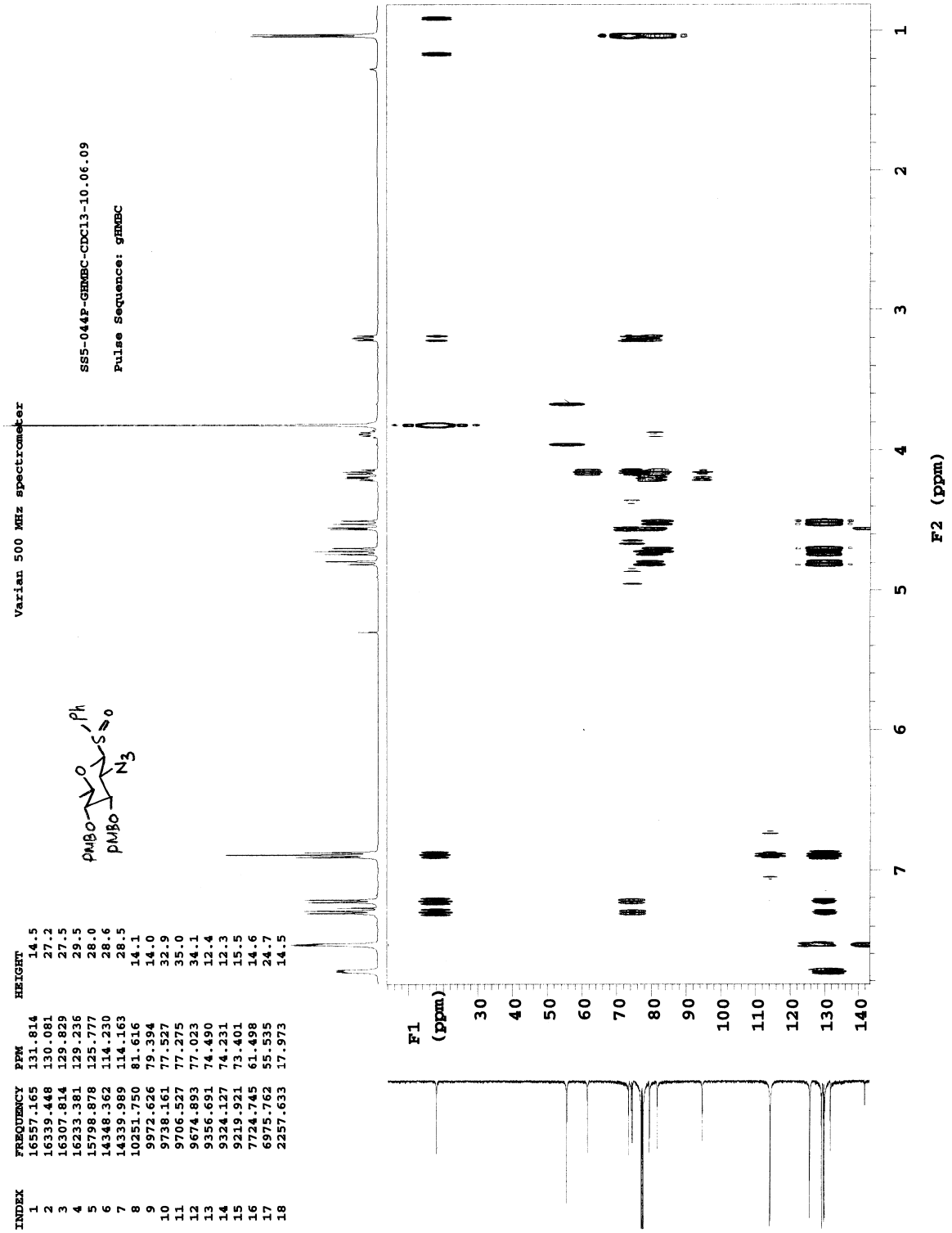


GHMQC NMR (Compound 582)



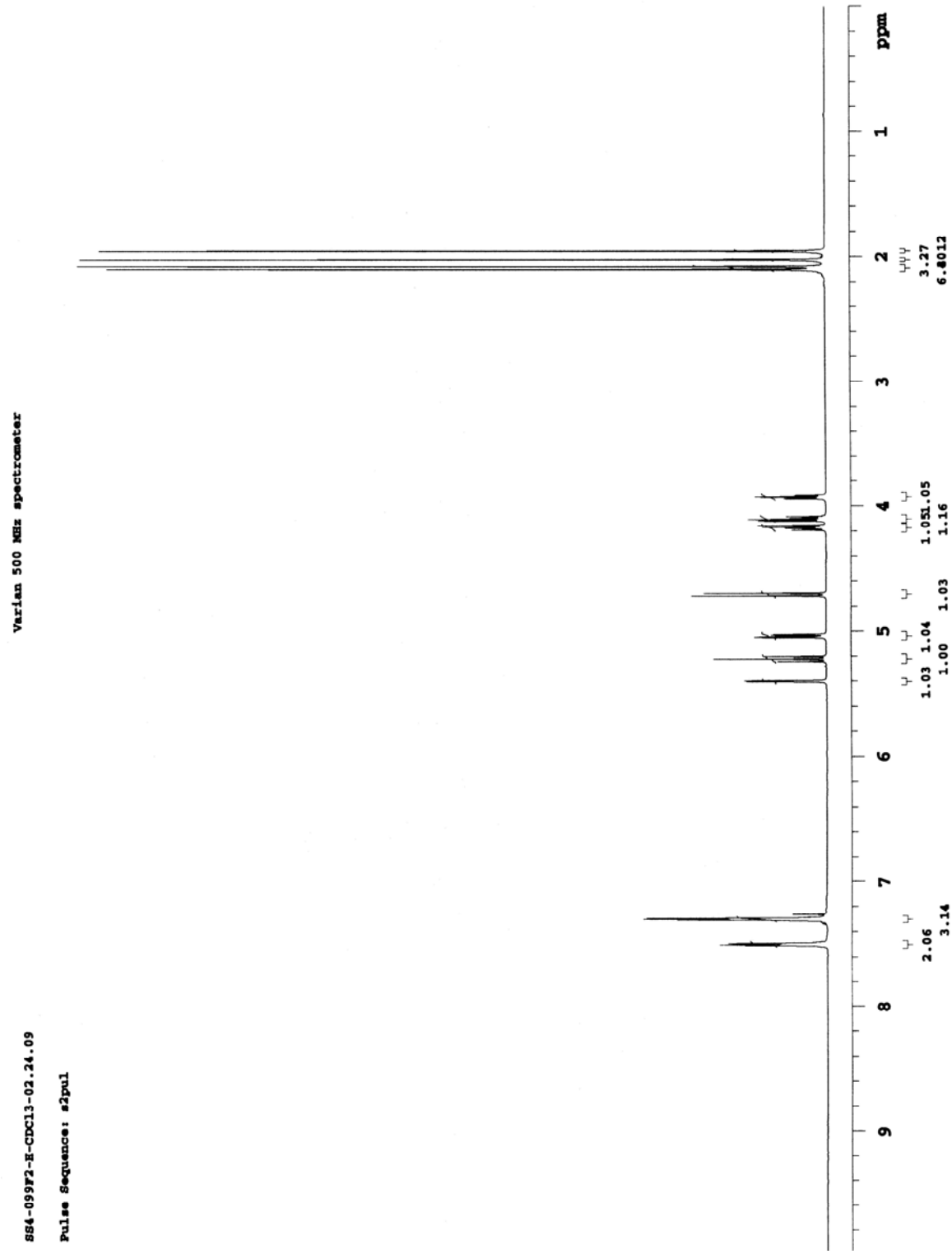
INDEX	FREQUENCY	PPM	HEIGHT
1	16557.630	131.818	15.7
2	16339.914	130.085	32.8
3	16308.279	129.833	32.9
4	16233.846	129.240	31.8
5	15798.878	125.777	32.1
6	14348.362	114.230	33.8
7	14339.989	114.163	33.6
8	11884.161	94.612	16.0
9	10251.750	81.616	17.9
10	9972.626	79.394	17.6
11	9356.691	74.490	-19.5
12	9324.127	74.231	-19.2
13	9219.921	73.401	17.1
14	7724.745	61.498	17.1
15	6976.227	55.539	34.2
16	2257.633	17.973	16.6

GHMBC NMR (Compound 582)

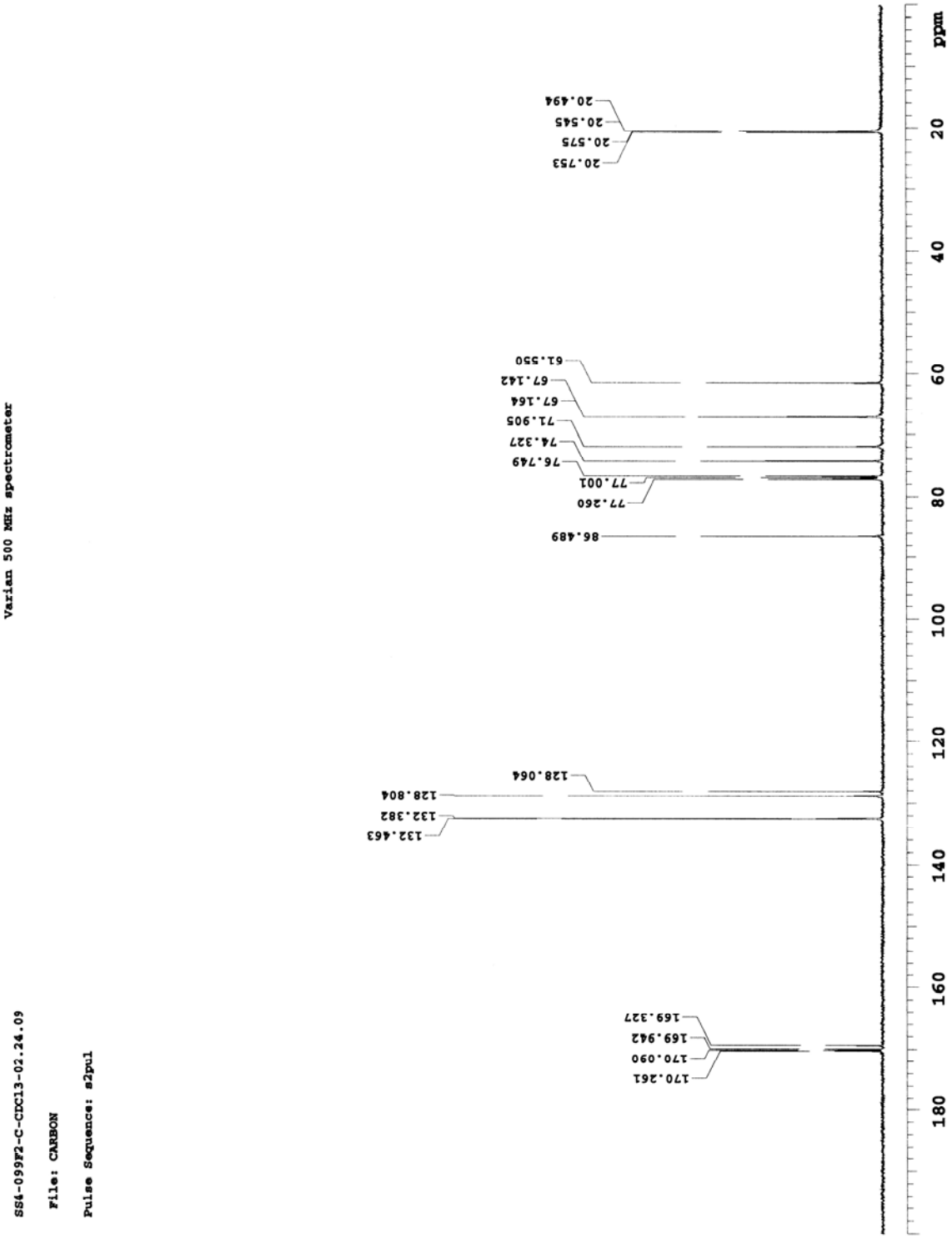


INDEX	FREQUENCY	PPM	HEIGHT
1	16557.165	131.814	14.5
2	16339.448	130.081	27.2
3	16307.814	129.829	27.5
4	16233.381	129.236	29.5
5	15798.878	125.777	28.0
6	14348.362	114.230	28.6
7	14339.989	114.163	28.5
8	10251.750	81.616	14.1
9	9972.626	79.394	14.0
10	9738.161	77.527	32.9
11	9706.527	77.275	35.0
12	9674.893	77.023	34.1
13	9356.691	74.490	12.4
14	9324.127	74.231	12.3
15	9219.921	73.401	15.5
16	7724.745	61.498	14.6
17	6975.762	55.535	24.7
18	2257.633	17.973	14.5

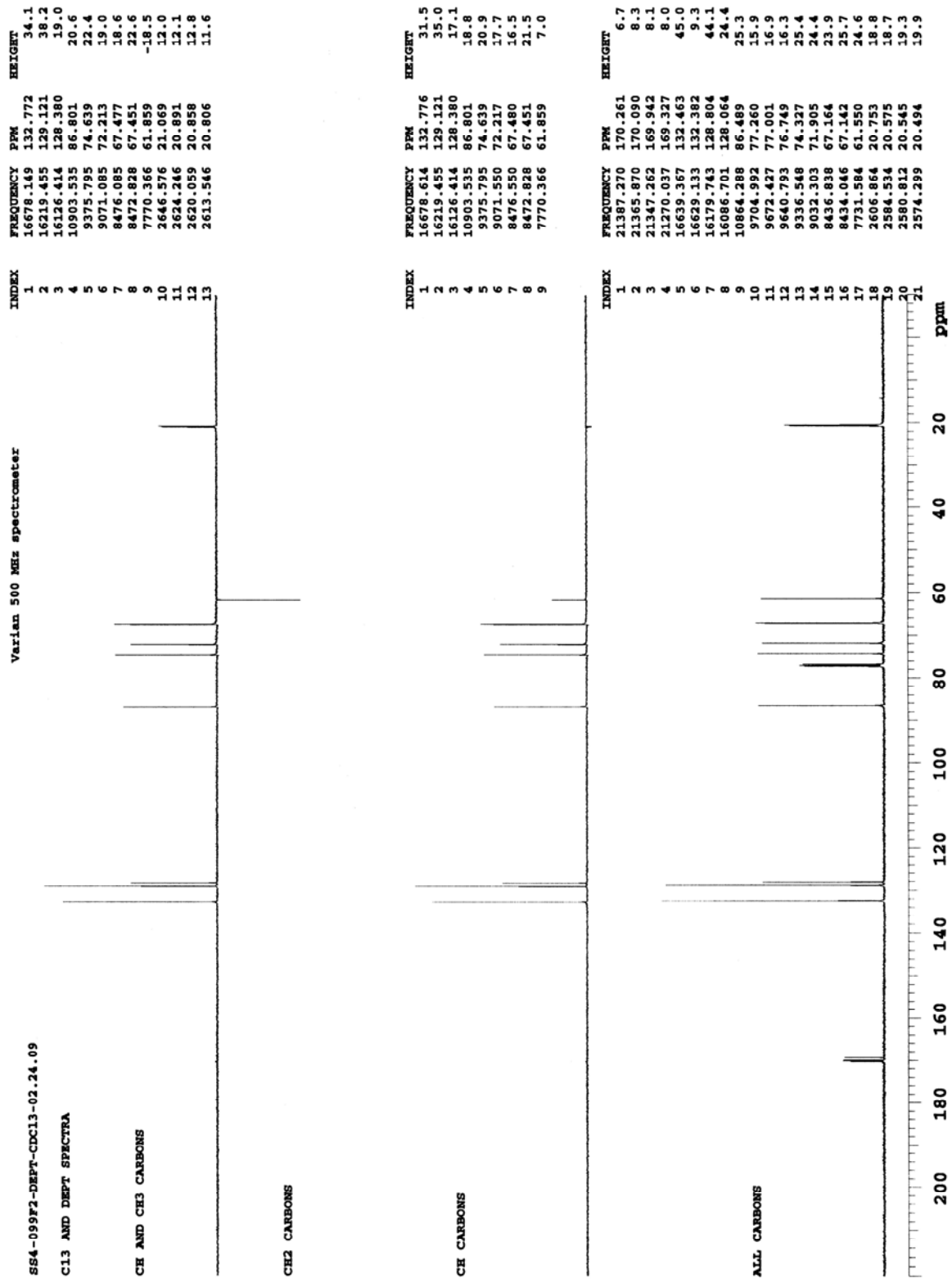
[1]H NMR (Compound 583)



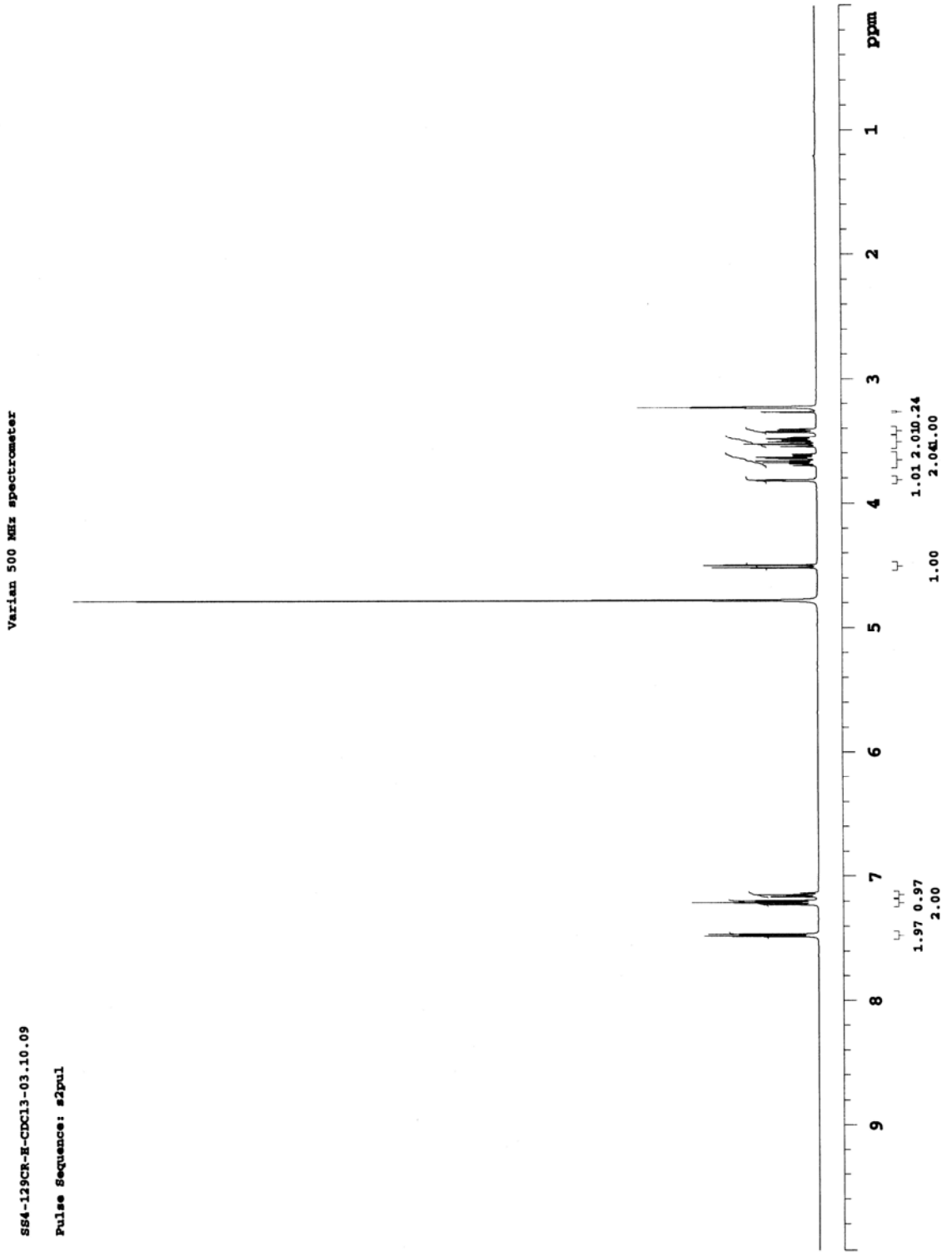
^{13}C NMR (Compound 583)



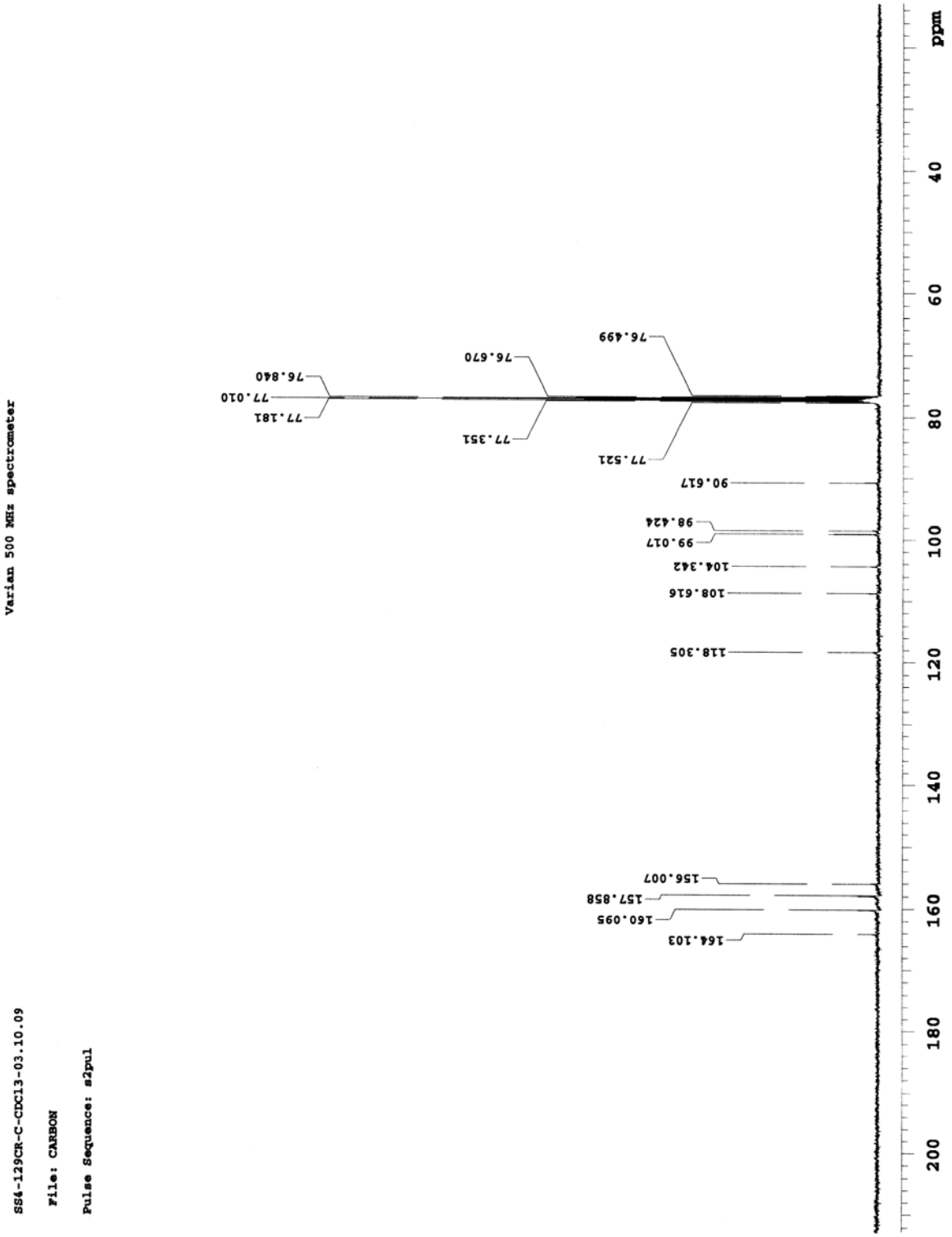
DEPT NMR (Compound 583)



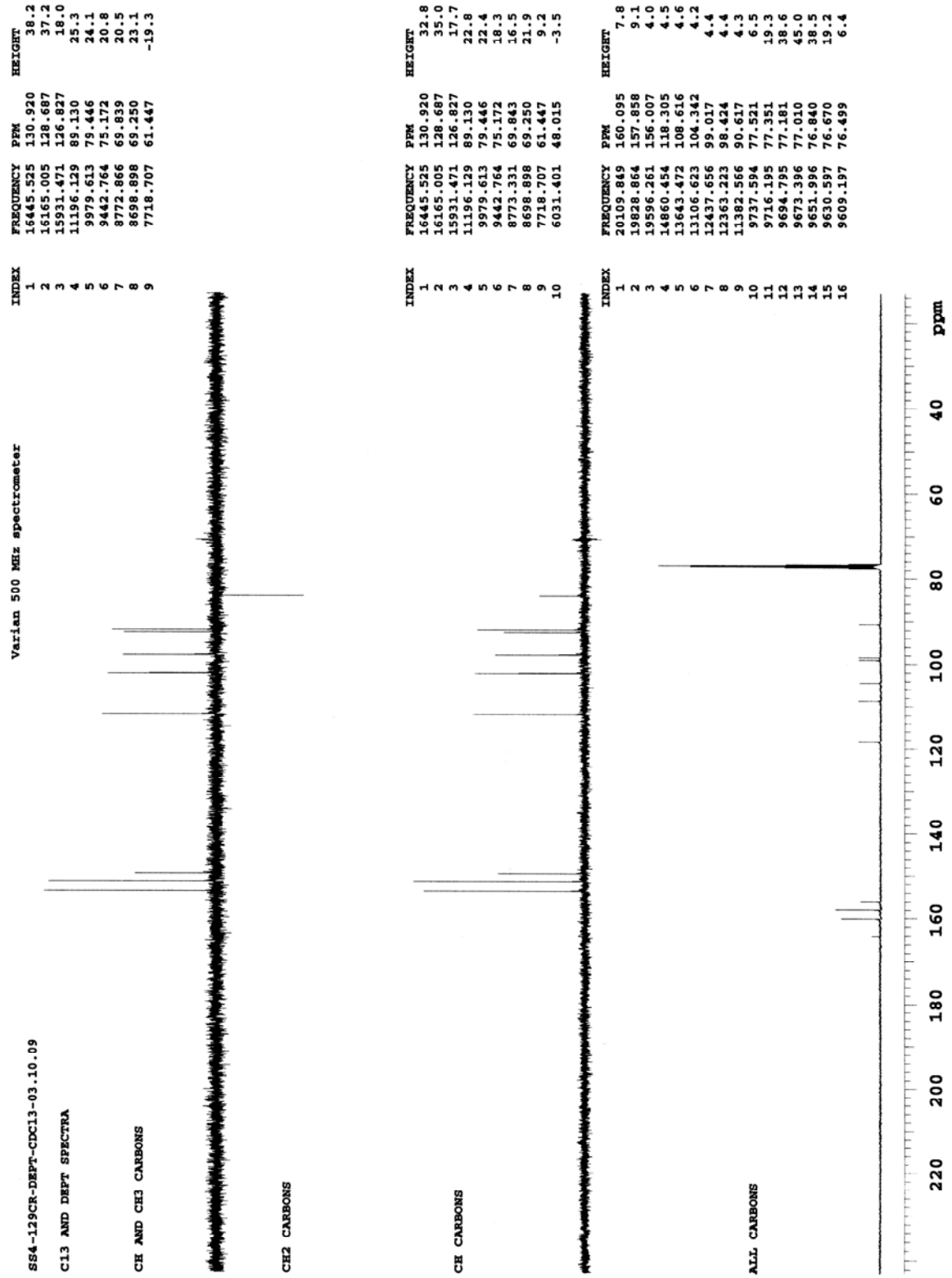
^{1}H NMR (Compound 584)



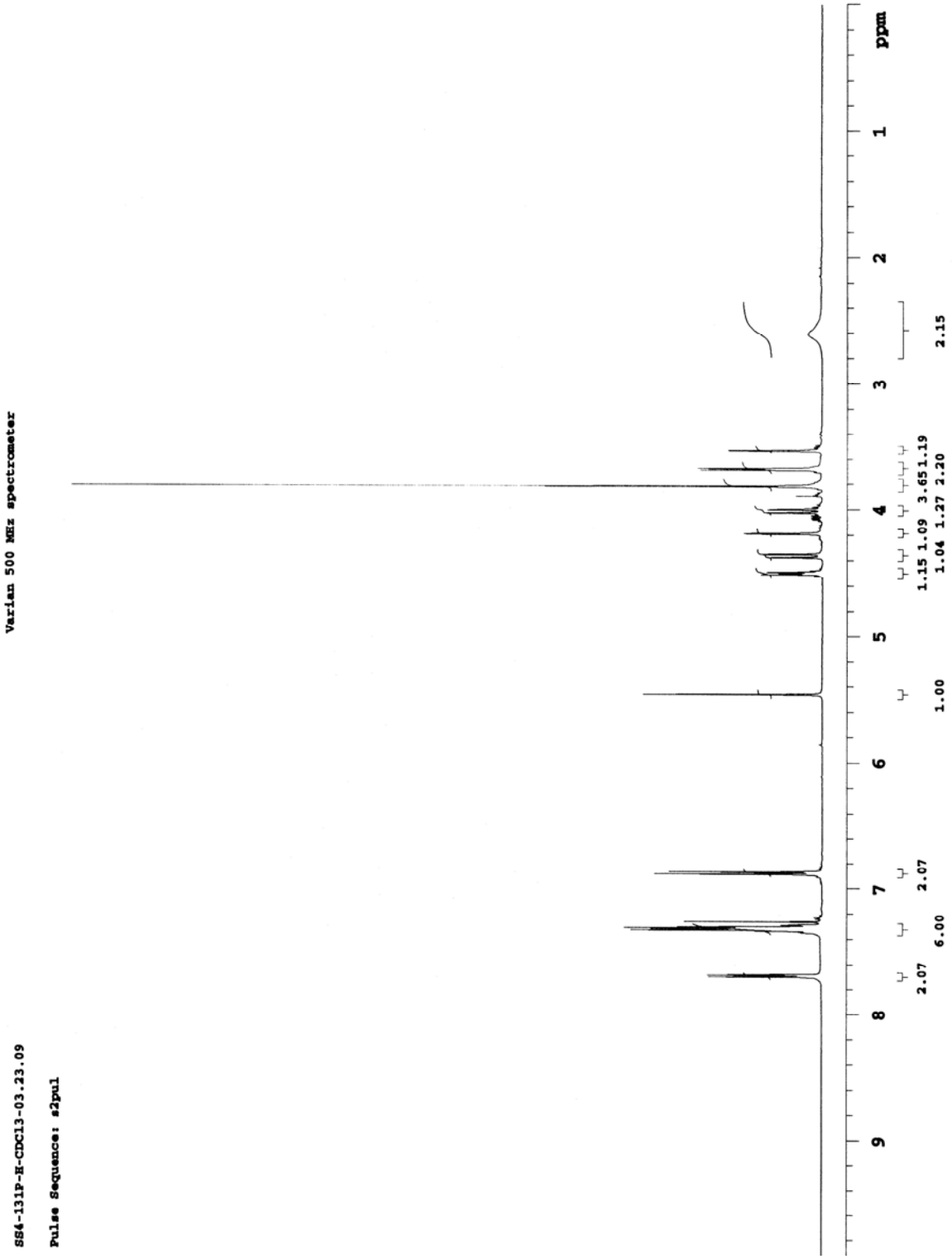
^{13}C NMR (Compound 584)



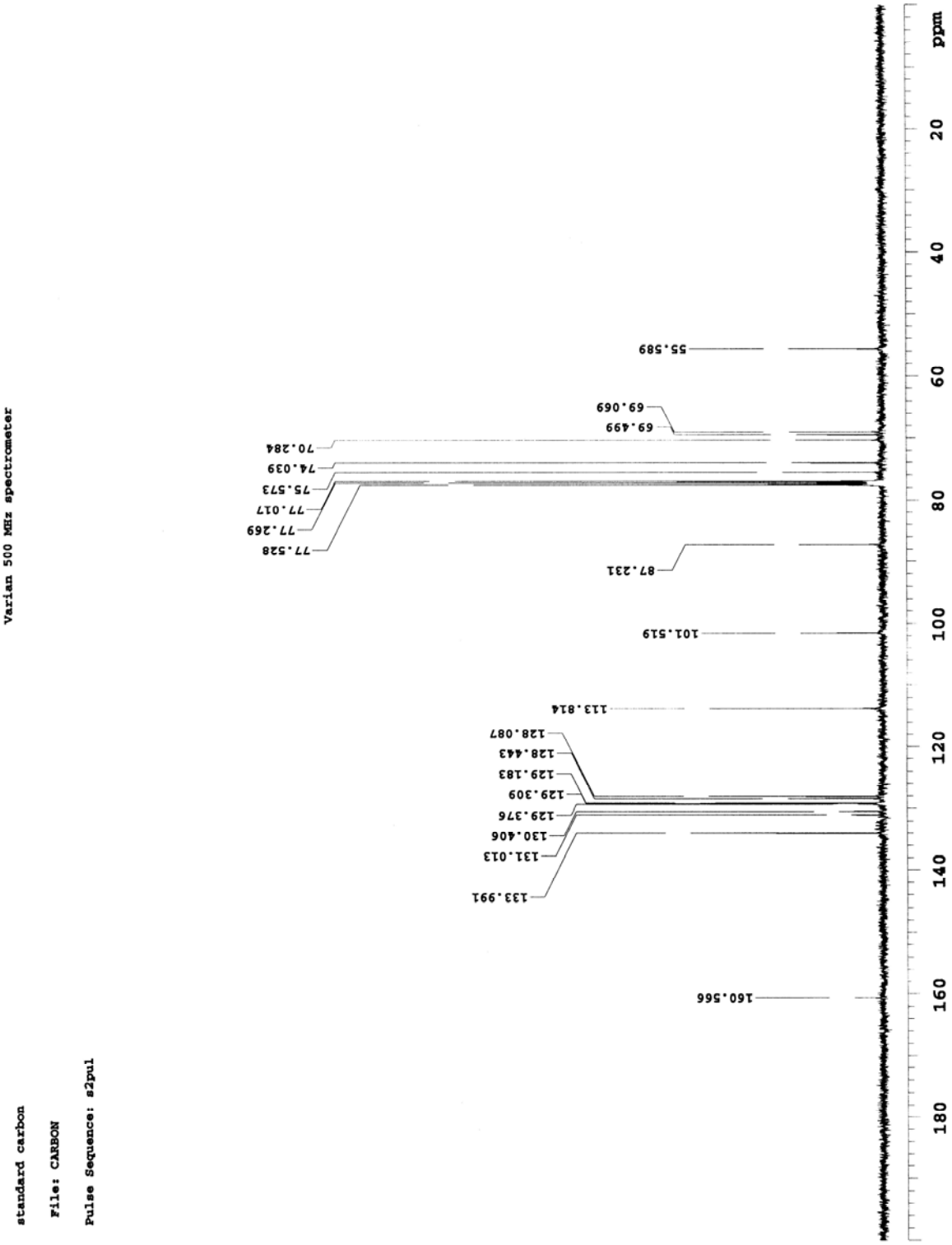
DEPT (Compound 584)



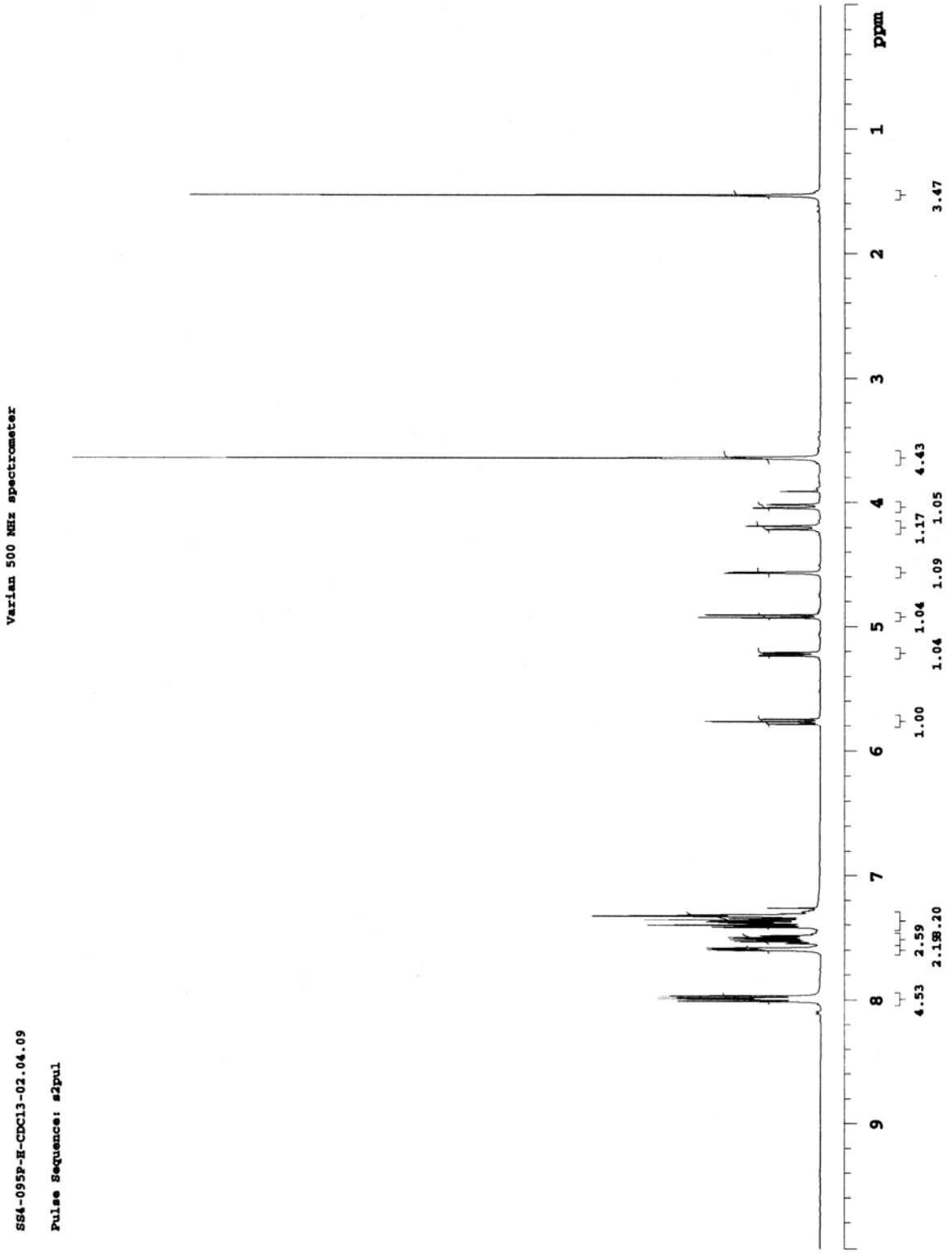
[1]H NMR (Compound 585)



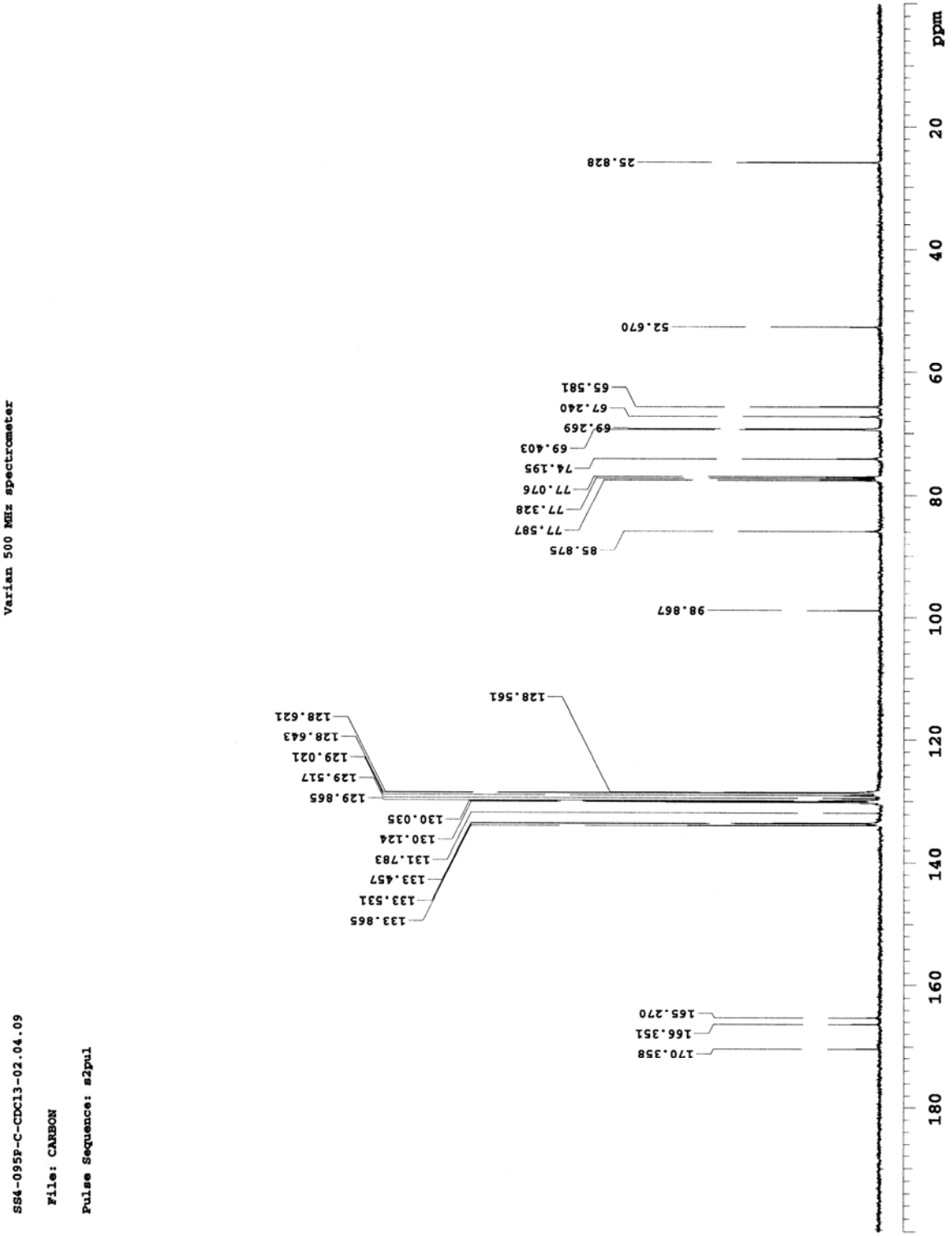
^{13}C NMR (Compound 585)



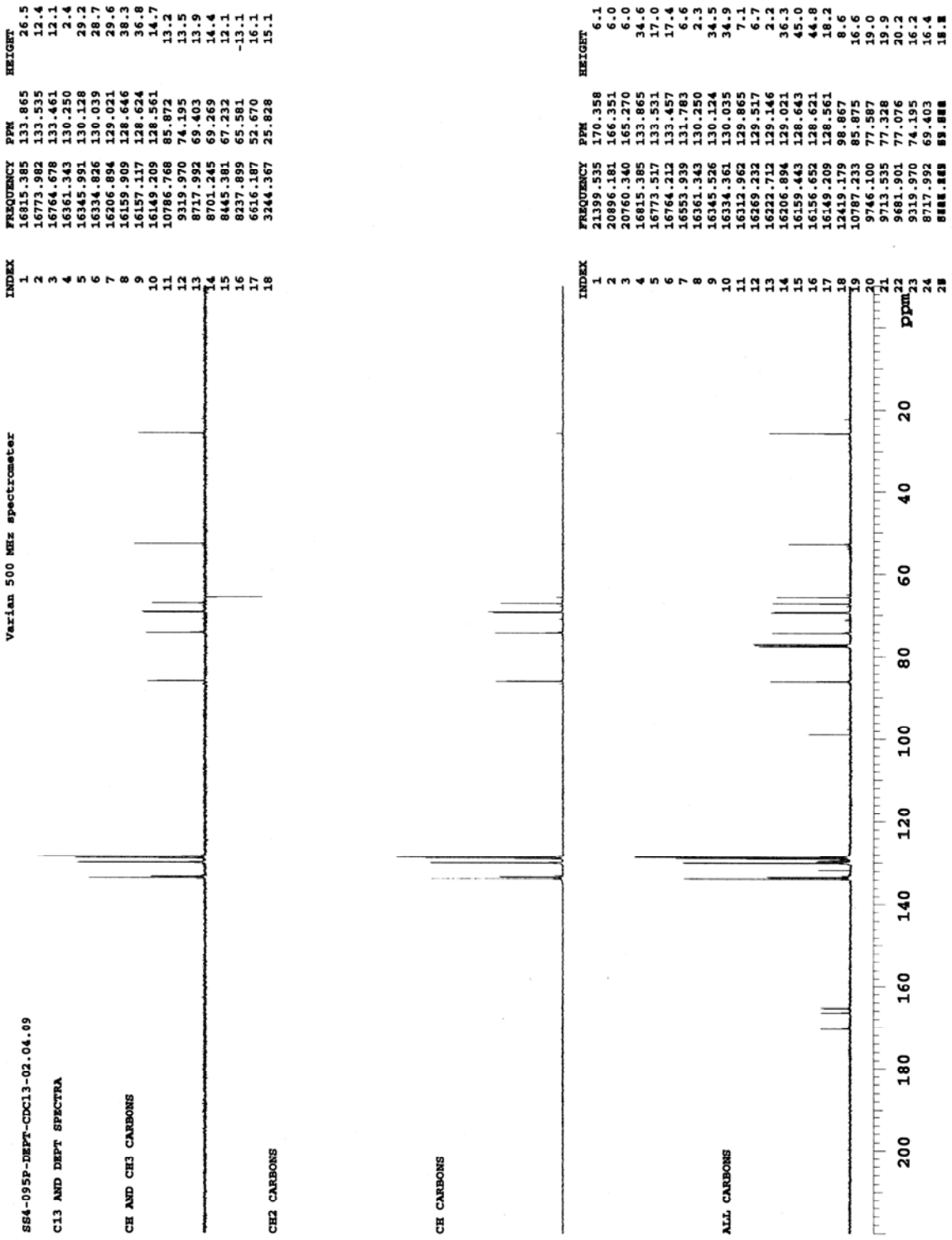
[1]H NMR (Compound 588)



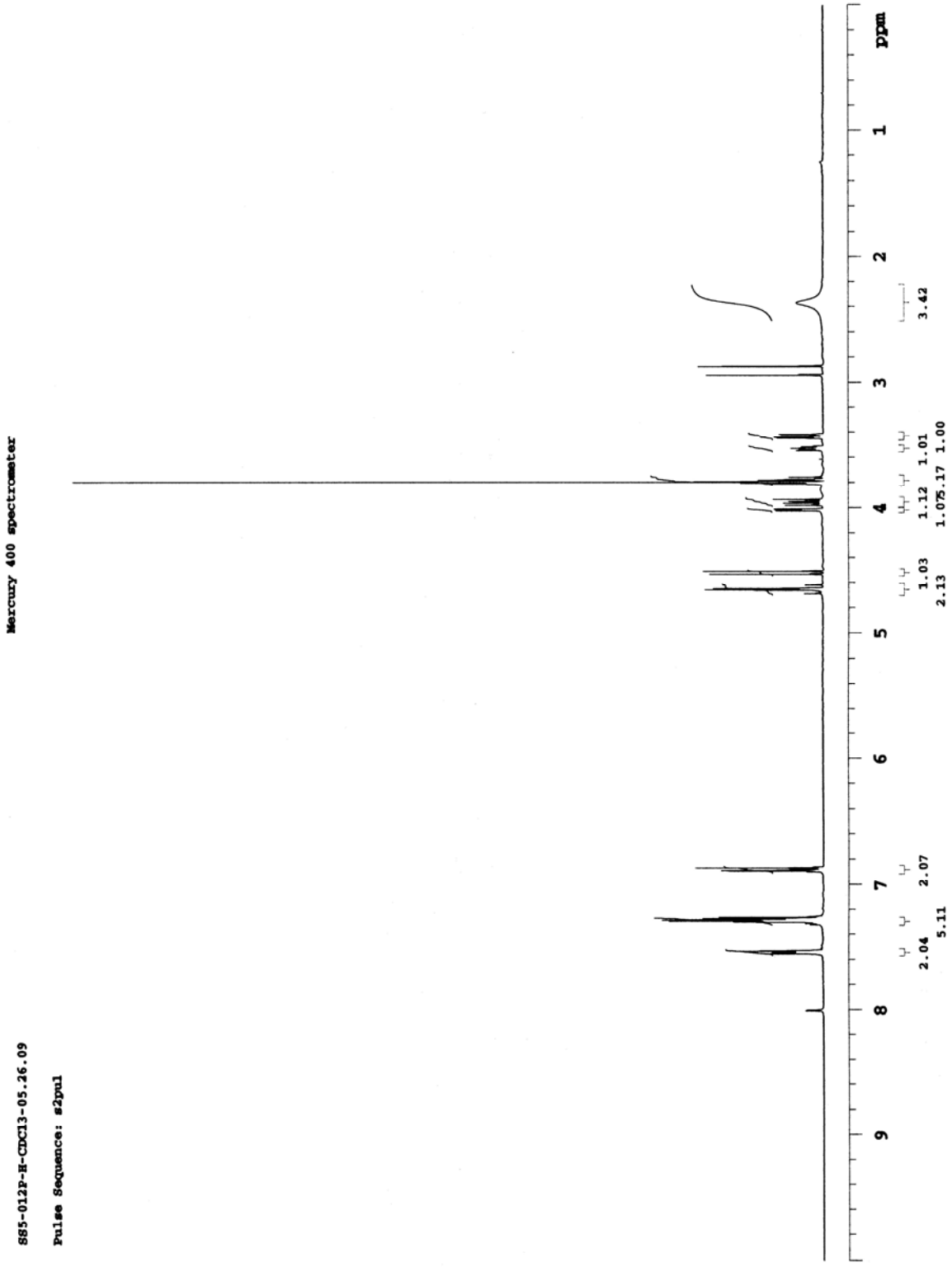
^{13}C NMR (Compound 588)



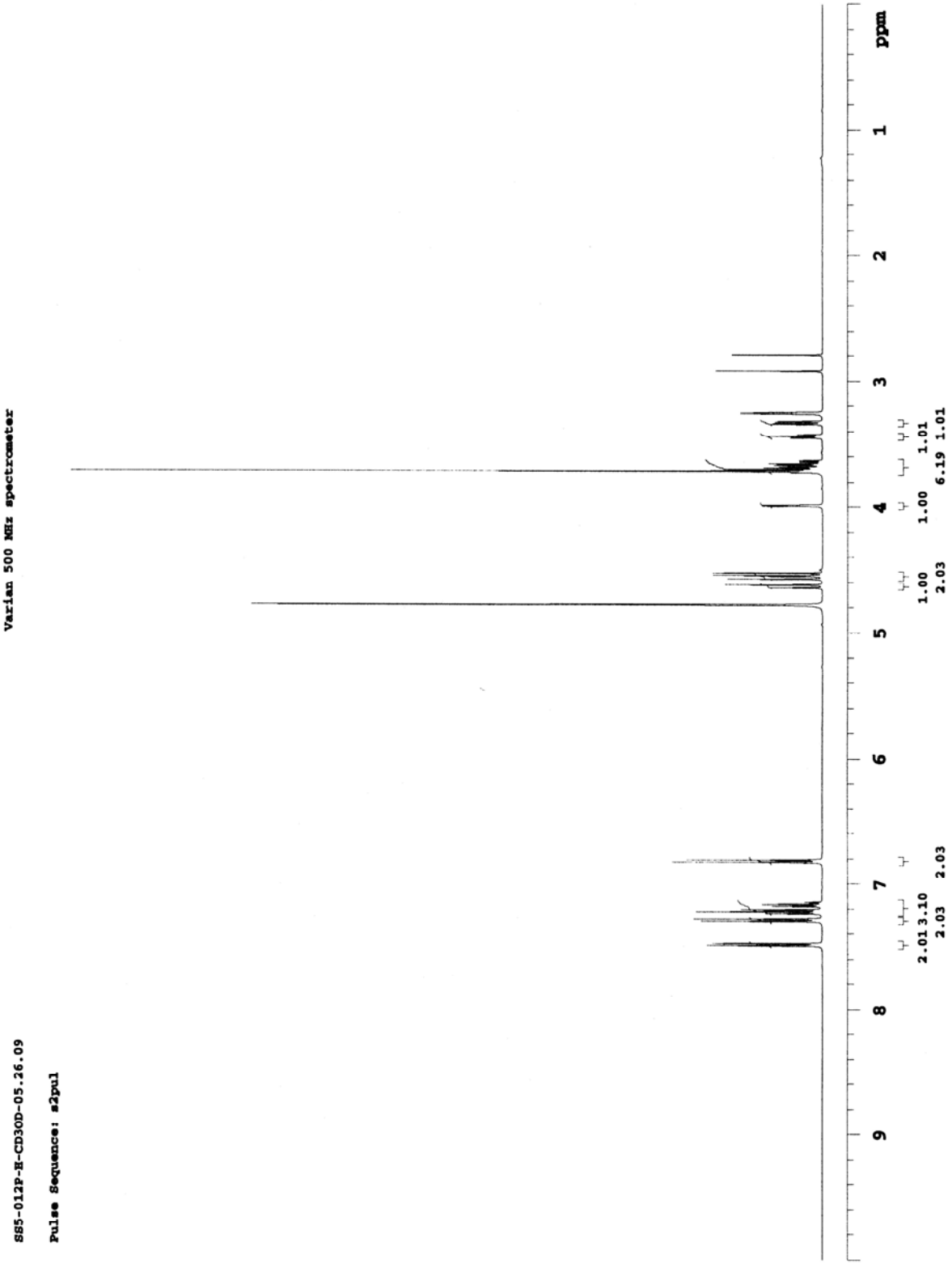
DEPT NMR (Compound 588)



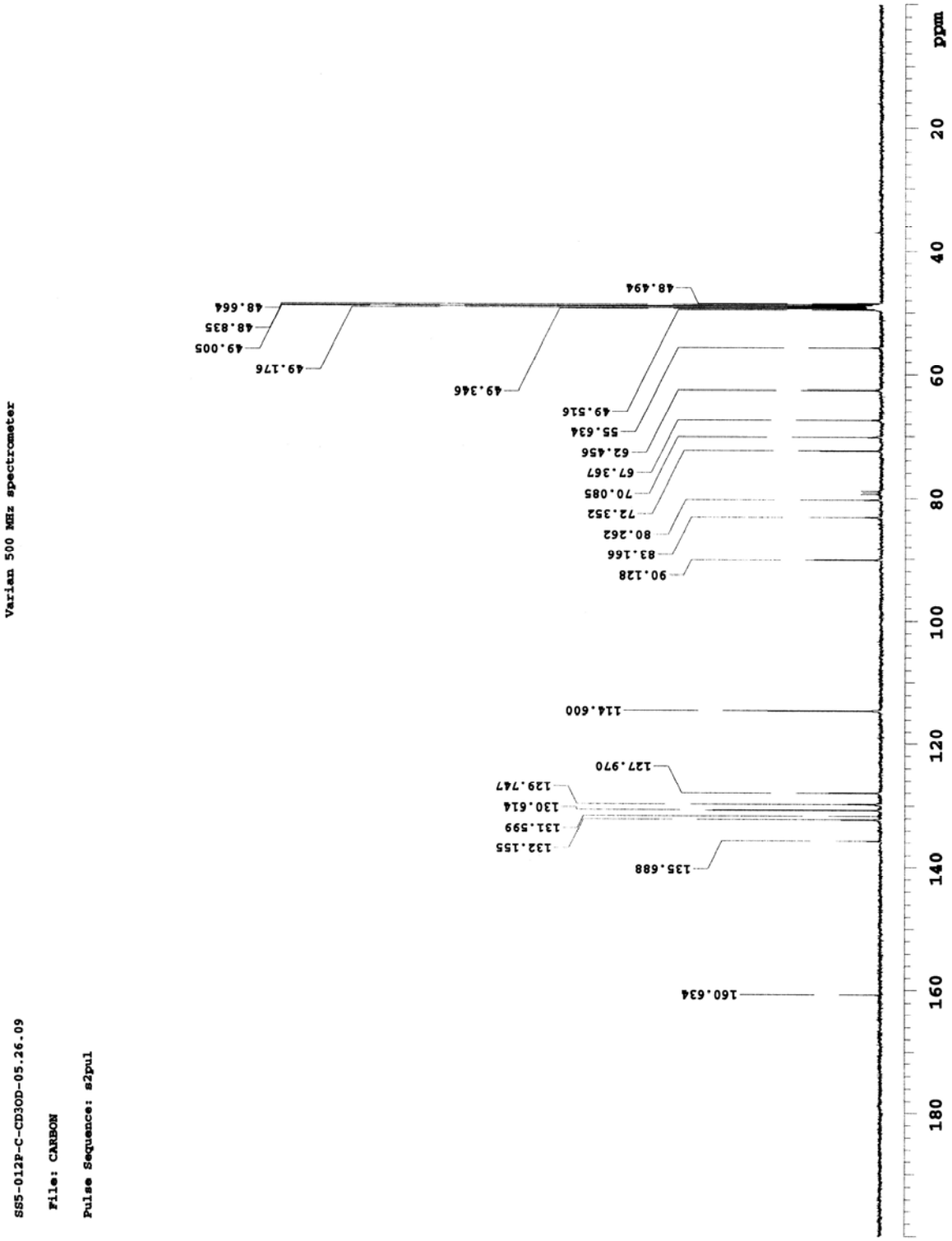
^{1}H NMR ($CDCl_3$, Compound 589)



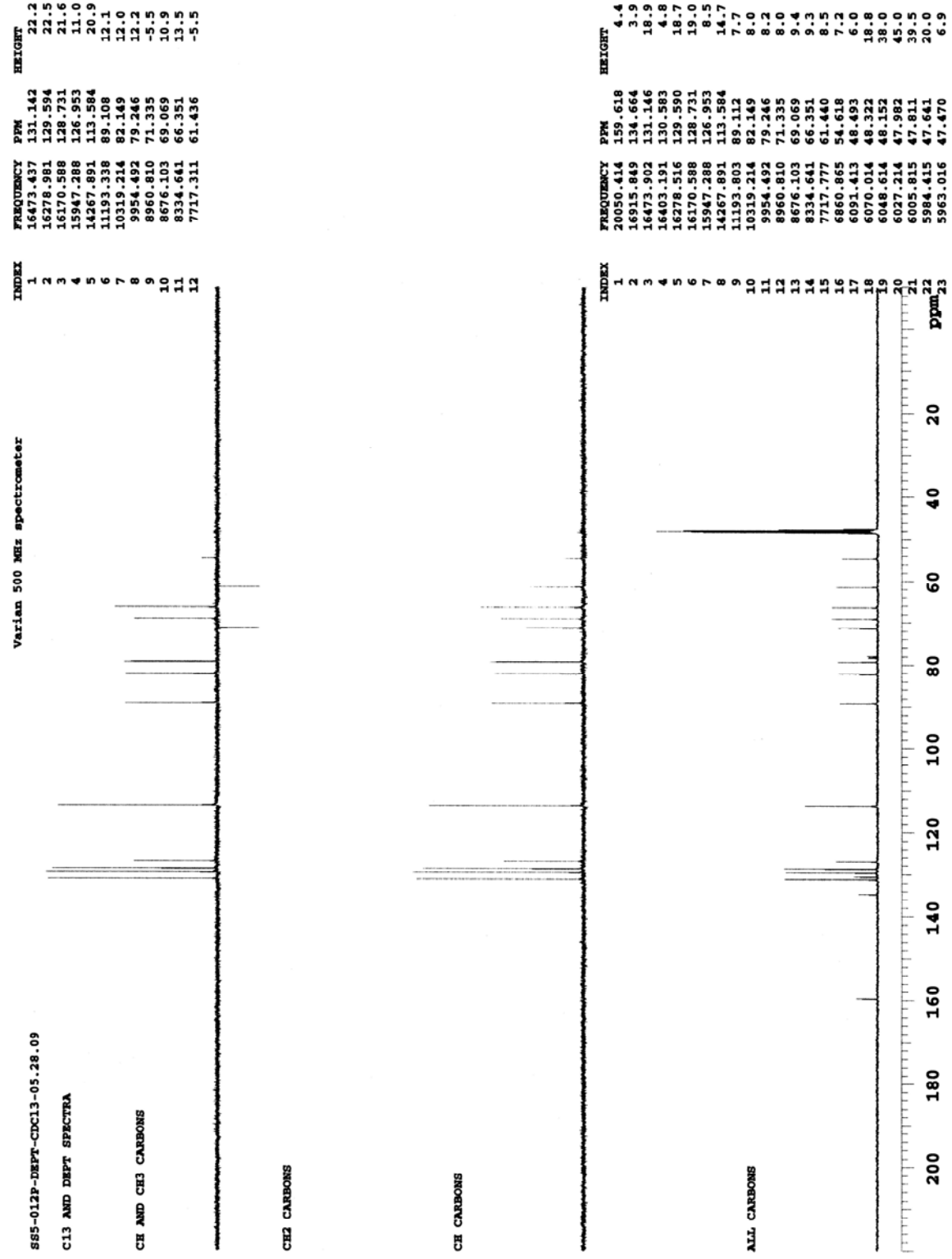
^{1}H NMR (CD_3OD, Compound 589)



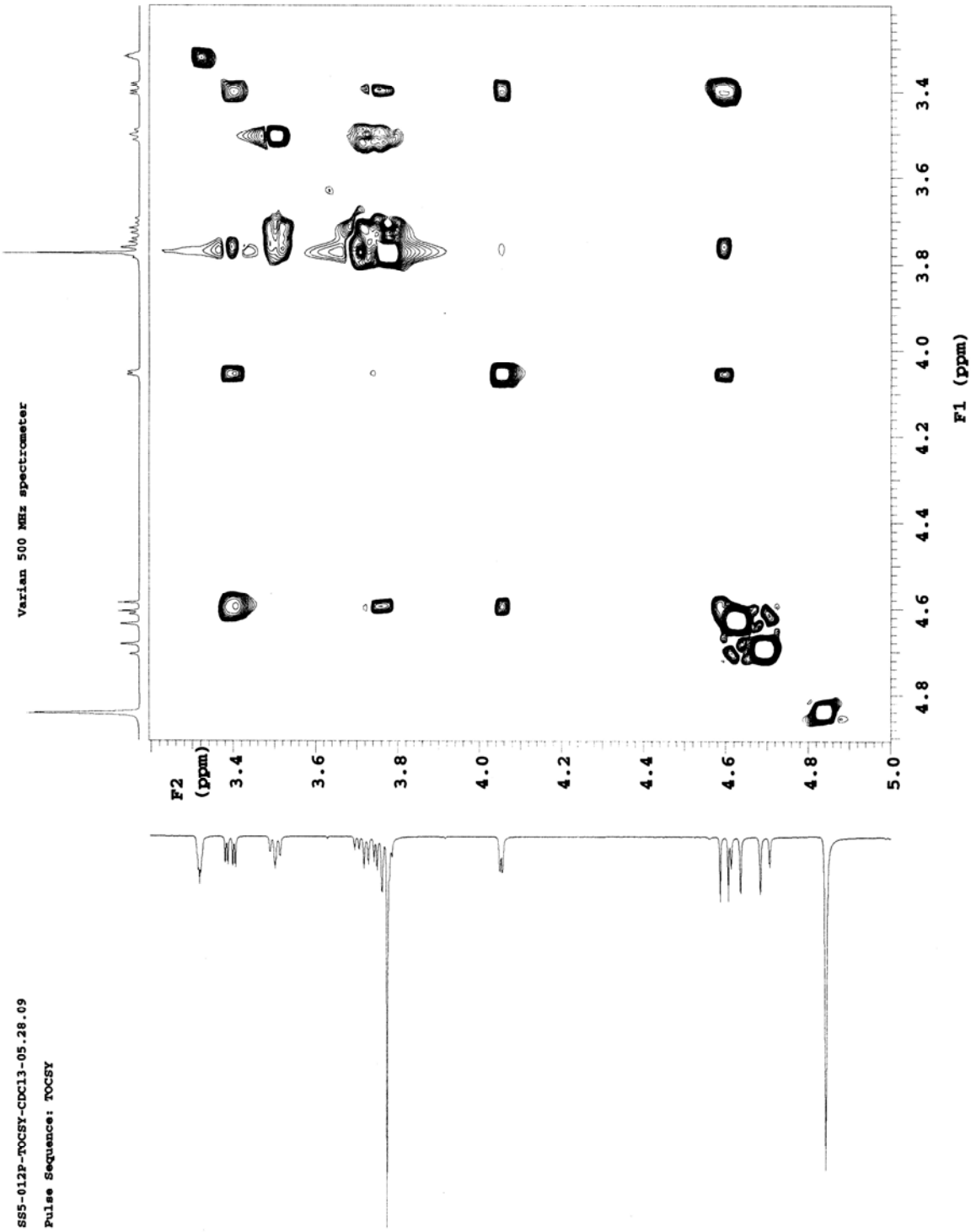
^{13}C NMR (CD_3OD, Compound 589)



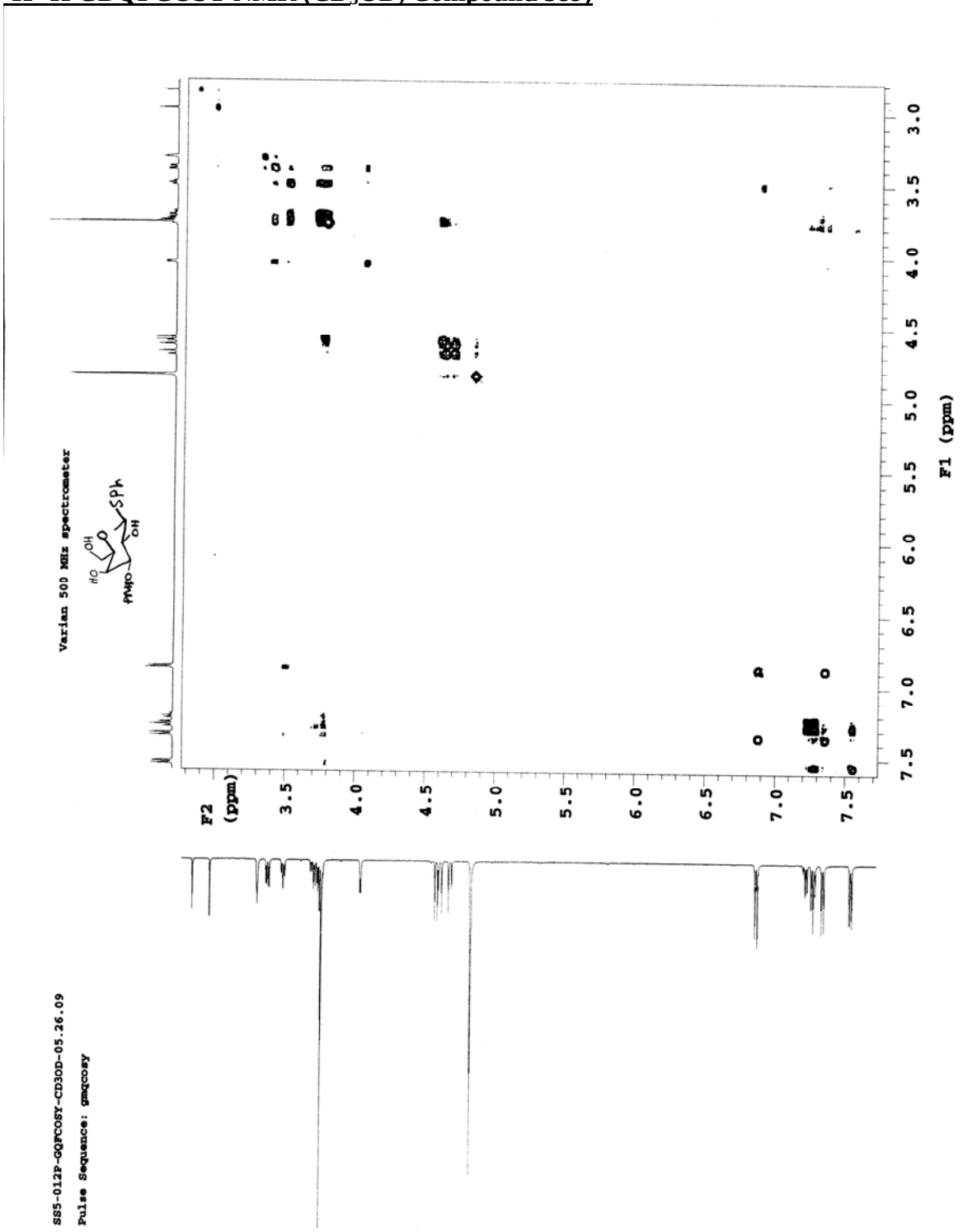
DEPT NMR (CD_3OD, Compound 589)



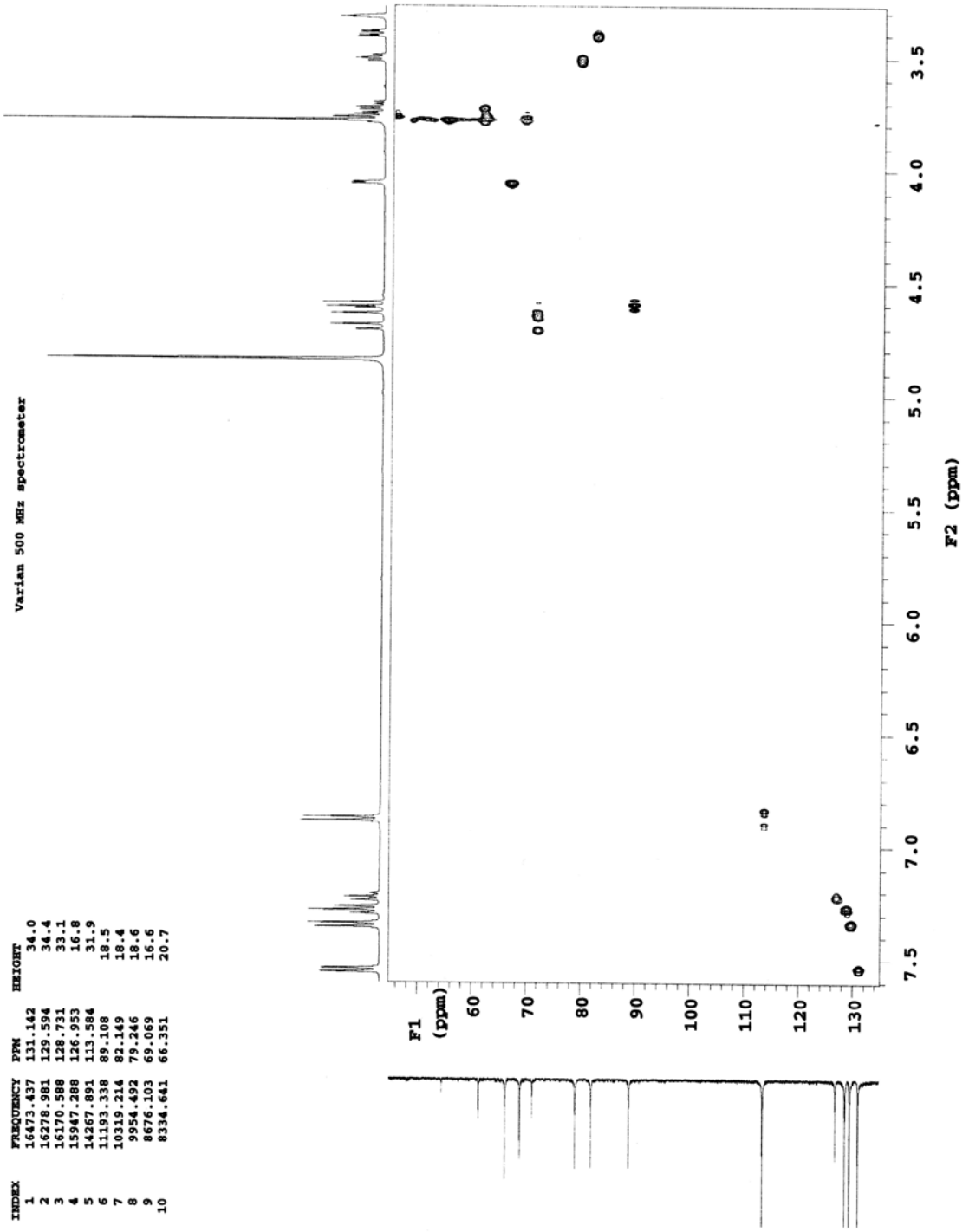
TOCSY NMR (CD_3OD, Compound 589)



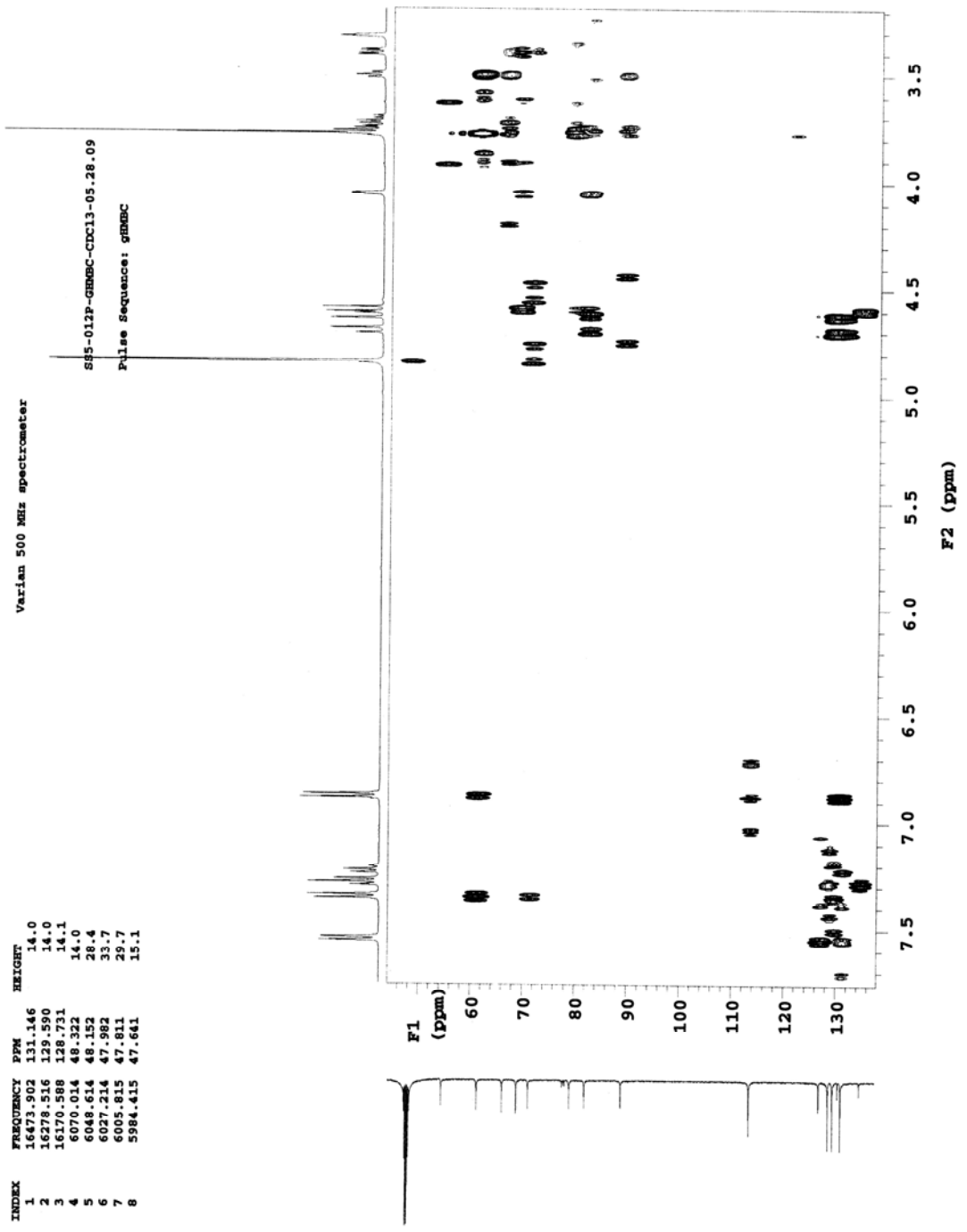
^{1}H-^{1}H GDQFCOSY NMR (CD_3OD, Compound 589)



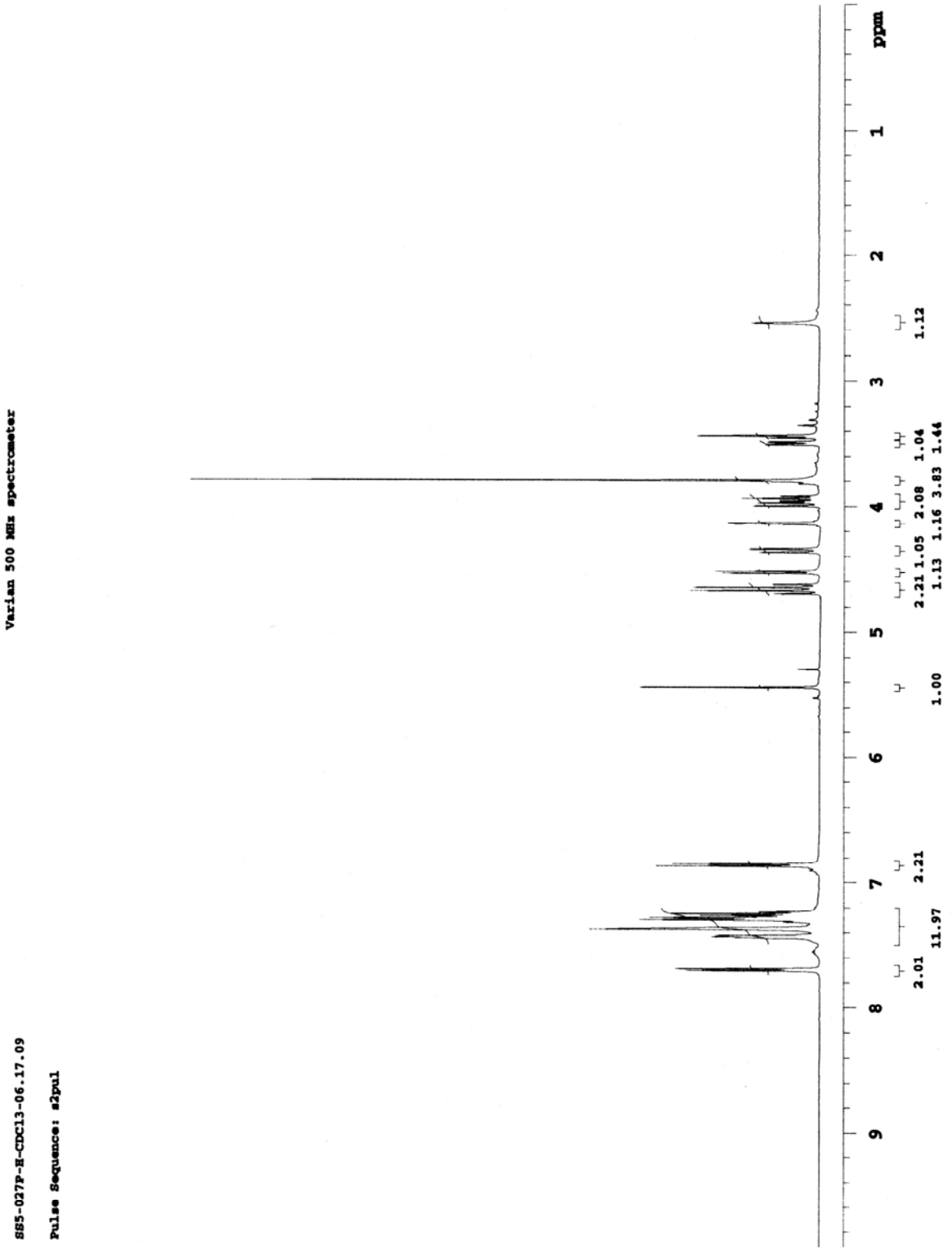
GHMQC NMR (CD_3OD, Compound 589)



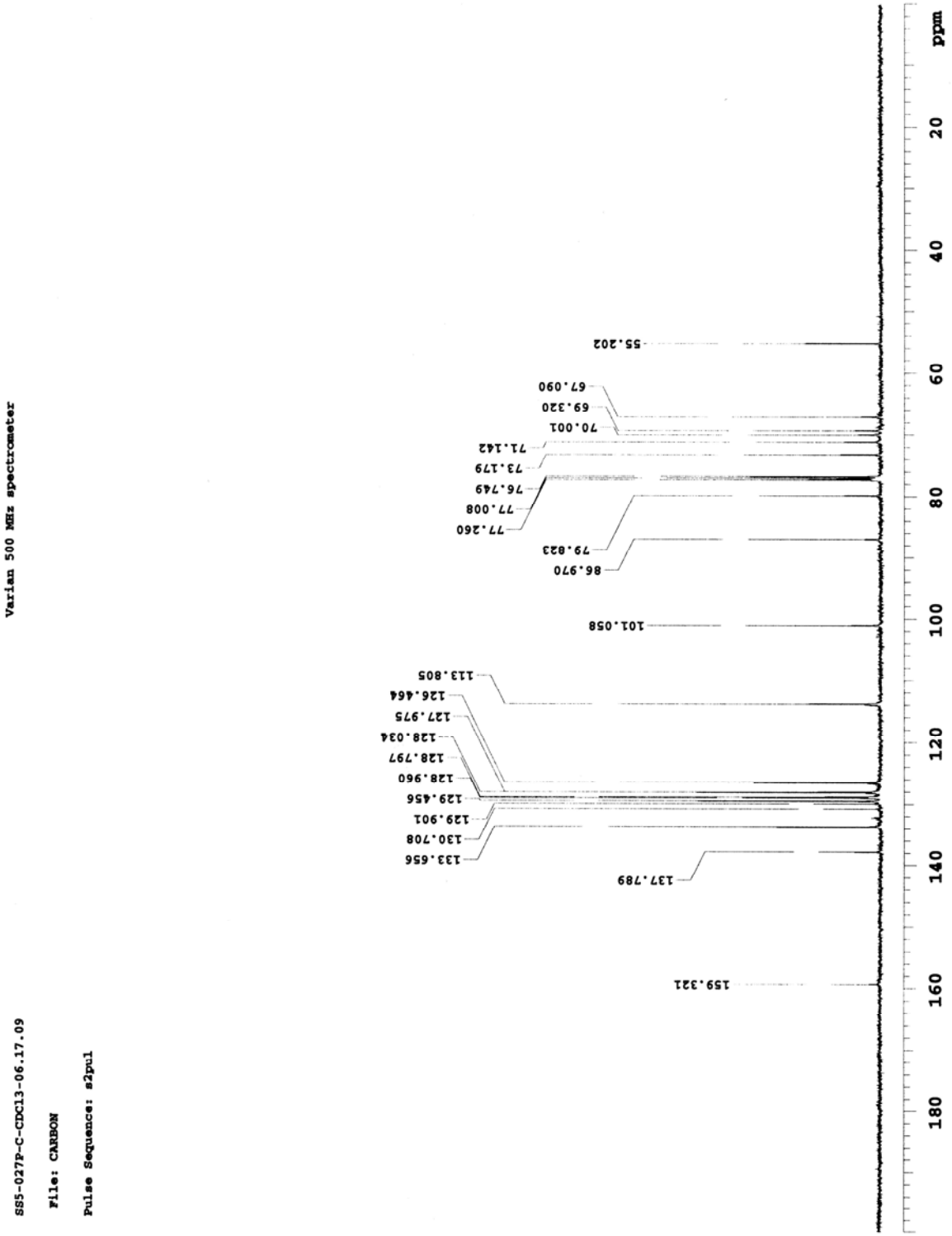
GHMBC NMR (CD_3OD, Compound 589)



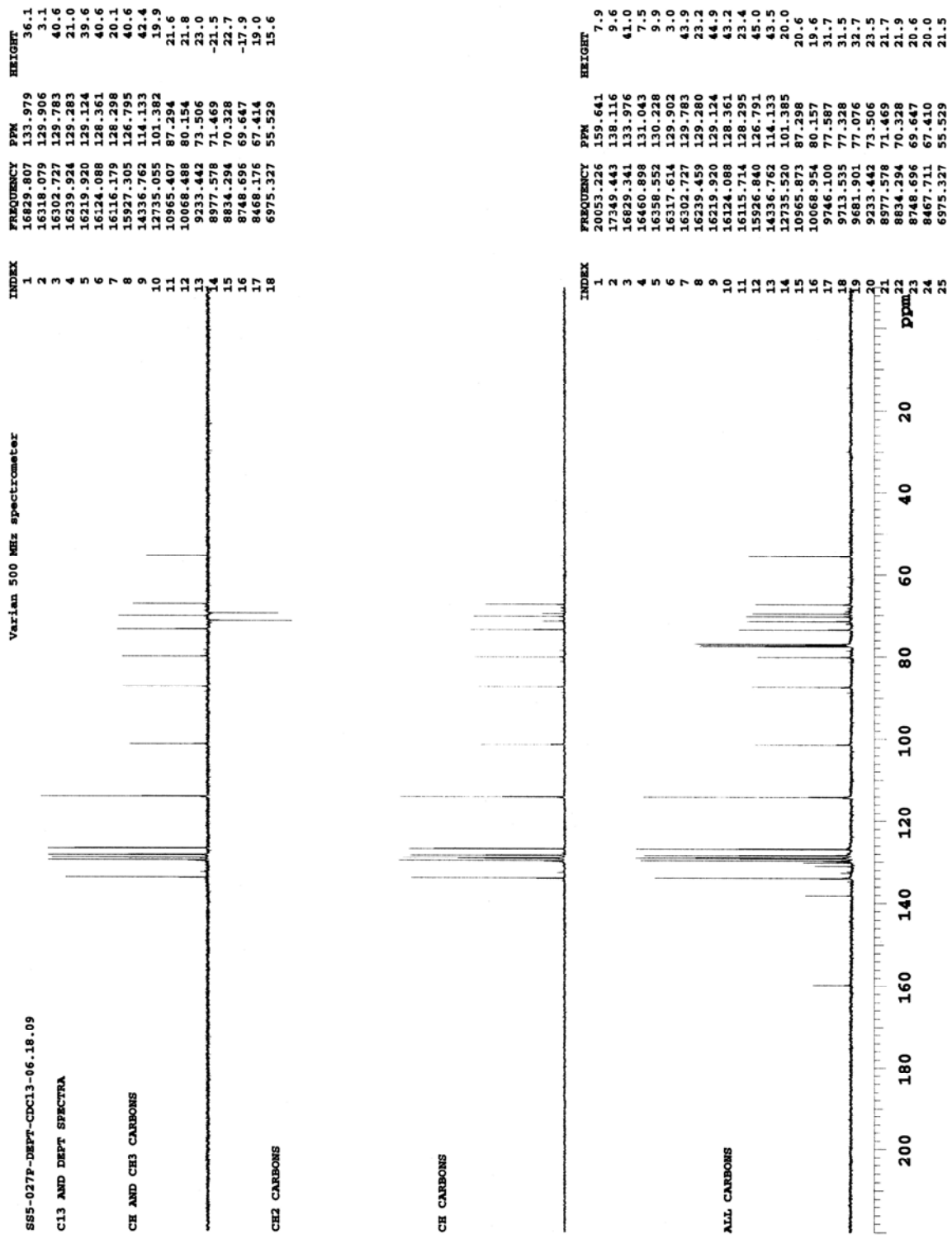
^{1}H NMR ((2R,4aR,6S,7R,8R,8aS)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol)



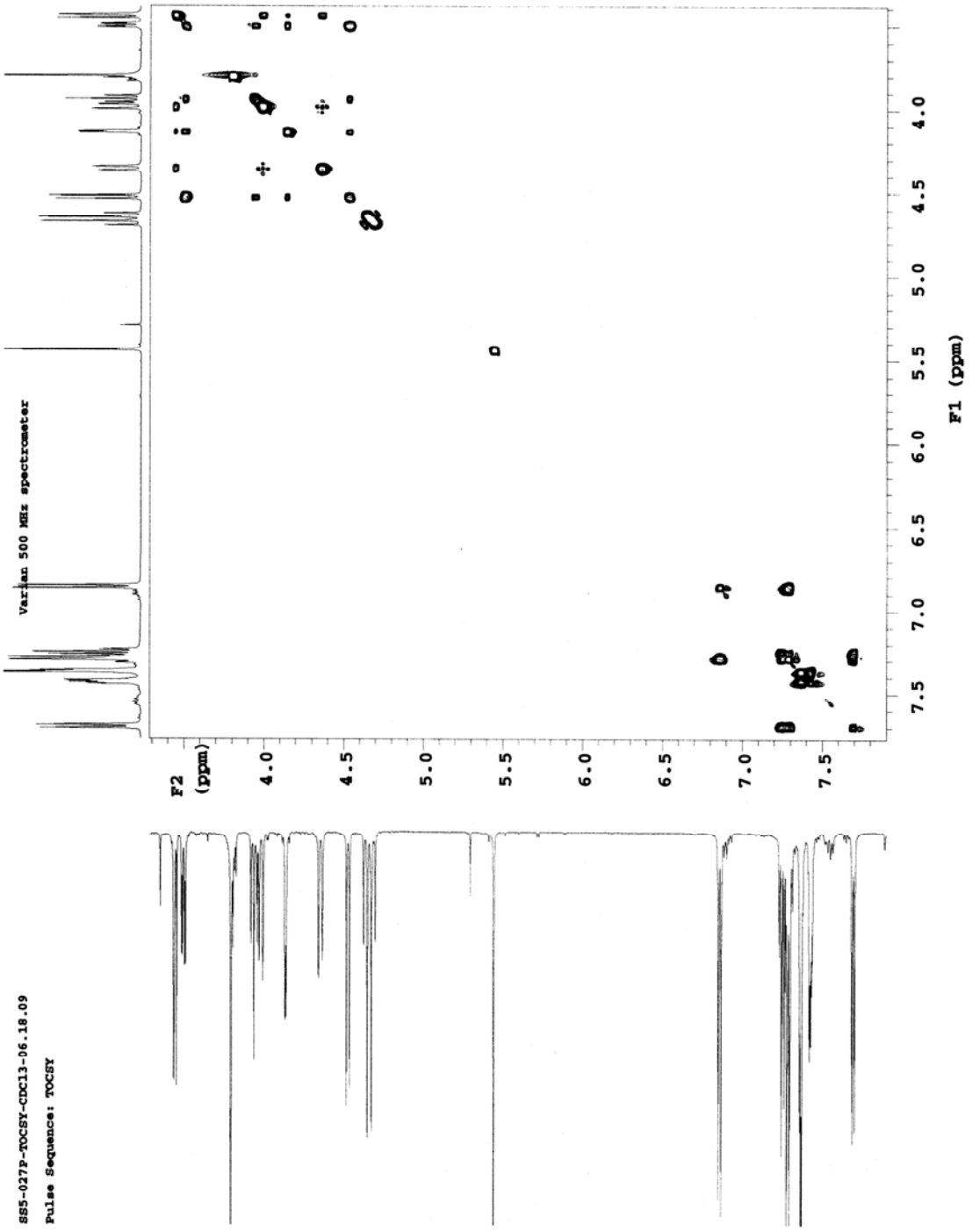
^{13}C NMR ((2R,4aR,6S,7R,8R,8aS)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol)



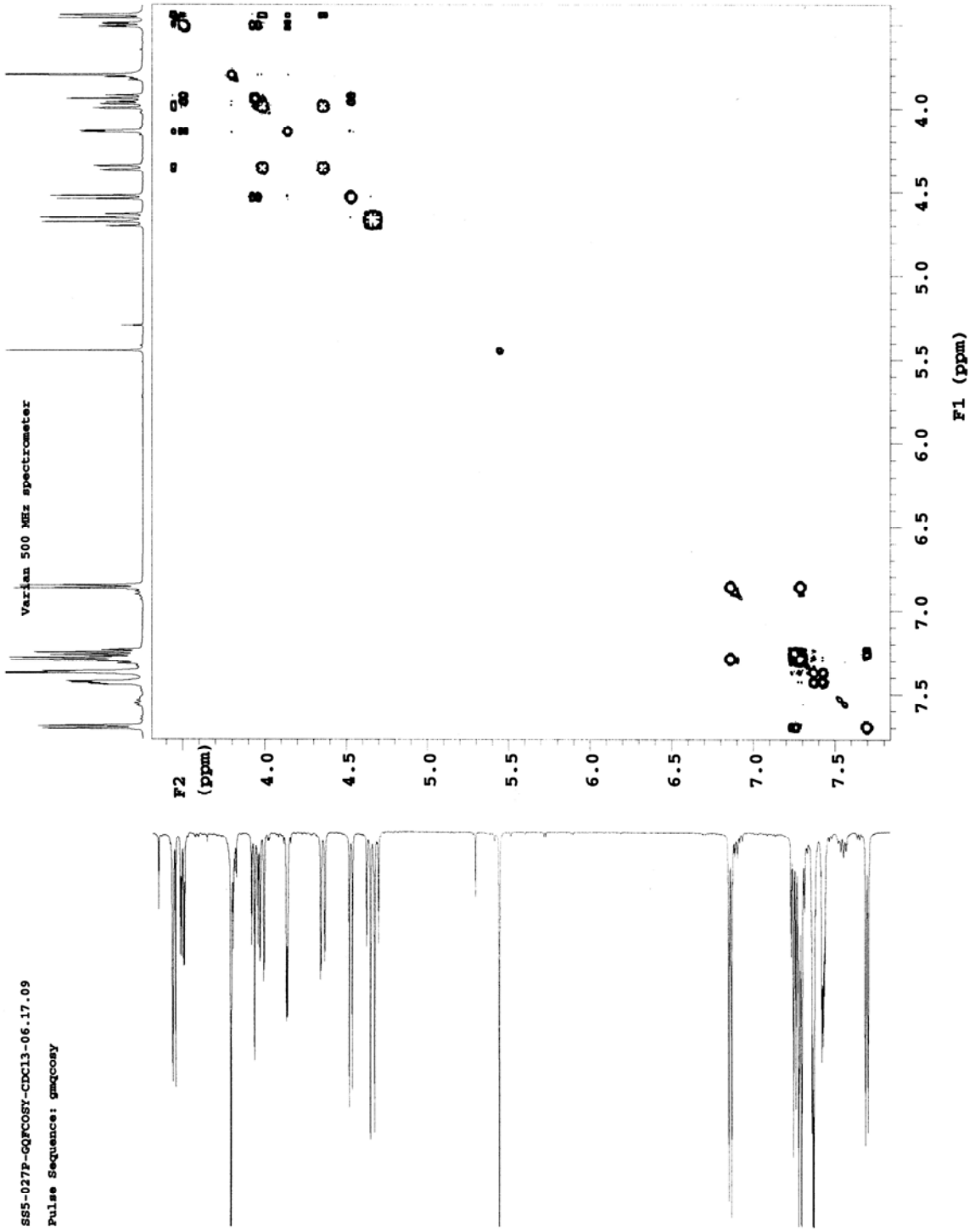
DEPT NMR ((2R,4aR,6S,7R,8R,8aS)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol)



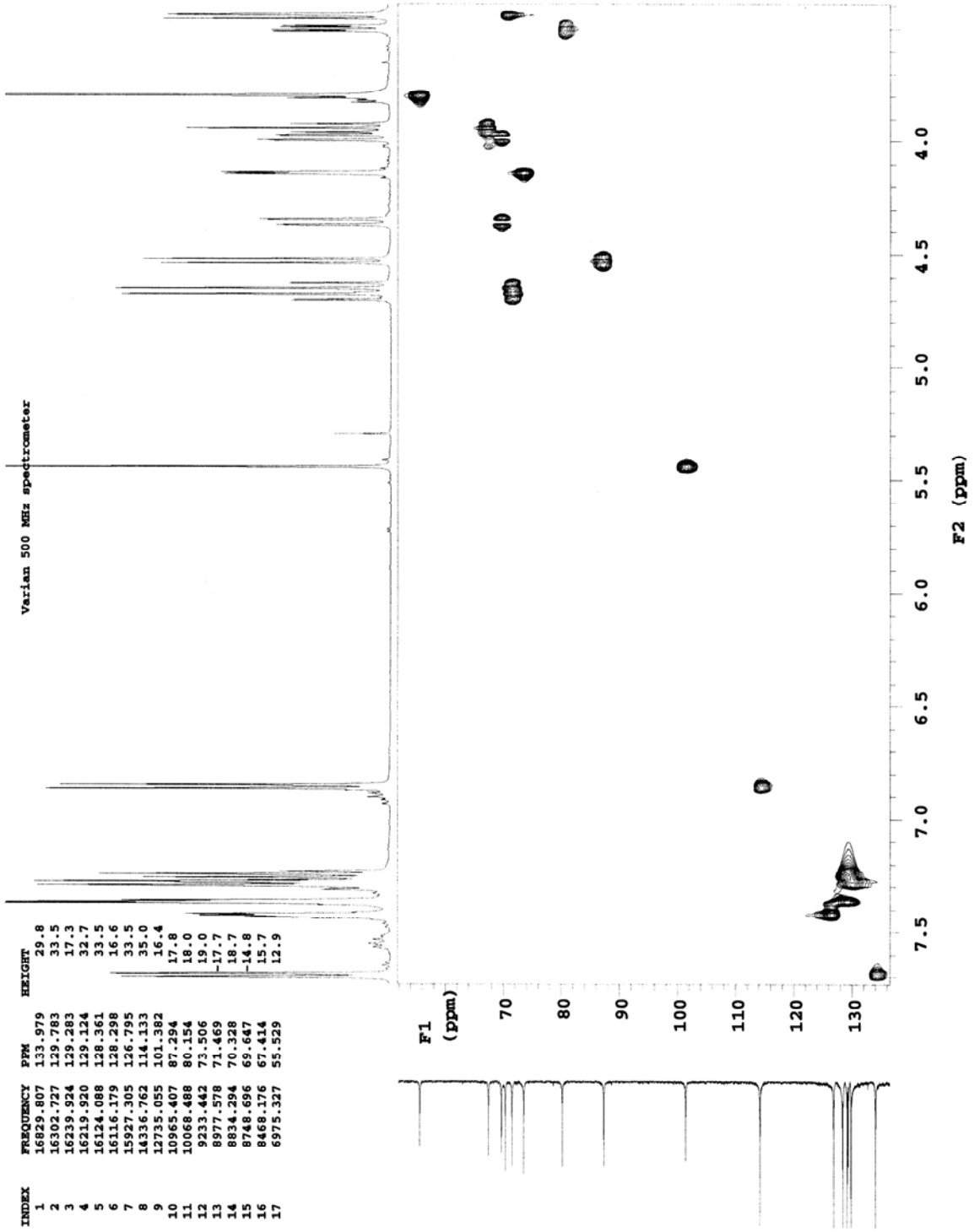
TOCSY NMR ((2R,4aR,6S,7R,8R,8aS)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol)



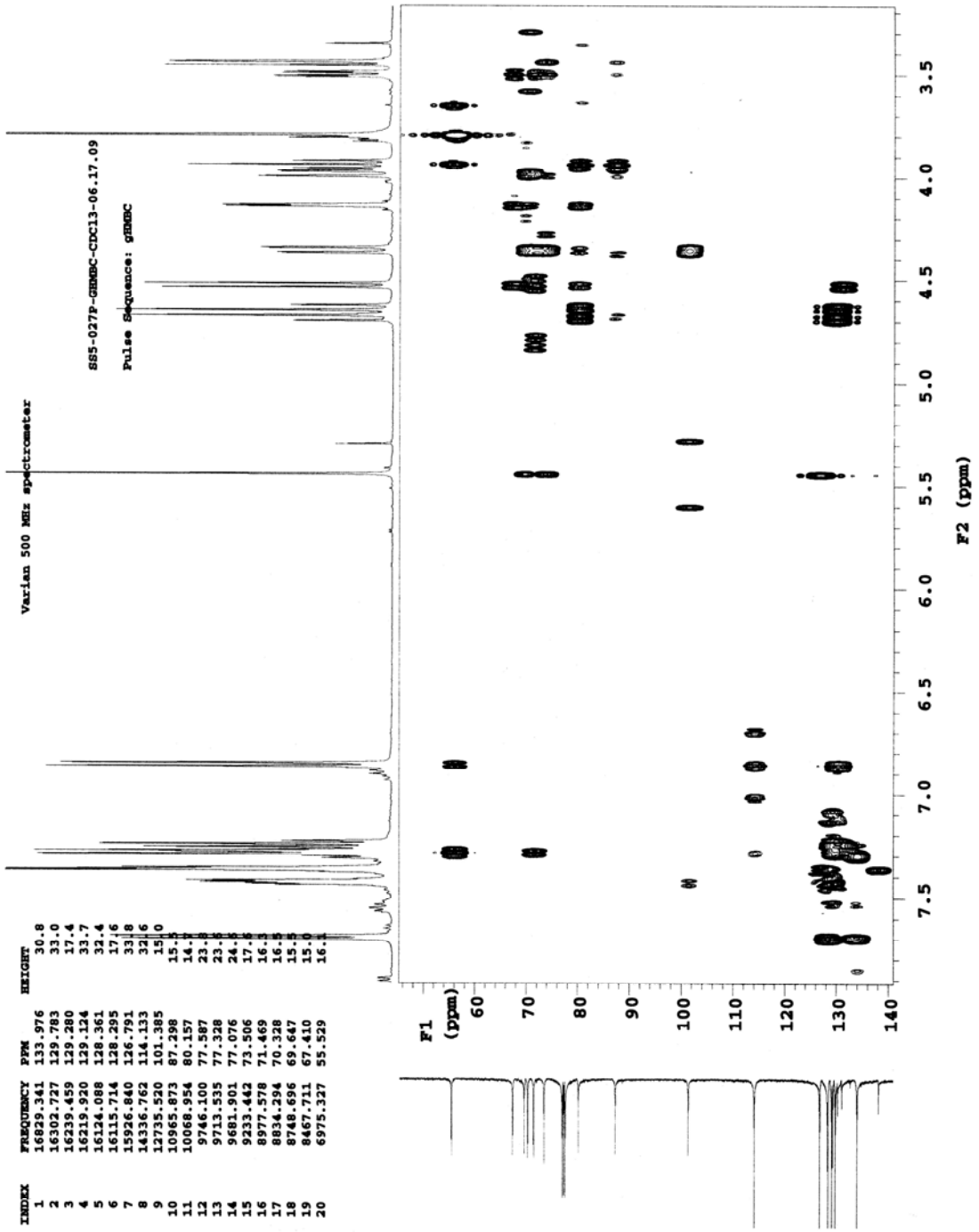
GDQFCOSY NMR ((2R,4aR,6S,7R,8R,8aS)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol)



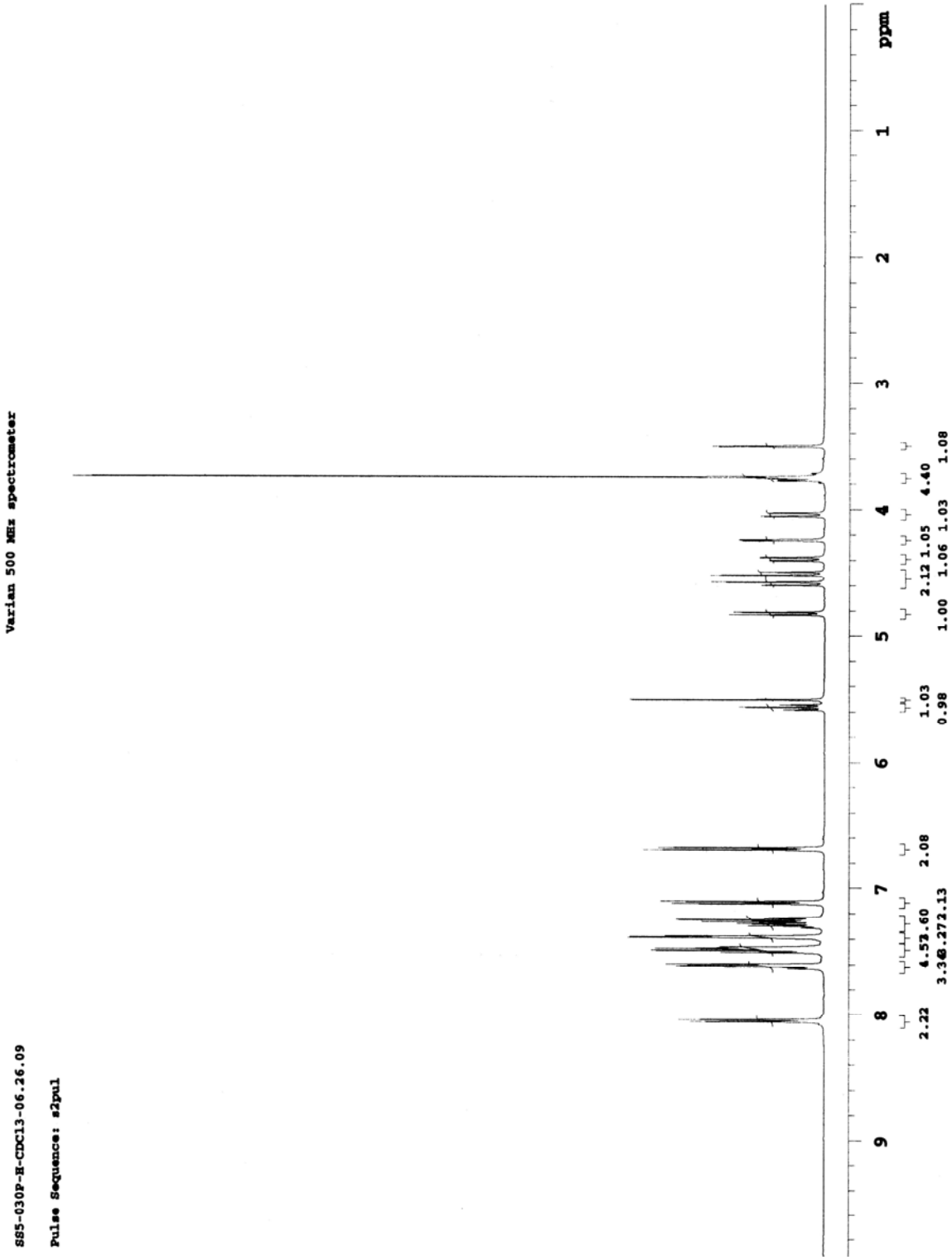
GHMQC NMR ((2R,4aR,6S,7R,8R,8aS)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol)



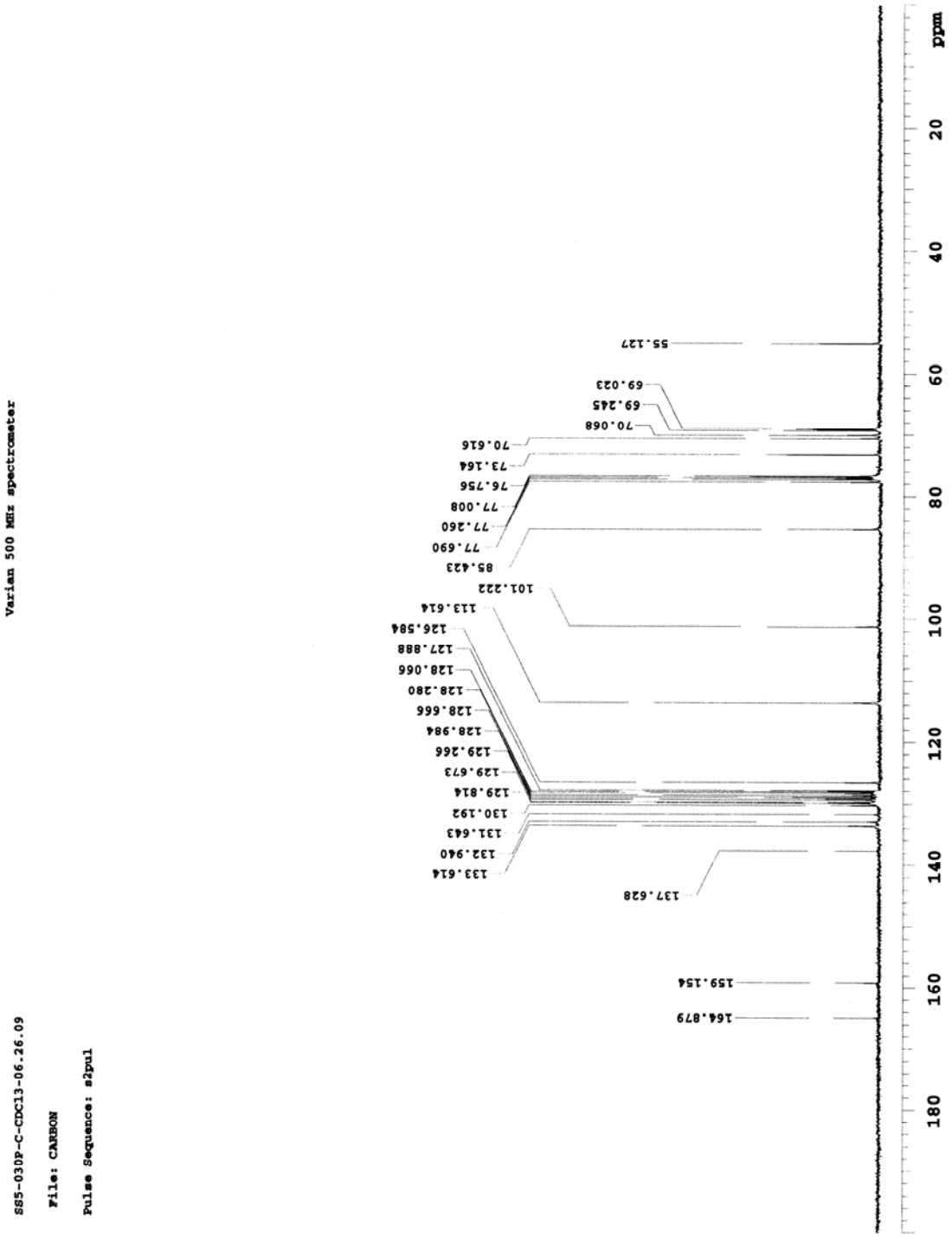
GHMBC NMR ((2R,4aR,6S,7R,8R,8aS)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol)



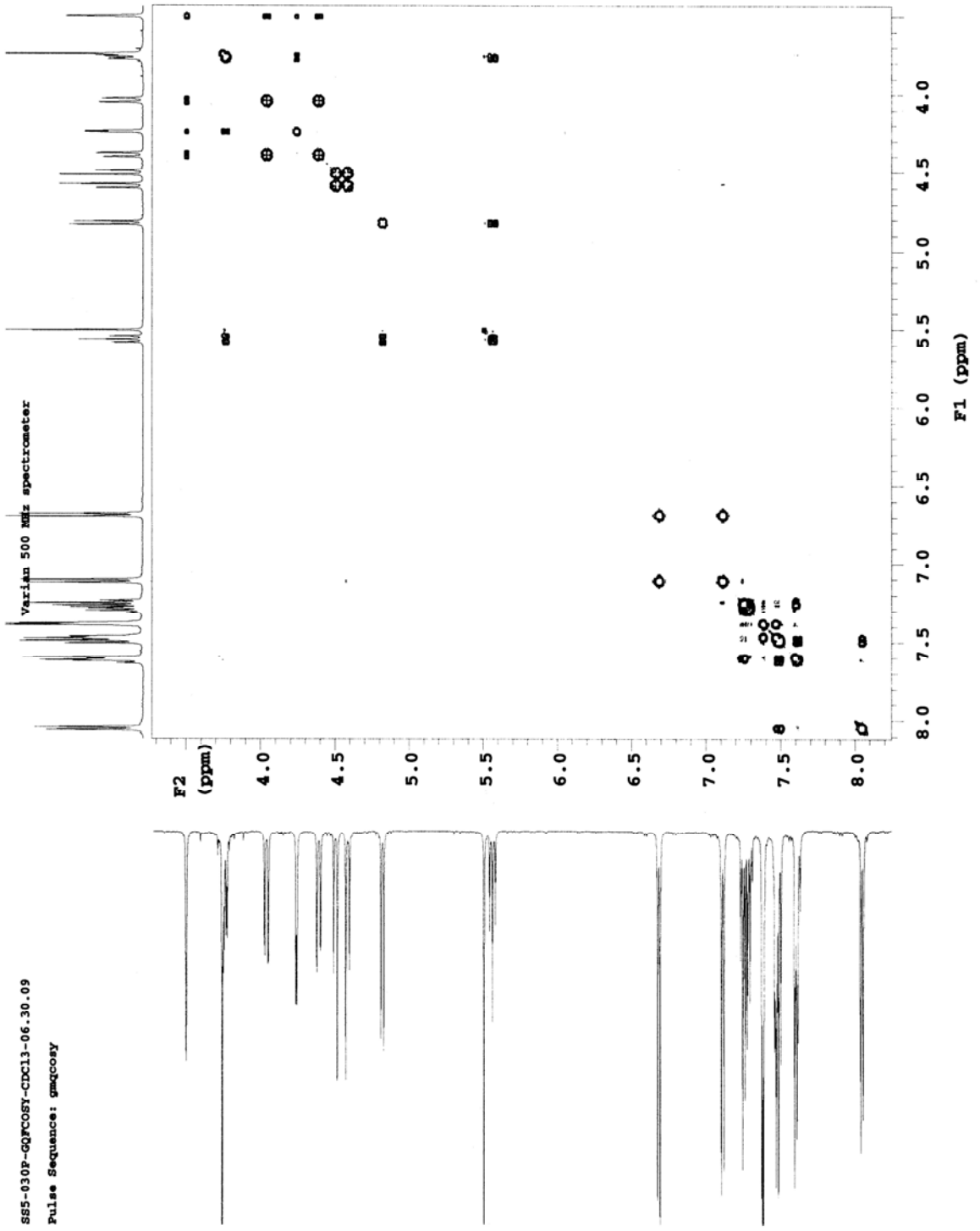
[1]H NMR (Compound 590)



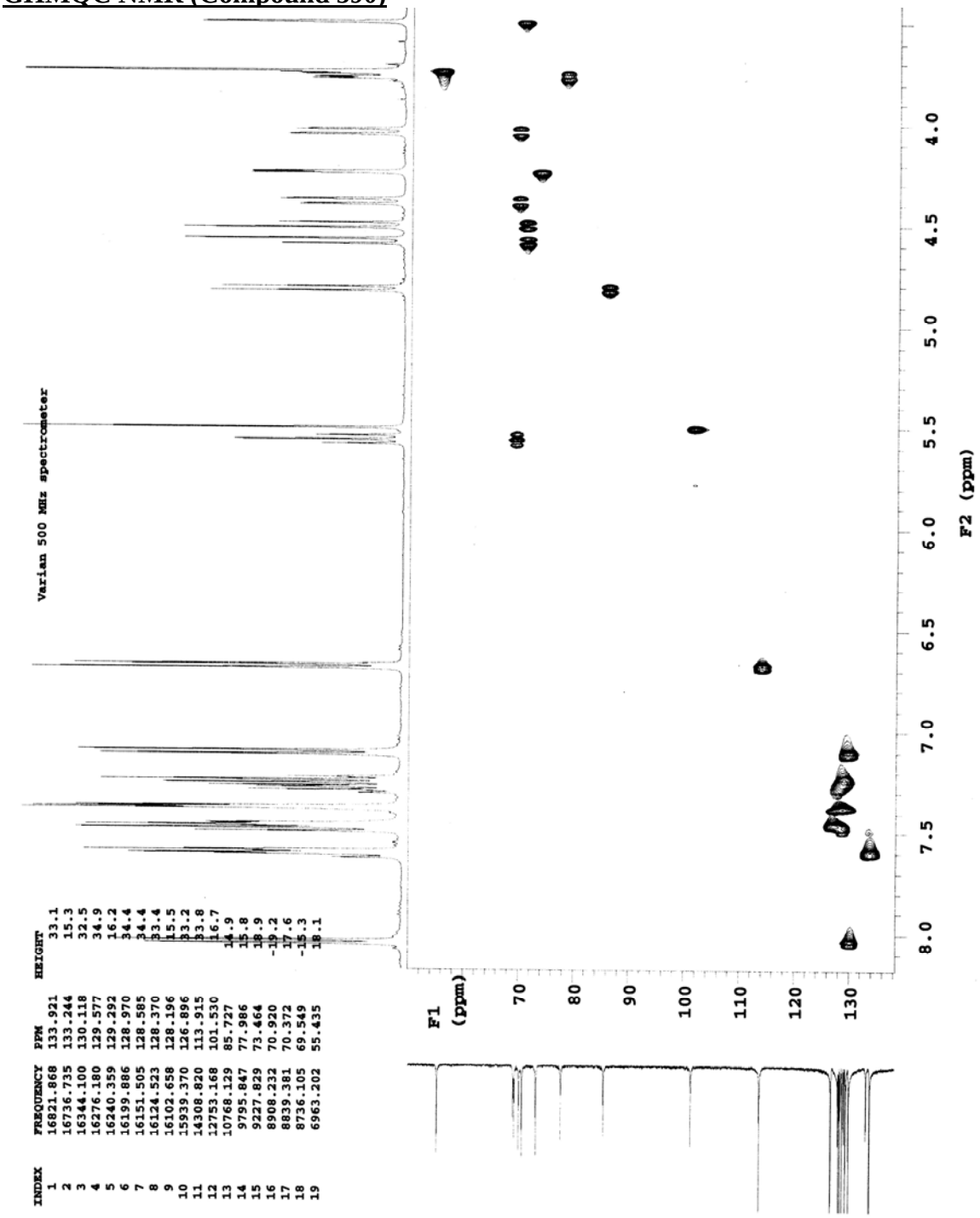
^{13}C NMR (Compound 590)



^{1}H-^{1}H GDQFCOSY NMR (Compound 590)

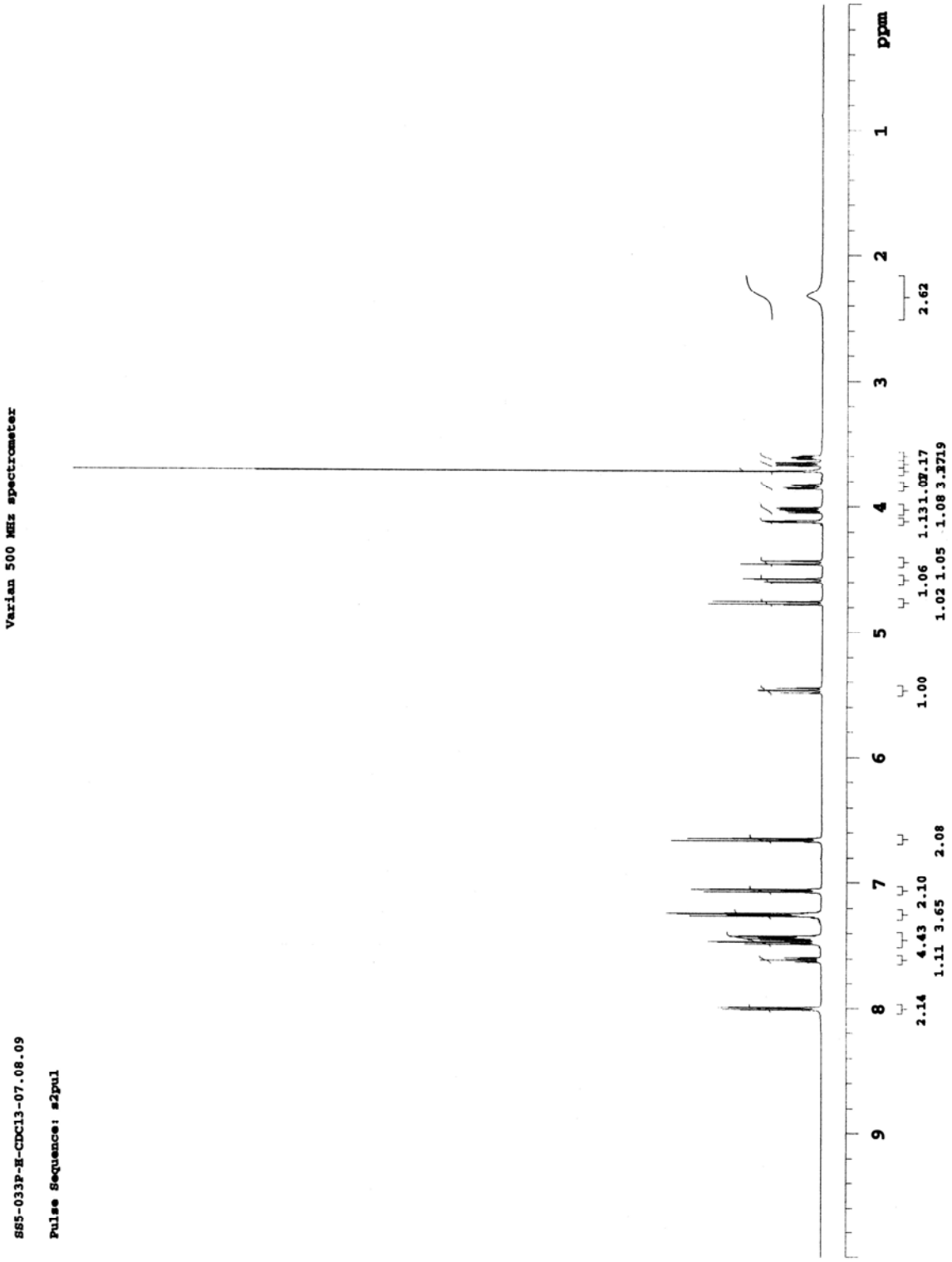


GHMQC NMR (Compound 590)

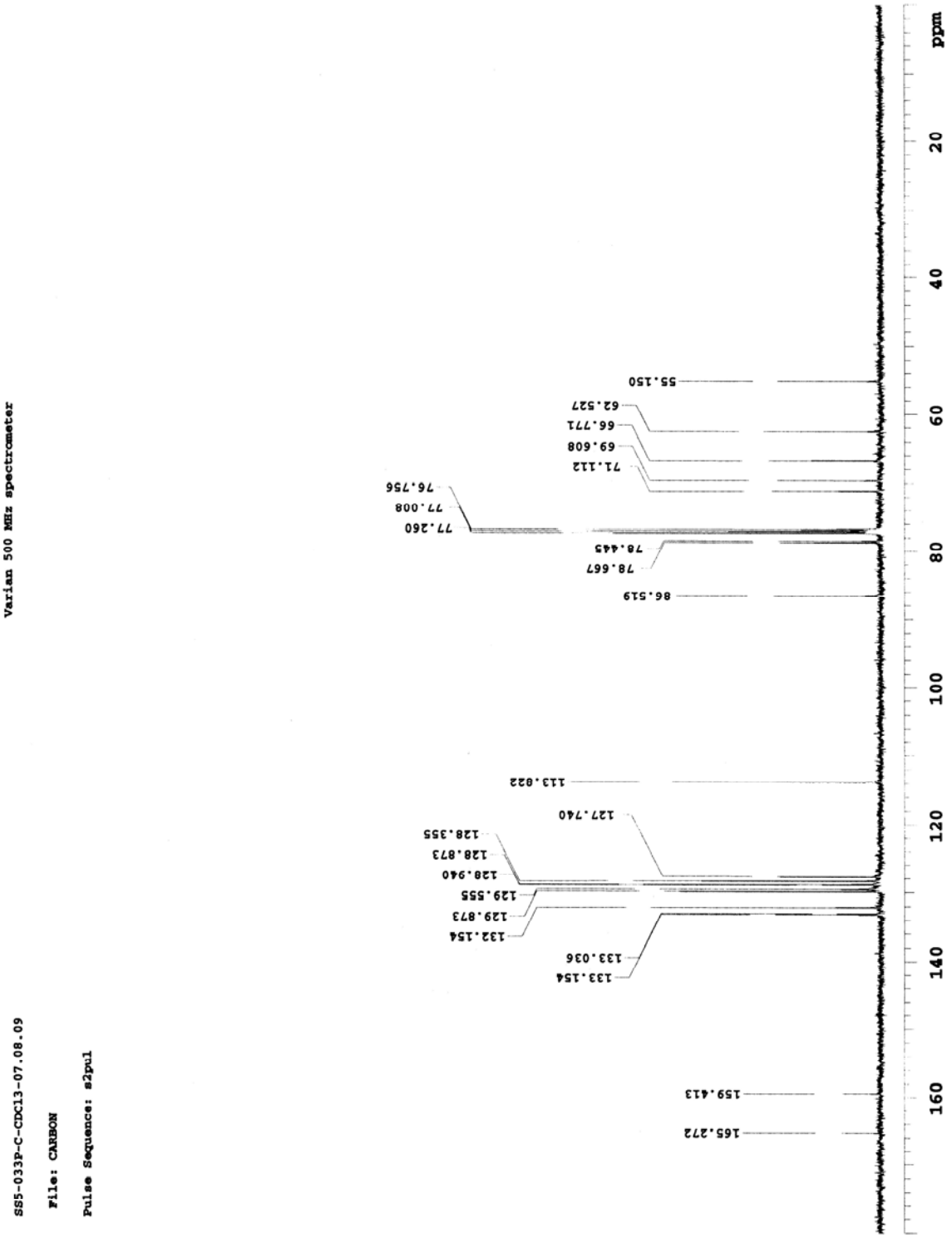


INDEX	FREQUENCY	PPM	HEIGHT
1	16821.868	133.921	33.1
2	16736.735	133.244	15.3
3	16344.100	130.118	32.5
4	16276.180	129.577	34.9
5	16240.359	129.292	16.2
6	16199.886	128.970	34.4
7	16151.505	128.585	34.4
8	16124.523	128.370	33.4
9	16102.658	128.196	15.5
10	15939.370	126.896	33.2
11	14308.820	113.915	33.8
12	12753.168	101.530	16.7
13	10768.129	85.727	14.9
14	9795.847	77.986	15.8
15	9227.829	73.464	18.9
16	8908.232	70.920	-19.2
17	8839.381	70.372	17.6
18	8736.105	69.549	-15.3
19	6963.202	55.435	18.1

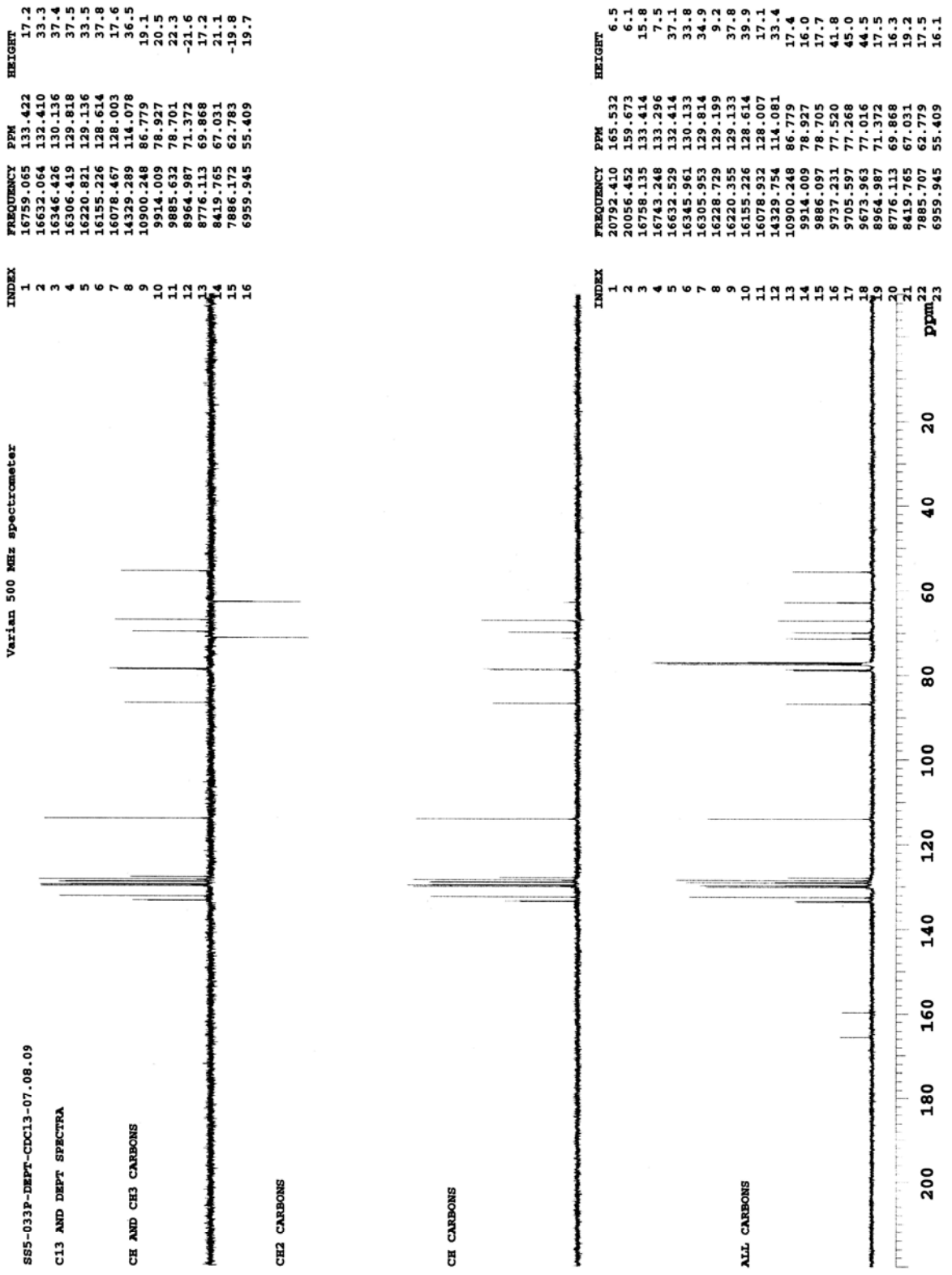
[1]H NMR (Compound 591)



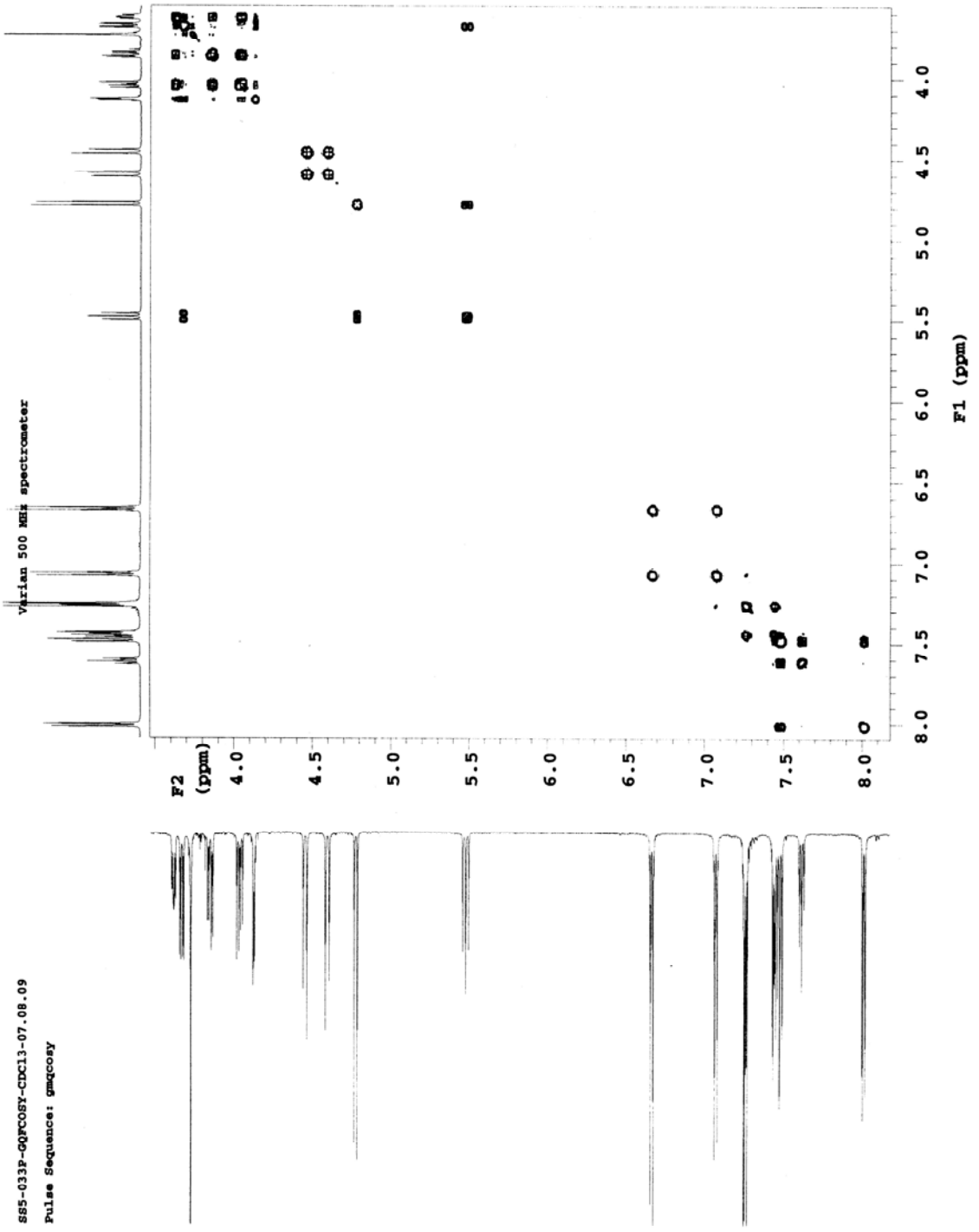
^{13}C NMR (Compound 591)



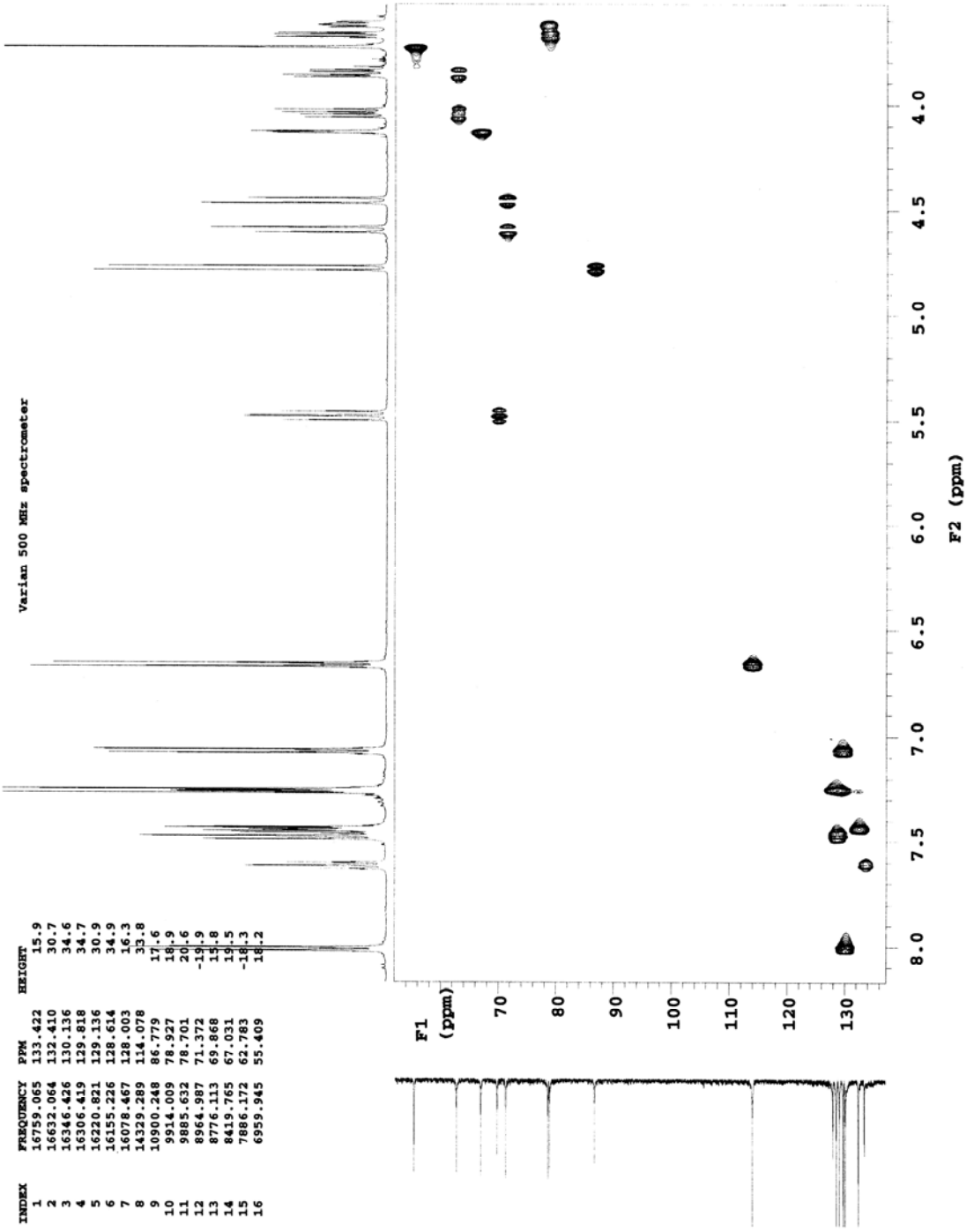
DEPT NMR (Compound 591)



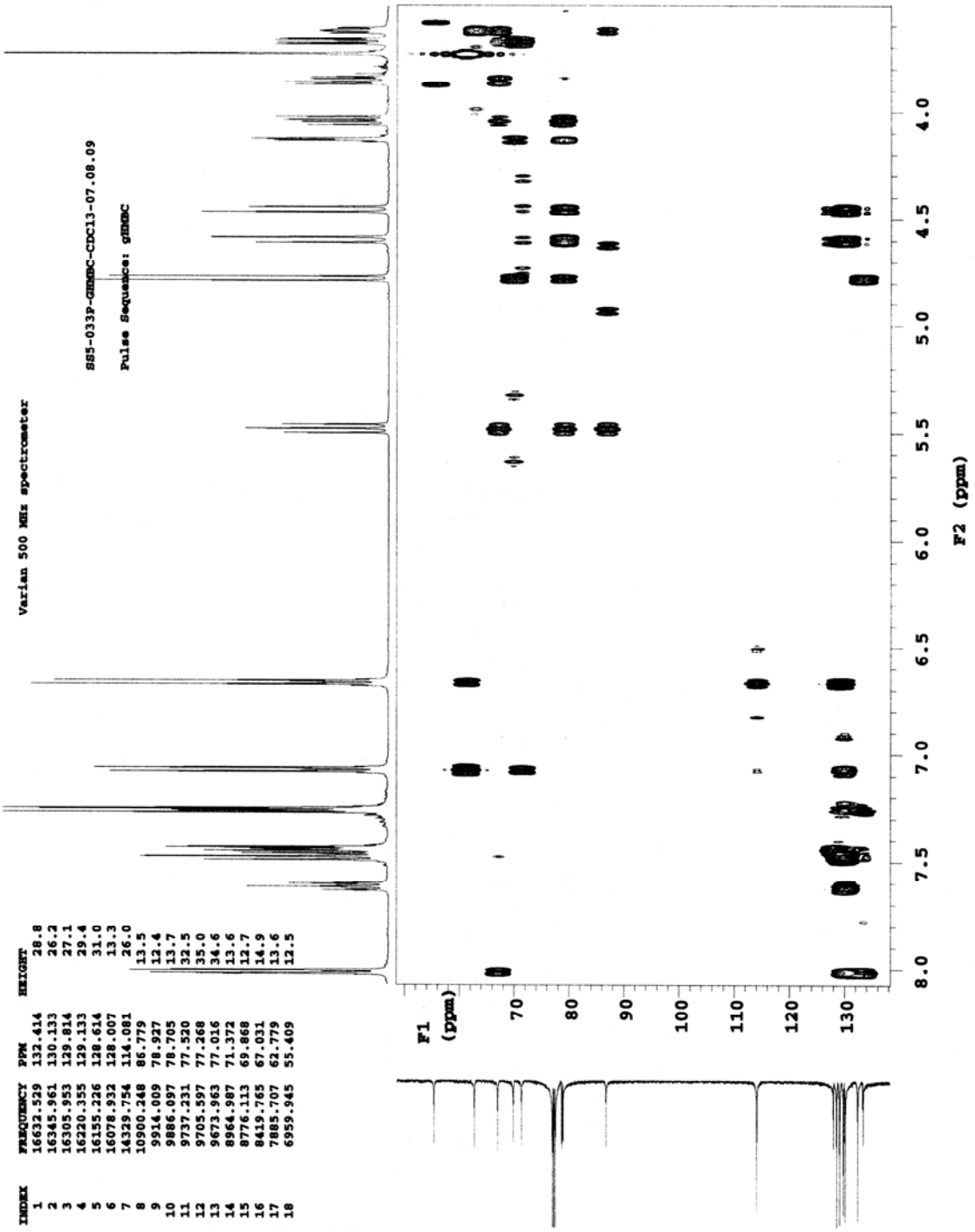
^{1}H-^{1}H GDQFCOSY NMR (Compound 591)



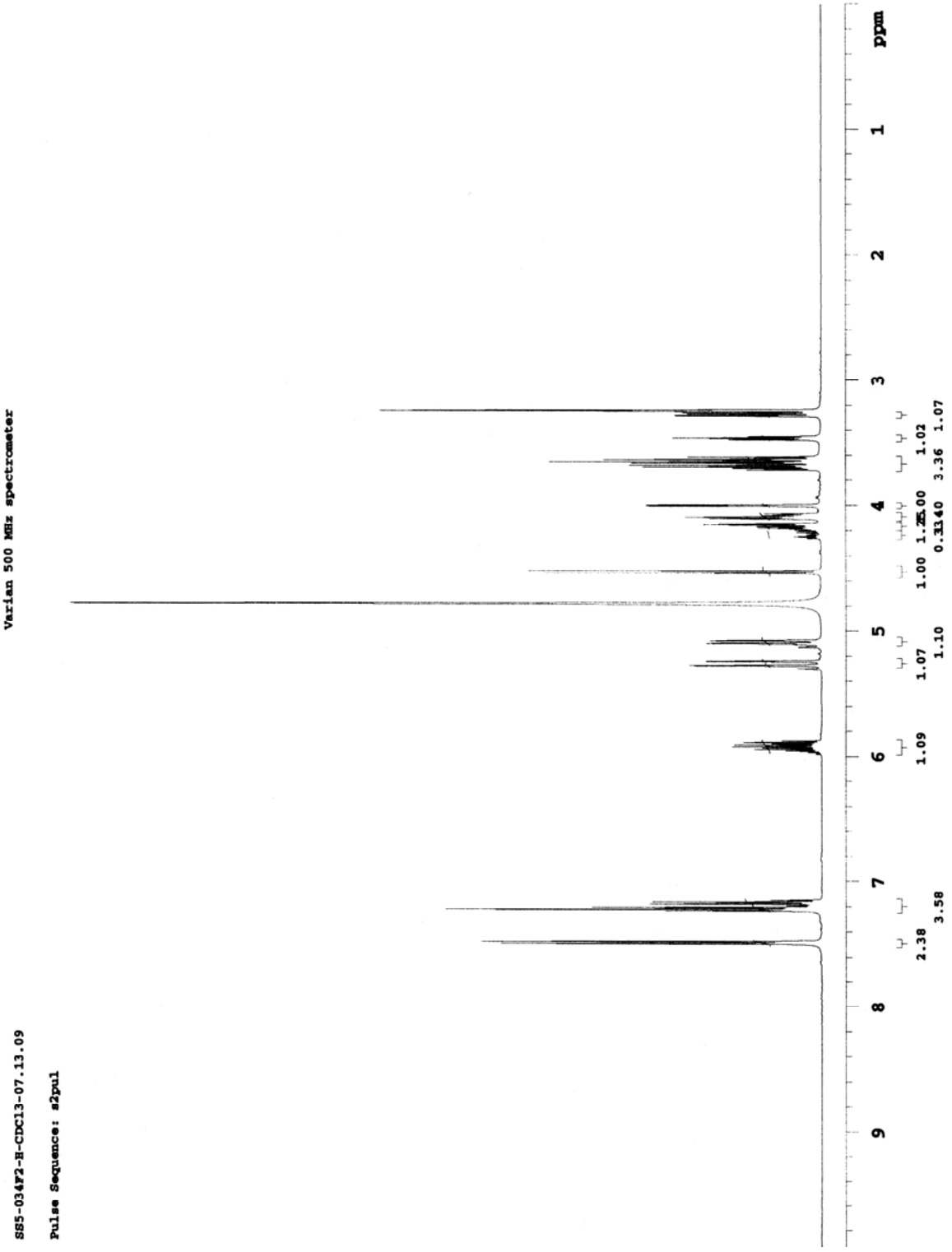
GHMQC NMR (Compound 591)



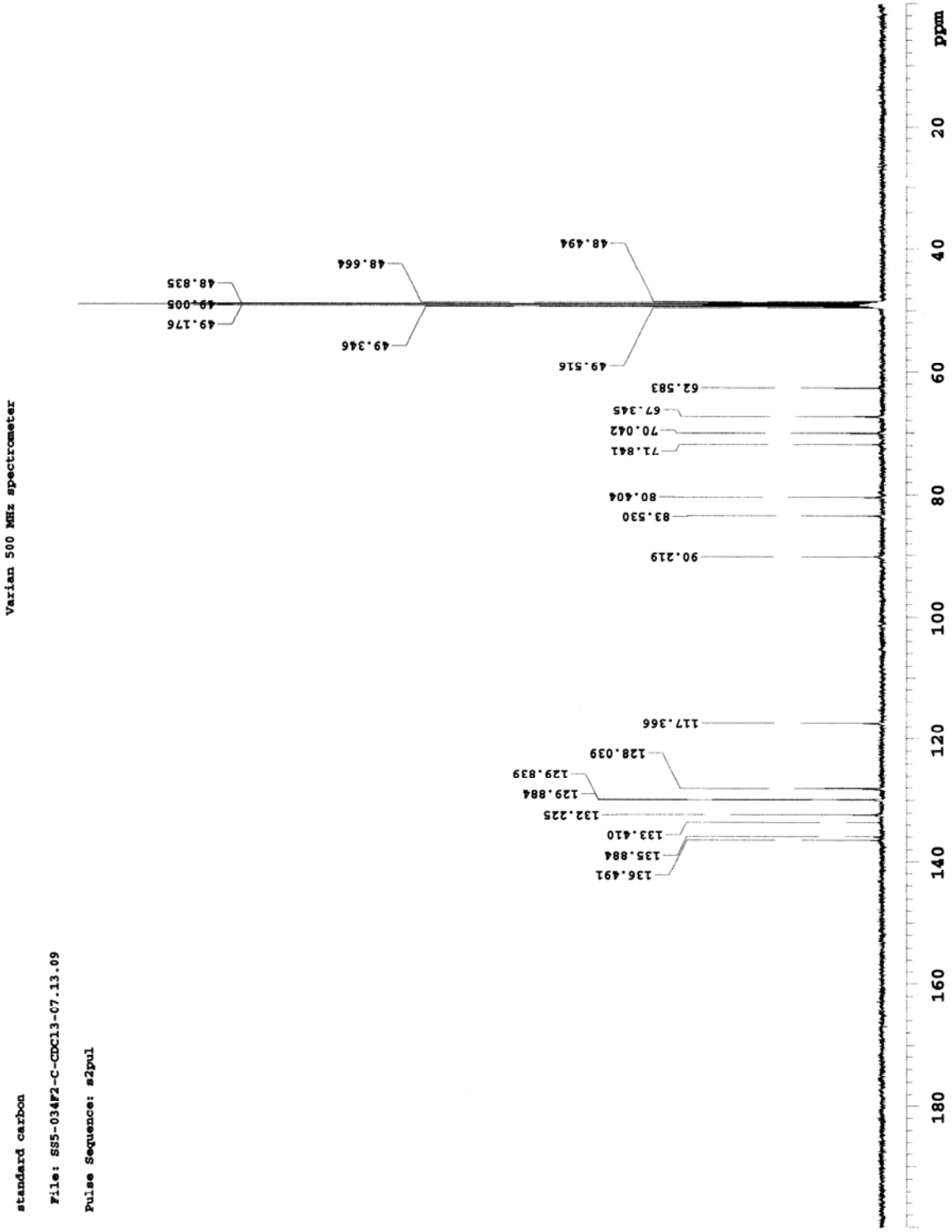
GHMBC NMR (Compound 591)



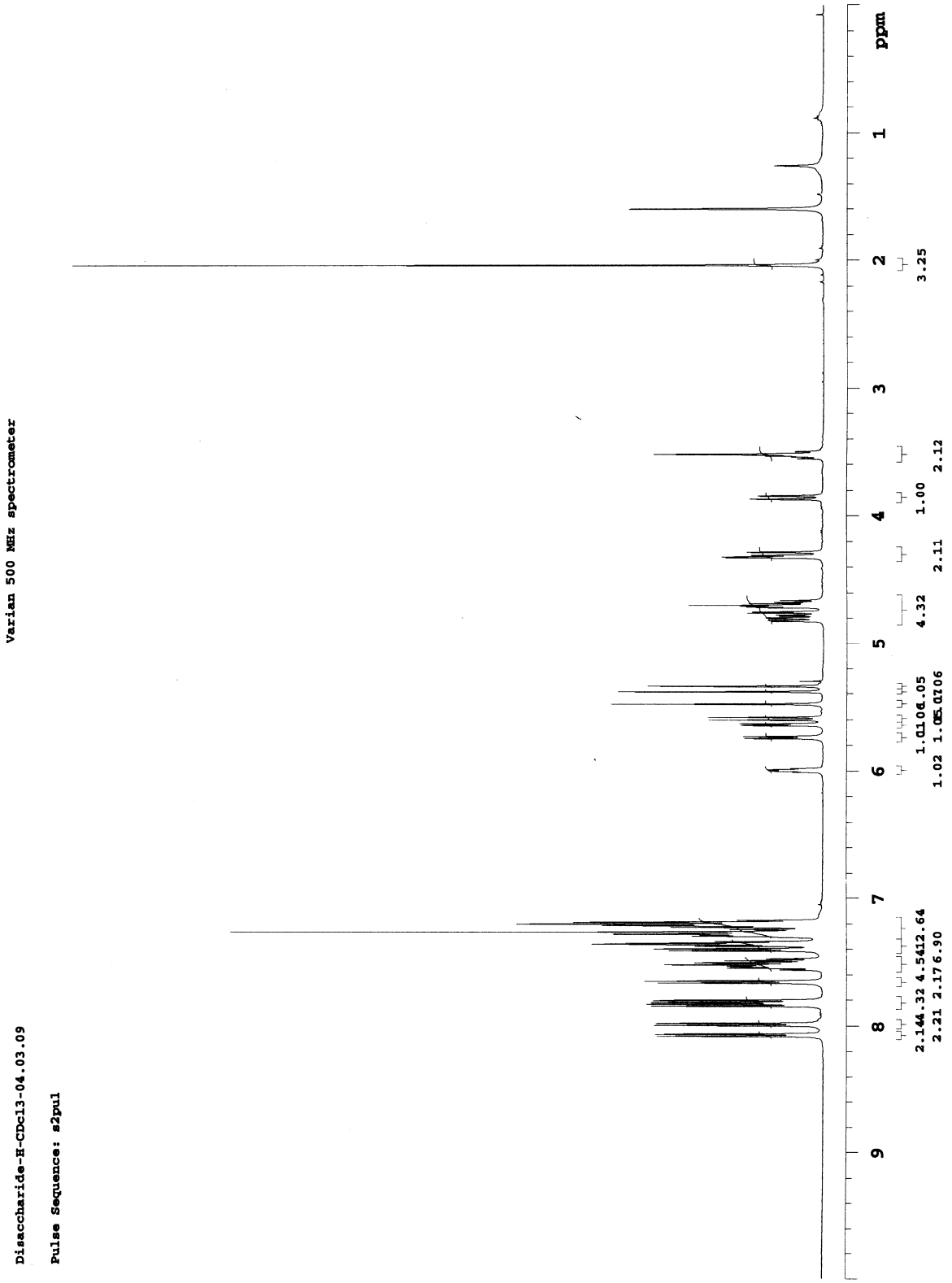
[1]H NMR (Compound 593)



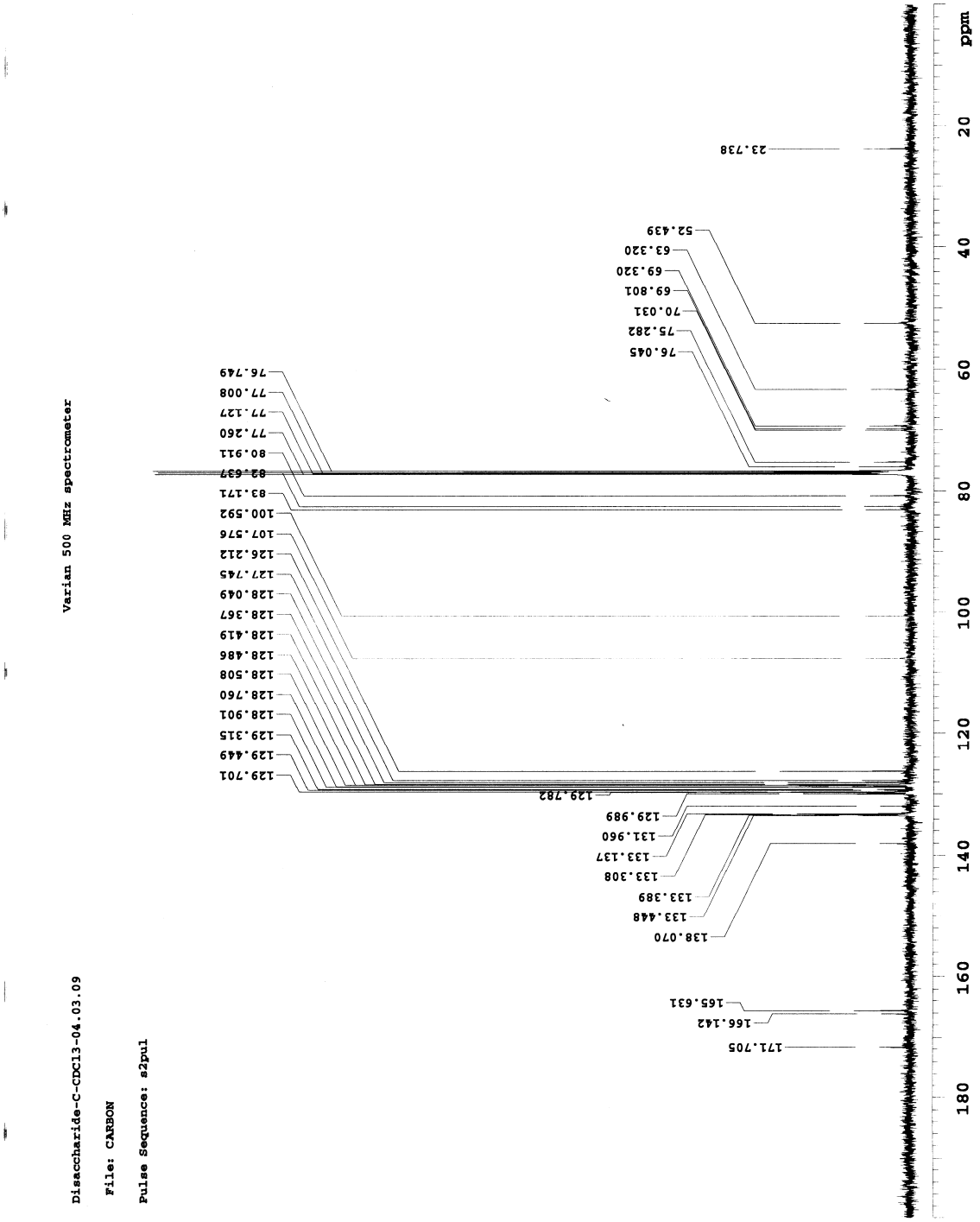
^{13}C NMR (Compound 593)



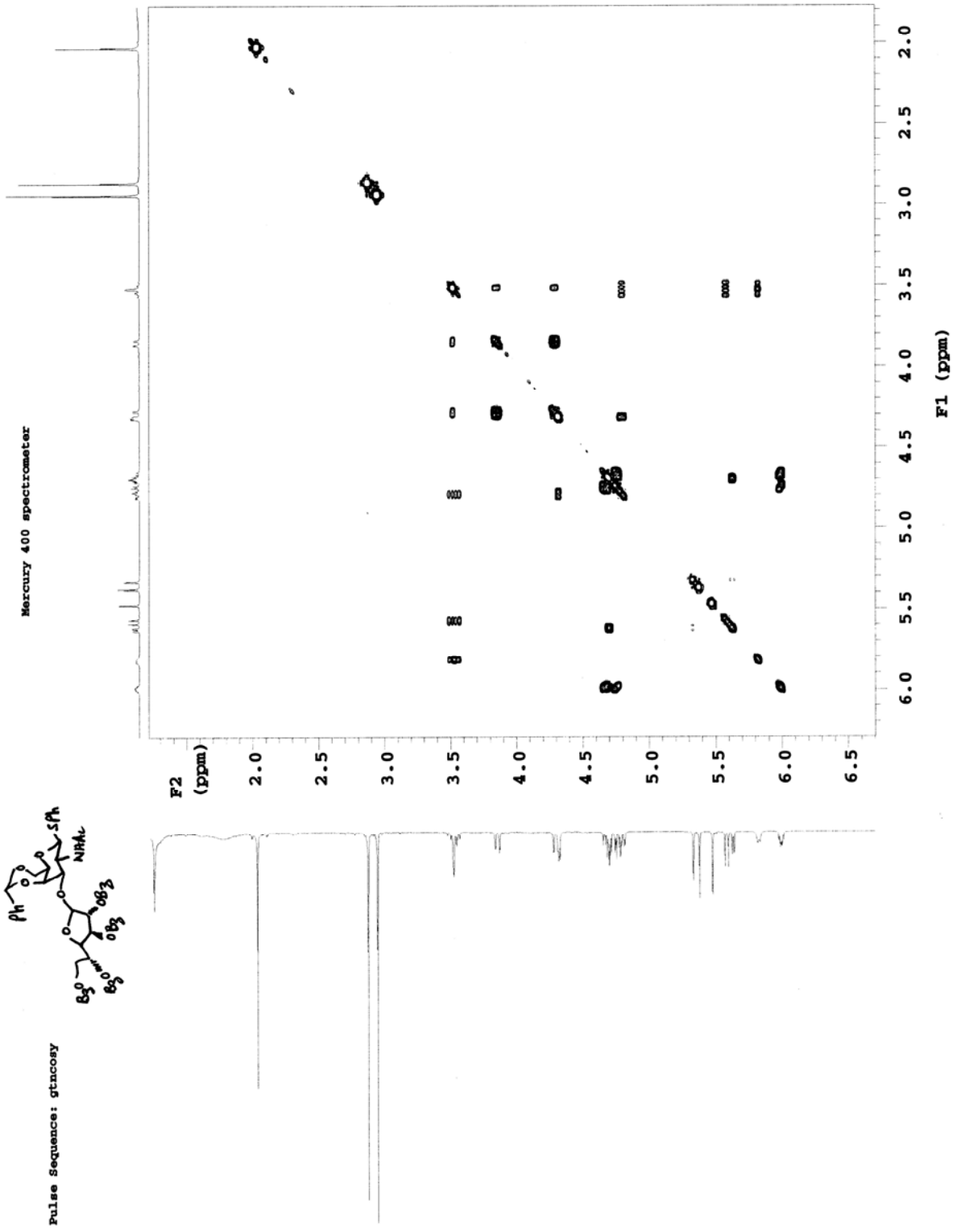
^{1}H NMR (Compound 598)



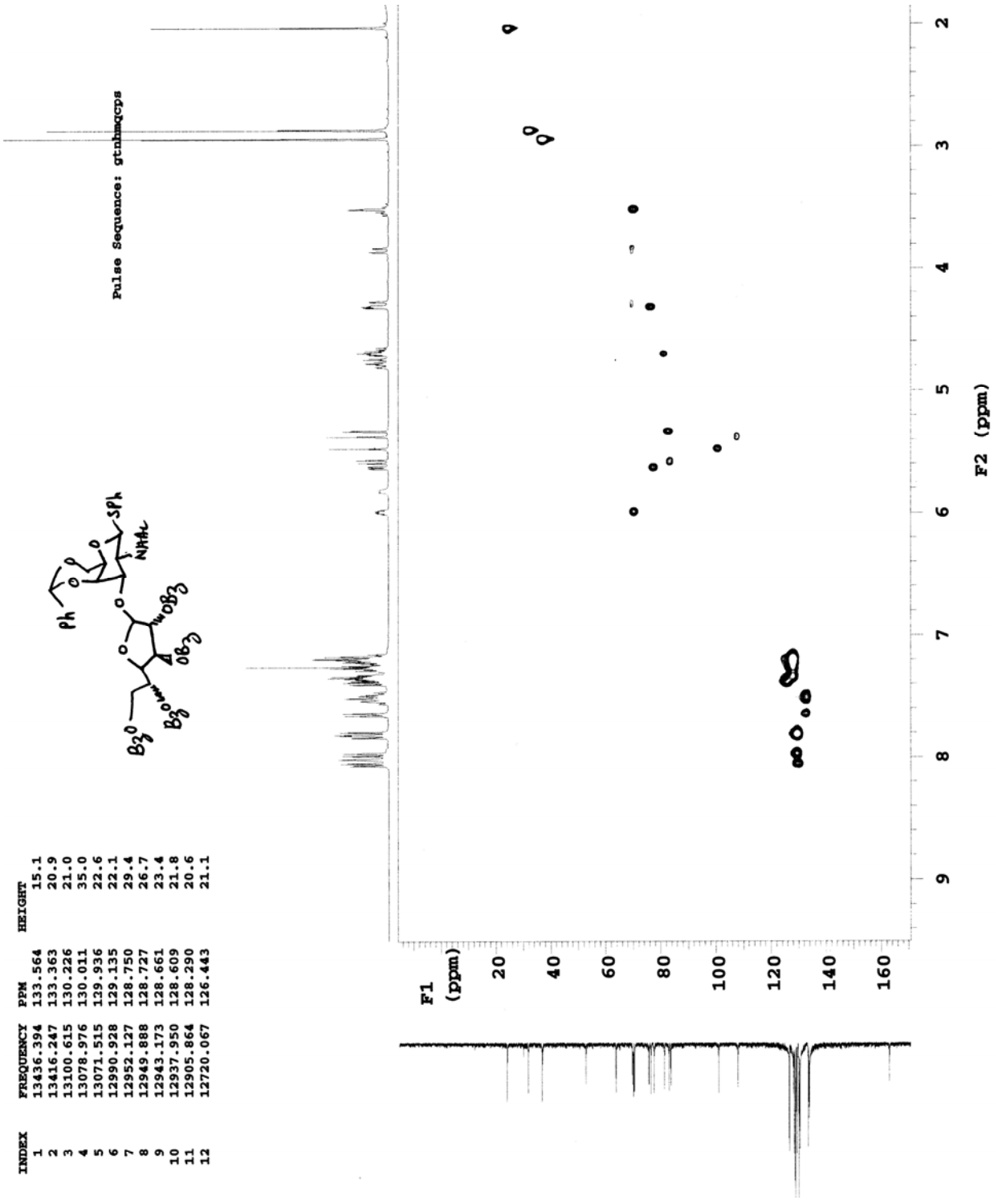
^{13}C NMR (Compound 598)



^{1}H-^{1}H GDQFCOSY NMR (Compound 598)

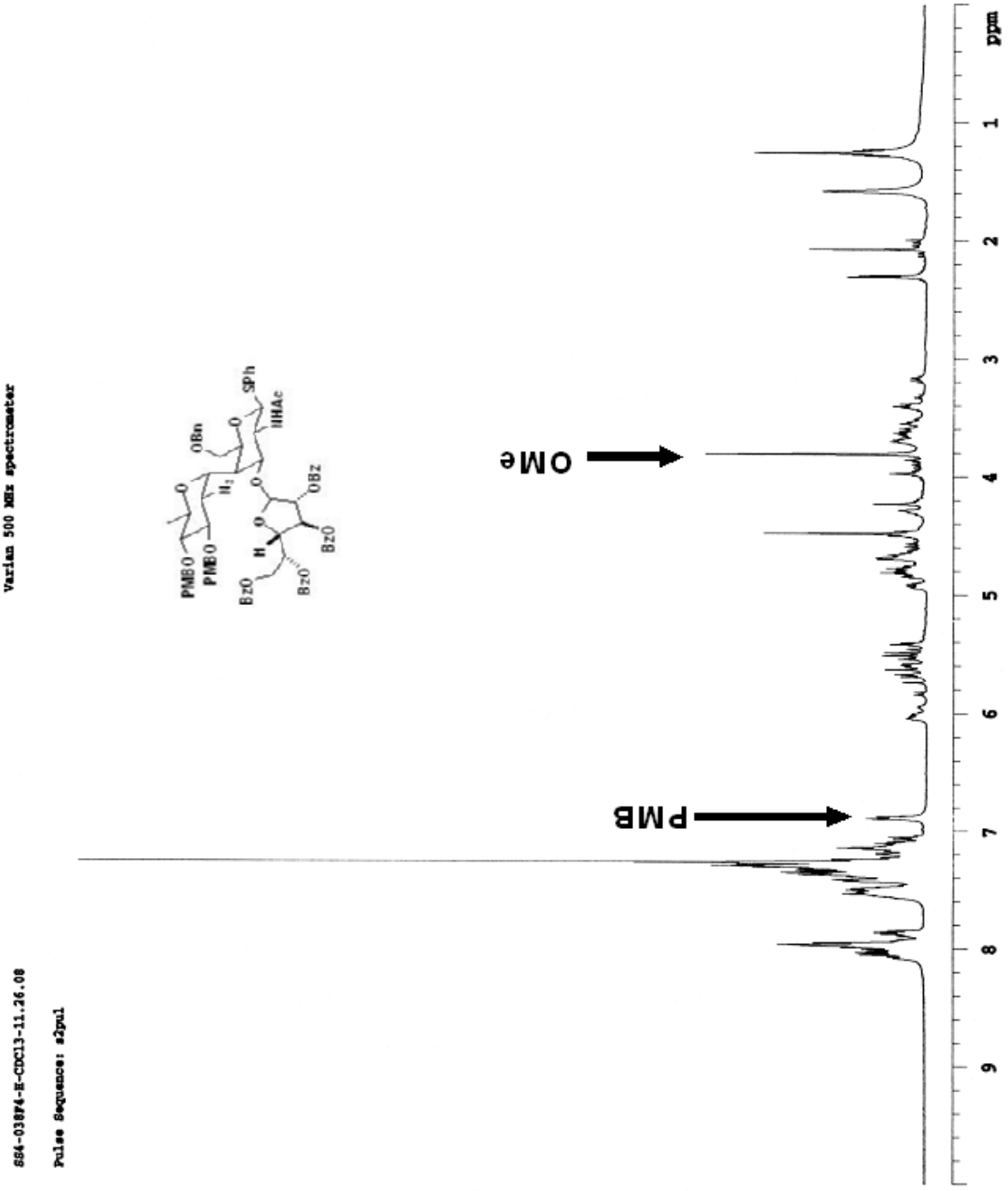


GHMQC NMR (Compound 598)

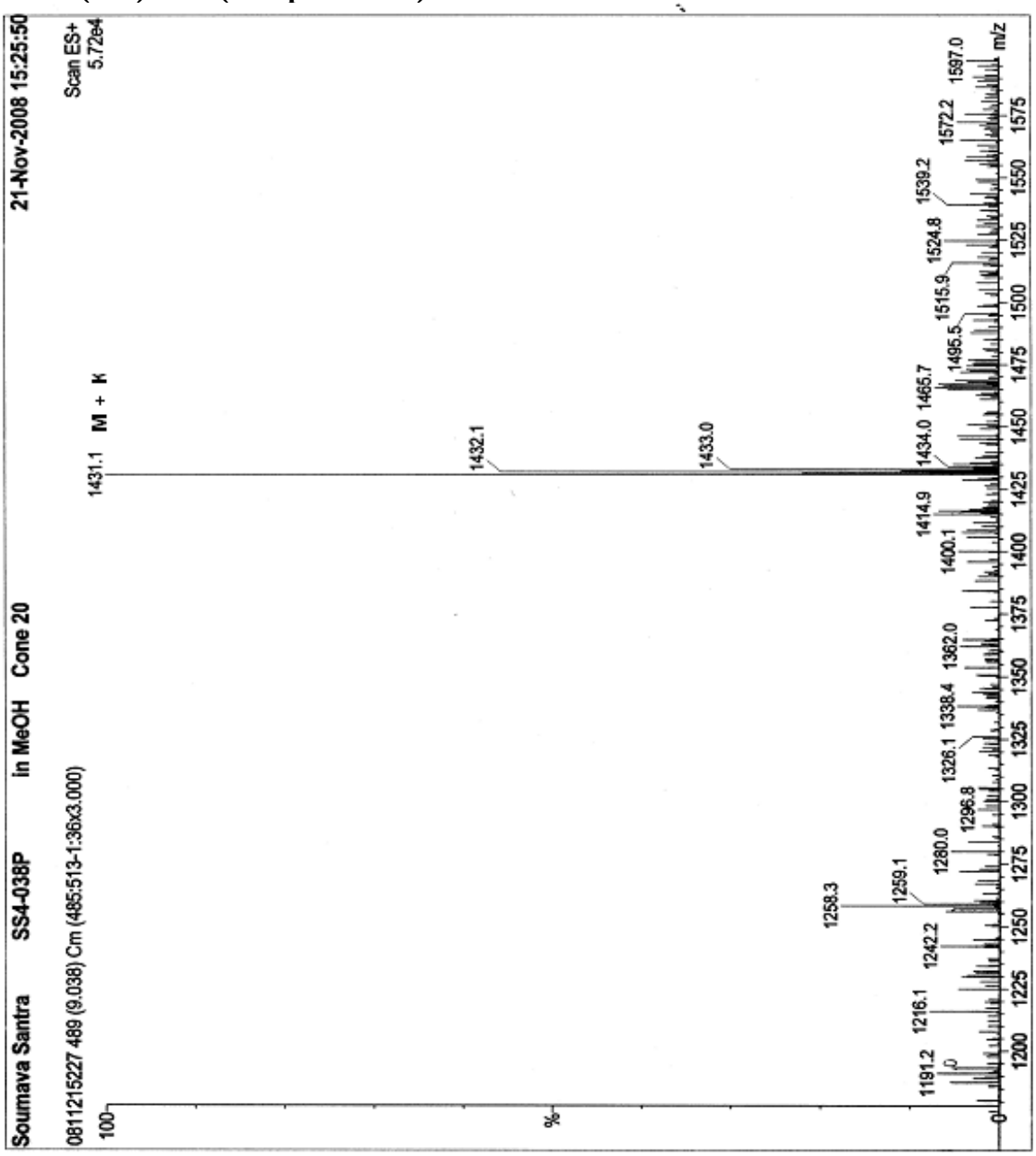


INDEX	FREQUENCY	PPM	HEIGHT
1	13436.394	133.564	15.1
2	13416.247	133.363	20.9
3	13100.615	130.226	21.0
4	13078.976	130.011	35.0
5	13071.515	129.936	22.6
6	12990.928	129.135	22.1
7	12952.127	128.750	29.4
8	12949.888	128.727	26.7
9	12943.173	128.661	23.4
10	12937.950	128.609	21.8
11	12905.864	128.290	20.6
12	12720.067	126.443	21.1

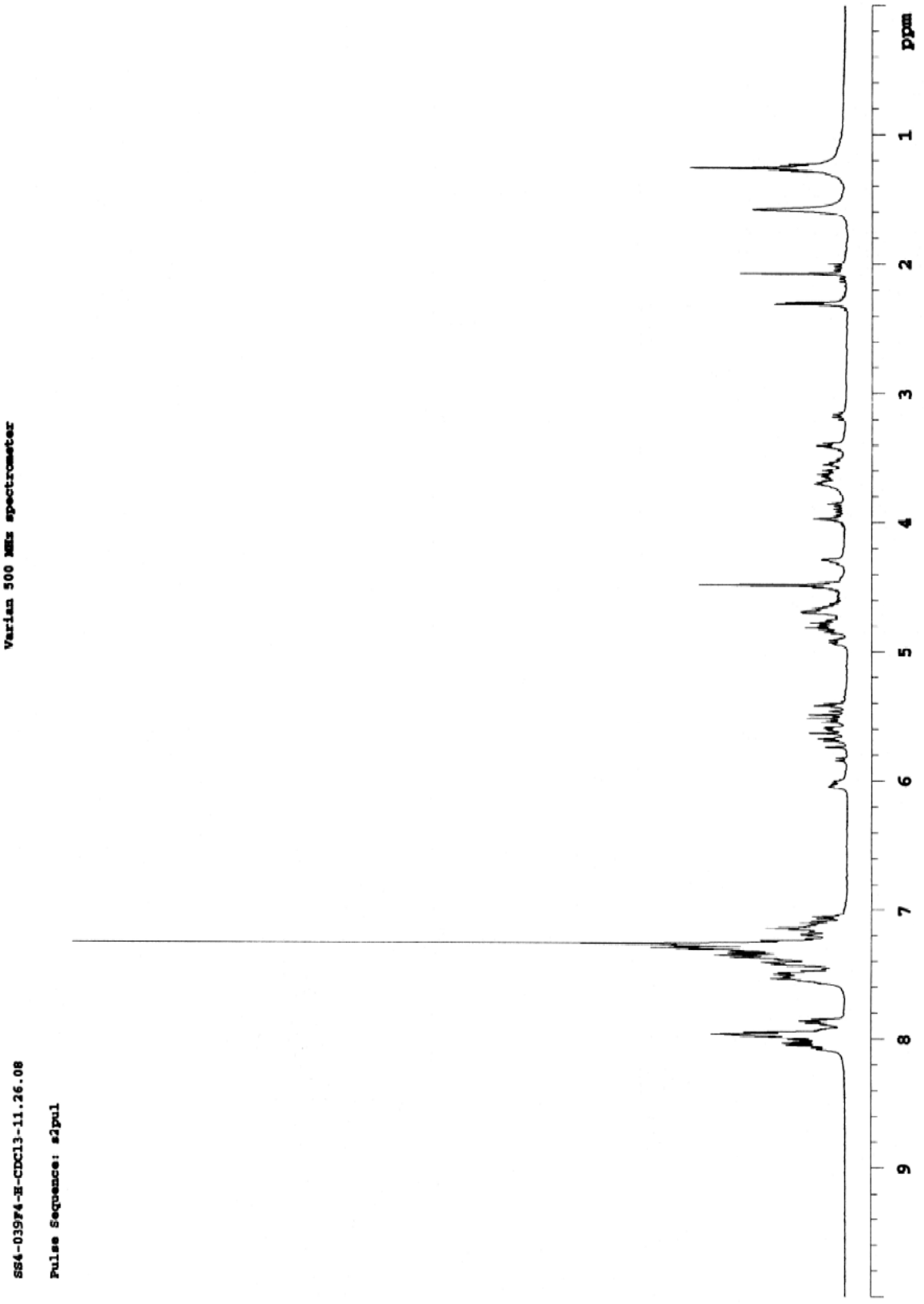
[1]H NMR (Compound 599)



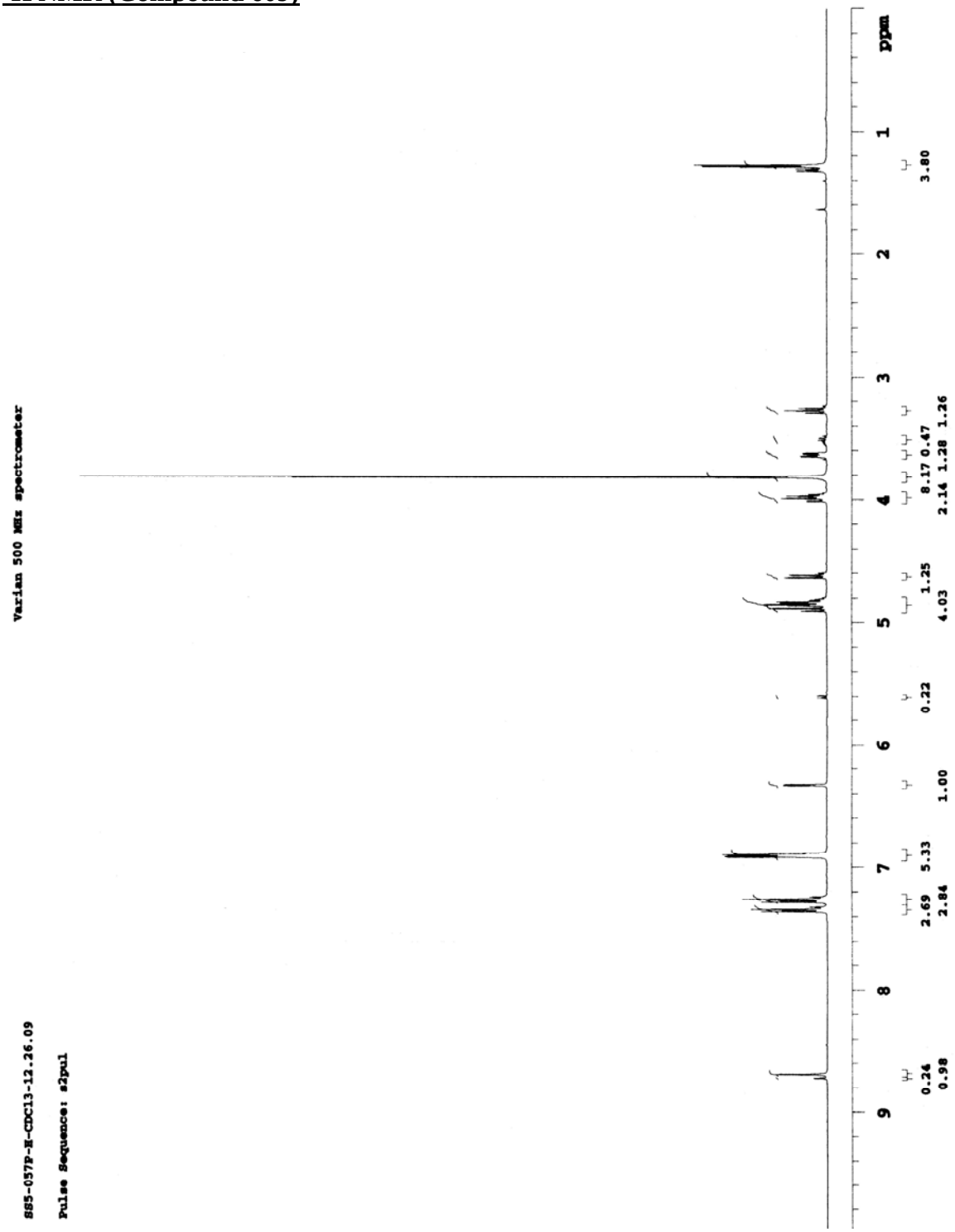
LRMS (ESI) Data (Compound 599)



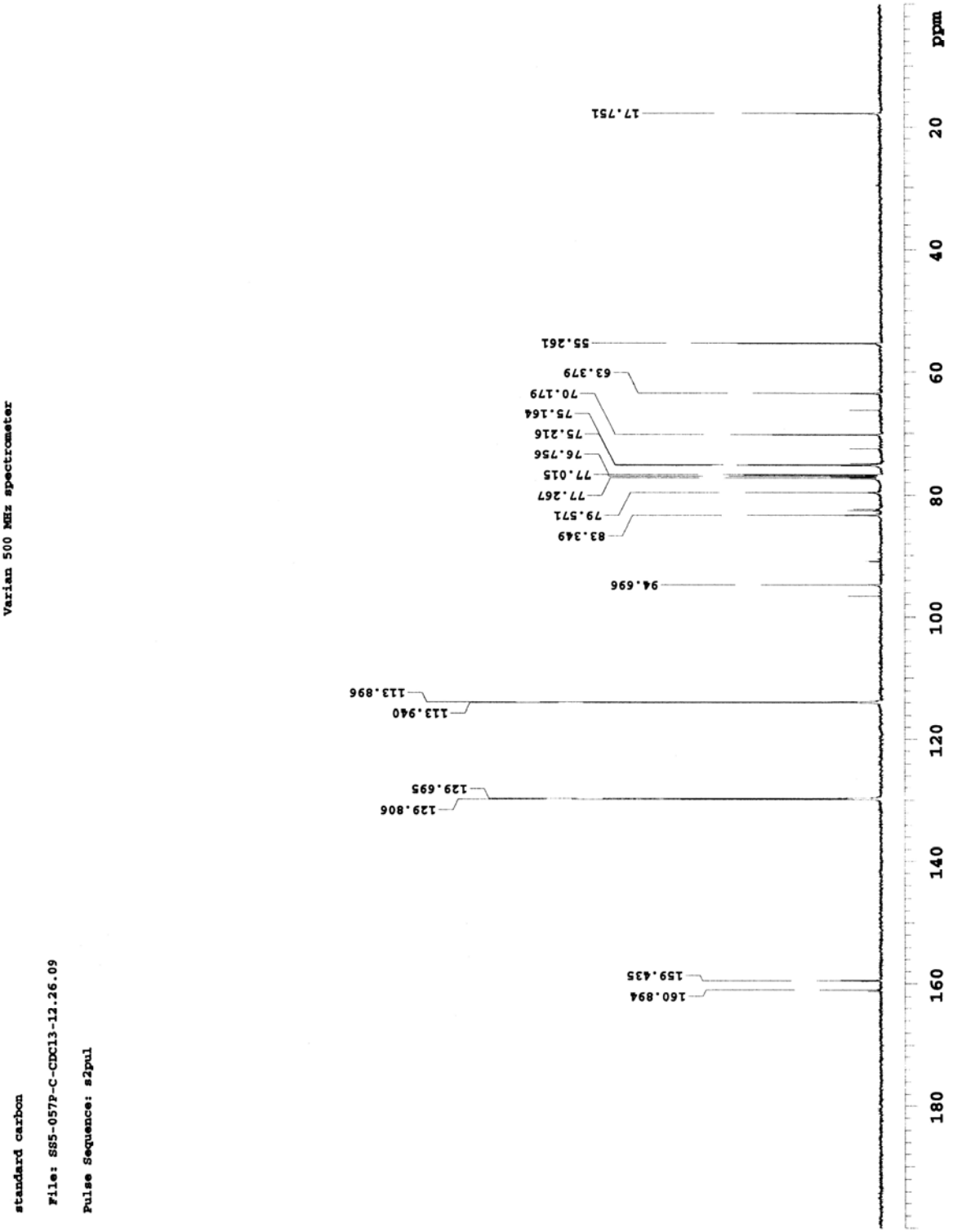
^{1}H NMR (Compound 600)



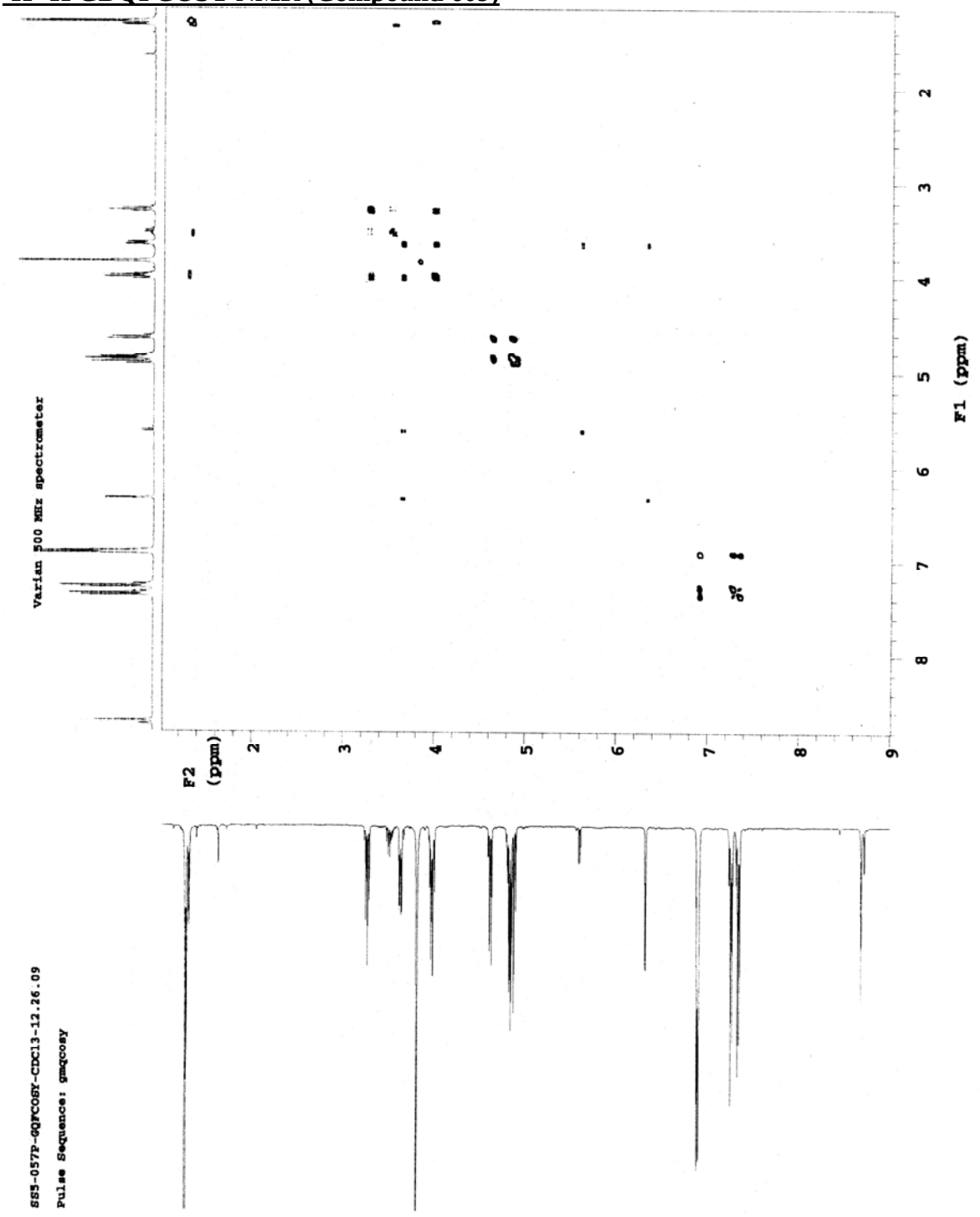
[1]H NMR (Compound 609)



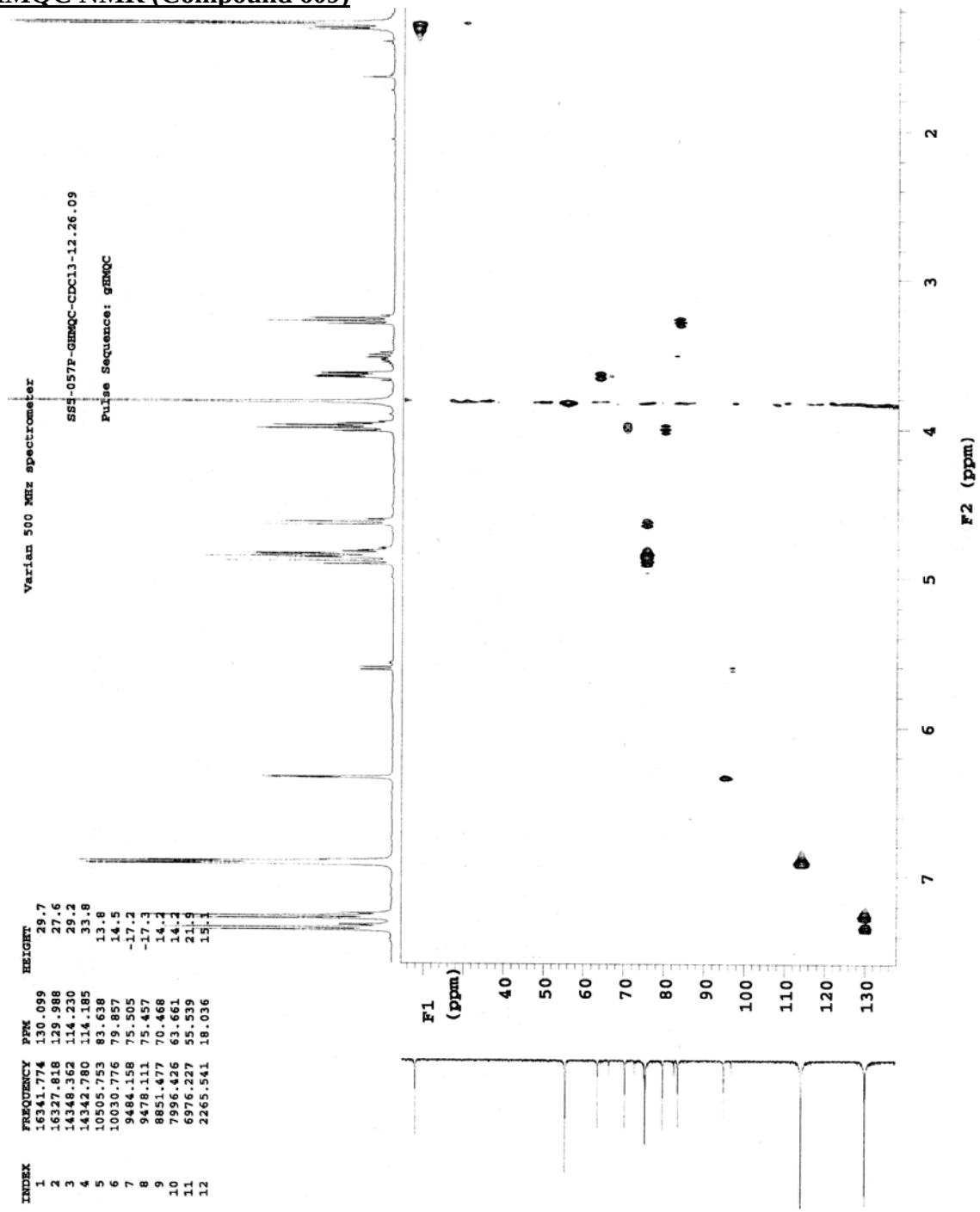
^{13}C NMR (Compound 609)



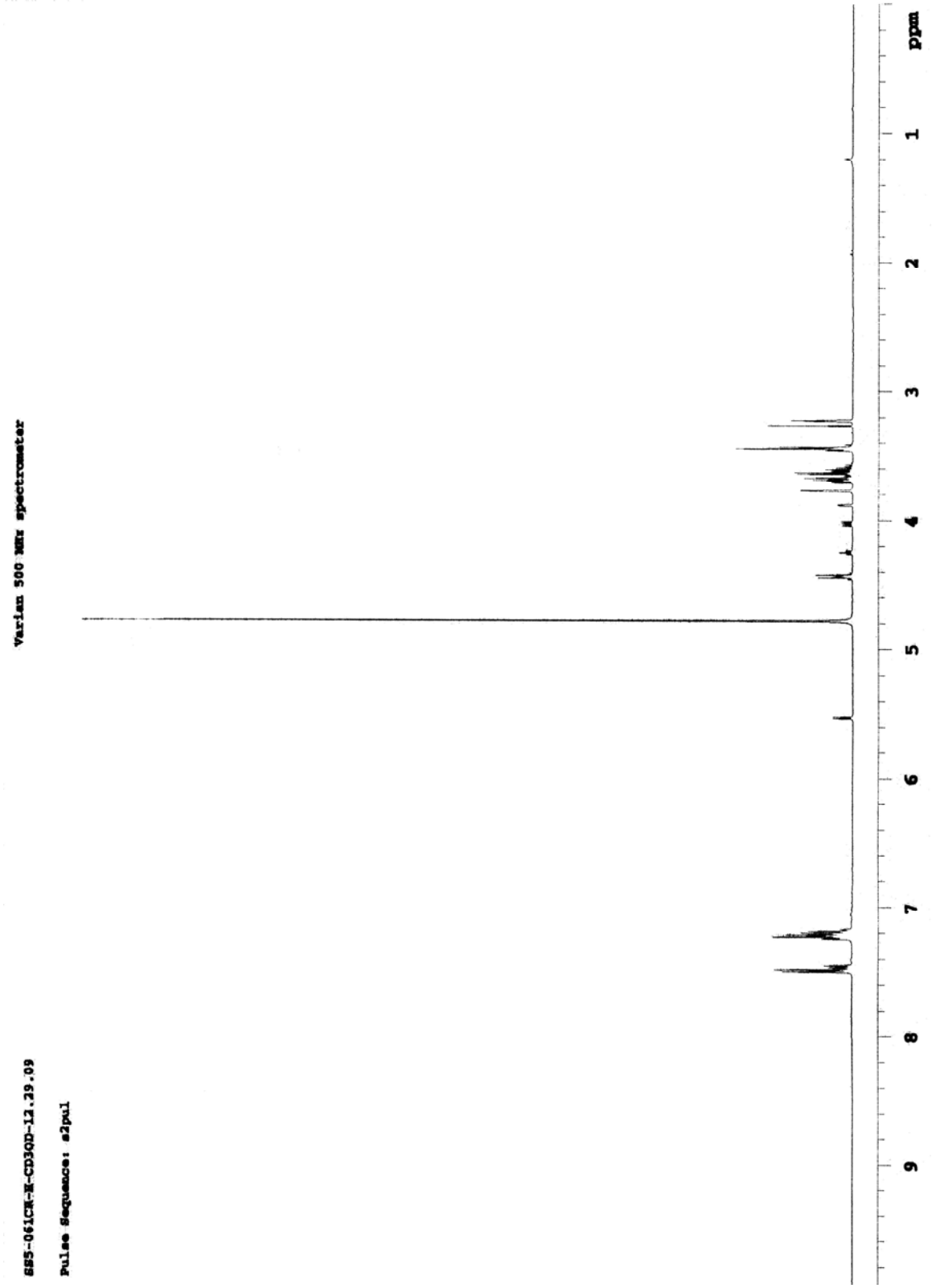
^{1}H-^{1}H GDQFCOSY NMR (Compound 609)



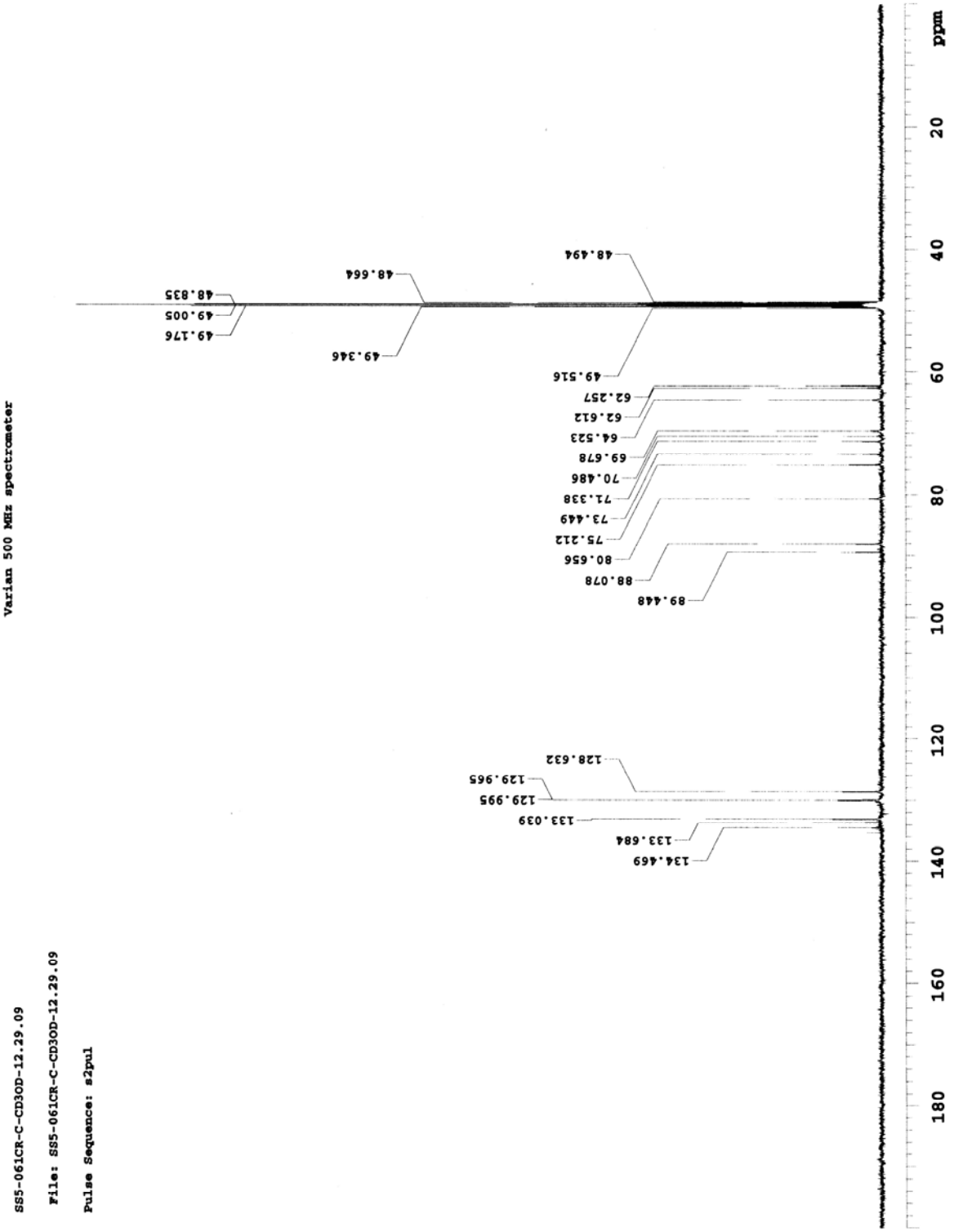
GHMQC NMR (Compound 609)



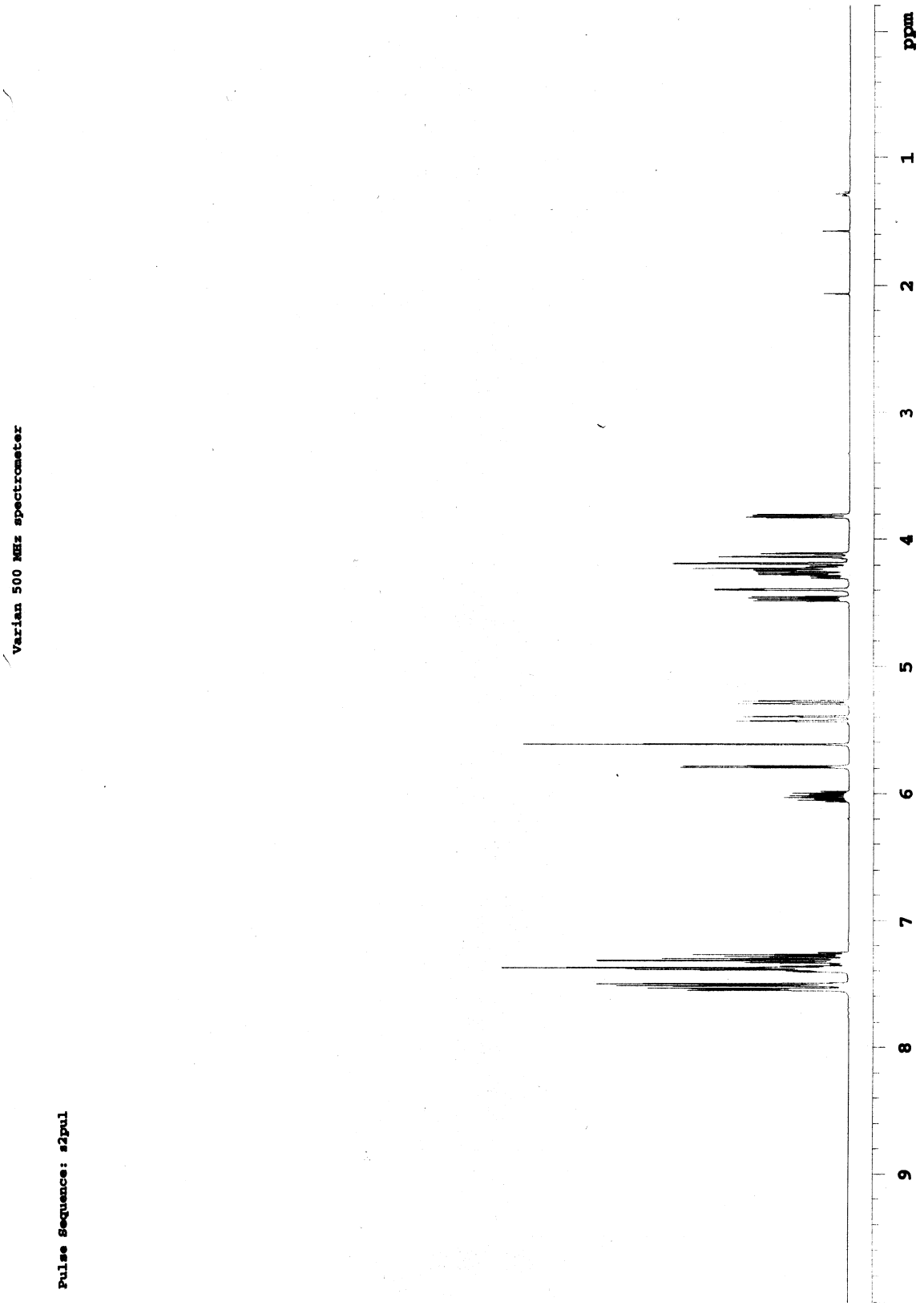
[1]H NMR (Compound 612)



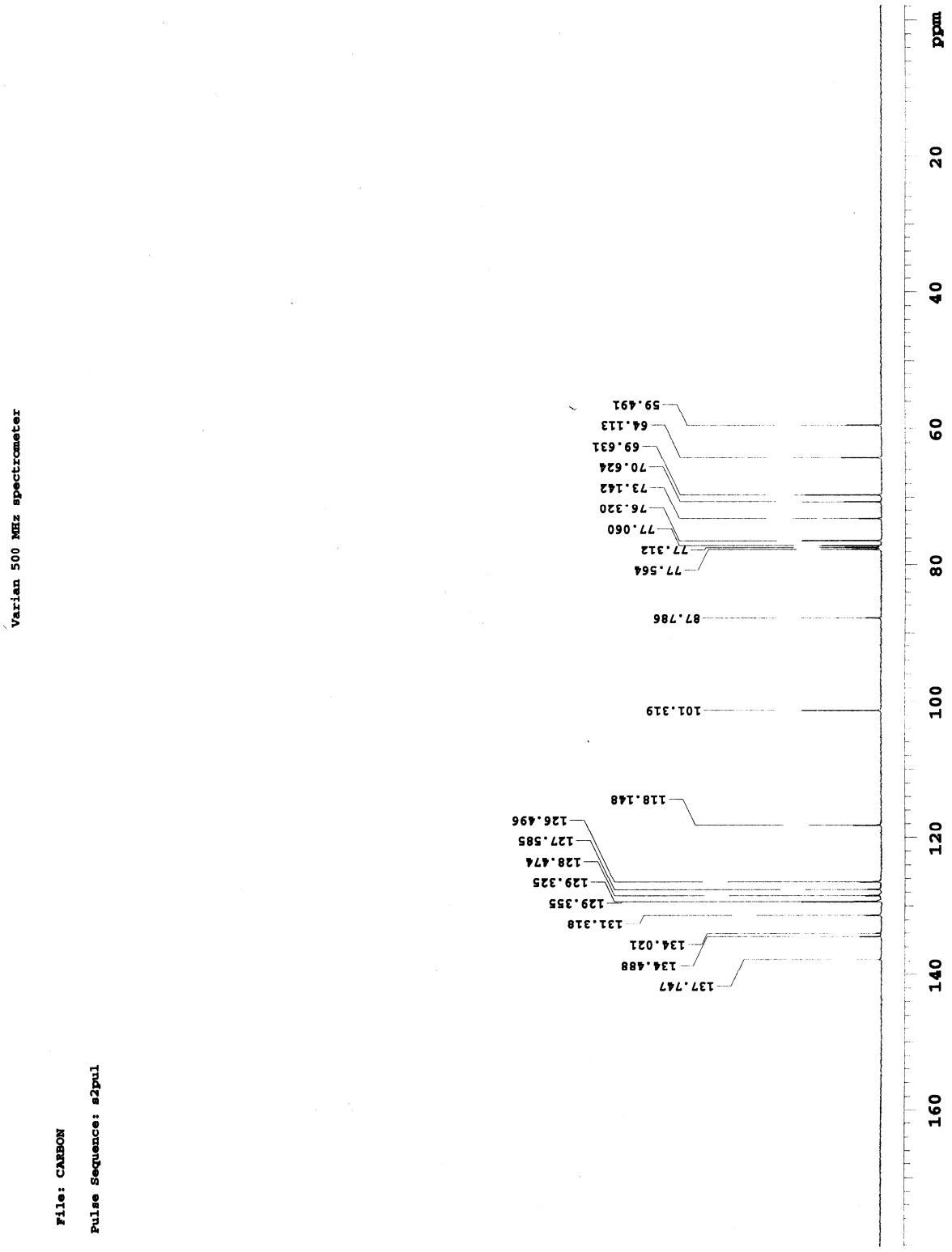
^{13}C NMR (Compound 612)



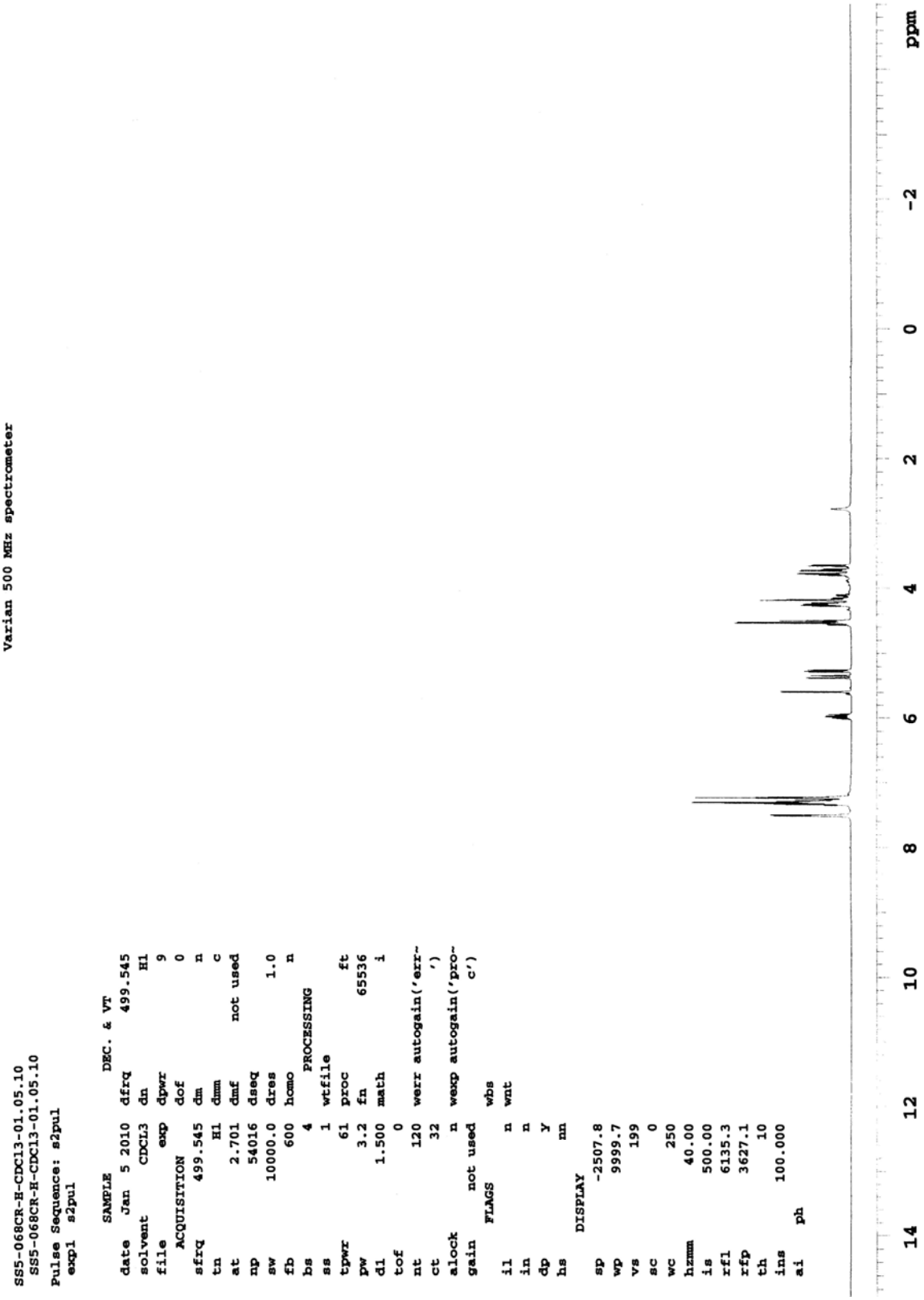
^{1}H NMR (Compound 614)



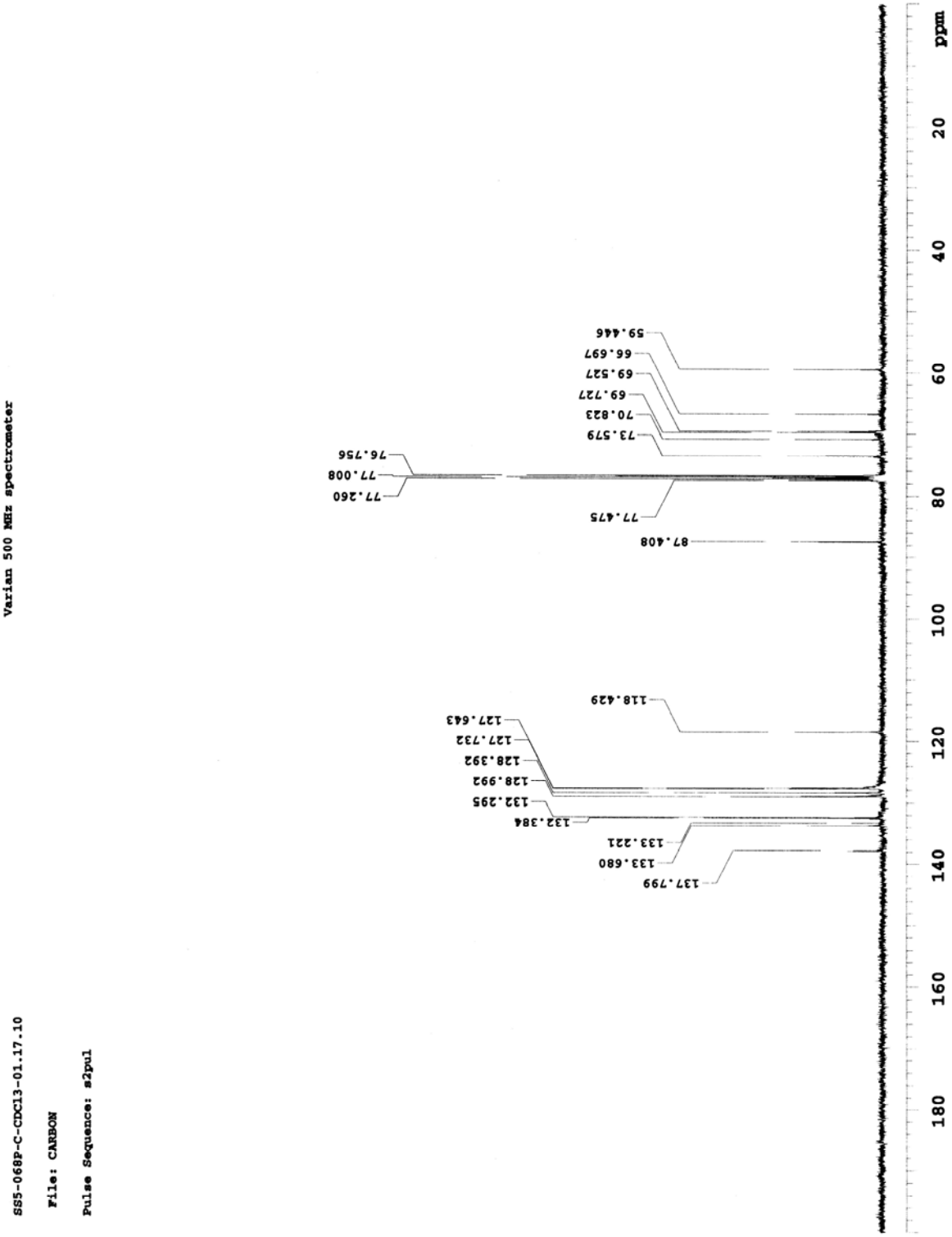
^{13}C NMR (Compound 614)



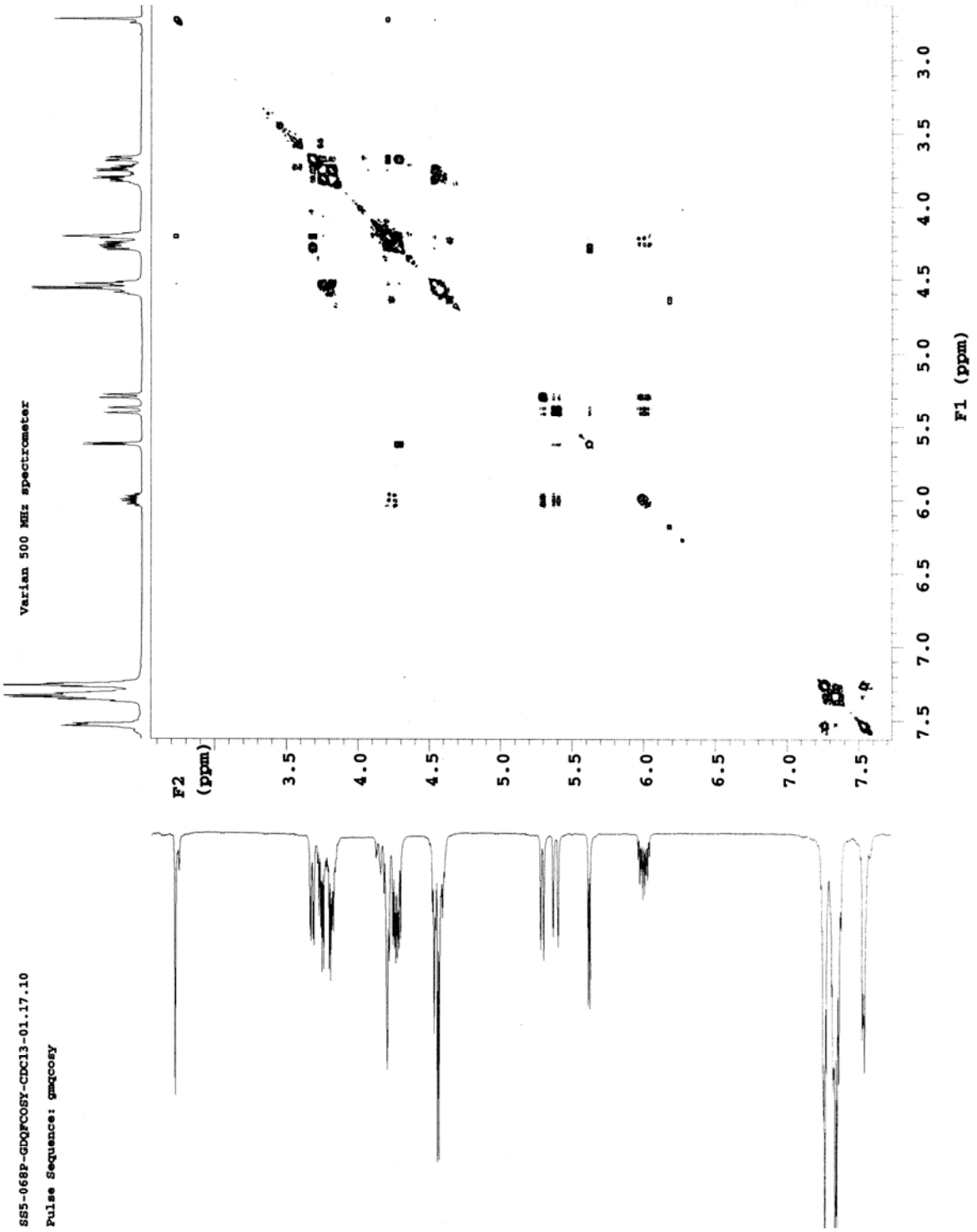
[1]H NMR (Compound 615)



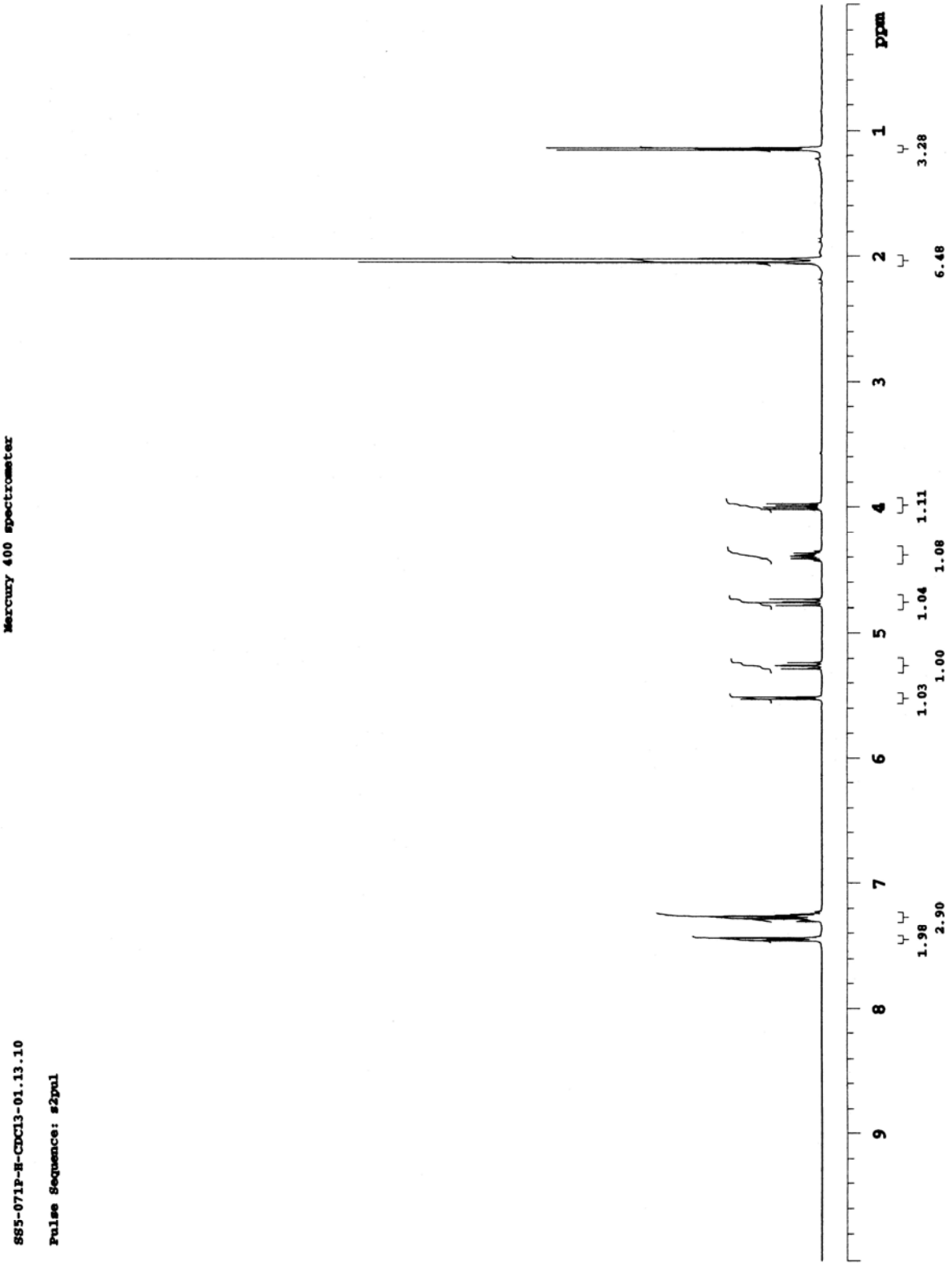
^{13}C NMR (Compound 615)



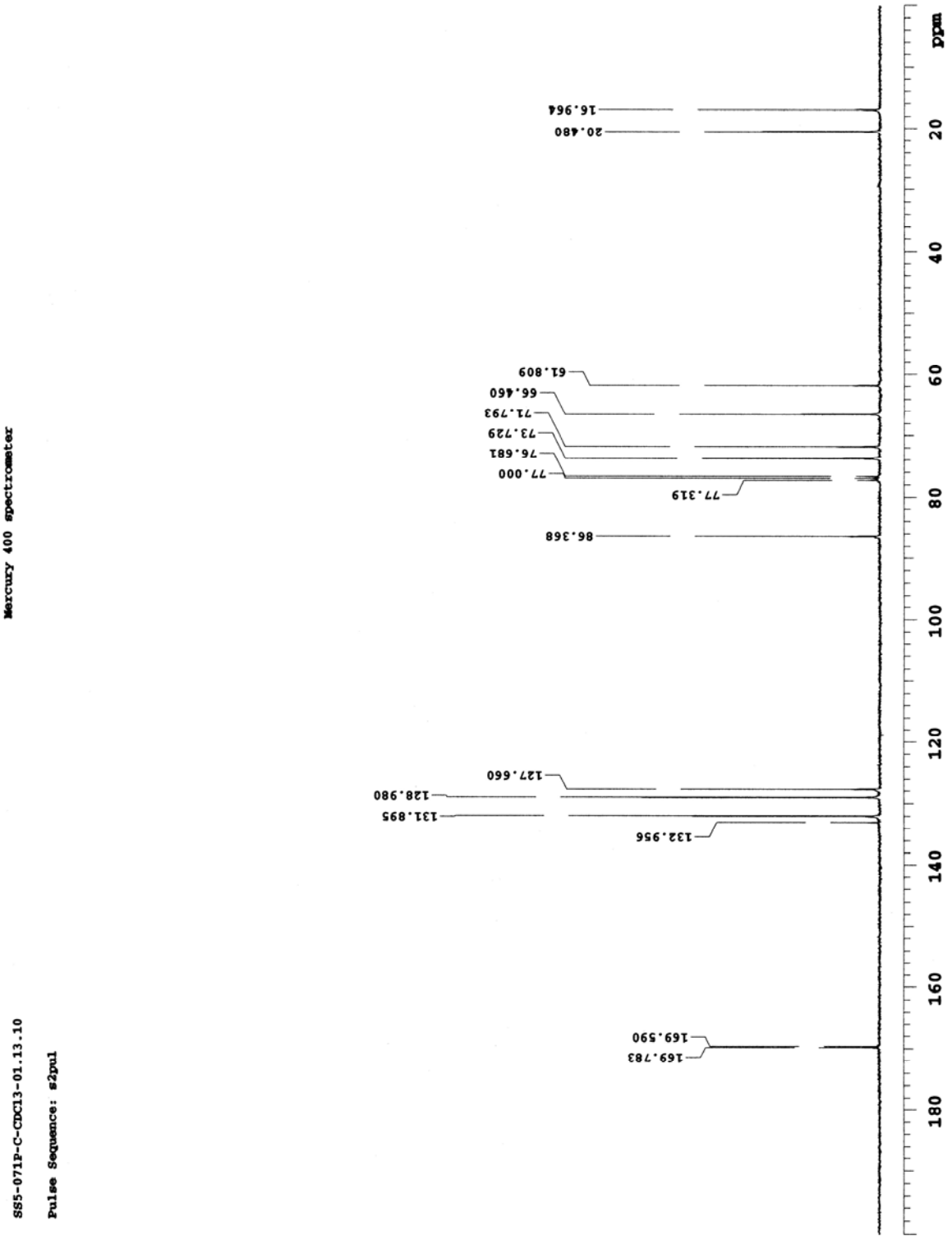
^{1}H-^{1}H GDQFCOSY NMR (Compound 615)



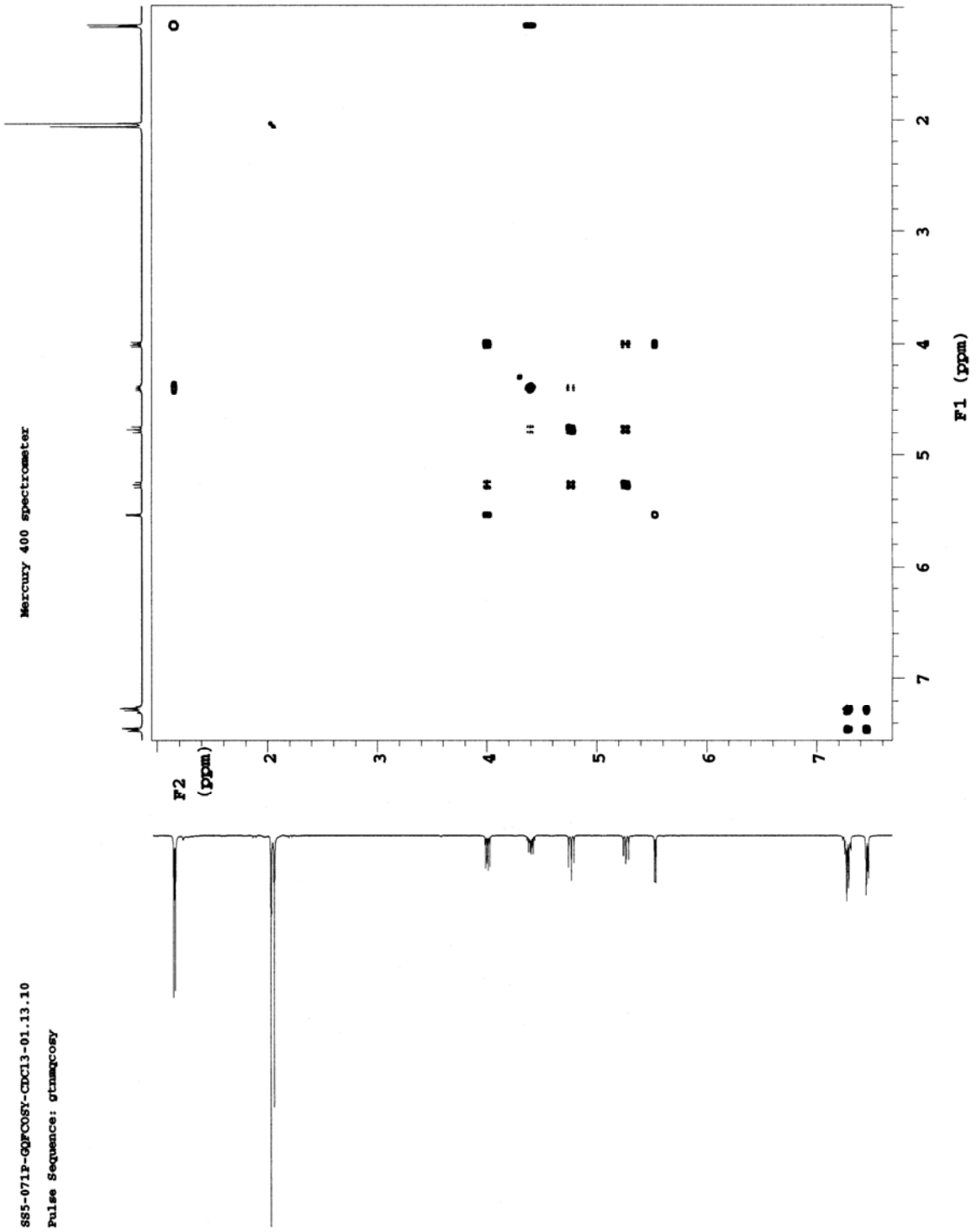
^{1}H NMR (Compound 617)



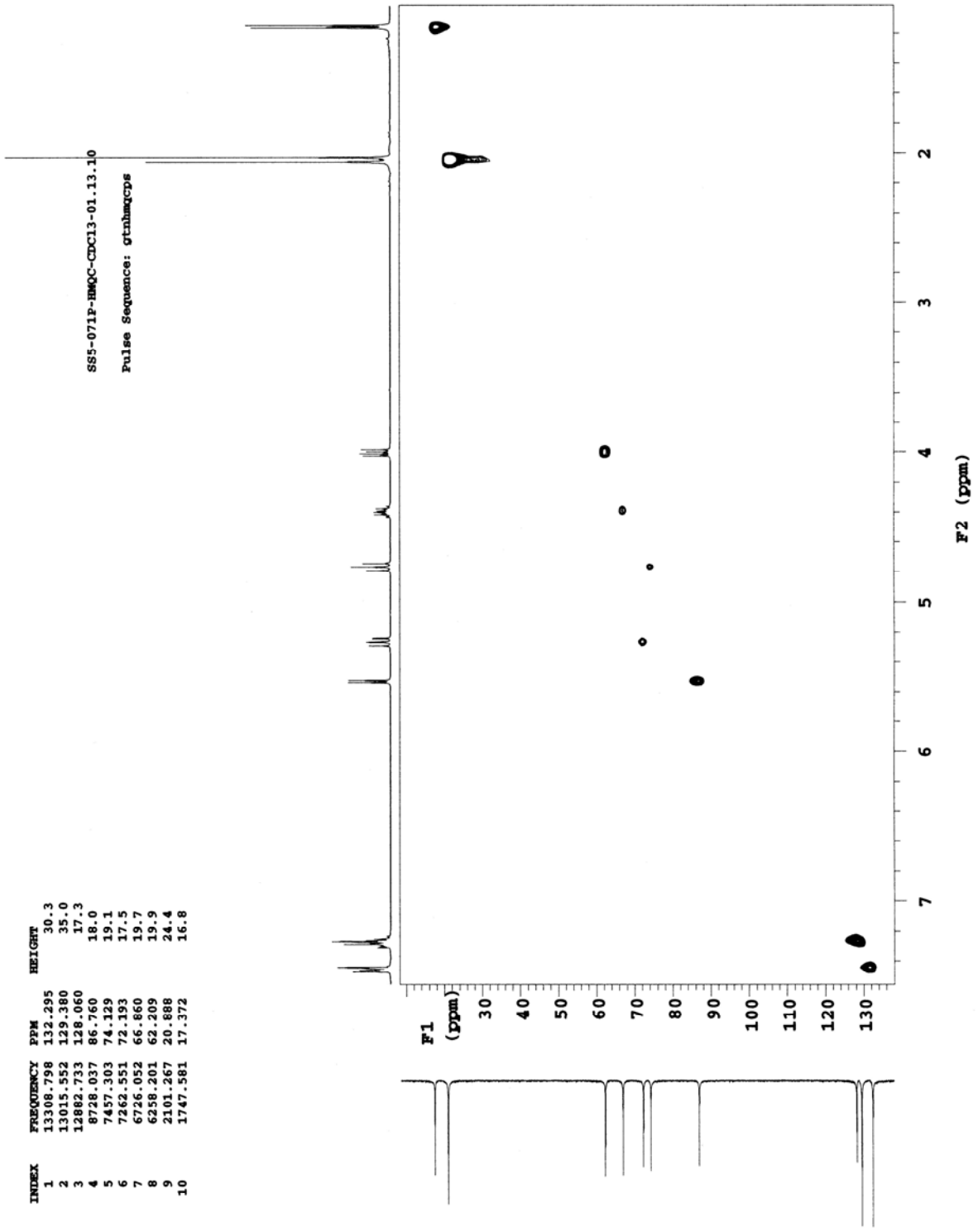
^{13}C NMR (Compound 617)



^{1}H-^{1}H GDQFCOSY NMR (Compound 617)

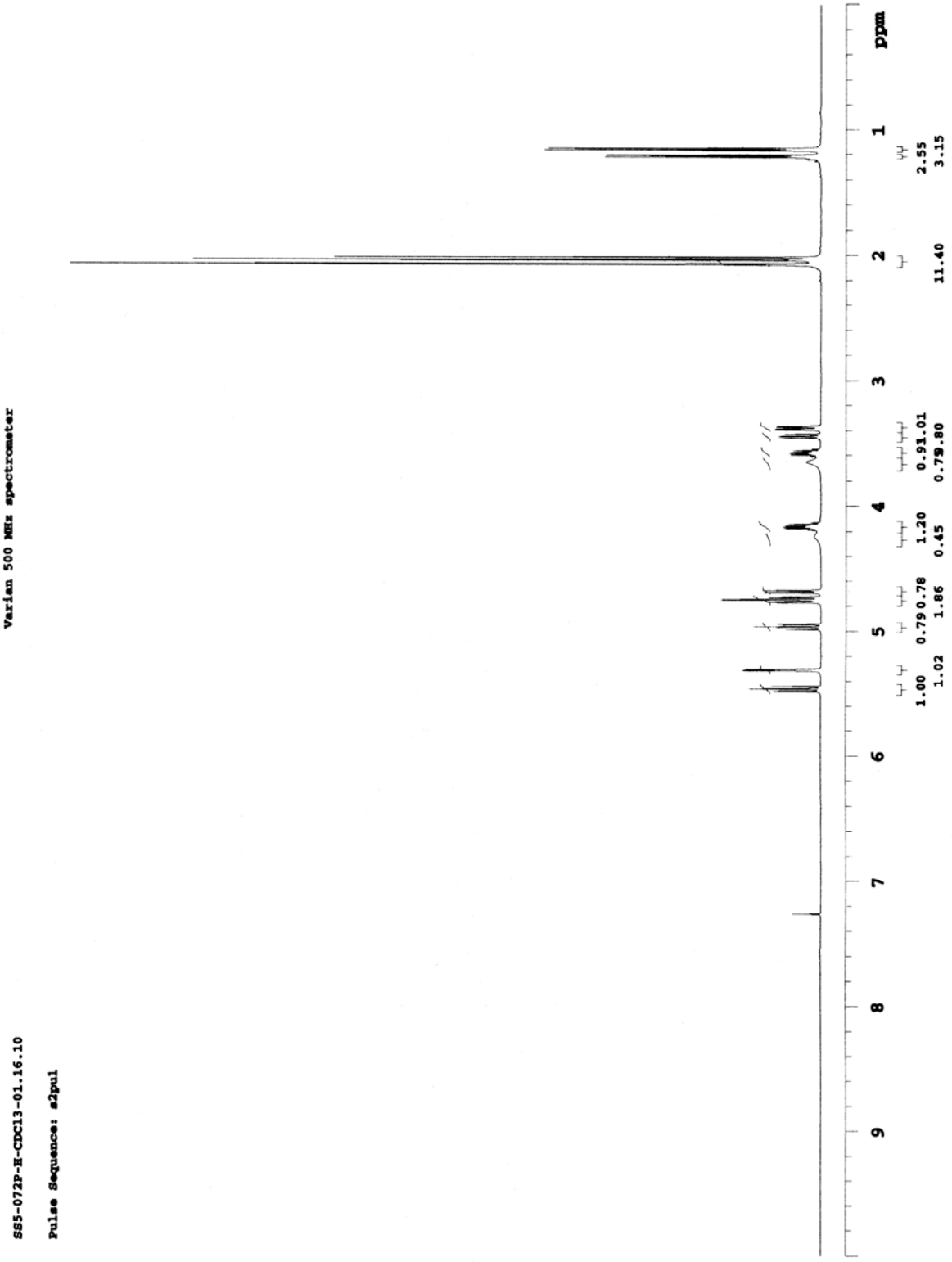


GHMQC NMR (Compound 617)

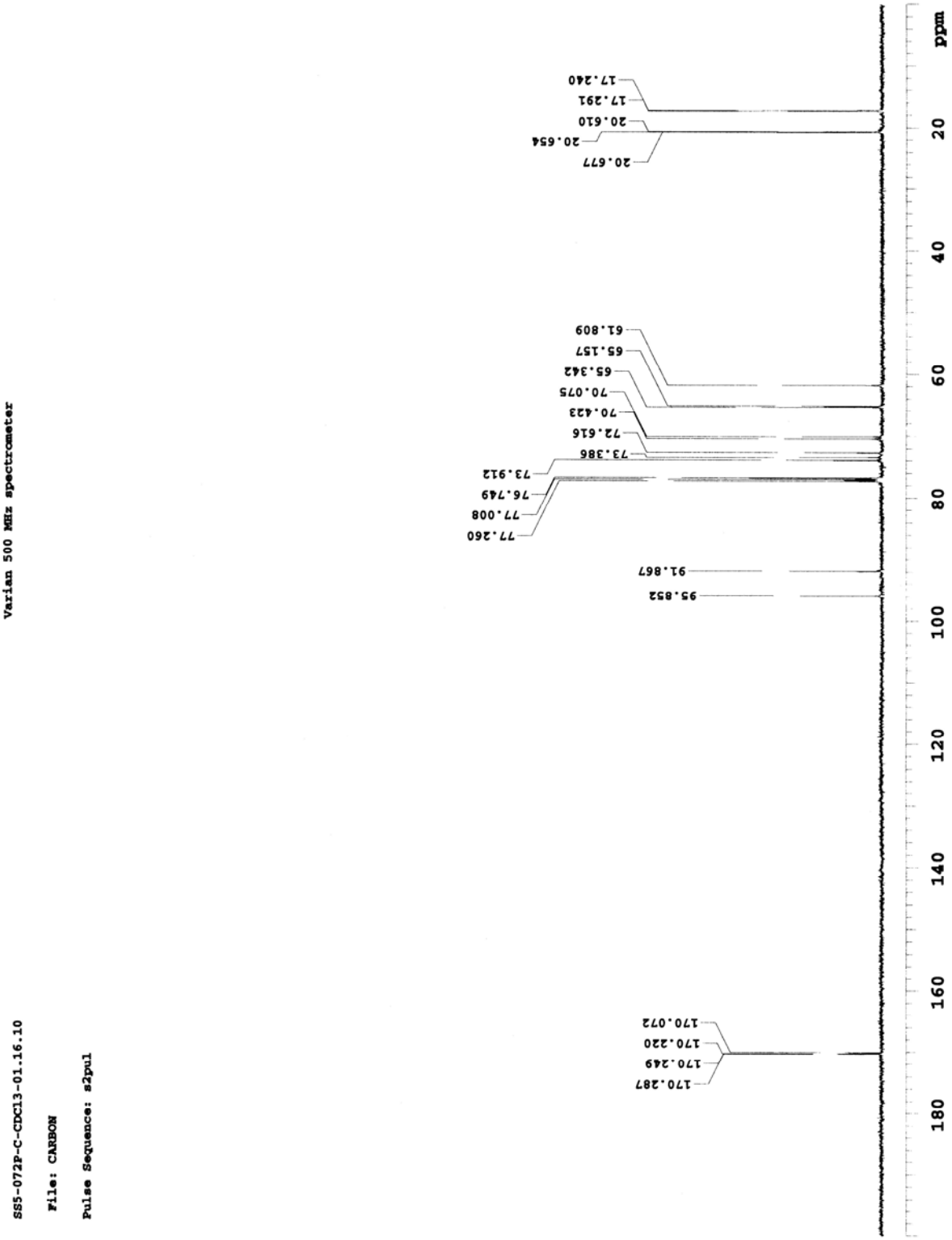


INDEX	FREQUENCY	PPM	HEIGHT
1	13308.798	132.295	30.3
2	13015.552	129.380	35.0
3	12882.733	128.060	17.3
4	8728.037	86.760	18.0
5	7457.303	74.129	19.1
6	7262.551	72.193	17.5
7	6726.052	66.860	19.7
8	6258.201	62.209	19.9
9	2101.267	20.888	24.4
10	1747.581	17.372	16.8

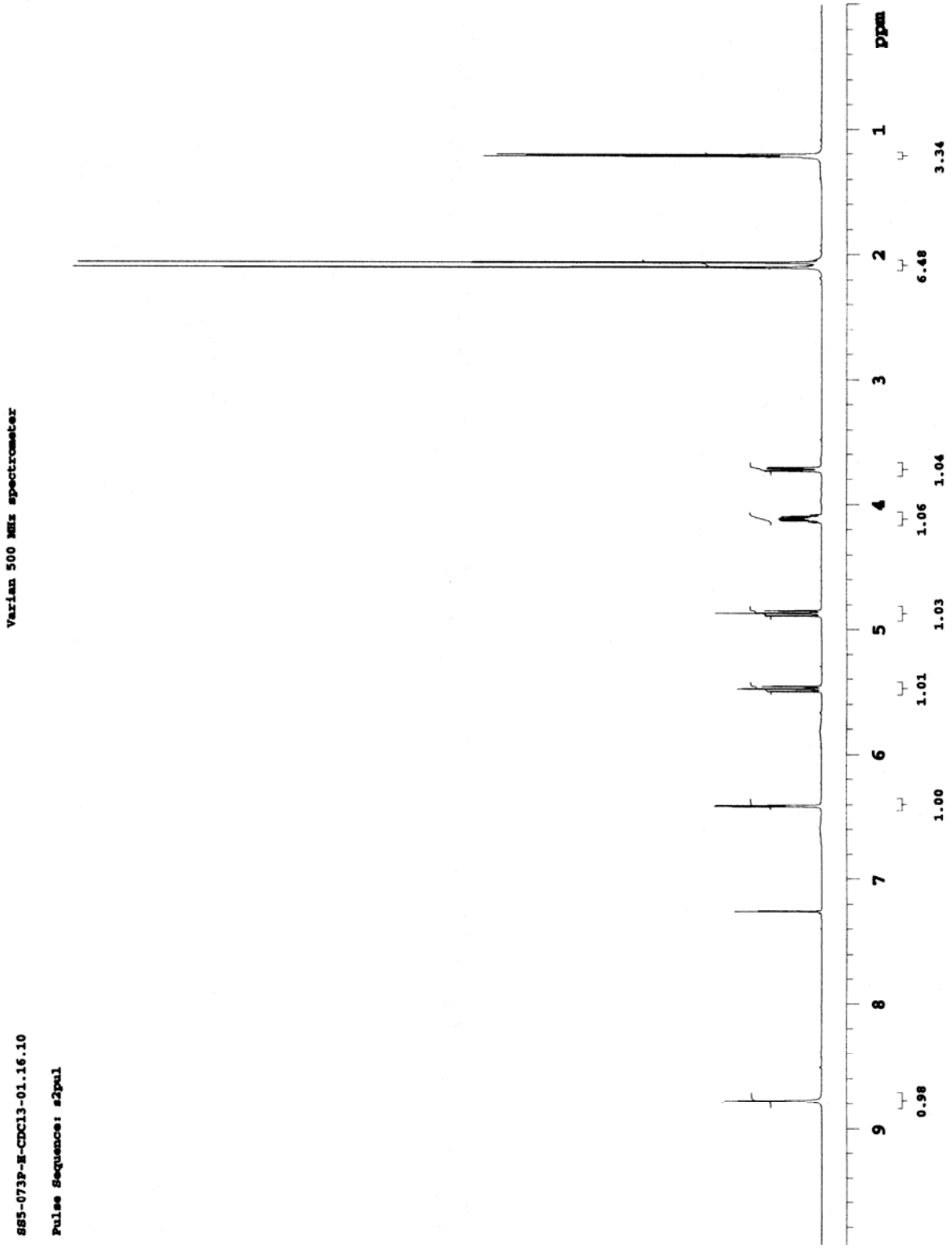
^{1}H NMR (Compound 618)



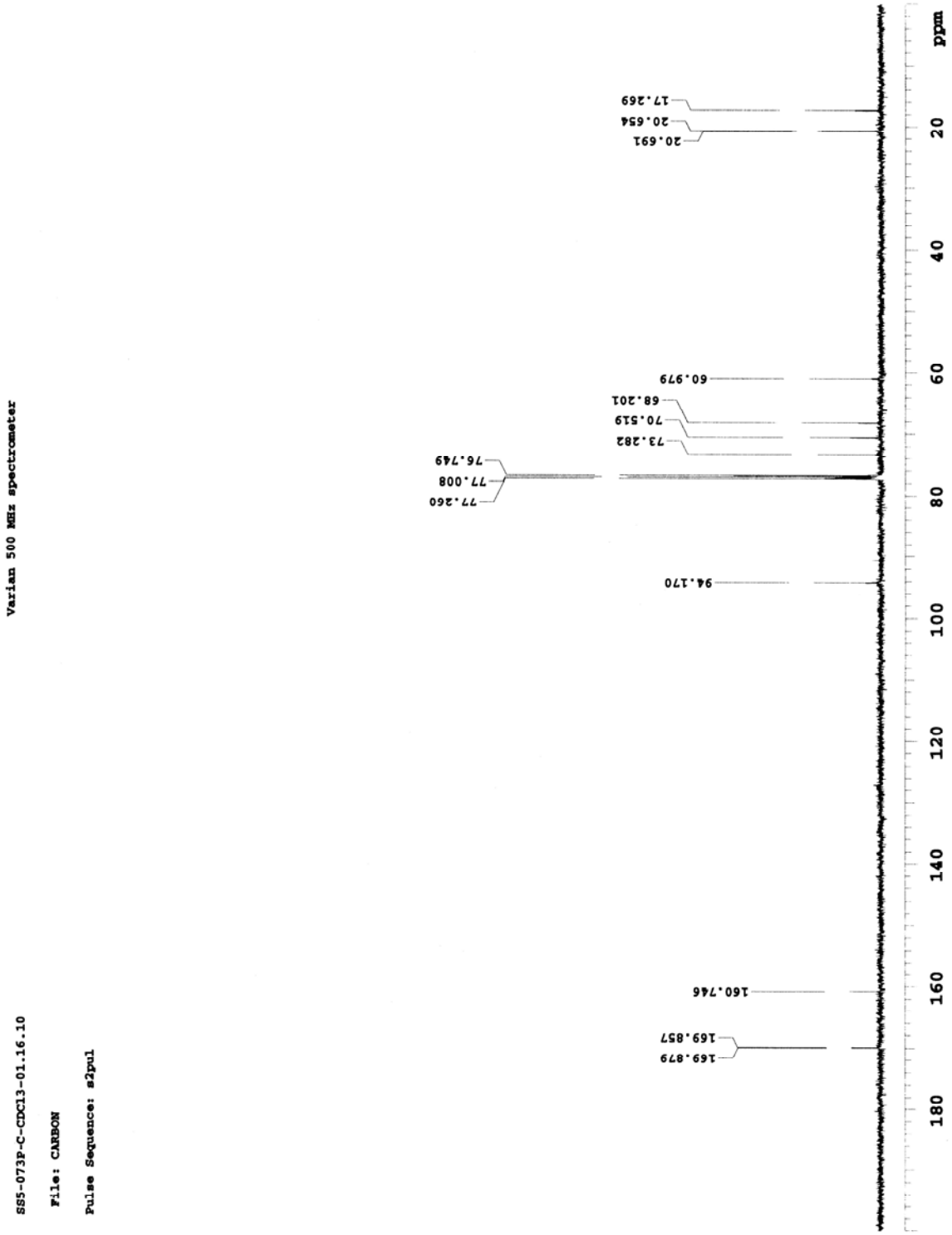
^{13}C NMR (Compound 618)



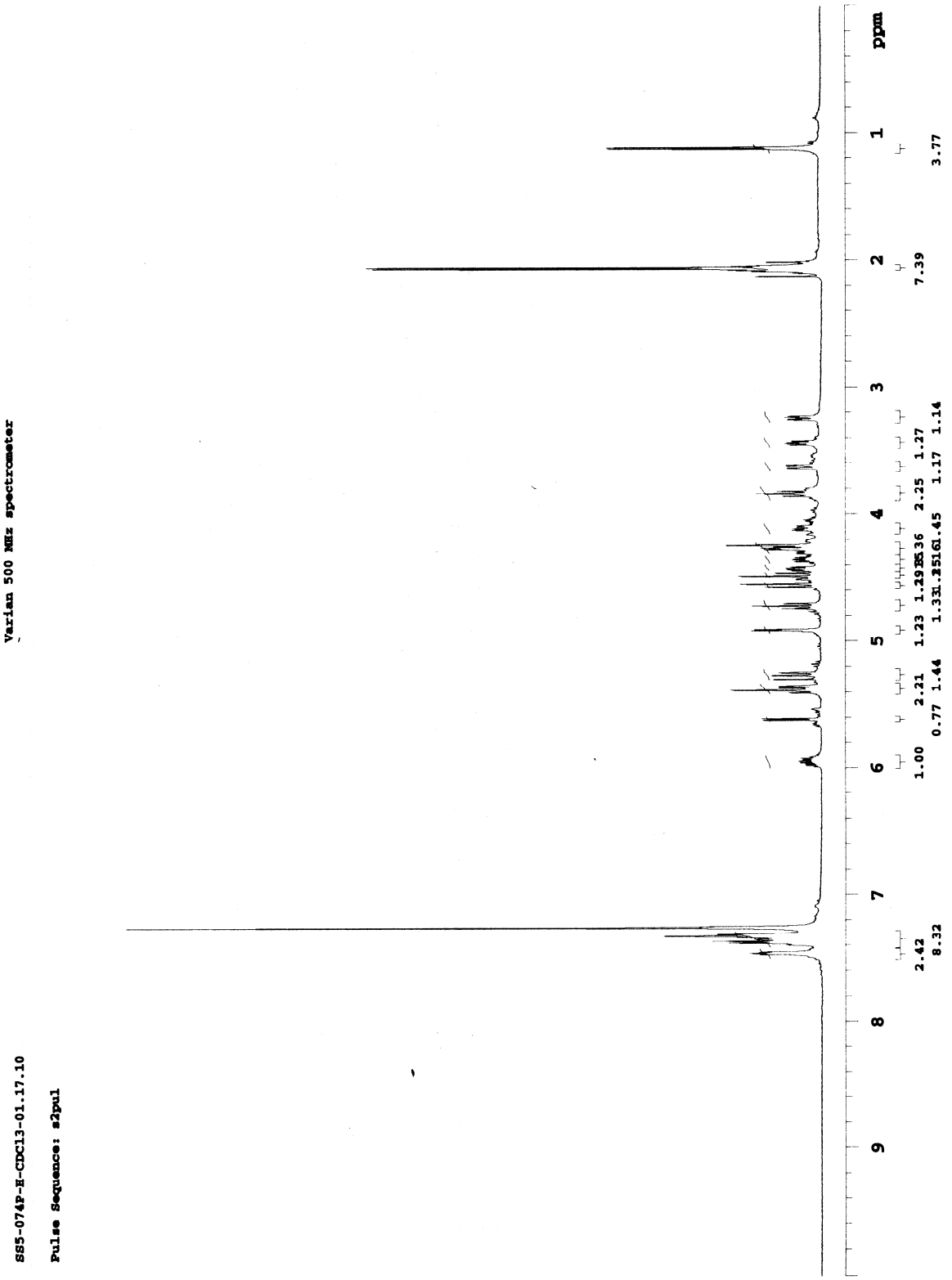
[1]H NMR (Compound 619)



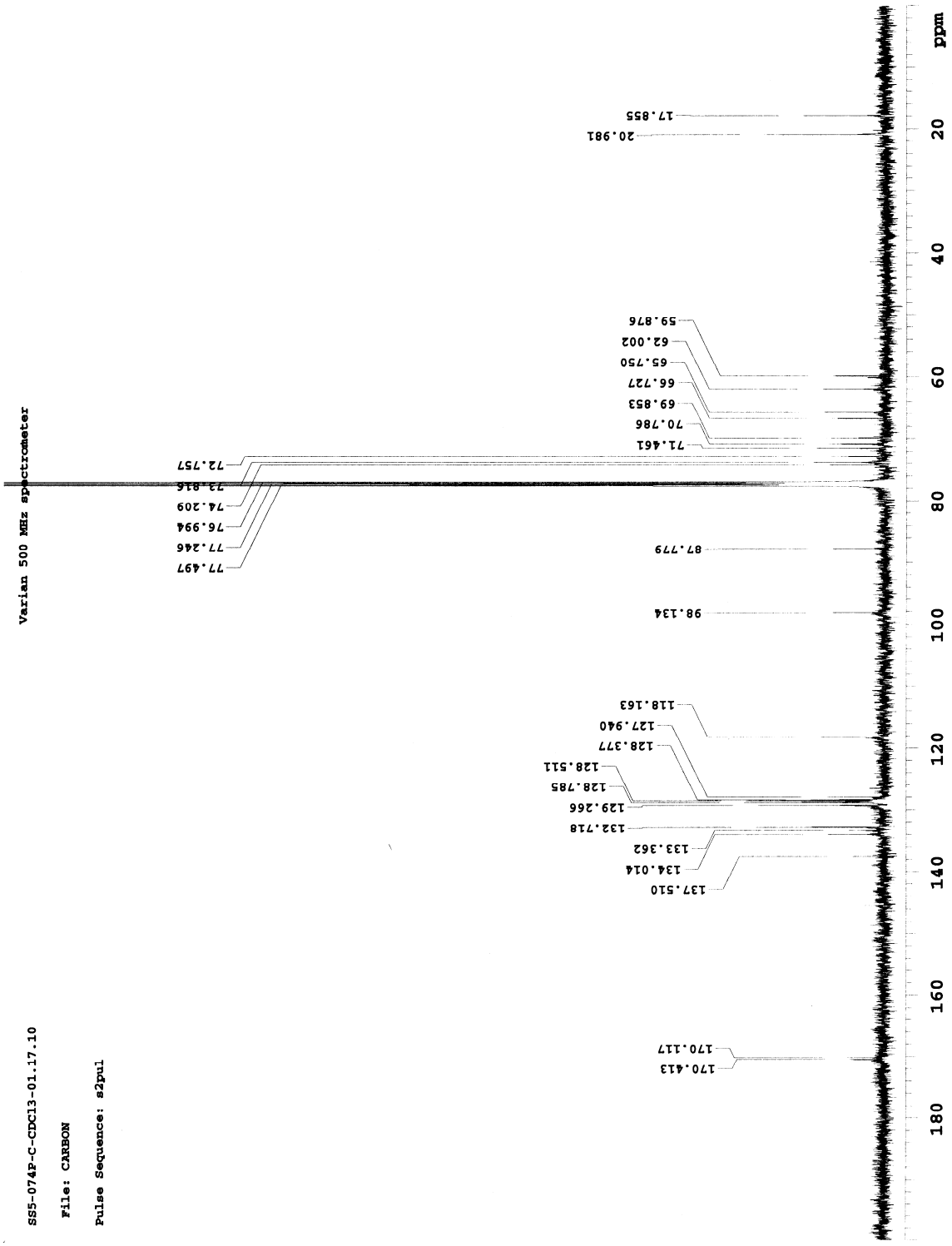
^{13}C NMR (Compound 619)



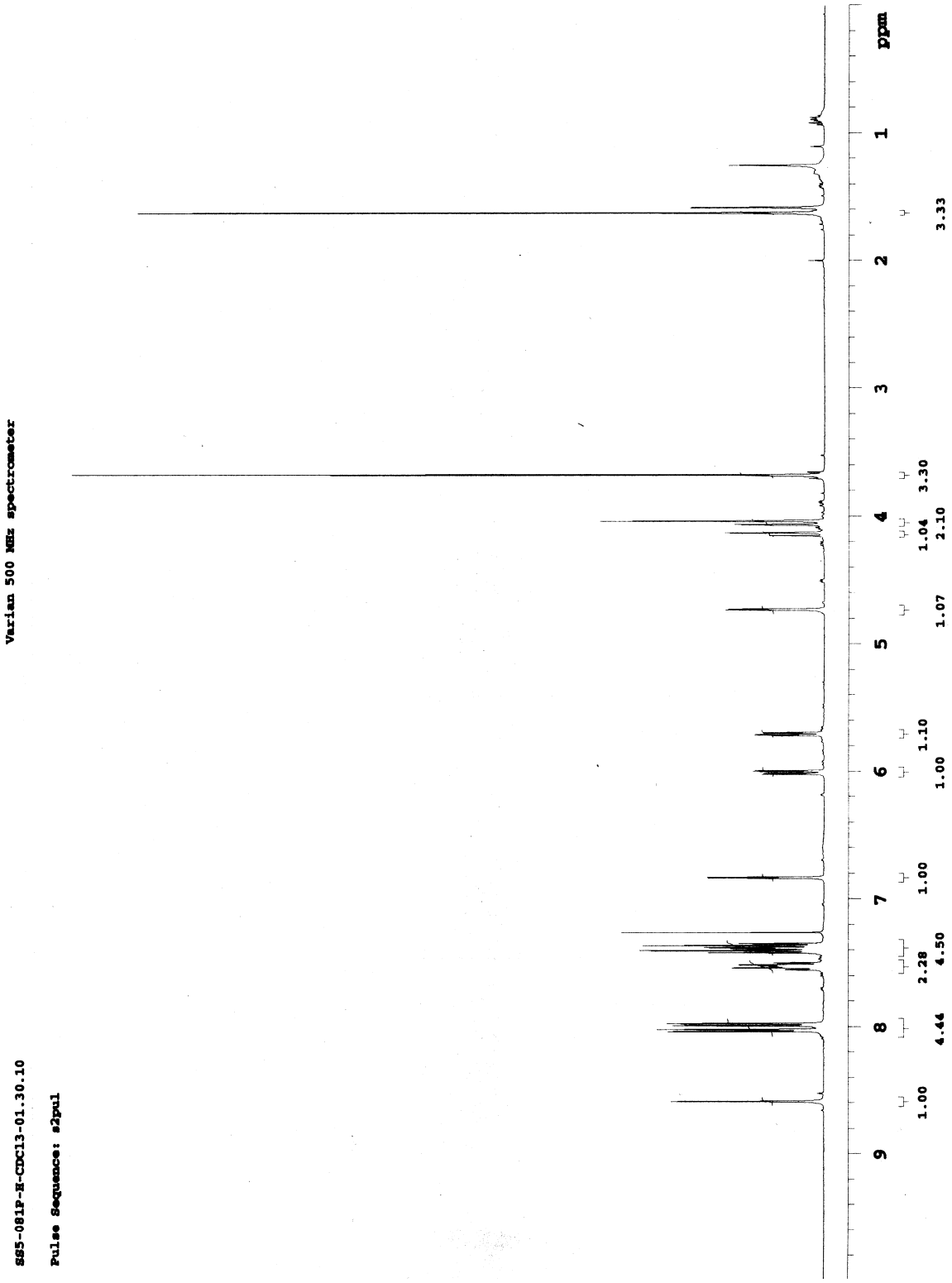
^{1}H NMR (Compound 620)



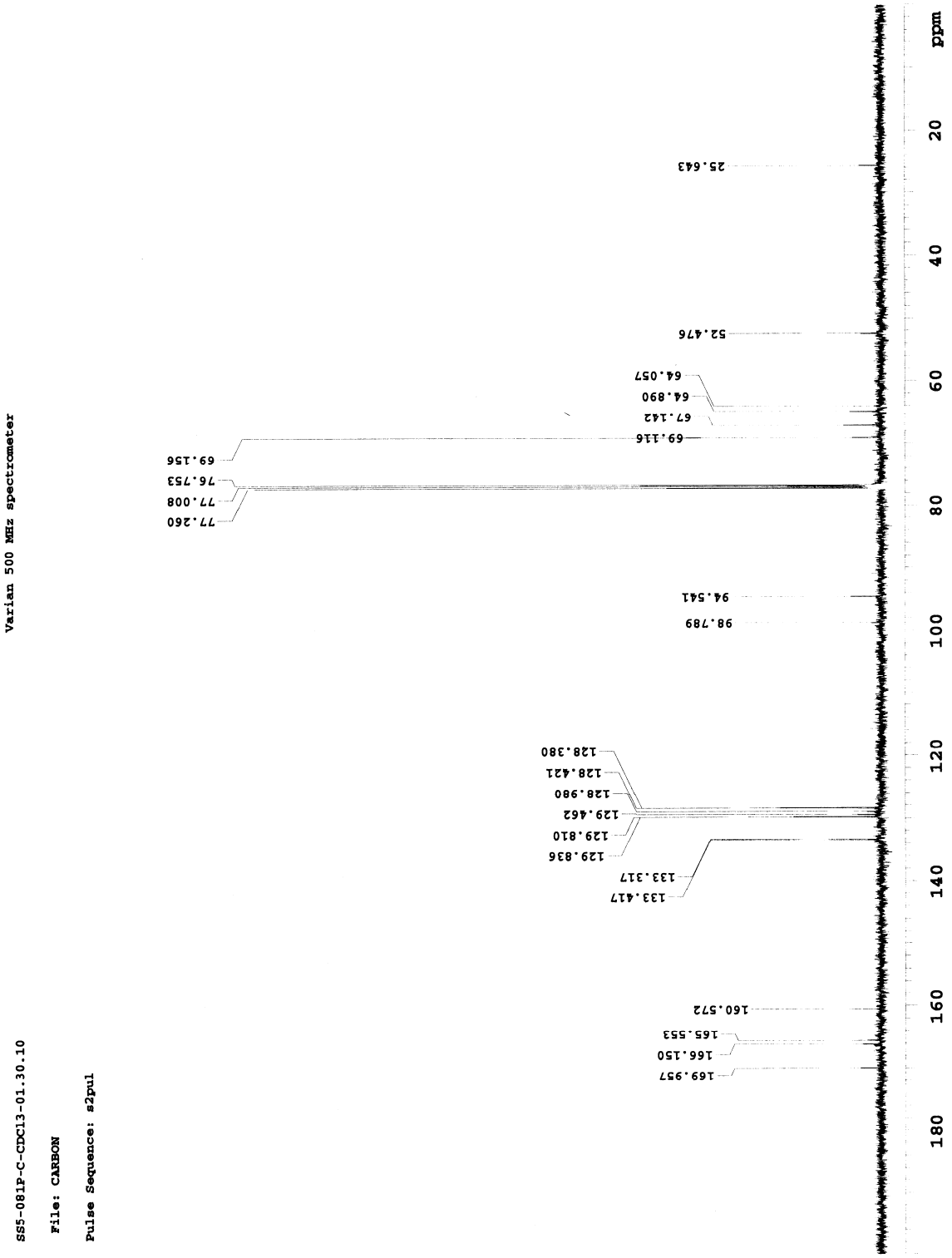
^{13}C NMR (Compound 620)



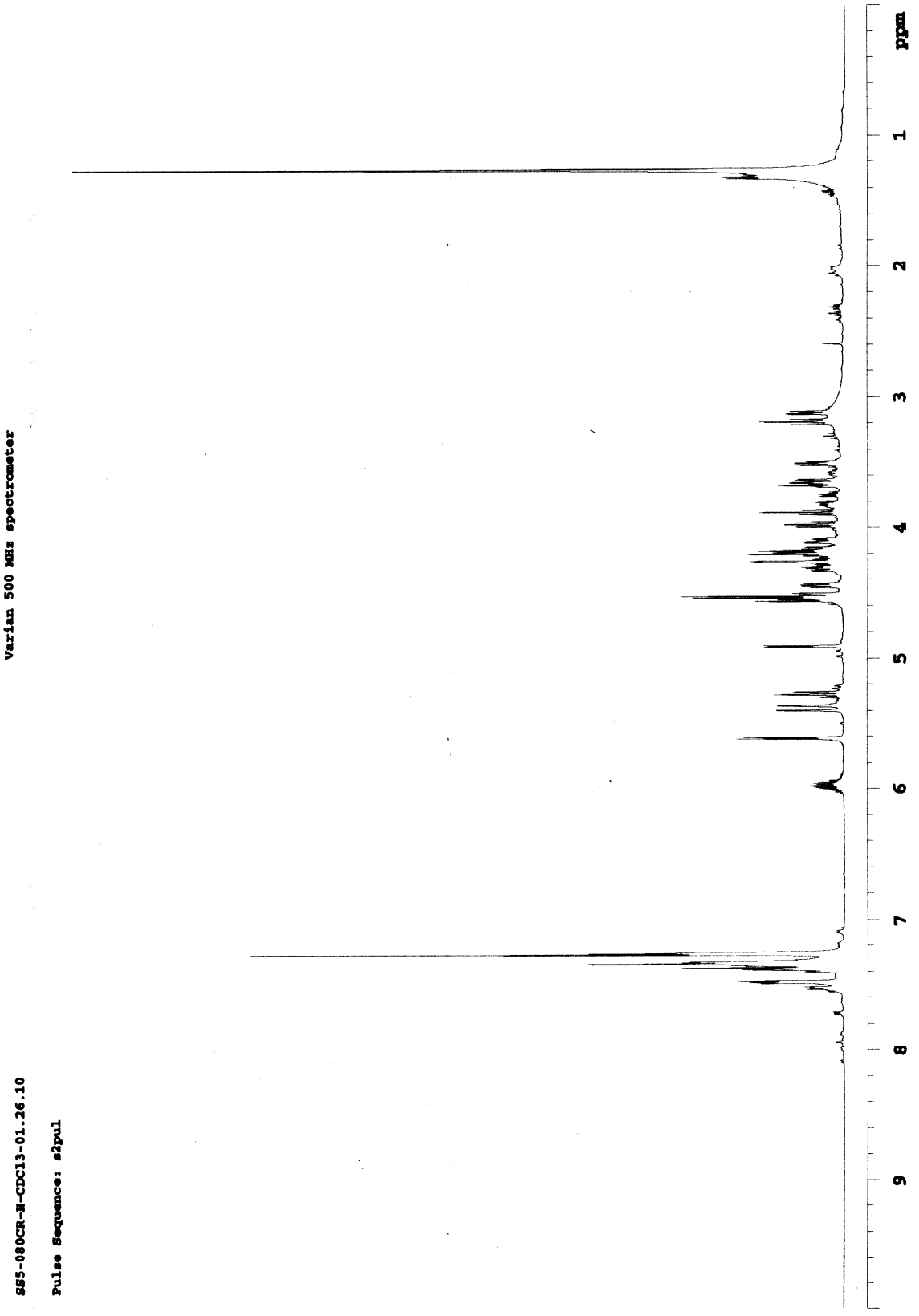
^{1}H NMR (Compound 622)



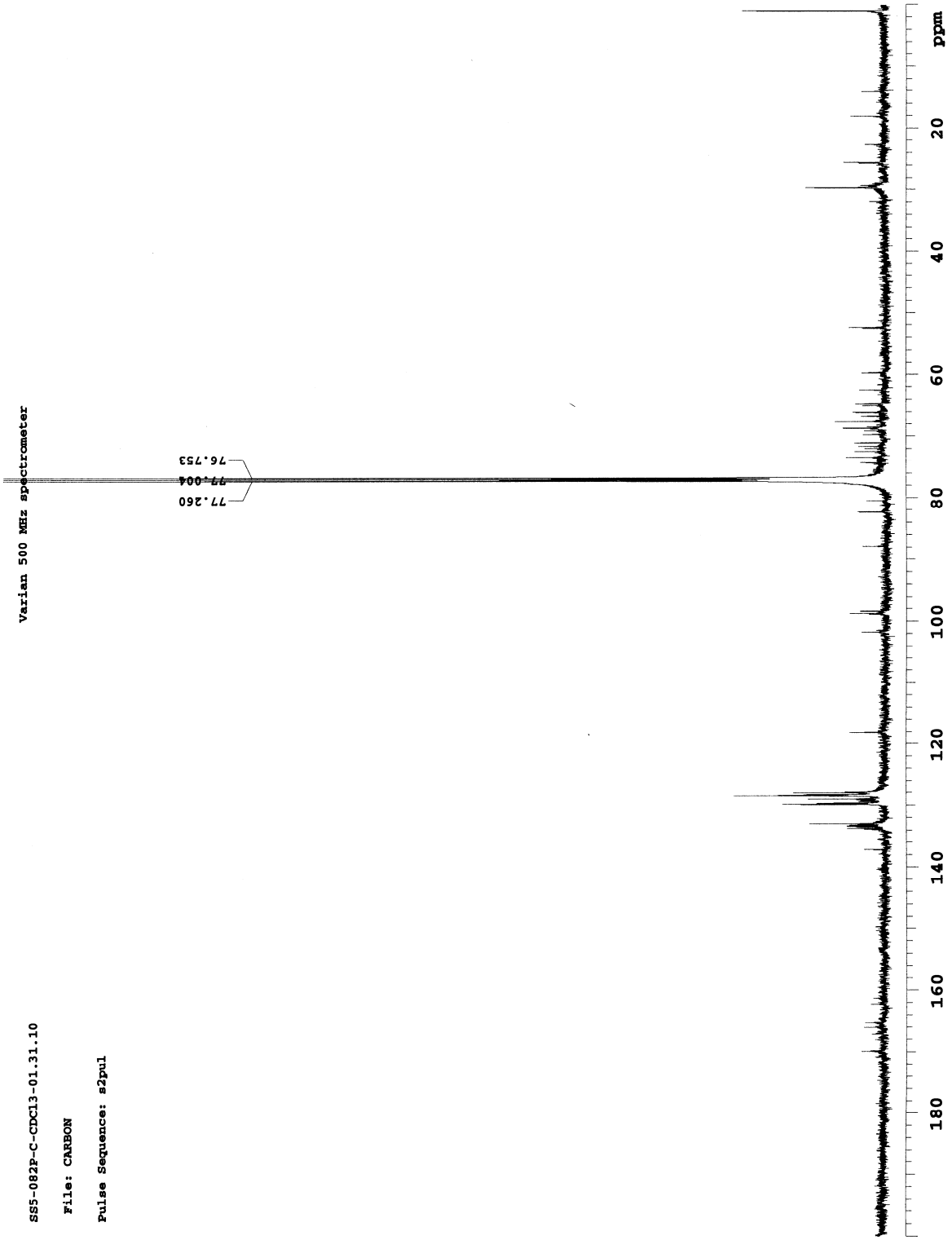
^{13}C NMR (Compound 622)



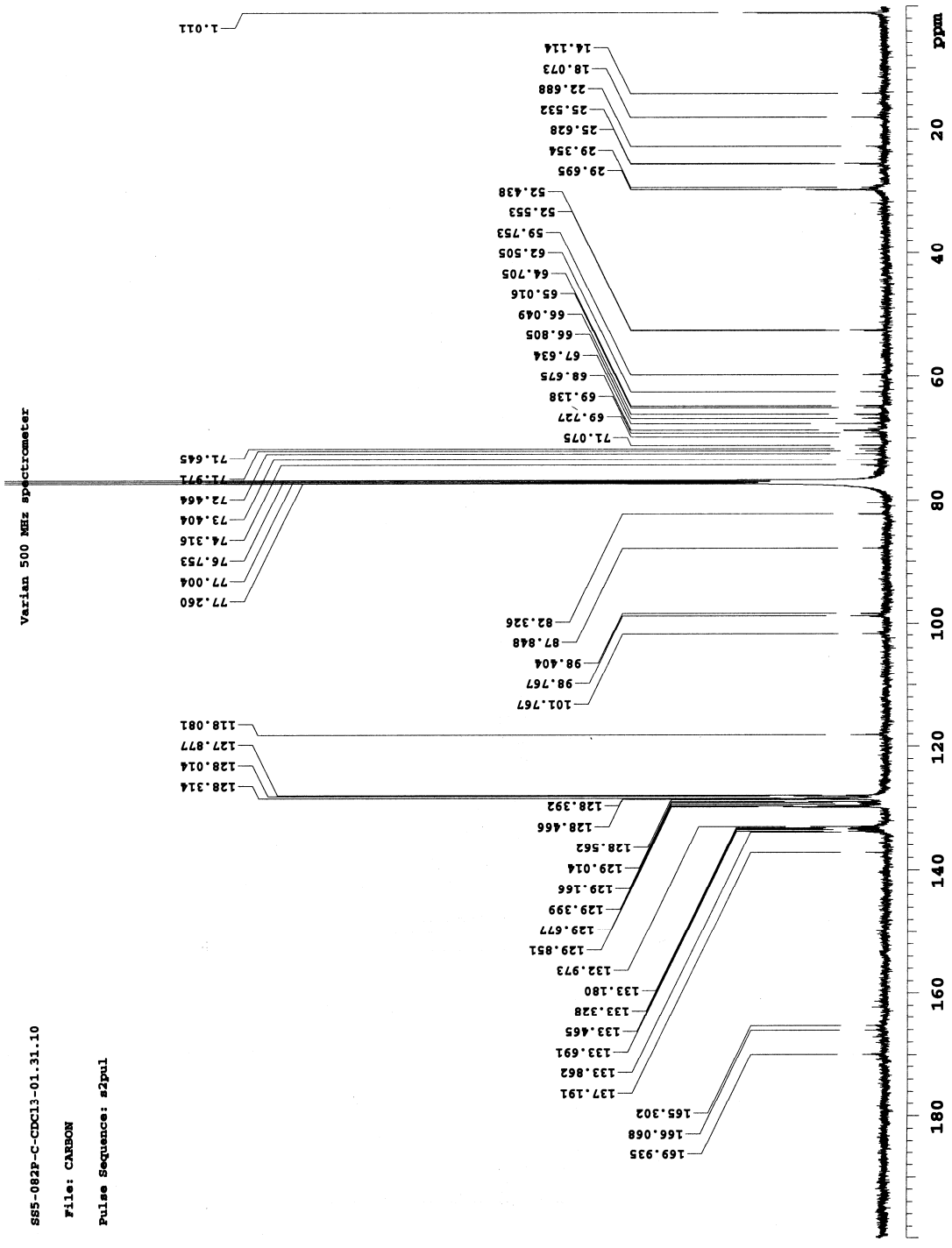
^{1}H NMR (Compound 623)



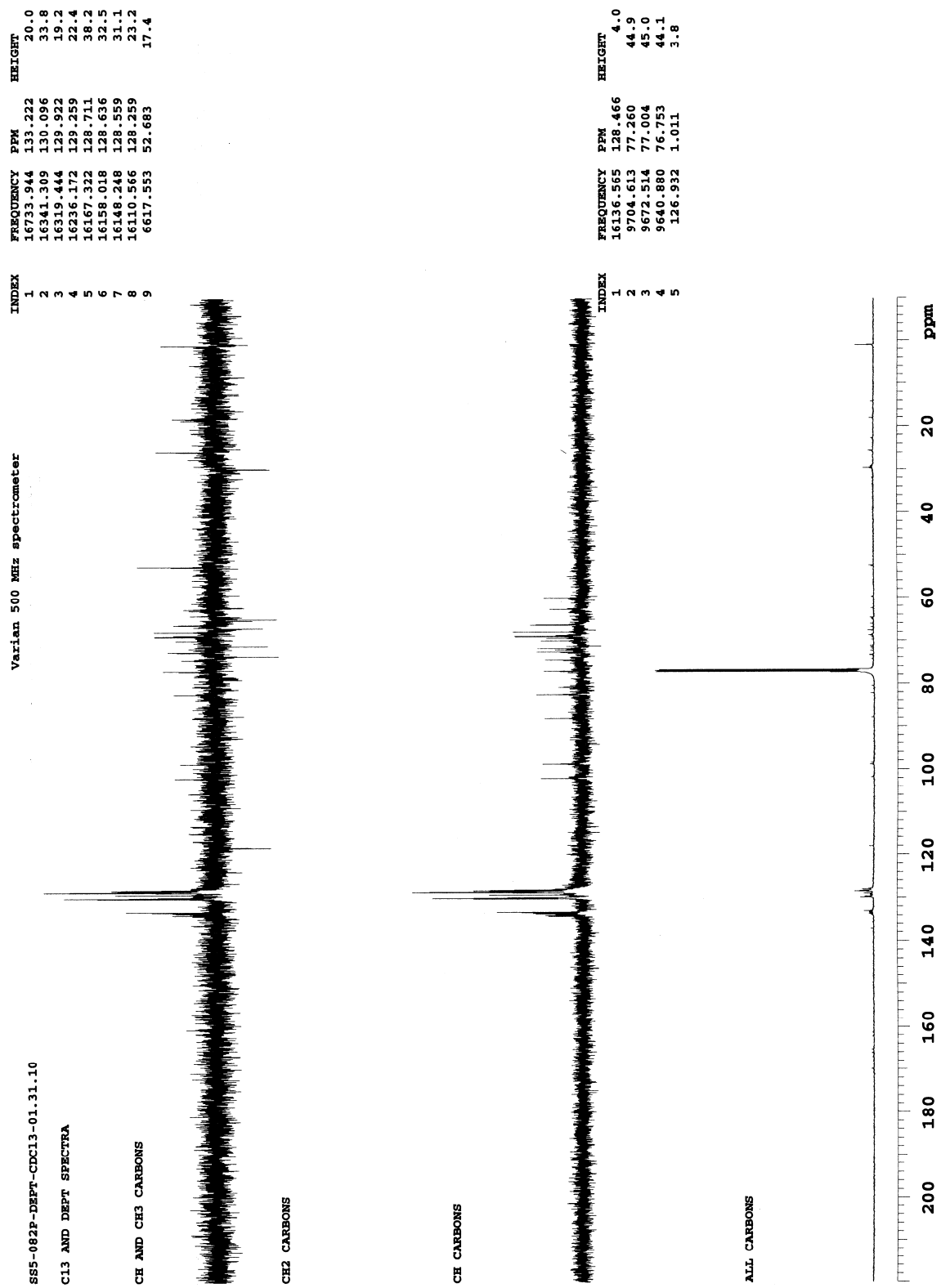
^{13}C NMR (Compound 623)



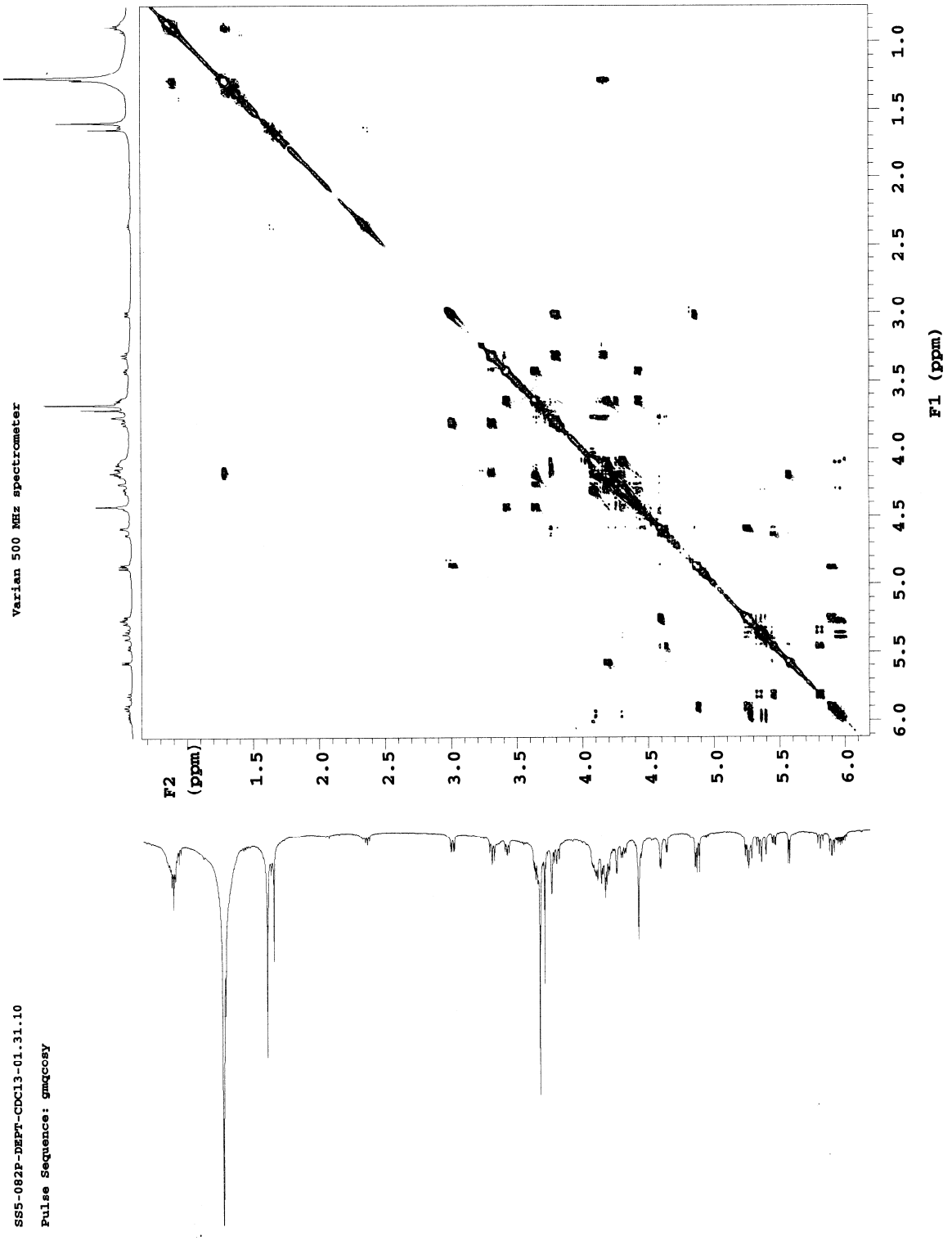
^{13}C NMR (Compound 623)



DEPT NMR (Compound 623)



^{1}H-^{1}H GDQFCOSY NMR (Compound 623)



APPENDIX VII

X-ray Crystallographic Data

1. Major diastereomer of diketopiperazine (±)-**12**

Table 1. Crystal data and structure refinement for BANT.

Identification code	bant
Empirical formula	C27 H34 N2 O5
Formula weight	466.56
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.3537(3) A alpha = 62.0420(10) deg. b = 12.2519(4) A beta = 82.9170(10) deg. c = 12.3436(4) A gamma = 88.012(2) deg.
Volume	1239.52(7) A^3
Z, Calculated density	2, 1.250 Mg/m^3
Absorption coefficient	0.086 mm^-1
F(000)	500
Crystal size	0.40 x 0.29 x 0.19 mm
Theta range for data collection	1.88 to 30.73 deg.
Limiting indices	-13<=h<=13, -15<=k<=17, 0<=l<=17
Reflections collected / unique	38899 / 7644 [R(int) = 0.0292]
Completeness to theta = 28.30	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9838 and 0.9664
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7644 / 0 / 317
Goodness-of-fit on F^2	1.093
Final R indices [I>2sigma(I)]	R1 = 0.0410, wR2 = 0.1114
R indices (all data)	R1 = 0.0503, wR2 = 0.1163
Largest diff. peak and hole	0.444 and -0.251 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for BANT.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	8557(1)	9338(1)	-49(1)	16(1)
O(2)	6560(1)	7862(1)	4456(1)	18(1)
N(1)	7265(1)	9525(1)	2621(1)	13(1)
C(1)	8319(1)	10059(1)	1480(1)	13(1)
C(2)	8585(1)	9086(1)	1036(1)	13(1)
N(2)	8858(1)	7943(1)	1934(1)	13(1)
C(3)	8668(1)	7642(1)	3251(1)	13(1)
C(4)	7419(1)	8359(1)	3501(1)	13(1)
C(5)	6053(1)	10238(1)	2747(1)	14(1)
C(6)	6169(1)	10946(1)	3353(1)	19(1)
C(7)	5033(1)	11720(1)	3340(1)	27(1)
C(8)	3844(1)	11780(1)	2759(1)	28(1)
C(9)	3721(1)	11030(1)	2210(1)	23(1)
C(10)	4816(1)	10225(1)	2218(1)	16(1)
C(11)	7441(1)	10864(1)	4020(1)	27(1)
C(12)	4657(1)	9338(1)	1709(1)	21(1)
C(13)	7849(1)	11272(1)	469(1)	14(1)
C(14)	8091(1)	12342(1)	721(1)	16(1)
O(3)	9081(1)	12429(1)	1219(1)	21(1)
O(4)	7097(1)	13198(1)	272(1)	25(1)
C(15)	7255(2)	14324(1)	382(1)	38(1)
C(16)	8206(2)	15258(1)	-722(1)	50(1)
C(17)	8842(1)	6887(1)	1656(1)	16(1)
C(18)	7418(1)	6180(1)	2148(1)	15(1)
C(19)	6210(1)	6631(1)	1527(1)	17(1)
C(20)	4876(1)	6033(1)	2019(1)	19(1)
C(21)	4726(1)	4957(1)	3156(1)	17(1)
C(22)	5918(1)	4487(1)	3785(1)	19(1)
C(23)	7252(1)	5098(1)	3274(1)	18(1)
O(5)	3388(1)	4411(1)	3594(1)	23(1)
C(24)	10078(1)	7662(1)	3809(1)	17(1)
C(25)	9689(1)	7197(1)	5205(1)	21(1)
C(26)	11142(1)	6774(1)	3603(1)	23(1)
C(27)	10827(1)	8932(1)	3246(1)	21(1)

Table 3. Bond lengths [A] and angles [deg] for BANT.

O(1)-C(2)	1.2294(10)
O(2)-C(4)	1.2385(10)
N(1)-C(4)	1.3456(11)
N(1)-C(5)	1.4451(12)
N(1)-C(1)	1.4903(11)
C(1)-C(13)	1.5198(12)
C(1)-C(2)	1.5302(12)
C(2)-N(2)	1.3581(11)
N(2)-C(3)	1.4763(11)
N(2)-C(17)	1.4874(11)
C(3)-C(4)	1.5255(13)
C(3)-C(24)	1.5676(13)
C(5)-C(6)	1.3987(12)
C(5)-C(10)	1.4011(13)
C(6)-C(7)	1.3956(15)
C(6)-C(11)	1.5035(15)
C(7)-C(8)	1.3781(18)
C(8)-C(9)	1.3874(16)
C(9)-C(10)	1.3948(14)
C(10)-C(12)	1.5074(13)
C(13)-C(14)	1.5127(12)
C(14)-O(3)	1.2069(12)
C(14)-O(4)	1.3362(12)
O(4)-C(15)	1.4610(13)
C(15)-C(16)	1.506(2)
C(17)-C(18)	1.5100(12)
C(18)-C(19)	1.3939(13)
C(18)-C(23)	1.3953(12)
C(19)-C(20)	1.3863(13)
C(20)-C(21)	1.3985(13)
C(21)-O(5)	1.3629(11)
C(21)-C(22)	1.3880(14)
C(22)-C(23)	1.3939(13)
C(24)-C(27)	1.5292(13)
C(24)-C(26)	1.5366(14)
C(24)-C(25)	1.5379(13)

C(4)-N(1)-C(5)	120.56(7)
C(4)-N(1)-C(1)	119.42(7)
C(5)-N(1)-C(1)	119.96(7)
N(1)-C(1)-C(13)	113.33(7)
N(1)-C(1)-C(2)	108.15(7)
C(13)-C(1)-C(2)	111.69(7)
O(1)-C(2)-N(2)	123.68(8)
O(1)-C(2)-C(1)	121.87(8)
N(2)-C(2)-C(1)	114.44(7)
C(2)-N(2)-C(3)	121.45(7)
C(2)-N(2)-C(17)	118.29(7)
C(3)-N(2)-C(17)	116.87(7)
N(2)-C(3)-C(4)	109.99(7)
N(2)-C(3)-C(24)	115.87(7)
C(4)-C(3)-C(24)	115.48(7)
O(2)-C(4)-N(1)	122.13(8)
O(2)-C(4)-C(3)	120.70(8)
N(1)-C(4)-C(3)	117.11(7)
C(6)-C(5)-C(10)	122.33(9)
C(6)-C(5)-N(1)	119.26(8)
C(10)-C(5)-N(1)	118.37(8)
C(7)-C(6)-C(5)	117.31(10)

C(7)-C(6)-C(11)	120.73(9)
C(5)-C(6)-C(11)	121.94(9)
C(8)-C(7)-C(6)	121.32(10)
C(7)-C(8)-C(9)	120.47(10)
C(8)-C(9)-C(10)	120.31(10)
C(9)-C(10)-C(5)	118.03(9)
C(9)-C(10)-C(12)	121.13(9)
C(5)-C(10)-C(12)	120.81(8)
C(14)-C(13)-C(1)	111.72(7)
O(3)-C(14)-O(4)	124.74(9)
O(3)-C(14)-C(13)	124.35(9)
O(4)-C(14)-C(13)	110.85(8)
C(14)-O(4)-C(15)	116.69(9)
O(4)-C(15)-C(16)	110.09(11)
N(2)-C(17)-C(18)	111.33(7)
C(19)-C(18)-C(23)	118.09(8)
C(19)-C(18)-C(17)	120.85(8)
C(23)-C(18)-C(17)	120.95(8)
C(20)-C(19)-C(18)	121.11(8)
C(19)-C(20)-C(21)	120.02(9)
O(5)-C(21)-C(22)	122.83(8)
O(5)-C(21)-C(20)	117.39(9)
C(22)-C(21)-C(20)	119.78(9)
C(21)-C(22)-C(23)	119.43(8)
C(22)-C(23)-C(18)	121.56(9)
C(27)-C(24)-C(26)	108.12(8)
C(27)-C(24)-C(25)	108.61(8)
C(26)-C(24)-C(25)	109.17(8)
C(27)-C(24)-C(3)	114.55(8)
C(26)-C(24)-C(3)	108.12(8)
C(25)-C(24)-C(3)	108.18(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for BANT. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	18(1)	18(1)	13(1)	-7(1)	0(1)	-1(1)
O(2)	18(1)	16(1)	14(1)	-4(1)	4(1)	-2(1)
N(1)	13(1)	13(1)	12(1)	-5(1)	1(1)	0(1)
C(1)	12(1)	12(1)	11(1)	-4(1)	1(1)	-2(1)
C(2)	10(1)	13(1)	15(1)	-6(1)	1(1)	-2(1)
N(2)	14(1)	12(1)	13(1)	-6(1)	0(1)	-1(1)
C(3)	13(1)	13(1)	12(1)	-4(1)	0(1)	-1(1)
C(4)	13(1)	14(1)	13(1)	-6(1)	-1(1)	-2(1)
C(5)	16(1)	12(1)	13(1)	-5(1)	2(1)	1(1)
C(6)	26(1)	16(1)	15(1)	-8(1)	4(1)	-4(1)
C(7)	36(1)	19(1)	26(1)	-14(1)	9(1)	-1(1)
C(8)	26(1)	18(1)	32(1)	-8(1)	9(1)	6(1)
C(9)	17(1)	19(1)	24(1)	-4(1)	3(1)	2(1)
C(10)	15(1)	15(1)	15(1)	-5(1)	2(1)	-1(1)
C(11)	38(1)	27(1)	19(1)	-14(1)	-3(1)	-7(1)
C(12)	17(1)	24(1)	23(1)	-12(1)	-2(1)	-3(1)
C(13)	15(1)	12(1)	12(1)	-4(1)	-1(1)	-1(1)
C(14)	20(1)	12(1)	13(1)	-4(1)	1(1)	0(1)
O(3)	23(1)	19(1)	23(1)	-10(1)	-5(1)	-2(1)
O(4)	32(1)	18(1)	30(1)	-13(1)	-13(1)	10(1)
C(15)	54(1)	23(1)	50(1)	-24(1)	-23(1)	16(1)
C(16)	85(1)	16(1)	47(1)	-10(1)	-31(1)	1(1)
C(17)	16(1)	13(1)	19(1)	-8(1)	2(1)	-1(1)
C(18)	16(1)	11(1)	16(1)	-7(1)	0(1)	-1(1)
C(19)	22(1)	13(1)	14(1)	-3(1)	-3(1)	-2(1)
C(20)	18(1)	16(1)	19(1)	-4(1)	-6(1)	-1(1)
C(21)	16(1)	13(1)	18(1)	-6(1)	-1(1)	-2(1)
C(22)	21(1)	12(1)	17(1)	-2(1)	-3(1)	-2(1)
C(23)	18(1)	13(1)	21(1)	-4(1)	-5(1)	1(1)
O(5)	17(1)	17(1)	26(1)	-2(1)	-2(1)	-4(1)
C(24)	14(1)	17(1)	15(1)	-3(1)	-2(1)	-1(1)
C(25)	19(1)	23(1)	15(1)	-4(1)	-4(1)	-1(1)
C(26)	16(1)	25(1)	24(1)	-8(1)	-3(1)	5(1)
C(27)	17(1)	20(1)	20(1)	-3(1)	-5(1)	-5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for BANT.

	x	y	z	U(eq)
H(1)	9249	10222	1708	15
H(3)	8323	6759	3702	16
H(7)	5082	12216	3739	32
H(8)	3102	12337	2735	34
H(9)	2888	11066	1826	28
H(11A)	7548	10004	4639	32
H(11B)	7288	11384	4430	32
H(11C)	8315	11150	3426	32
H(12A)	3773	9510	1311	25
H(12B)	4606	8488	2384	25
H(12C)	5489	9438	1101	25
H(13A)	8397	11434	-333	17
H(13B)	6813	11204	408	17
H(15A)	7684	14124	1145	46
H(15B)	6296	14674	437	46
H(16A)	9176	14932	-739	59
H(16B)	8256	16027	-667	59
H(16C)	7805	15421	-1480	59
H(17A)	9628	6323	2032	19
H(17B)	9019	7200	751	19
H(19)	6303	7360	754	21
H(20)	4064	6354	1584	23
H(22)	5825	3756	4556	22
H(23)	8068	4769	3703	22
H(105)	3431(18)	3697(16)	4287(16)	43(4)
H(25A)	10565	7161	5580	25
H(25B)	9238	6370	5583	25
H(25C)	9015	7763	5342	25
H(26A)	11418	7081	2714	28
H(26B)	10683	5951	3960	28
H(26C)	12003	6723	4002	28
H(27A)	11705	8863	3631	25
H(27B)	10177	9508	3391	25
H(27C)	11080	9241	2355	25

Table 6. Torsion angles [deg] for BANT.

C(4)-N(1)-C(1)-C(13)	168.55(7)
C(5)-N(1)-C(1)-C(13)	-8.55(11)
C(4)-N(1)-C(1)-C(2)	44.15(10)
C(5)-N(1)-C(1)-C(2)	-132.95(8)
N(1)-C(1)-C(2)-O(1)	132.48(8)
C(13)-C(1)-C(2)-O(1)	7.10(12)
N(1)-C(1)-C(2)-N(2)	-47.92(10)
C(13)-C(1)-C(2)-N(2)	-173.29(7)
O(1)-C(2)-N(2)-C(3)	-170.84(8)
C(1)-C(2)-N(2)-C(3)	9.57(11)
O(1)-C(2)-N(2)-C(17)	-12.29(13)
C(1)-C(2)-N(2)-C(17)	168.12(7)
C(2)-N(2)-C(3)-C(4)	33.36(11)
C(17)-N(2)-C(3)-C(4)	-125.48(8)
C(2)-N(2)-C(3)-C(24)	-99.89(10)
C(17)-N(2)-C(3)-C(24)	101.27(9)
C(5)-N(1)-C(4)-O(2)	-1.56(13)
C(1)-N(1)-C(4)-O(2)	-178.64(8)
C(5)-N(1)-C(4)-C(3)	175.71(7)
C(1)-N(1)-C(4)-C(3)	-1.37(11)
N(2)-C(3)-C(4)-O(2)	139.48(8)
C(24)-C(3)-C(4)-O(2)	-87.08(10)
N(2)-C(3)-C(4)-N(1)	-37.83(10)
C(24)-C(3)-C(4)-N(1)	95.61(9)
C(4)-N(1)-C(5)-C(6)	88.99(10)
C(1)-N(1)-C(5)-C(6)	-93.94(10)
C(4)-N(1)-C(5)-C(10)	-93.16(10)
C(1)-N(1)-C(5)-C(10)	83.91(10)
C(10)-C(5)-C(6)-C(7)	-4.41(13)
N(1)-C(5)-C(6)-C(7)	173.35(8)
C(10)-C(5)-C(6)-C(11)	174.17(9)
N(1)-C(5)-C(6)-C(11)	-8.07(13)
C(5)-C(6)-C(7)-C(8)	0.33(14)
C(11)-C(6)-C(7)-C(8)	-178.27(9)
C(6)-C(7)-C(8)-C(9)	2.45(16)
C(7)-C(8)-C(9)-C(10)	-1.25(15)
C(8)-C(9)-C(10)-C(5)	-2.64(14)
C(8)-C(9)-C(10)-C(12)	175.52(9)
C(6)-C(5)-C(10)-C(9)	5.56(13)
N(1)-C(5)-C(10)-C(9)	-172.22(8)
C(6)-C(5)-C(10)-C(12)	-172.60(8)
N(1)-C(5)-C(10)-C(12)	9.62(12)
N(1)-C(1)-C(13)-C(14)	77.71(9)
C(2)-C(1)-C(13)-C(14)	-159.83(7)
C(1)-C(13)-C(14)-O(3)	34.26(12)
C(1)-C(13)-C(14)-O(4)	-148.35(8)
O(3)-C(14)-O(4)-C(15)	1.17(15)
C(13)-C(14)-O(4)-C(15)	-176.21(9)
C(14)-O(4)-C(15)-C(16)	88.01(13)
C(2)-N(2)-C(17)-C(18)	-98.12(9)
C(3)-N(2)-C(17)-C(18)	61.41(10)
N(2)-C(17)-C(18)-C(19)	77.96(10)
N(2)-C(17)-C(18)-C(23)	-98.15(10)
C(23)-C(18)-C(19)-C(20)	0.89(14)
C(17)-C(18)-C(19)-C(20)	-175.33(8)
C(18)-C(19)-C(20)-C(21)	-0.14(15)
C(19)-C(20)-C(21)-O(5)	179.89(9)
C(19)-C(20)-C(21)-C(22)	-0.40(15)
O(5)-C(21)-C(22)-C(23)	179.85(9)

C(20)-C(21)-C(22)-C(23)	0.17(14)
C(21)-C(22)-C(23)-C(18)	0.62(15)
C(19)-C(18)-C(23)-C(22)	-1.14(14)
C(17)-C(18)-C(23)-C(22)	175.08(9)
N(2)-C(3)-C(24)-C(27)	64.56(11)
C(4)-C(3)-C(24)-C(27)	-66.12(10)
N(2)-C(3)-C(24)-C(26)	-56.05(10)
C(4)-C(3)-C(24)-C(26)	173.27(7)
N(2)-C(3)-C(24)-C(25)	-174.15(8)
C(4)-C(3)-C(24)-C(25)	55.16(10)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for BANT [A and deg.].

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O5-H105	0.896	1.810	170.91	2.699	O2 [-x+1, -y+1, -z+1]

2. 4-hydroxybenzyl alcohol (**14**) from μwave reaction

Table 1. Crystal data and structure refinement for xava.

Identification code	xava
Empirical formula	C7 H8 O2
Formula weight	124.13
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pna21
Unit cell dimensions	a = 9.3503(4) A alpha = 90 deg. b = 11.0090(5) A beta = 90 deg. c = 5.8847(3) A gamma = 90 deg.
Volume	605.76(5) A^3
Z, Calculated density	4, 1.361 Mg/m^3
Absorption coefficient	0.099 mm^-1
F(000)	264
Crystal size	0.10 x 0.09 x 0.09 mm
Theta range for data collection	2.86 to 28.31 deg.

Limiting indices	0<=h<=12, 0<=k<=14, -7<=l<=7
Reflections collected / unique	10949 / 1512 [R(int) = 0.0696]
Completeness to theta = 28.30	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9911 and 0.9901
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1512 / 1 / 90
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.0733
R indices (all data)	R1 = 0.0532, wR2 = 0.0776
Absolute structure parameter	-0.9(13)
Largest diff. peak and hole	0.166 and -0.165 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for xava.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	1607(1)	222(1)	6648(2)	18(1)
C(1)	2542(2)	709(1)	5100(3)	15(1)
C(2)	2791(2)	198(2)	2991(3)	15(1)
C(3)	3784(2)	731(1)	1531(3)	15(1)
C(4)	4517(2)	1779(1)	2142(3)	15(1)
C(5)	4240(2)	2283(2)	4273(3)	17(1)
C(6)	3263(2)	1764(2)	5750(3)	16(1)
C(7)	5562(2)	2368(1)	556(3)	16(1)
O(2)	4958(1)	3494(1)	-261(2)	18(1)

Table 3. Bond lengths [A] and angles [deg] for xava.

O(1)-C(1)	1.3716(19)
C(1)-C(2)	1.382(2)
C(1)-C(6)	1.397(2)
C(2)-C(3)	1.394(2)
C(3)-C(4)	1.390(2)
C(4)-C(5)	1.395(2)
C(4)-C(7)	1.499(2)
C(5)-C(6)	1.384(2)
C(7)-O(2)	1.4449(19)
O(1)-C(1)-C(2)	123.03(14)
O(1)-C(1)-C(6)	116.79(15)
C(2)-C(1)-C(6)	120.18(15)
C(1)-C(2)-C(3)	119.64(15)
C(4)-C(3)-C(2)	121.23(16)
C(3)-C(4)-C(5)	118.11(16)
C(3)-C(4)-C(7)	121.33(16)
C(5)-C(4)-C(7)	120.56(15)
C(6)-C(5)-C(4)	121.49(15)
C(5)-C(6)-C(1)	119.34(17)
O(2)-C(7)-C(4)	108.88(12)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for xava.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	22(1)	16(1)	17(1)	-3(1)	4(1)	-6(1)
C(1)	14(1)	13(1)	17(1)	3(1)	1(1)	1(1)
C(2)	15(1)	13(1)	16(1)	1(1)	-3(1)	0(1)
C(3)	16(1)	15(1)	13(1)	-1(1)	0(1)	4(1)
C(4)	15(1)	15(1)	15(1)	1(1)	-2(1)	4(1)
C(5)	17(1)	14(1)	20(1)	-1(1)	-3(1)	0(1)
C(6)	18(1)	17(1)	15(1)	-3(1)	-1(1)	0(1)
C(7)	15(1)	14(1)	20(1)	3(1)	2(1)	3(1)
O(2)	19(1)	14(1)	20(1)	2(1)	5(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for xava.

	x	y	z	U(eq)
H(01)	1170(20)	-364(16)	6050(40)	26(6)
H(2)	2288	-512	2538	17
H(3)	3963	370	93	17
H(5)	4733	2998	4721	20
H(6)	3084	2122	7191	20
H(7A)	6472	2530	1361	20
H(7B)	5764	1821	-739	20
H(02)	5560(20)	3849(17)	-1170(40)	37(7)

Table 6. Hydrogen bonds for xava [A and deg.].

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O1-H01	0.842	1.812	173.27	2.649	O2 [-x+1/2, y-1/2, z+1/2]
O2-H02	0.869	1.911	169.99	2.772	O1 [x+1/2, -y+1/2, z-1]

3. 2-azaspiro[4.5]deca-6,9-diene-3,8-dione (±)-**16**

Table 1. Crystal data and structure refinement for BTRA.

Identification code	btra
Empirical formula	C22 H32 N2 O5
Formula weight	404.50
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.9541(4) A alpha = 89.230(2) deg.
	b = 12.8285(5) A beta = 82.115(2) deg.
	c = 18.2464(7) A gamma = 78.410(2) deg.
Volume	2260.67(15) A^3
Z, Calculated density	4, 1.188 Mg/m^3

Absorption coefficient	0.084 mm^-1
F(000)	872
Crystal size	0.16 x 0.16 x 0.04 mm
Theta range for data collection	1.96 to 28.37 deg.
Limiting indices	-13<=h<=13, -17<=k<=17, 0<=l<=24
Reflections collected / unique	59289 / 11216 [R(int) = 0.0897]
Completeness to theta = 28.30	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9966 and 0.9867
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11216 / 0 / 553
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0723, wR2 = 0.1522
R indices (all data)	R1 = 0.1504, wR2 = 0.1791
Largest diff. peak and hole	0.347 and -0.346 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for BTRA.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	2489(2)	3262(1)	-388(1)	24(1)
C(1)	2595(2)	3863(2)	190(1)	25(1)
C(2)	4031(2)	3514(2)	406(1)	26(1)
C(3)	4497(2)	2364(2)	76(1)	27(1)
C(4)	3779(2)	2496(2)	-635(1)	28(1)
O(1)	1690(2)	4584(1)	495(1)	30(1)
C(5)	4085(3)	3660(2)	1221(1)	29(1)
C(6)	4006(3)	4810(2)	1420(2)	33(1)
O(2)	4498(2)	5435(2)	1034(1)	50(1)
O(3)	3349(2)	5041(1)	2105(1)	39(1)
C(7)	3338(3)	6104(2)	2382(2)	47(1)
C(8)	2401(4)	6233(2)	3103(2)	65(1)
C(9)	3917(3)	1595(2)	583(1)	28(1)
C(10)	4690(3)	814(2)	918(2)	32(1)
C(11)	6193(3)	643(2)	800(2)	38(1)
C(12)	6813(3)	1304(2)	253(2)	41(1)
C(13)	6039(3)	2078(2)	-87(2)	37(1)
O(4)	6915(2)	-33(2)	1152(1)	52(1)
C(14)	1318(3)	3514(2)	-806(1)	26(1)
C(15)	827(3)	2524(2)	-1041(1)	33(1)
C(16)	409(3)	1883(2)	-367(2)	38(1)

C(17)	-400(3)	2889(2)	-1467(2)	53(1)
C(18)	1724(3)	4175(2)	-1474(1)	36(1)
O(5)	2649(2)	3789(2)	-1963(1)	75(1)
N(2)	990(2)	5173(2)	-1462(1)	29(1)
C(19)	1091(3)	5952(2)	-2062(2)	38(1)
C(20)	96(3)	6969(2)	-1795(2)	44(1)
C(21)	2547(3)	6137(4)	-2218(3)	111(2)
C(22)	635(4)	5535(3)	-2744(2)	79(1)
N(3)	7549(2)	-1045(2)	4019(1)	29(1)
C(23)	7588(3)	-59(2)	4248(1)	28(1)
C(24)	8975(2)	187(2)	3953(1)	28(1)
C(25)	9502(2)	-615(2)	3296(1)	27(1)
C(26)	8872(3)	-1576(2)	3600(1)	32(1)
O(6)	6635(2)	552(1)	4629(1)	32(1)
C(27)	8952(3)	1352(2)	3785(1)	30(1)
C(28)	8784(3)	2026(2)	4466(2)	37(1)
O(7)	9059(2)	1715(2)	5063(1)	53(1)
O(8)	8305(2)	3038(2)	4308(1)	54(1)
C(29)	8220(5)	3800(3)	4897(2)	90(2)
C(30)	9099(7)	4413(7)	4892(4)	75(2)
C(30')	7559(11)	4779(5)	4679(4)	97(4)
C(31)	8874(3)	-199(2)	2618(1)	27(1)
C(32)	9596(3)	32(2)	1994(1)	29(1)
C(33)	11117(3)	-126(2)	1911(1)	31(1)
C(34)	11779(3)	-608(2)	2536(1)	30(1)
C(35)	11049(3)	-854(2)	3158(1)	30(1)
O(9)	11781(2)	136(2)	1351(1)	46(1)
C(36)	6446(3)	-1594(2)	4336(1)	34(1)
C(37)	6133(3)	-2379(2)	3790(2)	42(1)
C(38)	5648(3)	-1809(2)	3108(2)	48(1)
C(39)	5027(3)	-2947(3)	4170(2)	61(1)
C(40)	6862(3)	-2134(2)	5049(2)	41(1)
O(10)	7914(2)	-2836(2)	5015(1)	64(1)
N(4)	6013(2)	-1783(2)	5664(1)	36(1)
C(41)	6110(3)	-2211(2)	6417(2)	45(1)
C(42)	4973(3)	-1546(3)	6934(2)	54(1)
C(43)	7513(3)	-2144(4)	6642(2)	86(1)
C(44)	5905(4)	-3355(3)	6416(2)	78(1)

Table 3. Bond lengths [A] and angles [deg] for BTRA.

N(1)-C(1)	1.343(3)
N(1)-C(14)	1.460(3)
N(1)-C(4)	1.471(3)
C(1)-O(1)	1.233(3)
C(1)-C(2)	1.514(3)
C(2)-C(5)	1.510(3)
C(2)-C(3)	1.558(3)
C(3)-C(9)	1.490(3)
C(3)-C(13)	1.493(3)
C(3)-C(4)	1.557(3)
C(5)-C(6)	1.508(3)
C(6)-O(2)	1.195(3)
C(6)-O(3)	1.336(3)
O(3)-C(7)	1.458(3)
C(7)-C(8)	1.494(4)
C(9)-C(10)	1.331(3)
C(10)-C(11)	1.454(4)
C(11)-O(4)	1.241(3)

C(11)-C(12)	1.456(4)
C(12)-C(13)	1.332(3)
C(14)-C(18)	1.530(3)
C(14)-C(15)	1.535(4)
C(15)-C(16)	1.527(4)
C(15)-C(17)	1.529(3)
C(18)-O(5)	1.221(3)
C(18)-N(2)	1.340(3)
N(2)-C(19)	1.479(3)
C(19)-C(21)	1.504(4)
C(19)-C(20)	1.512(4)
C(19)-C(22)	1.521(4)
N(3)-C(23)	1.346(3)
N(3)-C(26)	1.469(3)
N(3)-C(36)	1.471(3)
C(23)-O(6)	1.238(3)
C(23)-C(24)	1.504(3)
C(24)-C(27)	1.518(3)
C(24)-C(25)	1.554(3)
C(25)-C(35)	1.494(3)
C(25)-C(31)	1.506(3)
C(25)-C(26)	1.556(3)
C(27)-C(28)	1.494(4)
C(28)-O(7)	1.202(3)
C(28)-O(8)	1.332(3)
O(8)-C(29)	1.445(4)
C(29)-C(30)	1.289(7)
C(29)-C(30')	1.377(7)
C(31)-C(32)	1.324(3)
C(32)-C(33)	1.474(3)
C(33)-O(9)	1.221(3)
C(33)-C(34)	1.462(3)
C(34)-C(35)	1.331(3)
C(36)-C(37)	1.530(4)
C(36)-C(40)	1.534(3)
C(37)-C(38)	1.523(4)
C(37)-C(39)	1.524(4)
C(40)-O(10)	1.231(3)
C(40)-N(4)	1.333(4)
N(4)-C(41)	1.481(3)
C(41)-C(42)	1.497(4)
C(41)-C(44)	1.521(4)
C(41)-C(43)	1.528(4)

C(1)-N(1)-C(14)	121.83(19)
C(1)-N(1)-C(4)	112.6(2)
C(14)-N(1)-C(4)	124.40(19)
O(1)-C(1)-N(1)	126.5(2)
O(1)-C(1)-C(2)	125.1(2)
N(1)-C(1)-C(2)	108.5(2)
C(5)-C(2)-C(1)	113.6(2)
C(5)-C(2)-C(3)	117.43(19)
C(1)-C(2)-C(3)	102.84(19)
C(9)-C(3)-C(13)	112.3(2)
C(9)-C(3)-C(4)	110.2(2)
C(13)-C(3)-C(4)	112.9(2)
C(9)-C(3)-C(2)	110.4(2)
C(13)-C(3)-C(2)	110.3(2)
C(4)-C(3)-C(2)	100.12(17)
N(1)-C(4)-C(3)	102.19(18)
C(6)-C(5)-C(2)	111.70(19)
O(2)-C(6)-O(3)	123.5(2)
O(2)-C(6)-C(5)	125.4(3)

O(3)-C(6)-C(5)	111.1(2)
C(6)-O(3)-C(7)	115.6(2)
O(3)-C(7)-C(8)	106.1(2)
C(10)-C(9)-C(3)	123.7(2)
C(9)-C(10)-C(11)	121.4(2)
O(4)-C(11)-C(10)	121.6(3)
O(4)-C(11)-C(12)	121.5(2)
C(10)-C(11)-C(12)	116.9(2)
C(13)-C(12)-C(11)	121.5(2)
C(12)-C(13)-C(3)	123.5(2)
N(1)-C(14)-C(18)	108.2(2)
N(1)-C(14)-C(15)	113.15(18)
C(18)-C(14)-C(15)	111.6(2)
C(16)-C(15)-C(17)	110.4(2)
C(16)-C(15)-C(14)	110.8(2)
C(17)-C(15)-C(14)	108.3(2)
O(5)-C(18)-N(2)	125.1(2)
O(5)-C(18)-C(14)	120.6(2)
N(2)-C(18)-C(14)	114.4(2)
C(18)-N(2)-C(19)	125.6(2)
N(2)-C(19)-C(21)	110.0(2)
N(2)-C(19)-C(20)	106.7(2)
C(21)-C(19)-C(20)	110.5(3)
N(2)-C(19)-C(22)	108.8(2)
C(21)-C(19)-C(22)	111.5(3)
C(20)-C(19)-C(22)	109.2(2)
C(23)-N(3)-C(26)	112.2(2)
C(23)-N(3)-C(36)	121.3(2)
C(26)-N(3)-C(36)	124.5(2)
O(6)-C(23)-N(3)	125.8(2)
O(6)-C(23)-C(24)	125.5(2)
N(3)-C(23)-C(24)	108.7(2)
C(23)-C(24)-C(27)	114.6(2)
C(23)-C(24)-C(25)	103.1(2)
C(27)-C(24)-C(25)	116.60(19)
C(35)-C(25)-C(31)	112.2(2)
C(35)-C(25)-C(24)	110.5(2)
C(31)-C(25)-C(24)	110.40(18)
C(35)-C(25)-C(26)	113.55(19)
C(31)-C(25)-C(26)	109.4(2)
C(24)-C(25)-C(26)	100.18(18)
N(3)-C(26)-C(25)	102.05(19)
C(28)-C(27)-C(24)	113.0(2)
O(7)-C(28)-O(8)	124.8(3)
O(7)-C(28)-C(27)	125.8(3)
O(8)-C(28)-C(27)	109.4(2)
C(28)-O(8)-C(29)	115.6(3)
C(30)-C(29)-C(30')	74.2(6)
C(30)-C(29)-O(8)	121.9(4)
C(30')-C(29)-O(8)	108.4(5)
C(32)-C(31)-C(25)	124.2(2)
C(31)-C(32)-C(33)	121.2(2)
O(9)-C(33)-C(34)	122.3(2)
O(9)-C(33)-C(32)	121.4(2)
C(34)-C(33)-C(32)	116.4(2)
C(35)-C(34)-C(33)	122.1(2)
C(34)-C(35)-C(25)	123.5(2)
N(3)-C(36)-C(37)	112.7(2)
N(3)-C(36)-C(40)	108.0(2)
C(37)-C(36)-C(40)	112.2(2)
C(38)-C(37)-C(39)	110.0(3)
C(38)-C(37)-C(36)	110.9(2)
C(39)-C(37)-C(36)	109.5(2)

O(10)-C(40)-N(4)	125.8(3)
O(10)-C(40)-C(36)	119.3(3)
N(4)-C(40)-C(36)	114.9(2)
C(40)-N(4)-C(41)	126.3(2)
N(4)-C(41)-C(42)	107.5(2)
N(4)-C(41)-C(44)	108.5(3)
C(42)-C(41)-C(44)	109.7(3)
N(4)-C(41)-C(43)	109.8(2)
C(42)-C(41)-C(43)	109.9(3)
C(44)-C(41)-C(43)	111.4(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for BTRA. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	26(1)	20(1)	25(1)	2(1)	-1(1)	-3(1)
C(1)	28(1)	20(1)	25(1)	6(1)	1(1)	-7(1)
C(2)	23(1)	25(1)	30(1)	2(1)	2(1)	-8(1)
C(3)	22(1)	23(1)	35(1)	2(1)	-2(1)	-5(1)
C(4)	27(1)	21(1)	32(1)	-2(1)	4(1)	-2(1)
O(1)	33(1)	24(1)	29(1)	-2(1)	0(1)	-1(1)
C(5)	30(1)	27(1)	34(1)	3(1)	-4(1)	-11(1)
C(6)	34(2)	34(2)	35(2)	0(1)	-13(1)	-10(1)
O(2)	64(1)	38(1)	53(1)	0(1)	1(1)	-29(1)
O(3)	58(1)	31(1)	30(1)	-2(1)	-15(1)	-9(1)
C(7)	78(2)	26(1)	42(2)	-6(1)	-31(2)	-7(1)
C(8)	118(3)	38(2)	36(2)	-5(1)	-25(2)	5(2)
C(9)	22(1)	29(1)	35(1)	1(1)	-4(1)	-7(1)
C(10)	31(2)	24(1)	44(2)	5(1)	-9(1)	-9(1)
C(11)	30(2)	25(1)	61(2)	-2(1)	-14(1)	-3(1)
C(12)	20(1)	33(2)	67(2)	-3(1)	-4(1)	-3(1)
C(13)	24(1)	38(2)	48(2)	-2(1)	4(1)	-9(1)
O(4)	38(1)	38(1)	82(2)	5(1)	-25(1)	-3(1)
C(14)	29(1)	27(1)	19(1)	2(1)	-2(1)	2(1)
C(15)	35(2)	32(1)	31(1)	-2(1)	-11(1)	2(1)
C(16)	38(2)	37(2)	43(2)	-3(1)	-6(1)	-15(1)
C(17)	60(2)	43(2)	58(2)	-11(2)	-35(2)	0(2)
C(18)	35(2)	39(2)	28(1)	9(1)	1(1)	6(1)
O(5)	80(2)	66(2)	46(1)	28(1)	31(1)	34(1)
N(2)	26(1)	31(1)	28(1)	8(1)	-1(1)	-3(1)
C(19)	33(2)	39(2)	39(2)	21(1)	-1(1)	-3(1)
C(20)	57(2)	35(2)	41(2)	14(1)	-6(1)	-10(1)
C(21)	39(2)	123(4)	168(5)	110(4)	-5(2)	-19(2)
C(22)	143(4)	52(2)	27(2)	13(2)	-13(2)	12(2)
N(3)	25(1)	32(1)	29(1)	6(1)	0(1)	-10(1)
C(23)	28(1)	37(2)	21(1)	10(1)	-6(1)	-9(1)
C(24)	28(1)	34(1)	24(1)	6(1)	-4(1)	-9(1)
C(25)	22(1)	33(1)	26(1)	6(1)	-3(1)	-6(1)
C(26)	29(1)	37(2)	31(1)	9(1)	-1(1)	-8(1)
O(6)	29(1)	41(1)	27(1)	2(1)	-2(1)	-9(1)
C(27)	31(1)	36(1)	25(1)	6(1)	-4(1)	-10(1)
C(28)	41(2)	44(2)	31(2)	7(1)	-2(1)	-26(1)
O(7)	69(2)	68(1)	33(1)	9(1)	-19(1)	-34(1)

O(8)	96(2)	35(1)	30(1)	-4(1)	9(1)	-27(1)
C(29)	168(5)	57(2)	50(2)	-23(2)	26(3)	-62(3)
C(30)	47(5)	101(6)	76(5)	-48(5)	8(4)	-23(4)
C(30')	195(10)	20(3)	48(4)	1(3)	35(5)	10(4)
C(31)	22(1)	30(1)	31(1)	4(1)	-6(1)	-5(1)
C(32)	30(1)	31(1)	27(1)	4(1)	-8(1)	-8(1)
C(33)	32(2)	32(1)	29(1)	-3(1)	1(1)	-12(1)
C(34)	22(1)	31(1)	37(2)	2(1)	-6(1)	-7(1)
C(35)	29(1)	29(1)	34(1)	7(1)	-9(1)	-6(1)
O(9)	36(1)	68(1)	35(1)	11(1)	5(1)	-20(1)
C(36)	30(2)	40(2)	33(2)	10(1)	0(1)	-15(1)
C(37)	37(2)	40(2)	50(2)	2(1)	2(1)	-16(1)
C(38)	49(2)	57(2)	43(2)	-10(2)	-4(2)	-22(2)
C(39)	60(2)	65(2)	67(2)	3(2)	-2(2)	-39(2)
C(40)	32(2)	47(2)	47(2)	20(1)	-5(1)	-14(1)
O(10)	43(1)	70(2)	66(2)	40(1)	11(1)	5(1)
N(4)	28(1)	48(1)	34(1)	17(1)	-5(1)	-12(1)
C(41)	31(2)	65(2)	40(2)	24(2)	-7(1)	-12(1)
C(42)	52(2)	78(2)	36(2)	21(2)	-12(2)	-18(2)
C(43)	43(2)	161(4)	59(2)	43(3)	-24(2)	-26(2)
C(44)	102(3)	64(2)	56(2)	31(2)	18(2)	-14(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for BTRA.

	x	y	z	U(eq)
H(2)	4636	3964	128	31
H(4A)	4351	2783	-1046	33
H(4B)	3589	1812	-795	33
H(5A)	3304	3403	1512	35
H(5B)	4957	3226	1352	35
H(7A)	2988	6650	2029	57
H(7B)	4283	6174	2456	57
H(8A)	1463	6188	3018	78
H(8B)	2386	6927	3324	78
H(8C)	2739	5668	3438	78
H(9)	2939	1666	673	34
H(10)	4250	358	1240	39
H(12)	7793	1181	136	49
H(13)	6492	2470	-454	44
H(14)	531	3967	-482	32
H(15)	1596	2067	-1373	40
H(16A)	-344	2327	-38	46
H(16B)	1206	1653	-101	46
H(16C)	97	1257	-529	46
H(17A)	-1134	3377	-1155	63
H(17B)	-755	2269	-1603	63
H(17C)	-100	3254	-1916	63
H(1N2)	250(30)	5320(20)	-1156(15)	44(9)
H(20A)	-846	6834	-1694	53
H(20B)	132	7512	-2176	53
H(20C)	359	7222	-1341	53
H(21A)	2796	6430	-1774	133
H(21B)	2609	6641	-2624	133
H(21C)	3184	5461	-2359	133
H(22A)	1230	4845	-2895	94

H(22B)	708	6041	-3148	94
H(22C)	-328	5450	-2629	94
H(24)	9595	-19	4341	34
H(26A)	8725	-2025	3193	39
H(26B)	9469	-2019	3925	39
H(27A)	9826	1414	3472	36
H(27B)	8180	1624	3500	36
H(29A)	7291	4266	4933	108
H(29B)	8246	3395	5362	108
H(30A)	9167	4782	4419	90
H(30B)	10008	3987	4957	90
H(30C)	8791	4937	5297	90
H(30D)	7453	5300	5082	117
H(30E)	6645	4729	4559	117
H(30F)	8111	5007	4242	117
H(31)	7897	-97	2639	33
H(32)	9124	306	1592	34
H(34)	12760	-750	2497	36
H(35)	11537	-1200	3535	36
H(36)	5584	-1043	4473	40
H(37)	6997	-2920	3633	50
H(38A)	5426	-2323	2774	58
H(38B)	6385	-1479	2852	58
H(38C)	4822	-1258	3257	58
H(39A)	4176	-2424	4327	73
H(39B)	5354	-3323	4603	73
H(39C)	4839	-3460	3823	73
H(1N4)	5190(30)	-1300(20)	5619(15)	49(9)
H(42A)	5094	-806	6922	65
H(42B)	5005	-1816	7438	65
H(42C)	4077	-1581	6781	65
H(43A)	8247	-2639	6335	103
H(43B)	7524	-2334	7163	103
H(43C)	7670	-1417	6571	103
H(44A)	5000	-3372	6269	93
H(44B)	5950	-3646	6913	93
H(44C)	6635	-3782	6065	93

Table 6. Torsion angles [deg] for BTRA.

C(14)-N(1)-C(1)-O(1)	9.9(3)
C(4)-N(1)-C(1)-O(1)	177.9(2)
C(14)-N(1)-C(1)-C(2)	-169.56(19)
C(4)-N(1)-C(1)-C(2)	-1.6(2)
O(1)-C(1)-C(2)-C(5)	30.9(3)
N(1)-C(1)-C(2)-C(5)	-149.60(19)
O(1)-C(1)-C(2)-C(3)	158.9(2)
N(1)-C(1)-C(2)-C(3)	-21.6(2)
C(5)-C(2)-C(3)-C(9)	43.5(3)
C(1)-C(2)-C(3)-C(9)	-82.0(2)
C(5)-C(2)-C(3)-C(13)	-81.2(3)
C(1)-C(2)-C(3)-C(13)	153.3(2)
C(5)-C(2)-C(3)-C(4)	159.6(2)
C(1)-C(2)-C(3)-C(4)	34.1(2)
C(1)-N(1)-C(4)-C(3)	24.0(2)
C(14)-N(1)-C(4)-C(3)	-168.31(19)
C(9)-C(3)-C(4)-N(1)	81.5(2)
C(13)-C(3)-C(4)-N(1)	-151.98(19)
C(2)-C(3)-C(4)-N(1)	-34.8(2)

C(1)-C(2)-C(5)-C(6)	-76.2(3)
C(3)-C(2)-C(5)-C(6)	163.8(2)
C(2)-C(5)-C(6)-O(2)	-34.9(4)
C(2)-C(5)-C(6)-O(3)	147.4(2)
O(2)-C(6)-O(3)-C(7)	-3.8(4)
C(5)-C(6)-O(3)-C(7)	174.0(2)
C(6)-O(3)-C(7)-C(8)	172.6(2)
C(13)-C(3)-C(9)-C(10)	7.1(4)
C(4)-C(3)-C(9)-C(10)	133.9(2)
C(2)-C(3)-C(9)-C(10)	-116.4(3)
C(3)-C(9)-C(10)-C(11)	-0.9(4)
C(9)-C(10)-C(11)-O(4)	174.6(3)
C(9)-C(10)-C(11)-C(12)	-5.1(4)
O(4)-C(11)-C(12)-C(13)	-175.3(3)
C(10)-C(11)-C(12)-C(13)	4.4(4)
C(11)-C(12)-C(13)-C(3)	2.4(4)
C(9)-C(3)-C(13)-C(12)	-7.9(4)
C(4)-C(3)-C(13)-C(12)	-133.2(3)
C(2)-C(3)-C(13)-C(12)	115.7(3)
C(1)-N(1)-C(14)-C(18)	94.5(2)
C(4)-N(1)-C(14)-C(18)	-72.1(3)
C(1)-N(1)-C(14)-C(15)	-141.3(2)
C(4)-N(1)-C(14)-C(15)	52.2(3)
N(1)-C(14)-C(15)-C(16)	58.4(3)
C(18)-C(14)-C(15)-C(16)	-179.3(2)
N(1)-C(14)-C(15)-C(17)	179.6(2)
C(18)-C(14)-C(15)-C(17)	-58.0(3)
N(1)-C(14)-C(18)-O(5)	65.1(3)
C(15)-C(14)-C(18)-O(5)	-60.0(4)
N(1)-C(14)-C(18)-N(2)	-114.8(2)
C(15)-C(14)-C(18)-N(2)	120.0(3)
O(5)-C(18)-N(2)-C(19)	5.2(5)
C(14)-C(18)-N(2)-C(19)	-174.9(2)
C(18)-N(2)-C(19)-C(21)	-58.9(4)
C(18)-N(2)-C(19)-C(20)	-178.8(3)
C(18)-N(2)-C(19)-C(22)	63.6(3)
C(26)-N(3)-C(23)-O(6)	-177.7(2)
C(36)-N(3)-C(23)-O(6)	-13.3(4)
C(26)-N(3)-C(23)-C(24)	3.2(3)
C(36)-N(3)-C(23)-C(24)	167.64(19)
O(6)-C(23)-C(24)-C(27)	-31.0(3)
N(3)-C(23)-C(24)-C(27)	148.1(2)
O(6)-C(23)-C(24)-C(25)	-158.8(2)
N(3)-C(23)-C(24)-C(25)	20.3(2)
C(23)-C(24)-C(25)-C(35)	-153.66(18)
C(27)-C(24)-C(25)-C(35)	79.9(3)
C(23)-C(24)-C(25)-C(31)	81.7(2)
C(27)-C(24)-C(25)-C(31)	-44.8(3)
C(23)-C(24)-C(25)-C(26)	-33.6(2)
C(27)-C(24)-C(25)-C(26)	-160.1(2)
C(23)-N(3)-C(26)-C(25)	-25.2(2)
C(36)-N(3)-C(26)-C(25)	170.9(2)
C(35)-C(25)-C(26)-N(3)	152.8(2)
C(31)-C(25)-C(26)-N(3)	-81.0(2)
C(24)-C(25)-C(26)-N(3)	35.0(2)
C(23)-C(24)-C(27)-C(28)	74.1(3)
C(25)-C(24)-C(27)-C(28)	-165.4(2)
C(24)-C(27)-C(28)-O(7)	22.4(4)
C(24)-C(27)-C(28)-O(8)	-158.9(2)
O(7)-C(28)-O(8)-C(29)	4.6(4)
C(27)-C(28)-O(8)-C(29)	-174.1(3)
C(28)-O(8)-C(29)-C(30)	104.6(6)
C(28)-O(8)-C(29)-C(30')	-172.9(5)

C(35)-C(25)-C(31)-C(32)	-6.5(3)
C(24)-C(25)-C(31)-C(32)	117.2(3)
C(26)-C(25)-C(31)-C(32)	-133.5(3)
C(25)-C(31)-C(32)-C(33)	1.3(4)
C(31)-C(32)-C(33)-O(9)	-176.3(3)
C(31)-C(32)-C(33)-C(34)	3.5(4)
O(9)-C(33)-C(34)-C(35)	177.2(3)
C(32)-C(33)-C(34)-C(35)	-2.5(4)
C(33)-C(34)-C(35)-C(25)	-3.3(4)
C(31)-C(25)-C(35)-C(34)	7.5(3)
C(24)-C(25)-C(35)-C(34)	-116.1(3)
C(26)-C(25)-C(35)-C(34)	132.2(3)
C(23)-N(3)-C(36)-C(37)	151.0(2)
C(26)-N(3)-C(36)-C(37)	-46.4(3)
C(23)-N(3)-C(36)-C(40)	-84.4(3)
C(26)-N(3)-C(36)-C(40)	78.1(3)
N(3)-C(36)-C(37)-C(38)	-60.8(3)
C(40)-C(36)-C(37)-C(38)	176.9(2)
N(3)-C(36)-C(37)-C(39)	177.6(2)
C(40)-C(36)-C(37)-C(39)	55.4(3)
N(3)-C(36)-C(40)-O(10)	-62.6(3)
C(37)-C(36)-C(40)-O(10)	62.3(3)
N(3)-C(36)-C(40)-N(4)	117.5(3)
C(37)-C(36)-C(40)-N(4)	-117.6(3)
O(10)-C(40)-N(4)-C(41)	-4.4(5)
C(36)-C(40)-N(4)-C(41)	175.4(2)
C(40)-N(4)-C(41)-C(42)	178.0(3)
C(40)-N(4)-C(41)-C(44)	-63.4(4)
C(40)-N(4)-C(41)-C(43)	58.5(4)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for BTRA [A and deg.].

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N2-H1N2	0.853	2.113	168.19	2.953	O1 [-x, -y+1, -z]
N4-H1N4	0.933	1.986	166.63	2.902	O6 [-x+1, -y, -z+1]

4. Compound (±)-**251**

Table 1. Crystal data and structure refinement for DAMI.

Identification code	dami
Empirical formula	C32 H39 N2 O5
Formula weight	531.65
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 10.138(3) A alpha = 79.039(9) deg. b = 11.923(4) A beta = 68.399(9) deg. c = 13.076(4) A gamma = 68.566(10) deg.
Volume	1365.1(7) A^3
Z, Calculated density	2, 1.293 Mg/m^3
Absorption coefficient	0.087 mm^-1
F(000)	570
Crystal size	0.40 x 0.20 x 0.06 mm
Theta range for data collection	1.68 to 28.46 deg.
Limiting indices	-12<=h<=13, -15<=k<=15, 0<=l<=17
Reflections collected / unique	13505 / 6540 [R(int) = 0.0541]
Completeness to theta = 28.30	95.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9948 and 0.9660
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6540 / 0 / 329
Goodness-of-fit on F^2	0.972
Final R indices [I>2sigma(I)]	R1 = 0.0640, wR2 = 0.1446
R indices (all data)	R1 = 0.1272, wR2 = 0.1671
Largest diff. peak and hole	0.245 and -0.251 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for DAMI.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	9137(2)	7026(2)	401(1)	34(1)
O(2)	10596(2)	7149(2)	3600(1)	35(1)
O(3)	5760(2)	4162(2)	5951(1)	36(1)
N(1)	10202(2)	6227(2)	1767(2)	27(1)
C(1)	9046(3)	6682(2)	1360(2)	28(1)
C(2)	7614(2)	6775(2)	2329(2)	25(1)
C(3)	8129(2)	5844(2)	3211(2)	24(1)
C(4)	9739(2)	5860(2)	2938(2)	24(1)
C(5)	9576(3)	6798(2)	3652(2)	28(1)
N(2)	8138(2)	7156(2)	4350(2)	26(1)
C(6)	7307(2)	6372(2)	4360(2)	27(1)
C(7)	7341(3)	5396(2)	5303(2)	28(1)
C(8)	6721(3)	4483(2)	5193(2)	29(1)
C(9)	7393(2)	3953(2)	4101(2)	26(1)
C(10)	7384(3)	2823(2)	4039(2)	31(1)
C(11)	8091(3)	2261(2)	3064(2)	33(1)
C(12)	8791(2)	2877(2)	2128(2)	29(1)
C(13)	8778(2)	4023(2)	2172(2)	27(1)
C(14)	8091(2)	4598(2)	3164(2)	24(1)
C(15)	11721(3)	6245(3)	1125(2)	35(1)
C(16)	12896(3)	5065(2)	1214(2)	30(1)
C(17)	13992(3)	5015(3)	1632(2)	40(1)
C(18)	15110(3)	3967(3)	1689(3)	56(1)
C(19)	15173(3)	2952(3)	1323(2)	59(1)
C(20)	14083(3)	2960(3)	901(2)	50(1)
C(21)	12943(3)	4027(3)	850(2)	37(1)
C(22)	6300(2)	6805(2)	2025(2)	29(1)
C(23)	4900(3)	7828(2)	2526(2)	29(1)
O(4)	4744(2)	8450(2)	3221(2)	40(1)
O(5)	3844(2)	7960(2)	2098(1)	34(1)
C(24)	2451(3)	8955(3)	2470(3)	50(1)
C(25)	2627(4)	10102(3)	1840(4)	72(1)
C(26)	7574(3)	8092(2)	5168(2)	31(1)
C(27)	5869(3)	8429(2)	5676(2)	34(1)
C(28)	8303(3)	7590(3)	6062(2)	40(1)
C(29)	7940(3)	9221(2)	4565(2)	38(1)

Table 3. Bond lengths [A] and angles [deg] for DAMI.

O(1)-C(1)	1.223(3)
O(2)-C(5)	1.225(3)
O(3)-C(8)	1.223(3)
N(1)-C(1)	1.354(3)
N(1)-C(4)	1.457(3)
N(1)-C(15)	1.463(3)
C(1)-C(2)	1.518(3)
C(2)-C(22)	1.511(3)
C(2)-C(3)	1.539(3)
C(3)-C(14)	1.514(3)
C(3)-C(4)	1.544(3)
C(3)-C(6)	1.550(3)
C(4)-C(5)	1.516(3)
C(5)-N(2)	1.361(3)
N(2)-C(6)	1.465(3)
N(2)-C(26)	1.501(3)
C(6)-C(7)	1.528(3)
C(7)-C(8)	1.492(3)
C(8)-C(9)	1.489(3)
C(9)-C(10)	1.369(3)
C(9)-C(14)	1.412(3)
C(10)-C(11)	1.374(3)
C(11)-C(12)	1.393(3)
C(12)-C(13)	1.374(3)
C(13)-C(14)	1.400(3)
C(15)-C(16)	1.492(4)
C(16)-C(21)	1.387(4)
C(16)-C(17)	1.386(3)
C(17)-C(18)	1.358(4)
C(18)-C(19)	1.356(5)
C(19)-C(20)	1.403(4)
C(20)-C(21)	1.382(4)
C(22)-C(23)	1.512(3)
C(23)-O(4)	1.211(3)
C(23)-O(5)	1.331(3)
O(5)-C(24)	1.458(3)
C(24)-C(25)	1.491(5)
C(26)-C(29)	1.523(4)
C(26)-C(28)	1.523(4)
C(26)-C(27)	1.529(3)

C(1)-N(1)-C(4)	113.10(18)
C(1)-N(1)-C(15)	123.0(2)
C(4)-N(1)-C(15)	123.5(2)
O(1)-C(1)-N(1)	126.1(2)
O(1)-C(1)-C(2)	126.5(2)
N(1)-C(1)-C(2)	107.3(2)
C(22)-C(2)-C(1)	114.6(2)
C(22)-C(2)-C(3)	120.97(19)
C(1)-C(2)-C(3)	104.25(19)
C(14)-C(3)-C(2)	114.04(19)
C(14)-C(3)-C(4)	112.28(19)
C(2)-C(3)-C(4)	101.29(18)
C(14)-C(3)-C(6)	114.88(19)
C(2)-C(3)-C(6)	109.9(2)
C(4)-C(3)-C(6)	103.04(18)
N(1)-C(4)-C(5)	112.51(19)
N(1)-C(4)-C(3)	104.60(18)
C(5)-C(4)-C(3)	104.68(18)

O(2)-C(5)-N(2)	126.9(2)
O(2)-C(5)-C(4)	124.4(2)
N(2)-C(5)-C(4)	108.72(19)
C(5)-N(2)-C(6)	112.30(19)
C(5)-N(2)-C(26)	123.14(18)
C(6)-N(2)-C(26)	123.56(17)
N(2)-C(6)-C(7)	111.45(19)
N(2)-C(6)-C(3)	103.01(17)
C(7)-C(6)-C(3)	112.6(2)
C(8)-C(7)-C(6)	110.9(2)
O(3)-C(8)-C(9)	121.9(2)
O(3)-C(8)-C(7)	122.9(2)
C(9)-C(8)-C(7)	115.2(2)
C(10)-C(9)-C(14)	121.5(2)
C(10)-C(9)-C(8)	119.0(2)
C(14)-C(9)-C(8)	119.4(2)
C(9)-C(10)-C(11)	121.0(2)
C(10)-C(11)-C(12)	118.6(2)
C(13)-C(12)-C(11)	121.0(2)
C(12)-C(13)-C(14)	121.1(2)
C(13)-C(14)-C(9)	116.8(2)
C(13)-C(14)-C(3)	120.6(2)
C(9)-C(14)-C(3)	122.6(2)
N(1)-C(15)-C(16)	112.9(2)
C(21)-C(16)-C(17)	119.4(3)
C(21)-C(16)-C(15)	121.2(2)
C(17)-C(16)-C(15)	119.4(2)
C(18)-C(17)-C(16)	121.1(3)
C(19)-C(18)-C(17)	119.8(3)
C(18)-C(19)-C(20)	121.0(3)
C(21)-C(20)-C(19)	118.9(3)
C(20)-C(21)-C(16)	119.8(3)
C(23)-C(22)-C(2)	112.1(2)
O(4)-C(23)-O(5)	123.9(2)
O(4)-C(23)-C(22)	125.4(2)
O(5)-C(23)-C(22)	110.7(2)
C(23)-O(5)-C(24)	116.6(2)
O(5)-C(24)-C(25)	109.9(3)
N(2)-C(26)-C(29)	108.73(19)
N(2)-C(26)-C(28)	109.4(2)
C(29)-C(26)-C(28)	111.1(2)
N(2)-C(26)-C(27)	109.40(18)
C(29)-C(26)-C(27)	108.0(2)
C(28)-C(26)-C(27)	110.2(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for DAMI. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	33(1)	46(1)	17(1)	4(1)	-1(1)	-17(1)
O(2)	26(1)	40(1)	41(1)	-9(1)	-6(1)	-13(1)
O(3)	33(1)	44(1)	24(1)	5(1)	1(1)	-18(1)
N(1)	20(1)	33(1)	22(1)	-2(1)	3(1)	-11(1)
C(1)	31(1)	22(1)	25(1)	-2(1)	-1(1)	-10(1)
C(2)	23(1)	27(1)	20(1)	0(1)	-2(1)	-10(1)
C(3)	17(1)	30(1)	24(1)	-2(1)	-3(1)	-9(1)
C(4)	21(1)	25(1)	22(1)	0(1)	-1(1)	-10(1)
C(5)	26(1)	30(2)	25(1)	1(1)	-7(1)	-8(1)
N(2)	24(1)	31(1)	23(1)	-6(1)	-4(1)	-10(1)
C(6)	23(1)	35(2)	20(1)	-3(1)	-3(1)	-9(1)
C(7)	31(1)	32(2)	17(1)	-2(1)	-5(1)	-8(1)
C(8)	24(1)	32(2)	23(1)	6(1)	-6(1)	-5(1)
C(9)	21(1)	28(2)	25(1)	-3(1)	-2(1)	-7(1)
C(10)	26(1)	36(2)	30(1)	5(1)	-7(1)	-14(1)
C(11)	32(1)	31(2)	33(2)	-1(1)	-7(1)	-11(1)
C(12)	25(1)	32(2)	28(1)	-4(1)	-3(1)	-9(1)
C(13)	26(1)	27(2)	24(1)	-2(1)	-4(1)	-8(1)
C(14)	19(1)	29(1)	22(1)	1(1)	-4(1)	-8(1)
C(15)	26(1)	47(2)	28(1)	-8(1)	4(1)	-19(1)
C(16)	25(1)	45(2)	16(1)	-4(1)	2(1)	-14(1)
C(17)	26(1)	67(2)	29(2)	-2(1)	-3(1)	-24(2)
C(18)	31(2)	88(3)	43(2)	-1(2)	-10(1)	-17(2)
C(19)	32(2)	76(3)	33(2)	8(2)	-1(1)	7(2)
C(20)	49(2)	46(2)	34(2)	-8(1)	2(1)	-7(2)
C(21)	32(1)	45(2)	29(2)	-8(1)	-6(1)	-7(1)
C(22)	27(1)	32(2)	24(1)	-2(1)	-5(1)	-8(1)
C(23)	28(1)	32(2)	27(1)	-2(1)	-5(1)	-13(1)
O(4)	37(1)	40(1)	41(1)	-16(1)	-9(1)	-6(1)
O(5)	26(1)	33(1)	43(1)	-8(1)	-11(1)	-7(1)
C(24)	29(1)	46(2)	75(2)	-22(2)	-17(1)	-3(1)
C(25)	64(2)	36(2)	132(4)	-12(2)	-56(2)	-5(2)
C(26)	32(1)	35(2)	26(1)	-7(1)	-7(1)	-9(1)
C(27)	33(1)	30(2)	31(2)	-9(1)	-6(1)	-2(1)
C(28)	37(1)	47(2)	33(2)	-15(1)	-10(1)	-5(1)
C(29)	37(1)	35(2)	38(2)	-10(1)	-2(1)	-13(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for DAMI.

	x	y	z	U(eq)
H(2)	7316	7580	2619	30
H(4)	10422	5049	3102	29
H(6)	6246	6866	4426	32
H(7A)	8387	4991	5299	34
H(7B)	6744	5772	6015	34
H(10)	6881	2421	4679	37
H(11)	8102	1469	3030	39
H(12)	9284	2498	1449	35
H(13)	9242	4433	1519	32
H(15A)	11913	6880	1384	42
H(15B)	11793	6456	341	42
H(17)	13959	5725	1882	48
H(18)	15847	3946	1984	67
H(19)	15967	2225	1354	70
H(20)	14127	2243	654	59
H(21)	12195	4051	566	44
H(22A)	6561	6895	1213	35
H(22B)	6099	6029	2282	35
H(24A)	2189	9035	3267	59
H(24B)	1628	8786	2360	59
H(25A)	3393	10296	1993	87
H(25B)	1670	10756	2063	87
H(25C)	2934	10006	1049	87
H(27A)	5492	9080	6172	41
H(27B)	5607	7722	6093	41
H(27C)	5417	8701	5089	41
H(28A)	9396	7321	5722	48
H(28B)	7983	6906	6477	48
H(28C)	7998	8222	6564	48
H(29A)	7468	9872	5071	46
H(29B)	7560	9470	3940	46
H(29C)	9029	9048	4295	46

Table 6. Torsion angles [deg] for DAMI.

C(4)-N(1)-C(1)-O(1)	-178.1(2)
C(15)-N(1)-C(1)-O(1)	9.1(4)
C(4)-N(1)-C(1)-C(2)	6.2(3)
C(15)-N(1)-C(1)-C(2)	-166.7(2)
O(1)-C(1)-C(2)-C(22)	26.3(4)
N(1)-C(1)-C(2)-C(22)	-157.9(2)
O(1)-C(1)-C(2)-C(3)	160.7(2)
N(1)-C(1)-C(2)-C(3)	-23.5(2)
C(22)-C(2)-C(3)-C(14)	40.0(3)
C(1)-C(2)-C(3)-C(14)	-90.7(2)
C(22)-C(2)-C(3)-C(4)	160.8(2)
C(1)-C(2)-C(3)-C(4)	30.1(2)
C(22)-C(2)-C(3)-C(6)	-90.7(2)
C(1)-C(2)-C(3)-C(6)	138.58(19)
C(1)-N(1)-C(4)-C(5)	-99.4(2)
C(15)-N(1)-C(4)-C(5)	73.4(3)
C(1)-N(1)-C(4)-C(3)	13.7(3)
C(15)-N(1)-C(4)-C(3)	-173.5(2)
C(14)-C(3)-C(4)-N(1)	95.4(2)
C(2)-C(3)-C(4)-N(1)	-26.7(2)
C(6)-C(3)-C(4)-N(1)	-140.46(19)
C(14)-C(3)-C(4)-C(5)	-146.1(2)
C(2)-C(3)-C(4)-C(5)	91.8(2)
C(6)-C(3)-C(4)-C(5)	-21.9(2)
N(1)-C(4)-C(5)-O(2)	-60.4(3)
C(3)-C(4)-C(5)-O(2)	-173.4(2)
N(1)-C(4)-C(5)-N(2)	120.4(2)
C(3)-C(4)-C(5)-N(2)	7.4(3)
O(2)-C(5)-N(2)-C(6)	-167.3(2)
C(4)-C(5)-N(2)-C(6)	11.8(3)
O(2)-C(5)-N(2)-C(26)	1.6(4)
C(4)-C(5)-N(2)-C(26)	-179.3(2)
C(5)-N(2)-C(6)-C(7)	95.2(2)
C(26)-N(2)-C(6)-C(7)	-73.7(3)
C(5)-N(2)-C(6)-C(3)	-25.7(3)
C(26)-N(2)-C(6)-C(3)	165.4(2)
C(14)-C(3)-C(6)-N(2)	150.54(19)
C(2)-C(3)-C(6)-N(2)	-79.2(2)
C(4)-C(3)-C(6)-N(2)	28.1(2)
C(14)-C(3)-C(6)-C(7)	30.4(3)
C(2)-C(3)-C(6)-C(7)	160.63(18)
C(4)-C(3)-C(6)-C(7)	-92.0(2)
N(2)-C(6)-C(7)-C(8)	-170.37(18)
C(3)-C(6)-C(7)-C(8)	-55.2(3)
C(6)-C(7)-C(8)-O(3)	-130.0(2)
C(6)-C(7)-C(8)-C(9)	51.9(3)
O(3)-C(8)-C(9)-C(10)	-24.4(4)
C(7)-C(8)-C(9)-C(10)	153.7(2)
O(3)-C(8)-C(9)-C(14)	158.8(2)
C(7)-C(8)-C(9)-C(14)	-23.1(3)
C(14)-C(9)-C(10)-C(11)	1.7(4)
C(8)-C(9)-C(10)-C(11)	-175.0(2)
C(9)-C(10)-C(11)-C(12)	-1.5(4)
C(10)-C(11)-C(12)-C(13)	0.0(4)
C(11)-C(12)-C(13)-C(14)	1.5(4)
C(12)-C(13)-C(14)-C(9)	-1.3(3)
C(12)-C(13)-C(14)-C(3)	177.9(2)
C(10)-C(9)-C(14)-C(13)	-0.3(3)
C(8)-C(9)-C(14)-C(13)	176.4(2)

C(10)-C(9)-C(14)-C(3)	-179.5(2)
C(8)-C(9)-C(14)-C(3)	-2.8(3)
C(2)-C(3)-C(14)-C(13)	51.1(3)
C(4)-C(3)-C(14)-C(13)	-63.4(3)
C(6)-C(3)-C(14)-C(13)	179.3(2)
C(2)-C(3)-C(14)-C(9)	-129.7(2)
C(4)-C(3)-C(14)-C(9)	115.8(2)
C(6)-C(3)-C(14)-C(9)	-1.5(3)
C(1)-N(1)-C(15)-C(16)	-134.0(2)
C(4)-N(1)-C(15)-C(16)	53.9(3)
N(1)-C(15)-C(16)-C(21)	62.2(3)
N(1)-C(15)-C(16)-C(17)	-120.2(2)
C(21)-C(16)-C(17)-C(18)	0.0(4)
C(15)-C(16)-C(17)-C(18)	-177.6(2)
C(16)-C(17)-C(18)-C(19)	0.6(4)
C(17)-C(18)-C(19)-C(20)	-1.0(5)
C(18)-C(19)-C(20)-C(21)	0.7(4)
C(19)-C(20)-C(21)-C(16)	0.0(4)
C(17)-C(16)-C(21)-C(20)	-0.3(4)
C(15)-C(16)-C(21)-C(20)	177.3(2)
C(1)-C(2)-C(22)-C(23)	-130.5(2)
C(3)-C(2)-C(22)-C(23)	103.3(3)
C(2)-C(22)-C(23)-O(4)	-10.6(4)
C(2)-C(22)-C(23)-O(5)	169.34(19)
O(4)-C(23)-O(5)-C(24)	2.7(4)
C(22)-C(23)-O(5)-C(24)	-177.2(2)
C(23)-O(5)-C(24)-C(25)	82.3(3)
C(5)-N(2)-C(26)-C(29)	52.9(3)
C(6)-N(2)-C(26)-C(29)	-139.5(2)
C(5)-N(2)-C(26)-C(28)	-68.6(3)
C(6)-N(2)-C(26)-C(28)	99.0(3)
C(5)-N(2)-C(26)-C(27)	170.5(2)
C(6)-N(2)-C(26)-C(27)	-21.8(3)

Symmetry transformations used to generate equivalent atoms:

5. Compound (±)-**252**

Table 1. Crystal data and structure refinement for SANA.

Identification code	sana
Empirical formula	C29 H32 N2 O5
Formula weight	488.57
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 6.8322(9) A alpha = 98.068(8) deg. b = 12.7786(17) A beta = 95.054(8) deg. c = 14.539(2) A gamma = 95.450(9) deg.
Volume	1244.4(3) A^3
Z, Calculated density	2, 1.304 Mg/m^3
Absorption coefficient	0.089 mm^-1
F(000)	520
Crystal size	0.26 x 0.13 x 0.07 mm
Theta range for data collection	1.99 to 28.40 deg.
Limiting indices	-9<=h<=9, -17<=k<=16, 0<=l<=19
Reflections collected / unique	19072 / 6149 [R(int) = 0.0504]
Completeness to theta = 28.30	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9938 and 0.9772
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6149 / 0 / 333
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0498, wR2 = 0.1077
R indices (all data)	R1 = 0.0869, wR2 = 0.1199
Largest diff. peak and hole	0.285 and -0.229 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for SANA.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	-2213(2)	10298(1)	8182(1)	17(1)
C(2)	-1951(2)	10677(1)	9140(1)	21(1)
C(3)	-2452(2)	10023(1)	9783(1)	25(1)
C(4)	-3184(2)	8972(1)	9497(1)	26(1)
C(5)	-3431(2)	8582(1)	8560(1)	27(1)
C(6)	-2974(2)	9236(1)	7896(1)	20(1)
C(7)	-3428(2)	8786(1)	6897(1)	24(1)
O(1)	-3958(2)	7838(1)	6641(1)	36(1)
C(8)	-3284(2)	9541(1)	6233(1)	22(1)
C(9)	-2572(2)	10552(1)	6495(1)	20(1)
C(10)	-1686(2)	11018(1)	7466(1)	17(1)
C(11)	609(2)	11232(1)	7429(1)	17(1)
C(12)	1245(2)	12194(1)	8160(1)	17(1)
N(1)	-356(2)	12696(1)	8330(1)	17(1)
C(13)	-2204(2)	12169(1)	7812(1)	17(1)
C(14)	1804(2)	10297(1)	7481(1)	22(1)
C(15)	1738(2)	9634(1)	6532(1)	21(1)
O(2)	2052(2)	10000(1)	5833(1)	27(1)
O(3)	1287(2)	8601(1)	6558(1)	24(1)
C(16)	1145(3)	7914(1)	5658(1)	26(1)
C(17)	636(3)	6800(1)	5830(1)	34(1)
O(4)	2949(2)	12501(1)	8511(1)	21(1)
C(18)	-264(2)	13740(1)	8898(1)	21(1)
C(19)	-1054(2)	13660(1)	9828(1)	19(1)
C(20)	-2960(2)	13868(1)	9981(1)	24(1)
C(21)	-3681(3)	13740(1)	10824(1)	29(1)
C(22)	-2505(3)	13398(1)	11519(1)	31(1)
C(23)	-601(3)	13182(1)	11371(1)	29(1)
C(24)	116(3)	13316(1)	10530(1)	25(1)
C(25)	-2767(2)	12822(1)	7045(1)	17(1)
O(5)	-1629(2)	12980(1)	6455(1)	23(1)
N(2)	-4493(2)	13228(1)	7114(1)	18(1)
C(26)	-5234(2)	14016(1)	6554(1)	20(1)
C(27)	-5471(3)	13568(2)	5520(1)	32(1)
C(28)	-7238(2)	14226(1)	6872(1)	27(1)
C(29)	-3794(3)	15033(1)	6764(1)	28(1)

Table 3. Bond lengths [A] and angles [deg] for SANA.

C(1)-C(6)	1.398(2)
C(1)-C(2)	1.399(2)
C(1)-C(10)	1.527(2)
C(2)-C(3)	1.382(2)
C(3)-C(4)	1.381(2)
C(4)-C(5)	1.373(3)
C(5)-C(6)	1.398(2)
C(6)-C(7)	1.479(2)
C(7)-O(1)	1.226(2)
C(7)-C(8)	1.460(2)
C(8)-C(9)	1.328(2)
C(9)-C(10)	1.503(2)
C(10)-C(13)	1.569(2)
C(10)-C(11)	1.573(2)
C(11)-C(12)	1.509(2)
C(11)-C(14)	1.516(2)
C(12)-O(4)	1.2337(18)
C(12)-N(1)	1.345(2)
N(1)-C(18)	1.459(2)
N(1)-C(13)	1.4647(19)
C(13)-C(25)	1.527(2)
C(14)-C(15)	1.509(2)
C(15)-O(2)	1.2050(19)
C(15)-O(3)	1.334(2)
O(3)-C(16)	1.460(2)
C(16)-C(17)	1.493(2)
C(18)-C(19)	1.512(2)
C(19)-C(20)	1.385(2)
C(19)-C(24)	1.387(2)
C(20)-C(21)	1.385(2)
C(21)-C(22)	1.381(3)
C(22)-C(23)	1.384(3)
C(23)-C(24)	1.382(2)
C(25)-O(5)	1.2321(19)
C(25)-N(2)	1.339(2)
N(2)-C(26)	1.480(2)
C(26)-C(28)	1.519(2)
C(26)-C(27)	1.520(2)
C(26)-C(29)	1.530(2)

C(6)-C(1)-C(2)	118.03(15)
C(6)-C(1)-C(10)	120.69(15)
C(2)-C(1)-C(10)	121.28(14)
C(3)-C(2)-C(1)	120.94(16)
C(4)-C(3)-C(2)	120.74(17)
C(5)-C(4)-C(3)	119.17(16)
C(4)-C(5)-C(6)	120.99(16)
C(1)-C(6)-C(5)	120.10(16)
C(1)-C(6)-C(7)	121.80(15)
C(5)-C(6)-C(7)	118.01(15)
O(1)-C(7)-C(8)	121.68(16)
O(1)-C(7)-C(6)	122.03(16)
C(8)-C(7)-C(6)	116.26(14)
C(9)-C(8)-C(7)	122.19(16)
C(8)-C(9)-C(10)	124.48(16)
C(9)-C(10)-C(1)	112.08(13)
C(9)-C(10)-C(13)	114.79(13)
C(1)-C(10)-C(13)	109.13(13)
C(9)-C(10)-C(11)	106.95(13)

C(1)-C(10)-C(11)	112.47(13)
C(13)-C(10)-C(11)	100.94(12)
C(12)-C(11)-C(14)	115.72(13)
C(12)-C(11)-C(10)	104.40(12)
C(14)-C(11)-C(10)	117.13(13)
O(4)-C(12)-N(1)	125.38(15)
O(4)-C(12)-C(11)	126.37(14)
N(1)-C(12)-C(11)	108.16(13)
C(12)-N(1)-C(18)	123.55(13)
C(12)-N(1)-C(13)	114.44(13)
C(18)-N(1)-C(13)	121.66(13)
N(1)-C(13)-C(25)	107.46(12)
N(1)-C(13)-C(10)	103.44(12)
C(25)-C(13)-C(10)	115.69(13)
C(15)-C(14)-C(11)	110.72(13)
O(2)-C(15)-O(3)	124.12(16)
O(2)-C(15)-C(14)	123.65(16)
O(3)-C(15)-C(14)	112.23(14)
C(15)-O(3)-C(16)	115.18(13)
O(3)-C(16)-C(17)	107.21(14)
N(1)-C(18)-C(19)	111.38(13)
C(20)-C(19)-C(24)	118.85(16)
C(20)-C(19)-C(18)	121.60(15)
C(24)-C(19)-C(18)	119.46(15)
C(19)-C(20)-C(21)	120.54(17)
C(22)-C(21)-C(20)	120.17(17)
C(21)-C(22)-C(23)	119.77(17)
C(24)-C(23)-C(22)	119.87(17)
C(23)-C(24)-C(19)	120.80(17)
O(5)-C(25)-N(2)	125.16(15)
O(5)-C(25)-C(13)	120.40(14)
N(2)-C(25)-C(13)	114.35(14)
C(25)-N(2)-C(26)	125.12(14)
N(2)-C(26)-C(28)	105.93(13)
N(2)-C(26)-C(27)	110.49(14)
C(28)-C(26)-C(27)	109.71(14)
N(2)-C(26)-C(29)	108.52(13)
C(28)-C(26)-C(29)	110.47(14)
C(27)-C(26)-C(29)	111.57(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for SANA. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	15(1)	17(1)	20(1)	5(1)	3(1)	6(1)
C(2)	22(1)	22(1)	20(1)	4(1)	2(1)	4(1)
C(3)	26(1)	31(1)	20(1)	9(1)	5(1)	8(1)
C(4)	28(1)	25(1)	31(1)	15(1)	8(1)	7(1)
C(5)	27(1)	20(1)	34(1)	7(1)	5(1)	2(1)
C(6)	19(1)	17(1)	26(1)	4(1)	3(1)	5(1)
C(7)	21(1)	20(1)	29(1)	-1(1)	3(1)	2(1)
O(1)	48(1)	20(1)	38(1)	-3(1)	5(1)	-4(1)
C(8)	21(1)	24(1)	20(1)	-2(1)	0(1)	3(1)
C(9)	20(1)	21(1)	18(1)	3(1)	1(1)	7(1)
C(10)	19(1)	18(1)	14(1)	2(1)	2(1)	4(1)
C(11)	18(1)	20(1)	15(1)	3(1)	3(1)	4(1)
C(12)	20(1)	19(1)	14(1)	6(1)	3(1)	2(1)
N(1)	20(1)	16(1)	14(1)	0(1)	1(1)	2(1)
C(13)	18(1)	17(1)	15(1)	2(1)	3(1)	3(1)
C(14)	20(1)	27(1)	19(1)	3(1)	1(1)	7(1)
C(15)	16(1)	27(1)	21(1)	4(1)	5(1)	7(1)
O(2)	33(1)	30(1)	20(1)	4(1)	8(1)	5(1)
O(3)	34(1)	22(1)	17(1)	1(1)	3(1)	7(1)
C(16)	36(1)	25(1)	17(1)	-2(1)	3(1)	7(1)
C(17)	52(1)	25(1)	26(1)	2(1)	2(1)	6(1)
O(4)	19(1)	25(1)	19(1)	3(1)	0(1)	0(1)
C(18)	28(1)	16(1)	18(1)	0(1)	2(1)	1(1)
C(19)	26(1)	12(1)	17(1)	-1(1)	1(1)	-1(1)
C(20)	25(1)	24(1)	23(1)	-2(1)	0(1)	3(1)
C(21)	24(1)	32(1)	27(1)	-3(1)	7(1)	-2(1)
C(22)	39(1)	32(1)	19(1)	-1(1)	7(1)	-7(1)
C(23)	40(1)	26(1)	20(1)	3(1)	0(1)	1(1)
C(24)	27(1)	24(1)	23(1)	0(1)	2(1)	3(1)
C(25)	23(1)	13(1)	16(1)	0(1)	1(1)	2(1)
O(5)	24(1)	27(1)	20(1)	8(1)	8(1)	6(1)
N(2)	21(1)	17(1)	17(1)	6(1)	3(1)	4(1)
C(26)	24(1)	20(1)	20(1)	8(1)	4(1)	7(1)
C(27)	39(1)	35(1)	23(1)	7(1)	-1(1)	12(1)
C(28)	26(1)	26(1)	32(1)	12(1)	4(1)	9(1)
C(29)	34(1)	22(1)	31(1)	10(1)	5(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for SANA.

	x	y	z	U(eq)
H(2)	-1421	11393	9352	25
H(3)	-2291	10301	10430	30
H(4)	-3512	8525	9942	32
H(5)	-3920	7858	8359	32
H(8)	-3713	9299	5593	27
H(9)	-2627	11014	6037	23
H(11)	792	11468	6812	21
H(13)	-3269	12137	8240	20
H(14A)	3193	10562	7715	26
H(14B)	1267	9852	7925	26
H(16A)	2420	7978	5384	32
H(16B)	108	8117	5219	32
H(17A)	1709	6594	6237	41
H(17B)	457	6320	5234	41
H(17C)	-590	6756	6132	41
H(18A)	-1048	14204	8557	25
H(18B)	1124	14069	9005	25
H(20)	-3781	14099	9505	29
H(21)	-4989	13889	10924	34
H(22)	-3001	13310	12097	37
H(23)	211	12943	11846	35
H(24)	1426	13170	10432	30
H(1N2)	-5170(20)	13070(13)	7603(12)	21(5)
H(27A)	-4169	13468	5310	38
H(27B)	-6104	14065	5165	38
H(27C)	-6294	12883	5418	38
H(28A)	-8143	13568	6731	33
H(28B)	-7772	14772	6544	33
H(28C)	-7091	14471	7546	33
H(29A)	-3650	15290	7436	34
H(29B)	-4306	15577	6425	34
H(29C)	-2504	14881	6564	34

Table 6. Torsion angles [deg] for SANA.

C(6)-C(1)-C(2)-C(3)	-0.7(2)
C(10)-C(1)-C(2)-C(3)	179.24(14)
C(1)-C(2)-C(3)-C(4)	1.5(3)
C(2)-C(3)-C(4)-C(5)	-0.7(3)
C(3)-C(4)-C(5)-C(6)	-0.7(3)
C(2)-C(1)-C(6)-C(5)	-0.7(2)
C(10)-C(1)-C(6)-C(5)	179.36(14)
C(2)-C(1)-C(6)-C(7)	175.79(15)
C(10)-C(1)-C(6)-C(7)	-4.2(2)
C(4)-C(5)-C(6)-C(1)	1.4(3)
C(4)-C(5)-C(6)-C(7)	-175.18(15)
C(1)-C(6)-C(7)-O(1)	174.52(16)
C(5)-C(6)-C(7)-O(1)	-9.0(2)
C(1)-C(6)-C(7)-C(8)	-7.7(2)
C(5)-C(6)-C(7)-C(8)	168.77(15)
O(1)-C(7)-C(8)-C(9)	-174.85(16)
C(6)-C(7)-C(8)-C(9)	7.4(2)
C(7)-C(8)-C(9)-C(10)	5.4(3)
C(8)-C(9)-C(10)-C(1)	-16.4(2)
C(8)-C(9)-C(10)-C(13)	-141.61(16)
C(8)-C(9)-C(10)-C(11)	107.33(18)
C(6)-C(1)-C(10)-C(9)	15.3(2)
C(2)-C(1)-C(10)-C(9)	-164.69(14)
C(6)-C(1)-C(10)-C(13)	143.60(14)
C(2)-C(1)-C(10)-C(13)	-36.39(19)
C(6)-C(1)-C(10)-C(11)	-105.25(16)
C(2)-C(1)-C(10)-C(11)	74.76(18)
C(9)-C(10)-C(11)-C(12)	148.45(13)
C(1)-C(10)-C(11)-C(12)	-88.08(15)
C(13)-C(10)-C(11)-C(12)	28.10(15)
C(9)-C(10)-C(11)-C(14)	-82.12(17)
C(1)-C(10)-C(11)-C(14)	41.34(19)
C(13)-C(10)-C(11)-C(14)	157.52(14)
C(14)-C(11)-C(12)-O(4)	32.8(2)
C(10)-C(11)-C(12)-O(4)	163.11(15)
C(14)-C(11)-C(12)-N(1)	-150.30(14)
C(10)-C(11)-C(12)-N(1)	-20.04(16)
O(4)-C(12)-N(1)-C(18)	6.0(2)
C(11)-C(12)-N(1)-C(18)	-170.90(13)
O(4)-C(12)-N(1)-C(13)	179.26(14)
C(11)-C(12)-N(1)-C(13)	2.36(17)
C(12)-N(1)-C(13)-C(25)	-106.53(15)
C(18)-N(1)-C(13)-C(25)	66.87(17)
C(12)-N(1)-C(13)-C(10)	16.32(17)
C(18)-N(1)-C(13)-C(10)	-170.28(13)
C(9)-C(10)-C(13)-N(1)	-141.04(13)
C(1)-C(10)-C(13)-N(1)	92.19(14)
C(11)-C(10)-C(13)-N(1)	-26.43(15)
C(9)-C(10)-C(13)-C(25)	-23.82(19)
C(1)-C(10)-C(13)-C(25)	-150.59(13)
C(11)-C(10)-C(13)-C(25)	90.79(15)
C(12)-C(11)-C(14)-C(15)	-153.33(14)
C(10)-C(11)-C(14)-C(15)	82.82(18)
C(11)-C(14)-C(15)-O(2)	48.9(2)
C(11)-C(14)-C(15)-O(3)	-130.82(14)
O(2)-C(15)-O(3)-C(16)	-1.3(2)
C(14)-C(15)-O(3)-C(16)	178.43(13)
C(15)-O(3)-C(16)-C(17)	179.93(14)
C(12)-N(1)-C(18)-C(19)	-108.34(17)

C(13)-N(1)-C(18)-C(19)	78.87(18)
N(1)-C(18)-C(19)-C(20)	-99.13(18)
N(1)-C(18)-C(19)-C(24)	77.34(18)
C(24)-C(19)-C(20)-C(21)	0.4(2)
C(18)-C(19)-C(20)-C(21)	176.91(15)
C(19)-C(20)-C(21)-C(22)	-0.4(3)
C(20)-C(21)-C(22)-C(23)	0.0(3)
C(21)-C(22)-C(23)-C(24)	0.3(3)
C(22)-C(23)-C(24)-C(19)	-0.3(3)
C(20)-C(19)-C(24)-C(23)	-0.1(2)
C(18)-C(19)-C(24)-C(23)	-176.66(15)
N(1)-C(13)-C(25)-O(5)	58.57(18)
C(10)-C(13)-C(25)-O(5)	-56.38(19)
N(1)-C(13)-C(25)-N(2)	-118.19(14)
C(10)-C(13)-C(25)-N(2)	126.87(15)
O(5)-C(25)-N(2)-C(26)	-6.3(3)
C(13)-C(25)-N(2)-C(26)	170.30(13)
C(25)-N(2)-C(26)-C(28)	179.59(15)
C(25)-N(2)-C(26)-C(27)	60.8(2)
C(25)-N(2)-C(26)-C(29)	-61.8(2)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for SANA [A and deg.].

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N2-H1N2	0.918	2.075	168.81	2.981	O4 [x-1, y, z]

6. Compound (±)-**370a**

Table 1. Crystal data and structure refinement for YANT.

Identification code	yant
Empirical formula	C9 H16 O6
Formula weight	220.22
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 9.2341(2) A alpha = 90 deg. b = 9.4269(2) A beta = 90 deg. c = 12.2070(3) A gamma = 90 deg.
Volume	1062.61(4) A^3
Z, Calculated density	4, 1.377 Mg/m^3
Absorption coefficient	0.116 mm^-1
F(000)	472
Crystal size	0.30 x 0.16 x 0.10 mm
Theta range for data collection	2.73 to 29.13 deg.
Limiting indices	-12<=h<=12, 0<=k<=12, 0<=l<=16
Reflections collected / unique	22079 / 2846 [R(int) = 0.0409]
Completeness to theta = 28.30	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9885 and 0.9660
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2846 / 0 / 160
Goodness-of-fit on F^2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0310, wR2 = 0.0753
R indices (all data)	R1 = 0.0349, wR2 = 0.0775
Absolute structure parameter	-0.1(7)
Largest diff. peak and hole	0.299 and -0.174 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for YANT.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3728(1)	-1535(1)	7807(1)	14(1)
C(1)	4978(1)	-764(1)	7447(1)	13(1)
C(2)	4541(1)	-110(1)	6355(1)	12(1)
C(3)	2950(1)	225(1)	6559(1)	12(1)
C(4)	2476(1)	-1123(1)	7151(1)	12(1)
O(2)	5299(1)	359(1)	8154(1)	16(1)
C(5)	5981(1)	-94(1)	9156(1)	18(1)
C(6)	5935(2)	1105(1)	9945(1)	18(1)
C(7)	7092(2)	1638(2)	10428(1)	29(1)
O(3)	5413(1)	1041(1)	6016(1)	15(1)
O(4)	2175(1)	447(1)	5572(1)	16(1)
C(8)	1140(1)	-970(1)	7866(1)	13(1)
O(5)	1275(1)	130(1)	8651(1)	15(1)
C(9)	733(1)	-2372(1)	8403(1)	17(1)
O(6)	-601(1)	-2256(1)	8988(1)	18(1)

Table 3. Bond lengths [A] and angles [deg] for YANT.

O(1)-C(1)	1.4334(15)
O(1)-C(4)	1.4588(14)
C(1)-O(2)	1.3979(15)
C(1)-C(2)	1.5222(17)
C(2)-O(3)	1.4136(14)
C(2)-C(3)	1.5239(16)
C(3)-O(4)	1.4161(14)
C(3)-C(4)	1.5260(16)
C(4)-C(8)	1.5185(16)
O(2)-C(5)	1.4404(15)
C(5)-C(6)	1.4853(18)
C(6)-C(7)	1.320(2)
C(8)-O(5)	1.4168(14)
C(8)-C(9)	1.5230(17)
C(9)-O(6)	1.4283(15)
C(1)-O(1)-C(4)	109.56(9)
O(2)-C(1)-O(1)	111.43(10)
O(2)-C(1)-C(2)	106.88(9)
O(1)-C(1)-C(2)	105.09(9)
O(3)-C(2)-C(1)	114.62(10)
O(3)-C(2)-C(3)	115.98(9)
C(1)-C(2)-C(3)	101.37(9)
O(4)-C(3)-C(2)	112.27(9)
O(4)-C(3)-C(4)	112.41(10)
C(2)-C(3)-C(4)	100.42(9)
O(1)-C(4)-C(8)	110.75(9)
O(1)-C(4)-C(3)	104.77(9)
C(8)-C(4)-C(3)	115.22(10)
C(1)-O(2)-C(5)	113.13(9)
O(2)-C(5)-C(6)	108.22(10)
C(7)-C(6)-C(5)	123.76(13)
O(5)-C(8)-C(4)	112.73(10)
O(5)-C(8)-C(9)	111.50(10)
C(4)-C(8)-C(9)	111.42(10)
O(6)-C(9)-C(8)	111.16(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for YANT. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	14(1)	14(1)	15(1)	4(1)	-1(1)	1(1)
C(1)	14(1)	13(1)	13(1)	0(1)	0(1)	0(1)
C(2)	14(1)	11(1)	12(1)	0(1)	1(1)	0(1)
C(3)	14(1)	12(1)	10(1)	1(1)	0(1)	1(1)
C(4)	13(1)	12(1)	11(1)	0(1)	-1(1)	0(1)
O(2)	20(1)	14(1)	12(1)	1(1)	-4(1)	0(1)
C(5)	21(1)	18(1)	15(1)	2(1)	-5(1)	0(1)
C(6)	23(1)	18(1)	14(1)	3(1)	-1(1)	0(1)
C(7)	37(1)	20(1)	30(1)	-2(1)	-16(1)	3(1)
O(3)	18(1)	15(1)	12(1)	0(1)	0(1)	-5(1)
O(4)	17(1)	19(1)	11(1)	1(1)	-2(1)	5(1)
C(8)	14(1)	14(1)	11(1)	0(1)	0(1)	0(1)
O(5)	18(1)	15(1)	13(1)	-3(1)	-1(1)	1(1)
C(9)	19(1)	16(1)	17(1)	1(1)	4(1)	-2(1)
O(6)	18(1)	21(1)	15(1)	-3(1)	3(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for YANT.

	x	y	z	U(eq)
H(1)	5831	-1407	7358	16
H(2)	4597	-865	5781	15
H(3)	2852	1067	7052	15
H(4)	2290	-1878	6594	14
H(5A)	6997	-372	9013	22
H(5B)	5463	-924	9462	22
H(6)	5019	1510	10113	22
H(8)	321	-703	7371	15
H(9A)	641	-3114	7833	21
H(9B)	1511	-2663	8913	21
H(7A)	7020(20)	2420(20)	10961(17)	43(5)
H(7B)	8020(20)	1230(20)	10238(17)	45(6)
H(03)	5650(20)	1510(20)	6547(16)	32(5)
H(04)	1570(20)	1174(19)	5666(16)	30(5)
H(05)	1880(20)	-99(18)	9102(14)	26(4)
H(06)	-510(20)	-1760(20)	9481(19)	46(6)

Table 6. Torsion angles [deg] for YANT.

C(4)-O(1)-C(1)-O(2)	102.02(11)
C(4)-O(1)-C(1)-C(2)	-13.38(12)
O(2)-C(1)-C(2)-O(3)	42.47(13)
O(1)-C(1)-C(2)-O(3)	160.98(9)
O(2)-C(1)-C(2)-C(3)	-83.24(10)
O(1)-C(1)-C(2)-C(3)	35.27(11)
O(3)-C(2)-C(3)-O(4)	73.15(13)
C(1)-C(2)-C(3)-O(4)	-162.05(9)
O(3)-C(2)-C(3)-C(4)	-167.24(10)
C(1)-C(2)-C(3)-C(4)	-42.43(10)
C(1)-O(1)-C(4)-C(8)	-138.89(10)
C(1)-O(1)-C(4)-C(3)	-14.06(12)
O(4)-C(3)-C(4)-O(1)	154.77(9)
C(2)-C(3)-C(4)-O(1)	35.25(11)
O(4)-C(3)-C(4)-C(8)	-83.28(12)
C(2)-C(3)-C(4)-C(8)	157.20(10)
O(1)-C(1)-O(2)-C(5)	76.32(12)
C(2)-C(1)-O(2)-C(5)	-169.39(9)
C(1)-O(2)-C(5)-C(6)	-166.05(10)
O(2)-C(5)-C(6)-C(7)	-124.39(14)
O(1)-C(4)-C(8)-O(5)	63.68(12)
C(3)-C(4)-C(8)-O(5)	-54.99(13)
O(1)-C(4)-C(8)-C(9)	-62.56(13)
C(3)-C(4)-C(8)-C(9)	178.77(10)
O(5)-C(8)-C(9)-O(6)	58.68(14)
C(4)-C(8)-C(9)-O(6)	-174.41(10)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for YANT [A and deg.].

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O3-H03	0.814	2.086	148.64	2.813	O1 [-x+1, y+1/2, -z+3/2]
O3-H03	0.814	2.264	113.18	2.691	O2
O4-H04	0.891	1.782	170.03	2.664	O6 [-x, y+1/2, -z+3/2]
O5-H05	0.813	2.023	160.09	2.801	O4 [-x+1/2, -y, z+1/2]
O6-H06	0.767	1.993	161.74	2.732	O3 [-x+1/2, -y, z+1/2]

7. Compound (±)-**417**

Table 1. Crystal data and structure refinement for saat.

Identification code	saat
Empirical formula	C16 H28 N2 O4
Formula weight	312.40
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P21/n
Unit cell dimensions	a = 9.4522(4) A alpha = 90 deg. b = 15.3510(7) A beta = 94.172(3) deg. c = 13.2985(6) A gamma = 90 deg.
Volume	1924.51(15) A^3
Z, Calculated density	4, 1.078 Mg/m^3
Absorption coefficient	0.077 mm^-1
F(000)	680
Crystal size	0.25 x 0.15 x 0.10 mm
Theta range for data collection	2.03 to 28.45 deg.
Limiting indices	-12<=h<=12, 0<=k<=20, 0<=l<=17
Reflections collected / unique	60608 / 4809 [R(int) = 0.0900]
Completeness to theta = 28.30	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9923 and 0.9810
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4809 / 0 / 234
Goodness-of-fit on F^2	1.150
Final R indices [I>2sigma(I)]	R1 = 0.0785, wR2 = 0.1926
R indices (all data)	R1 = 0.1174, wR2 = 0.2106
Largest diff. peak and hole	0.396 and -0.230 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for saat.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	3281(4)	-5782(2)	10474(4)	62(1)
C(2)	2157(3)	-5132(2)	10164(3)	33(1)
O(1)	2817(2)	-4277(1)	10279(2)	28(1)
C(3)	1936(3)	-3594(2)	10190(2)	24(1)
O(2)	673(2)	-3646(1)	10032(2)	36(1)
C(4)	2751(3)	-2767(2)	10292(2)	23(1)
C(5)	2101(3)	-2003(2)	10290(2)	21(1)
C(6)	2928(2)	-1174(2)	10349(2)	19(1)
O(3)	4238(2)	-1177(1)	10347(2)	28(1)
N(1)	2146(2)	-451(1)	10383(2)	19(1)
C(7)	2760(2)	421(2)	10388(2)	20(1)
C(8)	2697(3)	879(2)	11427(2)	26(1)
C(9)	1212(3)	853(2)	11811(2)	35(1)
C(10)	3153(4)	1834(2)	11321(2)	37(1)
C(11)	3751(3)	413(2)	12175(2)	36(1)
C(12)	2012(2)	923(2)	9509(2)	20(1)
O(4)	704(2)	938(1)	9388(1)	26(1)
N(2)	2870(2)	1318(1)	8906(2)	23(1)
C(13)	2439(3)	1838(2)	8000(2)	28(1)
C(14)	3799(3)	2107(3)	7542(3)	53(1)
C(15)	1546(4)	1294(3)	7248(2)	54(1)
C(16)	1632(4)	2640(2)	8286(3)	56(1)

Table 3. Bond lengths [A] and angles [deg] for saat.

C(1)-C(2)	1.494(5)
C(2)-O(1)	1.458(3)
O(1)-C(3)	1.339(3)
C(3)-O(2)	1.199(3)
C(3)-C(4)	1.485(3)
C(4)-C(5)	1.324(3)
C(5)-C(6)	1.492(3)
C(6)-O(3)	1.238(3)
C(6)-N(1)	1.336(3)
N(1)-C(7)	1.460(3)
C(7)-C(12)	1.529(3)
C(7)-C(8)	1.555(4)
C(8)-C(9)	1.528(4)
C(8)-C(11)	1.532(4)
C(8)-C(10)	1.538(4)
C(12)-O(4)	1.236(3)
C(12)-N(2)	1.328(3)
N(2)-C(13)	1.477(3)
C(13)-C(15)	1.512(4)
C(13)-C(16)	1.512(4)
C(13)-C(14)	1.519(4)
O(1)-C(2)-C(1)	106.4(3)
C(3)-O(1)-C(2)	115.9(2)
O(2)-C(3)-O(1)	124.6(2)
O(2)-C(3)-C(4)	125.2(2)
O(1)-C(3)-C(4)	110.2(2)
C(5)-C(4)-C(3)	121.3(2)
C(4)-C(5)-C(6)	120.9(2)
O(3)-C(6)-N(1)	123.9(2)
O(3)-C(6)-C(5)	121.1(2)
N(1)-C(6)-C(5)	114.9(2)
C(6)-N(1)-C(7)	122.8(2)
N(1)-C(7)-C(12)	107.27(19)
N(1)-C(7)-C(8)	112.2(2)
C(12)-C(7)-C(8)	114.0(2)
C(9)-C(8)-C(11)	109.9(2)
C(9)-C(8)-C(10)	109.0(2)
C(11)-C(8)-C(10)	109.3(2)
C(9)-C(8)-C(7)	112.4(2)
C(11)-C(8)-C(7)	107.5(2)
C(10)-C(8)-C(7)	108.6(2)
O(4)-C(12)-N(2)	124.2(2)
O(4)-C(12)-C(7)	120.8(2)
N(2)-C(12)-C(7)	115.0(2)
C(12)-N(2)-C(13)	126.6(2)
N(2)-C(13)-C(15)	110.4(2)
N(2)-C(13)-C(16)	110.4(2)
C(15)-C(13)-C(16)	110.3(3)
N(2)-C(13)-C(14)	106.4(2)
C(15)-C(13)-C(14)	109.5(3)
C(16)-C(13)-C(14)	109.7(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for saat. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	70(3)	18(2)	95(3)	0(2)	-20(2)	2(2)
C(2)	44(2)	14(1)	41(2)	-3(1)	-5(1)	-6(1)
O(1)	32(1)	13(1)	40(1)	-1(1)	-1(1)	0(1)
C(3)	29(1)	16(1)	27(1)	1(1)	1(1)	-3(1)
O(2)	28(1)	20(1)	59(1)	-2(1)	2(1)	-4(1)
C(4)	22(1)	19(1)	27(1)	1(1)	1(1)	-2(1)
C(5)	17(1)	17(1)	28(1)	1(1)	1(1)	-2(1)
C(6)	19(1)	15(1)	23(1)	3(1)	2(1)	-1(1)
O(3)	16(1)	19(1)	49(1)	3(1)	1(1)	0(1)
N(1)	13(1)	14(1)	31(1)	2(1)	2(1)	-2(1)
C(7)	17(1)	15(1)	28(1)	1(1)	3(1)	-1(1)
C(8)	31(1)	18(1)	27(1)	-2(1)	2(1)	-4(1)
C(9)	39(2)	31(2)	35(2)	-4(1)	12(1)	0(1)
C(10)	54(2)	21(1)	37(2)	-5(1)	3(1)	-10(1)
C(11)	44(2)	36(2)	28(2)	1(1)	-6(1)	-1(1)
C(12)	18(1)	15(1)	26(1)	-1(1)	1(1)	0(1)
O(4)	17(1)	24(1)	36(1)	8(1)	3(1)	1(1)
N(2)	15(1)	26(1)	29(1)	6(1)	0(1)	-3(1)
C(13)	27(1)	30(2)	25(1)	8(1)	0(1)	-4(1)
C(14)	34(2)	79(3)	47(2)	34(2)	-1(1)	-14(2)
C(15)	66(2)	62(2)	31(2)	9(2)	-8(2)	-31(2)
C(16)	79(3)	38(2)	53(2)	21(2)	14(2)	21(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for saat.

	x	y	z	U(eq)
H(1A)	4070	-5724	10040	74
H(1B)	2886	-6372	10409	74
H(1C)	3624	-5678	11177	74
H(9A)	913	246	11877	42
H(9B)	546	1156	11332	42
H(9C)	1227	1140	12470	42
H(10A)	3169	2121	11979	45
H(10B)	2479	2133	10844	45
H(10C)	4103	1856	11071	45
H(11A)	4708	456	11940	44
H(11B)	3484	-202	12224	44
H(11C)	3736	687	12840	44
H(14A)	4367	2472	8023	64
H(14B)	3566	2437	6921	64
H(14C)	4342	1587	7387	64
H(15A)	2089	784	7059	64
H(15B)	1284	1644	6647	64
H(15C)	684	1103	7553	64
H(16A)	783	2464	8616	67
H(16B)	1350	2977	7678	67
H(16C)	2238	2999	8750	67
H(2A)	1820(30)	-5200(20)	9480(20)	32(8)
H(2B)	1340(30)	-5160(20)	10570(20)	31(8)
H(4)	3780(30)	-2854(18)	10360(20)	23(7)
H(5)	1090(30)	-1970(20)	10220(20)	34(8)
H(1N1)	1240(30)	-530(20)	10380(20)	32(8)
H(7)	3800(20)	341(15)	10277(17)	7(6)
H(1N2)	3790(30)	1266(18)	9060(20)	18(7)

Table 6. Torsion angles [deg] for saat.

C(1)-C(2)-O(1)-C(3)	-170.0(3)
C(2)-O(1)-C(3)-O(2)	0.4(4)
C(2)-O(1)-C(3)-C(4)	-178.3(2)
O(2)-C(3)-C(4)-C(5)	5.4(4)
O(1)-C(3)-C(4)-C(5)	-175.9(2)
C(3)-C(4)-C(5)-C(6)	-177.4(2)
C(4)-C(5)-C(6)-O(3)	3.9(4)
C(4)-C(5)-C(6)-N(1)	-177.3(2)
O(3)-C(6)-N(1)-C(7)	2.1(4)
C(5)-C(6)-N(1)-C(7)	-176.6(2)
C(6)-N(1)-C(7)-C(12)	124.7(2)
C(6)-N(1)-C(7)-C(8)	-109.4(3)
N(1)-C(7)-C(8)-C(9)	-50.9(3)
C(12)-C(7)-C(8)-C(9)	71.3(3)
N(1)-C(7)-C(8)-C(11)	70.2(3)
C(12)-C(7)-C(8)-C(11)	-167.6(2)
N(1)-C(7)-C(8)-C(10)	-171.6(2)
C(12)-C(7)-C(8)-C(10)	-49.4(3)
N(1)-C(7)-C(12)-O(4)	49.8(3)
C(8)-C(7)-C(12)-O(4)	-75.0(3)
N(1)-C(7)-C(12)-N(2)	-129.6(2)
C(8)-C(7)-C(12)-N(2)	105.6(3)
O(4)-C(12)-N(2)-C(13)	0.0(4)
C(7)-C(12)-N(2)-C(13)	179.3(2)
C(12)-N(2)-C(13)-C(15)	-58.1(4)
C(12)-N(2)-C(13)-C(16)	64.1(4)
C(12)-N(2)-C(13)-C(14)	-176.9(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for saat [A and deg.].

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1N1	0.862	1.989	165.88	2.833	O4 [-x, -y, -z+2]
N2-H1N2	0.881	1.978	169.75	2.849	O3 [-x+1, -y, -z+2]

APPENDIX VII

Summary of Results

- Efficient and environmentally benign methodology has been developed for rapid synthesis of small molecules.
- Structural and skeletal diversity have been achieved without any extraneous additives except only two cases.
- Microwave irradiation can influence reactivity of molecules and can be used as a reagent.
- A new paradigm of diversity-activity relationships (DARs) has been established.
- PDMAB and PMNPAB groups have been developed as novel functional handles in organic synthesis and orthogonal to PMB group.
- Synthesis of the trisachharide unit of the repeating tetrasachharide unit of the ZPS PS A1 has been achieved *via* linear approach.

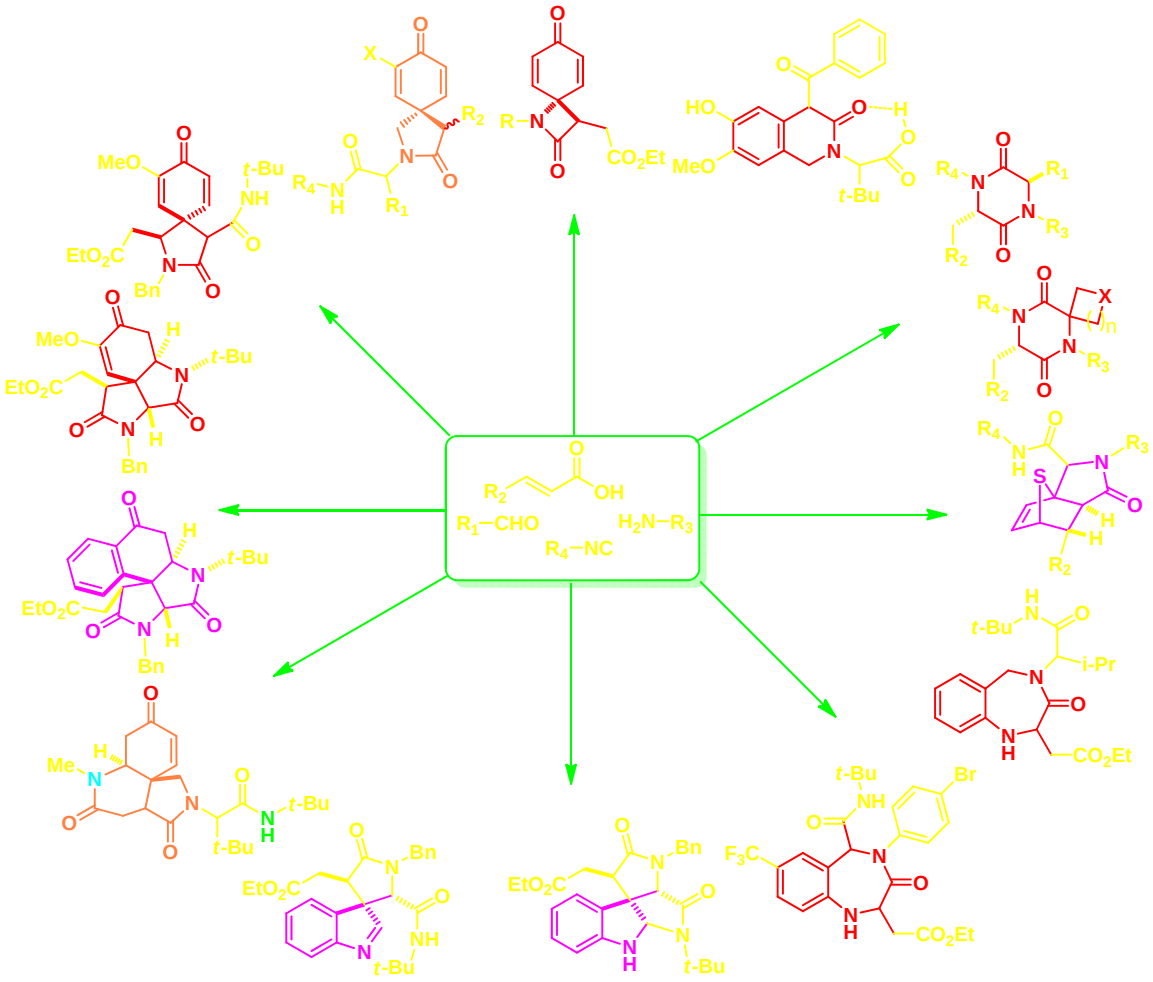


Figure 41. Structural and skeletal diversity from readily available starting materials

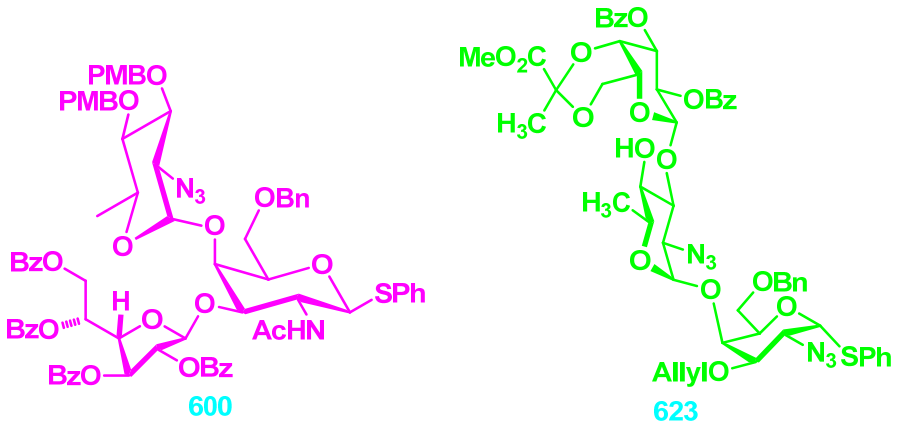


Figure 42. Synthesis of the trisachharide units have been achieved

APPENDIX IX

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Panagiotis Ioannidis, Ph D
Senior Scientist
Biotage Sweden AB
Kungsgatan 76
SE-753 18 Uppsala
Sweden

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On 26 Apr 2010, at 04:59, soumava@chem.wayne.edu wrote:

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Phone: +43-316-3805352; Fax: +43-316-3809840
email: oliver.kappe@uni-graz.at

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Phone: +43-316-3805352; Fax: +43-316-3809840
email: oliver.kappe@uni-graz.at

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Wayne State University
Detroit, MI 48201

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ABSTRACT

I. MICROWAVE-INFLUENCED DIVERSITY-ORIENTED SYNTHESIS OF BIOLOGICALLY RELEVANT SMALL AND NATURAL-PRODUCT-LIKE MOLECULES VIA MULTICOMPONENT COUPLING REACTIONS

II. SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF THE REPEATING TETRASACCHARIDE UNIT OF ZWITTERIONIC POLYSACCHARIDE PS A1

by

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Degree: Doctor of Philosophy

Microwave-influenced diversity-oriented synthesis of biologically relevant small and natural-product-like molecules via multicomponent coupling reactions (MCCRs) have been investigated. Cheap, readily available starting materials in conjunction of microwave irradiation and employment of environmentally benign solvent (e.g. water) provided a common platform that allowed to access a wide array of structurally and skeletally diverse molecules. The investigation allowed us to establish a new paradigm of diversity-activity relationships (DARs) by tuning reacting components of the MCCRs and proved that in contrary to the conventional use of microwave as a rate accelerating tool, it can be used to influence reactivity of molecules. The method was also extended to develop new protecting groups (PGs, PDMAB, PMNPAB) that can be useful in

carbohydrate as well as other areas of synthetic organic chemistry. Additionally, the new *p*-*N*,*N*-diemethylaminobenzyl (PDMAB) PG was employed to develop an alkoxide-based neutral glycosylation and further extended to study entirely neutral glycosylation *via* oxocarbenium ion.

We also investigated the total synthesis of the repeating tetrasaccharide unit of zwitterionic polysaccharide PS A1 using different strategies. PS A1 is known to modulate T-cell response via MHC-II pathway and shown to prevent tumor growth. The synthesis is quite challenging and we have been able to construct the trisaccharide unit of the repeating tetrasaccharide unit of PS A1.

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