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Synthesis of 3'-deoxy- and 2',3'-dideoxy-4'-C-alkyl-D-nucleosides: potential antiviral agents

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SYNTHESIS OF 3'-DEOXY- AND 2',3'-DIDEOXY-4'-*C*-ALKYL-D-NUCLEOSIDES: POTENTIAL ANTIVIRAL AGENTS

by

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To Mom and Dad

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Chapter 1

Introduction

1.1. HIV Infections: Historical Perspective and Scope of Problem.

In 1981, the first cases of the illness now known as acquired immunodeficiency syndrome (AIDS) were reported by Gottlieb.[1] This new illness was characterized by a diagnoses of *Pneumocystis Carinii* pneumonia (PCP), a condition caused by a generally harmless fungus. Because cases of PCP generally occur only in immune suppressed individuals, the occurrence of so many cases was termed "unusual".[2] Furthermore, the dramatic increase in pneumonia among individuals with life style similarities including homosexuality and intravenous drug use indicated that an infectious form of immune deficiency may be the culprit.

In January of 1983 Montagnier and colleagues working at the Pasteur Institute in Paris isolated a virus that they attributed as the agent causing AIDS. As the virus was isolated form a patient with lymphadenopathy, an early condition typical of individuals who progress into full blown AIDS, Montagnier named the virus lymphadenopathy-associated virus or LAV.[3] Nearly simultaneous to Montagnier's report, Gallo and co-workers also reported isolating the virus causing AIDS and named it Human T Cell Lymphotropic Virus (HTLV III).[4] Because of the collection of names given the virus created some confusion, the committee on the Taxomity of Viruses reduced all the names to one: Human Immunodeficiency Virus or HIV. This term has now been accepted for use world wide, and at present there is little doubt that HIV-I (or HIV-II) is responsible for a spectrum of progressive immunological disorders of which AIDS is the final and most severe manisfestation.[5]

As of 1995 it is estimated that some 1.5 million North Americans are infected with HIV. In third world countries with poorly developed health services the situation is even

bleaker. For example, it is believed that the number of HIV infected individuals in Africa is well over 14 million and these numbers continue to rise. The World Health Organization estimates by the year 2000 there will be over 40 million HIV-infected adults.[6] To slow the rapid growth of HIV infections, education on how HIV is transmitted from one individual to another is the only clear answer. For those that are already infected little can be done. Until quite recently people diagnosed with HIV were in effect given a death sentence as there was nothing that could be done to significantly slow the progression of the disease. However, combinations of certain antiviral drugs which are now available appear as if they may substantially slow and possibly stop the replication of HIV and the development of AIDS.[7] Unfortunately, the cost of these drugs is very high and this will limit their use.

1.2. HIV Replication

The human immunodeficiency virus, like all viruses, is nothing more than a protein shell that encases a small amount of genetic material. All viruses rely on the machinery of infected cell to produce duplicate copies. The HIV belongs to a class of viruses known as retroviruses, so named as they store genetic information in the form of a single strand of RNA, instead of DNA as is the case with all other viruses and living organisms. This requires that one of the first steps in replication of the HIV is a process referred to as reverse transcription in which the viral RNA is transcribed into proviral DNA (Figure 1).

A schematic diagram detailing the steps of HIV infection and replication is shown in Figure 2.[9,10,11] The first step is attachment of the virus to the target T Lymphocyte cell. This attachment results form the selective binding of a glycoprotien on the virus surface known as gp 120 with a CD4 antigen displayed by the T lymphocyte cells. After attaching, a process of uncoating occurs during which the contents of the virus -viral RNA and some viral enzymes- are released into the cytoplasm of the host cell.

The viral RNA, now within the cytoplasm of the host cell, will undergo the reverse transcription process. This involves a viral enzyme known as HIV reverse transcriptase (HIV-RT) which is responsible for performing three unique steps in the process. (1) HIV-

RT, using the single stranded viral RNA as a template, synthesizes a complementary single strand of DNA. (2) The HIV-RT hydrolyzes the viral RNA from the RNA-DNA complex. (3) HIV-RT acts as a DNA-dependent polymerase and transcribes a second DNA strand

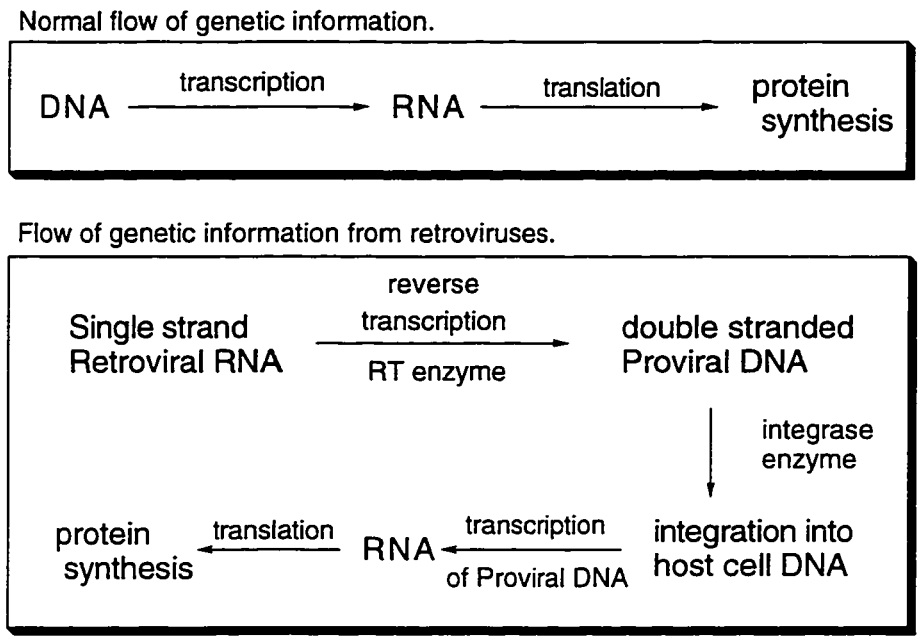


Figure 1. Human and Retroviral Flow of Genetic Information. The general directional flow of genetic information in all living species is from DNA, where the information is stored, into RNA, which serves as a messenger for the construction of proteins which are the cell's functional molecules. This unidirectional flow of genetic information has been referred to as the "central dogma" of molecular biology. In the 1960's Howard Temin and colleagues discovered an enzyme that copied RNA into DNA, a reverse of what was normally expected, thus the name reverse transcriptase.[8]

complementary to the first. This complex process of viral RNA transcription, when completed, affords a double stranded proviral DNA.

The proviral DNA then migrates into the cellular nucleus and becomes inserted (integrated) into the cellular genome. Once proviral DNA is integrated, the host cell is infected for life as the genetic information for the production of HIV particles is contained within the very chromosomes of the infected cell. Here, the proviral DNA will undergo a period of latency which can vary greatly in time and is characterized by no transcription of

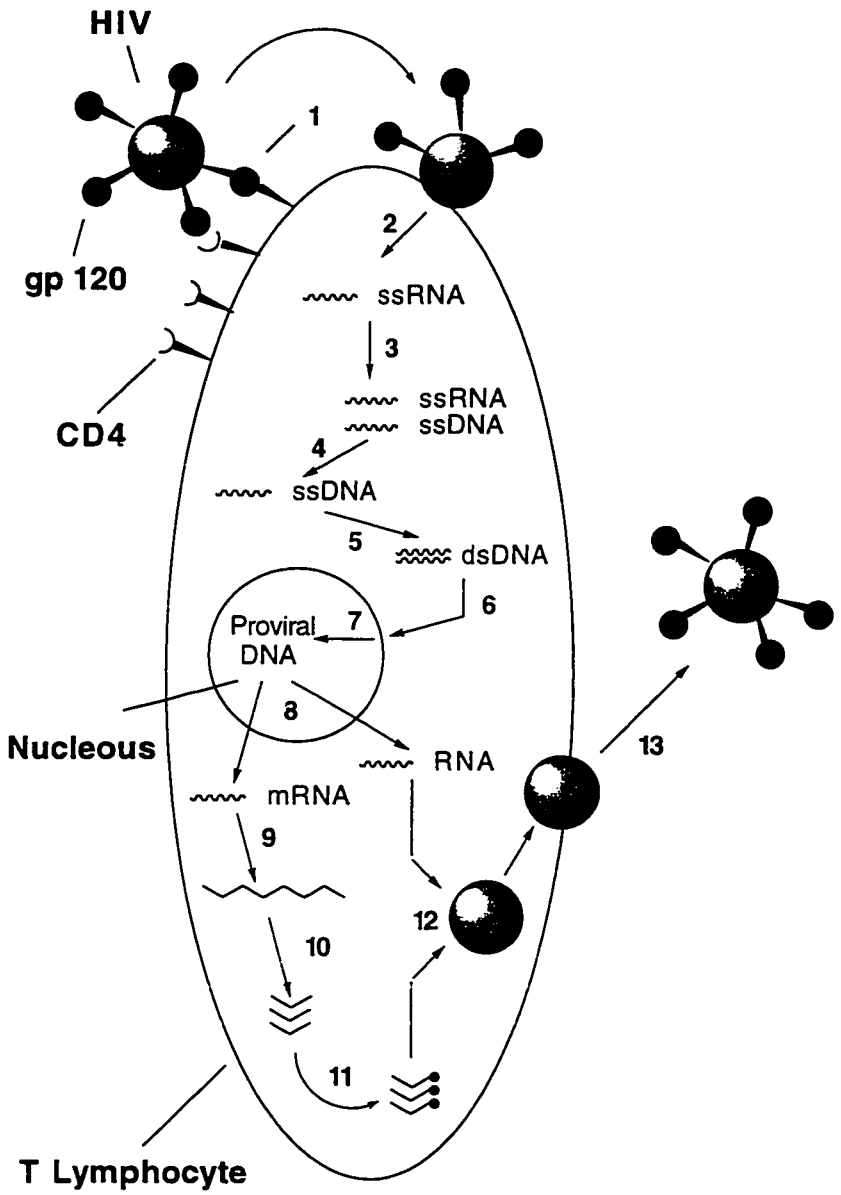


Figure 2. The Steps in HIV Replication. (1) Binding, (2) Uncoating, (3) Reverse transcription of single stranded RNA, (4) Hydrolysis of RNA, (5) DNA synthesis of second strand, (6) Migration to nucleus, (7) Integration, (8) Transcription of Proviral The proviral DNA, (9) Protein synthesis, (10) Protein slicing (HIV protease), (11) Protein glycosylation, (12) RNA packaging and viron assembly, (13) Budding and release of mature HIV.

the proviral DNA. The period of latency continues until various activating proteins initiate the transcription of the proviarl DNA into proviral RNA.

Some of these recently transcribed proviral RNA molecules will behave as messenger RNA and travel through the cytoplasm to the ribosome where they are translated to viral proteins. These freshly minted viral proteins are then sliced into the appropriate segments by another viral enzyme known as HIV-protease. These protein segments then undergo a process of glycosylation, and together with a complete strand of viral RNA are assembled into a new virus particle. The HIV particle will bud from the surface of the cell taking a piece of the cellular membrane to become the viral membrane and then be released into the intercellular media as a fully formed and mature HIV particle.

1.3. HIV Pathogenesis.

The hallmark of AIDS is a reduction of T lymphocyte cells that display the CD4 antigen. The loss of these cells severely compromises the effectiveness of the immune system of HIV infected individuals, making them susceptible to opportunistic infections and cancers.[12] Left without immune defenses, such afflictions will eventually result in death.

The mechanism by which HIV depletes T lymphocytes remains to be conclusively elucidated. The simplest explanation for the loss of T lymphocytes is direct killing by HIV. The virus might induce "lysis" (causing infected cells to implode or burst) or it might cause cells to fuse together into clumps called "syncytia". Both have been detected *in vitro*. The lysis of infected cells is attributed to the viral glycoprotein, gp 120, complexing freshly minted CD4 within the cell and this complex fusing to cellular organelles such as the Golgi apparatus. Syncytia formation results from freshly minted gp 120 budding through the cellular membrane of infected cells and complexing CD4 bearing T lymphocytes. In this way infected cells may fuse with innocent bystanders and, in doing so, destroy the immune function of T lymphocytes.[13, 14, 15]

1.4. Anti-HIV Chemotherapy.

Antimicrobial chemotherapy usually capitalizes on some biochemically unique life cycle event or structure of a living infecting organism. It serves as a target for intervention by weakening the pathogen but not the host. This approach has been highly successful in the discovery and development of antibacterial chemotherapeutics as well as chemotherapeutics for other life forms such as fungi.

Viral diseases, such as HIV infection, present very different problems because viruses depend largely on the host's cellular machinery for their existence. Interference with these processes often interferes with other important host physiological processes. HIV poses other challenges as well because its pathogenic properties include destruction of the human immune system.

With the elucidation of the HIV life cycle many potential targets for chemotherapeutic intervention have been recognized and explored. Several excellent reviews detailing such strategies for intervention of HIV infections have appeared.[11, 16, 17, 18] Only two targets to date however, have resulted in the development of useful antiviral agents. These two viral processes are inhibition of the HIV reverse transcriptase enzyme (step 3 in Figure 2) and inhibition of the HIV protease enzyme (step 10 in Figure 2). These two processes are particularly attractive points to intervene in the HIV life cycle as they are mediated by enzymes unique to HIV. Since these enzymes have no identical counterparts or function in the biochemistry of the host, a chemotherapeutic agent that is a highly selective inhibitor of the viral enzymes should, in theory, have no effect on the host.

The first anti-HIV agent to receive approval from the United States Food and Drug Administration was 3'-Azidothymidine (AZT).[19,20] AZT has been shown to be a substrate of the viral reverse transcriptase enzyme and an inhibitor of the reverse transcription process (HIV-RT inhibitor). Since the arrival of AZT, four additional substrate HIV-RT inhibitors have been approved by the FDA; dideoxyinosine (ddI),[21] dideoxycytidine (ddC),[22] didehydro-dideoxythymidine (d4T),[23] and 3'-thiocytidine (3TC).[24] Together these five nucleoside analogs, shown in Figure 3, make up more than half of the nine drugs

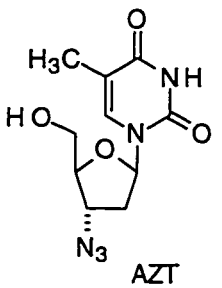
currently approved for treatment of HIV. The remaining four drugs which are approved for treatment of HIV consist of a nonsubstrate HIV-RT inhibitor known as Nevirapine[25] and three protease inhibitors; indinavir, ritonavir, and saquinavir.[26, 27]

While monotherapy with any one of the currently approved drugs offers only modest therapeutic benefit, combination therapy with two or more drugs can result substantial improvements in health. Particularly effective is the use of a protease inhibitor with one or more substrate HIV-RT inhibitors. These combinations have been shown to reduce viral loads in HIV infected individuals to nearly undetectable levels despite the fact that these same individuals were near death with full blown AIDS only months prior to initiation of combination therapy. The long term benefit from such combination therapies remains to be observed.[7, 28]

1.4.1. Nucleoside Analogs as Reverse Transcriptase Inhibitors.

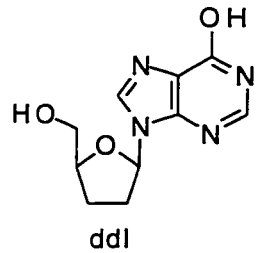
This body of work focuses on the preparation of modified nucleoside analogs as potential anti-HIV agents. Therefore, a thorough discussion on the mechanism by which nucleoside analogs can inhibit HIV replication is pertinent. Shown in Figure 3 are the five substrate HIV-RT inhibitors that are currently approved to treat HIV infection. All five have obvious similarities. First they are all nucleosides consisting of either a purine (as in ddI) or a pyrimidine heterocyclic base which is linked by a glycosidic bond to a modified ribose analog. The second similarity is that all are lacking a hydroxyl functionality at both the 2' as well as the 3' position (see Figure 4 for numbering of nucleosides). Natural nucleosides in the case of DNA contain a hydroxyl at the 3' position, and in the case of RNA both the 2' and 3' positions contain a hydroxy functionality. It is the deoxygenation of the 3' position which has been attributed as the key modification which imparts these dideoxynucleosides (ddN's) with potent anti-HIV activity.[29]

The mechanism by which dideoxynucleosides (ddN's) are thought to inhibit viral replication is shown if Figure 5. An important point to recognize is that ddN's are not the active form of the drugs. Rather they are prodrugs requiring cellular metabolism to be



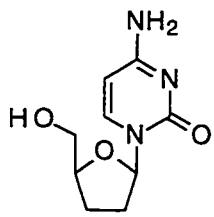
AZT

(Glaxo Wellcome 1987)



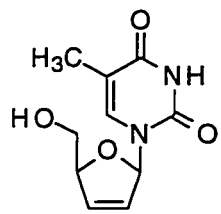
ddI

(Bristol-Myers Squibb 1991)



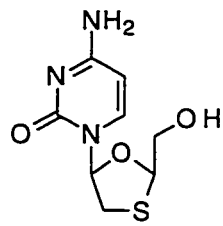
ddC

(Hoffman-La Roche 1992)



d4T

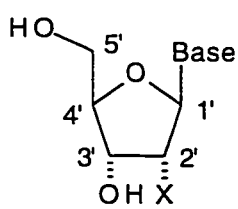
(Bristol-Myers Squibb 1994)



3TC

(Glaxo Wellcome 1995)

Figure 3. Nucleoside Analogs Approved by FDA for Treatment of HIV.



DNA X = H
RNA X = OH

Figure 4. Ribose Numbering of Nucleosides.

converted into their active forms. This metabolism is the sequential phosphorlation of the 5'-hydroxyl by cellular kinase enzymes to ddN-5'-triphosphates or ddNTP's. Each ddN

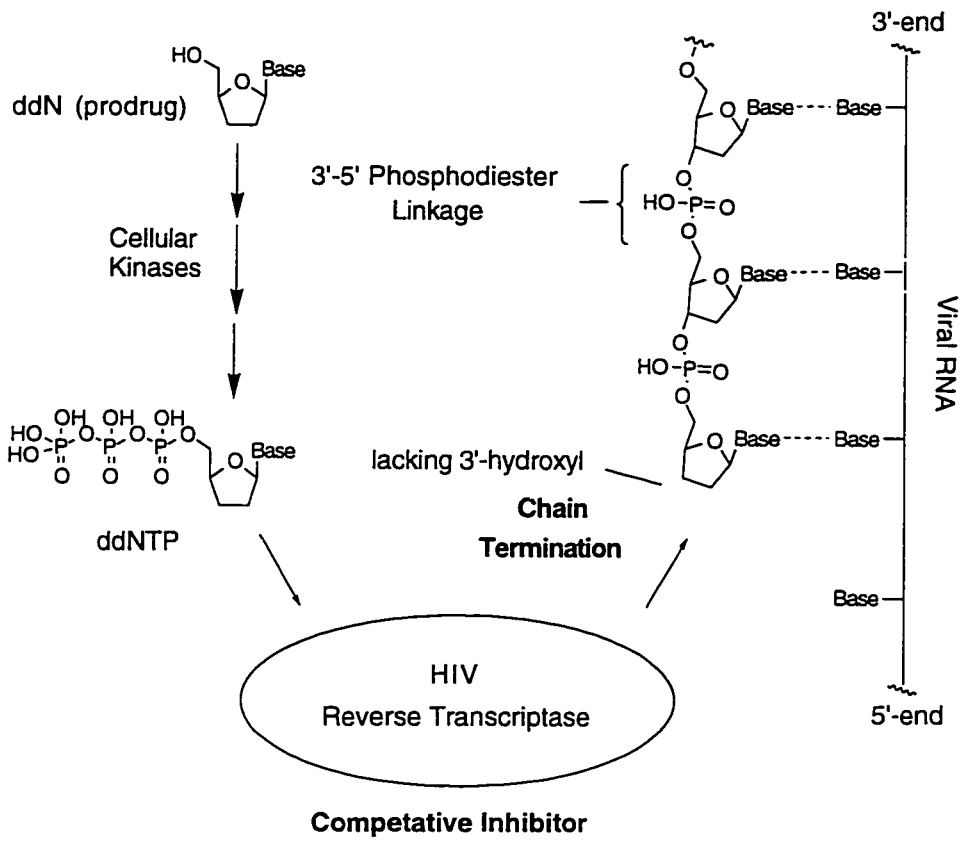


Figure 5. Mechanism by Which Dideoxynucleosides Inhibit HIV Replication. Sequential phosphorlation to the corresponding dideoxynucleoside triphosphates results in a substrate capable of competing with natural deoxynucleoside triphosphates for the active site of HIV-RT (**competitive inhibition**). More likely, ddNTP's function as **chain terminators.** If inserted into the growing viral DNA chain ddN's lack the 3'-hydroxyl necessary for formation of the 3'-5' phosphodiester linkage to the next nucleotide and will result in termination of the viral DNA chain.

must be considered as a different drug, as each has a different metabolic pathway. Cellular kinase enzyme activities influence an important determinant of ddN antiretroviral activity, that is, the intracellular ratio of the active ddNTP species to that of the corresponding

endogenous ddN. Therefore, despite their structural similarities and common mechanisms of action, each ddN exhibits unique molecular, cellular and clinical pharmacological features which are highly dependent on cell type and the enzyme activities of those cells (see Table 1).[30]

Once metabolized to their 5'-triphosphates ddNTP's represent a suitable substrate for the binding of the active site of the HIV-RT enzyme. As a substrate for HIV-RT, ddNTP's compete with natural dNTP's (deoxynucleoside triphosphates) for the HIV-RT active sight and can be considered a competitive inhibitor of that enzyme. However, it is believed that the main mechanism of anti-HIV activity arises form the ddNTP's functioning as alternative substrates for the HIV-RT enzymes. The role of the HIV-RT enzyme is to synthesize a strand of viral DNA using the viral RNA as a template. If a ddNTP is accepted by the HIV-RT and becomes inserted into a growing viral DNA chain, the chain will become terminated as the ddN lacks the 3'-hydroxyl necessary for formation of the 3'-5' phosphodiester linkage to the next nucleotide.[31] This inhibits the replication of viral DNA therefore stopping HIV from infecting cells.

1.4.2. Clinical Utility of Dideoxynucleosides as Anti-HIV Agents.

Despite the fact that dideoxynucleosides are very potent inhibitors of HIV (Table 1) they suffer two serious pitfalls that limit their *in vivo* utility as anti-HIV agents. First, all five approved ddN's have rather serious toxic side effects associated with their therapeutic use. Secondly, all nucleoside analogs, as well as any other anti-HIV compound that has been examined in a clinical setting, have been shown to be susceptible to the emergence of drug resistant strains of HIV.[16]

Given the structural similarities of ddN's to natural nucleosides, and the many important biochemical process that natural nucleosides are involved with in living organisms, it is of little surprise that ddN's display a range of toxic side effects. Due to differing rates of phosphorlation, dependent on cell types and enzyme activities, no two ddN's display identical toxicological profiles.[30] Use of AZT, for example, results in bone

Table 1. Anti-HIV-I Activities of Dideoxynucleosides.

Compound[a]	Cell[b]	EC_{50}[c]	CC_{50}[d]	Index[e]
AZT	CEM	-	-	-
	PBM[f]	0.004	200	50000
	MT4[f]	0.004	20	5000
ddI	CEM	-	-	-
	PBM[g]	4.3	>100	>23
	MT4[g]	10	>500	>50
ddC	CEM[g]	0.66	-	-
	PBM[g]	0.01	>100	>10000
	MT4[g]	0.06	37	616
d4T	CEM	-	-	-
	PBM[g]	0.005	65	13000
	MT4[g]	0.13	7.9	60
3TC	CEM[h]	0.07	>100	>1428
	PBM[h]	0.002	>100	>50000
	MT4	-	-	-

(*a*) Structures shown in Figure 3 (*b*) Cell type assay preformed with (*c*) Effective concentration (*d*) Cytotoxic concentration (*e*) IC_{50}/EC_{50}. (*f*) ref. 42 (*g*) ref. 43 (*h*) ref. 24.

marrow suppression leading to conditions such as anemia and neutropenia. This requires patients on long term AZT treatment to undergo regular blood transfusions.[32] The major life threatening side effect attributed to ddI is pancreatitis.[33] In the case of ddC, it has been shown that ddCTP is a poor substrate for cellular DNA polymerase α, β, and δ. It is however, a good substrate for both the HIV-RT as well as mitochondria DNA polymerase (DNA polymerase γ). So while inhibiting HIV DNA synthesis, ddC also inhibits the synthesis of mitochondria DNA resulting in painful peripheral neuropathy as a pathological side effect.[34]

Side effects, such as these, severely limit the dosage of a ddN that an individual can withstand. This requires the use of dosages insufficiently large to completely suppress viral replication. Only by carefully controlling dose regiments can these side effects be managed, while at the same time retain beneficial anti-HIV activity.

Medicinal chemist have had some success in decreasing the toxic side effects associated with ddN's by preparing ddN's that are optical isomers to natural nucleosides.

A few of these analogs with an L-ribose configuration have been shown to be active against HIV. Such is the case with 3TC (Figure 4). The recent surge of interest in L-nucleosides was spurred by the expectation that they would be recognized not by normal mammalian enzymes, but would be recognized as substrates by virus encoded enzymes. As 3TC has good activity against HIV, it is clearly still metabolized by cellular kinase enzymes to the 5'-triphosphate and accepted as substrate by HIV-RT. While at the same, time the observed reduction of toxic side effects suggests that it is less likely accepted by cellular DNA polymerases. [24, 35, 36]

The emergence of drug resistant strains of HIV, the second pitfall limiting the clinical utility of ddN's, is due to the HIV's remarkable ability to mutate. HIV replicates at a very high rate and the HIV-RT enzyme is highly prone to making errors in the transcription of viral RNA into viral DNA. Estimates put the predicted error rate of HIV-RT at 5 to 10 per HIV genome per round of replication *in vivo*.[37] Rapid replication and high rate of error in reverse transcription leads to large amounts of genetically diverse strains of HIV within a single HIV positive individual.

These genetically different strains of HIV are referred to as "quasispecies". Treatment with an anti-HIV agent selects for the survival of any quasispecies with mutations conferring resistance to that give agent. An example of the Darwinian forces anti-HIV drugs can exert on HIV has long been recognized with AZT in that it's clinical effectiveness in each individual decreases over time. Viral isolates form patients receiving AZT for as little as six months can demonstrate up to a 100-fold decreased susceptibility to AZT.[38]

Even more troubling is a related phenomenon known as "cross resistance". Cross resistance implies that a strain of HIV containing a mutation conferring resistance to, for example, AZT will also demonstrate reduced susceptibility to other ddN's due to the presence of the mutation conferring AZT resistance.[39] This has been demonstrated in a study in which viral isolates were obtained from individuals who had received only AZT as therapy. For every 10-fold decrease in AZT susceptibility, these same isolates

demonstrated a 2.2-fold decrease susceptibility to ddI and a 2.0-fold decrease in ddC susceptibility.[40]

The mutations conferring resistance to ddN's have been shown to be occurring in the protein of the HIV-RT enzyme. The actual sight specific genotype changes which confer resistance can be identified by the cloning and sequencing of the reverse transcriptase coding regions of these virus varients.[41] Some data of the codon of mutation and the compounds to which that mutation confers resistance has been assembled and is shown in Table 2.[22]

Table 2. HIV Mutations Associated with Decresed *In Vitro* Sensitivity to Didiexoynucleosides.

Mutation Codon(s)	Confers decreased sensitivity to:	Selected by *in vivo* therapy with:
65	ddC, ddI 3TC (low level)	ddC, ddI
69	ddC (low level)	intermittent ddC. alternating AZT/ddC
74	ddI, ddC	ddI, AZT/ddI
75	d4T, ddC, ddI	d4T (*in vitro*)
62, 75, 77 116, 151	AZT, ddI and ddC	alternating AZT/ddC concurrent AZT/ddI
184	ddC, ddI (low level) 3TC (high level)	3TC, ddC

Despite the pitfalls of toxicity and drug resistance there is still room for optimism in the use of ddN's as antiviral chemotherapeutics. This optimism is born from the logical extension to use combinations of two or more anti-HIV agents that have different antiretroviral mechanisms or have different metabolic pathways. Three virtues are associated with the combined use of different anti-HIV drugs: (i) diminished toxicity, due to a reduction in the dosage of an individual compound; (ii) reduced risk of developing virus-drug resistance since the statistical probability of a quasispecies containing mutations conferring resistance to two compounds is less likely to occur; (iii) synergistic antiviral

activity.[16,18] As discussed earlier, the clinical benefit of combination therapies with dideoxynucleosides and protease inhibitors has already proven to be highly successful.[7,28]

Chapter 2

4'-*C*-Alkyl Nucleoside Analogs: Potential Anti-HIV Agents; Synthetic Methodology

2.1. 4'-*C*-Alkyl Nucleosides as Potential Anti-HIV Agents.

This research interest centered on synthesizing novel nucleoside analogs to observe what effect structural modification of the ribose moiety would play on anti-HIV activity. At the time this project was initiated three modified nucleosides; AZT, ddC, and ddI had already received the approval of the FDA for the treatment of HIV. During the course of this work two additional nucleoside analogs, d4T and 3TC, received approval as well. These five compounds strongly suggest that the lack of a 3'-hydroxyl is invaluable in imparting anti-HIV activity. It was apparent that deoxygenation of the 3' position should be an important structural feature to include in the design of other ribose modified nucleosides targeted at inhibiting HIV. It appears that another important design criteria for new anti-HIV nucleosides be a distinct dissimilarity in structure to the current family of anti-HIV nucleosides (Figure 3). Such a dissimilarity in structure might result in an agent of increased anti-HIV potency. Other latent benefits may arise with a structural dissimilarity, such as the decreased propensity for the development of cross resistant viral strains. Furthermore, the adverse toxic side effects uniquely associated with the clinical use of other anti-HIV nucleoside analogs may be diminished with a structural dissimilarity as well (see Section 1.4).

Novel nucleosides having the potential to inhibit HIV led to interest in nucleosides substituted at the 4'-position. Despite a large amount of published work involving the synthesis of anti-HIV nucleosides modified at the 2', 3' and 5' positions, prior references to modification of the 4'-position have been infrequent. Verheyden *et al.* described the first synthesis of a 4'-substituted nucleoside in the preparation of nucleocidin, a naturally occurring nucleoside antibiotic which contains a fluorine at the 4'-position.[44]

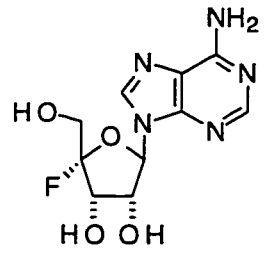


Figure 6. Nucleocidin; A Naturally Occurring Nucleoside Antibiotic.

Another 4'-substituted nucleoside was a reported by researchers at Syntex Pharmaceutical Company. This report detailed the synthesis and anti-HIV activity of 4'-azidothymidine (ADRT).[45, 46] Preclinical evaluations suggest that ADRT is as potent an inhibitor of the HIV as AZT, while at the same time appearing to be less toxic and possessing a longer half life *in vivo*.[47]

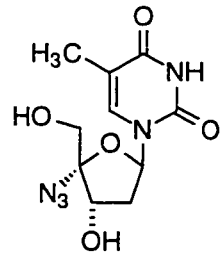


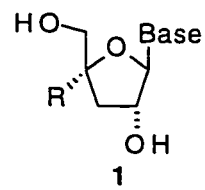
Figure 7. 4'-Azidothymidine (ADRT).

An interesting feature of ADRT is that it is not deoxygenated at the 3'-position, therefore it can not inhibit HIV replication by viral DNA chain termination resulting from the lack of a 3'-hydroxyl (see Figure 5). Rather, the anti-HIV activity results for chain termination of viral DNA due to a DNA "pucker". This pucker arises when two ADRT molecules are inserted consecutively into a growing viral DNA chain by the HIV-RT (HIV reverse transcriptase enzyme). Cellular DNA polymerases have a very low affinity for ADRT-5'-triphosphate, and have been shown to be incapable at inserting consecutive ADRT molecules when assembling cellular DNA. These two factors combined are attributed with the low cytotoxicity observed with ADRT therapy. They also suggest that

the active site of HIV-RT has a much higher degree of structural flexibility in comparison to cellular DNA polymerases.[46, 48]

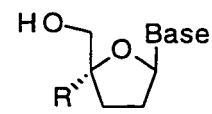
The flexibility of the HIV-RT active site and the precedence established by 4'-azidothymidine led to the postulate that nucleosides with alkyl substituents at the 4'-positions, once metabolized by cellular kinase enzymes to their 5'-triphosphate, may still be acceptable substrates for HIV-RT. While at the same time 4'-alkylnucleosides should be poor substrates for the conformational rigid active sites of cellular DNA polymerases. If the 4'-alkyl nucleosides were deoxygenated at the 3'-position they can then function as DNA chain terminators by a mechanism identical to that of the current family of FDA approved anti-HIV nucleosides. This would result in a preference for inhibition of HIV-RT processes over cellular DNA polymerase processes, thus limiting cytotoxicity of 4'-alkylnucleoside analogs. Furthermore, a 4'-*C*-alkyl group would qualify as a substantial structural dissimilarity to the current family of anti-HIV nucleoside analogs and perhaps impart 4'-*C*-alkylnucleosides with effectiveness against virus variants that display cross-resistance to other anti-HIV nucleosides.

A program to prepare novel nucleoside analogs was initiated. The key ribose modifications that are desired consist of a 4'-*C*-alkyl substituent, as well as deoxygenation of the 3'-position alone, and both the 2' and 3'-positions. As the heterocyclic base plays an important role in the rate at which nucleosides are metabolized[30] to their corresponding 5'-triphosphates (which are the active form of the drugs) a number of analogs with identical ribose moieties, but different purine or pyrimidine bases were prepared to explore



1

4'-*C*-alkyl-3'-deoxy



2

4'-*C*-alkyl-2',3'-dideoxy

Figure 8. Target Nucleoside Analogs. R = alkyl; Base = either a purine or pyrimidine heterocyclic base.

the effect the base may play in anti-HIV activity. The remainder of this document deals with the synthesis of the target 4'-*C*-alkyl-3'-deoxy and 4'-*C*-alkyl-2',3'-dideoxynucleoside analogs (**1** and **2**), which are shown in Figure 8.

2.2. Synthetic Methodology to Prepare 4'-C-Alkyl Nucleoside Analogs.

As mentioned above, there are numerous literature examples involving the preparation of nucleosides modified at the 2', 3' and 5' positions of the ribose moiety. In comparison, very little work has been reported involving modification of the 4'-position.[45] This may be attributed to the fact that the vast majority of approaches to modified ribose nucleosides employ either intact nucleosides (the glycosidic bond linking a heterocylic base and ribose analog already exists) or ribose itself as starting materials (Figure 9). These

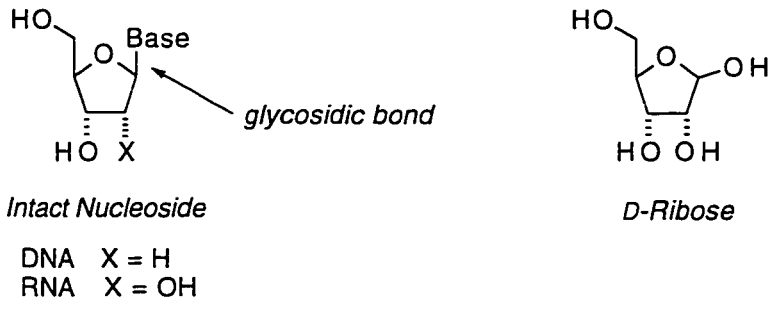


Figure 9. Common Starting Materials for the Preparation of Ribose Modified Nucleosides.

readily available and obvious choices for starting materials are, unfortunately, nonconducive to the efficient introduction of alkyl substituents to the 4'-position. The difficulties of using these starting materials for preparing a C-C bond at the 4'-position of nucleoside analogs can be observed in the literature reports detailing such work. [49-55] In general these difficulties include poor yields, and poor stereoselectivity.

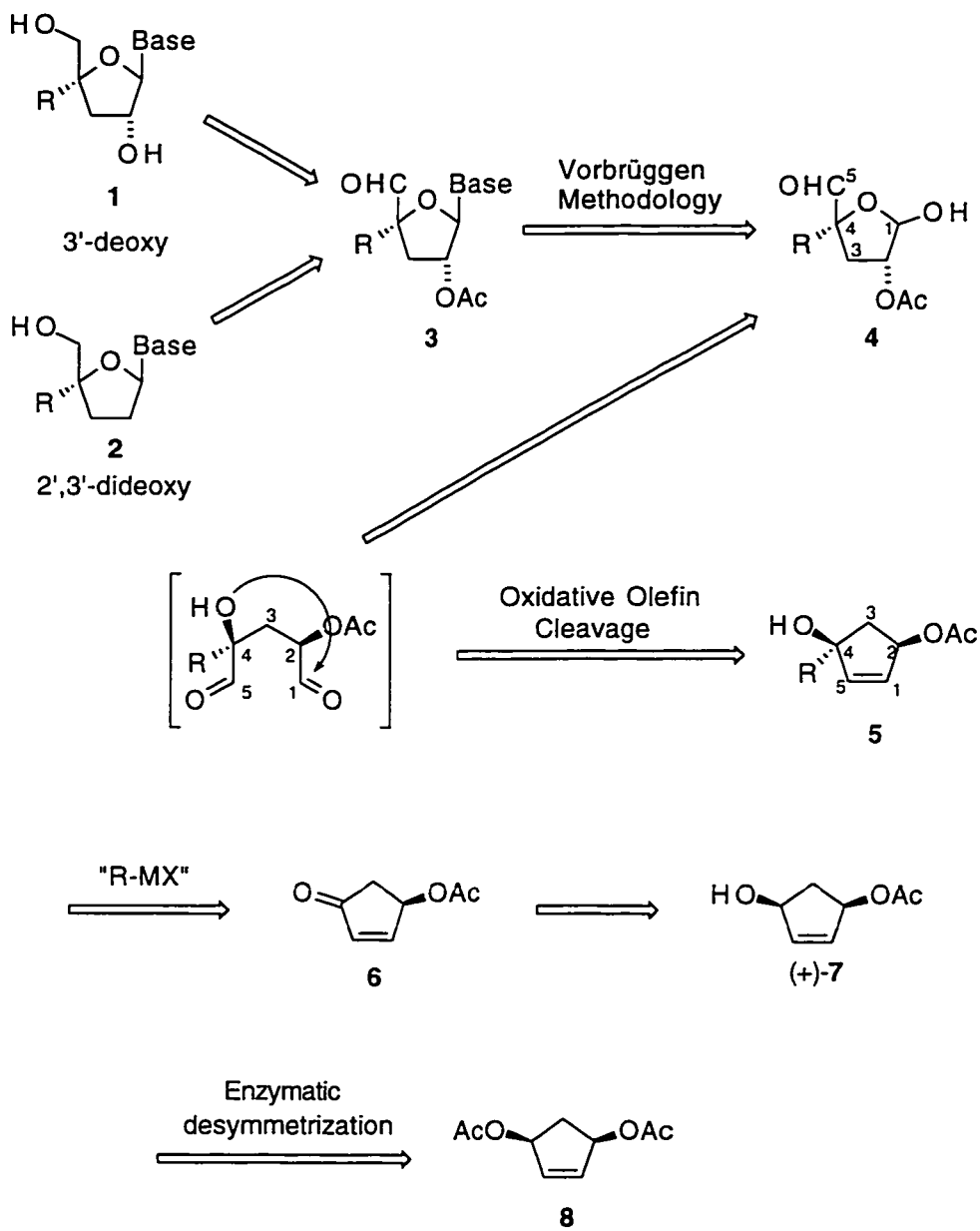
Given the lack of literature examples reporting the introduction of 4'-*C*-alkyl substituents to nucleosides, the goal of developing a general synthetic methodology to

accomplish this was paramount. Such methodology, to reach the highest level of utility for our purposes, needs to address four issues. First, the methodology must allow for the smooth introduction of a variety of alkyl groups to the 4'-position with an excellent degree of stereocontrol. Second, the preparation of an enantiopure nucleoside with an absolute configuration matching that of natural D-nucleosides was desired. (L-Nucleosides have been shown to inhibit HIV, ei. 3TC, but the first goal was the synthesis of D-nucleosides). Third, as the preparation of analogs consisting of different heterocyclic bases for each modified ribose is desired, a convergent synthesis in which the glycosidic bond between the modified ribose and heterocycle base is formed late in the process is beneficial. Fourth, the methodology must allow for the preparation of nucleosides deoxygenated at the 3' and both the 2' and 3' positions. A synthetic method to prepare the target 4'-alkyl nucleosides which addresses these four issues is shown in a retrosynthetic fashion in Scheme 1.

Appealing as an efficient means by which to introduce an alkyl substituent was to prepare a carbocyclic precursor such as **5**, in which the alkyl group and C-4 stereochemistry are already established. Oxidative cleavage of the olefin contained within **5**, followed by *in situ* lactolization, resulting from the tertiary alcohol closing onto the newly formed aldehyde at C1, can then unveil the 4-alkyl-3-deoxy ribose **4**. The advantage of this approach lies in the fact that the alkyl substituent and C-4 stereochemistry are introduced by a carbonyl alkylation of the rigid cyclopentenone **6**. Good stereocontrol can be expected resulting from a steric interaction between the acetoxy group and the incoming nucleophile, favoring carbonyl alkylation from the cyclopentenone face opposite the acetoxy. Furthermore, a variety of alkyl groups can be introduced by simply using the appropriate alkyl nucleophiles.

The use of enzymes to perform enantioselective hydrolysis and transesterification reactions is proving to be an important method for generation of useful chiral pool intermediates. From a synthetic viewpoint, *meso*-diacetates, such as **8**, are particularly laboratories have reported the enzymatic hydrolysis of **8** to prepare (+)-**7** in an enantiopure attractive substrates for enzymes because they frequently provide nearly quantitative yields

to the corresponding mono-acetates with very high enantiomeric purity.[56, 57] Several form,[58-61] making (+)-7 an excellent choice as a chiral pool intermediate for our purposes.



Scheme 1. Retrosynthetic analysis for the preparation of 4'-*C*-alkyl-3'-deoxy and 4'-*C*-alkyl-2',3'-dideoxynucleosides.

Simple oxidation of the allylic alcohol contained with in (+)-**7** then affords the cyclopentenone **6**.

The methodology outlined in the Scheme 1 is advantageous in that it is semi-convergent allowing for the late stage introduction of the heterocyclic base. This will facilitate the preparation of nucleoside analogs that are identical in the ribose moiety, but contain different heterocyclic bases. Often problematic in convergent approaches to ribose modified nucleosides is achieving high levels of β-stereoselectivity in the formation of the glycosidic bond.[62] Ribose **4**, however, appears to be an ideal substrate to obtain very high levels of β-selectivity in the glycosylation of either a pyrimidine or purine heterocycle by the protocol developed by Vorbrüggen *et al.*[63-70] This stereoselectivity is due to the presence of the acetoxy at C-2.

After glycosylation affording nucleosides of type **3**, simple hydride reduction of the aldehyde at C-5' to the primary alcohol can give the 4'-*C*-alkyl-3'-deoxynucleoside analogs of type **1**. Alternatively, the 4'-*C*-alkyl-2',3'-dideoxynucleosides of type **2** can be accessed by deoxygenation of the 2'-position of **3** using the procedure of Robins *et al.*, followed by reduction at C-5'. Note that the 2'-hydroxyl functionality is crucial in controlling the stereoselectivity of the glycosilation, so deoxygenation of this position must be preformed after glycosylation.

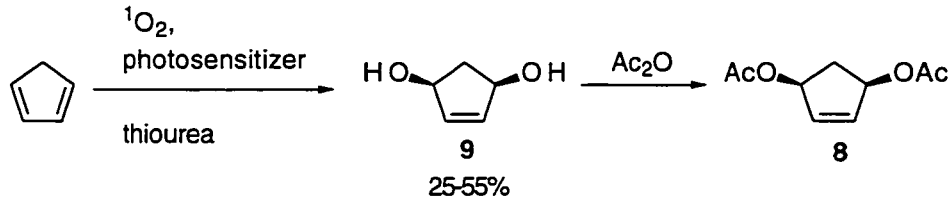
Chapter 3

Synthesis of 3'-Deoxy-4'-*C*-methyl and 2',3'-Dideoxy-4'-*C*-methyl Nucleoside Analogs: Results and Discussion.

The first 4'-alkyl nucleosides prepared were those in which the alkyl substituent is a methyl. These were prepared by the method outlined in the retrosynthetic analysis (Scheme 1). This chapter presents the results and discuses the synthesis of the target 4'-*C*-methyl nucleosides of type **1** and **2** (Scheme 1) in which the heterocyclic base is any of the following; uracil, thymine, 5-fluorouracil, cytosine, 5-fluorocytosine, adenine and hypoxanthine.

3.1. Synthesis of the Enantiopure 4-Methyl Carbocyclic Precursor.

The starting material for the preparation of the 4-methyl carbocyclic precursor is the *meso*-diacetate **8**. This material has found prior applications in our laboratory in the preparation of prostaglandins,[72] bioactive polyols,[73] and carbocyclic nucleosides.[74] In these instances, **8** was prepared by the singlet oxygen addition of cyclopentadiene and reduction of the resulting endoperoxide to afford *meso*-diol **9**. This was then treated with acetic anhydride to afford the *meso*-diacetate **8** (Scheme 2). While the singlet oxygen

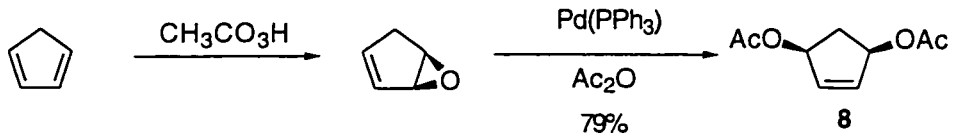


Scheme 2. Synthesis of *meso*-diacetate **8** by singlet oxygen addition.

oxidation precedes with very high stereoselectivity,[75] it requires copious amounts of solvent, is difficult to reproduce and yields are generally poor.[58] Therefore a more efficient

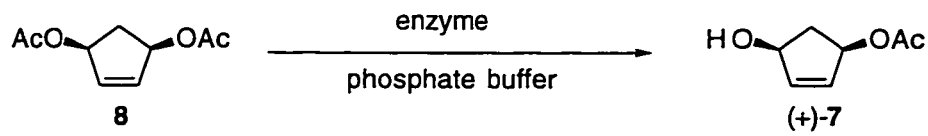
preparation of **8** was sought.

A two step literature preparation of *meso*-diacetate **8**[76,77] offered an alternative and was found to be amenable to scale up, allowing the preparation of up to 100 g of **8** with a reproducible yield of 79%. The preparation involves the monoepoxidation of cyclopentadiene with peracetic acid, followed by opening of the epoxide as a π-allyl system with tetrakis(triphenylphosphine)palladium(0) catalyst in the presence of acetic anhydride (Scheme 3). It was observed that freshly prepared tetrakis(triphenylphosphine)-palladium(0)[78] catalyst resulted in a much more rapid reaction and proceeded in an overall more satisfactory yield in comparison to the use of catalyst purchased from a commercial vender.



Scheme 3. Alternative preparation of *meso*-1,4-diacetoxycyclopente (**8**).

Our plan was to introduce optical purity by enzymatic desymmetrization of *meso*-diacetate **8**. Scheme 4 shows three enzymes known in the literature to effect this transformation. Good yields and very high enantiomeric excesses of monoacetate (+)-**7** are obtainable with both acetylcholine esterase from electric eel (EEAC) and Lipase B from the genetic code of *Candida antartica*; however, both are very expensive. On the other hand, porcine pancreatic lipase (PPL) is available as an inexpensive crude enzyme. Although the enantioselectivity obtained with crude PPL is not as impressive as that achievable with EEAC or Lipase B, monoacetate **7** is a highly crystalline material. This allows the enantioenriched (+)-**7** obtained by PPL desymmetrization to be easily crystallized, affording absolute enantiopure (+)-**7**. Therefore, due to PPL's low cost it was selected as the enzyme to perform the desymmetrization.

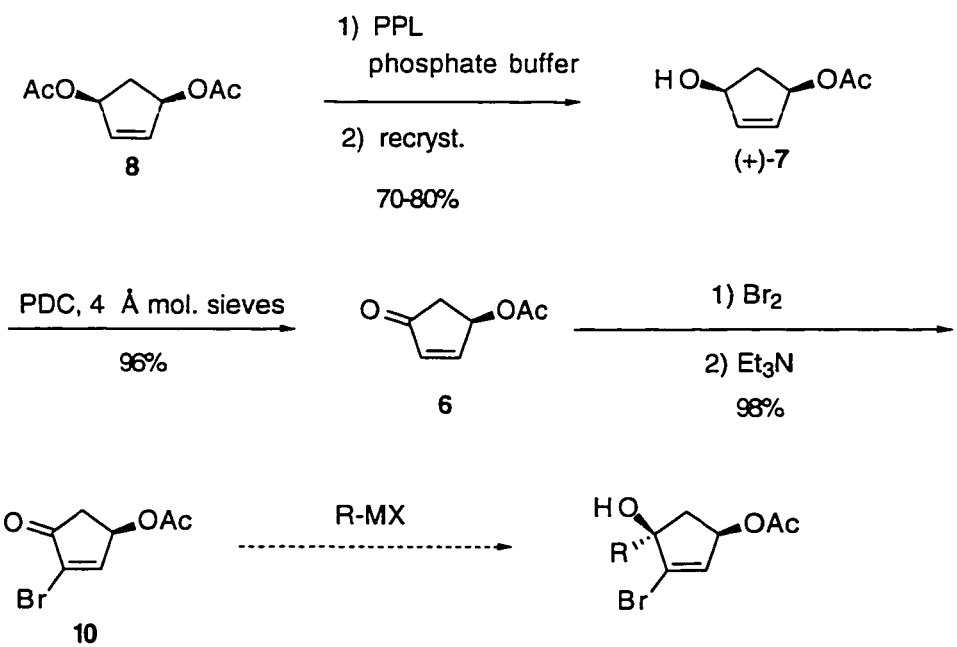


8 (+)-7

enzyme	yield	% e.e.	
Electric Eel Acetylcholine esterase	86%	96%	ref. 56
Candida antartica Lipase B (SP-435)	90%	99%	ref. 57
Porcine Pancreatic Lipase	87%	92%	ref. 59

Scheme 4. Some enzymes known to effect the desymmetrization of *meso*-diacetate **8**.

Treatment of *meso*-diacetate **8** with PPL (30 wt. %) in an aqueous phosphate buffer (1.0 M, pH 7.2) afforded, after column chromatography, enantioenriched (+)-**7** in an 84% yield (Scheme 5). A single recrystalization from 1 : 1 diethyl ether / pentane then gave white needles of enantiopure (+)-**7**. The enantiomeric excess of (+)-**7** was confirmed to be >99% by preparation of the *R*-(+)-methoxy(trifluoromethyl)phenylacetic acid ester and subsequent analysis by 500 MHz ^{1}H-NMR.[79] Oxidation of the allylic alcohol contained within (+)-**7** by treatment with pyridinium dichromate over crushed 4 Å molecular sieves

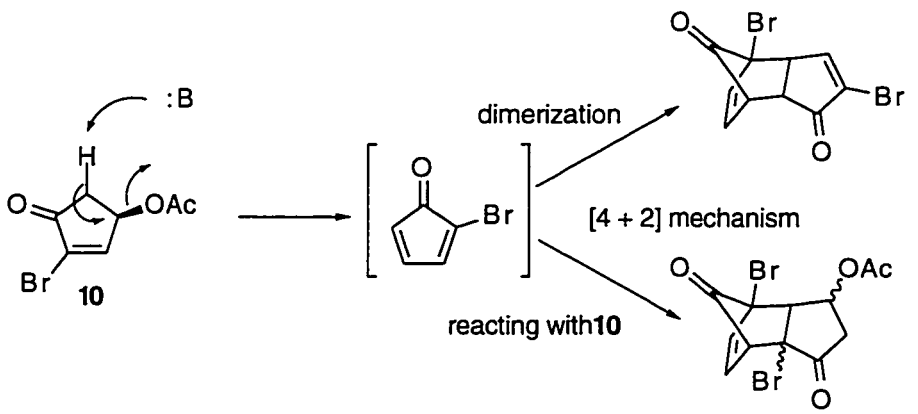


8 (+)-7 6 10

Scheme 5.

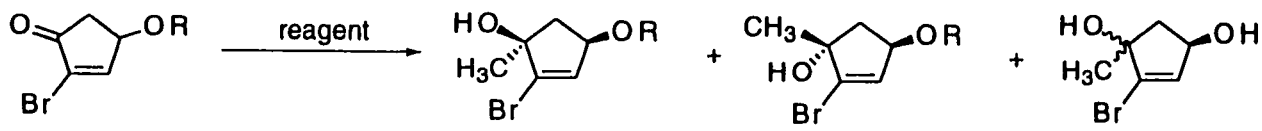
afforded acetoxycyclopentenone **6** in a 96% yield. At this point it was found to be necessary that **6** be brominated at the α-position. This was accomplished by treating the enone **6** with bromine followed by the addition of triethylamine to afford α-bromoenone **10** in an excellent yield. The presence of the α-bromine is crucial for obtaining good yields in the oxidative cleavage of the olefin contained within the carbocyclic precursor that will result from carbonyl alkylation of α-bromoenone **10**. The rational for this yield improving effect will be discussed in detail in section 3.2.

The carbonyl alkylation of **10** with a methyl nucleophile was next explored. Since this is the key step in which the alkyl substituent is introduced and C-4' stereochemistry established a number of methyl nucleophiles at a variety of temperatures were examined to identify optimum conditions. These findings are shown in Table 3. Initial results with methylmagnesium bromide were very disappointing, giving poor yields and poor diastereoselectivity in the formation of the inseparable diastereomeric pair **11a** and **11b**. The carbonyl alkylation with methyllithium at -100 °C gave good diastereomeric selectivity, but the yield of **11** was still unacceptably low (Table 3, entry 4). A reasonable explanation for the poor yields obtained in the carbonyl alkylation of **10** could be the β-elimination of the acetoxy group promoted by the strongly basic nature of either methylmagnesium bromide or methyllithium. This would result in the formation of a highly reactive cyclopentadienone which, under normal conditions, generally dimerizes[80] or in the



Scheme 6. Possible reaction pathways for β-elimination product of **10**.

Table 3. Stereoselective Addition of Methyl Nucleophiles to α-Bromoenone **10** or **13**.



10, R = Ac
13, R = TBS

11a, R = Ac
14a, R = TBS

11b, R = Ac
14b, R = TBS

12

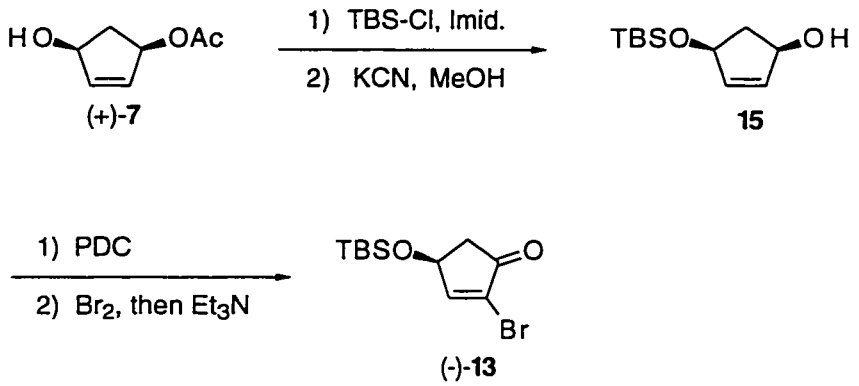
entry	substrate	reagent	temperature °C	yield% (**11a+11b** or **14a+14b**)	yield% **12**	ratio a:b
1	**10**	MeMgBr	-78	28	6	6:1
2			-40	26	12	3:1
3		MeLi	-78	39	-	12:1
4			-100	47	4	16:1
5		$MeCeCl_2$	-78	42	24	4:1
6			-100	51	16	4:1
7	**13**	MeMgBr	-78	47	-	11:1
8		MeLi	-78	71	-	29:1
9			-100	88	-	>50:1

examples at hand could polymerize with the starting substrate by a [4 + 2] mechanism (Scheme 6). It was also apparent that substrate **10** suffered from regioselectivity issues as **12**, resulting from nucleophilic attack of the acetate carbonyl of **11ab**, was often isolated and identified in the product mixture in low yields (Table 1). In the hope of diminishing β-elimination of the acetoxy, the non basic organocerium reagent, CH_3CeCl_2, was prepared and utilized in the addition.[81] This nucleophile did result in modest yield improvements, but showed poor diastereomeric selectivity (Table 3, entry 5 and 6).

It was rationalized that both improved yields as well as better diastereoselectivity may be achievable with the 4-*tert*-butyldimethylsilyloxy-2-bromo-2-cyclopenten-1-one (**13**) as the substrate for carbonyl alkylation. Improved yields were anticipated due to a decreased propensity of the *tert*-butyldimethylsilyloxy group to undergo β-elimination. Furthermore, the previous isolated diol by-product **12** would be prohibited from forming. An increase in diastereoselectivity was foreseen arising from the substantial steric bulk of the *tert*-butyl further biasing nucleophilic attack of the enone face opposite the protecting group. As seen in entries 7-9 of Table 3, substrate **13** did indeed show both improved yields and diastereoselectivities in comparison to the acetoxy protected α-bromoenone **10** when treated with either methylmagnesium bromide or methyllithium. The optimal conditions identified (Table 3, entry 9) were treatment of **13** with methyllithium at -100 °C affording an 88% combined yield of **14a** and **14b**, with an outstanding diastereomeric ratio of >50 : 1.

Employing the TBS protected **13** as the substrate for carbonyl alkylation proved to be a viable solution to the poor yields that were initially encountered using acetate protected **10** (Table 3). The problem that remained was how to prepare the correct enantiomer of **13**. The results reported in Table 3 were obtained using (-)-**13** as substrate, which was prepared as shown in Scheme 7.[82] This involved the protection of the allylic alcohol present in (+)-**7** as the TBS ether, followed by acetate deprotection to give **15**. The allylic alcohol of **15** was then oxidized with pyridinium dichromate, and the resulting enone brominated by treatment with bromine then triethylamine to afford (-)-**13**. While (-)-**13**

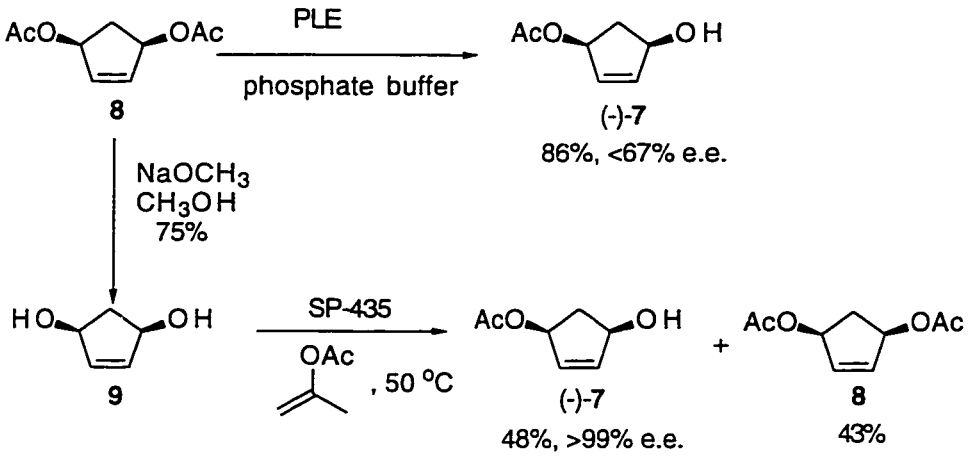
was an excellent substrate for a model study of carbonyl alkylation, it has the opposite absolute configuration to that which is required to approach D-nucleosides. Therefore an efficient preparation of the enantiomer (+)-**13** was needed to allow the preparation of D-nucleoside analogs.



Scheme 7. Synthesis of TBS-protected α-bromoenone (-)-**13**.

The most obvious method to prepare (+)-**13** would be by a method identical to that shown in Scheme 7, where (-)-**7** is employed as the starting material. There are two enzymes that have been reported to prepare (-)-**7** by enzymatic desymmetrization, and these are shown in Scheme 8. Enzymatic hydrolysis of *meso*-diacetate **8** with Porcine Liver Esterase (PLE) affords a good yield of (-)-**7**,[82, 83] but the enantiomeric excess is a maximum of 67%.[61] This necessitates multiple yield-reducing crystallization's to obtain enantiopure (-)-**7**. The second enzyme that has been used in the preparation of (-)-**7** is SP-435, a commercially available immobilized form of Lipase B rom the genetic code of *Candida antartica*.[59] In this case the enzyme is not effecting a hydrolysis, but rather an enantioselective acetylation of the *meso*-1,4-diol **9**; therefore requiring the transformation be performed in the presence of an acetate donor such as isopropenyl acetate. The enantioselectivity reported for this transformation is very high (>99% e.e.), but a poor yield of only 48% is reported in the formation of (-)-**7**. The origin of the low yield lies in the fact that the reaction must be driven past consumption of the starting material to achieve

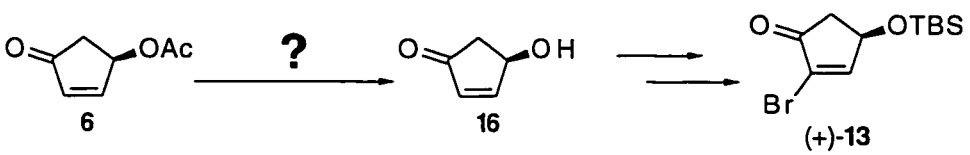
such high levels of enantioselectivity. This results in the formation of substantial amounts of the over acetylated *meso*-diacetate **8**. Attempts to reproduce this enantioselecitve



Scheme 8. Literature preparations of (-)-**7**.

acetylation were unsuccessful at obtaining the level of enantiomeric excess reported in the literature. The best example achieved only 85% e.e., which was calculated using the measured optical rotation.[84] So again, multiple yield-reducing crystallization's were required to obtain enantiopure (-)-**7**.

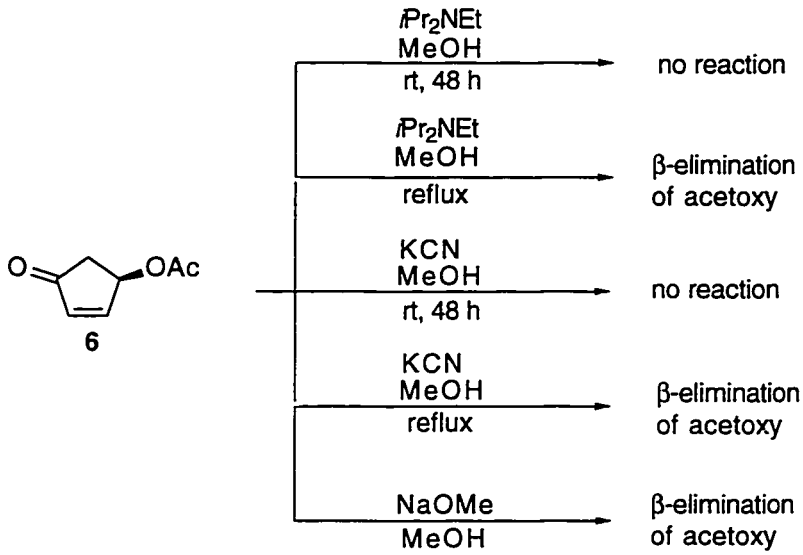
Perhaps the most efficient preparation of (+)-**13** would be the deprotection of the acetate of cyclopentenone **6** to generate the 4-hydroxyenone **16**. The hydroxyl of **16** could then be reprotected as a silyl ether followed by α-bromination to afford (+)-**13** as shown in



Scheme 9.

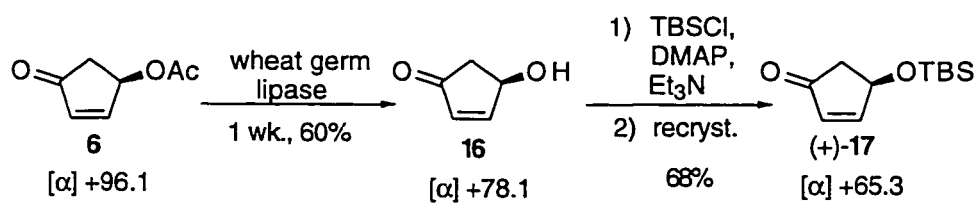
Scheme 9. This is an attractive route to (+)-**13** as **6** can be easily prepared in enantiopure form in which the absolute configuration matches that of (+)-**13**. Difficulties arise when

attempting to deprotect the acetate of **6**, however. Normal acetate deprotecting conditions such as basic methanolysis resulted in no reaction. Attempts to force the reactions to proceed by using stronger base conditions and / or higher temperatures resulted only in β-elimination of the acetoxy (Scheme 10).



Scheme 10. Attempts to deprotect acetoxycyclopentenone **6**.

Despite the fact that cyclopentenones of type **6** and **13** are exceptionally valuable as chiral pool intermediates in the synthesis of many natural products[85] the first and only

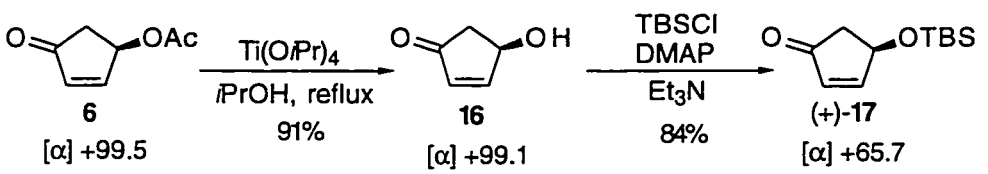


Scheme 11. Literature report for conversion of **6** into **13**.[86]

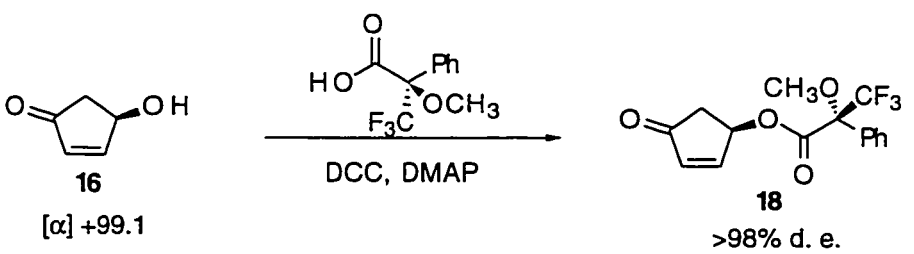
literature report for the conversion of **6** into **13** appeared in 1995.[86] In the report, **6** was deprotected by an enzymatic hydrolysis (Scheme 11). The yield of this deprotection is only

60% and the reaction is exceedingly sluggish. Furthermore, another report has appeared suggesting this deprotection results in some degree of racemization of the chiral center;[88] therefore, explaining why the authors perform a difficult low temperature crystallization in the purification of the silyl ether **17**, which has a melting point close to room temperature (Scheme 11).

Eventually a high yielding method of deprotecting **6** was identified. This involved the use of Seebach's transesterification catalyst $Ti(O\textit{i}Pr)_4$ in refluxing 2-propanol to afford the desired 4-hydroxyenone **16** in a 91% yield within 2 hours (Scheme 12). This mild method to deprotect **6** was determined to proceed without any loss of enantiopurity by the preparation of the *R*-(+)-methoxy(trifluoromethyl)phenylacetic acid ester **18** and subsequent analysis by 500 MHz ^{1}H-NMR (Scheme 13).[89]



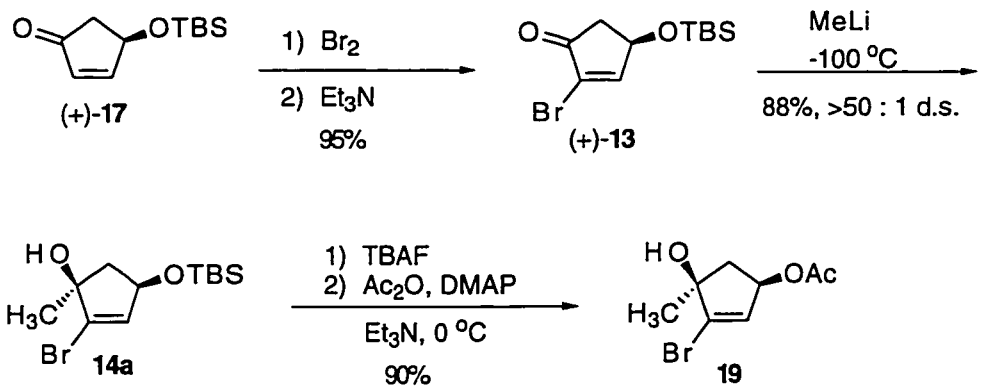
Scheme 12. Efficient conversion of **6** to (+)-**17**.



Scheme 13. Preparation of the MTPA derived ester of **16** to verify enantiopurity.

The 4-hydroxyclyclopentenone **16** was then protected as the TBS ether (+)-**12** by a procedure identical to that shown in Scheme 11 with the exception that the crystallization

was omitted (Scheme 12). Treatment of (+)-**17** with bromine followed by triethylamine then gave (+)-**13** in a 95% yield with the correct absolute configuration required to prepare D-ribose analogs. Addition of mehtyllithium to (+)-**13** as optimized (Table 3, entry 9) gave the nearly diastereomerically pure carbocyclic precursor **14a** in which the secondary alcohol is protected as a TBS ether. As an acetoxy is required at the 2-position of the ribose to control the stereochemistry of the glycosylation of heterocyclic bases, conversion



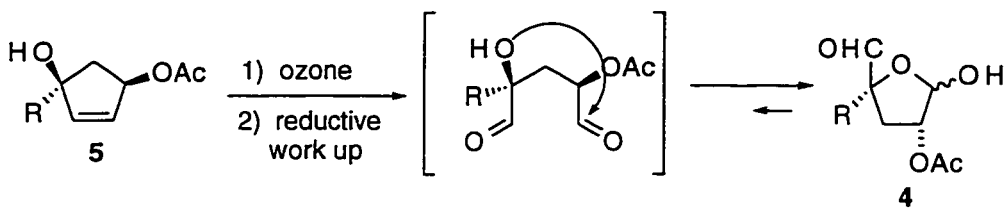
Scheme 14.

of the TBS protecting group to an acetate was required. This was easily accomplished by treating **14a** with tetrabutylammonium fluoride, followed by acetic anhydride, catalytic dimethylaminopyridine, and triethylamine at 0 °C to give **19** in a 90% yield (Scheme 14).

3.2. Oxidative Olefin Cleavage.

The initial approach envisioned for the synthesis of 4'-*C*-alkyl nucleosides called for the preparation of an enantipure cyclopentene in which all desired substituents and stereocenters of the ribose moiety were established. The five continuous carbons of the cyclopentene ring would then be exposed as the five continuous carbons of the desired ribose moiety. This would be achieved by oxidatively cleaving the olefin contained within **5** by treatment with ozone followed by a reductive work up (Scheme 15). The resulting

intermediate dialdehyde would exist in an open-closed equilibrium favoring the furanose ring form **4**.

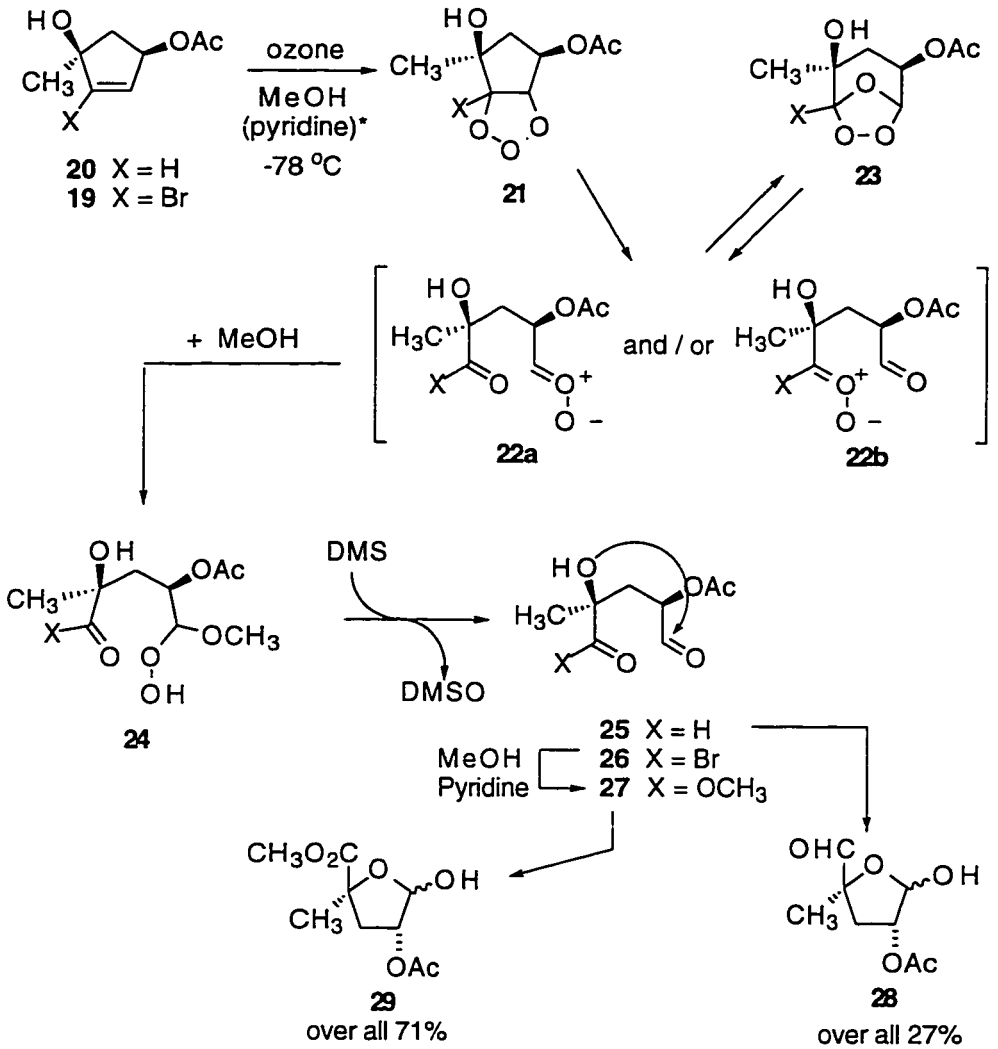


Scheme 15. Proposed oxidative olefin cleavage to afford the desired ribose moiety.

Previous experience within our laboratories involving the ozonolysis of a cyclopentene similar to **5** suggested that the the transformation proposed in Scheme 15 may prove difficult.[90] Therefore, upon initiating the project, this was one of the first steps to be examined by employing the methyl substituted cyclopentene **20**[91] as the substrate for ozonolysis. Treatment of **20** with ozone at -78 °C in methanol could only be optimized to afford 4-methyl ribose **28** in a 27% yield (Scheme 16). This transformation is thought to proceed first by addition of ozone to the olefin of **20** to give trioxolane **21.** The latter opens to carbonyl oxide intermediates **22a** and / or **22b** which then closes to afford the ozonide **23**. In the presence of methanol the favored product formation is believed to be the hydroperoxy methylacetal **24**.[92] A reductive work up by treatment with dimethyl sulfide then gives dialdehyde **25** which upon warming to room temperature favors the cyclized furanose form, ribose **28**.

The origin of the poor yield in the formation of ribose **28** from substrate **20** can be explained by one, or both, of two possible problems inherit to the oxidative olefin cleavage of substrate **20**. First, the dialdehyde **25,** formed upon reductive work up, or one of the intermediates that leads to its formation, may be unstable.[90] Or second, given that both vinyl carbons of **20** are electronically identical, the opening of the trioxarane **21** proceeds with little regioselectivity to give both **22a** and **22b**, and it is feasible that **22b** (or possibly

22a) does not lead to the formation of product. A solution to these problems would be to increase the oxidation state of one of the vinyl carbons present in **20** prior to olefin cleavage. This would avoid the formation of the dialdehyde **25**. It will also



Scheme 16. Mechanism of ozonolysis of substrates **19** and **20**.
*Pyridine only added for substrate **19**.

electronically differentiate the bridgehead carbons of trioxolane **21**, encouraging **21** to open with regioselectivity favoring formation of either **22a** or **22b**. This technique of increasing the oxidation level of a vinyl carbon has proven to result in improved yields over

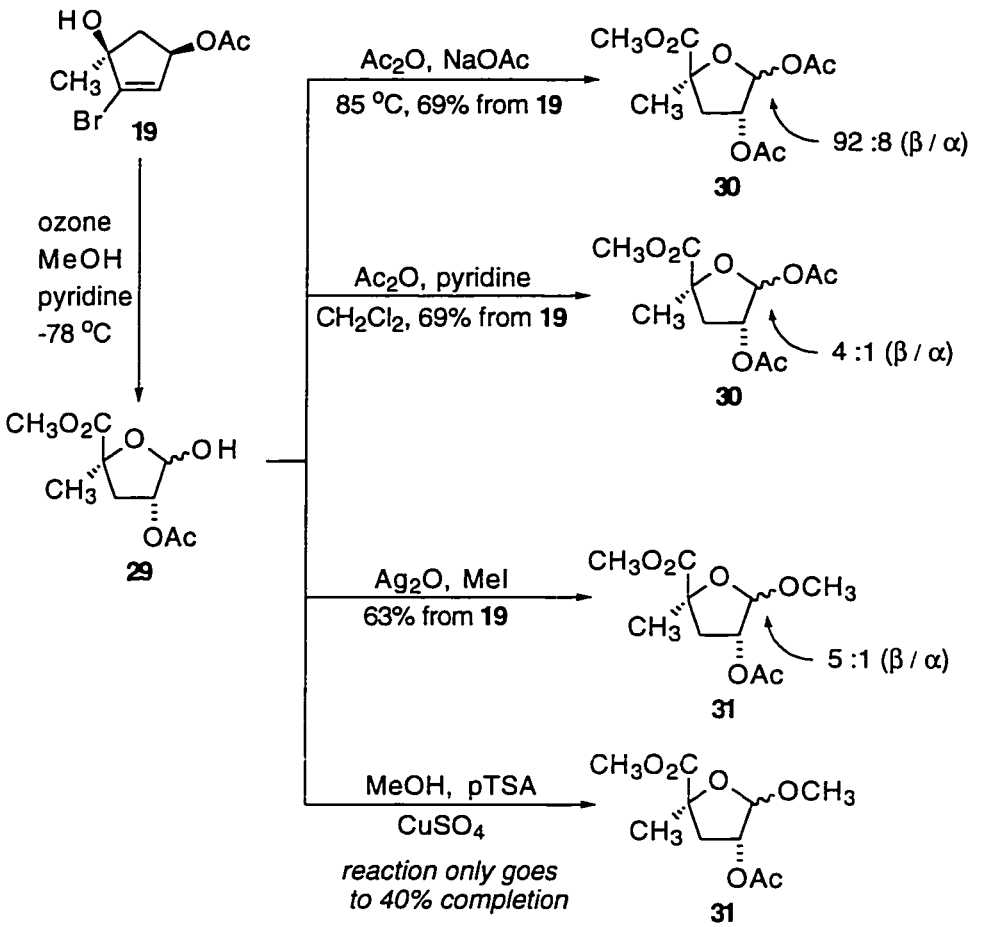
the unsubstituted olefin in prior experiences with oxidative olefin cleavage of cyclopentenes reported from this laboratory.[93]

The ideal substituent to introduce to a vinyl carbon of **20** would be a methoxy. This would afford an aldehyde-methyl ester (identical to **27** in Scheme 16) directly upon ozonolysis and reductive work up. Furthermore, a vinyl methoxy substituent would afford an electron rich olefin making an ideal partner for reaction with electron deficient ozone. However, the introduction of such a methoxy substituent appeared to be a formidable task.[94]

An alternative was to increase the oxidation state of one of the vinyl carbons of **20** by introducing a halogen atom. The ease with which this can be accomplished has already been demonstrated in Scheme 14 (Section 3.1) by the preparation of vinyl bromide **19**. Vinyl bromide **19** dissolved in methanol was treated with ozone at -78 °C in the presence of pyridine (Scheme 16) to form the acyl bromide-aldehyde **26**. The acyl bromide in the presence of methanol and pyridine was converted *in situ* to the methyl ester-aldehyde **27**, which upon warming to room temperature gave ribose **29** in a much improved yield of 71% (Scheme 16). Two notes regarding the oxidative olefin cleavage of substrate **19** are: (1) the bromine substituent makes for an electron deficient olefin which reacts slowly with ozone requiring reaction times as long as 2 hours; (2) the *N*-oxide of pyridine forms as a precipitate in the course of oxidizing the olefin; however, treatment with dimethyl sulfide immediately reduces this back to pyridine.

Ribose **29** was generally not isolated and characterized as it consists of an inseparable mixture of anomers (~ 1 : 3 α / β). Instead crude ribose **29** was carried on and the anomeric hydroxyl protected to give either the acetyl glycoside **30** or the methyl glycoside **31** (Scheme 18). It was found that heating ribose **29** in acetic anhydride buffered with sodium acetate gave the most satisfactory results in the formation of the protected ribose **30** and was selected as the general protocol. An overall yield of 69% for 2 steps could thus be obtained for the oxidative olefin cleavage and subsequent protection of the anomeric hydroxyl. Heating in sodium acetate buffered acetic anhydride also gave

the highest selectivity for the formation of the thermodynamically favored β-anomer of **30**, in which it was favored over the α-anomer of **30** by a ration of 92 : 8. This greatly simplified interpretation of NMR spectra as the α and β anomers of both **30** and **31** could not be separated by column chromatography. Interestingly, treatment of crude **29** with



Scheme 17. Protection of anomeric hydroxyl.

catalytic toluenesulfonic acid in methanol would only proceed to approximately 40% completion in the formation of **31** as judged by thin layer chromatography. The reaction could not be encouraged to completion even by additional acid catalyst, heat or anhydrous $CuSO_4$.

3.3. Analogs of Uridine, 5-Methyluridine and 5-Fluorouridine Nucleoside.

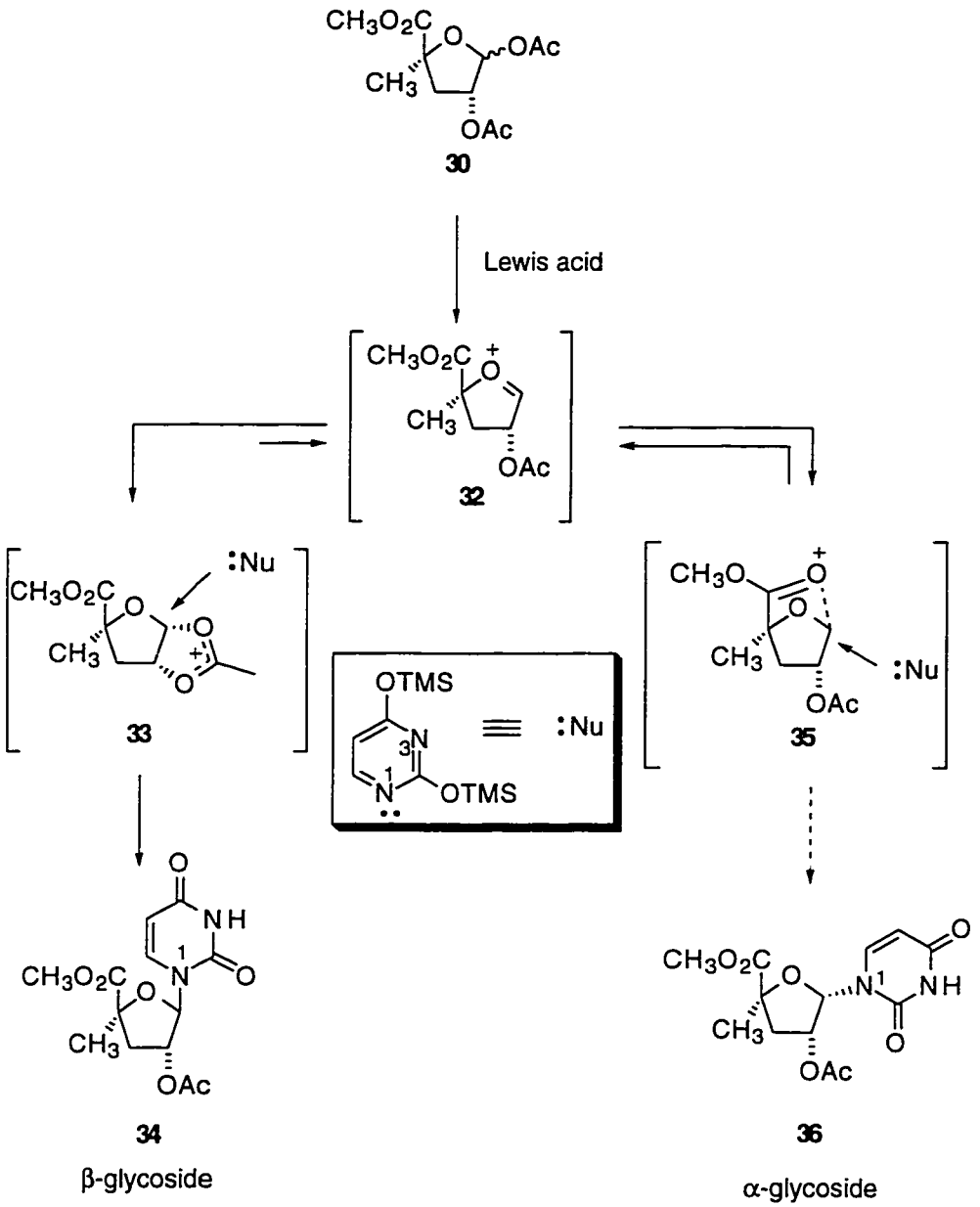
3.3.1. Glycosylation of Heterocyclic Bases.

Probably the most important reaction in nucleoside synthesis is formation of the *N*-glycosidic bond.[62] A great deal of research aimed at accomplishing this in a stereocontrolled fashion has appeared. Some of the classical methods include the Hilbert-Johnson reaction,[95] the mercuri-procedure developed by Fox and co-workers,[96] and the protocol of Vorbrüggen.[63-69] More recently, interest in nucleosides deoxygenated at both the 2' and 3' position have resulted in several elegant stereocontrolled glycosylation procedures of synthetic ribose analogs as well.[97, 98]

The method affording the highest level of stereocontrol and in general the most satisfactory yield in the formation of the *N*-glycosidic bond is that reported by Vorbrüggen. Ribose **30** was designed specifically to include a 2-acetoxy group to permit *N*-glycosylation by the standard Vorbrüggen type coupling. The predicted stereodirecting effect of the 2-acetoxy is shown in Scheme 19. Treatment of ribose **30** with a Lewis acid activates the anomeric acetate and results in formation of oxonium ion **32**. Due to the neighboring acetoxy substituent, a bridging oxonium ion **33** is formed, which is favored over the other cation **32** due to resonance stabilization. The reactive intermediate **33** then undergoes nucleophilic attack at C1 by a silylated nitrogen heterocycle in a stereocontrolled fashion, and results in the formation of **34** after the reaction is quenched. The β-selectivity is explained through formation of the bridged oxonium ion **33**, which due to its concave nature effectively blocks the α-face of the ribose from nucleophilic attack.

Standard Vorbrüggen couplings usually result in *N*-glycosylations with complete β-stereoselectivity. Substrate **30** raised concerns regarding the stereochemical outcome of the Vorbrüggen type *N*-glycosylation; however, due to the methyl ester at C5. A second bridged oxonium ion **35**, which is also resonance stabilized, may also participate to stabilize oxonium ion **32** (Scheme 16). Oxonium ion **35** would favor nucleophilic attack

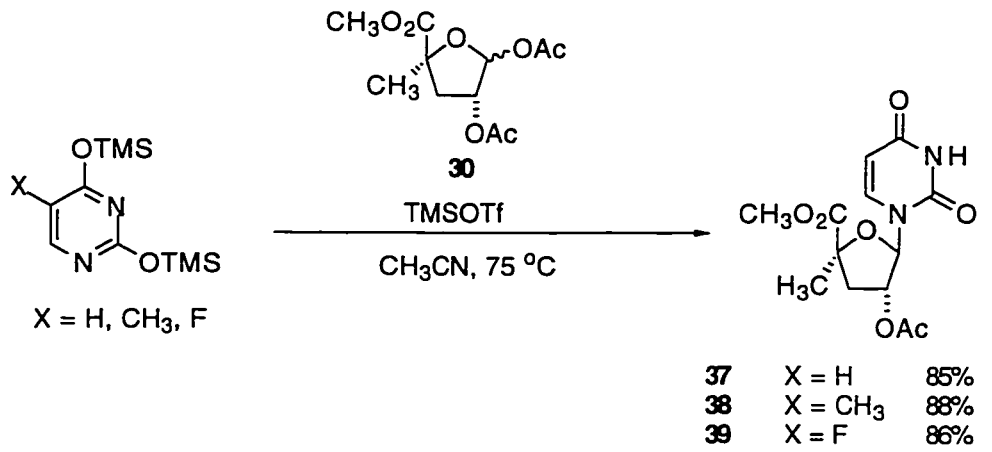
of the α-ribose face by effectively blocking the β-face, and would lead to the α-glycosylated nucleoside **36**.



Scheme 19. Mechanism of Vorbrüggen coupling with silylated uracil.

Uracil, 5-methyluracil and 5-fluorouracil were separately silylated. This was accomplished by boiling the heterocyclic base in hexamethyldisilazane (HMDS) and a catalytic amount of trimethylchlorosilane followed by the removal of excess reagents by

vacuum distillation. The silylated heterocycles each in a separate flask, were then charged with **30** and trimethylsilyl (trifluoromethane)sulfonate in acetonitrile. Consumption of the starting ribose **30** occurred rapidly at 45 °C with formation of single product in each case (Scheme 20). Isolation of the reaction products by chromatography afforded good yields



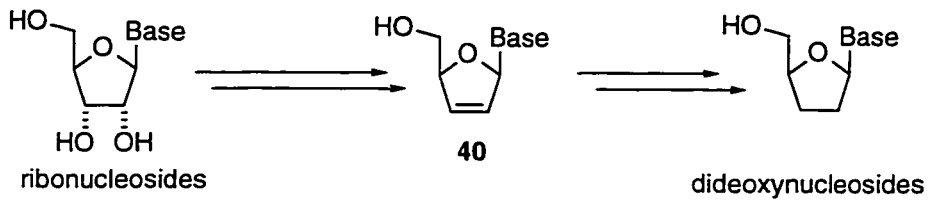
Scheme 20. Vorbrüggen type *N*-glycosylation of uracils with ribose **30**.

of nucleosides **37**, **38** and **39** in which the newly formed N^1-glycosidic bond had a β-configuration. No trace of nucleosides of type **36** (Scheme 19) constituting an α-*N*-glycosylation could be identified in any of the experiments, nor could any nucleosides resulting from N^3-glycosylation. These findings suggest that either oxonium ion **35** does not form to an appreciable extent, or if it does that it is non-reactive and equilibrates to oxonium ion **32** which is then attacked by the nucleophilic silylated base (Scheme 19) to give the observed product. Most importantly, the experiments afforded the desired N^1-glycosylated nucleoside products in good yield with complete β-stereoselectivity.

3.3.2. Deoxygenation of the 2'-Position.

The discovery that many dideoxynucleosides poses potent antiviral activity has precipitated a wealth of preparations of these compounds. The most strait forward means to prepare such compounds is by the deoxygenation of intact nucleosides. The classical

method for accomplishing this is the dideoxygenation of ribonucleic acids by the Corey-Winter reaction to afford 2',3'-dideoxy-didehydronucleosides **40** which are then hydrogenated to give dideoxynucleosides (Scheme 21).[99, 100] A number of other methods



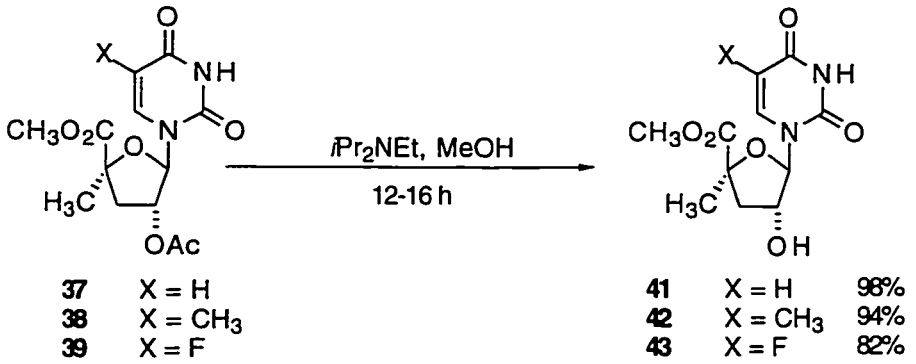
Scheme 21. Classical approach to dideoxynucleosides.

to prepare 2',3'-dideoxy-didehydronucleosides have appeared more recently.[100-104] All of these methods require vicinal diols and afford the 2',3'-unsaturated nucleosides as products; they, therefore, are unsuited for the deoxygenation of nucleosides **37**, **38**, or **39** at the C2' position.

The regioselective chemical 2'-deoxygenation of ribonucleosides has been pursued for many years, but with variable success.[105, 106] In general, the major difficulty is that the glycosidic bond is liable under acidic or basic conditions. This is particularly true of the desired 2'-deoxynucleoside products which lack the inductive effect stabilization the 2'-hydroxyl imparts on the glycosidic bond.[107] Other problems include poor overall yields reported for S_N2 displacement-reduction sequences at C2'.[105, 106, 108] Additionally, the electron deficient nature of C2', which is adjacent to the *N,O*-acetal at C1', precludes cationic S_N1 approaches.

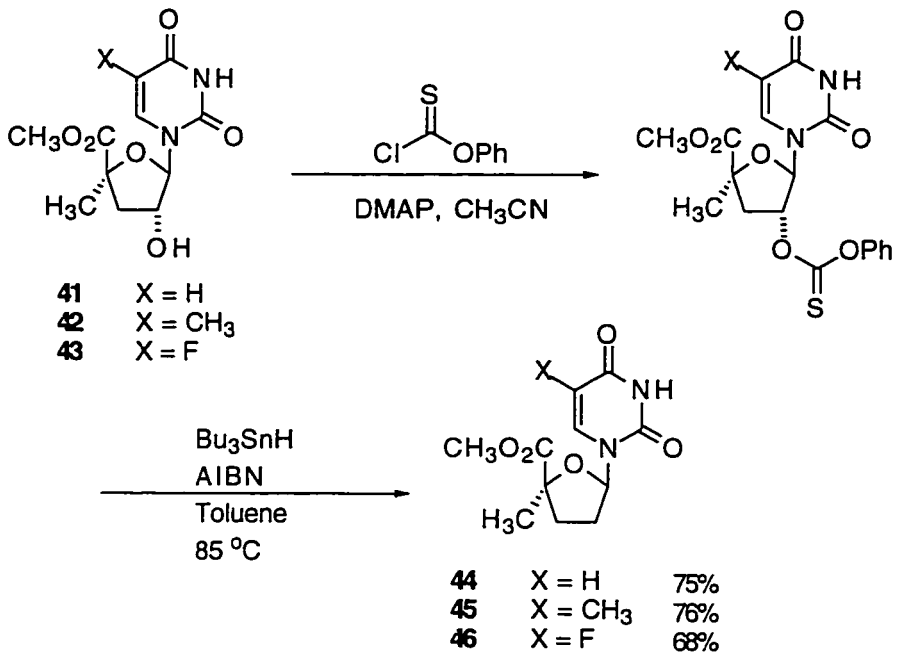
The solution to these problems has been the homolytic cleavage of the C2'-O bond. This was first demonstrated by Robins *et al.*[109, 110] by a modified Barton reduction.[111, 112] Robins' procedure for the 2'-deoxygenation of nucleosides requires the formation of the 2'-thionocarbonate of the nucleosides followed by treatment with tributyltin hydride and a radical initiator. This method of 2'-deoxygenation appeared well suited for nucleosides **37**, **38** and **39** and was investigated. The first step in attempting the deoxygenation was

the removal of the acetate protecting groups on the 2'-hydroxyl of **37**, **38** and **39** to allow for thioacylation at this position. This was efficiently accomplished by the action of catalytic Hunig's base (iPr$_2$NEt) in methanol (Scheme 22). Treatment of the resulting



Scheme 22. Deprotection of the 2'-acetate.

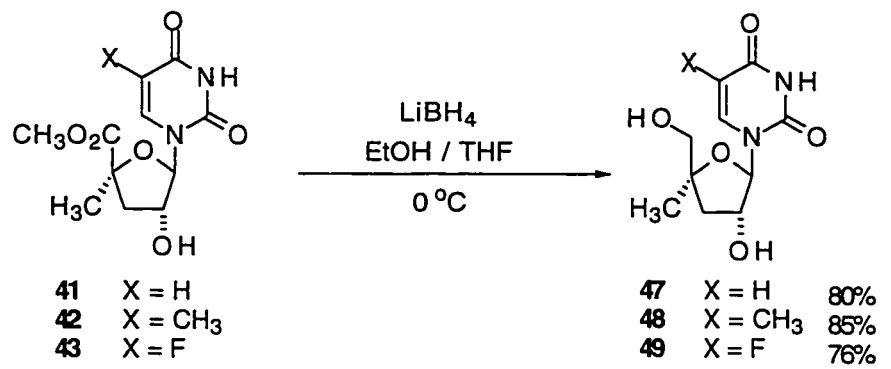
2'-hydroxyl nucleosides **41**, **42** and **43** with phenyl chlorothionoformate and dimethylamino-pyridine in acetonitrile gave 2'-phenyoxythionocarbonates (Scheme 23). These were generally not isolated or characterized as they proved sufficiently pure after work up to be carried on directly to the reduction step. Initial results in the Barton type reductions by treatment with tributyltin hydride as the source of hydrogen atom and 2,2'-azobis(2-methylpropionitrile) (AIBN) as the radical initiator in toluene at 85 °C were disappointing in that the yields of dideoxygenated nucleosides obtained were poor (20-36%). It was found that the use of freshly distilled tributyltin hydride and careful deoxygenation of the reaction solution prior to initiation of heat resulted in much improved yields of the desired dideoxygenated nucleosides **44**, **45**, and **46**. In the hope of avoiding the troublesome distillation of toxic tributyltin hydride, diphenylsilane was examined as a source of hydrogen atom in the radical reduction,[113] but proved unsatisfactory in terms of the yield of dideoxynucleoside that was obtained. A possible third source of hydrogen atom in Barton type reductions, dialkylphosphites,[114] were not explored.



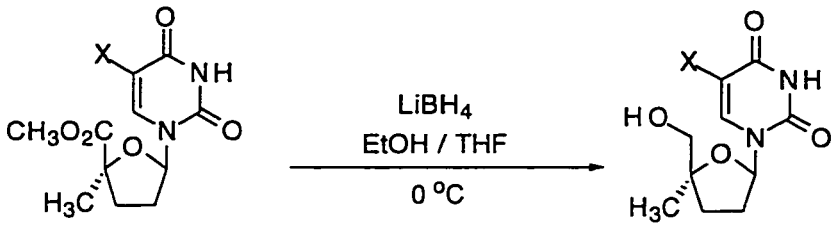
Scheme 23. Deoxygenation of the 2'-hydroxyl by Robins *et al.* procedure.

3.3.3. Reduction of the C5' Methyl Ester.

All that remained in the preparation of the target nucleosides was the successful reduction of the methyl ester at C5' of the 3'-deoxyuridines **41**, **42** and **43** and the 2',3'-dideoxyuridines **44**, **45** and **46**. After some initial difficulties, general conditions were identified allowing the reduction of **41**, **42** and **43** to give the 3'-deoxy-4'-*C*-methyluridine analogs **47**, **48** and **49** in satisfactory yields (Scheme 24). The optimum



Scheme 24. Reduction of C5' methyl ester to give the target 3'-deoxy-4'-*C*-methyluridine analogs.



44 X = H
45 X = CH_3
46 X = F

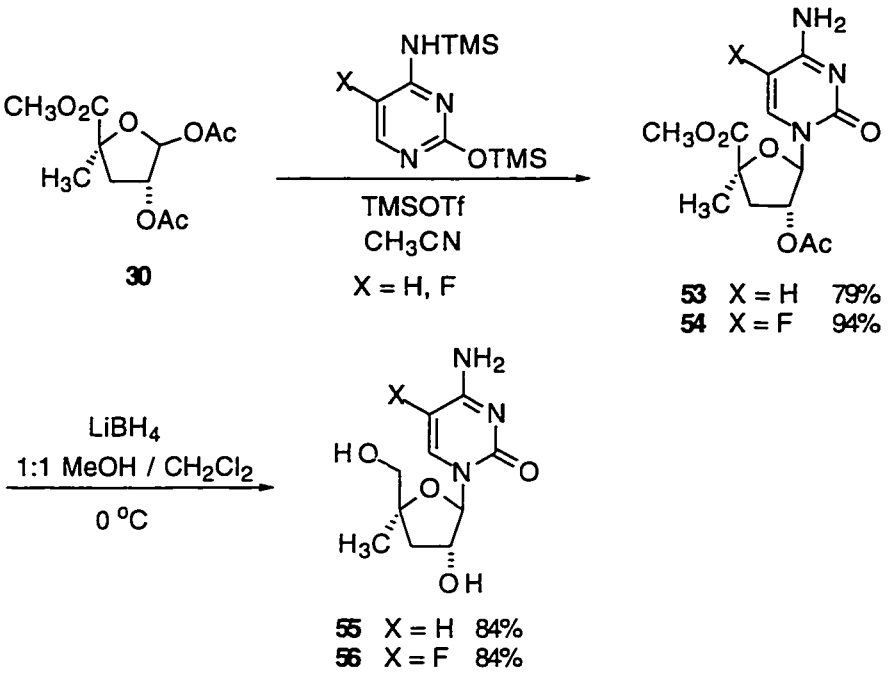
50 X = H 87%
51 X = CH_3 82%
52 X = F 81%

Scheme 25. Reduction of C5' methyl ester to give the target 2',3'-dideoxy-4'-*C*-methyluridine analogs.

conditions were treatment with lithium borohydride in tetrahydrofuran / ethanol (1 : 1) at 0 °C. These conditions proved equally effective for the carbonyl reduction of **44**, **45**, and **46** giving the 2',3'-dideoxyuridine analogs **50**, **51** and **52** (Scheme 25).

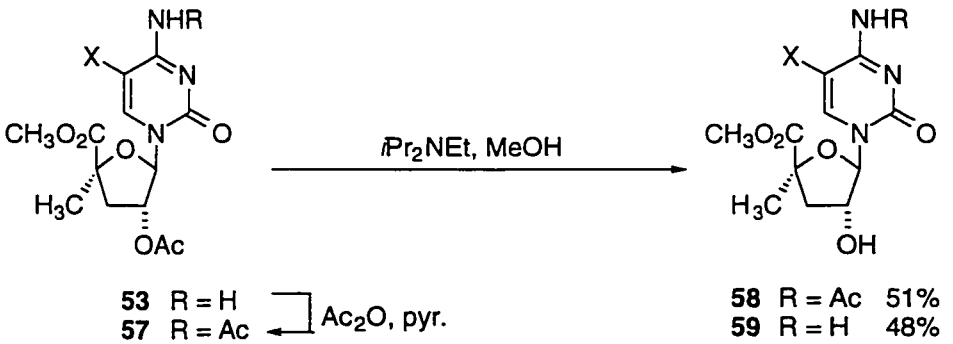
3.4. Cytidine and 5-Fluorocytidine Analogs.

The preparation of the 4'-*C*-methylcytidine and 4'-*C*-methyl-5-fluorocytidine analogs of type **1** and **2** was next attempted by the method outlined in the retrosynthetic analysis (Scheme 1) and nearly identical to that used to prepared the 4'-*C*-methyluridine analogs presented in section 3.3. These syntheses began with the N^1-glycosylation of cytosine and 5-fluorocytosine with the 4-*C*-methyl ribose analog **30**. This was accomplished by treating either silylated cytosine or silylated 5-fluorocytosine with ribose **30** and trimethylsilyl trifluoromethanesulfonate in acetonitrile, and afforded the desired β-N^1-glycosylated nucleosides **53** and **54** in satisfactory yields (Scheme 26). Again, no trace N^3-glycosylated nucleosides or nucleosides with an α-glycosidic configuration could be detected as reaction products. The 3'-deoxy-4'-*C*-methylcytidine analogs **55** and **56** were then obtained by the reducing action of lithium borohydride on the C5' methyl ester of **53** and **54**. Due to solubility problems the standard solvent mixture (1 : 1 THF / EtOH)used in the previous hydride reductions of the C5' methyl ester (sec. 3.3.3) was switched to MeOH / CH_2Cl_2 (1 : 1). This switch in solvent resulted in a much slower reaction rate, but appeared to have no deleterious effect on yields.



Scheme 26. Preparation of 3'-deoxy-4'-*C*-methylcytidine analogs.

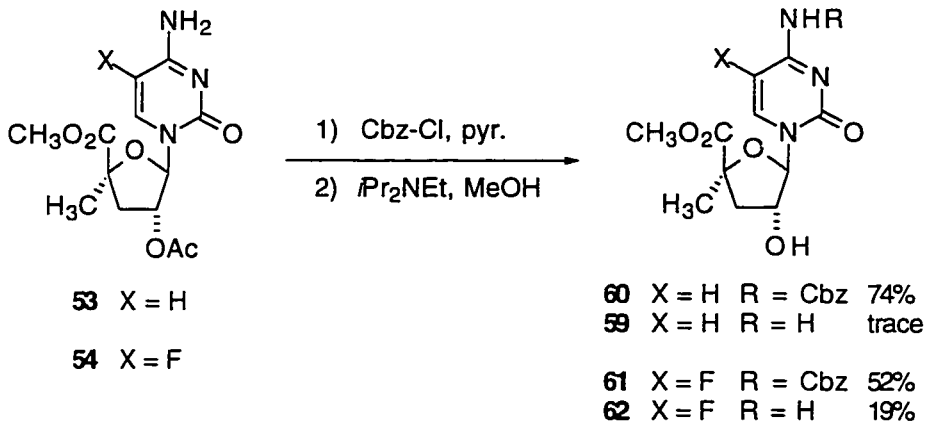
Before attempting to deoxygenate the 2'-positions of the cytidine analogs, it was required that the amino group at the 4-position of the nitrogen heterocycle be protected so as to avoid thionoacylation of this group. Using **53** for investigational purposes, a number



Scheme 27. Attempted regioselective methanolysis of 2'-acetoxy.

of conditions were examined in an effort to protect the 4-amino position. Protecting the amino group of **53** as an acetamide gave **57**. An attempt at the regioselectively methanolysis of the 2'-acetoxy proved unsatisfactory selectivity giving only a 51% yield of

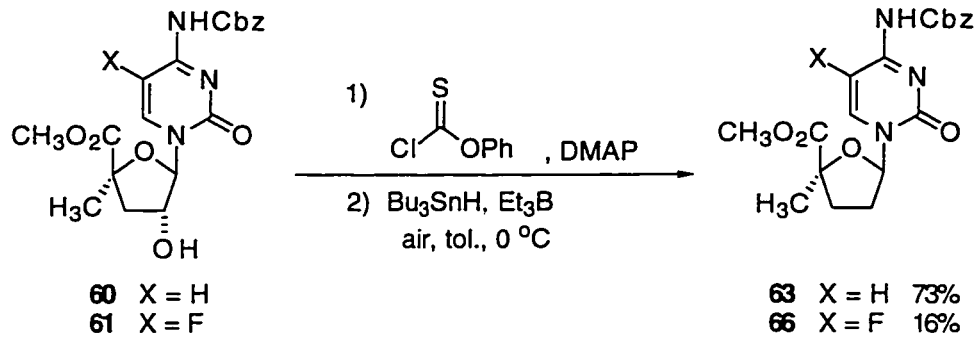
the desired 2'-hydroxyl cytidine **58** along with a 48% yield of di-deprotected cytidine **59**. A literature report describing the near quantitative yield for the regioselective acylation of the 4-amino group of cytidine by treatment with acetic anhydride in refluxing methanol appeared promising,[115] but submitting **59** to these conditions afforded a maximum 53% yield of **58**. Finally an acceptable yield of the 4-amino protected cytidine analog was achieved by protecting the 4-amino as a benzyl carbonate, followed by methanolysis of the 2'-acetoxy affording **60** in a yield of 74% for the two steps (Scheme 28). This same protection / deprotection protocol was performed with the 5-fluorocytidine **54** to afford the benzyl carbamate **61** in a 52% yield along with a 19% yield of the di-deprotected **62**.



Scheme 28. Regioselective protection of the 4-amino group.

In order to effect the deoxygenation of the cytidine analog **60**, formation of the 2'-thionocarbonate was first required. This was accomplished by treating **60** with phenyl chlorothionoformate and dimethylaminopyridine. The resulting crude product was then submitted to the Barton reduction conditions, consisting of treatment with tributyltin hydride and catalytic AIBN in deoxygenated toluene at 85 °C. Such conditions resulted in could only be isolated in yields of 20-25%. It was found; however, that if the Barton reduction was performed at 0 °C good yields of the dideoxygenated cytidine analog **63** a

complex mixture of reaction products from which the desired dideoxygenated cytidine **63** could be obtained. This required catalytic triethylborane / air as a low temperature radical initiator,[116, 117] and afforded a respectable 73% yield of **63** (Scheme 29).

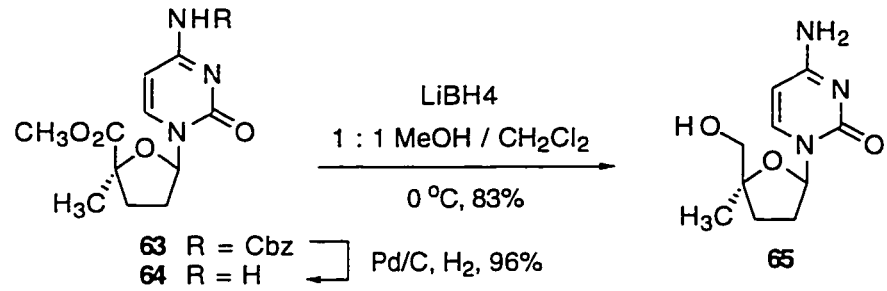


60 X = H
61 X = F

63 X = H 73%
66 X = F 16%

Scheme 29. 2'-Deoxygenation of cytidine analogs.

The dideoxygenated cytidine analog **63** was then deproteced by hydrogenolysis of the 4-benzylcarbamate to afford **64** and subsequent lithium borohydride reduction of the C5' methyl ester gave the target 2',3'-dideoxy-4'-*C*-methylcytidine **65** (Scheme 30).



63 R = Cbz
64 R = H

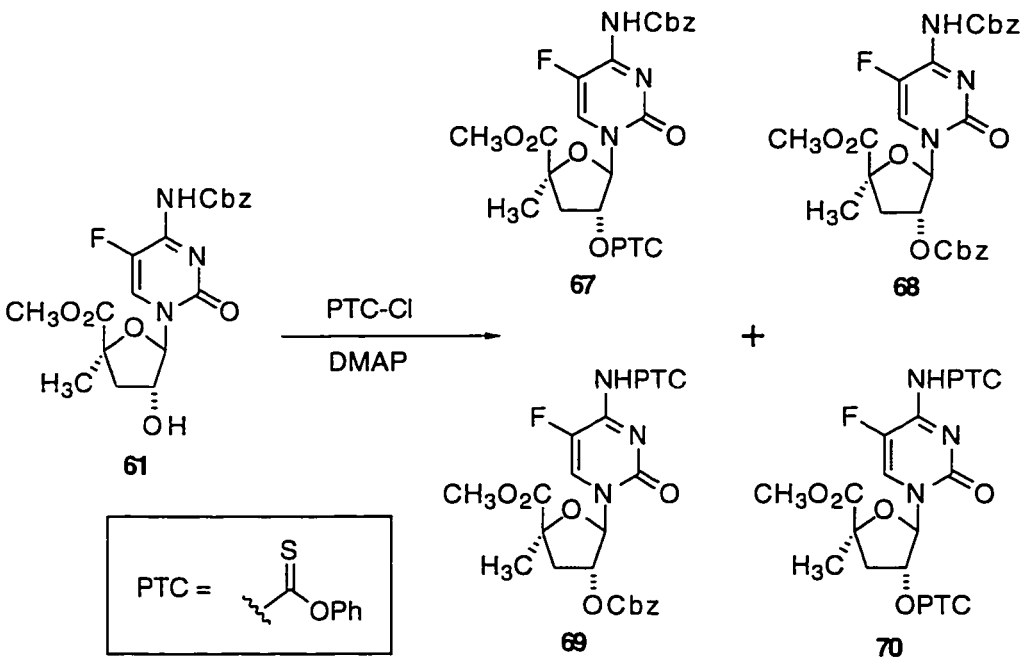
Pd/C, H_2, 96%

65

Scheme 30.

Surprisingly, attempted deoxygenation of the 5-fluorocytidine analog **61** by a two step procedure identical to that used to successfully deoxygenate the cytidine analog **53** only afforded the dideoxygenated 5-fluorocytidine analog **66** in a 16% yield (Scheme 29). Initially it was suspected that reduction of the 5-fluoro group may be occurring, but no product attributable to defluorination could be identified in the product mixture. After

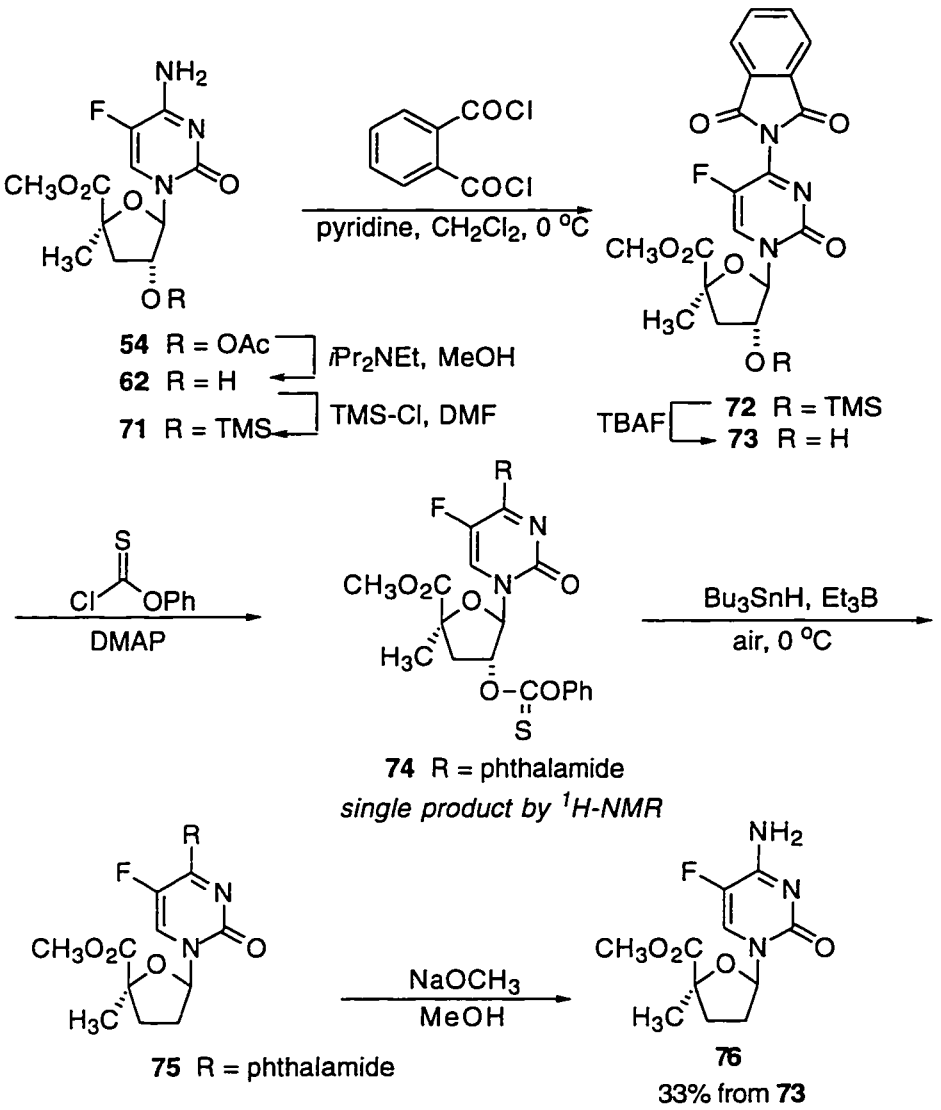
repeated attempts at the deoxygenation of **61** by the method in Scheme 29 it soon became clear that the problem lie with the thionoacylation of the 2'-hydroxyl. Analysis of this step by TLC suggested the formation of several products. These could not be separated by chromatography, but analysis of the product mixture by ^{1}H-NMR showed three different signals attributable to methylene protons of benzyl carbamates in a ratio of ~ 1 : 1 : 1. A possible explanation for this observation could be that under the conditions for thionoacylation, an intermolecular transfer of the 4-benzyl carbamate protecting group to the 2'-hydroxyl of **61** may be occurring. The material consisting of an unprotected 4-amino group could then be thionoacylated at this position resulting in the formation of the inseparable products **67-70** (Scheme 70). Of these possible products only **67** would then



Scheme 31. Inter molecular transfer of the benzylcarbamate protecting the 4-amino group of **61**. Acetyl, pivaloyl, and *t*-butylcarbamate were examined as protecting groups for the 4-amino functionality, but gave similar results to those observed for the **61**.

lead to the formation of the desired dideoxygenated **66** under the Barton reduction conditions, thus explaining the poor yield observed. A number of other protecting groups were examined for the 4-amino group of **61** including; acetyl, pivaloyl, and *t*-butyl

carbamoyl; but all appeared to give a product mixture similar to **67-70**. Ultimately, the 5-fluorocytidine analog **73** in which the 4-amino was protected with a phthaloyl group was prepared as shown in Scheme 32. Due to the bidentante nature of the phthaloyl protecting

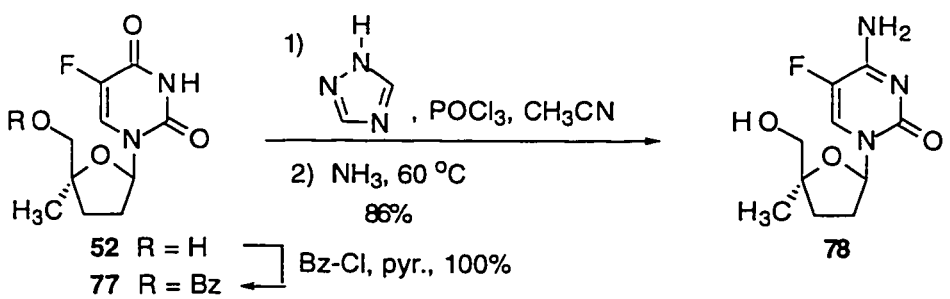


Scheme 31. Successful deoxygenation of the 5-fluorocytidine analog.

group, intermolecular transfer should be prohibited. Indeed, submission of **73** to thionoacylaction conditions as before resulted in the clean formation of a single product **74** as determined by crude ^{1}H-NMR analysis of this material. The deoxygenated of **74** was then accomplished by the action of tributyltin hydride and Et_3B / air at 0 °C to give **75**.

Unfortunately, **75** could not be obtained pure, as the tin by-products formed in the Barton reduction, co-alluted with **73** in attempts to purify by column chromatography. In order to separate the tin by-products, the 4-amino had to first be de-blocked requiring the strongly basic conditions of sodium methoxide in methanol. This afforded **76** which could now be purified by column chromatography, but only in a 33% yield form **73**.

In general the 4-amino group of the cytidine analogs makes these nucleosides difficult to work with. This is due to both the high polarity of the unprotected nucleoside, as well as the propensity of the 4-amino group to undergo acylation requiring that this functionality be protected. Alternatively, uridine nucleosides in which the pyrimidine ring is substituted with an oxygen at the 4-position, are far less troublesome to handle. Given that the preparation of 2',3'-dideoxy-4'-*C*-methyluridine (**52**) was smoothly accomplished (sec. 3.3), literature reports detailing the two step conversion of uridine to cytidine attracted our attention as a potentially more efficient method to prepare the dideoxy 5-fluorocytidine (Scheme 33).[118-120] To accomplish this transformation, the 5-fluorouridine analog **52** was protected as the 5'-benzoyl **77**, followed by treatment with phosphorus oxychloride and

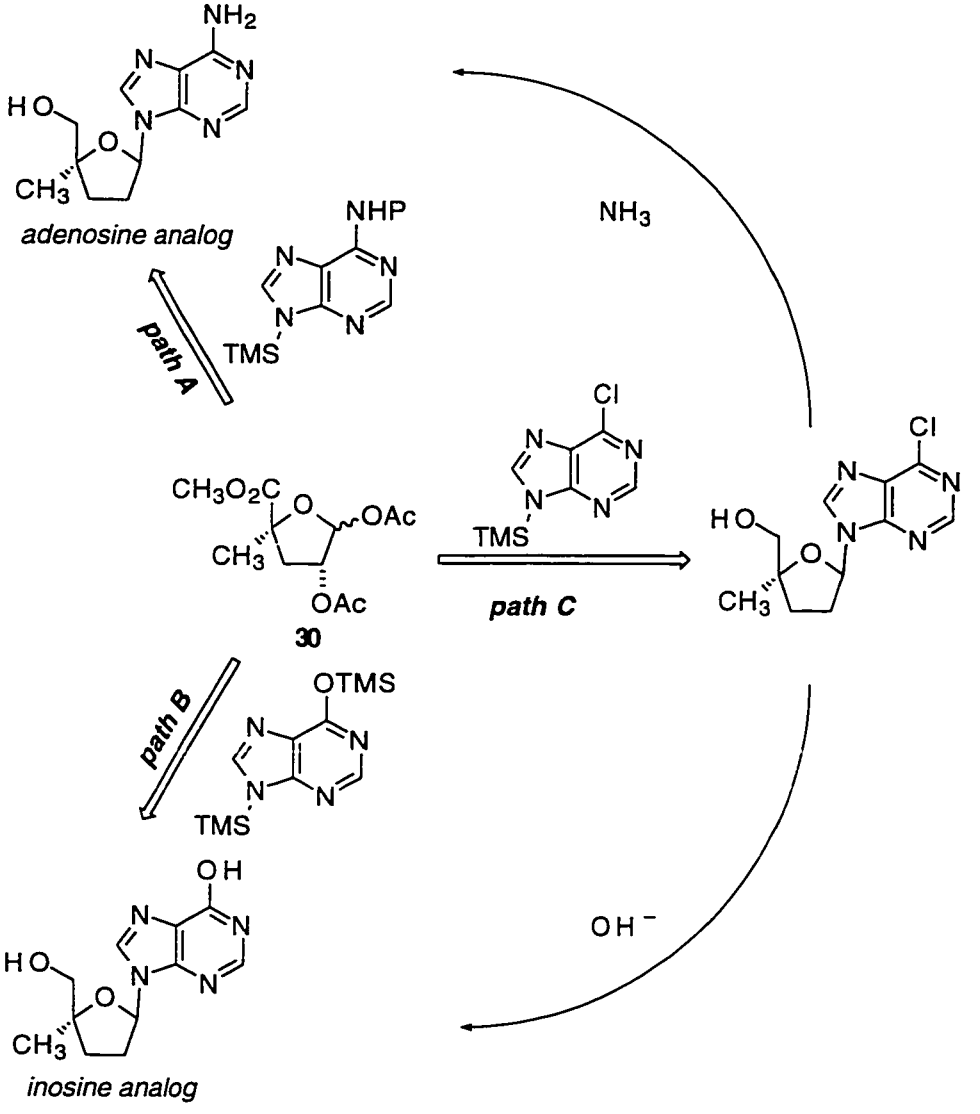


Scheme 32. Conversion of dideoxyuridine **52** to dideoxycytidine **78**.

triazole. The resulting crude product was then charged to a stainless steel bomb and heated at 60 °C in liquid ammonia to give the target 2',3'-dideoxy-5-fluoro-4'-*C*-methylcytidine(**78**) in an 86% two step yield (Scheme 32). In this example at least, converting uridine **52** to cytidine **78** proved vastly superior over the attempts to prepare dideoxy-5-fluorocytidine by the 2'-deoxygenation of **54** as shown in Scheme 31.

3.5. Adenosine and Inosine Analogs.

It was hoped that both adenosine and inosine analogs of type **1** and **2** (Scheme 1) could be prepared by reaction paths that did not diverge at ribose **30** (Scheme 34). Diverging at ribose **30** would require the separate glycosylation of both silylated N^6-protected adenine (path A) and silylated hypoxanthine (path B). Beyond the unattractive

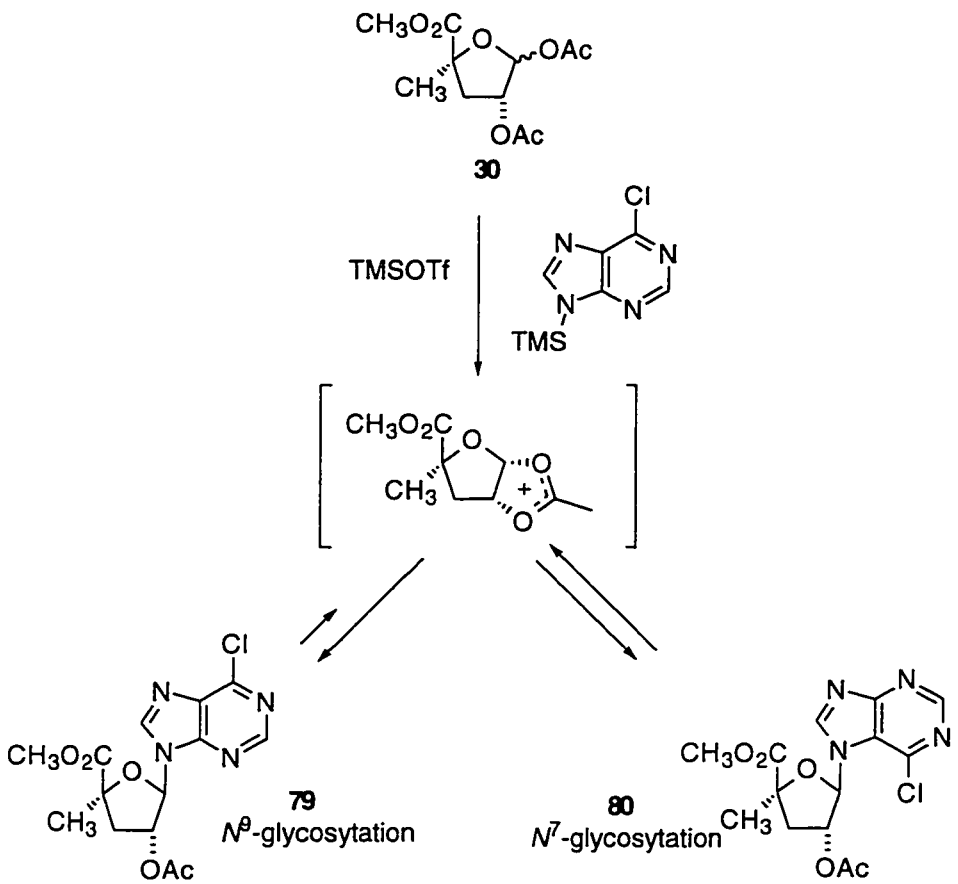


Scheme 34. Approaches to inosine and adenosine analogs.

divergent nature of paths A and B, it was feared that difficulties with the protection of the heteroatom at the 6-position of the purine heterocycle, similar to those encountered with the

protection of the 4-amino group of the cytidine analogs, would plague both reaction paths A and B. Attractive as a method to avoid both the divergent nature of paths A and B, as well as the need to protect the heteroatom at the 6-position of the purine heterocycle was path C. This would involve the glycosylation of silylated 6-chloropurine with ribose **30**. The 6-chloropurine nucleoside that would result, could then be carried down a single reaction path which diverges at the final step by either displacing the 6-chloro with ammonia to give adenosine analogs, or with hydroxide to give inosine analogs. Furthermore, it has been observed that the Vorbrüggen type glycosylation of 6-chloropurine generally proceed with yields superior to the glycosylation of N^6-protected adenine.[121]

The two concerns that question the feasibility of path C existed. First, could the 6-chloro substituent survive the Barton reduction conditions required to effect 2'-deoxygenation? Secondly, could the 6-chloro substituent survive the metal hydride reduction of the C5' methyl ester? In order to examine weather path C was workable, the glycosylation of 6-chloropurine with ribose **30** was attempted. Treatment of silylated 6-chloropurine with ribose **30** at 45 °C resulted in the formation of two products as determined by TLC analysis. After separating the products by column chromatography, high resolution mass spectrometry and ^{1}H-NMR analysis suggested that the products were either stereoisomers or structural isomers. The possibility for the formation of stereoisomers exists as the glycosidic bond, in theory, could form with either an α or β configuration, but this seemed unlikely as prior experience in the glycosylation of pyrimidine heterocycles with ribose **30** gave only nucleosides consisting of a β-anomeric configuration (sec. 3.3.1). A more fitting assignment of structures for the two products would be the formation of constitutional isomers **79** and **80** arising form either N^7-glycosylation or N^9-glycosylation of 6-cloropurine.[63, 122] It was found that longer reaction time and higher reaction temperature could drive the equilibrium to favor the thermodynamically favored N^9-glycosylated product. Such conditions allowed for the isolation of **79** in an excellent yield of 91%.

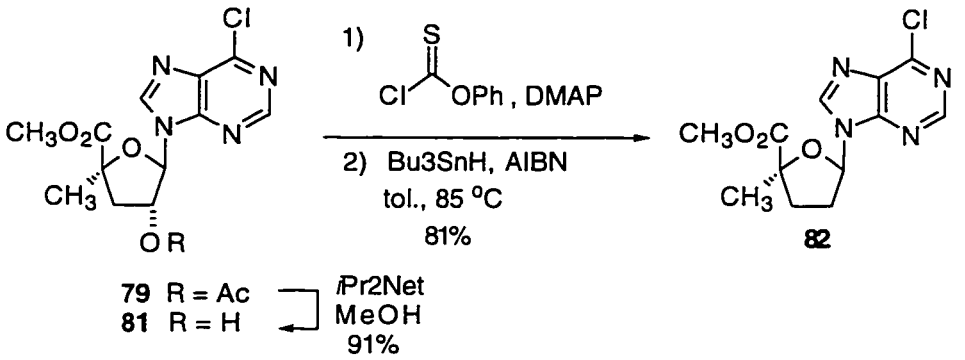


temperature	time	%N^9	%N^7
45 °C	1 h	54	42
75 °C	3 h	91	7

Scheme 35. N^9 vs. N^7 glycosylation of 6-chloropurine.

Deoxygenation of the 6-chloropurine nucleoside **79** was next attempted by a procedure identical to that used for the uridine analogs (sec. 3.3.2). This required that the 2'-hydroxyl of **79** first be deprotected by the action of catalytic Hunig's base in methanol to give **81**. Next the formation of the 2'-thionocarbonate was accomplished by treatment with phenyl chlorothionoformate and dimethylaminopyridine. The resulting crude material was then submitted to the Barton reduction. Much to our satisfaction the conditions of

tributyltin hydride and, AIBN at 85 °C in degassed toluene afforded dideoxygenated nucleoside **82** in a good yield of 81% for the two steps. Despite initial concerns, no reduction of the 6-chloro group was observed.

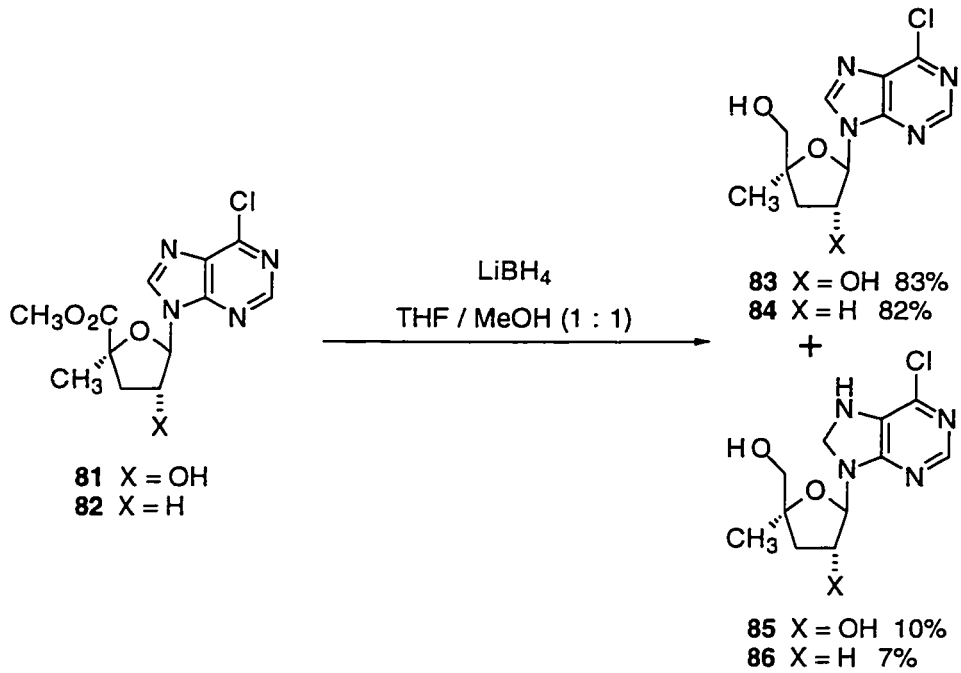


Scheme 36. 2'-Deoxygenation of 6-chloropurine nucleoside.

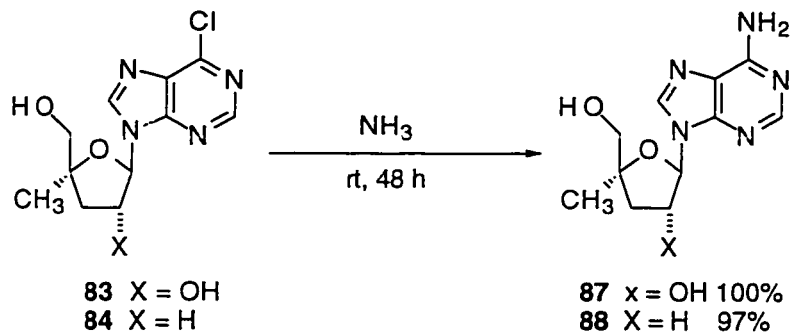
The second and last concern regarding path C (scheme 34) was the chemoselective reduction of the C5' methyl ester in the presence of the 6-chloro substituent. Initial attempts using aluminum hydride reducing agents at low temperatures (lithium aluminum hydride or diisobutylaluminum hydride at -78 °C) suggested this may prove difficult as mixtures of products resulting from reduction of either or both the C5' methyl ester and 6-chloro group were obtained. Using lithium borohydride at 0 °C, however, gave good yields in the chemoselective reduction of the C5' methyl ester contained within substrates **81** or **82** to afford either **83** or **84**. Surprising, the only over reduced products obtained from the lithium borohydride conditions were **85** and **86** resulting from the reduction of the C8-N^7 unsaturation of the purine ring.

All that remained for the preparation of the adenosine and inosine analogs was the nucleophilic displacement of the 6-chloro substituent of either **83** or **84** with the appropriate nucleophile. This was easily accomplished by treating either **83** or **84** in a stainless steel bomb with liquid ammonia at room temperature to give the 6-aminopurine nucleosides **87** or **88** in near quantitative yields. Introduction of a hydroxyl group to the

6-position of the purine ring of substrates **83** and **84** to prepare inosine analogs proved to



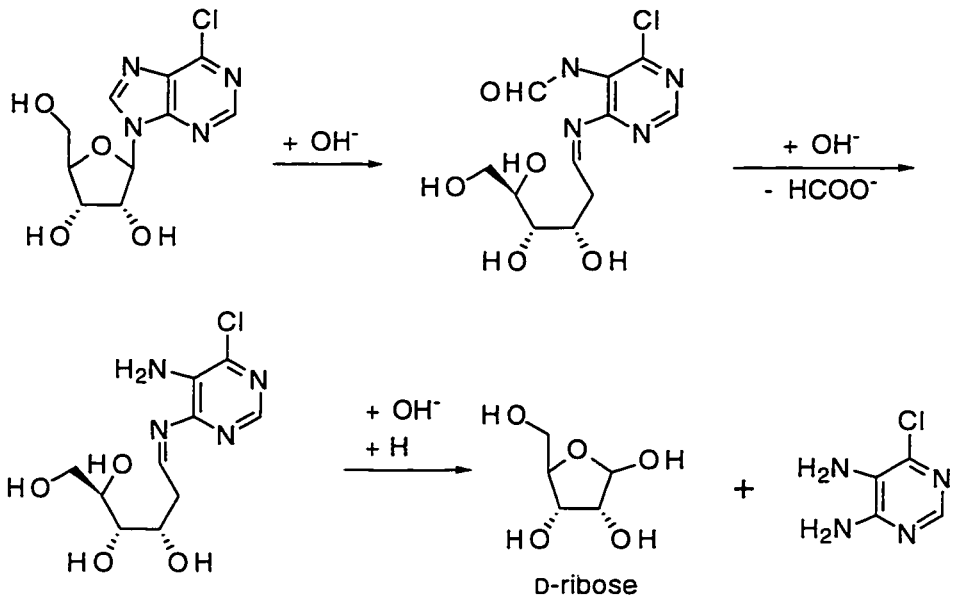
Scheme 36.



Scheme 37.

be much more difficult. Numerous attempts to displace the 6-chloro group directly by treatment with aqueous sodium hydroxide in a variety of organic solvents failed to give the desired inosine products. Submitting **84** to the biphasic reaction conditions of chloroform, 50% aqueous sodium hydroxide and the phase transfer catalyst, tetrabutylammonium chloride, failed to give the 6-oxopurine nucleoside as well. Literature examples involving

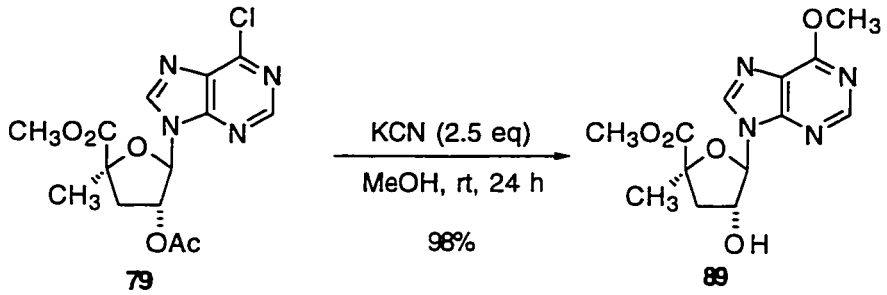
treatment of 6-chloropurine ribonucleosides with aqueous base confirmed our observations, reporting only very low yields of 6-oxopurine nucleosides.[123, 124] Instead the major products obtained in these examples were those resulting from the hydrolysis of the glycosidic bond which occurs by the mechanism shown in scheme 39.



Scheme 39. Mechanism for alkaline hydrolysis of glycosidic bond of 6-chloropurine ribonucleoside.

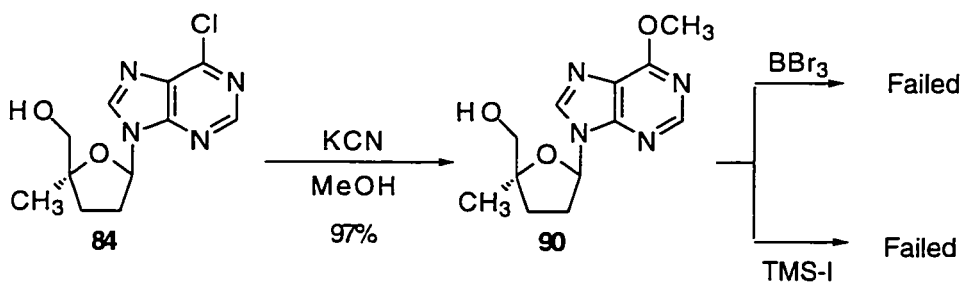
The successful conversion of 6-chloropurine ribonucleosides to 6-oxopurine ribonucleosides is known in the literature. Three general approaches exist: (1) an enzymatic transformation employing adenosine deaminase in aqueous buffer;[125, 126] (2) treatment of 6-chloropurine ribonucleosides with 2-mercaptoethanol and sodium methoxide in refluxing methanol;[127, 128] and (3) the chemical conversion of 6-chloro- to 6-alkoxypurine ribonucleosdies and subsequent ether cleavage to give 6-oxopurine ribonucleosides.[129, 130] All three of these methods report very good overall yields in the preparation of 6-oxopurine ribonucleosides, but the third method appeared particularly attractive. The reason for this is that it had incidentally been found in the process of attempting to de-block the 2'-hydroxyl of 6-chloronucleoside **79**, that treatment of **79** with excess potassium cyanide in methanol afforded the 6-methoxypurine nucleoside **89** in near quantitative yield (Scheme 40). Given

the ease with which 6-methoxypurine nucleosides could be prepared by this technique,



Scheme 40. Attempted de-blocking of 2'-hydroxyl with KCN / MeOH resulting in good yields of 6-methoxypurine nucleoside **89**.

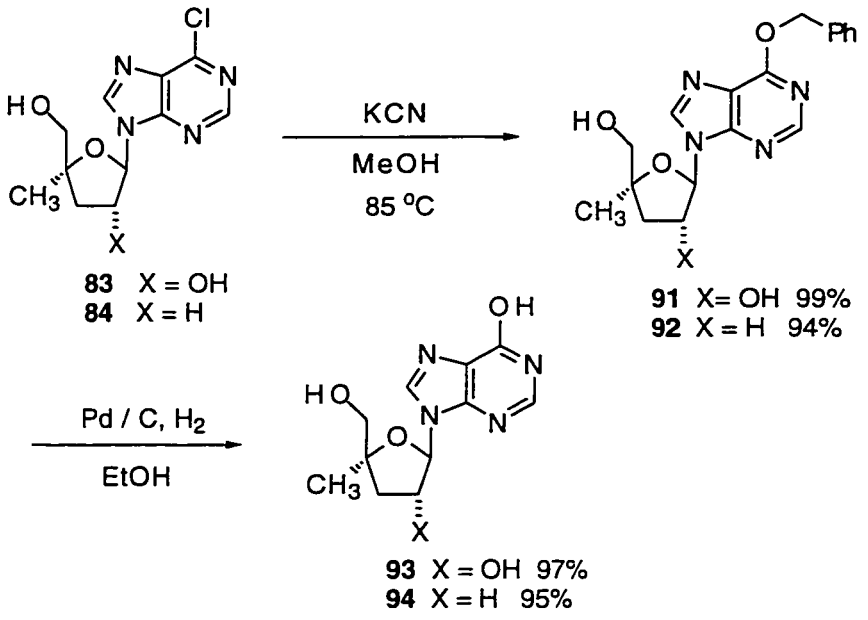
attempted de-methylation was logical. As shown in Scheme 41, attempts at de-methylation of **90** by the action of either boron tribromide or iodotrimethylsilane failed to give the



Scheme 41. Attempted de-methylation of **90**.

desired 6-oxopurine nucleoside. It is believed that treatment of **90** with these Lewis acidic reagents resulted in cleavage of the glycosidic bond, as this is especially liable under acidic conditions in the case of dideoxygenated purine nucleosides.[107] For this approach to the inosine analog to be successful, the introduced 6-alkoxy substituent must result in an ether which can be cleaved under neutral and mild conditions. A benzyl ether would fit these criteria, and it was found that heating either 6-chloropurine nucleoside **83** or **84** in benzyl alcohol and excess potassium cyanide gave excellent yields of the 6-benzyloxypurine nucleosides **91** and **92** (Scheme 42). Finally, submitting either **91** or **92** to

hydrogenolysis over palladium on carbon under one atmosphere of hydrogen cleanly afforded the desired 3'-deoxy-4'-*C*-methylinosine analog **93** or the 2',3'-dideoxy-4'-*C*-methylinosine analog **94** in near quantitative yields.



Scheme 42.

Chapter 4

4'-*C*-Phenyl and 4'-*C*-Trifluoromethyl Uridine Analogs

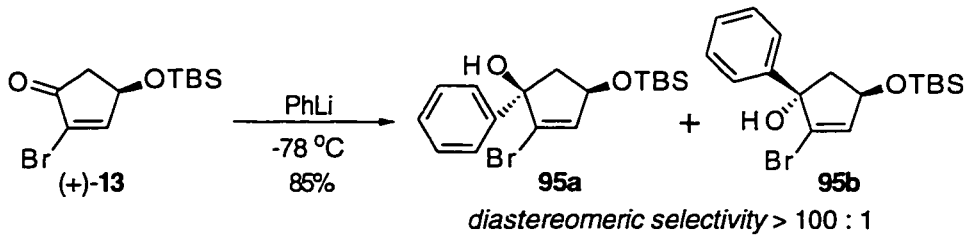
The preparation of 4'-*C*-substituted nucleosides discussed up to this point has dealt solely with 4'-*C*-methyl nucleosides. One of the goals of this project was to create methodology allowing for the synthesis of a variety of 4'-*C*-alkyl nucleosides. Therefore, it became important to synthesize nucleoside analogs bearing 4'-*C*-substituents other than methyl to demonstrate the generality of the synthetic methodology. The successful preparation 4'-*C*-methyl nucleosides presented in Chapter 3 made it apparent that any unfunctionalized alkyl group could be introduced with the same success as the 4'-*C*-methyl substituents, so 4'-*C*-alkyl groups of more interest both from the point of view of a synthetic challenge, as well as, biologically activity were sought. Emerging as appealing targets addressing both interest were the preparation of 4'-*C*-phenyl nucleosides and 4'-*C*-trifluoromethyl nucleoside of both the 3'-deoxy and 2',3'-dideoxy series. Results and discussion regarding the preparation of these analogs are discussed in this chapter.

4.1. 4'-*C*-Phenyluridine Analogs.

The decision to pursue the synthesis of 4'-*C*-phenyluridines was based on the thought that such a 4'-*C*-substituent would be compatible with our general methodology. Furthermore, nucleosides in which the ribose moiety is substituted with a phenyl are not known in the literature. Given the planar and hydrophobic nature of the phenyl group, it was thought that such 4'-*C*-phenylnucleosides deoxygenated at the 3'-position or at both the 2'- and 3'-positions may poses some interest in terms of biological activity. As the predominant goal was to demonstrate the compatibility of our methodology for the introduction of a 4'-*C*-phenyl substituent, the preparation of only the thymine series of 4'-*C*-phenyl nucleoside analogs was attempted. The selection of thymine as the heterocyclic base was derived from both the strong precedence for biological activity (Figure 3; AZT,

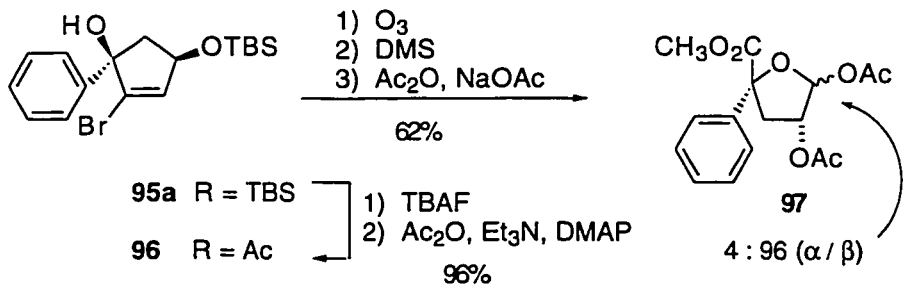
D4T) and the synthetic ease with which such nucleoside analogs can be handled (no protecting group manipulations are required, Section 3.3).

The synthesis of the 4'-*C*-phenyl nucleosides began with the carbonyl alkylation of the TBS-protected α-bromoenone (+)-**13** with a phenyl nucleophile. It was found that treatment of (+)-**13** with phenyllithium at -78 °C afforded the phenyl substituted carbocycle **95** as a single diastereomer (d. s. > 100 : 1) in an 85% yield (Scheme 43). The superior diastereomeric selectivity obtained in the carbonyl alkylation of (+)-**13** with phenyllithium, in comparison to that observed with methyllithium at the same temperature (Table 3, entry 8) is undoubtedly an a reflection of the larger size of phenyllithium.



Scheme 43.

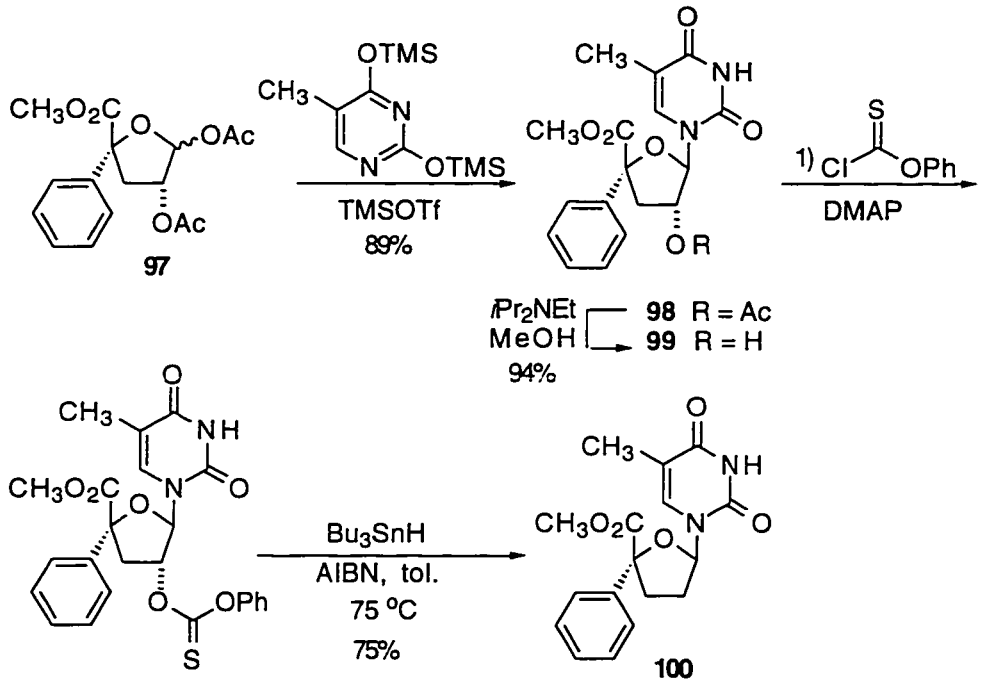
Next, converting the silyl ether of **95** to an acetate was required, as the acetate will control the stereochemistry of the *N*-glycosylation of a heterocylic base (Section 3.2). This was accomplished by treating **95a** with tetrabutlyammonium fluoride to cleave the silyl ether. The crude diol that resulted was then treated with acetic anhydride, triethylamine and



Scheme 44. Oxidative olefin cleavage of cyclopentene **96**.

dimethylaminopyridine to regioselectively acylate the secondary alcohol affording **96** (Scheme 45). Submitting cyclopentene **96** to the oxidative olefin cleaving conditions of ozone gave the 4-phenyl ribose which was heated in acetic anhydride buffered with sodium acetate prior to purification to give the 4-phenyl acylglycoside **97**. Acylglycoside **97** was isolated as an inseparable mixture of anomers [4 : 96 (α / β)] in a in a yield of 62% form **96**.

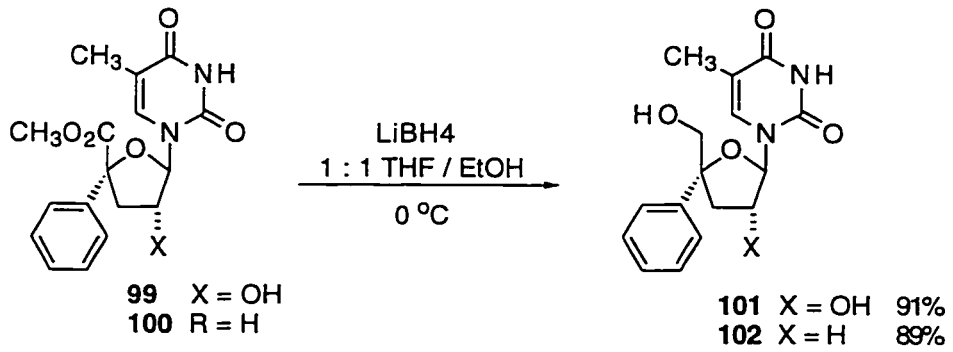
Glycosylation of silylated thymine with the 4-phenyl ribose **97** proceeded smoothly to give the β-N^1-glycosylated nucleoside **98** in a good yield (Scheme 15). De-blocking of the 2'-hydoxyl of **98** was accomplished by basic methanolysis of the acetate functionality to give **99** (Scheme 45). Thionoacylation of the 2'-hydroxyl by treatment with



Scheme 45.

phenyl chlorothionoformate and dimethylaminopyridine, followed by the high temperature Barton reduction conditions gave dideoxygenated **100** in a satisfactory yield. The final step was the reduction of the C5' methyl ester of **99** to give the 3'-deoxy-4'-*C*-phenyluridine (**101**) or reduction of the C5' methyl ester of **100** to give 2',3'-dideoxy-4'-

C-phenylthymidine (**102**). In both cases it was found that the conditions used previously for C5' ester reduction (lithium borohydride; 1 : 1 ethanol / tetrahydrofuran) cleanly afforded the target nucleosides **101** or **102** in good yields (Scheme 46).



Scheme 46. Reduction of the C5' methyl ester.

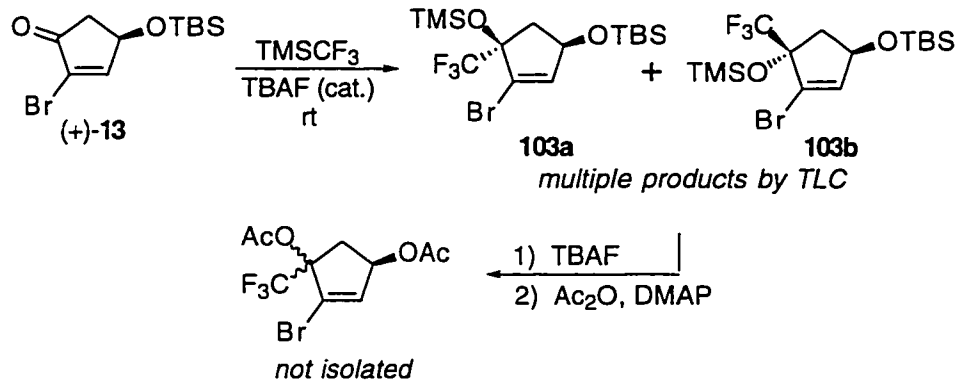
4.2. Analogs of 4'-*C*-Trifluoromethyluridine.

Another class of 4'-*C*-substituted nucleosides that appeared interesting, are those in which the substituent is a trifluoromethyl group. From a biological point of view, the presence of a small perfluoroalkyl group often confers unique properties to a molecule in terms of increased lipophilicity, which inturn alters *in vivo* absorption and transport rates. In addition, while small perfluoroalkyl groups are stable and sterically similar to their hydrocarbon analogs, they posses a strong electron withdrawing nature which can significantly alter the chemistry of the molecule to which they are introduced. As with the case of a 4'-*C*-phenyl substituent, it appeared that a 4'-*C*-trifluoromethyl group would be compatible with the general synthetic methodology employed in this research.

In order to introduce a trifluoromethyl group, a source of trifluoromethyl nucleophile (CF_3^-) capable of alkylating the carbonyl of TBS protected α-bromoenone (+)-**13** was required. Unfortunately, trifluoromethyllithium[131] and the coresponding Grignard[132] reagents are reported to not be synthetically useful as they decompose readily, apparently to difluorocarbene, even when formed at low temperatures and in the presence

of a suitable electrophile.[133] Reports describing the carbonyl alkylation of aldehydes with transient trifluoromethyl zinc reagents have appeared, but the methodology is ineffective at alkylating ketones.[134, 135] Good yields of trifluoromethyl alkylated ketones have only been reported by exposing trifluoromethyltrimethylsilane ($TMSCF_3$) to catalytic tetrabutylammonium fluoride (TBAF) in the presence of the ketone.[136] This method appeared as if it would be suitable for the carbonyl alkylation of the (+)-**13**. The expected products from the transformation would be diastereomeric trifluoromethyl-silyloxy adducts **103ab** resulting from carbonyl alkylation and *in situ* silylation of the newly formed tertiary alkoxide that is formed (Scheme 47).

Treatment of (+)-**13** and $TMSCF_3$ with 0.1 mol % of TBAF at room temperature resulted in little reaction. An additional portion of TBAF (0.4 mol % more) was required to encourage the complete consumption of (+)-**13** in a reasonable time (20 h). Following the progress of the reaction by TLC, it was clear that multiple products were forming. The formation of multiple products seemed reasonable as the presence of fluoride ion in the

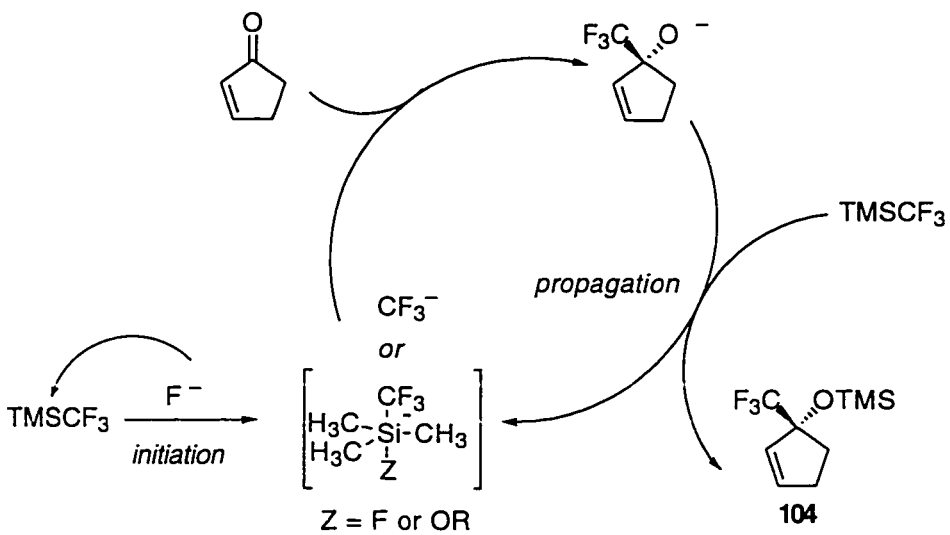


Scheme 47. Attempted carbonyl alkylation by generation of CF_3^- from $TMSCF_3$ / TBAF.

reaction mixture could cleave either of the silyl ethers of products **103a** or **b**, and the warm temperature required for the transformation might afford poor diastereomeric selectivity further complicating the product mixture. With the hope of isolating some form of a carbonyl alkylated product, the reaction mixture was treated with a large excess of

TBAF to cleave all silyl ethers and then treated with acetic anhydride / DMAP. However, no carbonyl alkylation products were isolated from this mixture.

Model studies in which cyclopentenone was treated with $TMSCF_3$ / catalytic TBAF gave satisfactory yields of the carbonyl alkylated trifluoromethyl-silyloxy adduct **104** (Scheme 48). So it became clear that either the α-bromo or the silyl ether functionalities of (+)-**13** are incompatible with the reaction conditions. Given that fluoride ion reacts readily with silicon, it seemed logical that an interaction between fluoride ion and the silyl ether of (+)-**13** was the origin of the poor results obtained in attempts to alkylate (+)-**13** with $TMSCF_3$ / catalytic TBAF. It was recognized upon consideration of possible reaction mechanisms, that the only role fluoride ion fulfills in the transformation is that of an

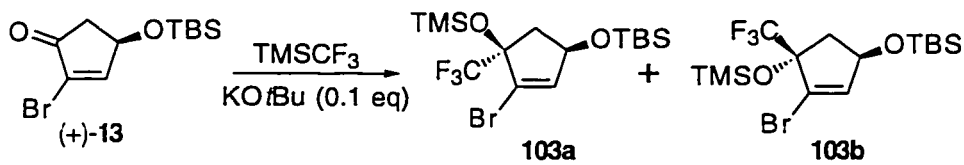


Scheme 49. Reaction mechanism for carbonyl alkylation with $TMSCF_3$ / catalytic TBAF.

initiator. That is fluoride ion attacks $TMSCF_3$ to irreversible form TMSF and CF_3^- (or a complexed carbanoid)(Scheme 48). The CF_3^- anion then adds to the carbonyl to generate a tertiary alkoxy, which in turn attacks another molecule of $TMSCF_3$ to generate the next CF_3^- and the trimethylsilyl ether **104**. The reaction is therefore propagated by the formation of alkoxide and fluorine plays no role in the catalytic cycle other than initiation. With this realization, it was logical to attempt the carbonyl alkylation of (+)-**13** by initiation

with an alkoxide and avoid any unproductive interactions between fluoride ion and the silyl ether present in (+)-**13**. The original report[136] of akylating ketones with $TMSCF_3$ / cat. TBAF, states in a footnote that the process may also be initiated by alkoxide, so this looked especially promising for the alkylation of (+)-**13**.

As seen in Scheme 49, treatment of a mixture of (+)-**13** and $TMSCF_3$ with 0.1 mol equivalent of potassium butoxide (based on (+)-**13**), resulted in the rapid consumption of (+)-**13** within 1 h to afford diasteriomers **103ab** in a combined yield of 46% with a diastereomic selectivity of 5 : 1 favoring **103a**. The substantial rate increase observed for the alkoxide initiated process compared to that initiated with fluoride ion was fortuitous, as it suggested that the transformation would proceed at much lower temperatures, which would allow for an improved diasteriomeric selectivity. Indeed treatment of (+)-**13** with $TMSCF_3$ / KO*t*Bu (0.1 mol %) at -78 °C cleanly afforded diasteriomerically pure **103a** (d. s. > 100 : 1) in a vastly improved yield of 94%. The improved diasteriomeric selectivity was gratifying, but the remarkable improvement in yield was surprising.

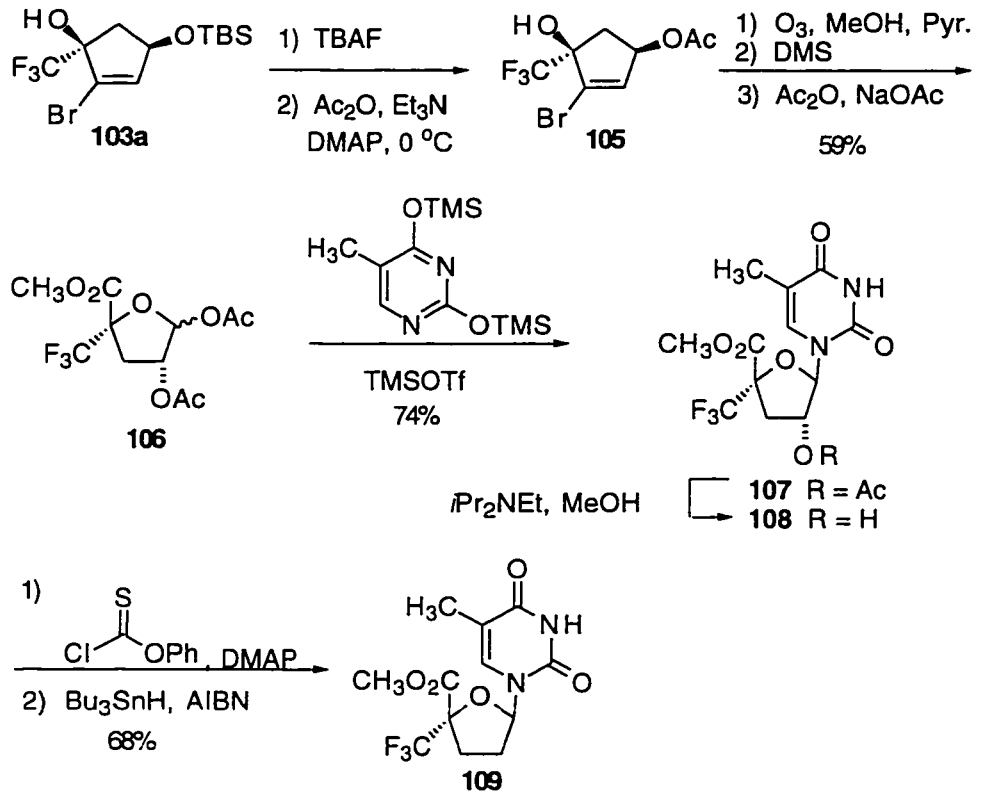


temperature	yield	selectivity
20 °C	46%	5 : 1
-20 °C	92%	20 : 1
-78 °C	94%	>100 : 1

Scheme 49. Alkylation of (+)-**13** with $TMSCF_3$ / catalytic KO*t*Bu.

The silyl ethers of **103a** were then cleaved by the action of TBAF, followed by the regioselective acylation of the secondary alcohol to afford monoacetate **106** (Scheme 50). Treatment of **106** with ozone in methanol / pyridine gave the crude 4-trifluoromethyl ribose which was then heated in sodium acetate buffered acetic anhydride prior to purification to give the 4-trifluoromethyl acylglycoside **107** in a two step yield of 59%. Acylglycoside

107 was isolated from these procedures as a 4 : 96 (α / β) mixture of anomers which could not be separated. Glycosylation of silylated thymine with ribose **107** was next attempted. This proceeded sluggishly at 75 °C and required a total of four equivalents of TMSOTf to reach completion, but still afforded a respectable 74% yield of the β-N^1-glycosylated uridine **107**. Deoxygenation of **107** at the 2'-position was accomplished as

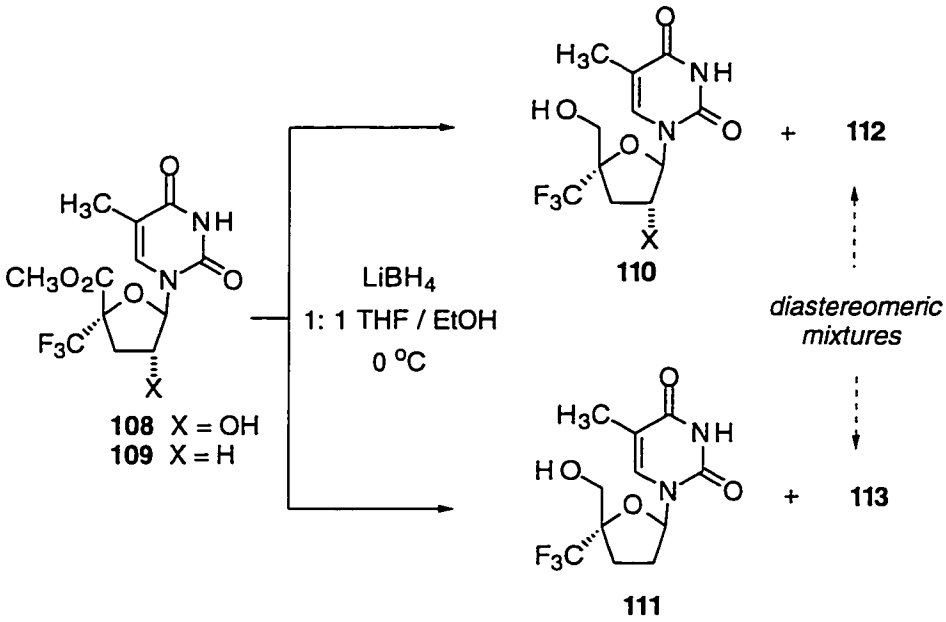


Scheme 50.

in the prior examples. This entailed de-blocking the 2'-hydroxyl, thionoacylation of the 2'-hydroxy and submission to Barton reduction conditions to give dideoxynucleoside **109**.

The last step in the syntheses of 3'-deoxy- and 2',3'-dideoxy-5-methyl-4'-C-trifluoromethylurines (**110** and **111**) was the reduction of the C5' methyl esters of substrates **108** and **109**. Treatment of either of these substrates with lithium borohydride in 1 : 1 THF / EtOH at 0 °C gave what appeared by thin layer chromatography analysis to be a single product in each case. Isolation of these products by chromatography and

subsequent analysis by NMR clearly supports the presence of the desired 5'-hydroxy-nucleosides **110** and **111**, but in each case these materials were contaminated with a by-product (**112** and **113**, Scheme 51). Despite several attempts the by-product could not be separated by chromatography, or crystallization. Examining the peaks attributed to the

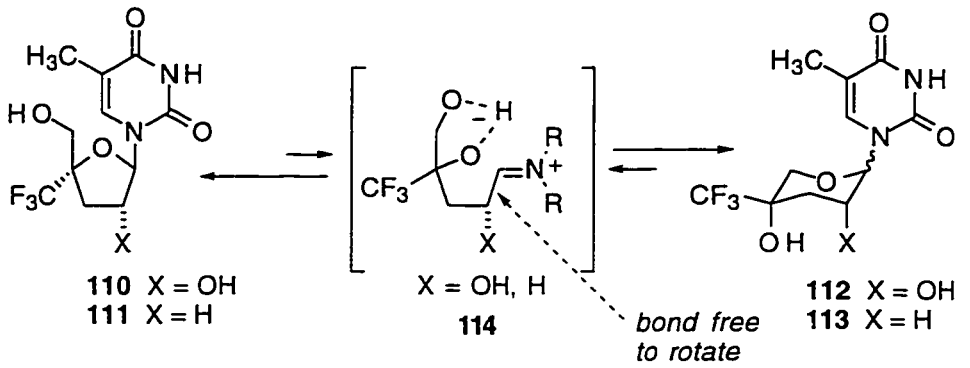


Scheme 51. Reduction of C5' methyl ester of substrates **107** and **108**.

contaminants **112 / 113** in the NMR spectra of the mixtures, some clues as to their possible structures were obtained. First, in each case the ratio of desired 5'-hydroxy nucleoside **110 / 111** to the respective contaminant **112 / 113** was 2 : 1. Second, it was clear that whatever the exact structure of the contaminant, it must be closely related to the desired product as all ^{1}H- and ^{13}C-NMR absorption's for the desired nucleosides **109 / 110** were closely matched with sister absorption's attributed to the contaminants **112 / 113**. Thirdly, in the ^{13}C-NMR, each carbon absorption attributed to the contaminant **111 / 112** is actually two signals suggesting that the contaminant is a mixture of diasteriomers.

Combining the limited physical data for **112 / 113** with possible mechanistic pathways that would be unique to 5-methyluridine nucleosides substituted with a 4'-*C*-

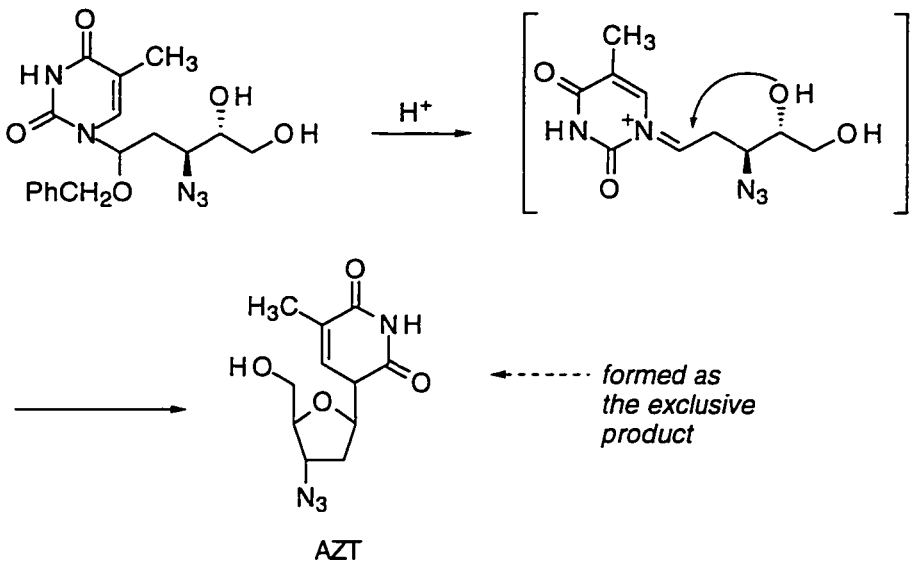
trifluoromethyl (5-methyluridine analogs substituted with a 4'-*C*-methyl or a 4'-*C*-phenyl gave clean products under identical borohydride reduction conditions) led to the proposed structures for **111 / 112** shown in Scheme 52. The formation of the pyranose ring of **111 / 112** could arise from the opening of the furanose ring of **110 / 111** which is



Scheme 52. Proposed structures of contaminants **112** and **113**, and proposed formation by isomerization.

encouraged by the electron withdrawing effect of the CF_3 substituent at C4' to give the transient species **114**. The 5'-hyroxyl can then close onto the iminium ion of **114** to form the pyranose ring of structures **112 / 113**. Since intermediate **114** is free to rotate about the C1'-C2' bond, a mixture of diasteriomers results in the formation of **112 / 113**. The fact that no product attributable to a furanose ring with an α-anomeric configuration is observed might suggest that the isomerization as proposed in Scheme 52 is unlikely, as the freedom of rotation about the C1'-C2' bond in **114** would allow racemization of the anomeric center of **110 / 111**. However, Liotta and co-workers, in a synthesis of the anti-HIV nucleoside AZT, reported the acid catalyzed cyclization of an acyclic nucleoside precursor proceeding through an intermediate similar to **114** to give exclusively the furanose nucleoside of β-anomeric configuration.[137] In this instance the β-selectivity is attributed to a low energy transition state favoring the formation of the observed product. While the substitution pattern for **114** is not identical to that of the Liotta intermediate, a

possible preferred transition state conformation may favor **114** closing preferentially to favor **110 / 111** as well.



Scheme 53. Liotta and co-workers' preparation of AZT

Whatever the origin of the contaminants **112 / 113** it is important to note that the structures in Scheme 52 are only proposed and have not been elucidated in any detail. It should also be noted that a group of Italian researchers have independently reported the preparation of 2',3'-dideoxy-4'-*C*-trifluoromethylthymidine (**111**) by an entirely different route.[138] In this instance **111** was obtained pure after chromatography. This report suggests that if in effect, the isomerization of **111** proposed in Scheme 52 is not occurring during chromatography on silica gel or upon standing alone in solution. It may be that Lewis acidic conditions, such as those present during the borohydride reduction, are require to effect the isomerization.

Chapter 5

Selective Agonists of the A_3 Adenosine Receptor.

5.1 Adenosine Receptor Antagonists and Agonists As Therapeutic Agents.

Adenosine is a chemical messenger involved in regulation of many physiological functions, including vasodilatation, vasoconstriction, cardiac depression, inhibition of platelet aggregation, inhibition of insulin release and inhibition of neurotransmitter release from nerve endings. There are three classes of adenosine receptors: A_1, A_2 and A_3. In recent years there have been tremendous advancements in the synthesis of adenosine

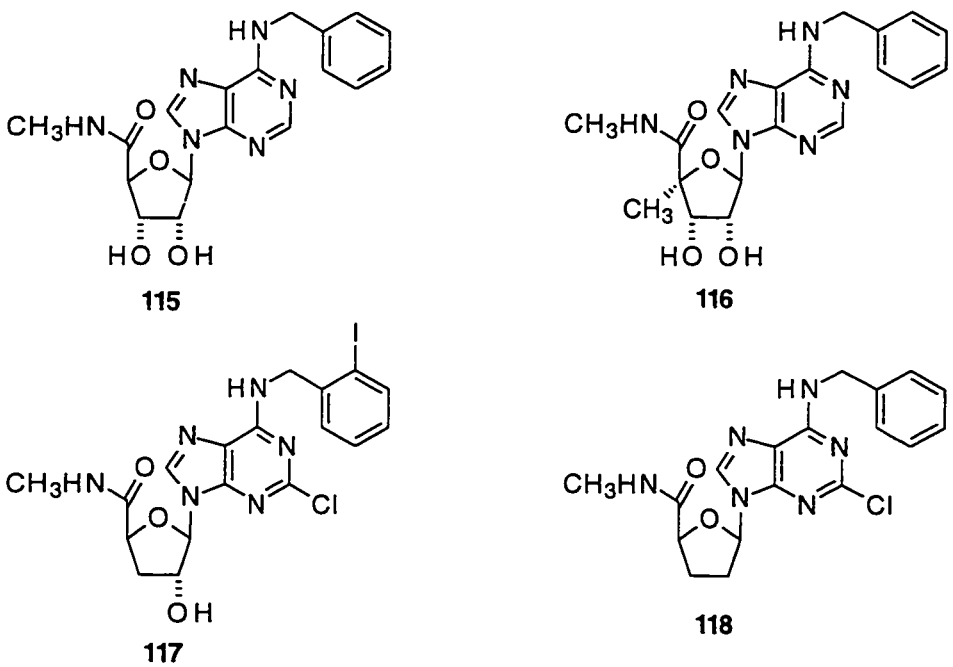


Figure 10. Some Adenosine Analogs that are Selective A_3 Agonist.

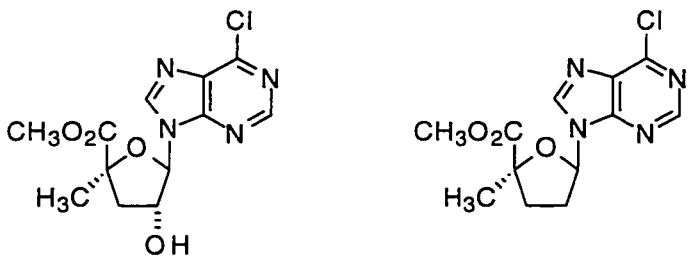
antagonists and agonists selective for a single receptor. These are being developed to treat diseases such as cognitive diseases (A_1), renal failure (A_1), Parkinson's and Huntington's

diseases (A_2) and cardiac arrhythmias (A_1). The A_3 receptor, which has only recently been discovered, has also been implemented in diverse physiological functions including; cardiac, CNS, reproductive and inflammatory functions.[139, 140]

The search for A_3 selective agonists and antagonists has lead to a collaborative effort among our laboratories and others to studied the structure-activity relationship of many ribose-modified adenosine analogs at adenosine receptors. This study identified the adenosine analog **115** and the 4'-C-methyl analog **116**[93] as highly A_3 selective agonists (Figure 10).[141] In latter work both the 3'-deoxy adenosine analog **117** and the 2',3'-dideoxy adenosine analog **118** were prepared and shown to be A_3 selective agonist as well.[142]

5.2. Synthesis of Adenosine Analogs as Potential A_3 Selective Agonists.

In Section 3.5 the synthesis of both the 3',-deoxy- and 2',3'-dideoxy-4'-*C*-methyladenosine analogs were discussed. These syntheses proceeded through the intermediates **81** and **82** (Figure 11). It was recognized that intermediates **81** and **82** may lend themselves to the easy preparation of both the 3'-deoxy- and 2',3'-dideoxy analogs of



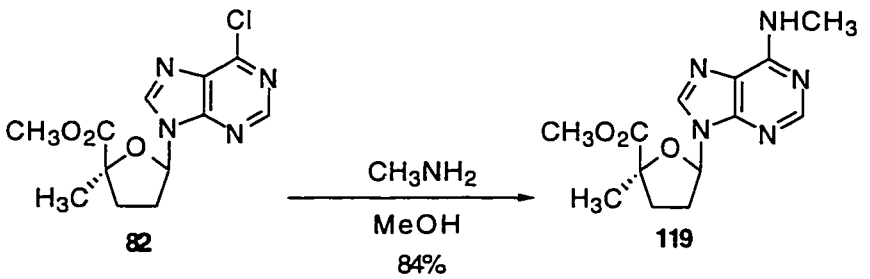
81 **82**

Figure 11. Intermediates for the Preparation of 3'-Deoxy- and 2',3'-Dideoxy Analogs of the A_3 Agonist **116**.

the selective A_3 agonist **116** (shown in Figure 10). This was dependent upon the rate difference in nucleophilic displacement of the methoxy of the methyl ester compared to the

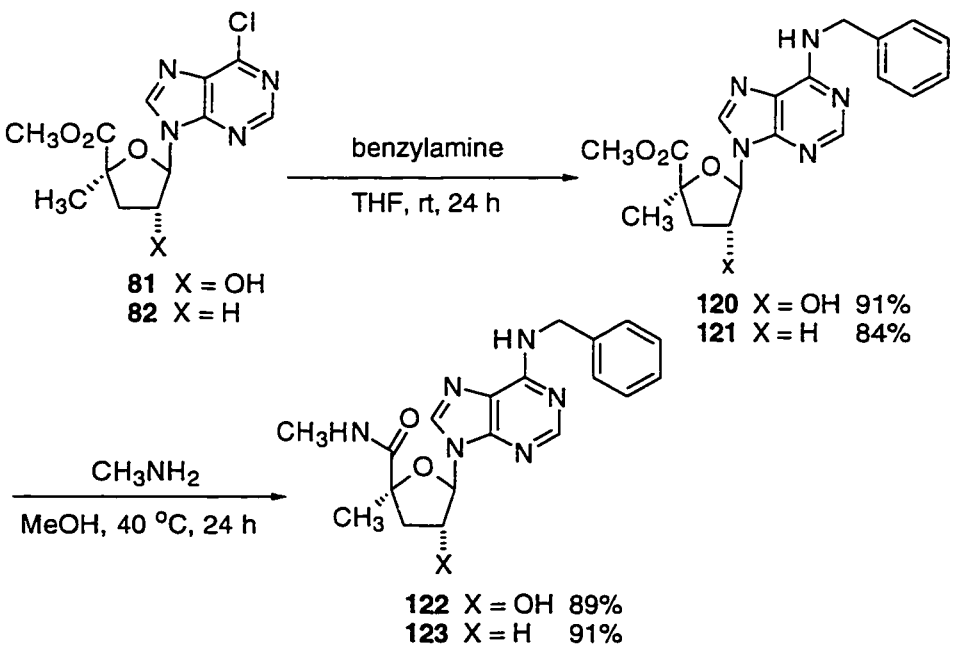
6-chloro of the purine ring by amines. If there is a substantial rate difference the appropriate amine can be regioselectively introduced to each position.

It was observed that treating **82** dissolved in methanol with an excess of methylamine for 3 h gave a good yield of 6-methylamino **119** as the only identifiable



Scheme 54. Nucleophilic attack occurs most rapidly at the 6-chloro.

product (Scheme 54). The results obtained in this experiment expose the 6-chloro as substantially more susceptible to nucleophilic attack. Dissolving either **81** or **82** in tetrahydrofuran and treating these solutions with an excess of benzylamine gave good yields of the 6-benzylamino adenosine analogs **120** or **121**, respectively. Interconversion



Scheme 55.

of the methyl esters of **120** and **121** to *N*-methyl-amides was then accomplished by heating these substrates in a solution of methylamine in methanol. This afforded the desired A_3 agonist analogs **122** and **123** in good yields. These were sent to Dr. Ken Jacobson at the National Institute of Health and are currently undergoing evaluation as A_3 selective agonists.

Chapter 6

Conclusions

This project had two main goals; (1) develop efficient methodology for the synthesis of novel 3'-deoxy- and 2',3'-dideoxy-4'-*C*-alkyl nucleosides, (2) screen such nucleoside analogs as antiviral agents.

6.1. Synthetic Methodology.

Achieving the first goal required the creation of methodology that would allow for the introduction of a variety of alkyl groups to the 4'-position, with particular emphasis on controlling the stereochemistry of C4' stereogenic center. This was accomplished by introducing the alkyl substituents and setting the stereogenic center at C4' in a cyclopentene precursor. The five carbons of the alkyl substituted cyclopentenes were then unveiled as the five continuous carbons of a synthetic ribose analog by oxidative cleavage of the olefin of the cyclopentene. The riboses prepared by these steps bear the introduced alkyl groups at the 4-position. The use of biocatalysis proved an efficient means to introduce enantiopurity and a judicial selection of a protecting group allowed for exceptionally high levels of diastereomeric selectivity in the carbonyl alkylation of the enantiopure cyclopentenone. This translated into complete control of the C4' stereogenic center of the 4-alkyl riboses as was demonstrated in the synthesis of the methyl, phenyl and trifluoromethyl 4-substituted ribose analogs.

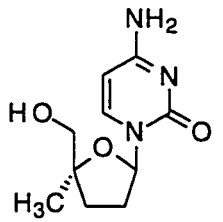
The semi-convergent nature of the methodology allowed for the synthesis of many nucleoside analogs of identical ribose moieties, but different heterocyclic bases. Excellent β-stereocontrol was achieved in the *N*-glycosylation of the heterocyclic bases with the 4-alkyl riboses by a Vorbrüggen type coupling to give, after adjustment of the C5' oxidation level, 3'-deoxy-4'-*C*-alkyl nucleosides. Obtaining the high level of stereocontrol accessible by the Vorbrüggen coupling was only possible due to the presence of the 2-acetoxy

functionality of the 4-alkyl riboses. This oxygenated functionality at the 2'-positions of the nucleosides was then removed by the protocol of Robins to afford the dideoxygenated 4'-*C*-alkyl nucleosides after adjustment of the C5' oxidation level.

The failure of the 4'-*C*-trifluoromethyl nucleoside analogs to undergo clean reductions of the C5' methyl ester was unique to the 4'-*C*-trifluoromethyl substituent. Other 4'-*C*-alkyl groups such as the methyl and phenyl gave clean products under identical reducing conditions. It may be that the methodology is not amenable to strongly electron withdrawing alkyl groups, or perhaps such products are not stable. The successful preparation of the methyl and phenyl 4'-*C*-substituted nucleoside analogs demonstrates the generality of the methodology for the preparation of nucleosides substituted at the 4'-position with unfunctionalized alkyl groups.

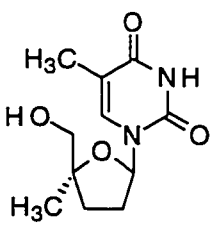
6.2. Anti-HIV Activity

To date the anti-HIV evaluation of only a single compound prepared in this body of work can be presented. The 4'-*C*-methyl analog (**65**) of the FDA approved, anti-HIV drug ddC (dideoxycytidine) was found to be moderately active against HIV-I by workers at the National Institute of Health. The 4'-*C*-methyl-ddC analog (**65**) displayed an EC_{50} value of 17.7 μM in T4 lymphocyte cells (CEM cell line) against HIV-I (Table 4), proving to be 27 times less effective than ddC at inhibiting HIV-I in identical cells. It should also be noted



65

4'-*C*-Methyl-ddC



51

4'-*C*-Methyl-ddT

Figure 12. Dideoxy-4'-*C*-methyl Nucleosides Screened Against HIV-I.

that a publication reporting the synthesis of 4'-*C*-methyl-ddT (**51**) appeared near the completion of the research reported here.[143] The authors describe 4'-*C*-methyl-ddT (**51**) to be inactive against HIV-I. From the biological data obtained with **65** and reported for **51**, it would appear that a 4'-*C*-methyl substituent does not result in an increase in anti-HIV activity.

Table 4. Anti-HIV-I Activity of 4'-C-Methyl-ddC (**65**).

Compound	EC_{50}	CC_{50}	Index	ref.
4'-*C*-Methyl-ddC (**65**)	17.7	>200	>11	this work
ddC	0.66	-	-	43
3TC	0.07	>100	>1428	24

(*a*) structures shown in Figure 3 or 12 (*b*) effective concentration (*c*) cytotoxic concentration (*d*) EC_{50} / CC_{50}.

Chapter 7

Experimental Section

7.1. General

7.1.1. General Techniques

All reactions requiring anhydrous solutions were carried out in flame or oven-dried glassware under a positive pressure of argon and in dry solvents. Air sensitive liquids were transferred via syringe or canuula. All reaction mixtures were stirred magnetically unless otherwise indicated.

7.1.2. Materials

Unless otherwise noted, commercial grade reagents and solvents were used without purification. Dry solvents were obtained by storing over or distilling from an appropriate desiccant:

Dimethylformamide (DMF), dichloromethane (CH_2Cl_2), triethylamine (Et_3N), acetonitrile (CH_3CN) and hexamethyldisilazane (HMDS) were distilled from calcium hydride (CaH_2). Pyridine and acetic anhydride were distilled from potassium hydroxide (KOH). Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl.

Enzymes were used as received and stored at -10 °C.

7.1.3. Chromatography

Thin layer chromatography (TLC) was performed on silica gel glass-backed plates containing a fluorescent indicator (0.25 mm, Whatman Silica Gel 60 A, KSF). The chromatograms were visualized by one or more of the following methods: (1) ultraviolet illumination (254 nm); (2) sprayed or dipped into a 10% solution of phosphomolybdic acid

(PMA) in ethanol followed by heating on a hot plate; (3) exposure to iodine vapor; (4) dipped in ceric sulfate dissolved in H_2SO_4 followed by heating on a hot plate; (5) dipped in K_2MnO_4 solution followed by heating under a heat gun. Column Chromatography was preformed under positive pressure (flash column chromatography) as described by Still[????] using chromatographic silica gel (170-400 mesh) purchased from Fisher Scientific.

7.1.4. Physical Data

Melting points (mp) were determined on a Thomas-Hoover melting point apparatus using open capillary tubes.

Optical rotations ($[\alpha]_D^{24}$) were measured on a Perkin-Elmer 241 MC polarimeter using spectrograde solvents. A one decimeter cell was used while maintaining the temperature with a constant temperature water bath (24 °C).

Infrared (IR) spectra were recorded on a Nicolet 20 DX Fourier Transform Spectrophotometer and are reported in wavenumbers (cm^{-1}).

Proton nuclear magnetic resonance spectra (^{1}H-NMR) were measured at 500 MHz on a Varian U-500 Fourier Transform Spectrometer in the indicated solvent. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS) using residual non-deuterated solvents as internal references. Multiplicity of signals are reported with the appropriate symbol as shown in Table 5. Coupling constants (J) are reported in hertz.

Carbon nuclear magnetic resonance spectra (^{13}C-NMR) were measured at 125 MHz

Table 5. Multiplicity / Symbol Table

multiplicity	symbol
singlet	s
doublet	d
triplet	t
quartet	q
multiplet	m
AB quartet	ABq
doublet of doublets	dd
doublet of triplet	dt

on a Varian U-500 Fourier Transform Spectrometer in the indicated solvents. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS) using residual non-deuterated solvents as internal references. Multiplicity of signals are reported with the appropriate symbol as shown in Table 5. Coupling constants (J) are reported in hertz.

Mass spectra were recorded on either a Kratos AEI-MS-902 or a Kratos MS50TC spectrometer at 20 or 70 ev for electronic ionization (EI) experiments. Isobutane was the reagent used for all chemical ionization (CI) experiments. Thioglycerol was used as matrix for all fast atom bombardment (FAB) experiments.

7.1.5. General Experimental Procedures

Procedure A: *N*-Gylcosylation Purine or Pyrimidine Bases with Methyl 1,2-*O*-Diacetyl-4-alkyl-3-deoxy-D*ribo*-furanuronate (**30**, alkyl = CH_3; **97** alkyl = Ph; **105**, alkyl = CF_3). A flame dried round-bottomed flask charged with a pyrimidine or purine base (3 equiv) was fitted with a flame dried reflux condenser, charged with freshly distilled HMDS (10 equiv) and one drop TMSCl. This slurry was heated at reflux for 1 h past homogeneity (2-16 h total). The heating bath was then removed and the flask quickly transferred to the rotary evaporator. The solvent was evaporated under reduced pressure and any residual solvent removed by vacuum drying of the residue. The vessel containing the silylated base was then flushed with argon, charged with ribose **30**, **97** or **105** (1 equiv) dissolved in CH_3CN (10 mL per mmol of **30**, **97** or **105**), and then charged with TMSOTf (2 equiv). The mixture was heated at 75 °C until TLC analysis showed no starting material remained (1-3 h). The heating bath was then removed and the reaction solution quenched by the addition of saturated aqueous $NaHCO_3$. The solvent was then evaporated under reduced pressure to give an oil, which was combined in a separatory funnel with EtOAc and H_2O. The aqueous layer was extracted and back extracted with

EtOAc (2x). The organic extracts were combined, dried over $MgSO_4$, and evaporated to give an oil which was then purified by column chromatography on silica gel.

Procedure B: Deprotection of 2'-*O*-Acetyl Nucleosides. A 2'-*O*-acetyl nucleoside (1 equiv) was dissolved in MeOH (10 ml per mmol of **30**) and treated with diisopropylethylamine (0.2 equiv). The solution was stirred at room temperature until TLC analysis showed no starting material remained (12-16 h). Evaporation of solvent under reduced pressure afforded a white foam which was submitted to column chromatography on silica gel.

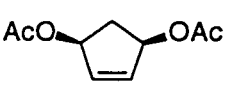
Procedure C: 2'-*O*-Phenoxythionocarbonylation of Nucleosides. The 3'-deoxynucleoside from Procedure B (1 equiv) dissolved in CH_3CN (10 mL per mmol substrate), was treated with DMAP (4 equiv) and cooled to 0 °C. The reaction solution was then charged with phenyl chlorothionoformate (1.15 equiv). When TLC analysis showed all starting material had been consumed (2-4 h) the solvent was evaporated by rotary evaporation and the remaining residue dissolved with ethyl acetate. This solution was then successively washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$, filtered, and evaporated to give the 2'-*O*-phenoxythiocarbonyl nucleoside as a yellow foam of sufficient purity to be used directly in the reduction step.

Procedure D: Reduction of 2'-*O*-Phenoxythionocarbonyl Nucleosides. Crude 2'-*O*-phenoxythiocarbonyl nucleoside (1 equiv) was dissolved in $PhCH_3$ (10 mL per mmol substrate) along with AIBN (0.2 equiv) and freshly distilled Bu_3SnH (1.2 equiv). This solution was degassed with oxygen free argon for 10 min before heating at 75 °C for 1 h. Solvent was then evaporated and the residue was dissolved in CH_3CN and extracted twice with pentane. The CH_3CN layer was then evaporated and the residue purified by column chromatography on silica gel.

Procedure E: Reduction of the 5'-*C*-Methyl Ester of Methyl uronates. A methyl uronate (1 equiv) was dissolved in 1 : 1 THF / absolute EtOH (10 mL per mmol substrate), and cooled to 0 °C by an ice bath. To this was slowly added $LiBH_4$ (1.0 M in THF, 2 equiv of BH_4). Upon completion as judged by TLC (2-4 h) saturated aqueous NH_4Cl was added and the mixture stirred for an additional 1 h at room temperature. Evaporation of solvent afforded a white residue which was dissolved in a minimal amount of H_2O and transferred to the body of a lighter than water continuous extraction apparatus whose pot was charged with EtOAc. After extracting for 12 h, the EtOAc solution was dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. The remaining residue was purified by column chromatography on silica gel.

7.2. Experimental Procedures of Chapter 3.

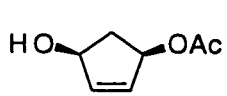
***Cis*-3,5-Diacetoxycyclopentene (8).**[76] A 2-L, 3 necked, round-bottomed flask was fitted with an overhead mechanical stirrer, a dry ice cold finger condenser, and a 250-mL addition funnel containing peracetic acid (170 mL of 35% aqueous solution, 0.808 mol) buffered with sodium acetate (8.0 g). The reaction vessel was charged with Na_2CO_3 (400 g) and stirred as a slurry in CH_2Cl_2 (600 mL). After cooling the reaction vessel to 0 °C, freshly cracked cyclopentadiene was added (69.0 g, 1.05 mol). (The cyclopentadiene was cracked by distillation from dicyclopentadiene through a short path condenser. The bath temperature was kept below 170 °C to avoid distillation of the dimmer. The monomer distilled at a head temperature of 48-51 °C, and was collected in a receiving flask cooled to -78 °C.) Immediately upon addition of the cyclopentadiene to the reaction slurry, the stopcock of the addition funnel was adjusted to allow a steady drip. An exothermic reaction and the evolution of CO_2 resulted. Upon completion of the addition (addition time 1 h) stirring was continued for 3 h, over which time the reaction slurry was allowed to slowly warm to room temperature. The slurry was then passed through a glass frit to filter solids The filtrate was dried over



$MgSO_4$ and filtered again. Taking care not to evaporate the volatile monoepoxide product, the solvent volume was gently reduced 50% by rotary evaporation. The solution was then cooled to 0 °C and deoxygenated by bubbling argon through it for 20 min.

A 3-L round-bottomed flask equipped with a magnetic stirrer was charged with dry THF (1 L) and freshly distilled acetic anhydride (92.0 mL, 0.975 mol). The reaction vessel was then placed under an argon atmosphere, cooled to 0 °C, and the solution deoxygenated by bubbling argon through it for 20 min. Taking care to minimize exposure of the solution to oxygen, tetrakis(triphenylphosphine)palladium(0) (1.51 g, 1.30 mmol) was quickly added. To this bright yellow solution, at a very slow dropwise rate, the monoepoxide solution was canulated over a period of 3 h. The reaction vessel was then allowed to warm to room temperature over night, after which it was opened to the atmosphere and 4-dimethylaminopyridine (500 mg, 4.09 mmol) was added followed by an additional 6 h of stirring. The reaction mixture was then concentrated under reduced pressure. The resulting oil was diluted with ethyl acetate (1.5 L) and washed successively with 1N HCl (700 mL), saturated aqueous $NaHCO_3$ (700 mL), and brine (700 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to give a pale yellow oil which purified by column chromatography on silica gel (15 x 40 cm column, 1 : 12 EtOAc / hex). Evaporation of the appropriate fractions afforded a yellow oil which was then vacuum distilled through a short path apparatus (91-94 °C at 1.5 mm Hg) to give **8** (117.6 g, 79%), as a slightly yellow oil: ^{1}H-NMR ($CDCl_3$) δ 5.99 (s, 2H), 5.44 (dd, 2H, J = 7.5, 4.0), 2.78 (Overlapping dt, 1H, J = 15.0, 7.5), 1.96 (s, 6H), 1.63 (dt, 1H, J = 15.0, 4.0); ^{13}C-NMR ($CDCl_3$) δ 170.48, 134.49, 76.49, 37.02, 20.98. These data are in agreement with literature values.[58]

(1*R*,4*S*)-(+)-4-Hydroxy-2-cyclopentenyl Acetate ((+)-7).[56]



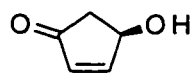
A 2-L, round-bottomed flask was charged with diacetate **8** (30.507g, 165 mmol), 1 L of phosphate buffer (1.0 M, pH 7.2) and type II, crude porcine pancreatic

lipase (purchased from Sigma, 9.0 g, 30 wt. %). (The phosphate buffer was made by dissolving $NaH_2PO_4 \cdot H_2O$ (10 g) and anhydrous Na_2HPO_4 (30 g) in 1 L distilled H_2O and adjusting the pH to 7.2 (as measured by a pH meter) by the addition of Na_2HPO_4.) This slurry was agitated mechanically for 24 h at room temperature, after which TLC showed no remaining diacetate **8**. The reaction was then saturated with sodium chloride and filtered by passing through a layer of sand / Celite, then diluted with an additional 1 L of H_2O. The aqueous filtrate was extracted with EtOAc (3 x 1 L). Organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crystalline residue was purified by flash column chromatography (1 : 2 going to 1 : 1 EtOAc / petroleum ether). Evaporation of the appropriate fractions gave (+)-**7** as a white crystalline solid (18.52 g, 79%): $[\alpha]_D^{24}$ +64.9 (c 1.070, $CHCl_3$). A single recrystallization from 1 : 1 Et_2O / pentane afforded white needles of (+)-**7** (15.987 g, 68%): mp 50-51 °C; $[\alpha]_D^{24}$ +73.6 (c 1.120, $CHCl_3$) [Lit.[58] $[\alpha]_D^{23}$ +73.8 (c 1.25, $CHCl_3$)]; ^{1}H-NMR ($CDCl_3$) δ 6.60 (m, 1H), 5.93 (m, 1H), 5.45 (m, 1H), 4.68 (m, 1H), 2.77 (overlapping dt, 1H, J = 14.5, 7.5), 2.46 (broad s, 1H), 2.01 (s, 3H), 1.61 (dt, 1H, J = 14.5, 4.0); ^{13}C-NMR ($CDCl_3$) δ 170.87, 138.56, 132.35, 77.08, 74.63, 40.42, 21.18. These data are in agreement with literature values.[58]

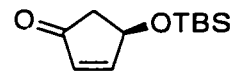
(4R)-(+)-Acetoxy-2-cyclopenten-1-one (6). To an oven dried, 2-L, round-bottomed flask was charged monoacetate (+)-**7** (15.32 g, 107.7 mmol), crushed 4 Å molecular sieves (50 g), and pyridinium dichromate (51.0 g, 135.5 mmol). This was stirred as a slurry in freshly opened CH_2Cl_2 (1 L) at room temperature for 14 h. Solids were filtered through a pad of Celite, and the filtrate concentrated under reduced pressure to give a brown sludge. This was poured into 2 : 3 EtOAc / petroleum ether (400 mL) to precipitate chromium salts, and passed through a plug of silica gel (4 cm in length, 8 cm width) which was then rinsed with 2 : 3 EtOAc / petroleum ether (600 mL). The colorless filtrate was successively washed with 1N HCl

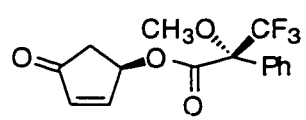
(500 mL), saturated aqueous $NaHCO_3$ (500 mL), and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to give **6** (14.56 g, 96%) as a low melting solid: mp 15 °C; $[\alpha]_D^{24}$ +99.5 (c 0.212, CH_3OH) [Lit.[82] $[\alpha]_D^{20}$ +96.1 (c 0.17, CH_3OH)]; ^{1}H-NMR ($CDCl_3$) δ 7.53 (dd, 1H, J = 5.5, 2.5), 6.28 (dd, 1H, J = 5.5, 1.0), 5.80 (m, 1H), 2.78 (dd, 1H, J = 18.5, 6.0), 2.28 (dd, 1H, J = 18.5, 2.0), 2.05 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 204.85, 170.37, 158.96, 136.94, 71.88, 40.95, 20.82; HRMS (EI) calcd. for $C_7H_8O_3$ 140.0473 (M^+), found 140.0473. These data are in agreement with literature values.[82]

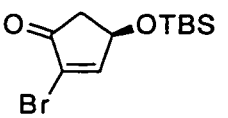
(4*R*)-(+)-Hydroxy-2-cyclopenten-1-one (16). To a 3-necked, 1-L, round-bottomed flask was charged acetoxyenone **6** (11.42 g, 81.50 mmol) which was dissolved in freshly opened 2-propanol (350 mL).



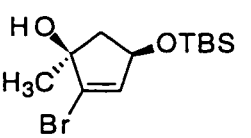
The vessel was fitted with a water cooled reflux condenser, and charged with $Ti(OiPr)_4$ (7.3 mL, 24.52 mmol). This was heated to reflux for 2 h then allowed to cool to approximately 45 °C, at which time H_2O (3.5 mL) was added followed by evaporation to dryness under reduced pressure. The resulting residue was suspended in EtOAc (400 mL), and filtered with the aid of sand / Celite. The filtrate was then dried over $MgSO_4$, filtered through a fresh layer of sand / Celite, and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography on silica gel (1 : 1 EtOAc / hex) to give **16** (7.25 g, 91%) as a colorless oil: $[\alpha]_D^{24}$ +99.1 (c 2.29, CH_3OH) [Lit.[87] $[\alpha]_D^{20}$ +78.1 (c 2.03, CH_3OH)]; ^{1}H-NMR ($CDCl_3$) δ 7.51 (dd, 1H, J = 5.5, 2.5), 6.09 (dd, 1H, J = 5.5, 1.0), 4.92 (m, 1H), 4.17 (broad s, 1H), 2.64 (dd, 1H, J = 18.5, 6.5), 2.15 (dd, 1H, J = 18.5, 2.5); ^{13}C-NMR ($CDCl_3$) δ 207.90, 164.60, 134.61, 70.04, 44.17; IR (neat) 3394, 3081, 2974, 2924, 2896, 2691, 1712, 1672, 1585, 1404, 1341, 1187, 1103, 1044, 946, 796, 658 cm^{-1}; HRMS (EI) calcd. for $C_5H_6O_2$ 98.0367 (M^+), found 98.0364. These data are in agreement with literature values.[87]

(4*R*)-(+)-*tert*-Butyldimethylsiloxy-2-cyclopenten-1-one (17).  Prepared from 4-hydroxyenone **16** (5.10 g, 51.99 mmol) according to the literature procedure[87] to give **17** (9.75 g, 88%) as a white crystalline solid: mp 27-28 °C [Lit.[87] mp 27-28 °C]; $[\alpha]_D^{24}$ +65.7 (c 1.32, CH_3OH) [Lit.[87] $[\alpha]_D^{20}$ +65.3 (c 0.40 CH_3OH)]; ^{1}H-NMR ($CDCl_3$) δ 7.45 (dd, 1H, J = 5.5, 2.0), 6.17 (dd, 1H, J = 5.5, 1.5), 4.98 (m, 1H), 2.70 (dd, 1H, J = 18.5, 6.0), 2.24 (dd, 1H, J = 18.0, 2.0), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 206.51, 163.85, 134.44, 70.86, 44.96, 25.73, 18.09, -4.71, -4.73; IR (neat) 2955, 2930, 2886, 2858, 1725, 1463, 1355, 1253, 1183, 1109, 1072, 900, 837, 778, 670 cm^{-1}; HRMS (EI) calcd. for $C_7H_8O_3$ 212.1232 (M^+), found 212.1230. These data are in agreement with literature values.[87]

(4*R*)-4-((*R*)-α-Methoxy-α-(trifluoromethyl)phenyl-acetoxy)-2-cyclopenten-1-one (18).  Prepared by dissolving hydroxyenone **16** (38 mg, 0.388 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (82 mg, 0.350 mmol), 1,3-dicyclohexylcarbodiimide (88 mg, 0.427 mmol), and 4-dimethylaminopyridine (5 mg, 0.040 mmol) with CH_2Cl_2 (4 mL). A white precipitate developed with in 20 min. After 2 h the reaction mixture was combined in a separatory funnel with EtOAc (50 mL). This was successively extracted with 1N HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was then dried over $MgSO_4$, filtered, and evaporated to afford a yellow oil. Column chromatography of this oil on silica gel (1 : 6 EtOAc / hex) gave **18** (92 mg, 76%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 7.60 (dd, 1H, J = 5.5, 2.0), 7.50-7.49 (m, 2H), 7.42-7.40 (m, 3H), 6.39 (dd, 1H, J = 5.5, 1.0), 6.07 (m, 1H), 3.54 (s, 3H), 2.87 (dd, 1H, J = 19.0, 7.0), 2.30 (dd, 1H, J = 18.5, 2.0).

(4*R*)-(+)-2-Bromo-4-*tert*-butyldimethylsiloxy-2-cyclopenten-1-one ((+)-13). 

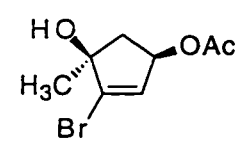
A 3-necked, 1-L, round-bottomed flask equipped with a pressure equalizing addition funnel was charged with enone **17** (9.93 g, 46.77 mmol) and CH_2Cl_2 (400 mL). The addition funnel was charged with a solution of bromine (6.39 g in 40 mL CH_2Cl_2). The reaction vessel was cooled to 0 °C and the bromine solution was added dropwise to the reaction solution until a yellow color persisted for 30 seconds between drops (approximately 24 mL of bromine solution added). At this point the reaction progress was carefully monitored by TLC every few drops until no starting material remained. Triethylamine was added (7.2 mL, 51.7 mmol) and the reaction solution was allowed to warm to room temperature with stirring over a 1 h period. The reaction solution volume was then reduced by 85%, diluted with pentane (500 mL) and extracted successively with 1 N HCl (250 mL), saturated aqueous $NaHCO_3$ (250 mL), and brine (250 mL). The organic layer was dried over $MgSO_4$, filtered, evaporated and the resulting oil submitted to flash chromatography (1 : 20 EtOAc / hex) to give (+)-**13** (12.891 g, 95%) as a low melting solid: mp 37-38 °C; $[\alpha]_D^{24}$ +30.4 (c 1.29, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.55 (d, 1H, J = 2.5), 4.93 (m, 1H), 2.87 (dd, 1H, J = 18.5, 6.0), 2.37 (dd, 1H, J = 18.5, 2.0), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 189.21, 161.17, 127.69, 69.515, 43.71, 25.68, 18.05, -4.73, -4.76; IR (neat) 2955, 2929, 2885, 2857, 1733, 1592, 1463, 1349, 1279, 1088, 922, 833, 779, 668 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{19}BrO_2Si$ 290.0338 (M^+), found 290.0342.

(1*S*,4*R*)-(+)-2-Bromo-4-*tert*-butyldimethylsiloxy-1-methyl-2-cyclopenten-1-ol (14a). 

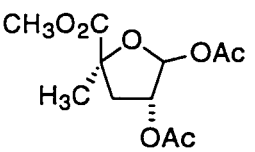
Enone (+)-**13** (12.366 g, 42.46 mmol) was charged to a oven dried 500-mL, round-bottomed flask. The vessel was charged next with Et_2O (125 mL) and THF (125 mL), and then placed in a 1% (vol / vol) MeOH / Et_2O bath cooled with liquid nitrogen to -100 °C. Using a syringe pump, methyllithium (1.6 M in Et_20, 27.0 mL, 43.2 mmol) was added over a 1 h period. Once the addition had been completed the bath was removed and the reaction

mixture was allowed to slowly warm to -60 °C (approximately 1h). Glacial acetic acid was added (3.0 mL, 51.6 mmol) and reaction mixture allowed to warm to room temperature with stirring. Next, the reaction mixture volume was reduced by 75% using rotary evaporation, then diluted with pentane (500 mL). Successive washing of this solution with 1 N HCl (400 mL), saturated aqueous $NaHCO_3$ (350 mL) and brine (350 mL) followed by drying of the organic layer over $MgSO_4$, filtration and concentration under reduced pressure gave a dark yellow oil. Purification by flash chromatography (1 : 15 EtOAc / hex) afforded **14a** (11.44 g, 88%) as a colorless oil: $[\alpha]_D^{24}$ +51.4 (c 1.035, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 5.94 (d, 1H, J = 2.0), 4.60 (m, 1H), 2.49 (dd, 1H, J = 13.5, 7.0), 2.18 (broad s, 1H), 1.95 (dd, 1H, J = 13.5, 4.0), 1.32 (s, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 134.82, 134.74, 80.98, 73.07, 49.49. 26.03, 25.80. 18.09. -4.69. -4.73; Ir (neat) 3417, 2955, 2929, 2894, 2858, 1620, 1472, 1463, 1361, 1298, 1257, 1172, 1088, 1045, 970, 903, 835, 777 cm^{-1}; HRMS (EI) calcd. for $C_{12}H_{23}BrO_2Si$ 306.0651 (M^+), calcd. for $C_8H_{14}BrO_2Si$ 248.9946 (M^+ - *t*Bu), found 248.9946.

(1*S*,4*R*)-(+)-4-Acetoxy-2-bromo-1-methyl-2-cyclopenten-1-ol (19). In a 500-mL, round-bottomed flask, **14a** (11.39 g, 37.08 mmol) was dissolved in THF (250 mL), and the solution was cooled to 0 °C by an ice bath. The slow addition of TBAF (1.0 M in THF, 41.0 mL, 41.0 mmol) by syringe resulted in the solution immediately turning dark green. Within 0.5 h of completing the addition, TLC analysis showed all starting material had been consumed. The reaction solution was brought to neutral pH by the dropwise addition of glacial acetic acid (2.5 mL). The solvent was then evaporated to give a viscous black oil, which was dissolved in CH_2Cl_2 (100 mL), cooled to 0 °C, and treated with 4-dimethylaminopyridine (255 mg, 1.84 mmol), triethylamine (6.2 mL, 44.5 mmol) and acetic anhydride (3.90 mL, 41.3 mmol). After 1.5 h, MeOH (5 mL) was added and reaction solution allowed to warm

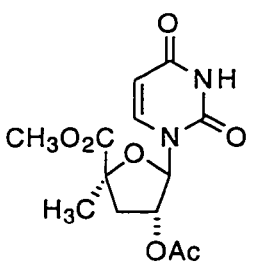


to room temperature. The reaction solvent volume was then reduced by 75% and diluted with EtOAc (500 mL). Successive washing of this solution with 1 N HCl (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL); followed by drying of the organic layer over $MgSO_4$, filtration, and evaporation afforded a black oil. The oil was then purified by column chromatography on silica gel (1 : 4 EtOAc / hex) to give **19** (7.84 g, 90%) as a white crystalline solid: mp 50-51 °C; $[\alpha]_D^{24}$ +114.3 (c 1.370, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 6.03 (d, 1H, J = 2.5), 5.41 (m, 1H), 2.63 (dd, 1H, J = 14.0, 7.0), 2.22 (broad s, 1H), 2.09 (dd, 1H, J = 14.5, 3.5), 2.04 (s, 3H), 1.38 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.70, 137.71, 130.43, 81.02, 74.94, 45.15, 26.72, 21.09; Ir (KBr) 3251 (broad), 3093, 2981, 2933, 2864, 2799, 1732, 1693, 1620, 1449, 1483, 1371, 1349, 1300, 1244, 1196, 1169, 1113, 1033, 967, 882; HRMS (EI) calcd. for $C_8H_{11}BrO_3$ 233.9892 (M^+), calcd. for $C_8H_{10}BrO_2$ 216.9864 (M^+ - OH), found 216.9868.

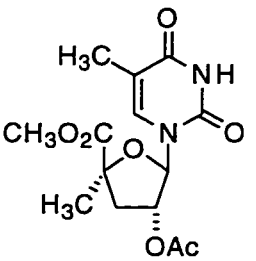


Methyl 1,2-*O*-Diacetyl-3-deoxy-4-methyl-D-ribofurano-uronate (30). Cyclopentene **19** (6.89 g, 29.3 mmol) was dissolved with MeOH (250 mL) in a 500-mL, round-bottomed flask equipped with a gas sparge inlet. Pyridine (12.5 mL) was added, and the flask cooled to -78 °C. A 1.0 L / min. flow rate of ozone was initiated through the gas sparge. After 2 h the ozone flow was ceased and the flask flushed with argon for 15 min. Dimethyl sulfide (7.0 mL) was added, rapidly changing the reaction mixture from a heterogeneous yellow-green to colorless solution. The reaction vessel was then allowed to warm to room temperature with stirring over a 2 h period. Evaporation of the solvent left a yellow oil that was diluted with EtOAc (400 mL), then extracted with 1N HCl (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a viscous syrup. This syrup was diluted with acetic anhydride (30 mL) and stirred as a slurry with sodium acetate (10 g). The solution was heated to 75 °C for 9 h, then codistilled twice with xylenes under reduced pressure. The

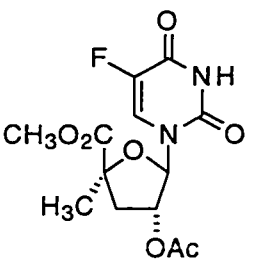
residue that remained was partitioned between EtOAc (300 mL) and H_2O (200 mL). The aqueous phase was extracted and back extracted with additional EtOAc (2 x 100 mL). Organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated to give a yellow oil. Purification of the oil by column chromatography on silica gel (1 : 3 EtOAc / hex) gave **30** (5.09 g, 67%) as a colorless oil consisting of an inseparable mixture of anomers in a ration of 8 : 92 (α : β) as determined by integration of the anomeric proton peaks in the ^{1}H-NMR spectra. The spectral data of the major β anomer follows: ^{1}H-NMR ($CDCl_3$) δ 6.17 (s, 1H), 5.14 (dd, 1H, J = 6.0, 1.0), 3.17 (s, 3H), 2.85 (dd, 1H, J = 15.5, 6.5), 2.06 (s, 3H), 2.00 (d, 1H, J = 14.5), 1.99 (s, 3H), 1.56 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.13, 169.87, 169.15, 99.86, 85.40, 77.06, 52.63, 39.28, 25.80, 20.87, 20.84; IR (neat) 3340, 3111, 3074, 2970, 2933, 2871, 1593, 1565, 1493, 1440, 1417, 1400, 1338, 1207, 1126, 1084, 935, 809, 787, 636 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{16}O_7$ 260.0895 (M^+), calcd. for $C_9H_{13}O_5$ 201.0762 (M^+ - OAc), found 201.0757.



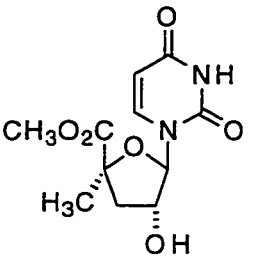
Methyl 2-*O*-Acetyl-1,3-dideoxy-1-(2,4-dioxypyrimidin-1-yl)-4-*C*-methyl- β-D-ribofuranuronate (37) was prepared from **30** (1.09 g, 4.20 mmol) and uracil (1.54 g, 13.73 mmol) as described in procedure A. Column chromatography on silica gel (1 : 2 EtOAc / CH_2Cl_2) afforded **37** (1.17 g, 85%) as a white foam: $[\alpha]_D^{24}$ +25.4 (c 1.17, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.42 (s, 1H), 7.87 (d, 1H, J = 8.0), 6.09 (d, 1H, J = 4.5), 5.78 (dd, 1H, J = 8.0, 2.0), 5.33 (m, 1H), 3.79 (s, 3H), 2.80 (dd, 1H, J = 14.0, 7.5), 2.17 (dd, 1H, J = 14.0, 6.5), 2.08 (s, 3H), 1.62 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.63, 170.13, 163.23, 150.60, 140.41, 103.07, 89.55, 84.20, 75.74, 53.04, 40,04, 40.76, 25.27. 20.76; IR (KBr) 3198, 3064, 3006, 2956. 2830, 1744, 1693, 1631, 1457, 1379, 1270, 1234, 1106, 1058, 921, 814, 731, cm^{-1}; HRMS (EI) calcd. for $C_{13}H_{16}N_2O_7$ 312.0957 (M^+), calcd. for $C_{11}H_{12}N_2O_5$ 252.0.746 (M^+-HOAc), found 252.0740.



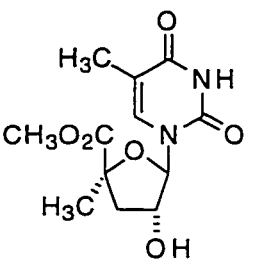
Methyl 2-*O*-Acetyl-1,3-dideoxy-1-(2,4-dioxy-5-methyl-pyrimidin-1-yl)-4-*C*-methyl-βD-ribofuranuronate (38) was prepared from **30** (711 mg, 2.73 mmol) and thymine (1.02 g, 8.07 mmol) as described in procedure A. Chromatography on silica gel (2 : 3 EtOAc / CH_2Cl_2) gave **38** (780 mg, 88%) as an amorphous white foam: $[\alpha]_D^{24}$ +8.25 (c 1.37, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.65 (s, 1H), 7.61 (d, 1H, J = 1.0), 6.08 (d, 1H, J = 5.0), 5.32 (m, 1H), 3.78 (s, 3H), 2.84 (dd, 1H, J = 13.5, 7.0), 2.13 (dd, 1H, J = 13.5, 7.0), 2.06 (s, 3H), 1.91 (d, 3H, J = 1.0), 1.59 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.60, 170.21, 163.97, 150.83, 136.17, 111.53, 89.37, 84.01, 75.61, 52.95, 40.80, 25.37, 20.78, 12.70; IR (neat) 3426, 3176, 3067, 3028, 2998, 2944, 2825, 1749, 1681, 1473, 1461, 1427, 1259, 1263, 1152, 1093 cm^{-1}; HRMS (EI) calcd. for $C_{14}H_{18}N_2O_7$ 326.1113 (M^+), calcd. for $C_{12}H_{14}N_2O_5$ 266.0902 (M^+-HOAc), found 266.0899.



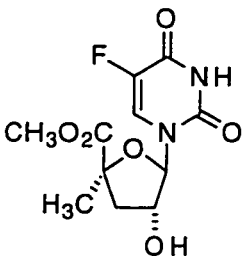
Methyl 2-*O*-Acetyl-1,3-dideoxy-1β-(-2,4-dioxy-5-fluoro-pyrimidin-1-yl)- 4-methyl-D-ribofuranuronate (39) was prepared from **30** (744 mg, 2.86 mmol) and 5-fluorouracil (1.05 g, 8.05 mmol) as described in procedure A. Column chromatography on silica gel (1 : 2 EtOAc / CH_2Cl_2) gave **39** (798 mg, 86%) as an amorphous white foam: $[\alpha]_D^{24}$ +35.6 (c 1.025, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.43 (s, 1H), 8.18 (d, 1H, J = 6.0), 6.11 (d, 1H, J = 5.5), 5.31 (m, 1H), 3.82 (s, 3H), 2.75 (dd, 1H, J = 14.0, 7.0), 2.20 (dd, 1H, J = 14.0, 8.0), 2.09 (s, 3H), 1.63 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.65, 170.15, 156.74 (d, J = 26.8), 149.32, 140.77 (d, J = 236.4), 124.54 (d, J = 35.1), 89.15, 84.02, 75.28, 53.15, 40.70. 25.09, 20.70; IR (neat) 3317, 3126, 3058, 2968, 2910, 2843, 1715, 1654, 1610, 1593, 1462, 1450, 1341, 1265, 1037, 817 cm^{-1}; HRMS (EI) calcd. for $C_{13}H_{15}N_2O_7F$ 330.0863 (M^+), found 330.0872.



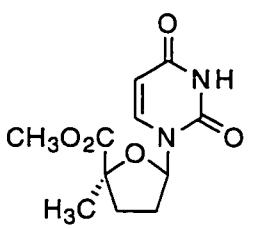
Methyl 1,3-Dideoxy-1-(2,4-dioxypyrimidin-1-yl)-4-*C*-methyl-β-D-ribofuranuronate (41) this was prepared from **37** (977 mg, 3.13 mmol) as described in procedure B. Chromatography on silica gel (2 : 1 EtOAc / CH_2Cl_2) gave **41** (839 mg, 98%) as an amorphous white foam: $[\alpha]_D^{24}$ +0.98 (c 1.020, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 11.13 (s, 1H), 8.16 (d, 1H, J = 8.0), 5.92 (d, 1H, J = 4.0), 5.64 (dd, 1H, J = 8.0, 1.5), 5.32 (s, 1H), 4.60 (m, 1H), 3.80 (s, 3H), 2.57 (dd, 1H, J = 13.5, 7.0), 2.22 (dd, 1H, J = 13.5, 6.5), 1.68 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.44, 163.58, 152.22, 140,82, 120.27, 92.77, 85.21, 75.61, 52.85, 41.40, 25.34; IR (neat) 3410, 3203, 3098, 3060, 2956, 1739, 1698, 1460, 1385, 1288, 1271, 1201, 1172, 1141, 1101, 1050, 815, 762, 577 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{14}N_2O_6$ 270.0851 (M^+), found 270.0853.



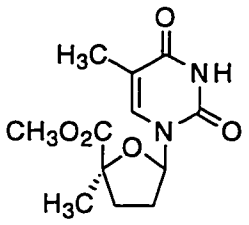
Methyl 1,3-Dideoxy-1-(2,4-dioxy-5-methylpyrimidine-1-yl)-4-*C*-methyl-β-D-ribofuranuronate (42) was prepared from **38** (745 mg, 2.28 mmol) as described in procedure B. Column chromatography on silica gel (1 : 1 EtOAc / CH_2Cl_2) gave **42** (610 mg, 94%) as a white solid: mp 126-128 °C; $[\alpha]_D^{24}$ -27.1 (c 1.60, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 11.23 (s, 1H), 8.00 (d, 1H, J = 1.0), 5.92 (d, 1H, J = 4.0), 5.15 (m, 1H), 3.81 (s, 3H), 2.66 (dd, 1H, J = 13.5, 6.5), 2.22 (dd, 1H, J = 13.5, 6.0), 1.82 (s, 3H), 1.69 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.47, 164.00, 152.18, 136.56, 110.22, 92.72, 85.14, 75.42, 52.73, 41.41, 25.50, 12.67; IR (neat) 3404, 3181, 3067, 3039, 3001, 2956, 2813, 1742, 1697, 1470, 1461, 1435, 1289, 1270, 1212, 1141, 1103 cm^{-1}; HRMS (EI) calcd. for $C_{12}H_{16}N_2O_6$ 284.1008 (M^+), found 284.1012.



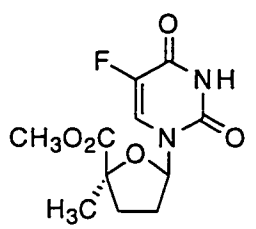
Methyl 1,3-Dideoxy-1β-(2,4-dioxy-5-fluoropyrimidin-1-yl)-4-methyl-β-D-ribofuranuronate (43) was prepared from **39** (708 mg, 2.14 mmol) as described in procedure B. Column chromatography on silica gel (1 : 1 EtOAc / CH_2Cl_2) gave **43** (508 mg, 82%) as an amorphous white foam: $[\alpha]_D^{24}$ -7.05 (c 1.05, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 11.35 (s, 1H), 8.45 (d, 1H, J = 6.0), 5.90 (s, 1H), 5.10 (s, 1H), 4.60 (s, 1H), 3.82 (s, 3H), 2.58 (dd, 1H, J = 13.5, 6.5), 2.22 (dd, 1H, J = 13.5, 6.5), 2.16 (s, 1H), 1.68 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.27, 157.14 (d, J = 25.9), 150.65, 140.27 (d, J = 237.3) 125.76 (d, J = 35.00), 92.89, 85.48, 75.52, 52.99, 41.46, 25.19; IR (neat) 3321, 3108, 3066, 3037, 2960, 2927, 2851, 1721, 1663, 1602, 1580, 1471, 1455, 1346, 1262, 1211, 1094, 820 cm^{-1}; FAB MS calcd. for $C_{11}H_{13}N_2O_6F$ (M^+), found (M^+ + H) 289 (34%).



Methyl 1-(2,4-Dioxypyrimidin-1-yl)-4-*C*-methyl-1,2,3-trideoxy-β-D-ribofuranuronate (44) was prepared from **41** (538 mg, 1.99 mmol) as described in procedure C and then subjected to reduction without further purification as described in procedure D. Chromatography on silica gel (1 : 2 EtOAc / CH_2Cl_2) gave **44** (382 mg, 75%) as a crispy white foam: mp 105-106 °C; $[\alpha]_D^{24}$ +35.2 (c 1.23, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.23 (d, 1H, J = 3.0), 6.17 (t, 1H, J = 6.0), 5.71 (d, 1H, J = 8.0) 3.77 (s, 3H), 2.51-2.39 (m, 2H), 2.13-2.00 (m, 2H), 1.52 (s, 3H); ^{13}C-NMR (CD_3OD) δ 174.72, 164.89, 150.81, 141.30, 100.86, 86.99, 84.74, 51.74, 35.22, 31.15, 23.41; IR (KBr) 3194, 3108, 3093, 3058, 3005, 2952, 2878, 2804, 1736, 1672, 1631, 1454, 1396, 1274, 1199, 1117, 856 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{14}N_2O_5$ 254.0902 (M^+), found 254.0897.

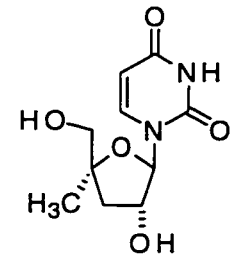


Methyl 1-(2,4-Dioxy-5-methylpyrimidin-1-yl)-4-*C*-methyl-1,2,3-trideoxy-β-D-ribofuranuronate (45) was prepared from **42** (505 mg, 1.78 mmol) as described in procedure C and then subjected to reduction without further purification as described in procedure D. Column chromatography on silica gel (1 : 2 EtOAc / CH_2Cl_2) gave **45** (361 mg, 76%) as a white solid: mp 112-114 °C; $[\alpha]_D^{24}$ +31.7 (c 1.22, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.44 (s, 1H), 7.96 (s, 1H), 6.23 (dd, 1H, J = 5.5, 2.0), 3.79 (s, 3H), 2.46-2.38 (m, 1H), 2.06-1.92 (m, 1H), 1.94 (s, 3H), 1.54 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.66, 164.07, 150.72, 136.15, 110.83, 86.37, 84.27, 52.72, 36.14, 31.82, 24.68, 12.76; IR (neat) 3176, 3038, 2982, 2956, 2934, 2893, 2831, 1739, 1698, 1469, 1454, 1295, 1276, 1196, 1168, 1119, 1103, 1054 cm^{-1}; HRMS (EI) calcd. for $C_{12}H_{16}N_2O_5$ 268.1059105 (M^+), found 268.1063.

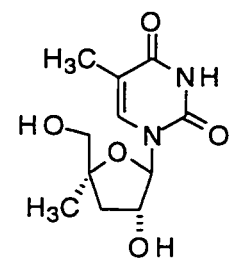


Methyl 1-(2,4-Dioxy-5-fluoro-pyrimidin-1-yl)-1,2,3-trideoxy-4-methyl-β-D-ribofuranuronate (46) was prepared from **43** (276 mg, 0.958 mmol) as described in procedure C and then subjected to reduction without further purification as described in procedure D. Chromatography on silica gel (1 : 3 EtOAc / CH_2Cl_2) gave **46** (178 mg, 68%) as a white solid: mp 142-144 °C; $[\alpha]_D^{24}$ +49.3 (c 0.990, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 10.04 (s, 1H), 8.43 (d, 1H, J = 6.5), 6.18 (t, 1H, J = 6.0), 3.79 (s, 3H), 2.50 (m, 1H), 2.36 (m, 1H), 2.04 (m, 1H),1.95 (m, 1H), 1.54 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.66, 157.20 (d, J = 26.8), 149.38, 140.52 (d, J = 231.5), 124.91 (d, J = 35.0), 87.04, 84.71, 52.86, 36.09, 31.96, 24.43; IR (KBr) 3176, 3051, 2960, 2850, 1718, 1679, 1482, 1411, 1358, 1269, 1209, 1103, 1061, 882 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{13}N_2O_5F$ 272.0808 (M^+), found 272.0814.

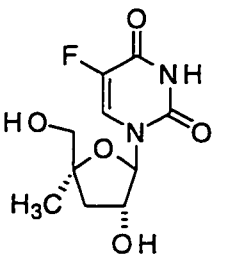
3'-Deoxy-4'-*C*-methyluridine (47) was prepared from **41** (110 mg, 0.410 mmol) as described in procedure E. Column chromatography on silica gel (1 : 10 MeOH / CH_2Cl_2) gave **47** (79 mg, 80%) as a colorless glass: $[\alpha]_D^{24}$ -20.5 (c 1.02, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.05 (d, 1H, J = 8.0), 5.87 (d, 1H, J = 5.0), 5.68 (d, 1H, J = 8.0), 4.43 (dd, 1H, J = 12.0, 6.5), 3.53 (ABq, 1H, J = 12.0), 3.46 (ABq, 1H, J = 12.0), 2.45 (dd, 1H, J = 13.0, 7.5), 1.80 (dd, 1H, J = 13.0, 6.0), 1.32 (s, 3H); ^{13}C-NMR (CD_3OD) δ 164.83, 151.20, 141,62, 101.13, 90.96, 85.21, 75.33, 67.62, 39.61, 23.59; IR (KBr) 3488, 3245, 3096, 3055, 2977, 2935, 2877, 2822, 1695, 1467, 1388, 1266, 1151, 1102, 1077, 1048, 870, 820, 774, 578 cm^{-1}; HRMS (EI) calcd. for $C_{10}H_{14}N_2O_5$ 242.0902 (M^+), calcd. for $C_{10}H_{12}N_2O_4$ 224.0787 (M^+-H_2O), found 224.0802.



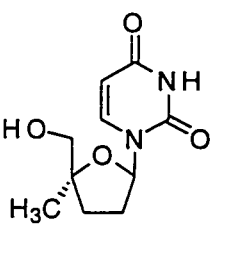
3'-Deoxy-4'-*C*-methyl-5-methyluridine (48) This was prepared from **42** (90 mg, 0.316 mmol) as described in procedure E. Column chromatography on silica gel (1 : 15 MeOH / CH_2Cl_2) gave **48** (69 mg, 85%) as a crispy white foam: $[\alpha]_D^{24}$ -30.8 (c 1.11, CH_3OH); ^{1}H-NMR (CD_3OD) δ 7.88 (d, 1H , J = 1.0), 5.87 (d, 1H, J = 5.0), 4.43 (m, 1H), 3.55 (ABq, 1H, J = 12.0), 3.45 (ABq, 1H, J = 11.5), 2.47 (dd, 1H, J = 13.0, 8.0), 1.87 (s, 3H), 1.80 (dd, 1H, J = 13.0, 6.5), 1.31 (s, 3H); ^{13}C-NMR (CD_3OD) δ 165.04, 151.39, 137.35, 109.98, 90.59, 84.80, 75.05, 67,65, 39.63, 23.64, 11.03; IR (KBr) 3407, 3196, 3055, 2963, 2928, 2830, 1689, 1470, 1372, 1259, 1104, 1076, 794, 752 cm^{-1}; FAB MS calcd. for $C_{11}H_{16}N_2O_5$ 256.1059 (M^+), found (M^+ + H) 257 (77%).



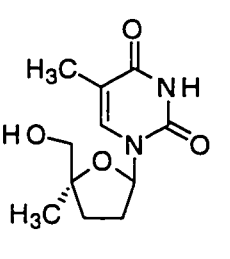
3'-Deoxy-5-fluoro-4'-*C*-methyluridine (49) was prepared from **43** (150 mg, 0.520 mmol) as described in procedure E. Column chromatography on silica gel (1 : 25 MeOH / CH_2Cl_2) gave **49** (103 mg, 76%) as a white solid: mp 206-208 °C; $[\alpha]_D^{24}$ +11.8 (c 1.180, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.38 (d, 1H, J = 7.0), 5.87 (d, 1H, J = 3.5), 4.41 (m, 1H,), 3.57 (ABq, 1H, J = 12.0), 3.47 (ABq, 1H, J = 12.0), 2.45 (dd, 1H, J = 13.0, 7.0), 1.80 (dd, 1H, J = 13.0, 6.0), 1.13 (s, 3H); ^{13}C-NMR (CD_3OD) δ 158.12 (d, J = 25.88), 149.81, 140.35 (d, J = 230.88), 125.31 (d, J = 34.13), 91.05, 85.68, 75,62, 67.43, 39.26, 23.66; IR (KBr) 3423, 3197, 3051, 2977, 2936, 2828, 1710, 1662, 1476, 1400, 1251, 1200, 1090, 1050, 802, 750 cm^{-1}; HRMS (EI) calcd. for $C_{10}H_{13}N_2O_5F$ 260.0808 (M^+), found 260.0814.



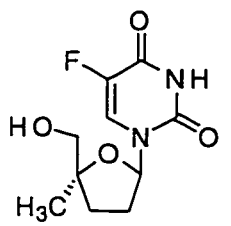
2',3'-Dideoxy-4'-*C*-methyluradine (50) was prepared from **44** (151 mg, 0.594 mmol) as described in procedure E. Chromatography on silica gel (1 : 20 MeOH / CH_2Cl_2) gave **50** (117 mg, 87%) as a crystaline white solid: mp 108-111 °C; $[\alpha]_D^{24}$ +31.8 (c 1.18, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.12 (d, 1H, J = 8.0), 6.09 (dd, 1H, J = 6.0, 4.5), 5.66 (d, 1H, J = 8.5), 3.64 (ABq, 1H, J = 11.5), 3.53 (ABq, 1H, J = 11.5), 2.51 (m, 1H), 2.18 (m, 1H), 2.08 (m, 1H), 1.75 (m, 1H), 1.21 (s, 3H); ^{13}C-NMR (CD_3OD) δ 164.98, 150.87, 141.42, 100.62, 86.28, 85.70, 66.92, 31.94, 30.56, 22.33; IR (KBr) 3506, 3113, 3088, 2998, 2968, 2931, 2871, 2803, 1698, 1472, 1388, 1179, 1069, 844 cm^{-1}; HRMS (EI) calcd. for $C_{10}H_{14}N_2O_4$ 226.0953 (M^+), found 226.0951.



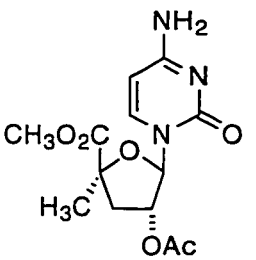
2',3'-Dideoxy-4'-*C*-methylthymidine (51) was prepared from **45** (156 mg, 0.581 mmol) as described in procedure E. Column chromatography on silica gel (1 : 25 MeOH / CH_2Cl_2) gave **51** (115 mg, 82%) as a white solid: mp 115-117 °C; $[\alpha]_D^{24}$ +24.5 (c 1.170, CH_3OH); ^{1}H-NMR (CD_3OD) δ 7.97 (d, 1H, J = 1.0), 6.11 (dd, 1H, J = 6.5, 5.0), 3.65



(ABq, 1H, J = 11.5), 3.54 (ABq, 1H, J = 11.5), 2.48 (m, 1H), 2.21 (m, 1H), 2.07 (m, 1H), 1.87 (d, 3H, J = 1.0), 1.75 (m, 1H), 1.20 (s, 3H); ^{13}C-NMR (CD_3OD) δ 165.13, 151,01, 137.17, 109.53, 85.89, 85.29, 66.92, 31.82, 30.57, 22.39, 11.06; IR (KBr) 3373, 3195, 3095, 3047, 2993, 2958, 2923, 2869, 1704, 1691, 1652, 1464, 1408, 1279, 1261, 1139, 1077, 1055, 1006, 926, 861, 837 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{16}N_2O_4$ 240.1109 (M^+), found 240.1099.

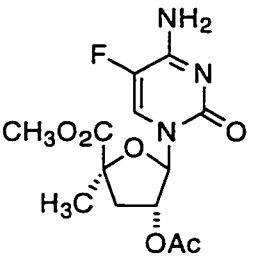


2',3'-Dideoxy-5-fluoro-4'-*C*-methyluridine (52) was prepared form **46** (115 mg, 0.422 mmol) as described in procedure E. Column chromatography on silica gel (1 : 1 EtOAc / CH_2Cl_2) gave **52** (83 mg, 81%) as a white solid: mp 151-153 °C; $[\alpha]_D^{24}$ +34.9 (c 0.960, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.46 (d, 1H, J = 6.5), 6.07 (s, 1H), 3.67 (ABq, 1H, J = 11.5), 3.55 (ABq, 1H, J = 11.5), 2.52 (m, 1H), 2.21 (m, 1H), 2.09 (m, 1H), 1.73 (m, 1H), 1.19 (s, 3H); ^{13}C-NMR (CD_3OD) δ 158.32, 149.41, 140.15 (d, J = 229.8), 125.36 (d, J = 34.4), 86.64, 85.89, 66.63, 32.06, 30.05, 22.35; IR (KBr) 3518, 3448, 3161, 3047, 3000, 2910, 2835, 1724, 1652, 1475, 1410, 1270, 1233, 1188, 1141, 1095, 1075, 869, 833 cm^{-1}; HRMS (EI) calcd. for $C_{10}H_{13}N_2O_4F$ 244.0859 (M^+), found 244.0862.

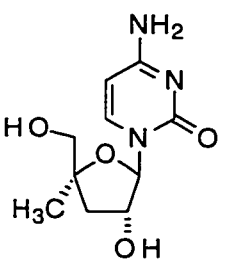


Methyl 2-*O*-Acetyl-1-(4-amino-2-oxypyrimidine-1-yl)-1,3-dideoxy-4-methyl-β-D-ribofuranuronate (53) was prepared form **30** (1.27 g, 4.87 mmol) and cytosine (1.60 g, 114.4 mmol) as described in procedure A. Column chromatography on silica gel (1 : 30 MeOH / CH_2Cl_2) gave **53** (1.19 g, 79%) as a amorphous white foam: $[\alpha]_D^{24}$ +31.5 (c 1.110, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.06 (d, 1H, J = 7.5), 5.99 (d, 1H, J = 3.0), 5.45 (m, 1H), 3.78 (s, 3H), 2.89 (dd, 1H, J = 14.0, 7.5), 2.39 (dd, 1H, J = 14.0, 4.5), 2.08 (s, 3H) 1.61 (s, 3H); ^{13}C-NMR (CD_3OD) δ

173.94, 170.35, 164.67, 154.78, 143.25, 94.79, 92.69, 85.65, 77.04, 51.91, 40.04, 24.60, 19.34; IR (KBr) 3552, 3351, 3217, 3092, 2997, 2958, 2850, 1743, 1654, 1613, 1527, 1496, 1459, 1441, 1378, 1287, 1249, 1168, 1135, 1110, 1031, 787, 639 cm^{-1}; FAB MS calcd. for $C_{13}H_{17}N_3O_6$ 311.1117 (M^+), found (M^+ + H) 312 (54%).

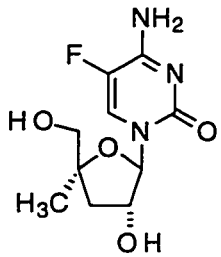


Methyl 2-*O*-Acetyl-1β-(4-amino-5-fluoro-2-oxypyrimidin-1-yl)-1,3-dideoxy-4-methyl-D-ribofuran-ouronate (54) was prepared from **30** (945 mg, 3.63 mmol) and 5-fluorocytosine (951 mg, 7.37 mmol) as described in procedure A. Chromatography on silica gel (1 : 25 MeOH / CH_2Cl_2) gave **54** (1.13 g, 94%) as an amorphous white foam: $[\alpha]_D^{24}$ +77.1 (c 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.20 (d, 1H, J = 6.0), 6.30 (broad s, 1H), 6.08 (d, 1H, J = 2.5), 5.33 (m, 1H), 3.80 (s, 3H), 2.64 (dd, 1H, J = 14.5, 5.0), 2.18 (dd, 1H, J = 14.5, 5.0), 2.08 (s, 3H), 1.62 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.81, 169.96, 157.66 (d, J = 14.75), 153.40, 136.63 (d, J = 241.00), 126.04 (d, J = 32.25), 90.93, 85.06, 76.71, 53.02, 40.45, 25.27, 20.88; IR (KBr) 3332, 3187, 3149, 3076, 2999, 2957, 2245, 1743, 1689, 1646, 1614, 1512, 1457, 1438, 1376, 1346, 1323, 1290, 1238, 1173, 1134, 1105, 1052, 1031, 915, 777, 733, 638; FAB MS for $C_{13}H_{16}FN_3O_6$ (M^+) 329.1023, found (M^++ H) 330 (17%).

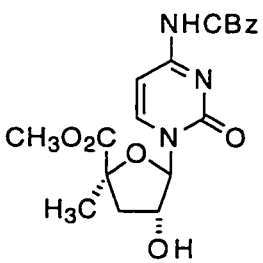


3'-Deoxy-4'-*C*-methylcytidine (55) was prepared from **53** (107 mg, 0.343 mmol) as described in procedure E. Chromatography on silica gel (1 : 5 MeOH / CH_2Cl_2) gave **55** (70 mg, 84%) as a white solid: mp 113-117 °C; $[\alpha]_D^{24}$ +2.06 (c 0.970, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.20 (d, 1H, J = 7.5), 6.02 (d, 1H, J = 6.5), 5.94 (s, 1H), 4.42 (m, 1H), 3.57 (ABq, 1H, J = 11.5), 3.48 (ABq, 1H, J = 12.0), 2.45 (dd, 1H, J = 13.0, 7.5), 1.82 (dd, 1H, J = 13.0, 5.5), 1.34 (s, 3H); ^{13}C-NMR (CD_3OD) δ 165.79, 155.78, 142.37, 94.38, 91.61, 84.98, 75.49, 67.82, 40.64, 25.27; IR (KBr)

3366, 3189, 2971, 2929, 1650, 1602, 1529, 1494, 1410, 1297, 1099, 1073, 1047, 1026, 789, 608 cm^{-1}; FAB MS calcd. for $C_{10}H_{15}N_3O_4$ (M^+), found (M^+ + H) 242 (36%).

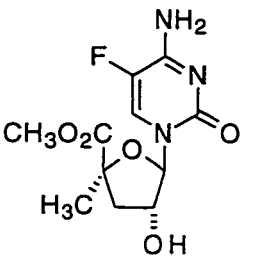


3'-Deoxy-5-fluoro-4'-*C*-methylcytidine (56) was prepared from **54** (54 mg, 0.188 mmol) as described in procedure E. Chromatography on silica gel (1 : 5 MeOH / CH_2Cl_2) gave **56** (41 mg, 84%) as a white solid: mp 206-208 °C; $[\alpha]_D^{24}$ +14.3 (c 1.58, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.37 (d, 1H, J = 7.0), 5.83 (dd, 1H, J = 3.5, 2.0), 4.38 (m, 1H), 3.60 (ABq, 1H, J = 12.0), 3.48 (ABq, 1H, J = 12.0), 2.42 (dd, 1H, J = 13.0, 7.5), 1.77 (dd, 1H, J = 13.0, 5.0), 1,33 (s, 3H); ^{13}C-NMR (CD_3OD) δ 158.11 (d, J = 26.75), 155.58, 136.95 (d, J = 240.12), 126.01 (d, J = 32.38), 92.90, 86.50, 76.69, 67.16, 38.68, 23.60; FAB MS calcd. for $C_{10}H_{14}FN_3O_4$ (M^+) 259.0968, found (M^+ + H) 260 (12%).

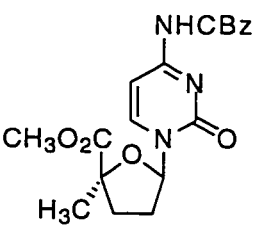


Methyl 1-(4-Benzyloxycarbonylamino-2-oxypyrim-idin-1-yl)-1,3-dideoxy-4-methyl-β-D-ribofuranuronate (60). A 100-mL, round-bottomed flask containing **53** (779 mg, 2.50 mmol) was charged with CH_2Cl_2 (20 mL), dry pyridine (1.60 mL, 19.78 mmol), and benzyl chloroformate (0.71 mL, 5.00 mmol). This solution was stirred for 4 h, after which it was combined with EtOAc (100 mL) in a separatory funnel and extracted with 1N HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and condensed to a viscous yellow oil. The oil was then diluted with MeOH (10 mL), and diisopropylethylamine (0.1 mL, .574 mmol) was added to the solution. After 12 h the sovent was evaporated to give a viscous yellow syrup. Column chromatography of the syrup on silica gel (1 : 1 EtOAc / CH_2Cl_2) gave **60** (743 mg, 74% for two steps) as an amorphous white foam: $[\alpha]_D^{24}$ -7.2 (c 1.23, $CDCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.52 (d, 1H, J = 7.0), 8.05 (broad s, 1H), 7.38-7.33 (m, 5H), 7.31 (d, 1H, J = 7.5), 5.71 (d, 1H, J =

4.5), 5.21 (s, 2H), 5.19 (broad s, 1H), 4.34 (m, 1H), 3.73 (s, 3H), 2.67 (dd, 1H, J = 13.5, 7.0), 2.20 (dd, 1H, J = 13.5, 8.5), 1.69 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.94, 162.70, 156.34, 152.44, 145.10, 135.01, 128.65, 128.62, 128.33, 96.13, 94.72, 86.19, 77.08, 67.96, 52.79, 43.23, 24.99; IR (KBr) 3292, 3140, 3088, 3034, 2954, 1744, 1657, 1622, 1557, 1499, 1383, 1322, 1271, 1199, 1140, 1098, 996 cm^{-1}; FAB MS calcd. for $C_{19}H_{21}N_3O_7$ 403.1379 (M^+), found (M^+ + H) 404 (32%).

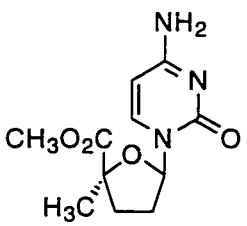


Methyl 1-(4-Amino-5-fluoro-2-oxypyrimidin-1-yl)-1,3-dideoxy-4-methyl-β-D-ribofuranuronate (62). This was prepared from **54** (343 mg, 1.04 mmol) as described in procedure B. Chromatography on silica gel (1 : 10 MeOH / CH_2Cl_2) gave **62** (287 mg, 96%) as a white solid: decomposes >250 °C; $[\alpha]_D^{24}$ +30.0 (c 0.88, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ 8.34 (d, 1H, J= 7.0), 5.86 (dd, 1H, J = 3.5, 1.5), 4.36 (m, 1H), 3.79 (s, 3H), 2.48 (dd, 1H, J = 13.5, 6.0), 2.10 (dd, 1H, J = 13.5, 5.0), 1.65 (s, 3H); ^{13}C-NMR (DMSO-*d6*) δ 174.61, 157,86 (d, J = 13.75), 154.10, 136.63 (d, J = 266.00), 126.07 (d, J = 32.25), 92.77, 84.19, 74.50, 52.99, 42.76, 25.84; HRMS (EI) calcd. for $C_{11}H_{14}N_3O_5F$ 287.0917 (M^+), found 287.0921

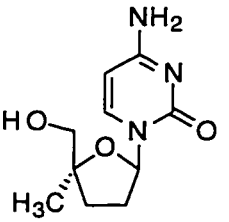


Methyl 1-(4-Benzyloxycarbonylamino-2-oxypyrimidine-1-yl)-4-methyl-1,2,3-trideoxy-β-D-ribofuranuronate (63). The 2'-*O*-phenoxythionocarbonyl derivative was prepared from **60** (570 mg, 1.41 mmol) as described in procedure C. The resulting crude 2'-*O*-phenoxythiocarbonyl nucleoside was then placed in a 100-mL, round-bottomed flask which was charged with toluene (30 mL) and fitted with a drying tube. The reaction vessel was cooled to 0 °C in an ice bath and charged with tributyltin hydride (0.40 mL, 1.487 mmol) followed by triethylborane (1.0 M in hexane, 0.50 mL, 0.50 mmol). After 7 h of stirring at 0 °C the solvent was evaporated and the resulting oil dissolved in acetonitrile (100 mL) and extracted with pentane (2 x 25 mL).

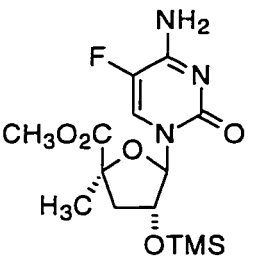
The acetonitrile layer was then evaporated to a viscous oil which was purified by column chromatography on silica gel (1 : 5 EtOAc / CH_2Cl_2) to give **63** (403 mg, 73%) as a white foam: $[\alpha]_D^{24}$ +59.1 (c 0.960, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.62 (d, 1H, J = 7.0), 7.85 (s, 1H), 7.35 (m, 5H), 7.24 (d, 1H, J = 7.0), 6.13 (t, 1H, J = 5.5), 5.19 (s, 2H), 3.77 (s, 3H), 2.70 (m, 1H), 2.27 (m, 1H), 2.05-1.93 (m, 2H), 1.55 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.45, 162.216, 155.03, 152.28, 144.97, 135.04, 128.33, 94.37, 88.87, 85.54, 67.86, 52.73, 35.38, 32.70, 24.43; IR (neat) 3191, 3143, 3067, 3034, 2983, 2954, 1744, 1727, 1678, 1630, 1612, 1564, 1549, 1402, 1327, 1275, 1199, 1110, 1068, 988, 799, 745, 698 cm^{-1}; FAB MS calcd. for $C_{19}H_{21}N_3O_6$ (M^+), found (M^+ + H) 388 (25%).



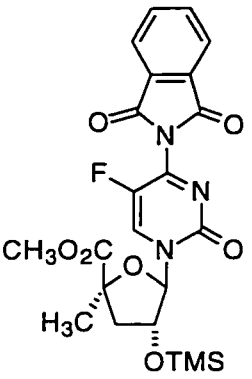
Methyl 1-(4-Amino-2-oxypyrimidin-1-yl)-4-methyl-1,2,3-trideoxy-β-D-ribofuranuronate (64). A 25-mL, round-bottomed flask was charged with **63** (171 mg, 0.460 mmol) and 10% palladium on carbon (25 mg, 15 wt. %). Absolute ethanol (5 mL) was added and the vessel was flushed with hydrogen. The reaction solution was stirred at room temperature under an atmosphere of hydrogen for 3 h. Solids were then filtered with the aid of Celite and the filtrate was concentrated under reduced pressure. The glass that resulted was purified by column chromatography (1 : 20 MeOH / CH_2Cl_2) to give **64** (112 mg, 96%) as a white powder: mp 208-209 °C, $[\alpha]_D^{24}$ +76.7 (c 1.02, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.28 (d, 1H, J = 7.5), 6.15 (t, 1H, J = 6.0), 5.90 (d, 1H, J = 7.5), 3.77 (s, 3H), 2.04 (m, 1H), 2.36 (m, 1H), 2.09 (m, 1H), 1.95 (m, 1H), 1.52 (s, 3H); ^{13}C-NMR (CD_3OD) δ 174.76, 166.28, 156.82, 141.40, 94.19, 87.88, 84.83, 51.68, 35.05, 31.88, 23.40; IR (KBr) 3350, 3107. 3079, 2992, 2951, 1747, 1735, 1668, 1523, 1487, 1402, 1358, 1289, 1252, 1198, 1118, 1090 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{15}N_3O_4$ 253.1062 (M^+), found 253.1066.



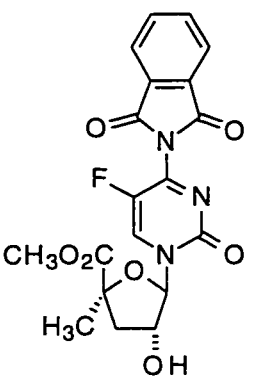
2',3'-Dideoxy-4'-*C*-methylcytidine (65) was prepared from **64** (151 mg, 0.596 mmol) as described in procedure E. Column chromatography on silica gel (1 : 20 MeOH / CH_2Cl_2) gave **65** (112 mg, 83%) as a amorphous white foam: $[\alpha]_D^{24}$ +64.3 (c 1.460, $CHCl_3$); ^{1}H-NMR (CD_3OD) δ 8.17 (d, 1H, J = 7.5) 6.07 (dd, 1H, J = 6.5, 4.5), 5.87 (d, 1H, J = 7.0), 3.65 (ABq, 1H, J = 12.0), 3.55 (ABq, 1H, J = 11.5), 2.55 (m, 1H), 2.13 (m, 1H), 2.00 (m, 1H), 1.73 (m, 1H), 1.22 (s, 3H); ^{13}C-NMR (CD_3OD) δ 165.95, 156.65, 141.66, 94,00, 86,60, 86.36, 66.86, 32.52, 30.27, 22.29; IR (neat) 3338, 3238, 3189, 2967, 2926, 2871, 1651, 1608, 1526, 1488, 1410, 1363, 1288, 1101, 1066, 779 cm^{-1}; FAB MS calcd. for $C_{10}H_{15}N_3O_3$ (M^+), found (M^+ + H) 226 (19%).



Methyl 1-(4-Amino-5-fluoro-2-oxypyrimidin-1-yl)-1,3-dideoxy-4-methyl-2-*O*-trimethylsilyl-β-D-ribofuran-uronate (71). To a flask containing **62** (254 mg, 0.844 mmol) and imidazole (150 mg, 2.203 mmol) dissolved with DMF (4 mL) was added chlorotrimethylsilane (0.17 mL, 1.377 mmol). After stirring at room temperature for 3 h, the reaction mixture was combined in a separatory funnel with EtOAc (75 mL). The mixture was extracted with water (25 mL) and the aqueous phase back extracted with EtOAc (2 x 25 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and evaporated to give a yellow oil. Column chromatography of this oil on silica gel (1 : 30 MeOH / CH_2Cl_2) gave **71** (176 mg, 60%) as a colorless oil and starting material **62** (97 mg, 34%) as a white solid. The spectral data for **71** are: ^{1}H-NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.20 (d, 1H, J = 6.5), 5.86 (t, 1H, J = 1.5), 5.77 (s, 1H), 4.43 (m, 1H), 3.79 (s, 3H), 2.20 (dd, 1H, J = 14.0, 6.0), 2.02 (dd, 1H, J = 13.5, 3.0), 1.67 (s, 3H), 0.12 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 174.52, 158.15 (d, J = 13.88), 154.04, 136,56 (d, J = 239.13), 125.67 (d, J = 33.25), 94.28, 86.10, 76.52, 52.76, 42.26, 25.50, -0.06.

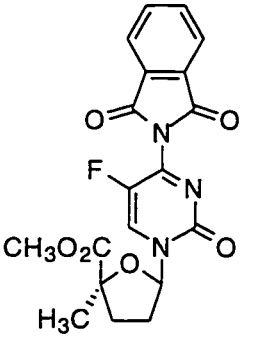


Methyl 1,3-Dideoxy-4-methyl-1-(4-phthalamido-5-fluoro-2-oxypyrimidin-1-yl)-2-*O*-trimethylsilyl-β-D-ribo-furanouronate (72). A 25-mL, round-bottomed flask containing **71** (156 mg, 0.471 mmol) dissolved in CH_2Cl_2 (5 mL) was charged with dry pyridine (0.15 mL, 1.376 mmol) and cooled to 0 °C with an ice bath. The vessel was charged with phthaloyl dichloride (82 μL, 0.569 mmol) and stirred until TLC analysis showed all starting material had been consumed (1 h). The reaction mixture was then combined with EtOAc (75 mL) in a separatory funnel and successively extracted with 1N HCl (20 mL), sat. aq. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a yellow oil. Column chromatography of this oil on silica gel (1 : 20 MeOH / CH_2Cl_2) gave **72** (145 mg, 63%) as a white foam: ^{1}H-NMR ($CDCl_3$) δ 9.09 (d, 1H, J = 5.5), 7.98 (m, 2H), 7.83 (m, 2H), 5.91 (s, 1H), 4.59 (m, 1H), 3.83 (s, 3H), 2.12-2.10 (m, 2H), 1.78 (s, 3H), 0.22 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 174.29, 164.24, 152.59, 150.52 (d, J = 14.75), 140.96 (d, J = 245.63), 135.07, 133.38 (d, J = 35.00), 131.70, 124.51, 96.71, 88.41, 77.07, 52.97, 41.78, 25.32, 0.02.

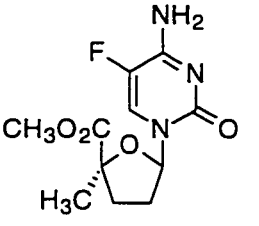


Methyl 1,3-Dideoxy-4-methyl-1-(4-phthalamido-5-fluoro-2-oxypyrimidin-1-yl)-β-D-ribofuranuronate (73). To a 25-mL, round-bottomed flask containing **72** dissolved in THF / H_2O (9 : 1, 3 mL) was slowly added tertrabutylammonium fluoride (1.0 M in THF, 0.30 mL, 0.30 mmol). After stirring for 0.5 h, the reaction mixture was combined with EtOAc (75 mL) in a separatory funnel and extracted once with brine (25 mL). The organic layer was then dried over Na_2SO_4, filtered and evaporated to give a brown oil. Purification of this oil by column chromatography on silica gel (1 : 2 EtOAc / CH_2Cl_2) gave **73** (80 mg, 74%) as an amorphous white foam: ^{1}H-NMR ($CDCl_3$) δ 8.89 (d, 1H, J = 8.5), 7.98 (m,

2H), 7.83 (m, 2H), 5.80 (d, 1H, J = 6.5), 4.81 (s, 1H), 4.50 (m, 1H), 3.78 (s, 3H), 2.71 (dd, 1H, J = 13.5, 7.5), 2.26 (dd, 1H, J = 13.5, 7.5), 1.72 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.94, 164.11, 154.14, 150.61, 141.16 (d, J = 245.93), 135.08, 133.87 (d, J = 34.20), 131.67, 124.51. 96.86, 86.94, 76.87, 52.94, 43.29, 24.90.



Methyl 4-Methyl-1-(4-phthalamido-5-fluoro-2-oxy-pyrimidin-1-yl)-1,2,3-trideoxy-β-D-ribofuranuronate (75). The 2'-*O*-phenoxythiocarbonyl derivative was prepared from **74** (76 mg, 0.182 mmol) as described in procedure C. The crude 2'-*O*-phenoxythiocarbonyl nucleoside was dissolved in dry toluene (3 mL) in a 25-mL round-bottomed flask and tributyltin hydride (59 μL, 0.219 mmol) was added. The reaction vessel was fitted with a drying tube to exclude atmospheric moisture. The reaction mixture was cooled to 0 °C by an ice bath and triethylborane (1.0 M in hexane, 73 μL, 0.073 mmol) was added. The reaction solution was stirred for 5 h at 0 °C, then combined in a separatory funnel with EtOAc (50 mL) and extracted with sat. aq. $NaHCO_3$ (10 mL) followed by extraction with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a viscous oil. Attempted purifcation of this oil by column chromatography (1 : 4 EtOAc / hex) was unsuccessful in separating the dideoxygenated nucleoside **75** from the tin by-products as determined by ^{1}H-NMR analysis. Therefore, **75** was carried on without further attempts at purification (see below).



Methyl 1-(4-Amino-5-fluoro-2-oxypyrimidin-1-yl)-4-methyl-1,2,3-trideoxy-β-D-ribofuranuronate (76) was prepared by dissolving the impure dideoxygenated nucleoside **75** (from above) in MeOH (3 mL) and treating the solution with sodium methoxide (20 mg, 0.354 mmol). After 1 h the reaction solution was neutralized by the addition of sat. aq. NH_4Cl (0.1 mL) and evaporated to dryness. The residue that remained

was dissolved in EtOAc (20 mL) and extracted once with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give a brown foam. Preparative thin layer chromatography of the foam (1 : 10 MeOH / CH_2Cl_2) gave **76** (16 mg, 33%) as a white solid: mp 143-147 °C; ^{1}H-NMR ($CDCl_3$) δ 8.46 (d, 1H, J = 7.0), 7.46 (s, 1H), 6.14 (m, 1H), 5.48 (s, 1H), 3.80 (s, 3H), 2.61 (m, 1H), 2.30 (m, 1H), 2.03 (m, 1H), 1.93 (m, 1H), 1.55 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.83, 157.81 (d, J = 13.88), 153.99, 136.39 (d, J = 238.13), 126.28 (d, J = 32.38), 88.16, 84.95, 52.75, 35.80, 32.52, 24.49; HRMS (EI) calcd. for $C_{11}H_{14}FN_3O_4$ 271.0968 (M^+), found 271.0972.

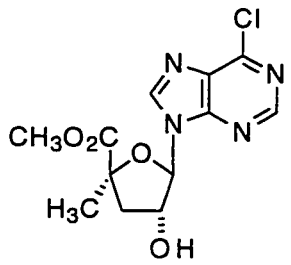
5'-*O*-Benzoyl-2',3'-dideoxy-5-fluoro-4'-*C*-methyluridine (77). was prepared by dissolving 2',3'-dideoxy-5-fluoro-4'-*C*-methyluridine (**52**) (40 mg, 0.163 mmol) in CH_2Cl_2 (1 mL) and treating this solution with dry pyridine (35 μL, 0.321 mmol), followed by benzoyl chloride (21 μL, 0.180 mmol). After stirring for 2 h at room temperature, the reaction solution was combined in a separatory funnel with EtOAc (50 mL) and extracted successively with 1N HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was then dried over $MgSO_4$, filtered and evaporated to give a viscous oil. Column chromatography of the oil on silica gel (1 : 2 EtOAc / CH_2Cl_2) gave **77** (58 mg, 100%) as a colorless glass: ^{1}H-NMR ($CDCl_3$) δ 9.86 (d, 1H, J = 4.0), 8.02 (dt, 2H, J = 8.0, 1.5), 7.78 (d, 1H, J = 6.0), 7.58 (m, 1H), 7.46 (m, 2H), 6.10 (m, 1H), 4.55 (ABq, 1H, J = 12.0), 4.38 (ABq, 1H, J = 12.0), 2.61 (m, 1H), 2.17 (m, 1H), 2.03 (m, 1H), 1.88 (m, 1H), 1.38 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 166.31, 157.02 (d, J = 26.75), 149.07, 140.47 (d, J = 236.38), 133.61, 129.50, 129.28, 128.73, 123.77 (d, J = 33.25), 85.87, 84.61, 68.72, 32.67, 31.66, 23.98.

2',3'-Dideoxy-5-fluoro-4'-*C*-methylcytidine (78) was prepared by dissolving **77** (55 mg, 0.157 mmol) in CH_3CN and stirring as a slurry with triazole (216 mg, 3.12 mmol). The slurry was then cooled to 0 °C with an ice bath and treated with phosphorus oxychloride (30 μL, 0.321 mmol). After 2 h of stirring at 0 °C, TLC analysis showed that all starting material had been consumed. The reaction slurry was then combined with EtOAc (50 mL) in a separatory funnel and extracted with sat. aq. $NaHCO_3$ (15 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to give a yellow glass which was transferred to a stainless steel bomb. The bomb was charged with liquid NH_3 (approx. 10 mL), sealed, and heated to 60 °C for 48 h. After which, the bomb was cooled to -78 °C, opened, and the liquid ammonia allowed to evaporate while slowly warming to room temperature in the back of a fume hood. The residue that remained in the bomb was then purified by column chromatography on silica gel (1 : 10 MeOH / CH_2Cl_2) to give **78** (33 mg, 86%) as a white powder: mp 95-98 °C; $[\alpha]_D^{24}$ +62.5 (c 0.610, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.48 (d, 1H, J = 7.5), 6.02 (m, 1H), 3.69 (ABq, 1H, J = 12.0), 3.56 (ABq, 1H, J = 12.0), 2.57 (m, 1H), 2.16 (dt, 1H, J = 12.5, 9.0), 2.02 (m, 1H), 1.70 (m, 1H), 1.19 (s, 3H); ^{13}C-NMR (CD_3OD) δ 158.06 (d, J = 13.87), 155.16, 136.82 (d, J = 235.00), 125.90 (d, J = 32.25), 86.76, 86.73, 66.54, 32.62, 29.66, 22.25; FAB MS for $C_{10}H_{14}FN_3O_3$ 243.1019 (M^+), found (M^+ + H) 244 (10%).

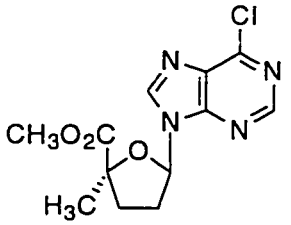
Methyl 2-*O*-Acetyl-1-(6-chloropurin-9-yl)-1,3-dideoxy-4-methyl-β-D-ribofuranuronate (79) was prepared from **30** (2.61 g, 10.02 mmol) and 6-chloropurine (4.67 g, 30.27 mmol) as described in procedure A. Chromatography on silica gel (1 : 3 EtOAc / CH_2Cl_2) gave **79** (3.24 g, 91%) as a viscous colorless oil: $[\alpha]_D^{24}$ -10.1 (c 0.910, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.50 (s, 1H), 6.33 (d, 1H, J = 3.5), 5.88 (m, 1H), 3.60 (s, 3H), 3.13 (dd, 1H, J = 14.5, 7.0), 2.30 (dd, 1H, J = 14.5, 5.0), 2.12 (s, 3H) 1.69 (s, 3H);

^{13}C-NMR ($CDCl_3$) δ 173.17, 169.92, 151.96, 151.26, 144.28. 132.04, 89.69, 86.15, 76.95, 52.91, 40.67, 25.47, 20.77; IR (KBr) 3470, 3122, 3071, 2992, 2955, 1745, 1591, 1561, 1490, 1438, 1338, 1233, 1130, 1077, 1051, 917, 801, 763, 637 cm^{-1}; HRMS (EI) calcd. for $C_{14}H_{15}N_4O_5Cl$ 354.0730 (M^+), found 354.0728.

Methyl 1-(6-Chloropurin-9-yl)-1,3-dideoxy-4-methyl-β-D-ribofuranuronate (81) was prepared from **79** (2.89 g, 8.09 mmol) as described in procedure B. Chromatography on silica gel (1 : 2 EtOAc / CH_2Cl_2) gave **81** (2.290 g, 91%) as an amorphous white foam: $[\alpha]_D^{24}$ -17.5 (c 0.960, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.70 (s, 1H), 8.58 (s, 1H), 6.05 (d, 1H, J = 5.0), 4.81 (m, 1H), 4.74 (d, 1H, J = 2.0), 3.70 (s, 3H), 2.85 (dd, 1H, J = 13.5, 7.0), 2.23 (dd, 1H, J = 13.5, 9.5), 1.73 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.59, 151.49, 151.24, 150.80, 143.97, 132.24, 93.30, 86.12, 76.40, 52.87, 42.81, 24.88; IR (KBr) 3383, 3126, 3077, 2991, 2954, 1738, 1592, 1564, 1491, 1440, 1339, 1217, 1141, 1112, 1047, 802, 636 cm^{-1}; FAB MS calcd. for $C_{12}H_{13}N_4O_4Cl$ 312.0625 (M^+), found (M^+ + H) 313 (70%).

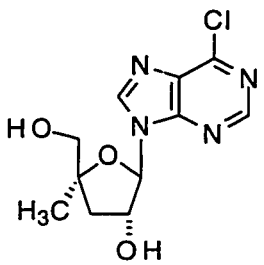


Methyl 1-(6-Chloropurine-9-yl)-4-methyl-1,2,3-trideoxy-β-D-ribofuranuronate (82) was prepared from **81** (2.04 g, 6.52 mmol) as described in procedure C and then subjected to reduction without further purification as described in procedure D. Chromatography on silica gel (1 : 5 EtOAc / CH_2Cl_2) gave **82** (1.57 g, 81%) as a crystalline white solid: mp 82-83 °C; $[\alpha]_D^{24}$ -3.15 (c 1.27, $CHCl_3$); ^{1}H-NMR ($CHCl_3$) δ 8.66 (s, 1H), 8.65 (s, 1H), 6.47 (t, 1H, J = 5.0), 3.70 (s, 3H), 2.67 (m, 1H), 2.55 (m, 2H), 2.13 (m, 1H), 1.56 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.04, 151.75, 151.15, 150.85, 144.24, 132.07, 86.36, 85.70, 52.76, 35.64, 35.38, 32.40, 24.48; IR (KBr) 3120, 3108, 2996, 2949, 1747, 1733, 1589, 1558, 1494, 1439, 1402, 1381, 1328,

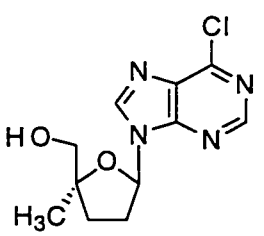


1313, 1278, 1202, 1111, 1055, 927, 853, 789, 735, 636 cm^{-1}; HRMS (EI) calcd. for $C_{12}H_{13}N_4O_3Cl$ 296.0676 (M^+), found 296.0678.

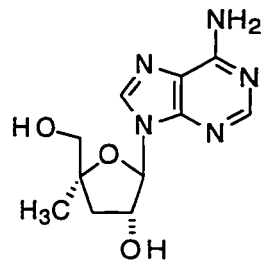
6-Chloro-9-(3'-deoxy-4'-*C*-methyl-β-D-ribosyl)purine (83) was prepared from **81** (390 mg, 1.25 mmol) as described in procedure E, with the exception that the work up involved partitioning the reaction products between EtOAc (50 mL) and H_2O (30 mL) in a separatory funnel. The aqueous phase was extracted and back extracted with EtOAc (2 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and evaporated. Column chromatography of the resulting residue on silica gel (1 : 25 MeOH / CH_2Cl_2) gave **83** (294 mg, 83%) as an amorphous white foam: $[\alpha]_D^{24}$ -47.7 (c 1.85, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ 8.58 (s, 1H), 8.22 (s, 1H), 5.76 (d, 1H, J = 6.5), 5.30 (broad s, 1H), 5.17 (q, 1H, J = 8.0), 4.82 (s, 1H), 3.66 (ABq, 1H, J = 12.5), 3.41 (ABq, 1H, J = 12.5), 2.71 (dd, 1H, J = 12.5, 8.0), 2.03 (dd, 1H, J = 12.5, 6.0), 1.35 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 151.44, 151.40, 149.99, 145.29, 132.35, 92.84, 86.30, 74.11, 69.49, 40.81, 24.84; IR (neat) 3340, 3111, 3074, 2970, 2933, 2871, 1593, 1565, 1493, 1440, 1417, 1400, 1338, 1207, 1126, 1084, 935, 809, 787, 636 cm^{-1}; FAB MS calcd. for $C_{11}H_{13}N_4O_3Cl$ 284.0676 (M^+), found (M^+ + H) 285 (19%).



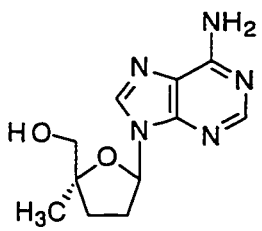
6-Chloro-9-(2',3'-dideoxy-4'-*C*-methyl-β-D-ribosyl)-purine (84) was prepared from **82** (446 mg, 1.50 mmol) in the same manner as described for **83**. Column chromatography on silica gel (3 : 2 EtOAc / CH_2Cl_2) gave **84** (331 mg, 82%) as a colorless syrup: $[\alpha]_D^{24}$ +1.44 (c 0.975, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.35 (s, 1H), 6.27 (t, 1H, J = 6.5), 4.60 (broad s, 1H), 3.80 (d, 1H, J = 12.0), 3.55 (ABq, 1H, J = 12.0), 3.55 (ABq, 1H, J = 12.0), 2.85-2.77 (m, 1H), 2.61-2.50 (m, 2H), 1.96-1.89 (m, 1H), 1.29 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 151.72, 151.54, 150.66, 144.53, 132.93, 87.15, 87.09, 69.01, 33.15, 32.34, 24.23; IR (neat) 3357, 3103, 3063, 2963,



2923, 2869, 1586, 1552, 1485, 1439, 1425, 1392, 1338, 1205, 1144, 1064, 924, 630 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{13}N_4O_2Cl$ 268.0726 (M^+), calcd. for $C_{10}H_{10}N_4OCl$ 237.0543 (M^+ - CH_3O), found 237.0541.

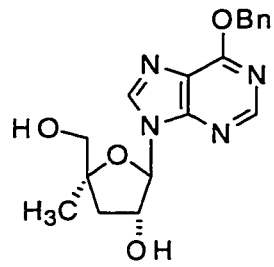


3'-Deoxy-4'-*C*-methyladenosine (**87**) was prepared by charging a stainless steal bomb with **83** (48 mg, 0.170 mmol) and liquid NH_3 (5 mL). The bomb was then sealed and placed in the back of a fume hood at room temperature for 48 h. After 48 h the bomb was cooled to -78 °C, opened and the ammonia was allowed to evaporate. The residue remaining in the bomb was purified by column chromatography on silica gel (1 : 10 MeOH / CH_2Cl_2) to give **87** (45 mg, 100%) as a flaky white solid: mp 117-120 °C; $[\alpha]_D^{24}$ -47.3 (c 1.11, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.30 (s, 1H), 8.17 (s, 1H), 5.87 (d, 1H, J = 5.5), 4.95 (dd, 1H, J = 13.5, 6.5), 3.62 (ABq, 1H, J = 12.5), 3.45 (ABq, 1H, J = 12.5), 2.64 (dd, 1H, J = 13.0, 8.0), 1.95 (dd, 1H, J = 13.0, 8.0), 1.35 (s, 3H); ^{13}C-NMR (CD_3OD) δ 156.13, 151.97, 148.48, 140. 63, 119.61, 91.67, 85.37, 74.32, 68.64, 40.30, 23.69; IR (KBr) 3319, 3172, 2971, 2932, 2867, 1694, 1602, 1577, 1479, 1425, 1375, 1303, 1248, 1210, 1086, 1048, 896, 822, 647 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{15}N_5O_3$ 265.1174 (M^+), found 265.1170.

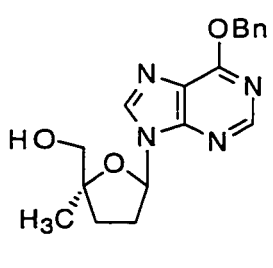


2',3'-Dideoxy-4'-*C*-methyladenosine (**88**) was prepared from **84** (88 mg, 0.327 mmol) in the same manner as described for **83**. Chromatography on silica gel (1 : 10 MeOH / CH_2Cl_2) gave **88** (79 mg, 97%) as a crispy white foam: mp 157-160 °C; $[\alpha]_D^{24}$ -12.4 (c 1.00, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.37 (s, 1H), 8.17 (s, 1H), 6.30 (t, 1H, J = 6.0), 3.66 (ABq, 1H, J = 12.0), 3.52 (ABq, 1H, J = 12.0), 2.59 (dd, 2H, J = 14.0, 7.5), 2.41 (dt, 1H, J = 13.0, 7.5), 1.89 (dt, 1H, J = 13.0, 7.5), 1.26 (s, 3H); ^{13}C-NMR (CD_3OD) δ 155.97, 152.03, 148.41, 139.86, 119.24, 86.49, 85.81, 67.82, 32.30, 31.45, 22.67; IR (KBr) 3309, 3181, 3003, 2972, 2930, 2869, 2385, 1681, 1636, 1604,

1573, 1476, 1418, 1374, 1337, 1295, 1245, 1215, 1055, 997, 932, 759, 648 cm^{-1}; HRMS (EI) calcd. for $C_{11}H_{15}N_5O_2$ 249.1225 (M^+), found 249.1224.

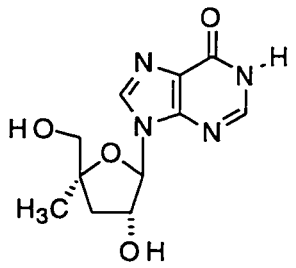


6-*O*-Benzyl-9-(3'-deoxy-4'-*C*-methyl-β-D-ribosyl)hypoxanthine (91) was prepared by treating **83** (49 mg, 0.156 mmol) dissolved with distilled benzyl alcohol (2.0 mL) with KCN (50 mg, 0.768 mmol) and heating at 80 °C for 16 h. The reaction mixture was then combined with EtOAc (30 mL) and extracted twice with H_2O (5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated by rotory evaporation followed by vacuum distillation to remove excess benzyl alcohol. The residue that remained in the vessel was purified by column chromatography on silica gel (1 : 30 MeOH / CH_2Cl_2) to give **91** (54 mg, 99%) as a colorless glass: $[\alpha]_D^{24}$ -44.5 (c 1.44, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.70 (s,1H), 7.52 (d, 2H, J = 7.5), 7.38 (t, 2H, J = 7.5), 7.34 (m, 1H), 5.76 (d, 1H, J = 11.5), 5.55 (d, 1H, J = 7.5), 5.37 (m, 2H), 3.65 (ABq, 1H, J = 12.0), 3.39 (ABq, 1H, J = 12.0), 2.63 (dd, 1H, J = 13.0, 8.5), 1.99 (dd, 1H, J = 12.0, 10.0), 1.31 (S, 3H); ^{13}C-NMR ($CDCl_3$) δ 159.75, 151.48, 149.55, 142.18, 135.32, 128.56, 128.52, 128.34, 121.66, 93.45, 85.61, 73.01, 69.92, 68.83, 40.40, 25.02; IR (neat) 3299, 3113, 3092, 2964, 2926, 2853, 1601, 1580, 1471, 1453, 1422, 1345, 1322, 1228, 1089, 1059, 1045, 802, 740, 644 cm^{-1}; HRMS (EI) calcd. for $C_{18}H_{20}N_4O_4$ 356.1484 (M^+), found 356.1489.

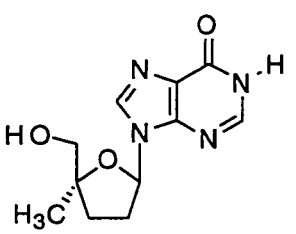


6-*O*-Benzyl-9-(2',3'-dideoxy-4'-*C*-methyl-β-D-ribosyl)-hypoxanthine (92) was prepared from **84** (136 mg, 0.506 mmol) in the same manner as described for **91**. Column chromatography on silica gel (1 : 30 MeOH / CH_2Cl_2) gave **92** (161 mg, 94%) as a white solid: mp 98-100 °C; $[\alpha]_D^{24}$ -9.1 (c 1.07, CH_3OH); ^{1}H-NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.06 (s,1H) 7.51 (m, 2H), 7.34 (m, 2H), 7.29 (m, 1H), 6.16 (dd, 1H, J = 8.0, 6.0), 5.65 (ABq, 2H, J = 13.0), 3.77 (ABq, 1H, J = 12.5), 3.48 (ABq,

1H, J = 12.5), 2.82 (m, 1H), 2.56 (m, 1H), 2.40 (m, 1H), 1.88 (m, 1H), 1.24 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 160.83, 151.57, 150.89, 141.67, 135.90, 128.45, 128.37, 128.19, 122.96, 87.22, 86.77 69.42, 68.58, 33.27, 32.82, 24.45; IR (KBr) 3611, 3556, 3283, 3140, 3089, 3062, 3030, 2964, 2926, 2869, 1604, 1473, 1457, 1411, 1346, 1222, 1113, 1063, 1006, 936, 738, 698, 643 cm^{-1}; FAB MS calcd. for $C_{18}H_{20}N_4O_3$ (M^+), found (M^+ + H) 341 (5%).



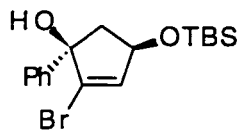
3'-Deoxy-4'-*C*-methylinosine (93) was prepared by treating **91** (44 mg, 0.124 mmol) in absolute ethanol (2 mL) with 10% palladium on carbon (6.6 mg, 15 wt. %) under one atmosphere of H_2 for 3 h. Next, solids were filtered by passing the reaction mixture through a plug of Celite. The filtrate was evaporated to give a colorless glass. This glass was purified by column chromatography on silica gel (1 : 8 MeOH / CH_2Cl_2) to give **93** (32 mg, 97%) as a white solid: mp 184-186 °C; $[\alpha]_D^{24}$ -47.6 (c 1.03, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.33 (S, 1H), 8.07 (s, 1H), 5.95 (d, 1H, J = 5.0), 4.86 (m, 1H), 3.58 (ABq, 1H, J = 11.5), 3.47 (ABq, 1H, J = 12.0) 2.62 (dd, 1H, J = 13.0, 7.5), 1.93 (dd, 1H, J = 13.0, 7.0), 1.37 (s, 3H); ^{13}C-NMR (CD_3OD) δ 157.41, 148.11, 145.37, 139.70, 124.55, 91.23, 85,73, 75.35, 68.17, 40.10, 23.60; IR (KBr) 3357, 3120, 3053, 2967, 2933, 2869, 1700, 1589, 1550, 1514, 1456, 1417, 1376, 1346, 1211, 1122, 1086, 1053, 895, 820, 789, 649 cm^{-1}; FAB MS calcd. for $C_{11}H_{15}N_4O_4$ 266.1014 (M^+), found (M^+ +H) 267 (11%).



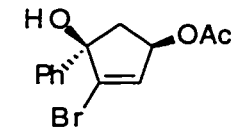
2',3'-Dideoxy-4'-*C*-methylinosine (94) was prepared from **92** (88 mg, 0.258 mmol) in the same manner as described for **93**. Column chromatography on silica gel (1 : 8 MeOH / CH_2Cl_2) gave **94** (62 mg, 95%) as a white solid: mp decomposes >250 °C; $[\alpha]_D^{24}$ -9.9 (c 1.06, CH_3OH); ^{1}H-NMR (CD_3OD) δ 8.39 (s, 1H), 8.04 (s, 1H), 6.33 (dd, 1H, J = 6.5, 4.5), 3.64 (ABq, 1H, J = 11.5), 3.53 (ABq, 1H, J =

11.5), 2.66 (m, 1H), 2.53 (m, 1H), 2.38 (m, 1H), 1.26 (s, 3H); ^{13}C-NMR (CD_3OD) δ 157.50, 147.91, 145.14, 139.12, 124.29, 86.77, 85.59, 67.36, 32.33, 31.04, 22.45; IR (KBr) 3381, 3124, 3049, 2968, 2932, 2869, 1697, 1589, 1548, 1510, 1480, 1415, 1375, 1341, 1217, 1128, 1066, 1000, 936, 787, 649, 610 cm^{-1}; FAB MS calcd. for $C_{11}H_{14}N_4O_3$ 250.1065 (M^+), found (M^+ + H) 251 (19%).

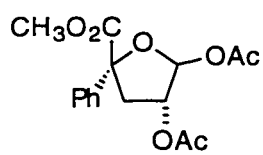
7.3. Experimental Procedures for Chapter 4.



(1*S*,4*R*)-(+)-2-Bromo-4-*tert*-butyldimethylsiloxy-1-phenyl-2-cyclopentene-1-ol (95a) was prepared by dissolving α-bromoenone (+)-**13** (1.99 g, 6.85 mmol) in THF (35 mL) and Et_2O (35 mL) in a 250-mL, round bottomed flask. The mixture was cooled to -78 °C with a dry ice / acetone bath. To the cold vessel was slowly added phenyllithium (1.8 M in hexane, 4.15 mL, 7.47 mmol) by syringe pump over a 1 h period. Upon completion of the addition, the cooling bath was removed and the vessel was allowed to warm to -60 °C, at which point glacial acetic acid (0.43 mL, approx. 7.48 mmol) was added. The solvent was then concentrated by rotary evaporation. The resulting oil was dissolved in pentane (300 mL) and then successively extracted with 1N HCl (75 mL), aqueous saturated $NaHCO_3$ (75 mL) and brine (75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The resulting oil was submitted to column chromatography on silica gel (1 : 25 EtOAc / petroleum ether) to give **95a** (2.148g, 85%) as a crystalline white solid: mp 101-102 °C; $[\alpha]_D^{24}$ +80.4 (c 1.09, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.36 (d, 1H, J = 4.0), 7.30 (m, 1H), 6.23 (d, 1H, J = 2.0), 4.78 (m, 1H), 2.76 (dd, 1H, J = 13.5, 7.0), 21.60 (s, 1H), 2.25 (dd, 1H, J = 13.5, 4.0), 0.902 (s, 9H), 0.99 (s, 3H), 0.086 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 143.29, 137.16, 133.13, 128.46, 1278.51, 124.92, 85.67, 73.56, 52.28, 25.81, 18.10, -4.68; HRMS (EI) calcd. for $C_{17}H_{25}BrO_2Si$ 368.0807 (M^+), calcd. for $C_{13}H_{16}BrO_2Si$ 311.0102 (M-*t*Bu)$^+$, found 311.0105.

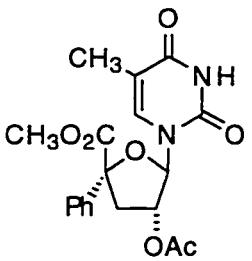


(1*S*,4*R*)-(+)-4-Acetoxy-2-bromo-1-phenyl-2-cyclopenten-1-ol (96) was prepared by dissolving vinyl bromide **95a** (2.174 g, 5.88 mmol) in THF (50 mL) in a 100-mL, round bottomed flask. The reaction vessel was then cooled to 0 °C with an ice bath, and charged with tetrabutylammonium fluoride (1.0 M in THF, 6.4 mL, 6.4 mmol) which was added slowly by syringe. Thin layer chromatography showed all starting material consumed with in 0.5 h of completing the TBAF addition. Glacial acetic acid was then added (0.35 mL, approx. 6.1 mmol), followed by removal of the cooling bath and rotary evaporation of the solvent to give a black oil. This oil was then diluted with CH_2Cl_2 (50 mL) and treated with 4-dimethylaminopyridine (180 mg, 0.1.47 mmol). The reaction vessel was cooled to 0 °C with an ice bath, and triethylamine (1.3 mL, 9.32 mmol) added, followed by the addition of acetic anhydride (0.85 mL, 9.01 mmol). After 1.5 h, MeOH (3 mL) was added, and the cooling bath removed. The reaction mixture was then combined in a separatory funnel with EtOAc (300 mL) and successively extracted with 1N NaOH (100 mL), 1N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). The organic layer was then dried over $MgSO_4$, filtered, and evaporated to give a black oil. Purification of this oil by column chromatography on silica gel (1 : 7 EtOAc / petroleum ether) gave **96** (1.68 g, 96%) as a colorless oil: $[\alpha]_D^{24}$ +122.4 (c 1.64, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.36 (m ,4H), 7.30 (m, 1H), 6.32 (d, 1H, J = 2.0), 5.59 (m, 1H), 2.87 (dd, 1H, J = 14.0, 7.5), 2.80 (s, 1H), 2.39 (dd, 1H, J = 14.0, 4.0), 2.08 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.75, 143.03, 136.08, 132.78, 128.60, 127.81, 124.82, 85.65, 75.34, 47.94, 21.09; HRMS (EI) calcd. for $C_{13}H_{13}BrO_3$ (M^+), found 296.0048.

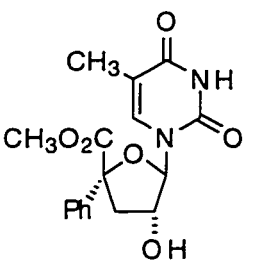


Methyl 1,2-*O*-Diacetyl-3-deoxy-4-phenyl-D-ribofuran-ouro-nate (97) was prepared by dissolving vinyl bromide **96** (1.66 g, 5.59 mmol) with MeOH (50 mL) and pyridine (2.5 mL) in a 100-mL, 3-necked, round bottomed flask equipped with a gas sparge inlet. The reaction

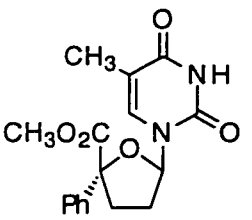
vessel was then cooled to -78 °C by a dry ice / acetone bath and ozone was bubbled into the reaction solution *via* the gas sparge at a 1.0 L / min. rate. After 2 h the reaction vessel was purged with argon for 10 min and treated with dimethyl sulfide (approx. 3 mL) which immediately changed the reaction mixture from an heterogeneous opaque green mixture to a colorless solution. The reaction mixture was then allowed to warm to room temperature with stirring over a 2 h period. Following this, solvent was removed by rotary evaporation and the resulting oil was dissolved with EtOAc (300 mL) and transferred to a separatory funnel. This solution was successively washed with 1 N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a yellow oil. The oil was dissolved in acetic anhydride (20 mL) an stirred as a slurry with sodium acetate (2.0 g) at 85 °C for 18 h. The mixture was then co-distilled twice with two 40-mL portions of xylenes under reduced pressure. The residue that remained was combined with EtOAc (200 mL) and extracted with saturated aqueous $NaHCO_3$ (75 mL) and then brine (75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The oil that resulted was submitted to column chromatography on silica gel (1 : 5 EtOAc / petroleum ether) to give **97** (1.115 g, 62%) as a yellow oil consisting of a mixture of anomers in a ratio of 94 : 6 (β / α). The spectral data for the major β anomer follows: ^{1}H-NMR ($CDCl_3$) δ 7.48 (m, 2H), 7.33 (m, 2H), 7.29 (d, 1H, J = 2.5), 6.42 (s, 1H), 5.20 (dd, 1H, J = 6.0, 1.5), 3.69 (s, 3H), 3.44 (dd, 1H, J = 14.5, 6.0), 2.40 (td, 1H, J = 14.5, 2.0, 0.5), 2.05 (s, 3H), 1.86 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.83, 169.91, 168.95, 140.05, 128.36, 128.06, 124.74, 99.84, 88.69, 77.07, 53.04, 40.99, 20.87, 20.64; HRMS (EI) calcd. for $C_{16}H_{18}O_7$ 322.1052 (M^+), calcd. for $C_{14}H_{15}O_5$ 263.0919 $(M\text{-}OAc)^+$, found 263.0916.



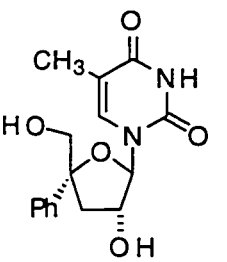
Methyl 2-*O*-Acetyl-1,3-dideoxy-1-(2,4-dioxy-5-methyl-pyrimidin-1-yl)-4-*C*-phenyl-β-D-ribofuranuronate (98) was prepared from 4-*C*-phenylribose **97** (507 mg, 1.57 mmol) and thymine (597 mg, 4.72 mmol) as described in procedure A. Chromatography on silica gel (1 : 25 MeOH / CH_2Cl_2) gave **98** (544 mg, 89%) as a sticky white foam: $[\alpha]_D^{24}$ +3.00 (c 1.26, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.22 (s, 1H), 7.50-7.48 (m, 3H), 7.39-7.31 (m, 3H), 6.05 (d, 1H, J = 4.0), 5.39 (m, 1H), 3.74 (s, 3H), 3.35 (dd, 1H, J = 14.0, 7.5) 2.26 (dd, 1H, J = 13.5, 5.5), 1.96 (d, 1H, J = 1.5) 1.88 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 171.91, 170.29, 163.77, 150.50, 139.74, 136.34, 128.53, 128.40, 124.98, 111.62, 90.63, 87.55, 75.80, 53.31, 41.16, 20.56, 12.73; HRMS (EI) calcd. for $C_{19}H_{20}N_2O_7$ 388.1270 (M^+), calcd. for $C_{17}H_{17}N_2O_5$ 329.1137 $(M\text{-}OAc)^+$, found 329.1135.



Methyl 1,3-dideoxy-1-(2,4-dioxy-5-methylpyrimidin-1-yl)-4-*C*-phenyl-β-D-ribofuranuronate (99) was prepared from **98** (520 mg, 1.34 mmol) as described in procedure B. Chromatography on silica gel (1 : 1 EtOAc / CH_2Cl_2) gave **99** (434 mg, 94%) as a white foam: $[\alpha]_D^{24}$ +6.67 (c 1.23, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 10.91 (s, 1H), 7.93 (d, 1H, J = 1.0), 7.51 (dt, 2H, J = 7.0, 1.5), 7.36 (m, 3H), 5.92 (d, 1H, J = 4.0), 5.02 (s, 1H), 4.63 (q, 1H, J = 4.5), 3.74 (s, 3H), 3.14 (dd, 1H, J = 13.5, 6.5), 2.62 (dd, 1H, J = 13.5, 7.5), 1.87 (d, 1H, J = 1.0); ^{13}C-NMR ($CDCl_3$) δ 172.79, 164.03, 152.16, 139.84, 136.43, 128.37, 128.27, 125.32, 110.49, 92.81, 87.85, 75.11, 53.13, 41.66, 12.73; HRMS (EI) calcd. for $C_{17}H_{18}N_2O_6$ 346.1164 (M^+), found 346.1165.

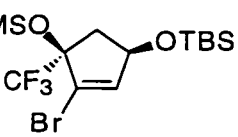


Methyl 1-(2,4-Dioxy-5-methylpyrimidin-1-yl)-4-*C*-phenyl-1,2,3-trideoxy-β-D-ribofuranuronate (100) was prepared from **99** (300 mg, 0.866 mmol) as described in procedure C followed by reduction without further purification as described in procedure D. Chromatography on silica gel (1 : 4 EtOAc / CH_2Cl_2) gave **100** (183 mg, 75%) as a sticky white foam: $[\alpha]_D^{24}$ +41.0 (c 2.41, $CHCl_3$); ^{1}H-NMR ($CDCl_3$), 9.54 (s, 1H), 7.79 (d, 1H, J = 1.0), 7.50 (m, 2H), 7.38-7.32 (m, 3H), 6.28 (t, 1H, J = 6.0), 3.76 (s, 3H), 2.92-2.87 (m, 1H), 2.50-2.38 (m, 2H), 2.06-1.97 (m, 1H), 1.98 (d, 1H, J = 1.5); ^{13}C-NMR ($CDCl_3$) δ 172.69, 164.11, 150.62, 139,57, 135.86, 128.52, 128.38, 125.25, 110.97, 88.25, 86.85, 53.14, 36.00, 31.72, 12.87; HRMS (EI) calcd. for $C_{17}H_{18}N_2O_5$ 330.1215 (M^+), found 330.1215.



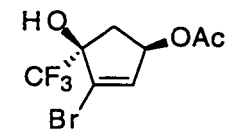
3'-Deoxy-5-methyl-4'-*C*-phenyluridine (101) was prepared from **99** (1.4 mg, 0.30 mmol) as described in procedure E, with the exception that the work up involved partitioning the reaction between EtOAc (50 mL) and water (30 mL) in a separatory funnel. The aqueous phase was extracted and back extracted with EtOAc (2 x 20 mL). Organic extracts were combined, dried over $MgSO_4$ and evaporated to give a yellow oil. Column chromatography of the oil on silica gel (1 : 15 MeOH / CH_2Cl_2) gave **101** (87 mg, 91%) as a fluffy white solid: mp 100-105 °C; $[\alpha]_D^{24}$ -30.7 (c 1.18, $CHCl_3$); ^{1}H-NMR ($CDlC_3$) δ 8.00 (d, 1H, J = 1.0), 7.41 (m, 2H), 7.34 (dt, 2H, J = 7.0, 1.5), 7.28 (m, 1H), 5.89 (d, 1H, J = 6.5), 4.56 (dt, 1H, J = 7.5, 4.0), 3.62 (ABq, 1H, J = 12.0), 3.56 (ABq, 1H, J = 12.0), 2.96 (dd, 1H, J = 13.0, 8.0), 2.23 (dd, 1H, J = 13.0, 7.5), 1.91 (d, 3H, J = 1.0); ^{13}C-NMR ($CDCl_3$) δ 165.01, 151.51, 144.05, 137.36, 127.95, 126.91, 124.48, 110.32, 89.73, 87.42, 74.29, 69.15, 40.62, 11.06; HRMS (EI) calcd. for $C_{16}H_{18}N_2O_5$ 318.1215 (M^+), calcd. for $C_{15}H_{15}N_2O_4$ 287.1031 (M^+ - CH_3O), found 287.1038.

2',3'-Dideoxy-4'-C-phenylthymidine (102) was prepared from **100** (125 mg, 0.378 mmol) as described in procedure E, with the exception that the work up involved partitioning the reaction between EtOAc (50 mL) and water (30 mL) in a separatory funnel. The aqueous phase was separated and extracted with EtOAc (2 x 20 mL). Organic extracts were combined, dried over $MgSO_4$ and evaporated. Chromatography of the resulting residue on silica gel (1 : 15 MeOH / CH_2Cl_2) gave **102** (102 mg, 89%) as a white foam: $[\alpha]_D^{24}$ +8.4 (c 0.62, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.36 (s, 1H), 7.71 (d, 1H, J = 1.0), 7.39-7.34 (m, 4H), 7.30-7.26 (m, 1H), 6.23 (dd, 1H, J = 7.0, 4.0), 3.83 (ABq, 1H, J = 12.0), 3.18 (s, 1H), 2.72-2.66 (m, 1H), 2.29-2.19 (m, 2H), 2.14-2.09 (m, 1H), 1.92 (d, 1H, J = 1.0); ^{13}C-NMR ($CDCl_3$) δ 164.17, 150.58, 142.13, 136.91, 128.58, 127.75, 125.00, 110.89, 90.12, 85.46, 68.13, 31.54, 31.41, 12.60; HRMS (EI) calcd. for $C_{16}H_{18}N_2O_4$ 302.1269 (M^+), found 302.1266.

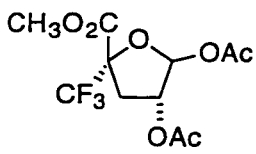


(1*S*,4*R*)-(+)-2-Bromo-4-*tert*-butyldimethylsiloxy-1-trifluoromethyl-2-cyclopenten-1-ol (103a) was prepared by dissolving α-bromoenone (+)-**13** (2.01 g, 6.90 mmol) and trimethyl(trifluoromethyl)silane (2.20 mL, 13.85 mmol) in THF (75 mL) in a 250-mL, round bottomed flask. The flask was then cooled to -78 °C with an dry ice / acetone bath and a solution of potassium *tert*-butoxide (76 mg, .680 mmol, dissolved in 4 mL of THF) was slowly added *via* canula. The solution was stirred for 4 h at -78 °C then the cooling bath was removed and the vessel allowed to slowly warm. Once the vessel had warmed to -20 °C saturated aqueous $NaHCO_3$ was added. The reaction solvent was then evaporated and the resulting oil was diluted with pentane (300 mL). This solution was then successively extracted with 1N HCl (75 mL), saturated aqueous $NaHCO_3$ (75 mL) and brine (75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The resulting oil was submitted to column chromatography on silica gel (1 : 60 EtOAc / petroleum ether) to give **103a** (2.80 g, 94%) as a colorless oil: $[\alpha]_D^{24}$ +55.7 (c 1.445,

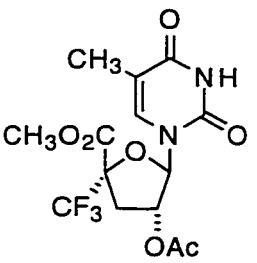
$CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 6.23 (d, 1H, J = 2.0), 4.64 (m, 1H), 2.91 (dd, 1H, J = 14.0, 7.0), 1.99 (m, 1H), 0.87 (s, 9H), 0.23 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 141.77, 124.56 (q, J = 284,38), 124.41, 84,89 (q, 31.38), 72.47, 44.88, 25.68, 17,93, 1.49, -4.78, -4.81; HRMS (EI) calcd. for $C_{15}H_{28}BrF_3O_2Si_2$ 432.0763 (M^+), calcd. for $C_{11}H_{19}BrF_3O_2Si_2$ 375.0059 (M - *t*Bu)$^+$, found 375.0065.



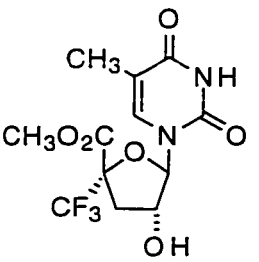
(1*S*,4*R*)-(+)-4-Acetoxy-2-bromo-1-trifluotomethyl-2-cyclo-penten-1-ol (105) was prepared by dissolving vinyl bromide **103a** (2.72 g, 6.27 mmol) in THF (60 mL) in a 100-mL, round bottomed flask. The reaction vessel was then cooled to 0 °C with an ice bath. Tetrabutylammonium fluoride (1.0 M in THF, 13.8 mL, 13.8 mmol) was added slowly by syringe. Thin layer chromatography showed all starting material was consumed within 0.5 h of completing the addition, so glacial acetic acid (0.40 mL, approx. 6.9 mmol) was added, the cooling bath was removed and the solvent evaporated by rotary evaporation to give a black oil. This oil was then diluted with CH_2Cl_2 (50 mL). To the CH_2Cl_2 solution was added 4-dimethylaminopyridine (76 mg, 0.622 mmol). The mixture was cooled to 0 °C and triethylamine (1.04 mL, 7.46 mmol) and acetic anhydride (0.71 mL, 7.52 mmol) were added. After 1.5 h, MeOH (3 mL) was added and the cooling bath removed. The reaction mixture was combined in a separatory funnel with EtOAc (300 mL) and successively washed with 1H NaOH (100 mL), 1N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a black oil. Column chromatography of this oil on silica gel (1 : 5 EtOAc / petroleum ether) gave **105** (1.71 g, 94%) of a colorless oil: $[\alpha]_D^{24}$ +71.4 (c 2.66, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 6.39 (d, 1H, J = 2.0), 5.49 (m, 1H), 3.39 (s, 1H), 3.05 (dd, 1H, J = 14.5, 7.5), 2.11 (td, 1H, J = 14.5, 5.0, 1.0), 2.07 (S, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.70, 138,08, 125.54, 124.35 (q, J = 283,38), 83.14 (q, J = 31.38), 74,17, 40.27, 20.85; HRMS (EI) calcd. for $C_8H_8BrF_3O_3$ 287.9608 (M^+), found 287.9606.



Methyl 1,2-*O*-Diacetyl-3-deoxy-4-trifluoromethyl-D-ribofuranuronate (106) was prepared by dissolving α-bromoenone **105** (1.49 g, 5.17 mmol) in MeOH (50 mL) and pyridine (2.5 mL) in a 100-mL, 3-necked, round bottomed flask equipped with a gas sparge inlet. The reaction vessel was then cooled to -78 °C with a dry ice / acetone bath, and a 1.0 L / min. flow rate of ozone was initiated through the reaction solution *via* the gas sparge. After 3 h the reaction vessel was purged with argon for 10 min, allowed to warm to -50 °C, and then treated with dimethyl sulfide (approx. 3 mL) which immediately changed reaction mixture from a heterogeneous opaque green mixture to a colorless solution. The reaction vessel was then allowed to warm to room temperature with stirring over a 2 h period. Following this, solvent was removed by rotary evaporation and the resulting oil was diluted with EtOAc (300 mL). This solution was then successively washed with 1 N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give a yellow oil. The oil was dissolved in acetic anhydride (25 mL) and stirred as a slurry with sodium acetate (2.5 g) at 85 °C for 18 h. The reaction mixture was then co-distilled twice with xylenes (40 mL) under reduced pressure. The residue that remained was combined with EtOAc (200 mL) and extracted with saturated aqueous $NaHCO_3$ (75 mL), and brine (75 mL). The organic layer was then dried over $MgSO_4$, filtered and evaporated. The resulting oil was submitted to column chromatography on silica gel (1 : 4 EtOAc / petroleum ether) to give **106** (956 mg, 59% based on recovered starting material) as a yellow oil consisting of a mixture of anomers in a ratio of 94 : 6 (β / α). The spectral data for the major β anomer follows: ^{1}H-NMR ($CDCl_3$) δ 6.36 (s, 1H), 5.17 (d, 1H, J = 6.5), 3.84 (s, 3H), 3.01 (dd, 1H, J = 16.0, 6.5), 2.53 (d, 1H, J = 15.5), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 169.96, 168.35, 167.43, 122.37 (q, J = 282.50), 100.57, 86.33 (q, J = 32.25), 75.61, 53.73, 35.23, 20.64, 20.63; HRMS (EI) calcd. for $C_{11}H_{13}F_3O_7$ 314.0613 (M+), calcd. for $C_9H_{10}F_3O_6$ 271.0429 (M^+ - C_2H_3O), found 271.0429.

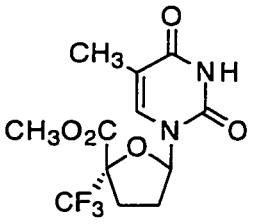


Methyl 2-*O*-Acetyl-1,3-dideoxy-1-(2,4-dioxy-5-methyl-pyrimidin-1-yl)-4-*C*-trifluoromethyl-β-D-ribofurano-uronate (107) was prepared from 4-trifluoromethylribose **106** (650 mg, 2.068 mmol) and thymine (780 mg, 6.185 mmol) as described in procedure A. An additional two equivalents of trimethylsilyl trifluoromethanesulfonate were added to the reaction mixture after 1.5 h to encourage complete consumption of starting material **106**. Chromatography on silica gel (1 : 25 MeOH / CH_2Cl_2) gave **107** (585 mg, 74%) as a crystalline solid: 146-147 °C; $[\alpha]_D^{24}$ -17.2 (c 1.07, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.05 (s, 1H), 7.28 (d, 1H, J = 1.0)5.85 (d, 1H, J = 4.0), 5.43 (m, 1H), 3.88 (s, 3H), 3.28 (dd, 1H, J = 14.5, 8.0), 2.58 (dd, 1H, J = 15.0, 5.5), 2.11 (s, 3H), 1.93 (d, 1H, J = 1.5); ^{13}C-NMR ($CDCl_3$) δ 170.72, 166.96, 163.75, 137.73, 122.87 (q, J = 283.55), 111.77, 95.23, 86.08 (q, J = 31.38), 75.75, 53.86, 35.86, 35.96, 20.64, 12.44; HRMS (EI) calcd. for $C_{14}H_{15}F_3N_2O_7$ 380.0831 (M^+), found 380.0833.



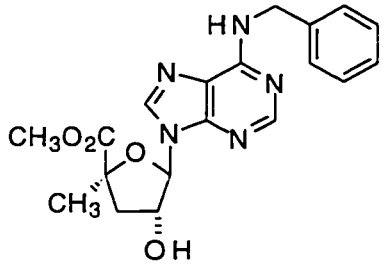
Methyl 1,3-Dideoxy-1-(2,4-dioxy-5-methylpyrimidin-1-yl)-4-*C*-trifluoromethyl-β-D-ribofuranuronate (108) was prepared from **107** (465 mg, 1.32 mmol) according to procedure B. Chromatography on silica gel (1 : 25 MeOH / CH_2Cl_2) gave **108** (433 mg, 97%) as a white foam: $[\alpha]_D^{24}$ -44.1 (c 1.16, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 11.20 (s, 1H), 7.90 (d, 1H, J = 1.0), 6.04 (d, 1H, J = 5.5), 5.53 (s, 1H), 4.73 (m, 1H), 3.93 (s, 3H), 2.88 (dd, 1H, J = 14.5, 7.5), 2.64 (dd, 1H, J = 14.5, 7.5), 1.82 (d, 1H, J = 1.0); ^{13}C-NMR ($CDCl_3$) δ 167.97, 163.81, 152.19, 136.28, 122.86 (q, J = 282.50), 110.99, 93.11, 84.75 (q, J = 32.38), 73.51, 53.82, 36.18, 12.64; HRMS (EI) calcd. for $C_{12}H_{13}F_3N_2O_6$ 338.0725 (M^+), found 338.0720.

Methyl 1,3-Dideoxy-1-(2,4-dioxy-5-methylpyrimidin-1-yl)-4-*C*-trifluoromethyl-β-D-ribofuranuronate (109) was prepared from **108** (148 mg, 0.437 mmol) as described in procedure C followed by reduction without prior purification as described in procedure D. Column chromatography on silica gel (1 : 35 MeOH / CH_2Cl_2) gave **109** (95 mg, 68%) as a colorless glass: mp 164-165 °C; $[\alpha]_D^{24}$ +9.1 (c 1.01, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 9.25 (s, 1H), 7.77 (d, 1H, J = 1.0), 6.38 (m, 1H), 3.91 (s, 3H), 2.56-2.52 (m, 3H), 2.08-2.02 (m, 1H), 1.96 (d, 3H, J = 1.0); ^{13}C-NMR ($CDCl_3$) δ 168.08, 163.69, 150,35, 135.58, 123.22 (q, J = 281.38), 111.78, 88.27, 84.53 (q, J = 31.38), 53.79, 30.65, 30.47, 121.76; HRMS (EI) calcd. for $C_{12}H_{13}F_3N_2O_5$ 322.0776 (M^+), found 322.0780.



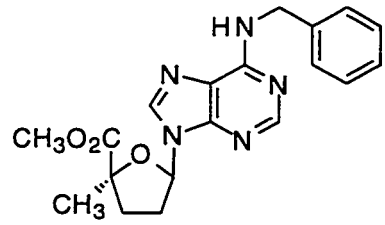
7.4. Experimental for Chapter 5.

Methyl 1-[6-(Benzylamino)purin-9H-yl]-1,3-dideoxy-4-methyl-β-D-ribofuranuronate (120) was prepared by dissolving **81** (94 mg, 0.300 mmol) in THF (3 mL) and treating this solution with benzylamine (0.16 mL, 1.46 mmol). After 24 h, the reaction mixture was combined in a separatory funnel with CH_2Cl_2 (50 mL) and water (25 mL). The organic layer was extracted, and the aqueous layer back extracted with two additional portions of CH_2Cl_2 (15 mL each). Organic extracts were combined, dried over $MgSO_4$, filtered and evaporated to give a yellow glass. Column chromatography of this residue on silica gel (3 : 2 EtOAc / CH_2Cl_2) gave **120** (105 mg, 91%) as an amorphous white foam: $[\alpha]_D^{24}$ -32.2 (c 0.640, $CHCl_3$), ^{1}H-NMR (CD_3OD) δ 8.36 (s, 1H), 8.24 (s, 1H), 7.36 (d, 2H, J = 7.5), 7.30 (t, 2H, J = 7.5), 7.23 (t, 2H, J = 7.5), 6.12 (d, 1H, J = 4.0), 4.88 (m, 1H), 4.80 (s, 2H), 3.71 (s, 3H), 2.83 (dd, 1H, J = 13.5, 6.5), 2.19 (dd, 1H, J = 13.5, 6.0), 1.65 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.76, 154.48, 152.56, 138.18, 138.08,



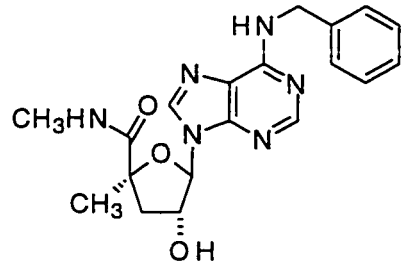
128.68, 127.73, 127.53, 93.03, 85.68, 76.25, 52.74, 44.49, 42.56, 25.06; HRMS (EI) calcd. for $C_{19}H_{21}N_5O_4$ 383.1593 (M^+), found 383.1588.

Methyl 1-[6-(Benzylamino)purin-9H-yl]-1,2,3-trideoxy-4-methyl-β-D-ribofuranuronate (121) was prepared from **82** (102 mg, 0.343 mmol) as described for the preparation of **120**. Column chromatography on silica gel (3 : 2 EtOAc / CH_2Cl_2) gave



121 (106 mg, 84%) as a white powder: mp 105-106 °C; $[\alpha]_D^{24}$ -17.0 (c 0.940, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.38 (s, 1H), 8.22 (s, 1H), 7.36 (d, 2H, J = 7.0), 7.31 (d, 2H, J = 7.0), 7.25 (t, 1H, J = 7.0), 6.44 (t, 1H, J = 5.5), 6.34 (s, 1H), 4.85 (s, 2H), 3.74 (s, 3H), 2.62-2.52 (m, 3H), 2.11 (m, 1H), 1.58 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.31, 154.59, 153.03, 138.59, 138.46, 128.65, 127.68, 127.44, 119.98, 85.67, 85.21, 52.66, 44.43, 35.65, 32.38, 24.66; HRMS (EI) calcd. for $C_{19}H_{21}N_5O_3$ 367.1644 (M^+), found 367.1650.

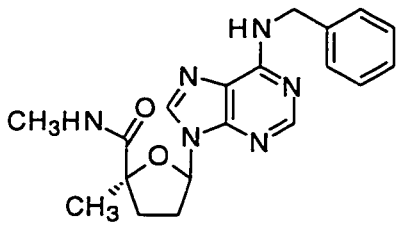
1-[6-(Benzylamino)-9H-purin-9-yl]-1,3-dideoxy-*N*,4-dimethyl-β-D-ribofuranuronamide (122) was prepared by treating **120** (99 mg, 0.258 mmol) with methylamine (2 mL, 2.0 M in MeOH) at 40 °C for 24 h. The solvent was evaporated to give a



colorless glass. Column chromatography of this residue on silica gel (1 : 2 MeOH / CH_2Cl_2) gave **122** (88 mg, 89%) as a colorless glass: $[\alpha]_D^{24}$ -36.9 (c 0.910, $CHCl_3$); ^{1}H-NMR (CD_3OD) δ 8.30 (s, 1H), 8.15 (s, 1H), 7.37 (d, 2H, J = 7.0), 7.30 (t, 2H, J = 7.5), 7.23 (t, 1H, J = 7.0), 5.95 (d, 1H, J = 4.5), 4.87 (m, 1H), 4.80 (s, 2H), 2.83 (dd, 1H, J = 13.0, 7.0), 2.75 (s, 3H), 2.12 (dd, 1H, J = 13.0, 7.5), 1.60 (s, 3H); ^{13}C-NMR (CD_3OD) δ 175.93, 154.65, 152.40, 140.22, 138.77, 128.13, 127.09, 126.84, 119.92,

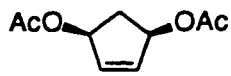
91.07, 84.30, 72.23, 43.61, 42.85, 25.01, 24.81; HRMS (EI) calcd. for $C_{19}H_{22}N_6O_3$ 382.1753 (M^+), found 382.1758.

1-[6-(Benzylamino)-9H-purin-9-yl]-1,2,3-trideoxy-*N*,4-dimethyl-β-D-ribofuranuronamide (123) was prepared from **121** (101 mg, 0.274 mmol) as described for the preparation of **122**. Column chromatography on silica gel (1 : 30 MeOH / CH_2Cl_2) gave **123** (91 mg, 91%) as an amorphous white foam: $[\alpha]_D^{24}$ -19.0 (c 0.890, $CHCl_3$); ^{1}H-NMR (CD_3OD) δ 8.28 (s, 1H), 8.14 (s, 1H), 7.37 (d, 2H, J = 7.5), 7.29 (t, 2H, J = 7.5), 7.23 (t, 1H, J = 7.5), 6.36 (t, 1H, J = 5.5), 4.79 (s, 2H), 2.68 (s, 3H), 2.67-2.60 (m, 2H), 2.53-2.48 (m, 1H), 2.14 (s, 1H), 1.49 (s, 3H); ^{13}C-NMR (CD_3OD) δ 176.23, 154.53, 152.30, 139.55, 138.75, 128.14, 127.12, 126.86, 119.72, 85.92, 85.82, 43.62, 34.99, 30.16, 24.79, 24.20; HRMS (EI) calcd. for $C_{19}H_{22}N_6O_2$ 366.1804 (M^+), found 366.1809.



Appendix:

^{1}H and ^{13}C NMR Spectra of Selected Compounds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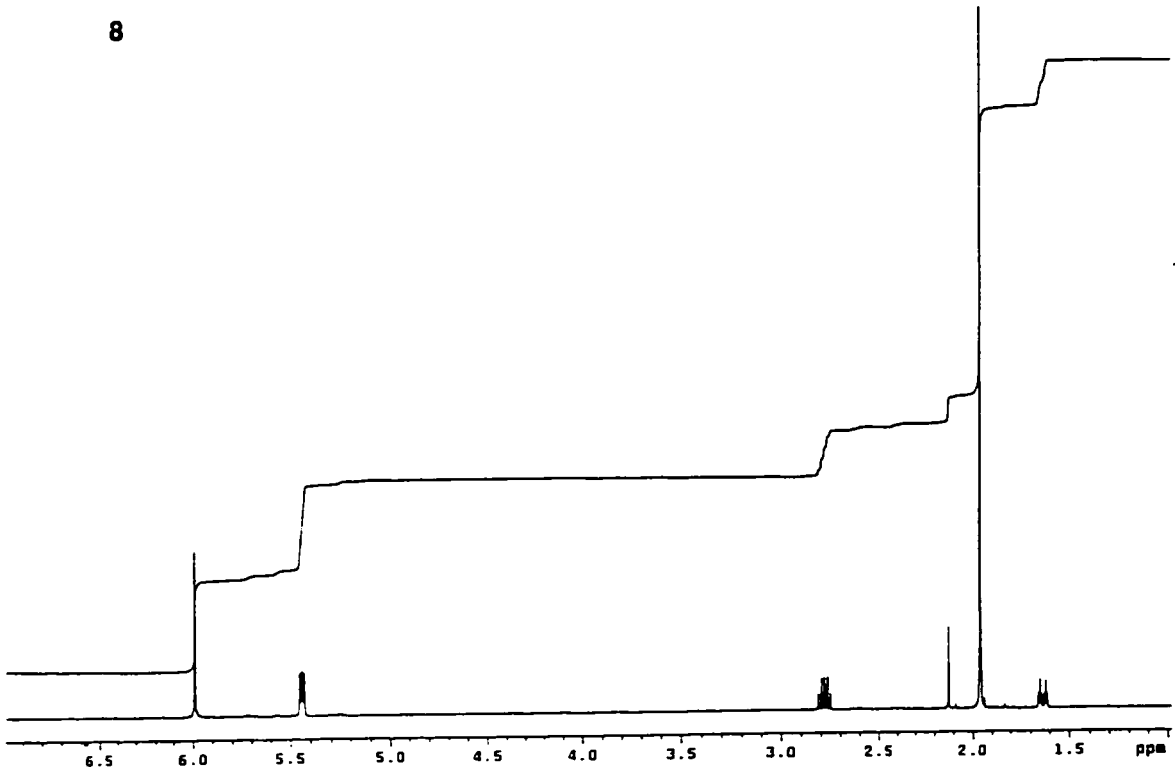
OAc

8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3.5
3.0
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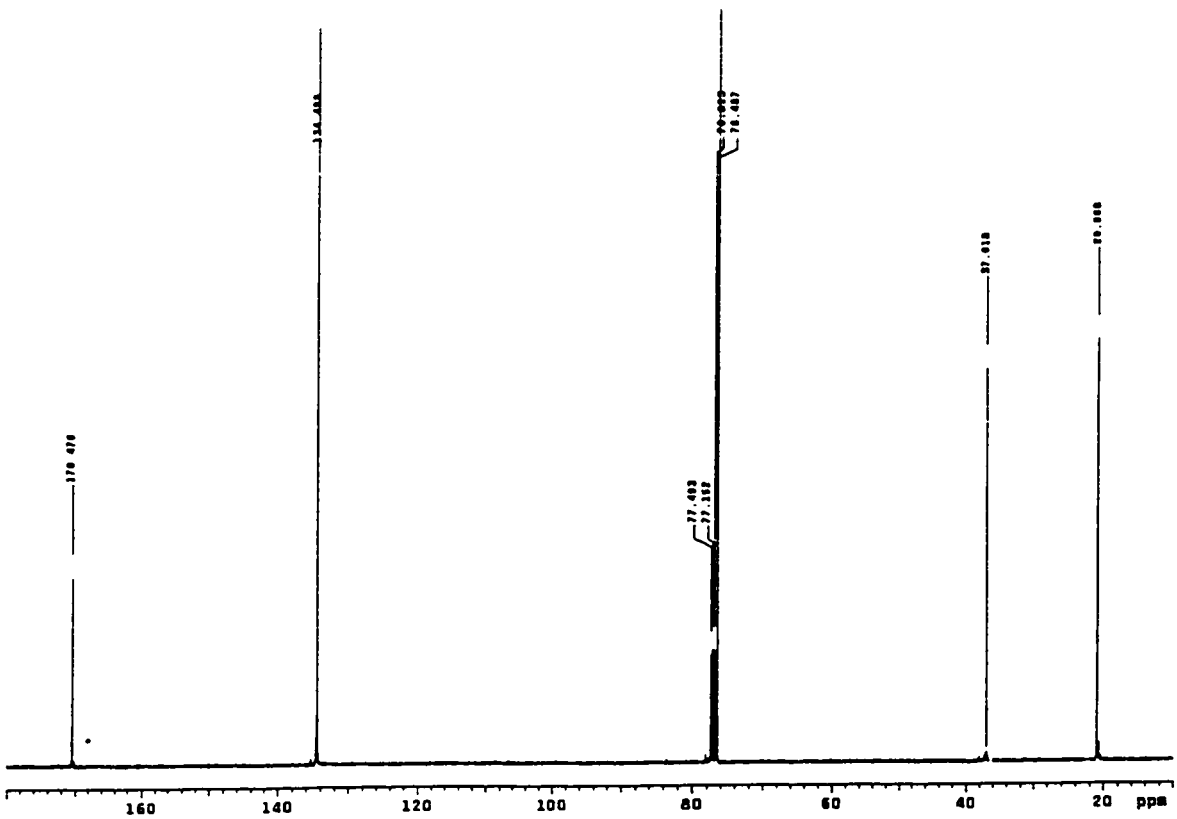
2.0
1.5
ppm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120
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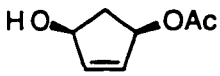
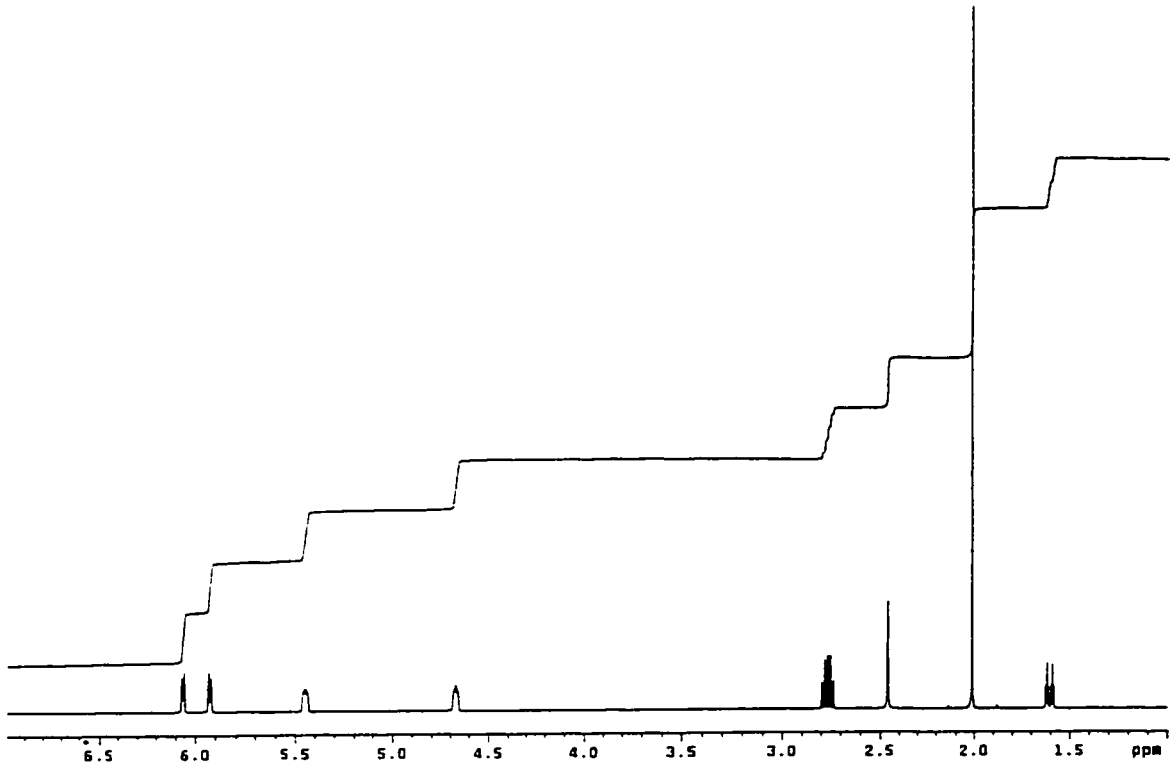
80
60
40
20
ppm


HO
OAc

(+)-7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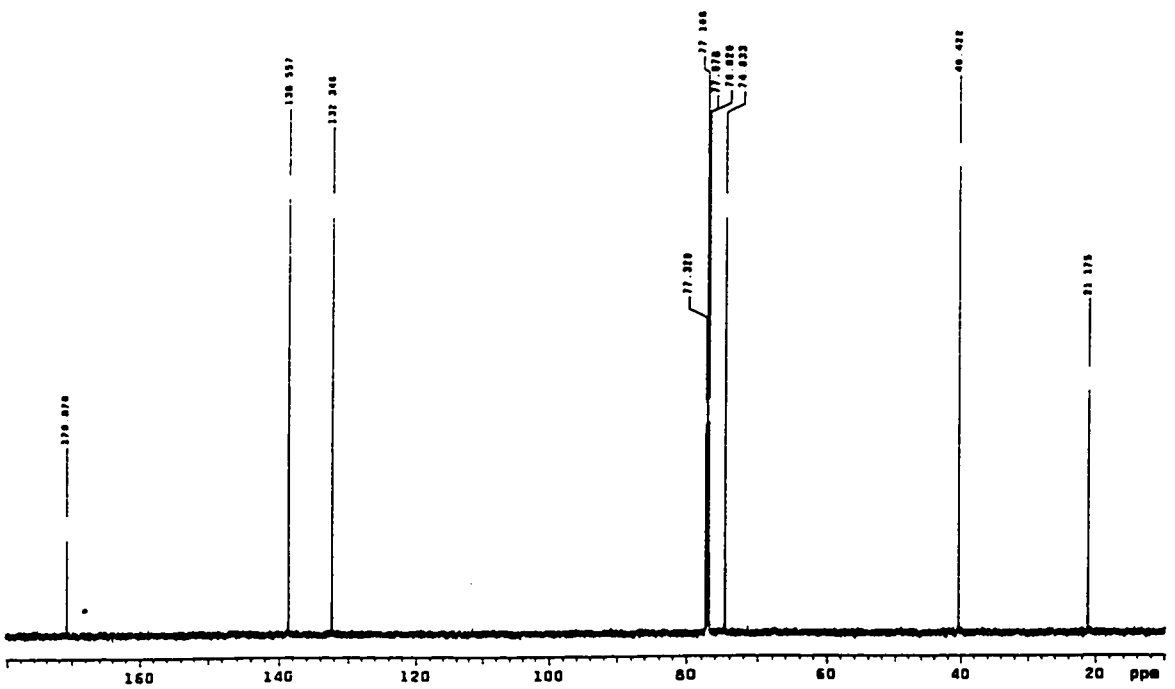
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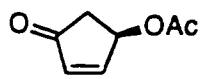
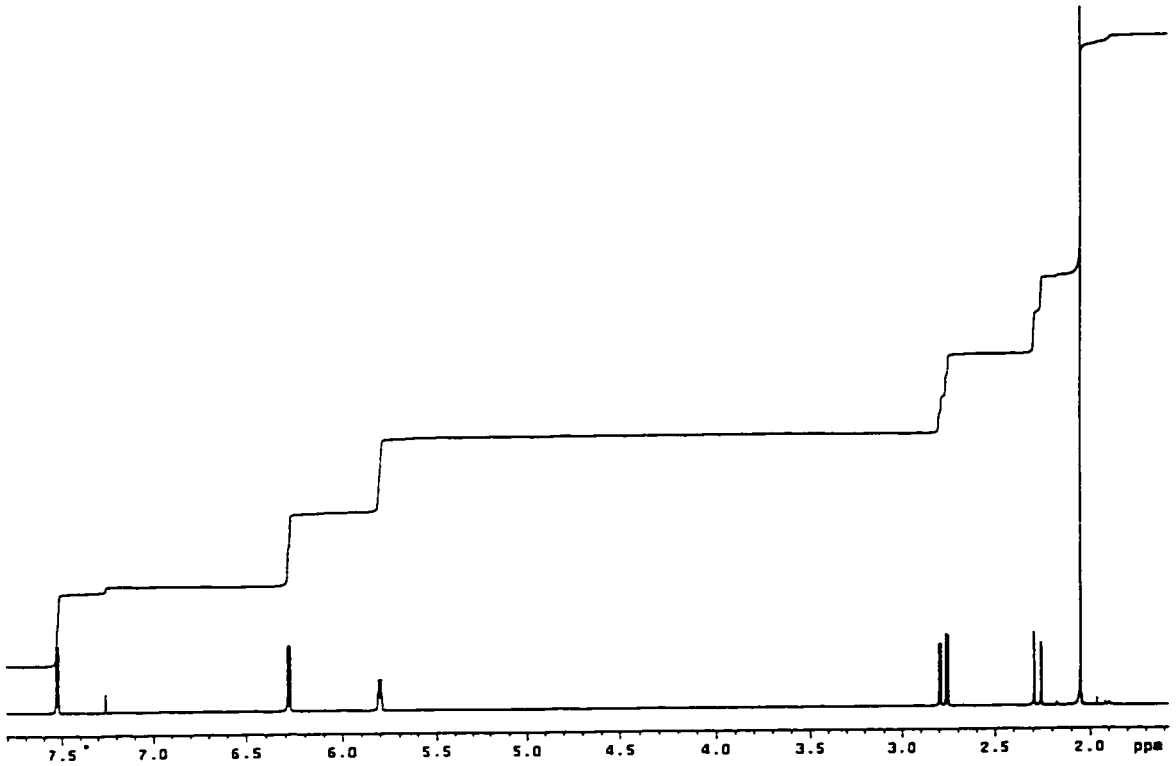
20
ppm


O
OAc

6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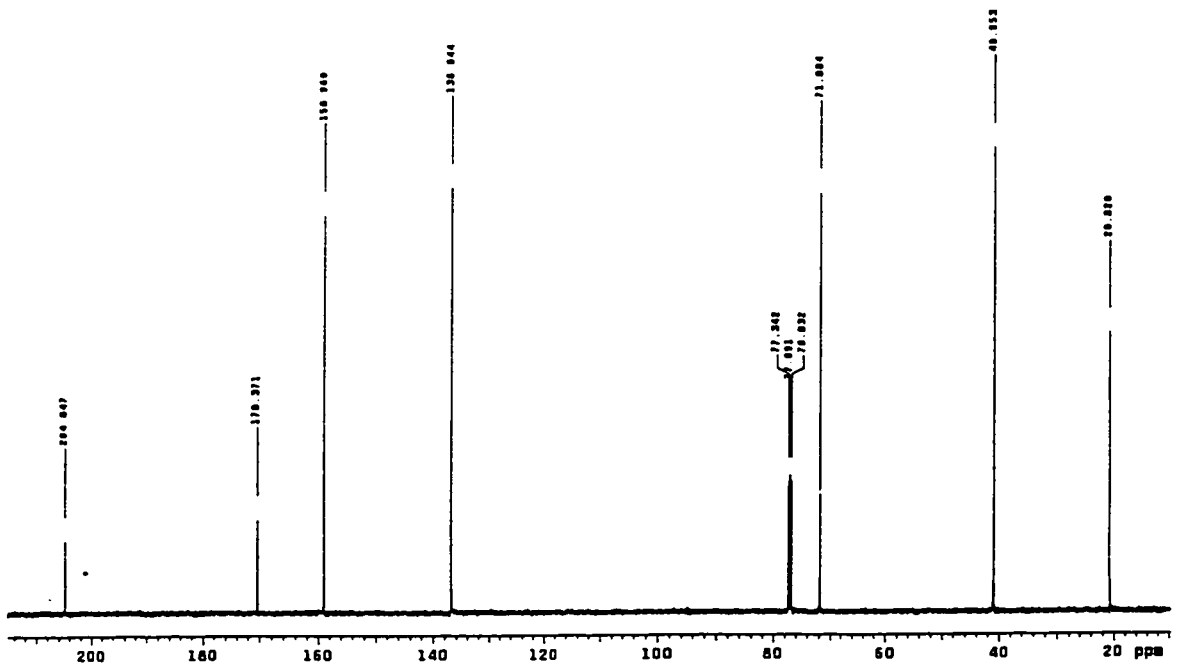
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120
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80
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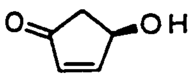
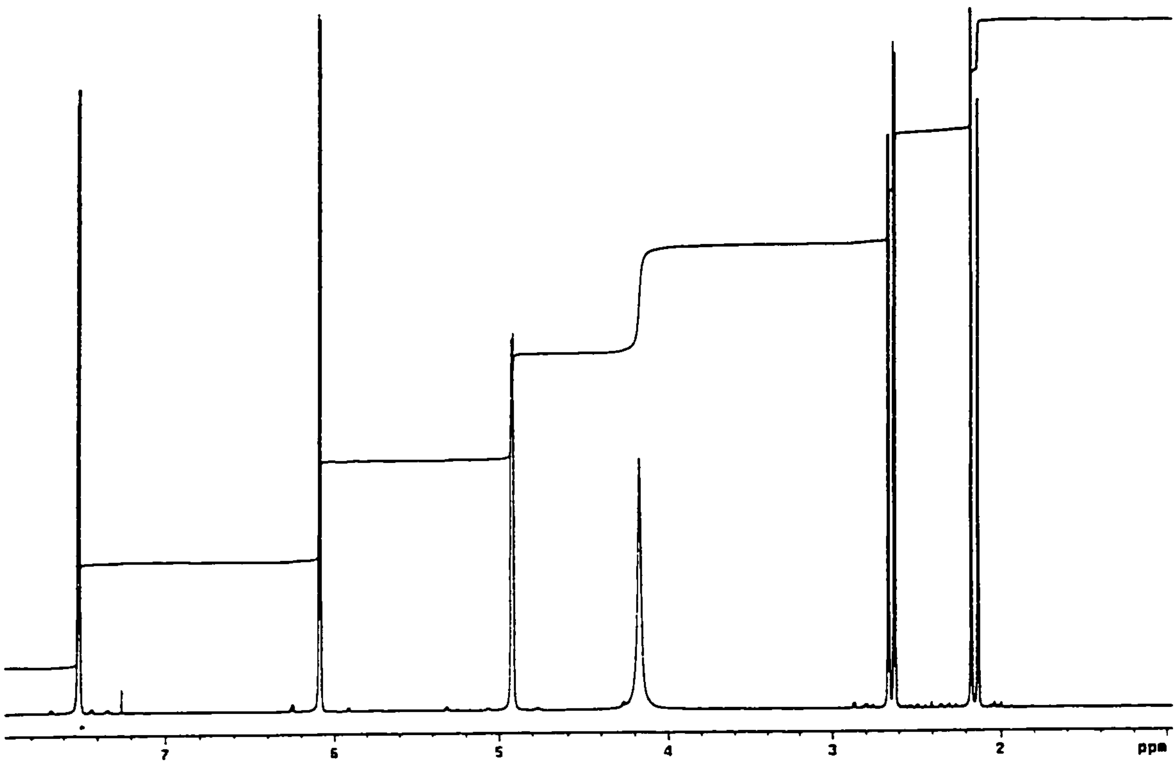
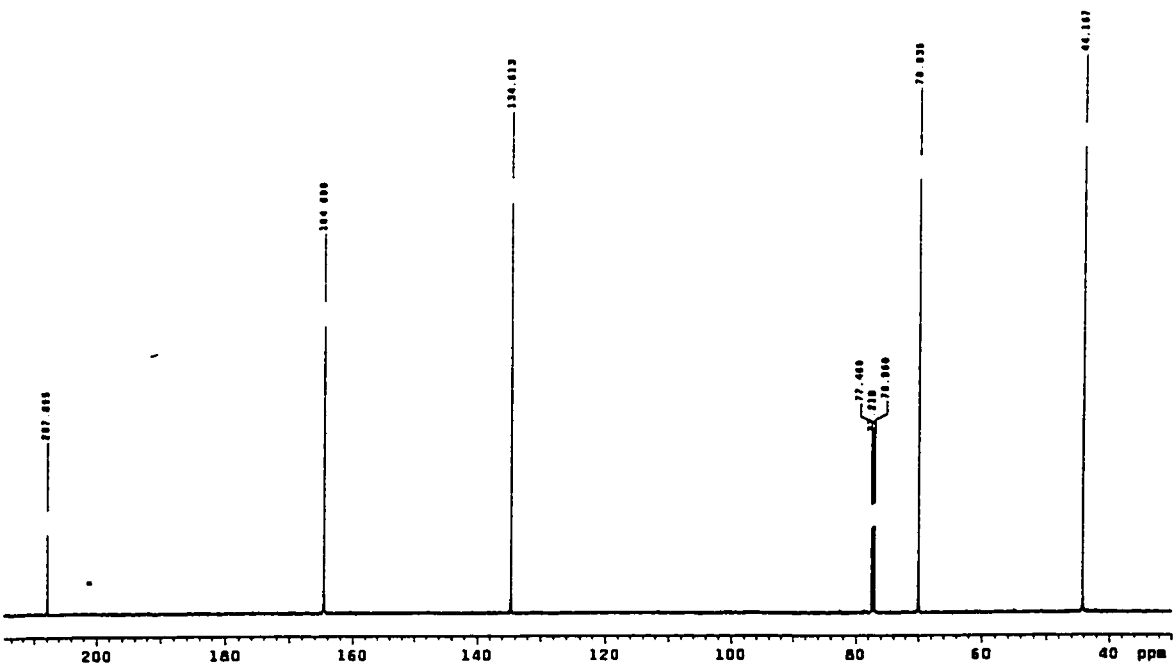
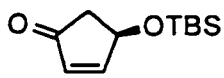
20
ppm



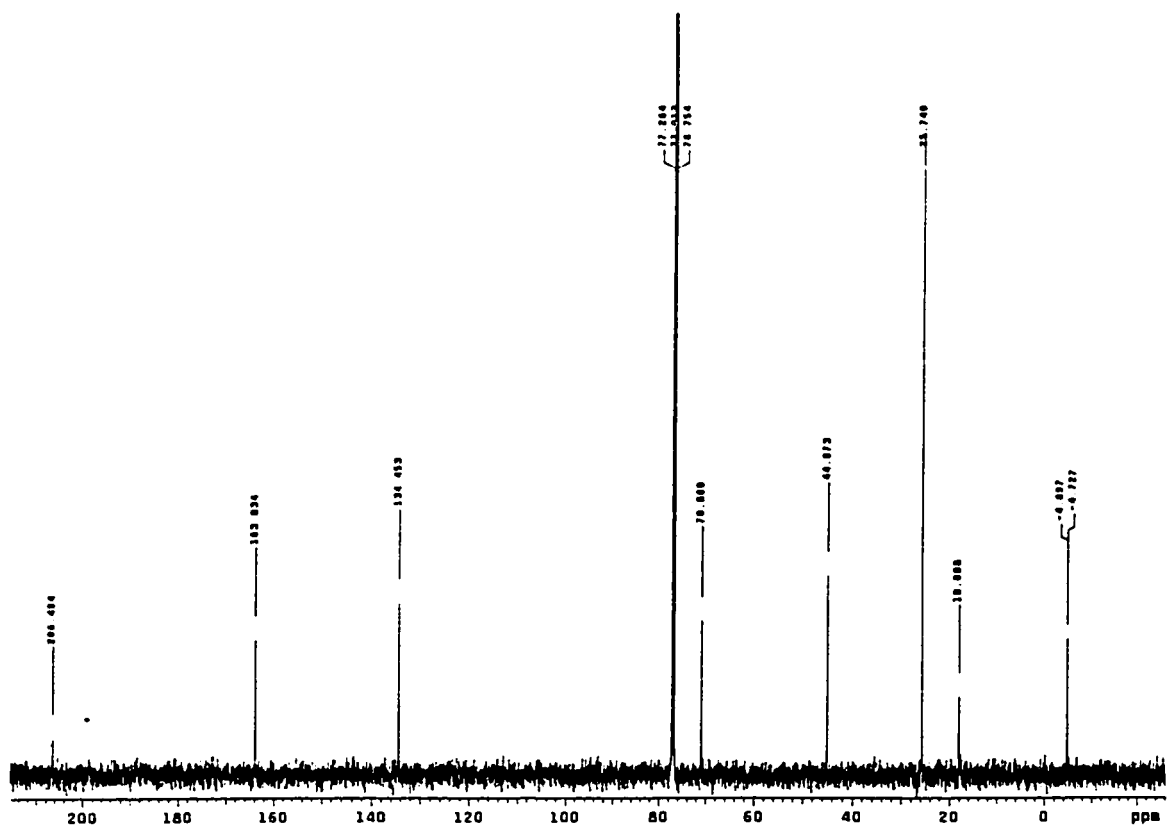
16

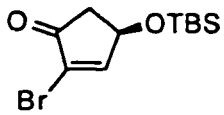




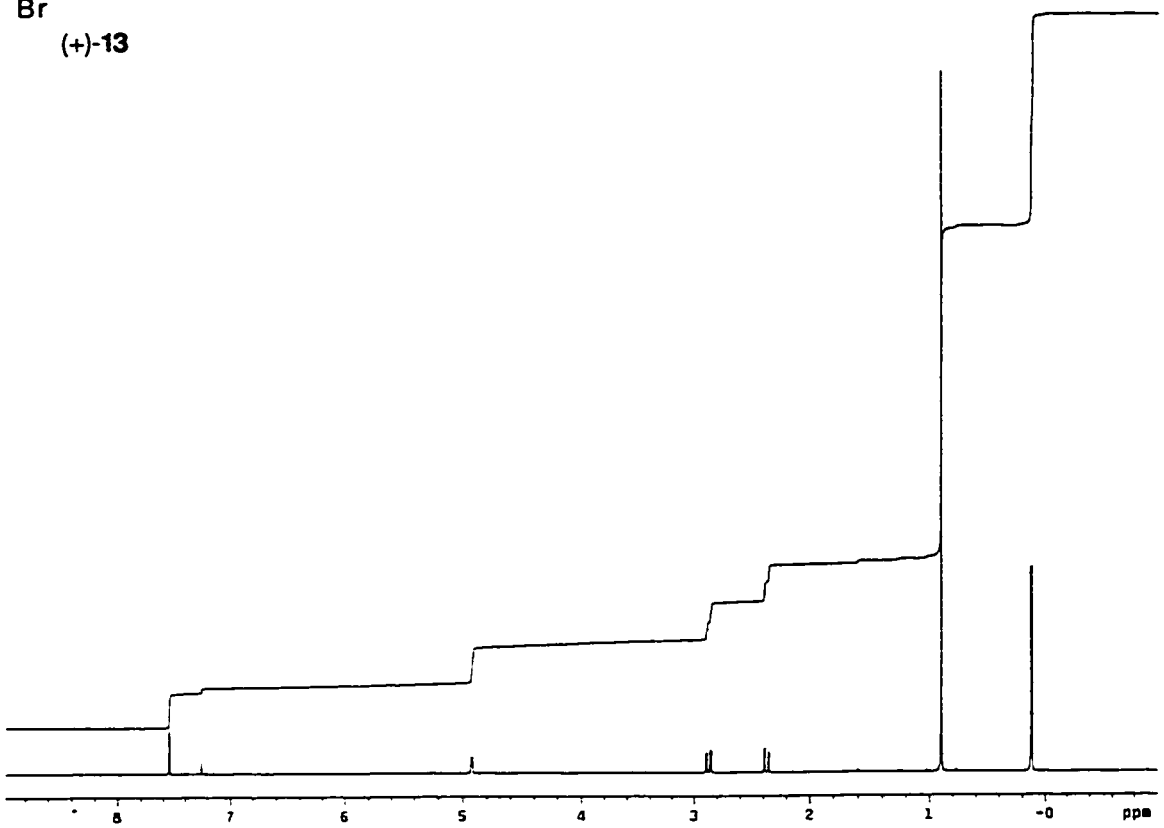


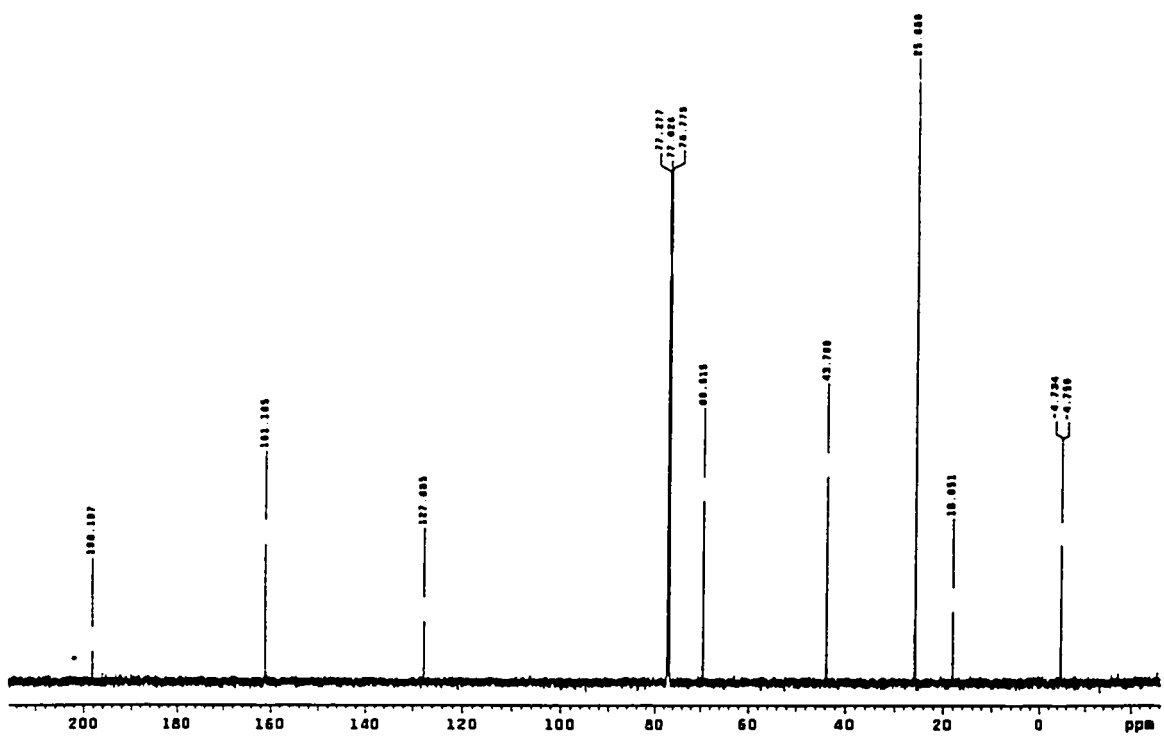
(+)-17

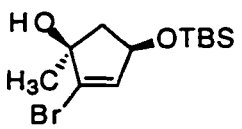




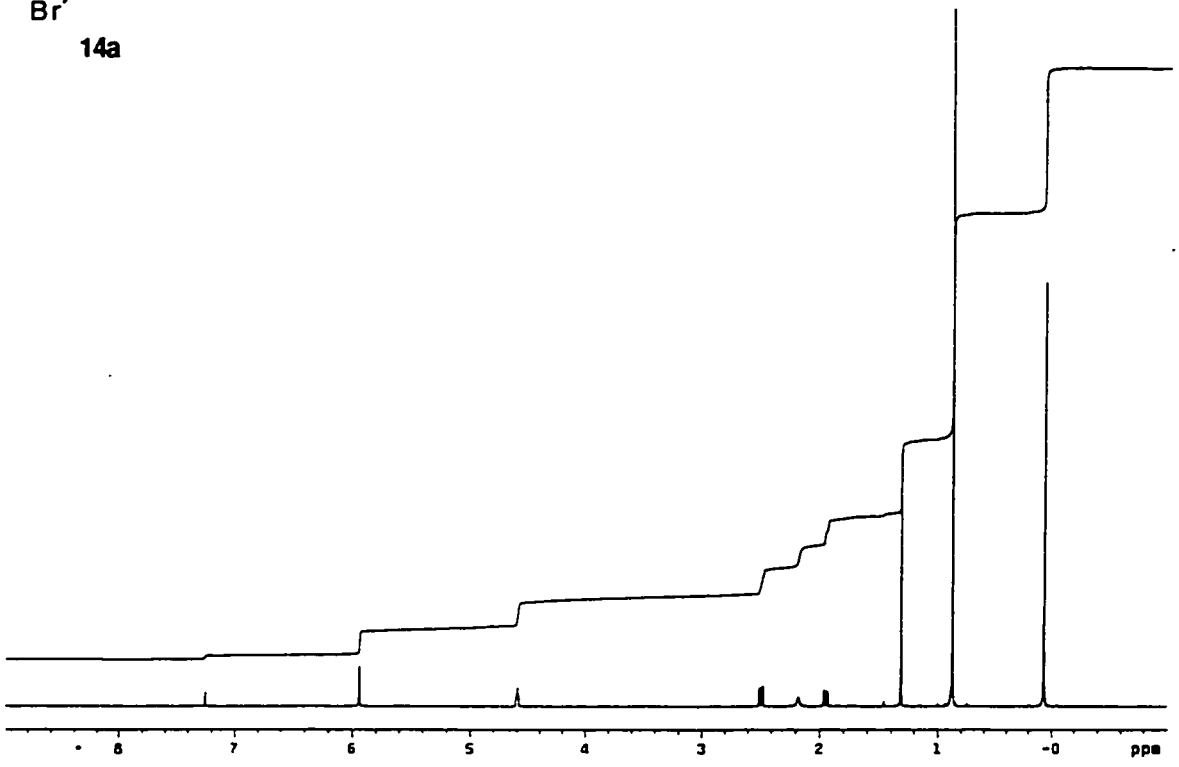
(+)-**13**

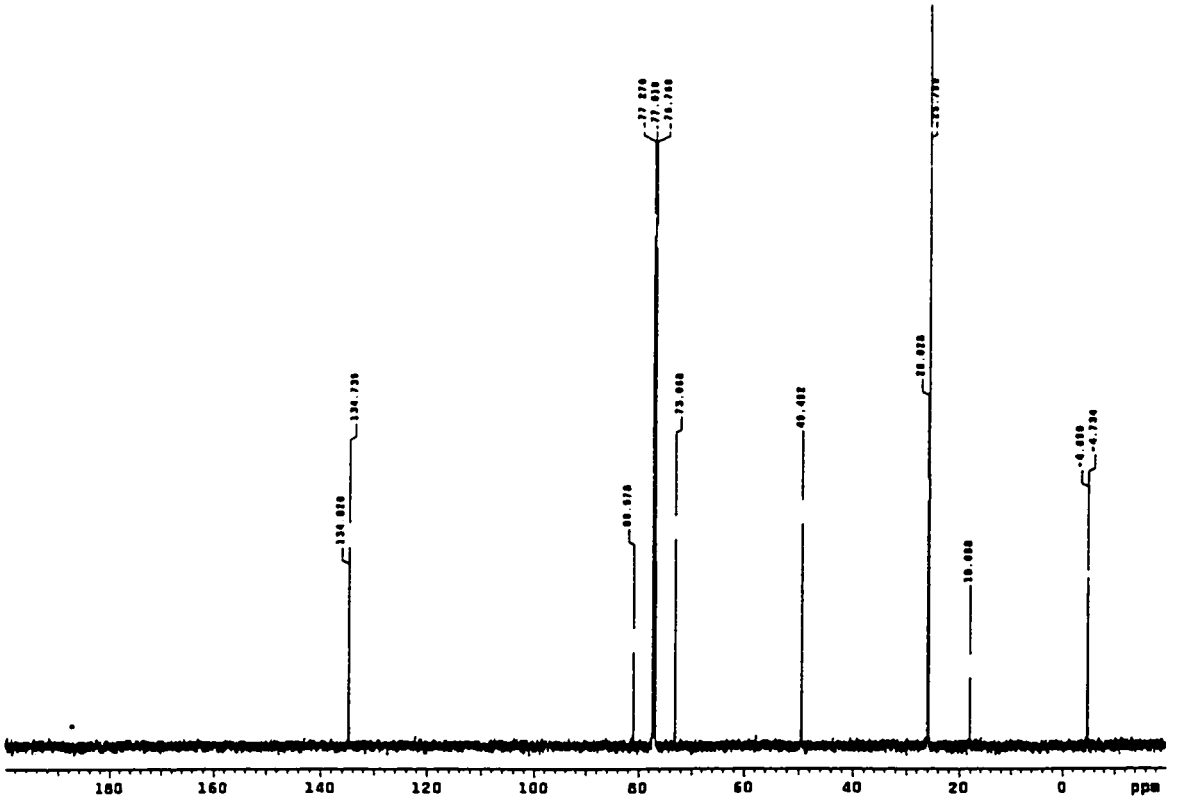


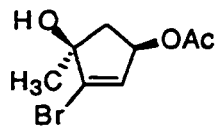



HO
OTBS
H3C
Br

14a

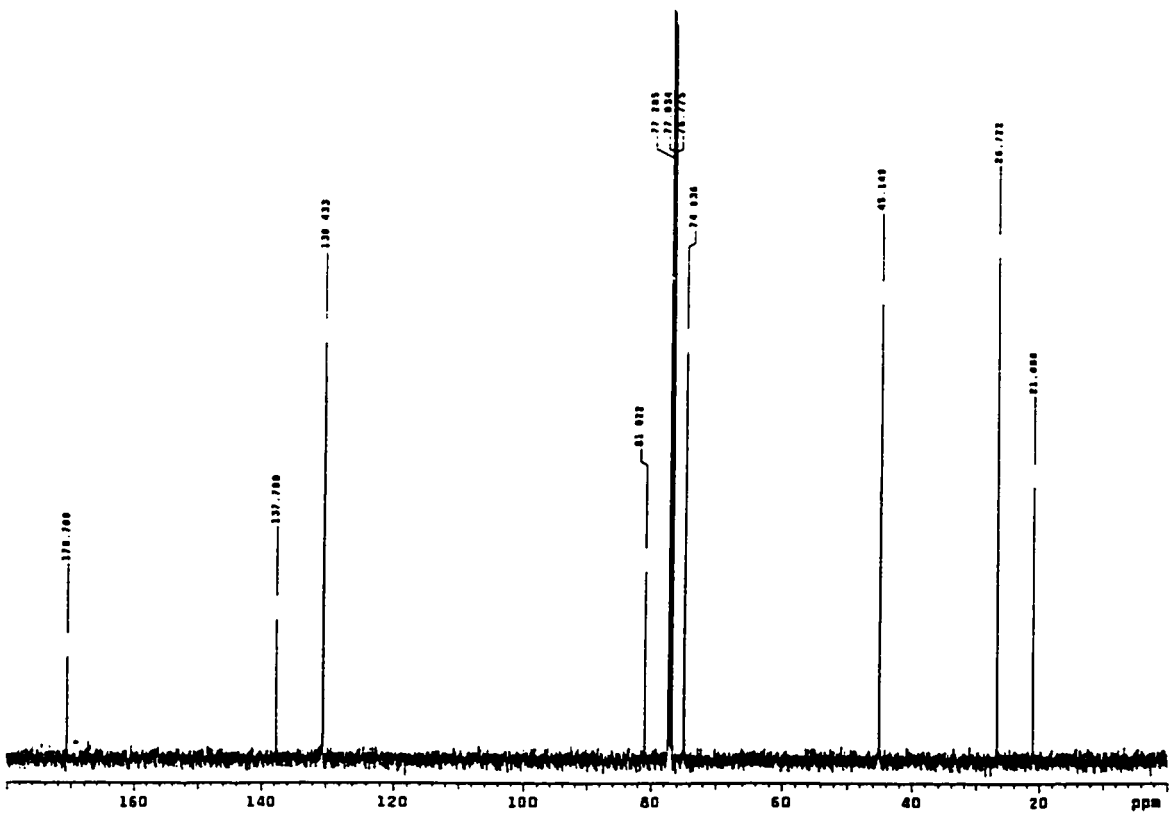

8
7
6
5
4
3
2
1
-0
ppm

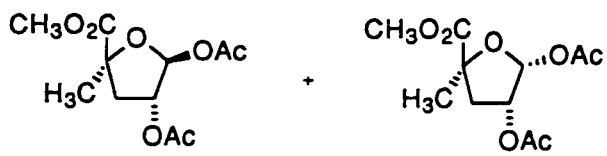

180
160
140
120
100
80
60
40
20
0
ppm


HO
OAc
H3C
Br

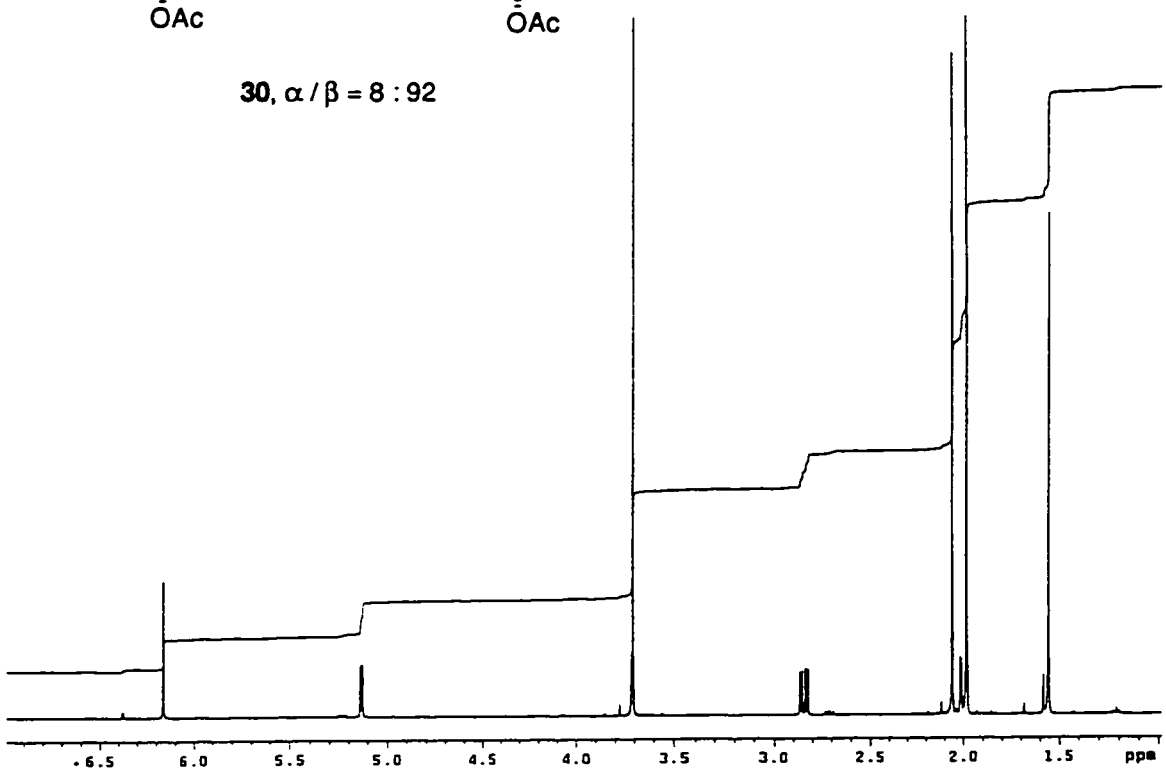
19

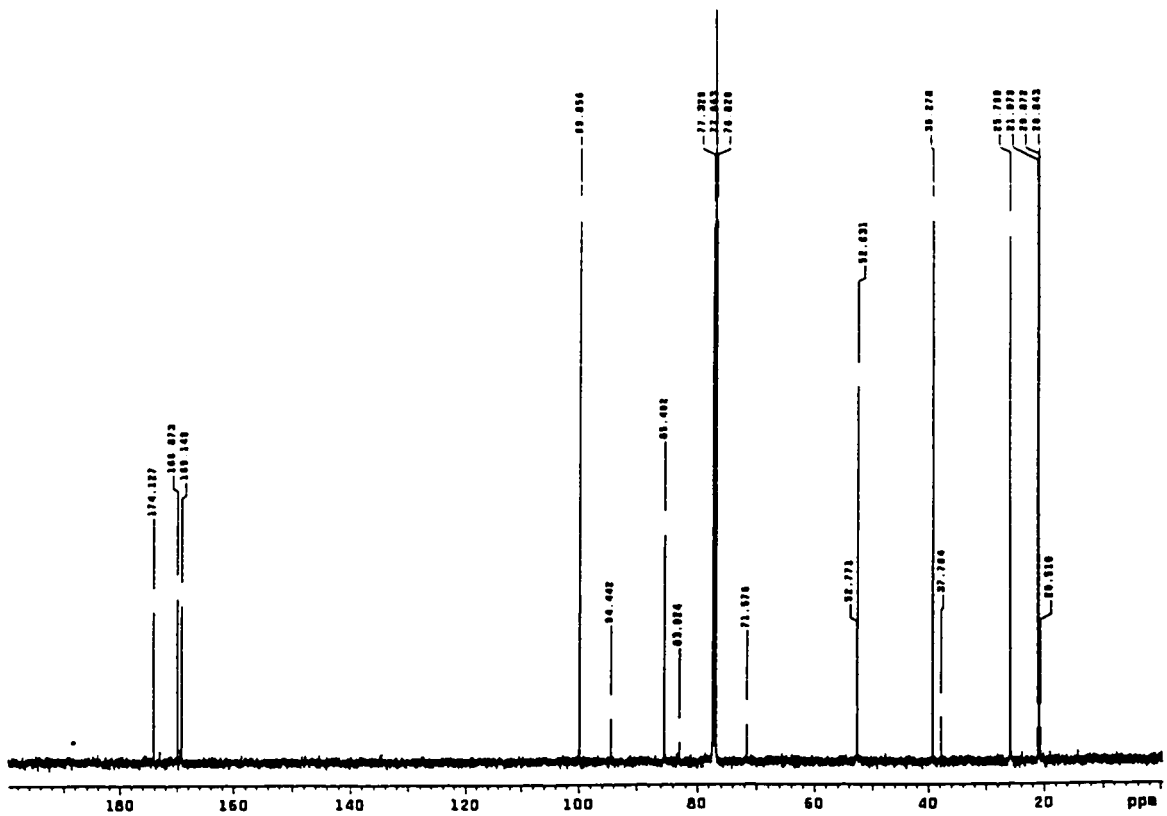
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

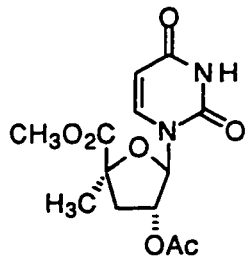

160
140
120
100
80
60
40
20
ppm



30, $\alpha / \beta = 8 : 92$

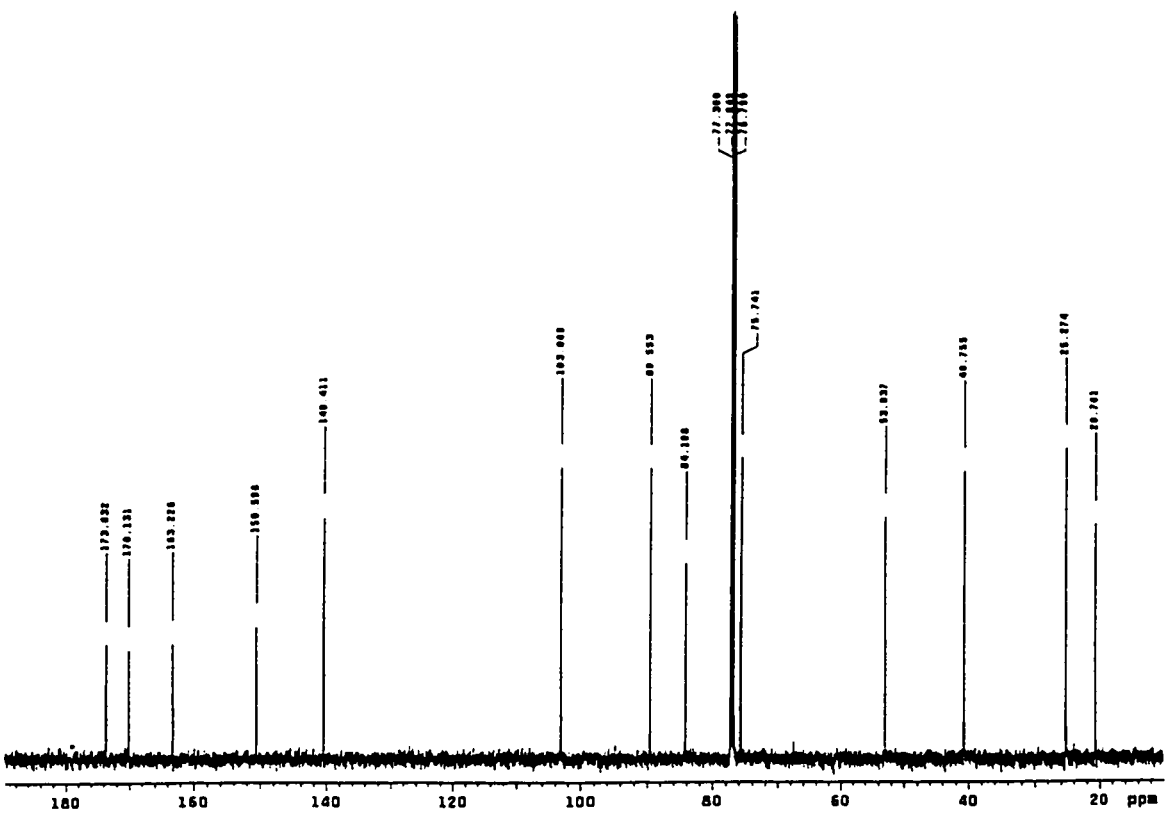


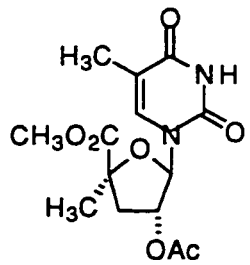



O
NH
CH3O2C
O
N
O
H3C
OAc

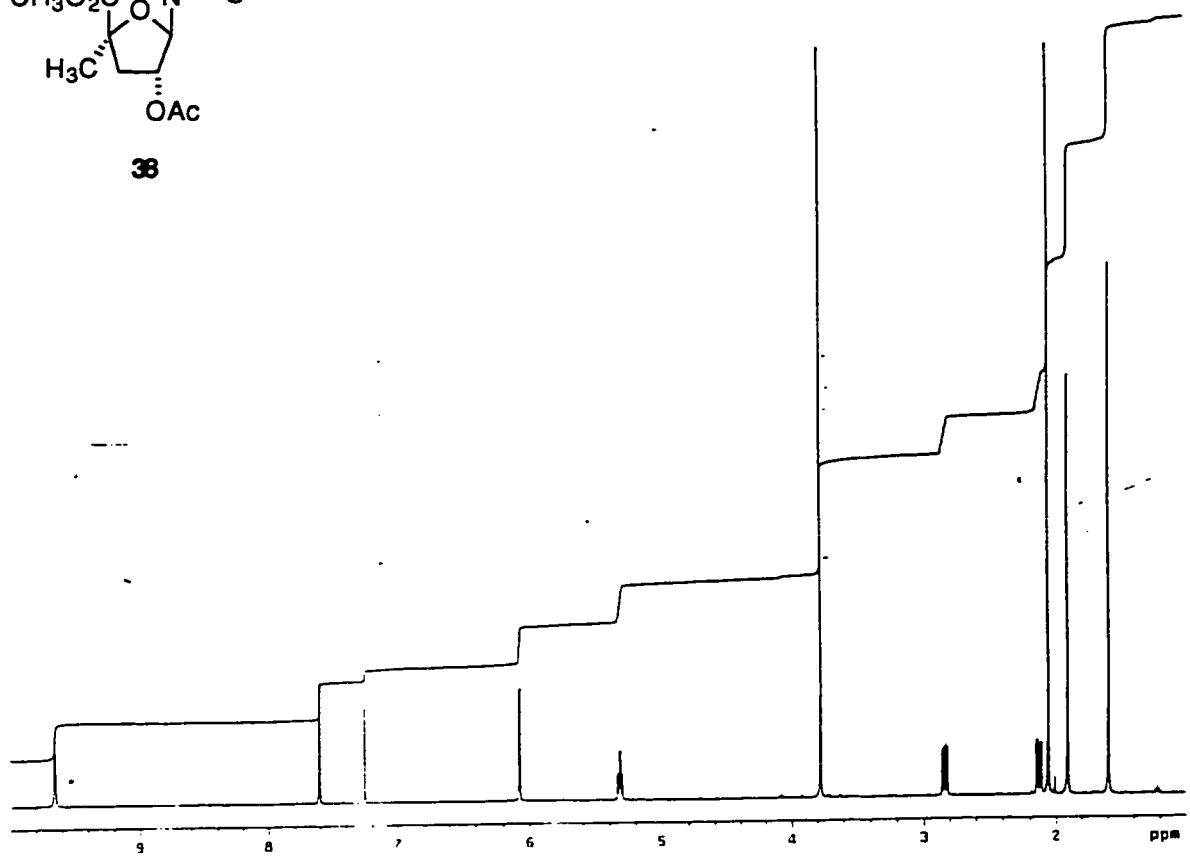
37

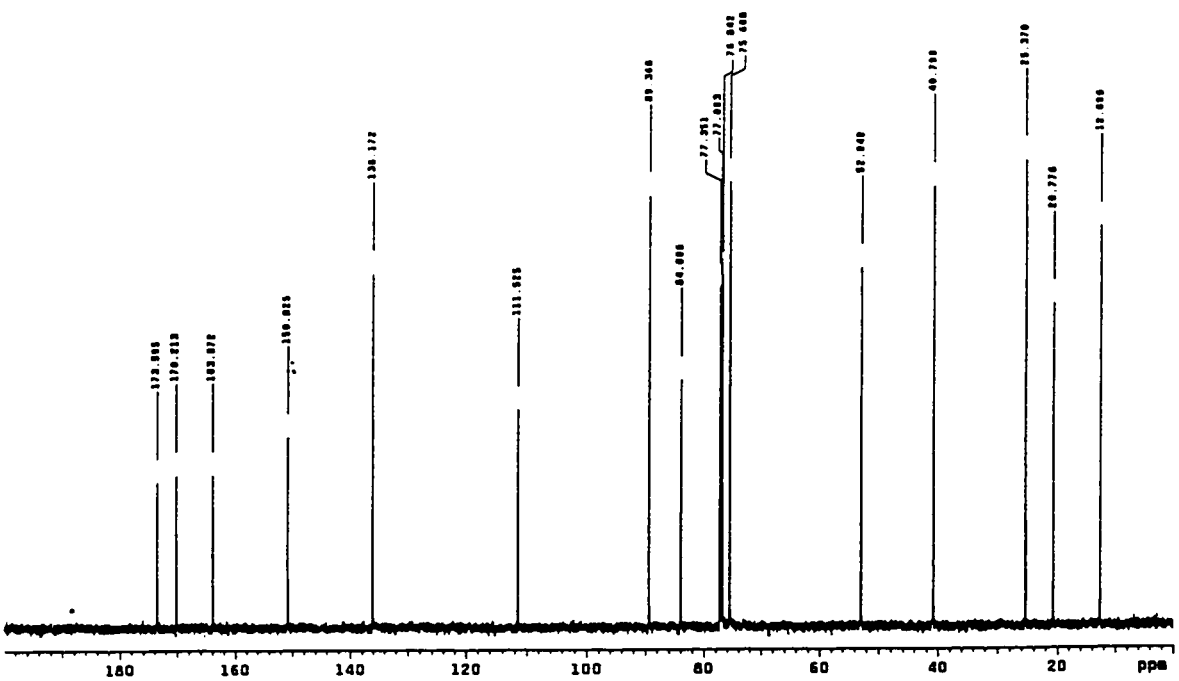
9
8
7
6
5
4
3
2
ppm

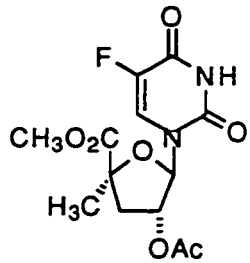

180
160
140
120
100
80
60
40
20
ppm


H3C
NH
CH3O2C
O
N
O
H3C
OAc

38

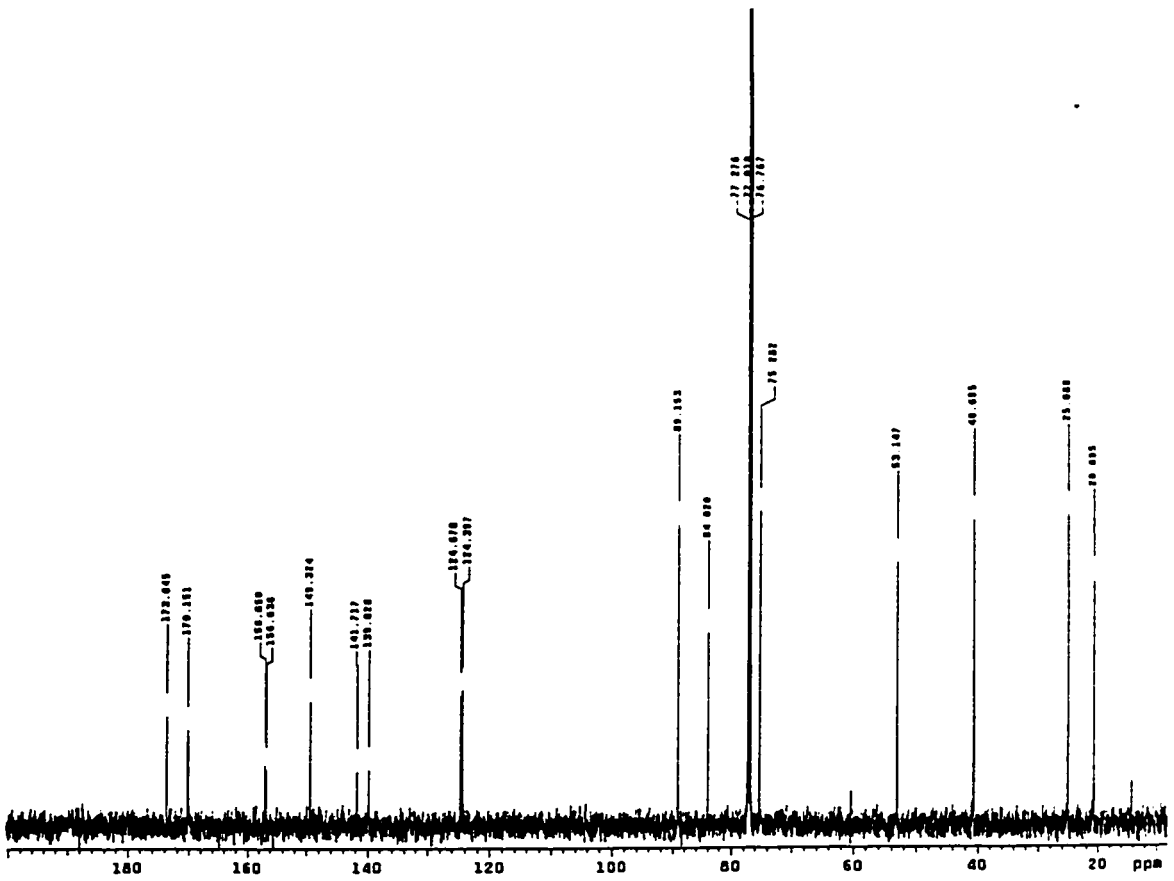

9
8
7
6
5
4
3
2
ppm

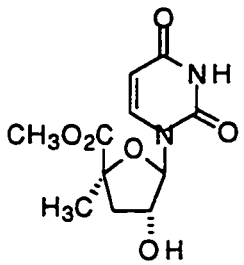

180
160
140
120
100
80
60
40
20
ppm


O
F
NH
O
CH_3O_2C
O
N
H_3C
OAc

39

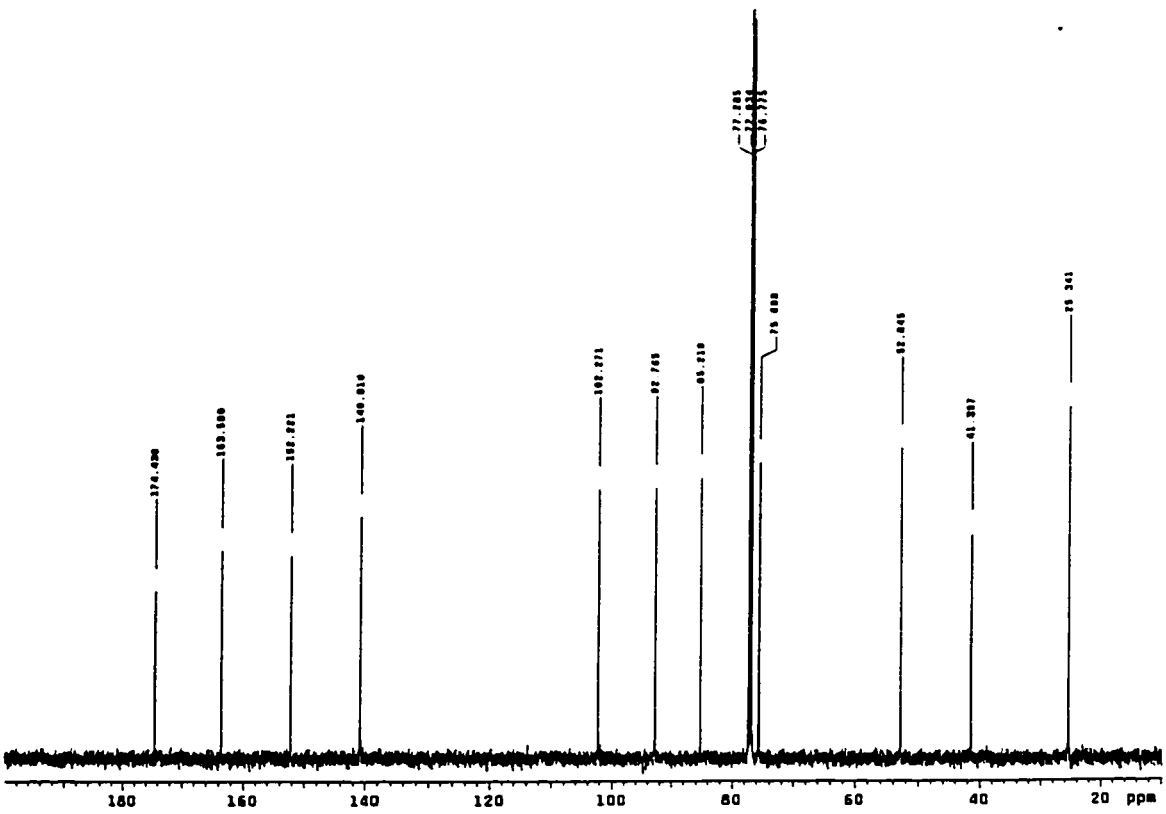
9
8
7
6
5
4
3
2
ppm

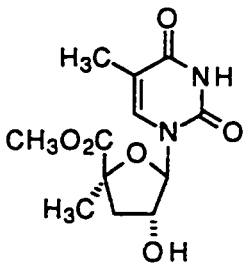

180
160
140
120
100
80
60
40
20
ppm


O
NH
CH3O2C
O
N
O
H3C
OH

41

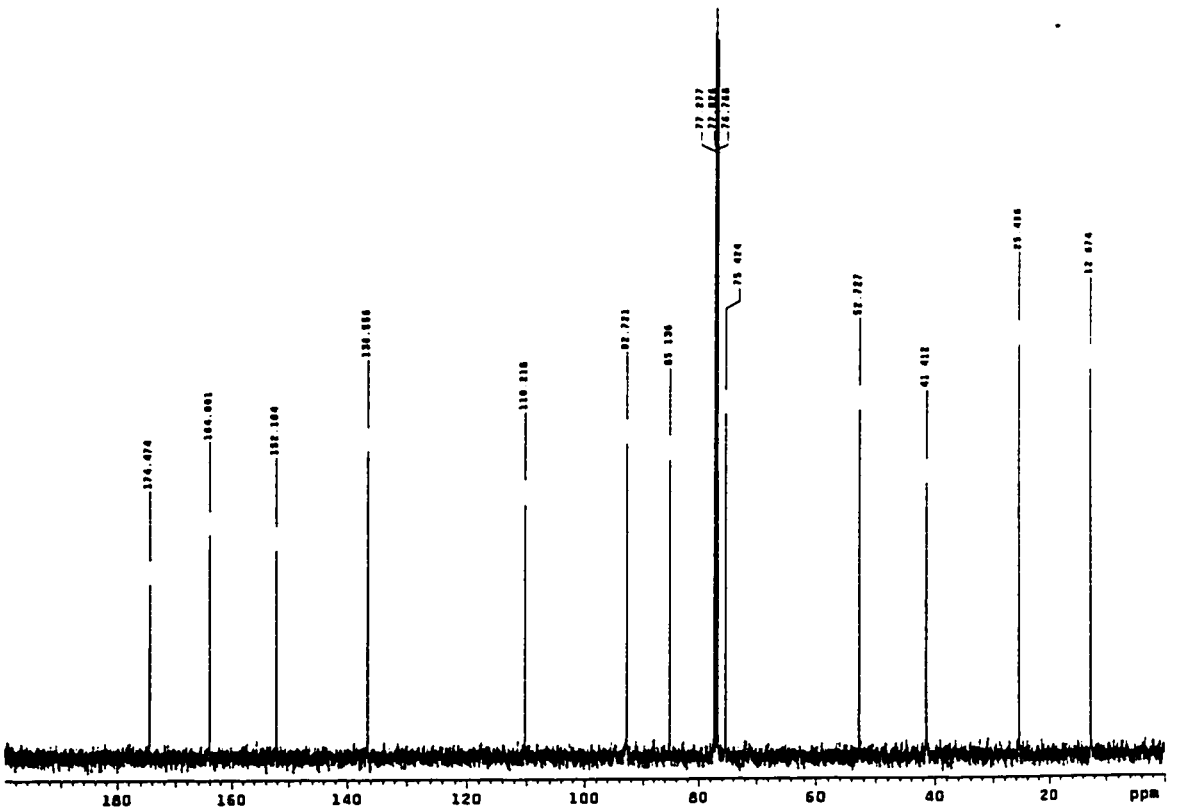
11
10
9
8
7
6
5
4
3
2
ppm

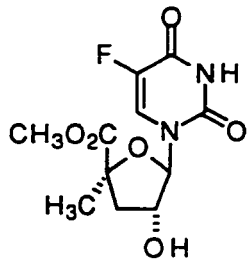

180
160
140
120
100
80
60
40
20 ppm


O
H3C
NH
CH3O2C
O
N
O
H3C
OH

42

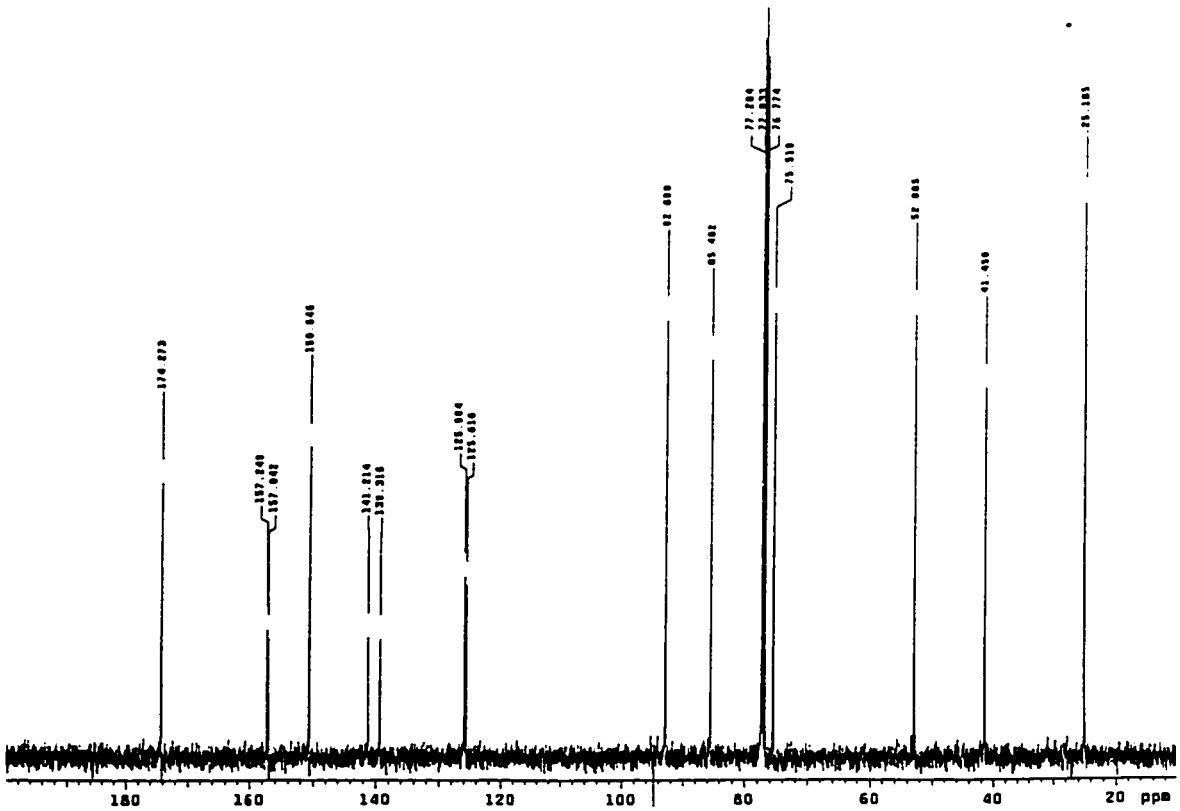
11
10
9
8
7
6
5
4
3
2
ppm

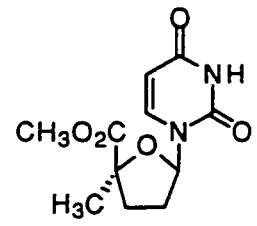

180
160
140
120
100
80
60
40
20
ppm


F
NH
O
O
CH_3O_2C
O
N
H_3C
OH

43

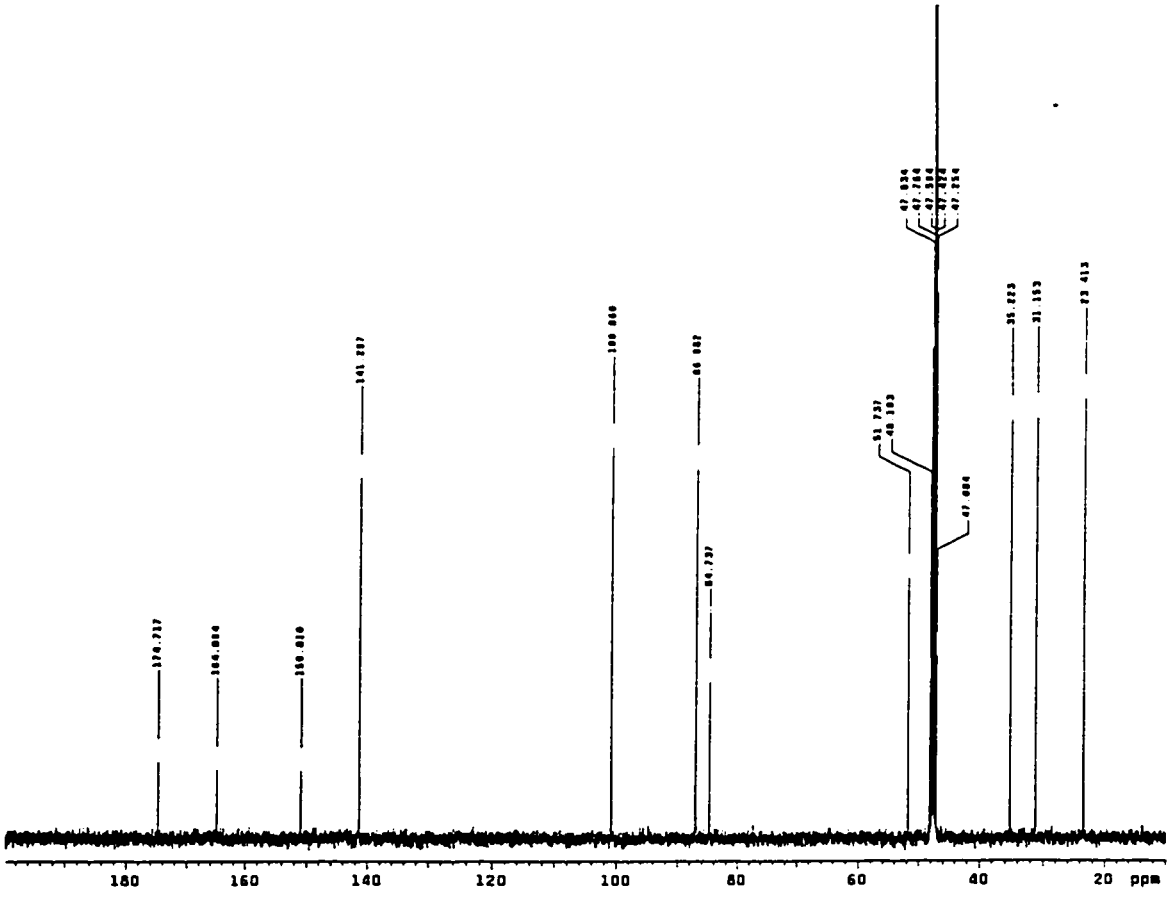
11
10
9
8
7
6
5
4
3
2
ppm

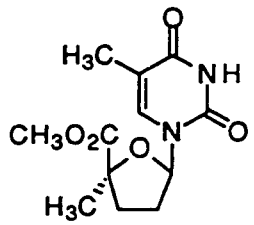

180
160
140
120
100
80
60
40
20 ppm


O
NH
CH3O2C
O
N
O
H3C

44

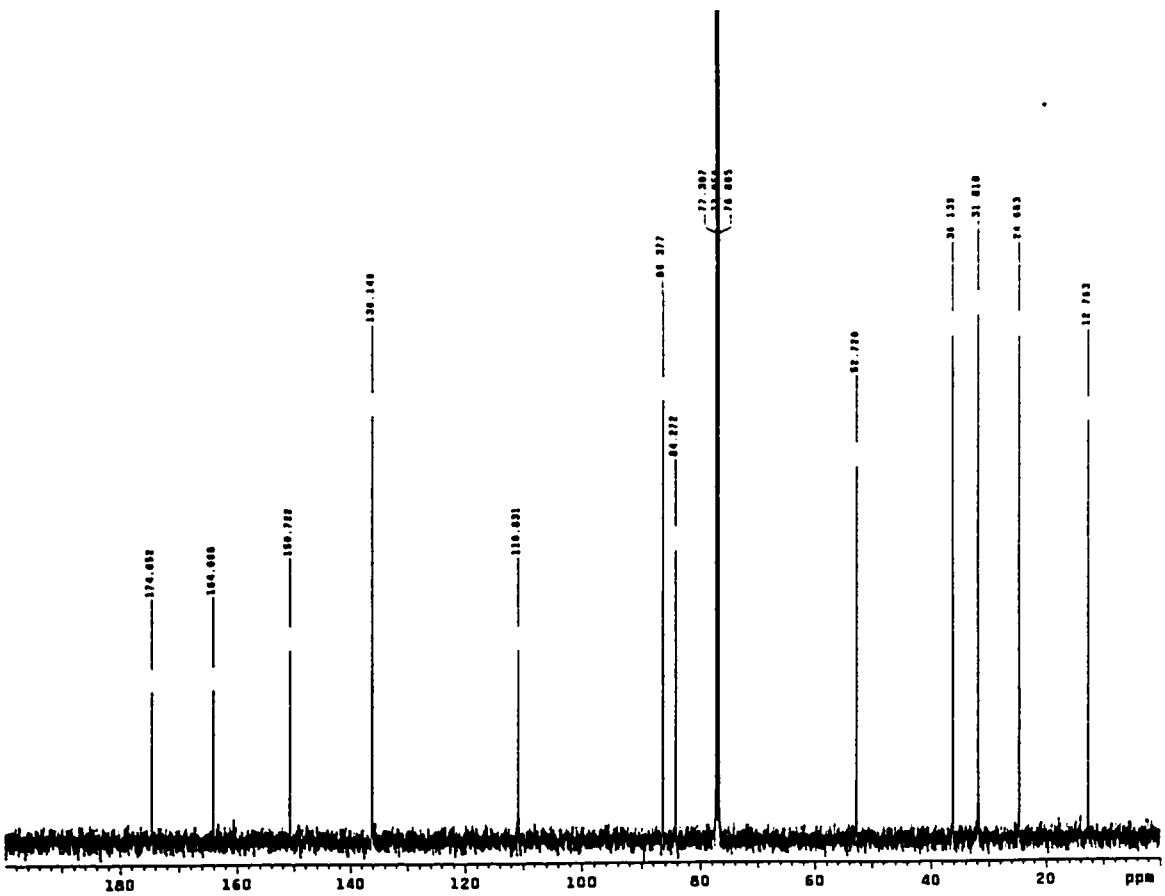
8
7
6
5
4
3
2
ppm

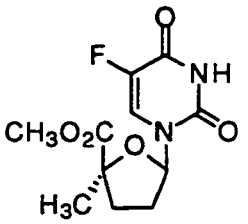

180
160
140
120
100
80
60
40
20 ppm


H3C
NH
CH3O2C
O
N
O
H3C

45

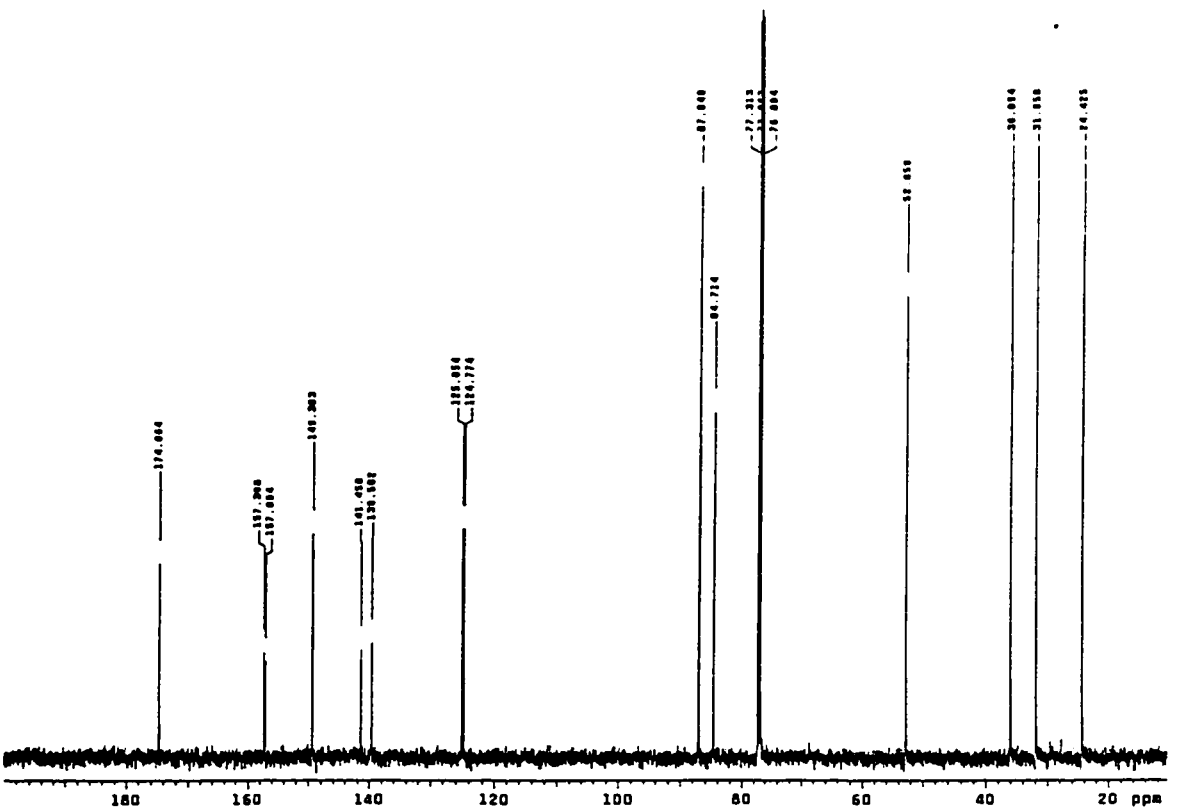
9
8
7
6
5
4
3
2
ppm

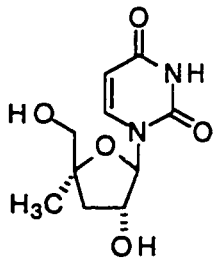

180
160
140
120
100
80
60
40
20
ppm


F
NH
O
O
N
O
CH_3O_2C
H_3C

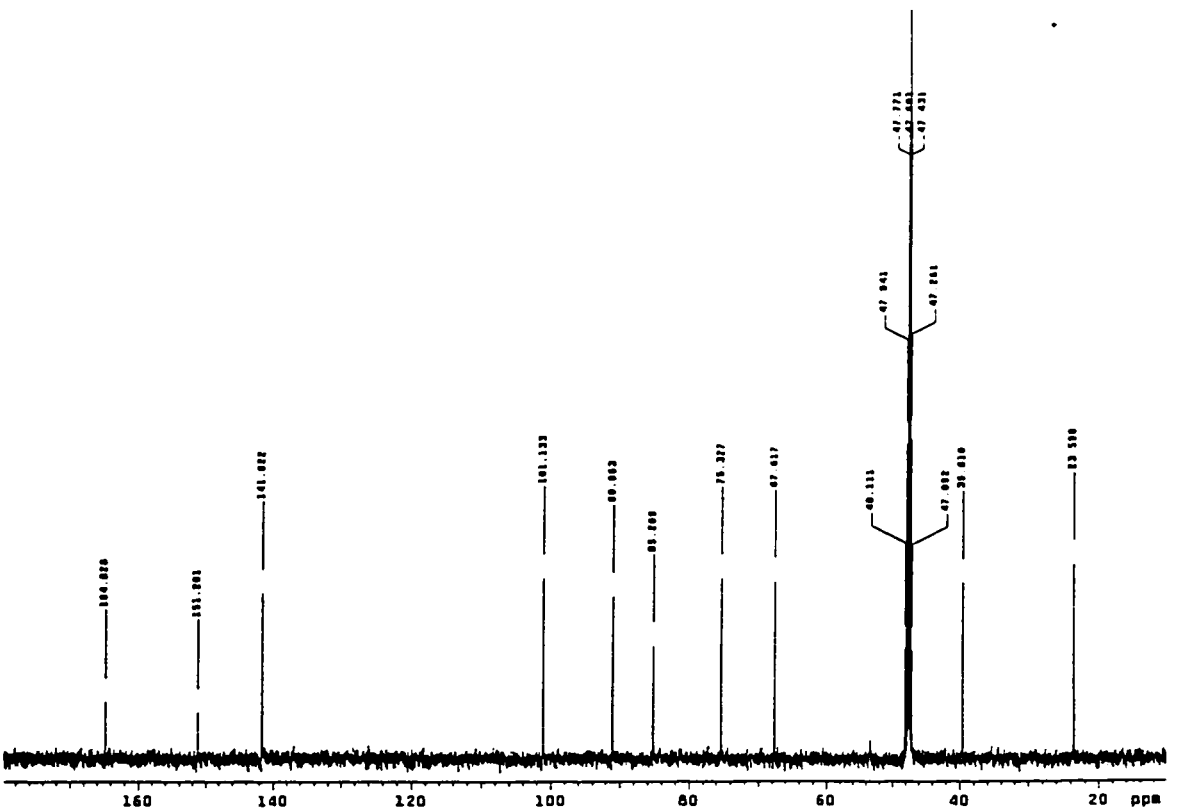
46

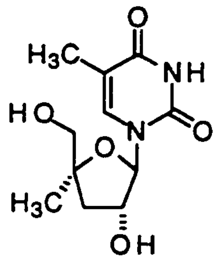
10
9
8
7
6
5
4
3
2
ppm


180
160
140
120
100
80
60
40
20 ppm

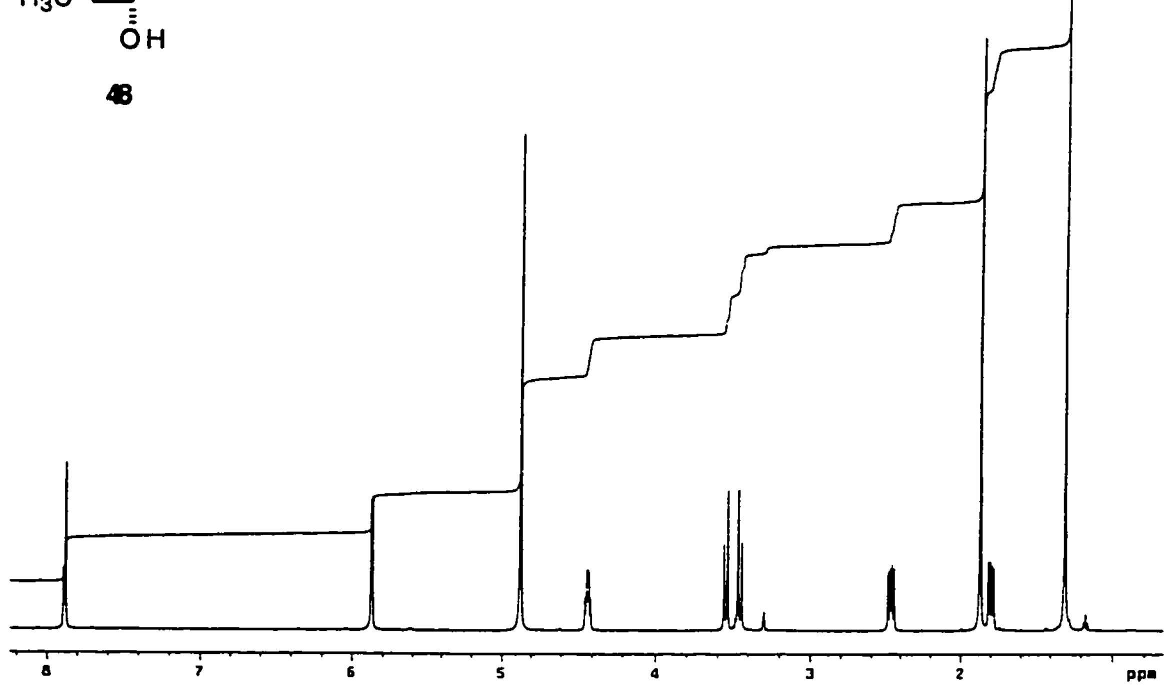


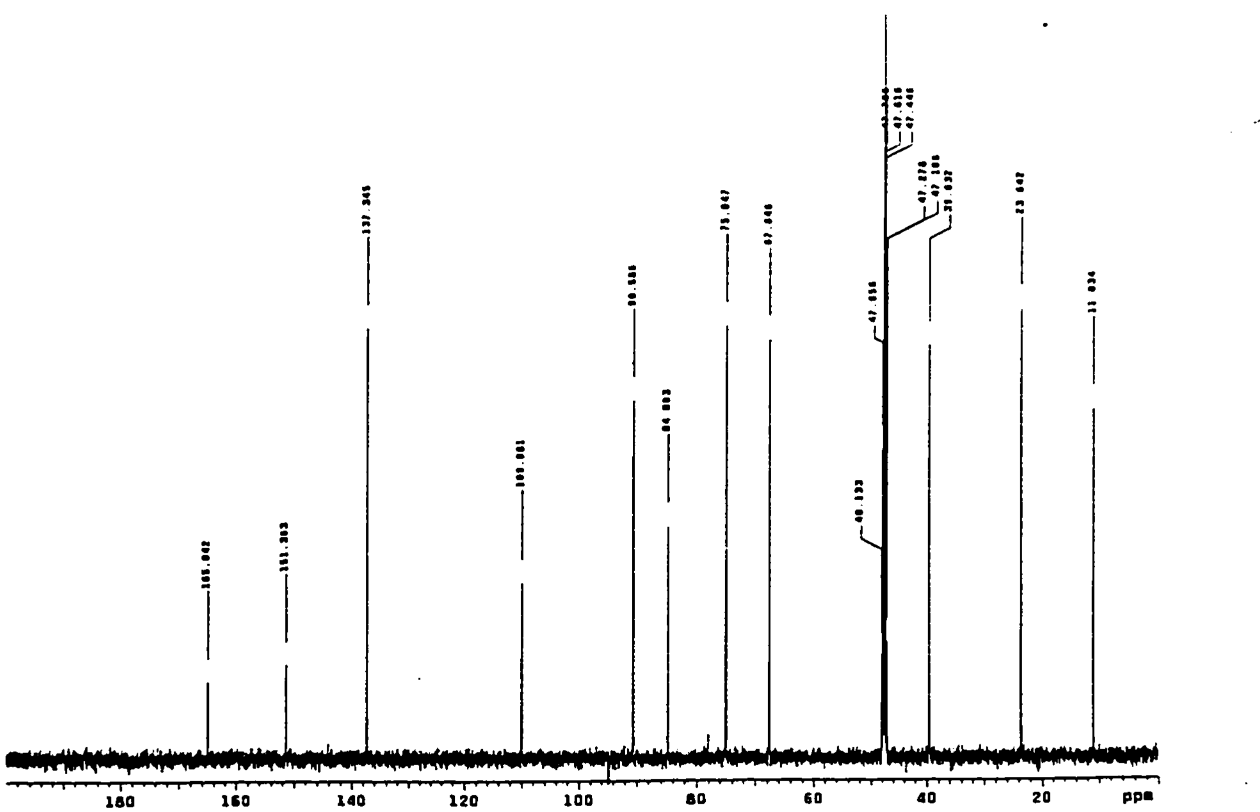
47




H3C
NH
O
HO
N
H3C
OH

48


8
7
6
5
4
3
2
ppm


180
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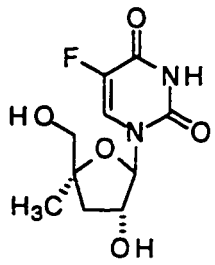
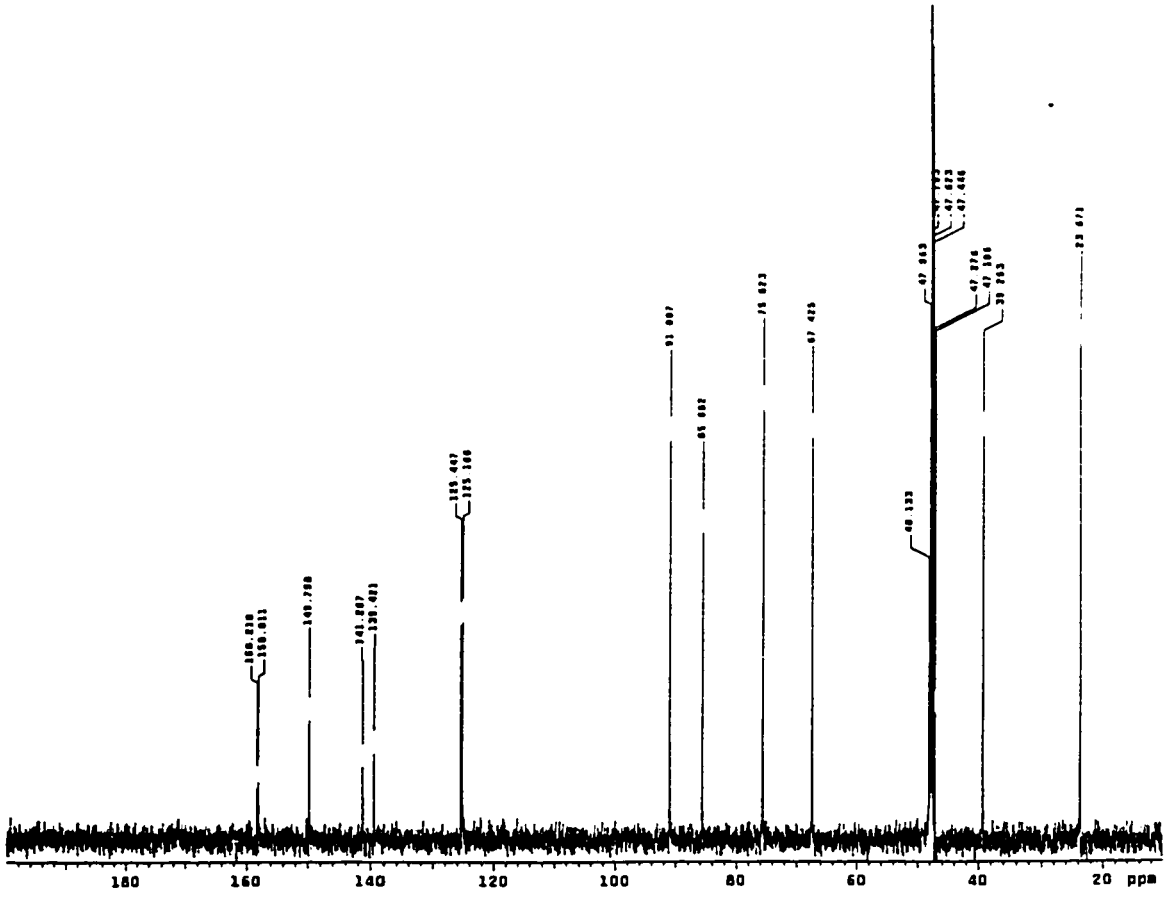
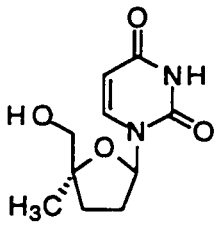
140
120
100
80
60
40
20
ppm

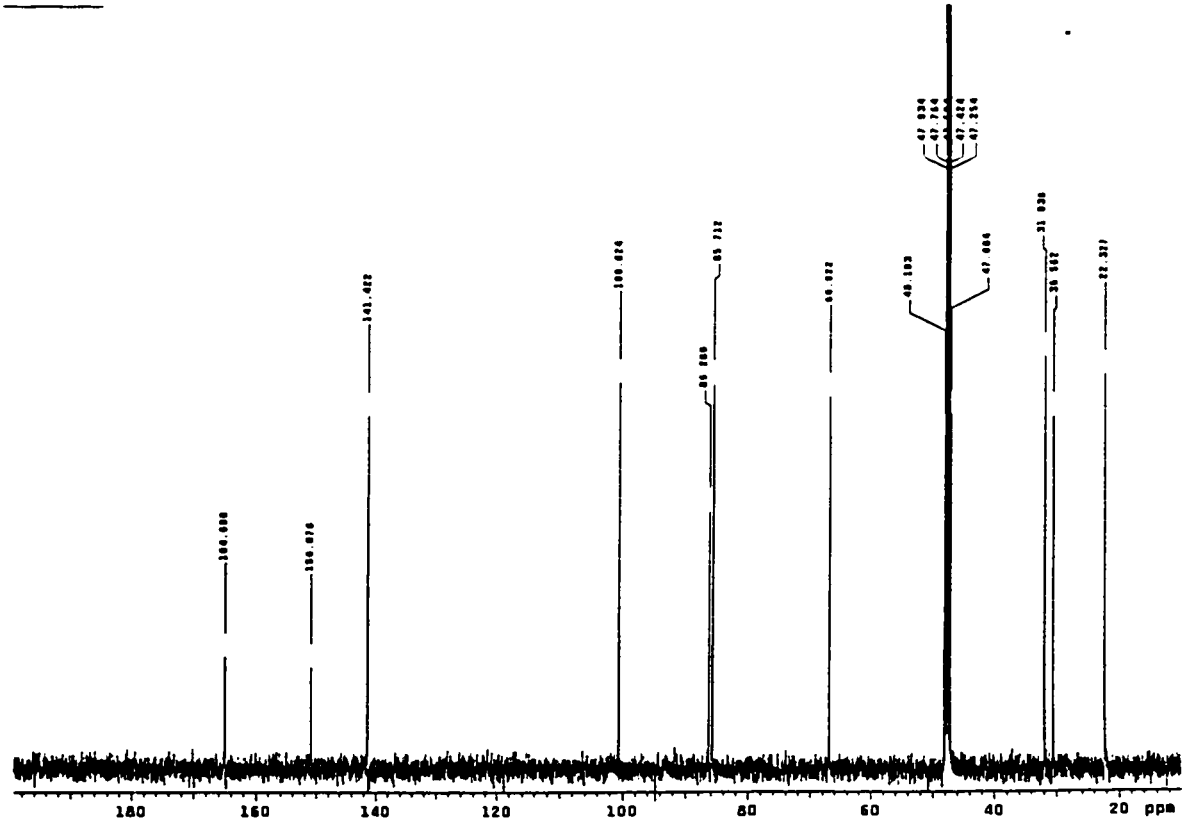


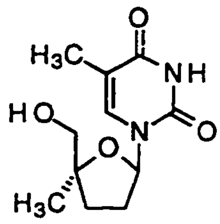
49



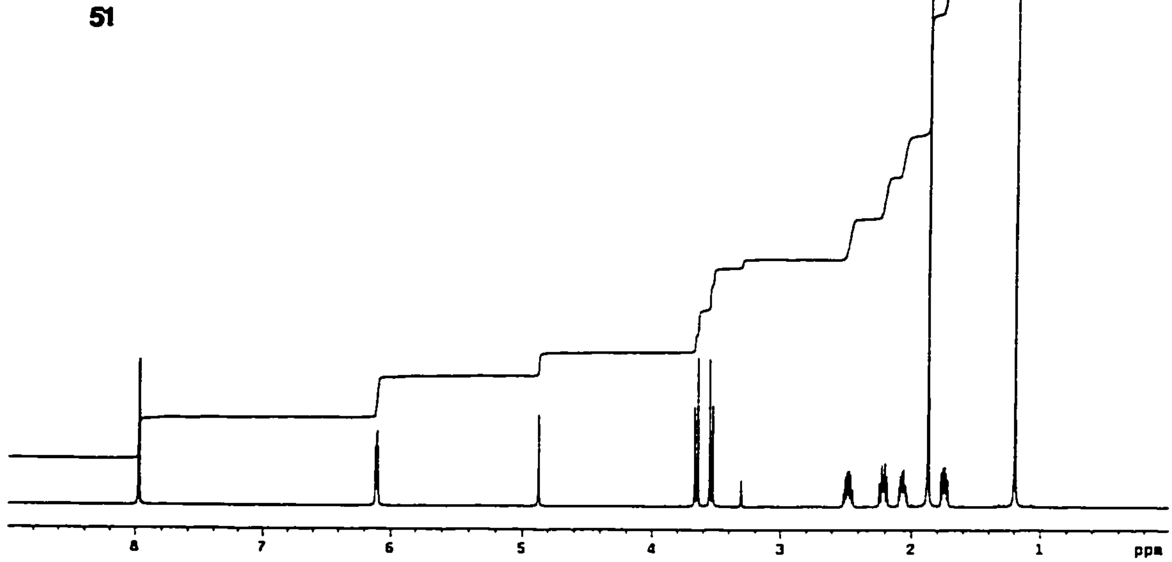


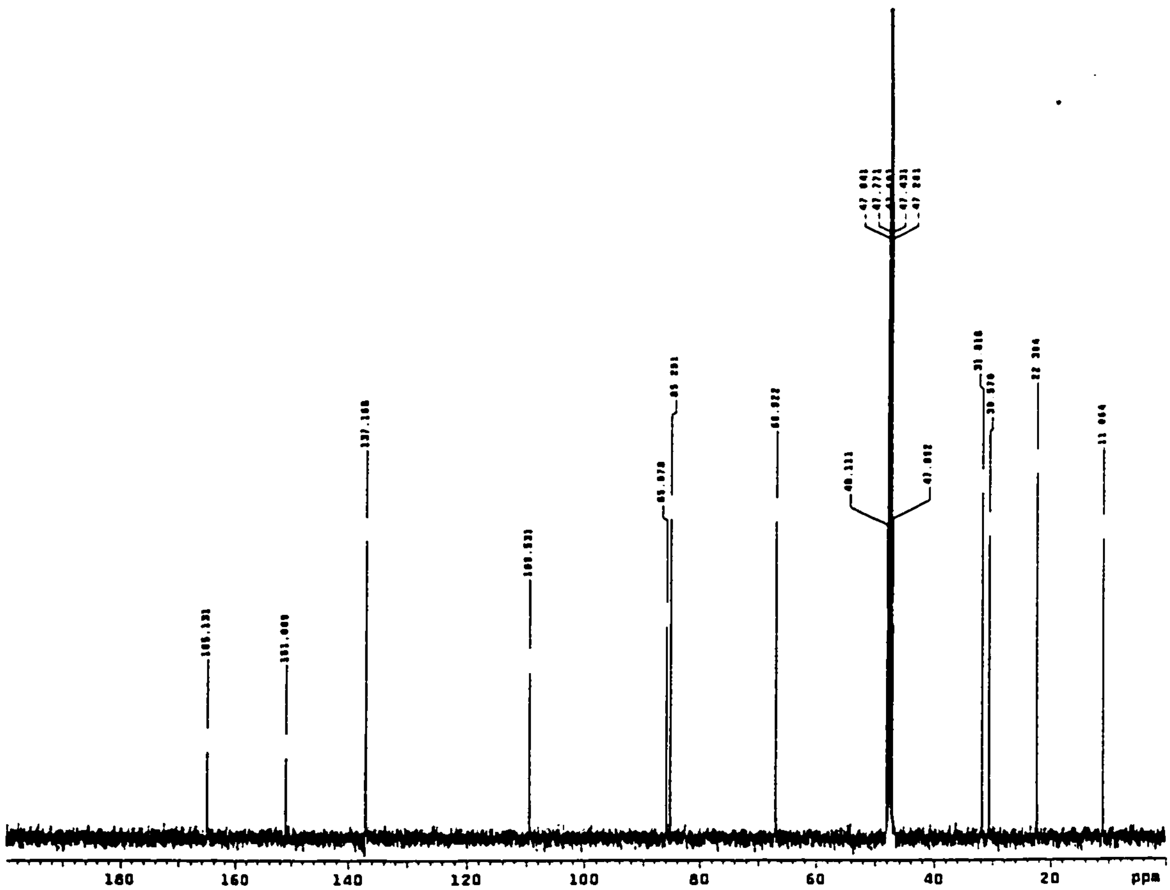
50

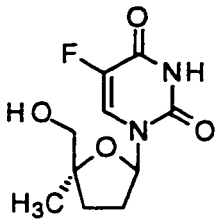



O
H_3C
NH
HO
O
N
O
H_3C

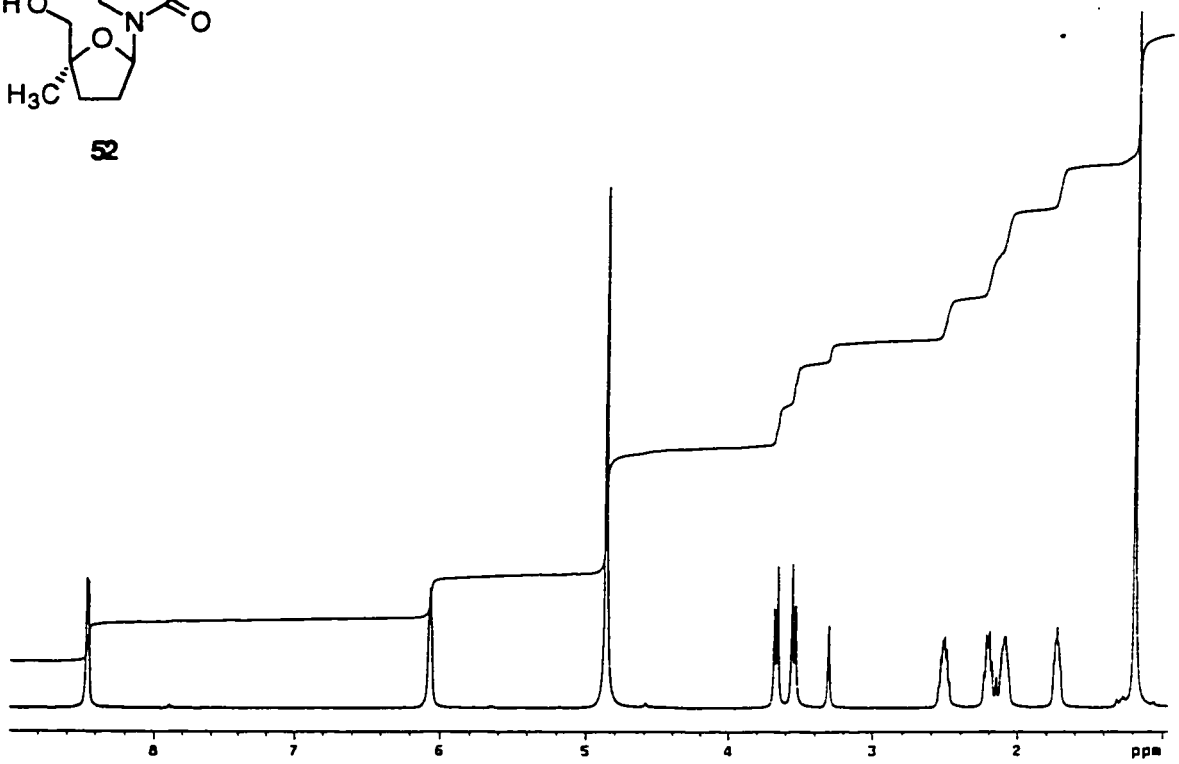
51

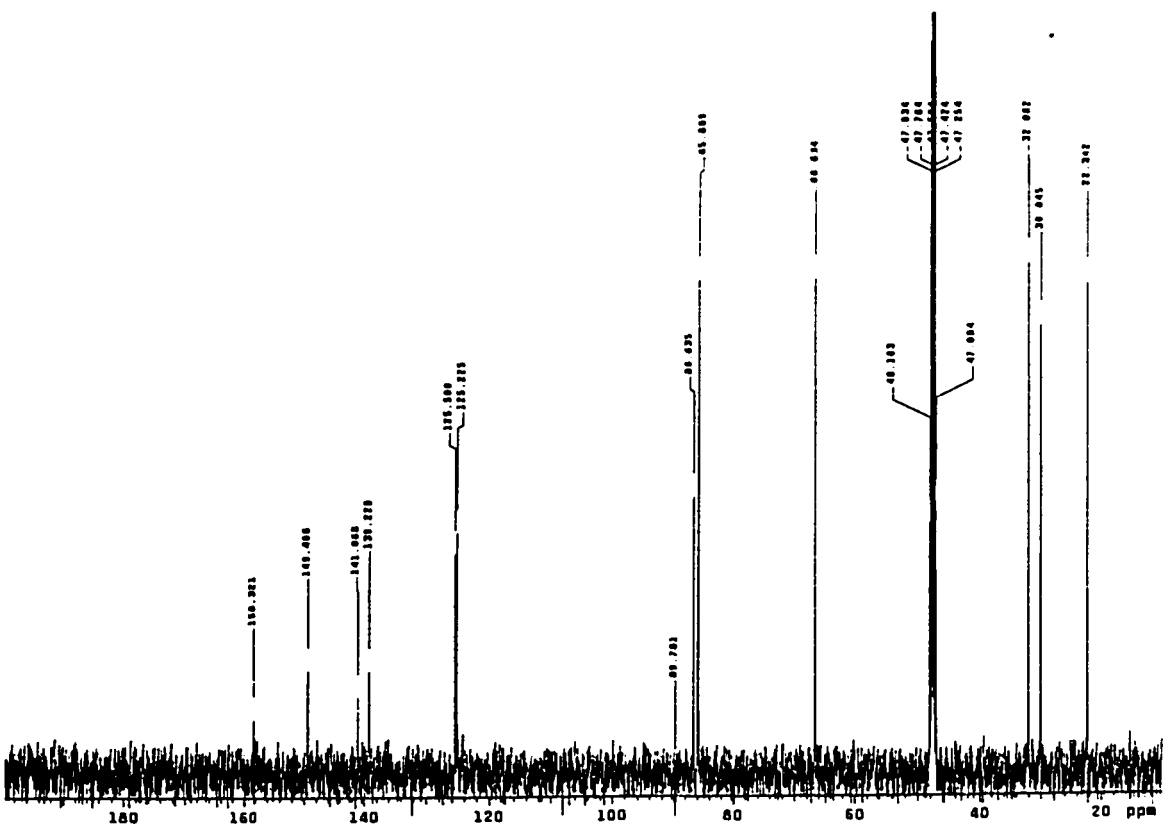

8
7
6
5
4
3
2
1
ppm

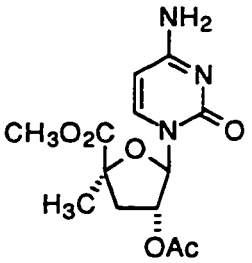

180
160
140
120
100
80
60
40
20
ppm



52

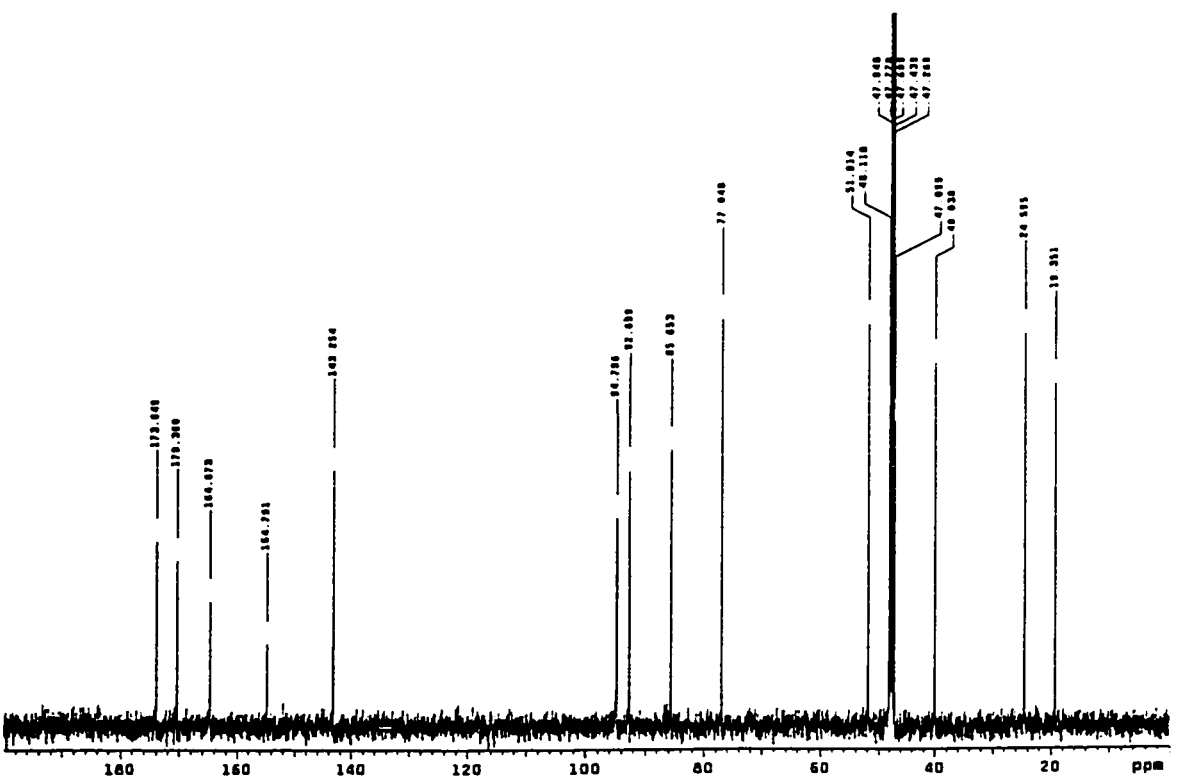


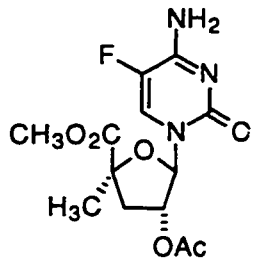



NH2
N
CH3O2C
N
O
O
H3C
OAc

53

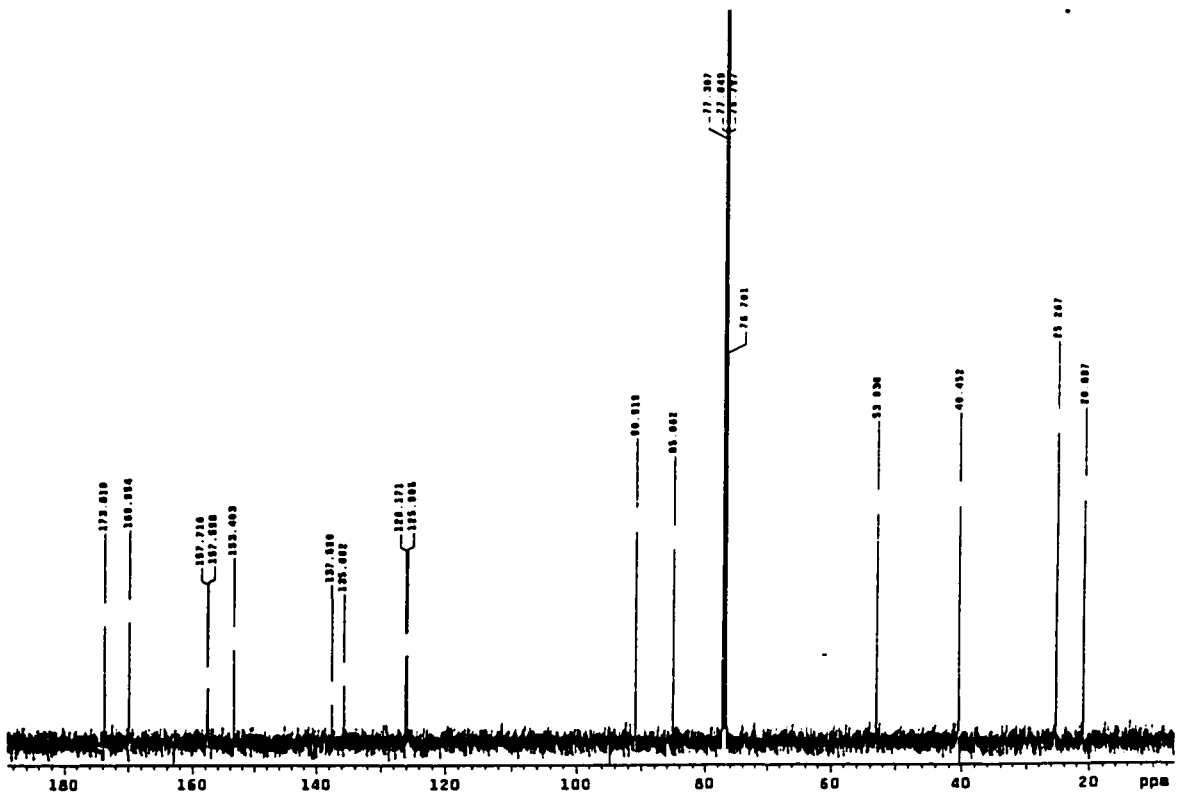
8
7
6
5
4
3
2
ppm

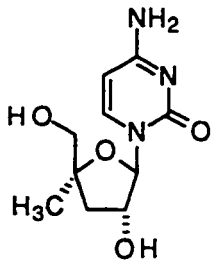

180
160
140
120
100
80
60
40
20
ppm


NH2
F
N
CH3O2C
O
N
O
H3C
OAc

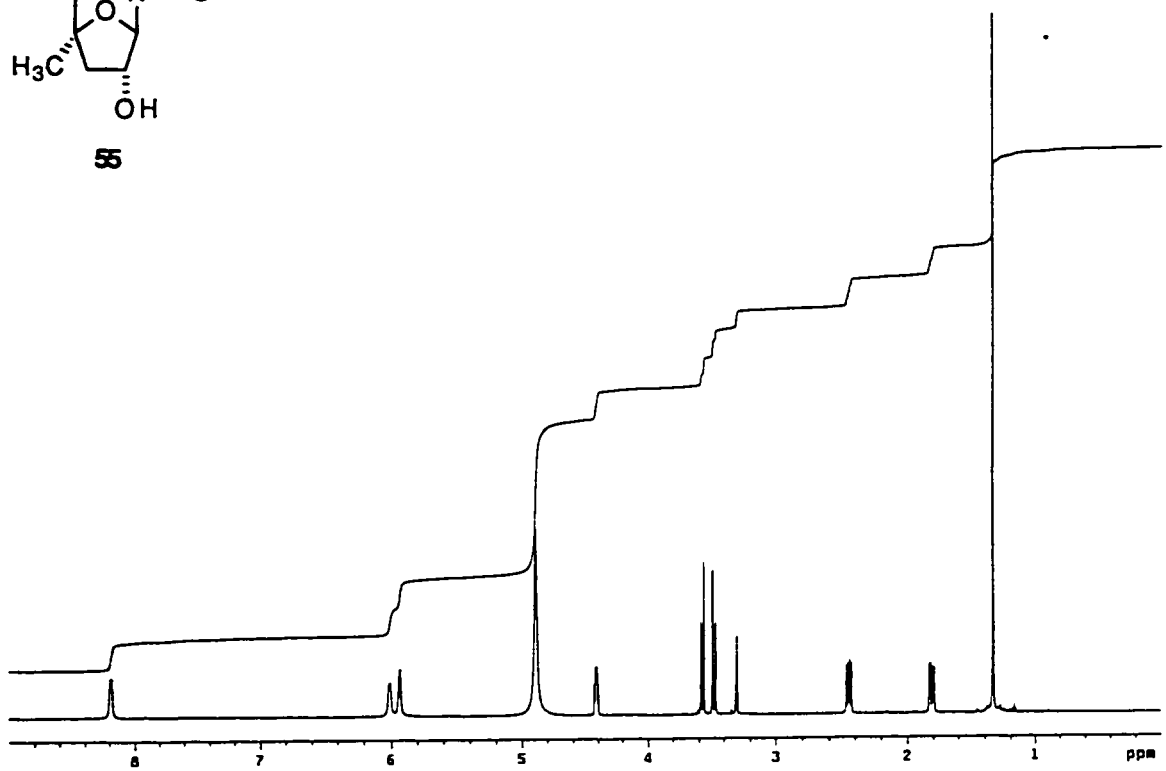
54

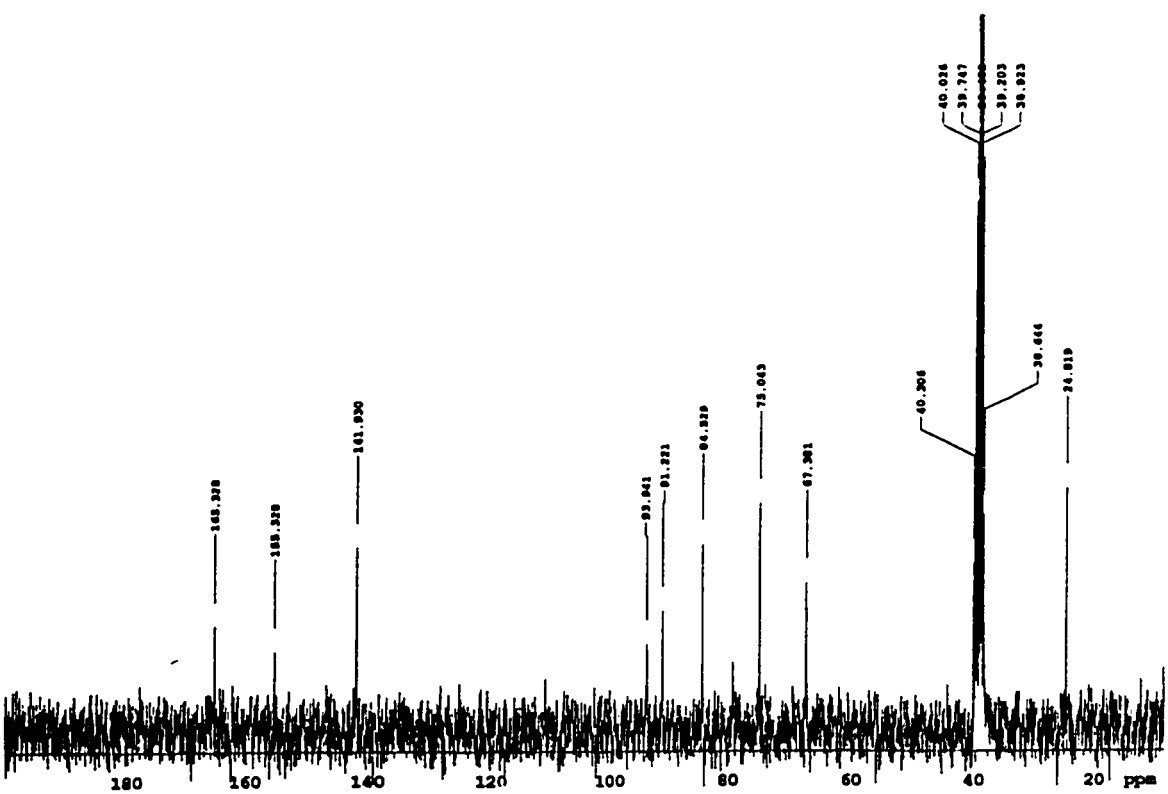
8
7
6
5
4
3
2
ppm


180
160
140
120
100
80
60
40
20
ppm


NH2
N
HO
O
N
O
H3C
OH

55


8
7
6
5
4
3
2
1
ppm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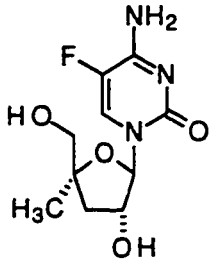
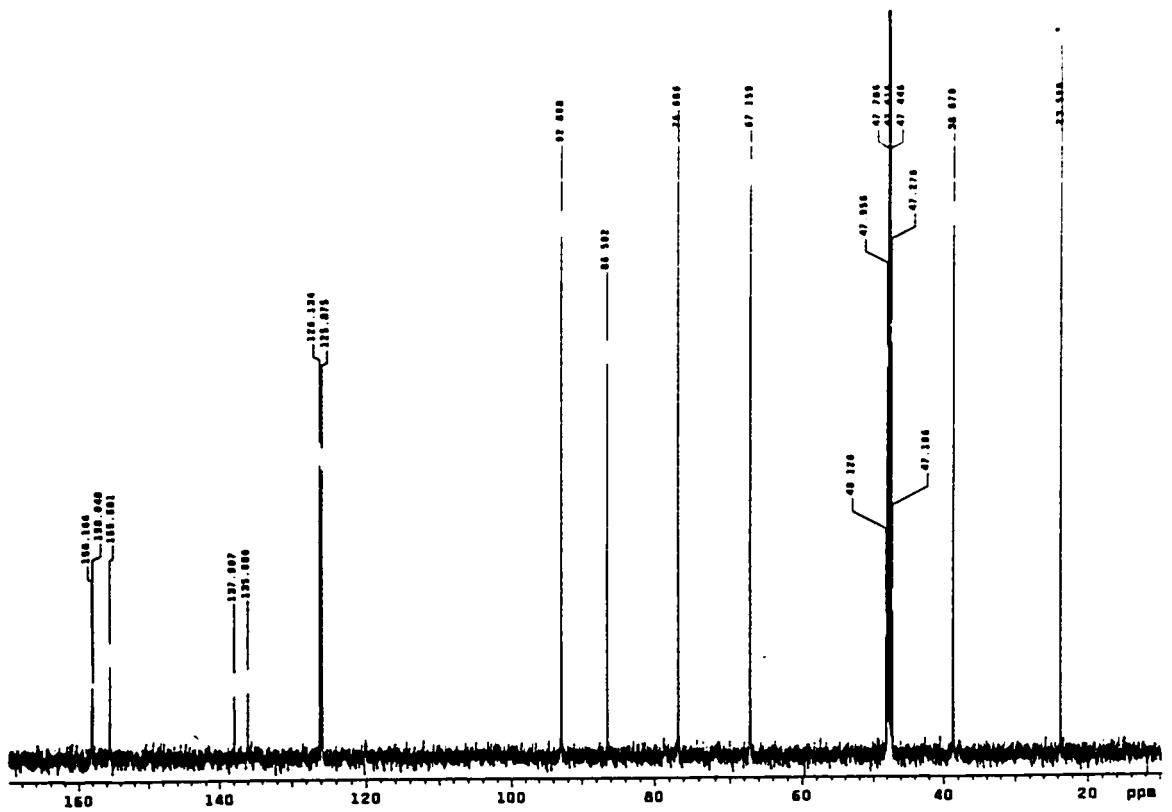
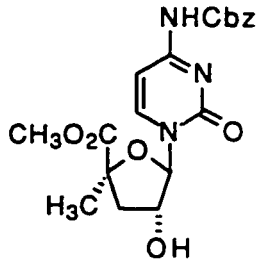
39.747
39.203
38.933
165.328
155.328
141.930
93.841
91.221
84.829
73.043
67.301
40.306
30.644
24.819
180
160
140
120
100
80
60
40
20
ppm

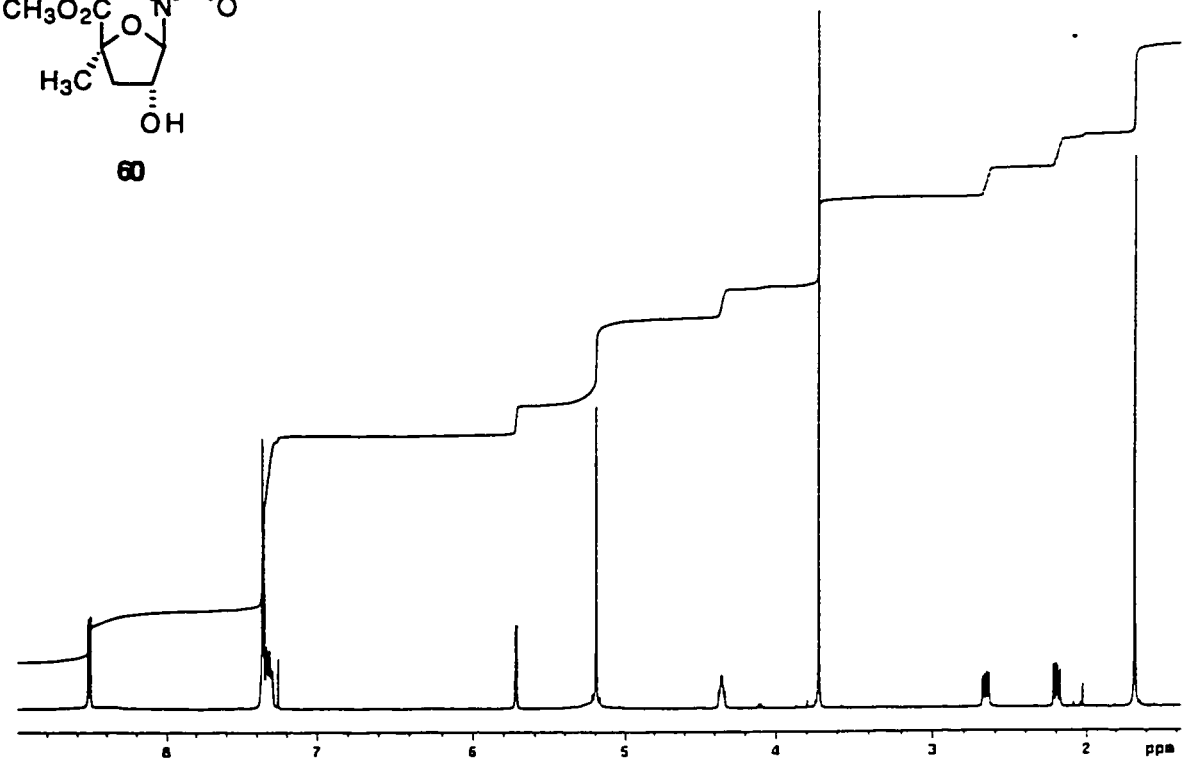


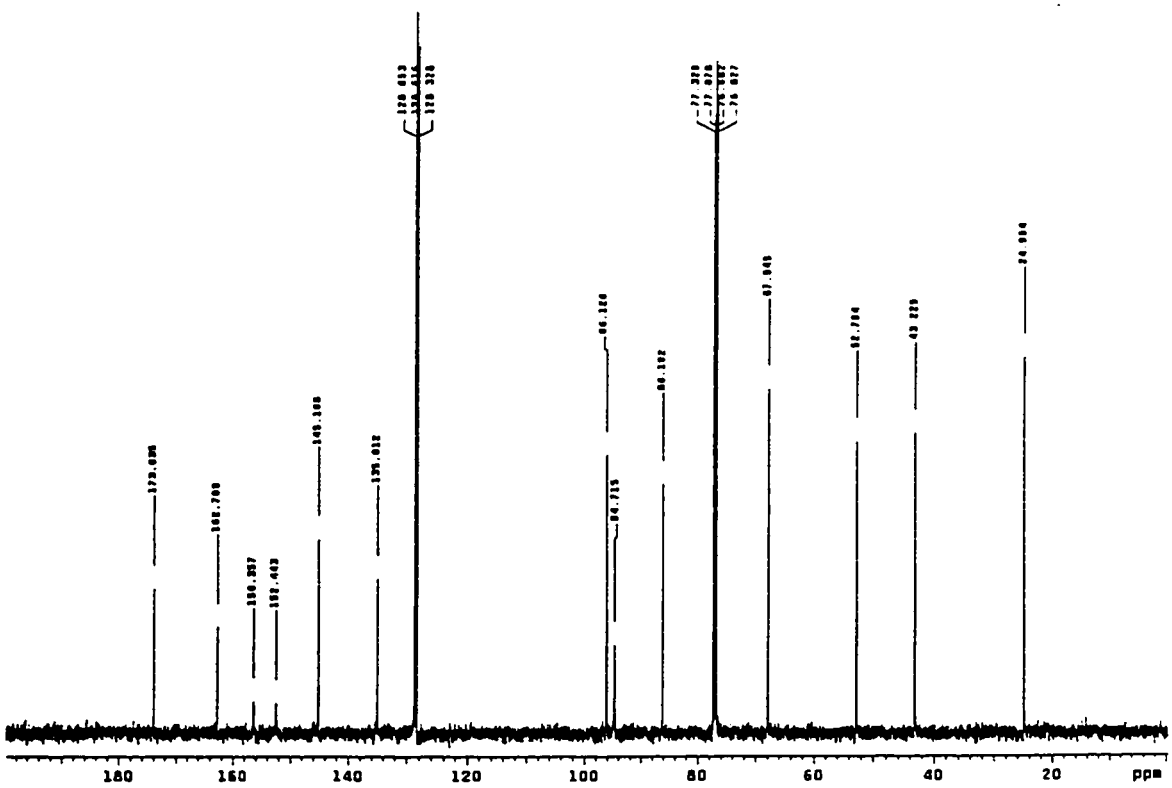
56

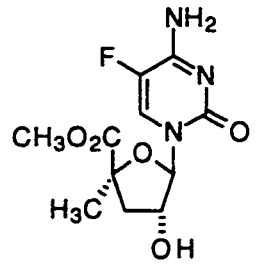



NHCbz
N
CH3O2C
O
N
O
H3C
OH

60

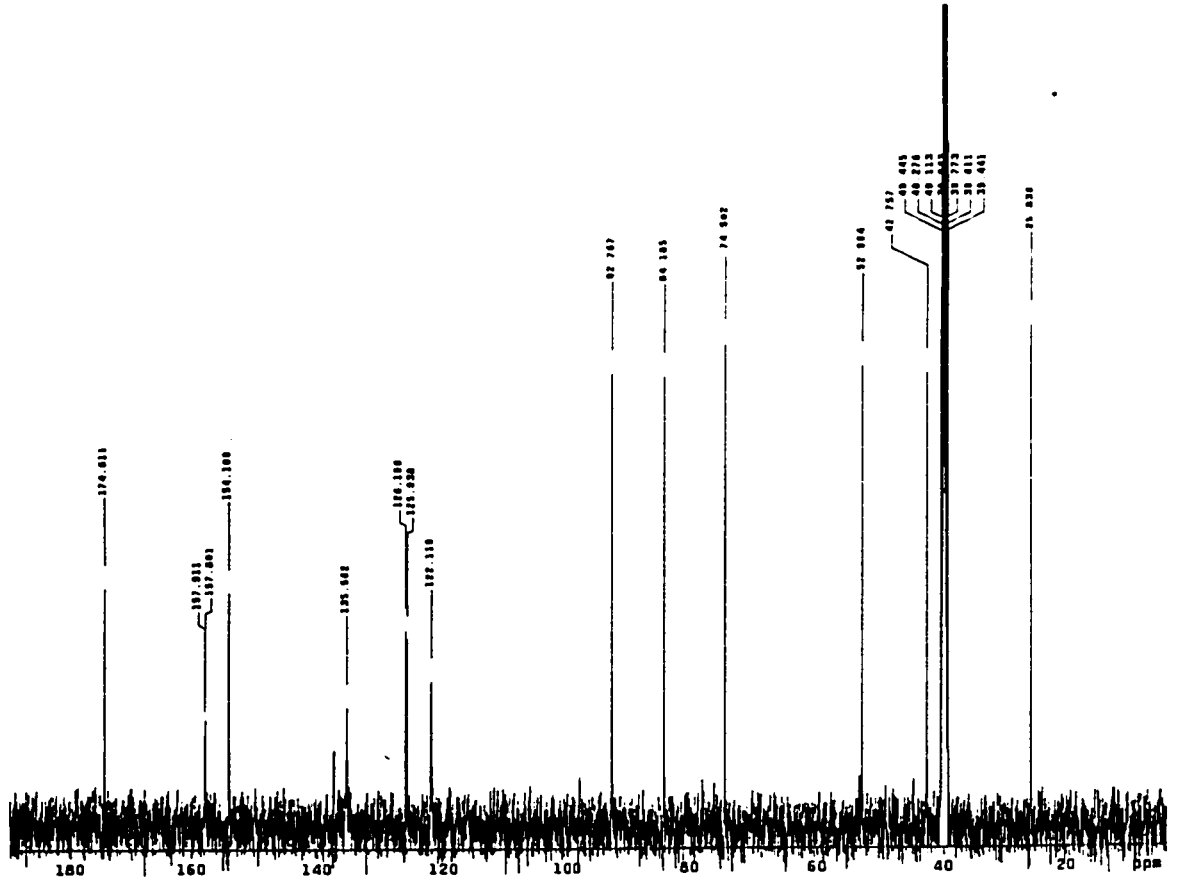

8
7
6
5
4
3
2
ppm

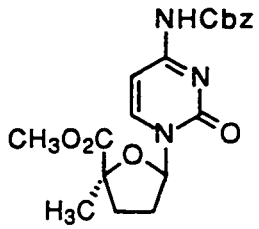

180
160
140
120
100
80
60
40
20
ppm


NH2
F
N
O
CH3O2C
O
N
H3C
OH

62

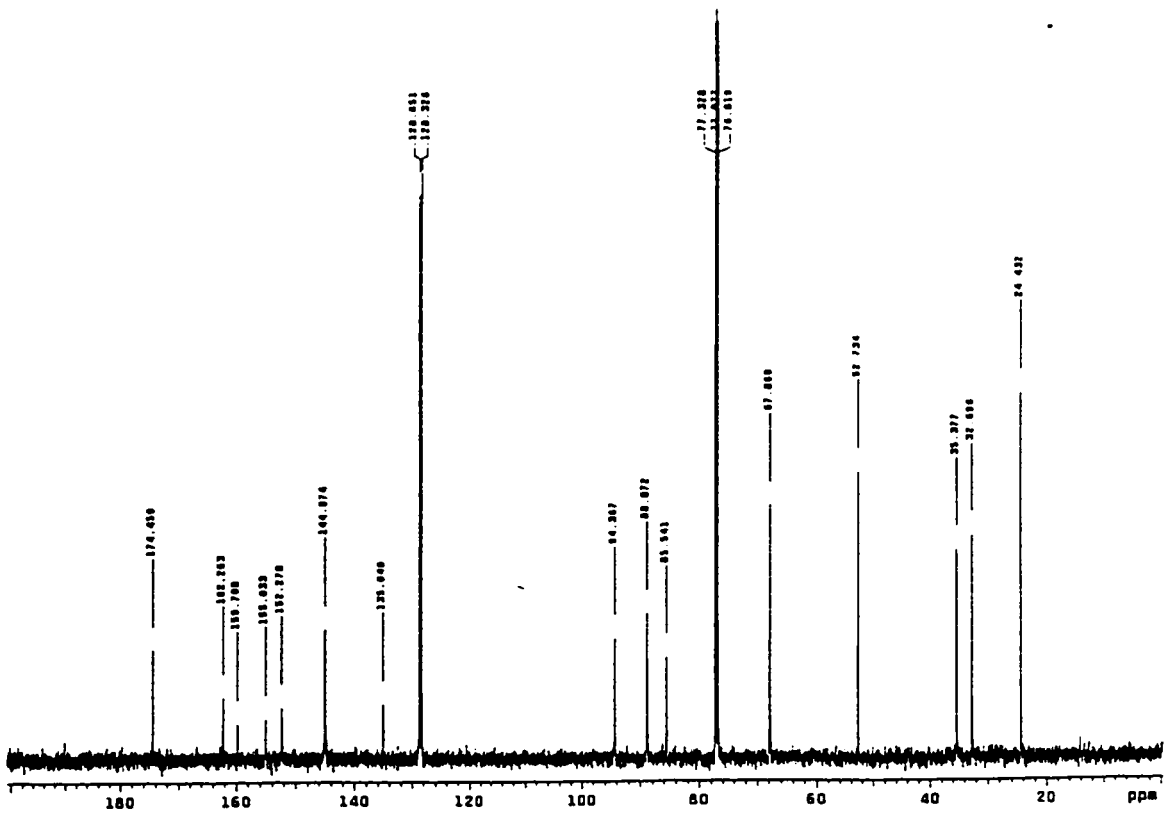
8
7
6
5
4
3
2
ppm

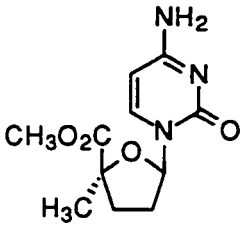

180
160
140
120
100
80
60
40
20
ppm


NHCbz
N
N
O
CH_3O_2C
O
H_3C

63

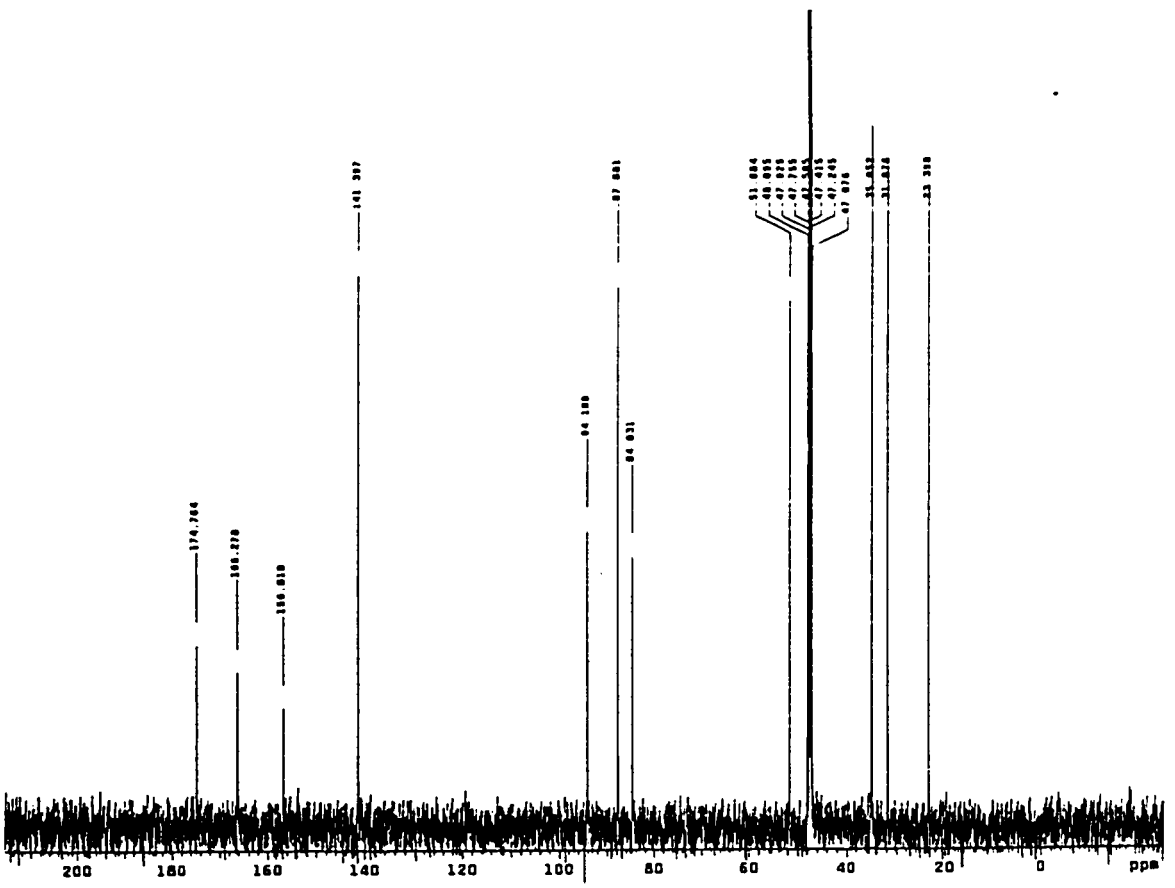
8
7
6
5
4
3
2
ppm

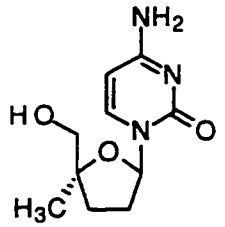

180
160
140
120
100
80
60
40
20
ppm


NH2
N
O
CH3O2C
O
N
H3C

64

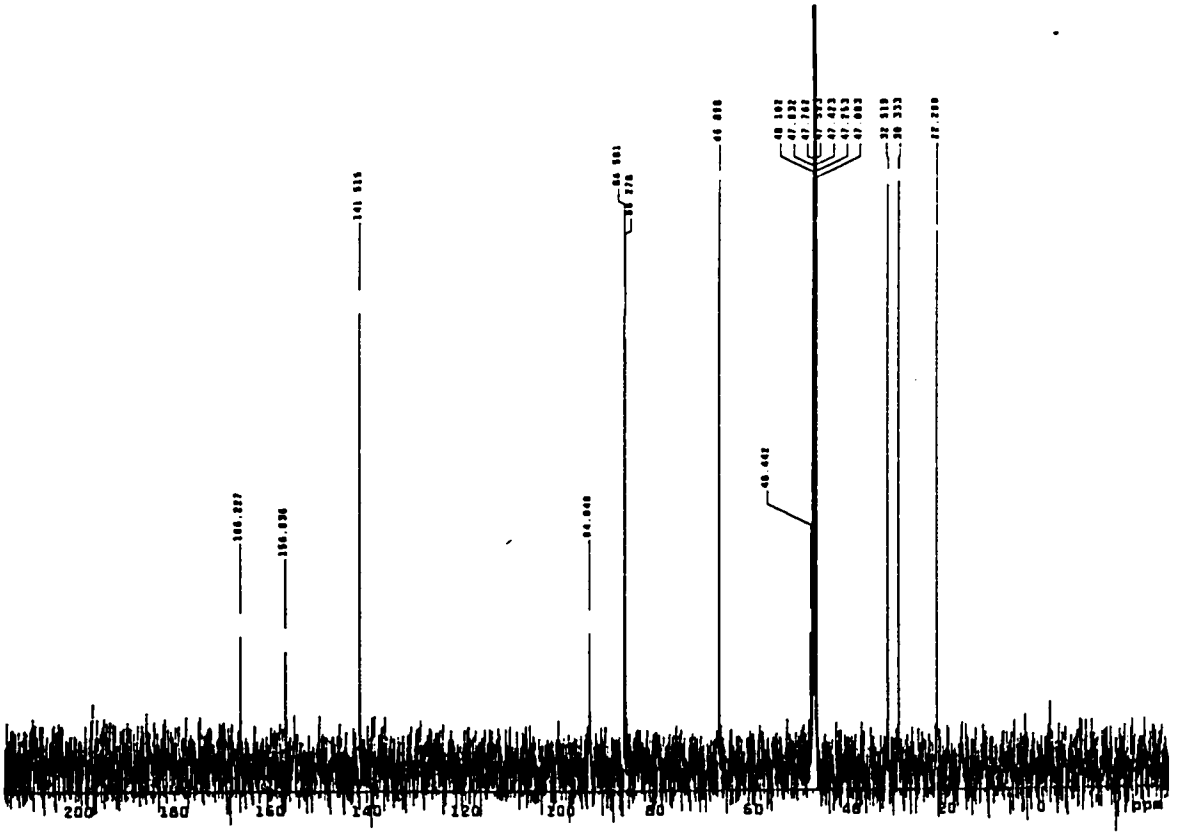
8
7
6
5
4
3
2
ppm

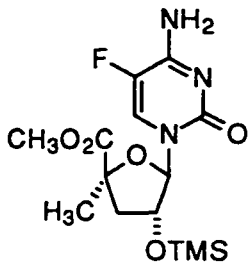

200
180
160
140
120
100
80
60
40
20
0
ppm


NH2
N
HO
N
O
O
H3C

65

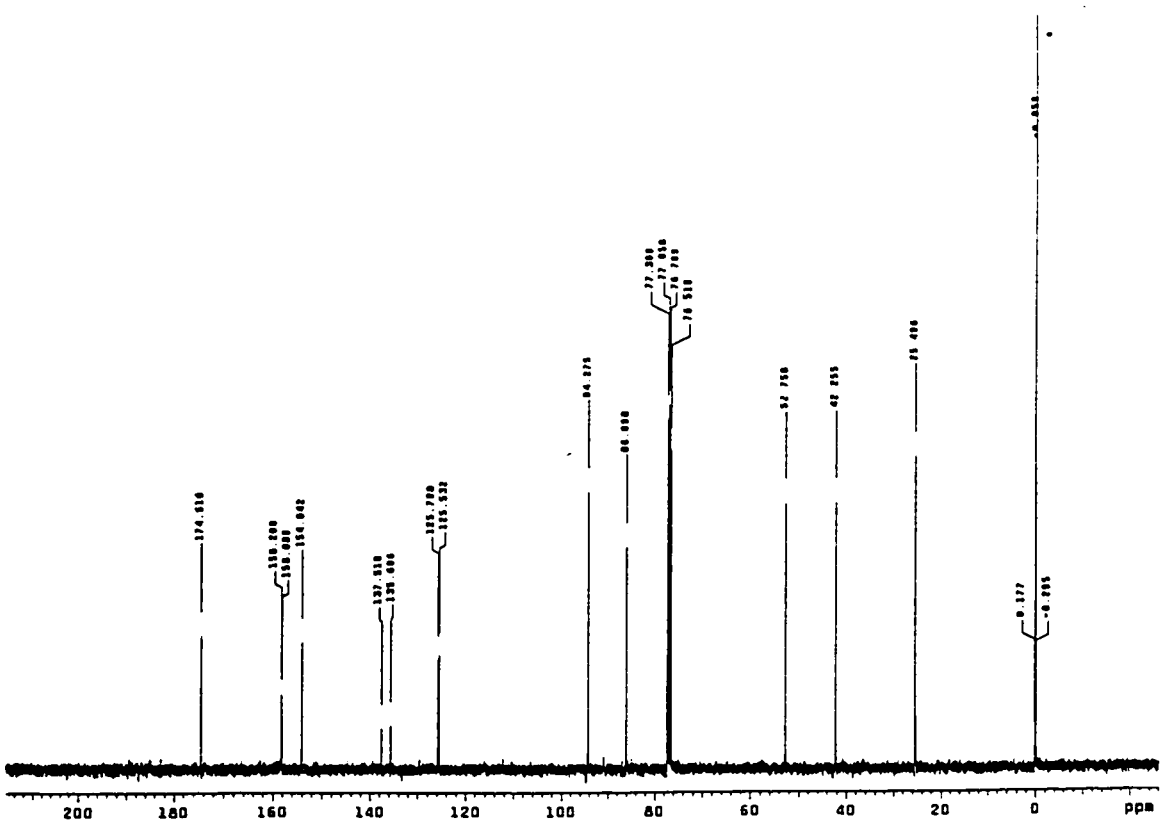
8
7
6
5
4
3
2
ppm

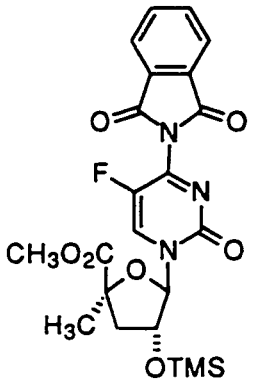

200
180
160
140
120
100
80
60
40
20
0
ppm


NH2
F
N
CH3O2C
O
N
O
H3C
OTMS

71

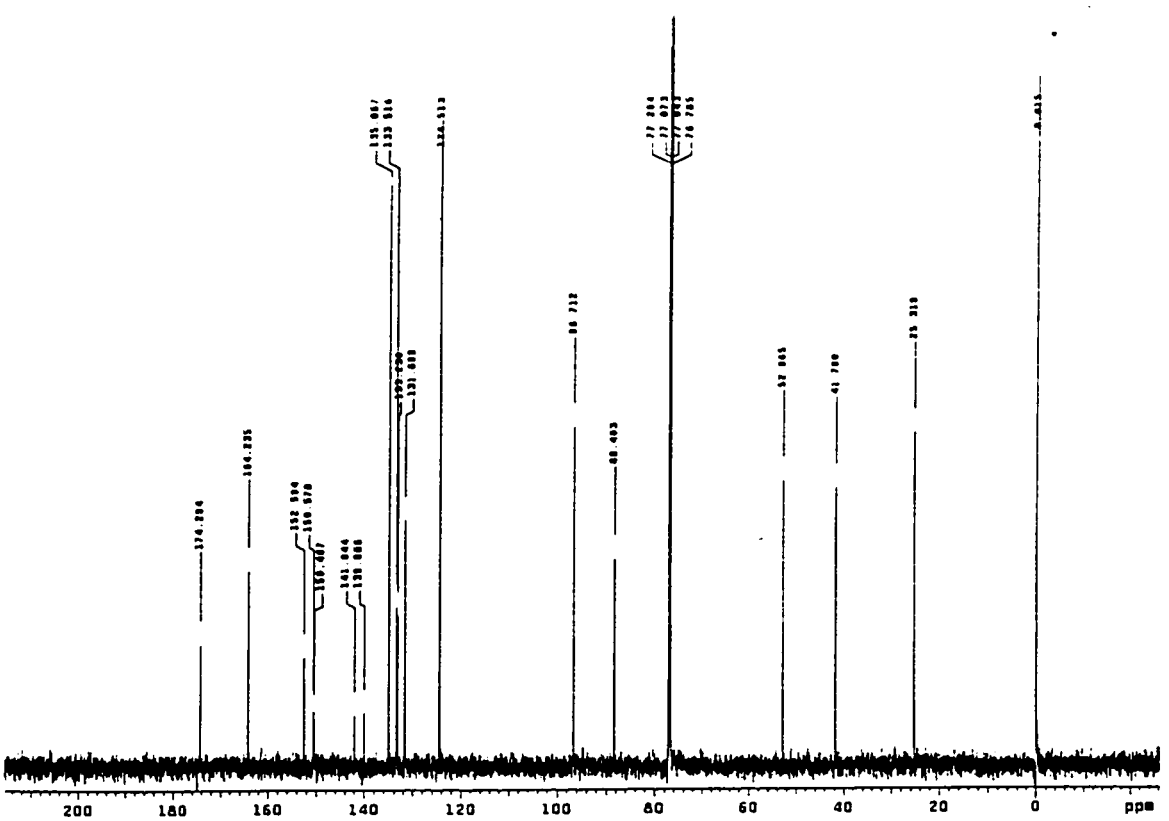
8
7
6
5
4
3
2
1
ppm

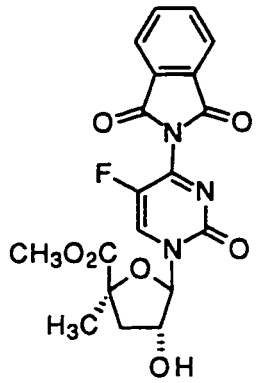

200
180
160
140
120
100
80
60
40
20
0
ppm


O
N
O
F
N
CH3O2C
O
N
O
H3C
OTMS

72

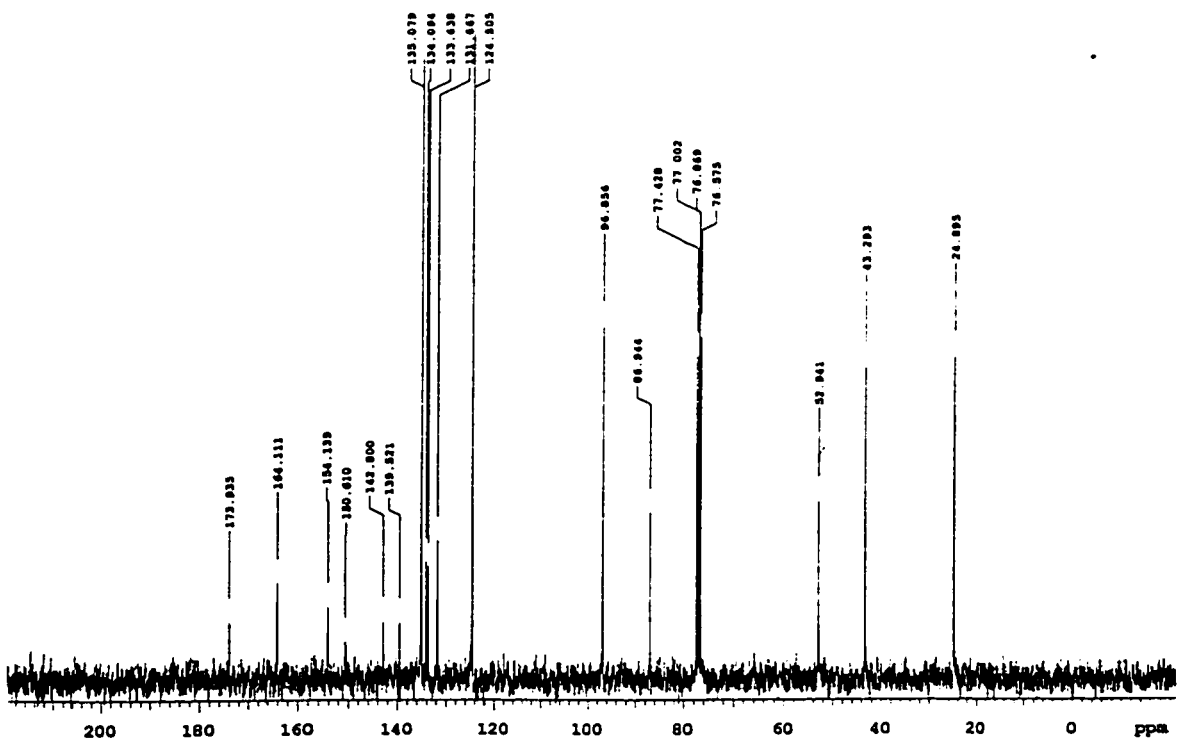
9
8
7
6
5
4
3
2
1
ppm

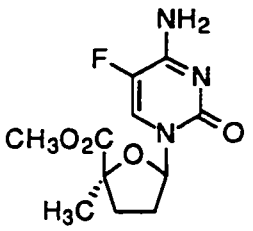

200
180
160
140
120
100
80
60
40
20
0
ppm


O
N
O
F
N
CH3O2C
O
N
O
H3C
OH

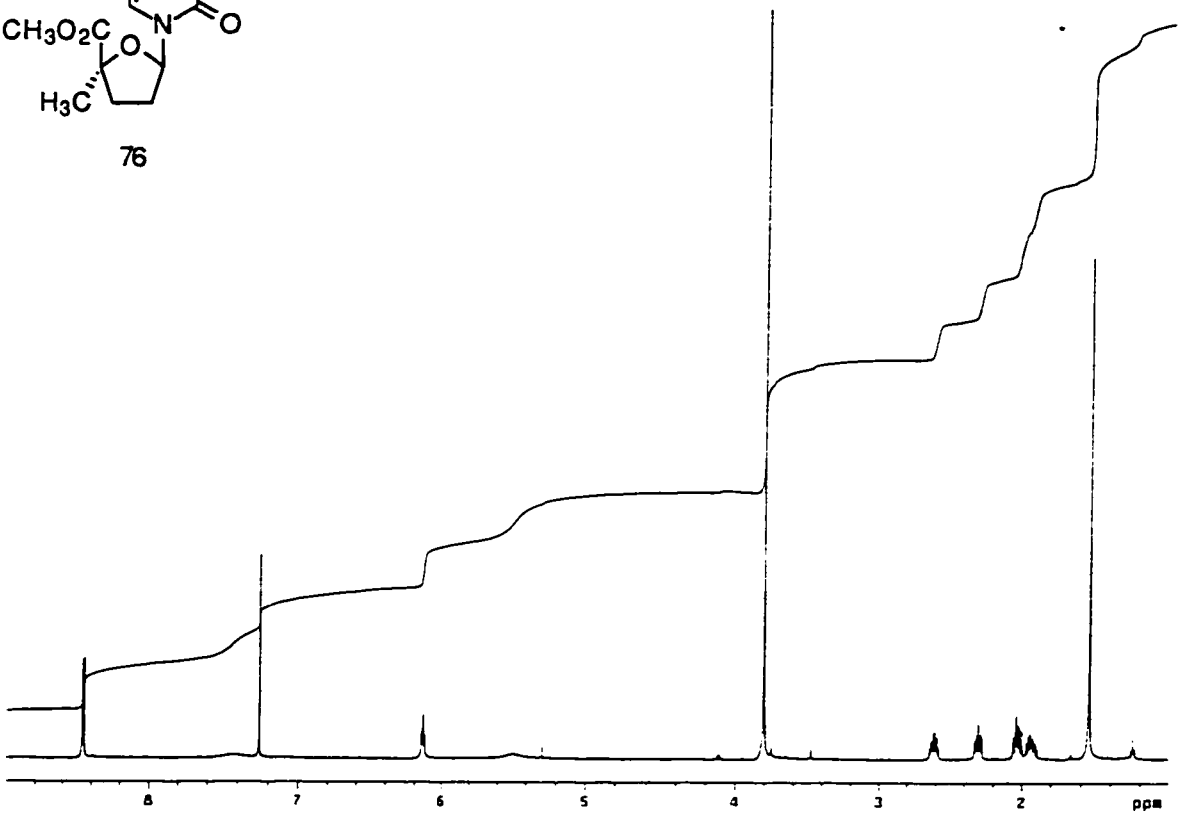
73

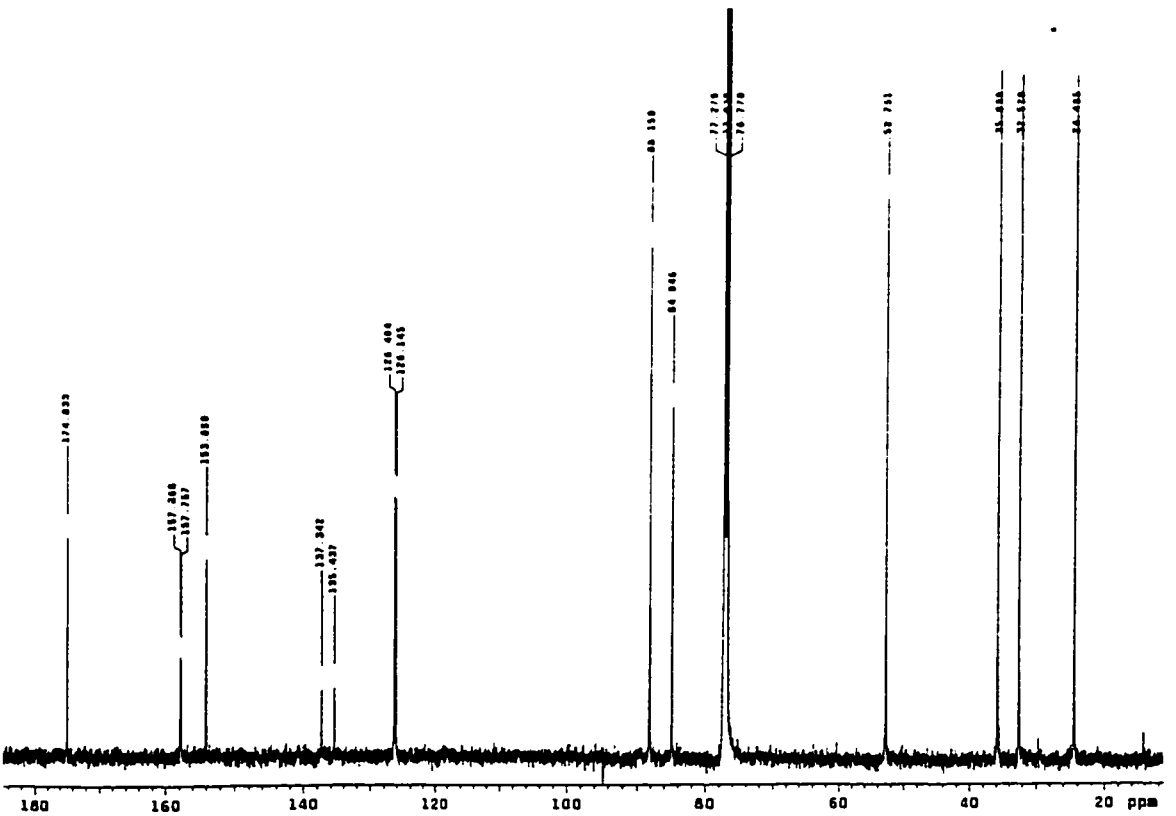
9
8
7
6
5
4
3
2
ppm

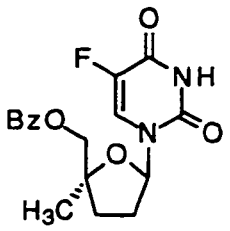

135.079
134.084
133.438
131.667
124.805
96.856
86.944
77.428
77.002
76.869
76.575
52.941
43.293
24.885
173.833
164.111
154.339
150.610
142.800
139.821
200
180
160
140
120
100
80
60
40
20
0
ppm


NH2
F
N
CH3O2C
O
N
O
H3C

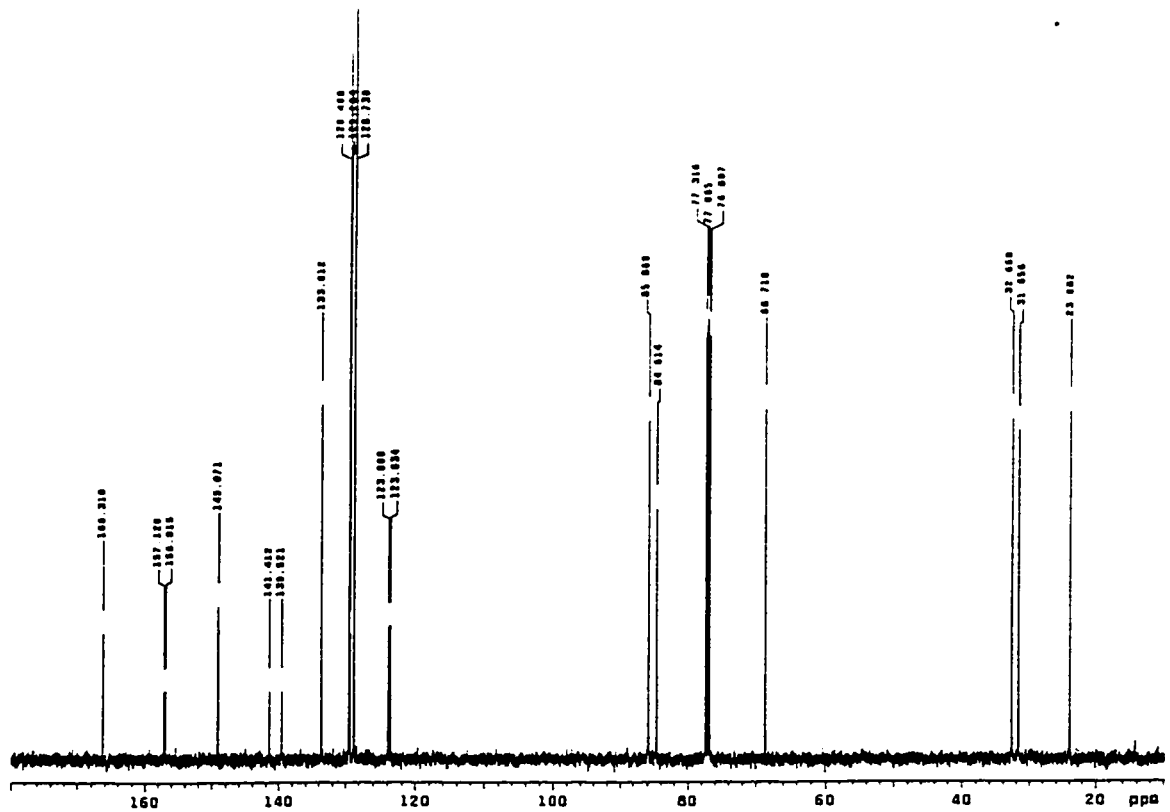
76

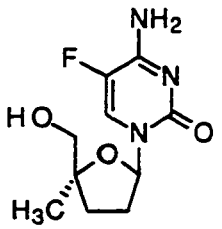

8
7
6
5
4
3
2
ppm


160
140
120
100
80
60
40
20 ppm



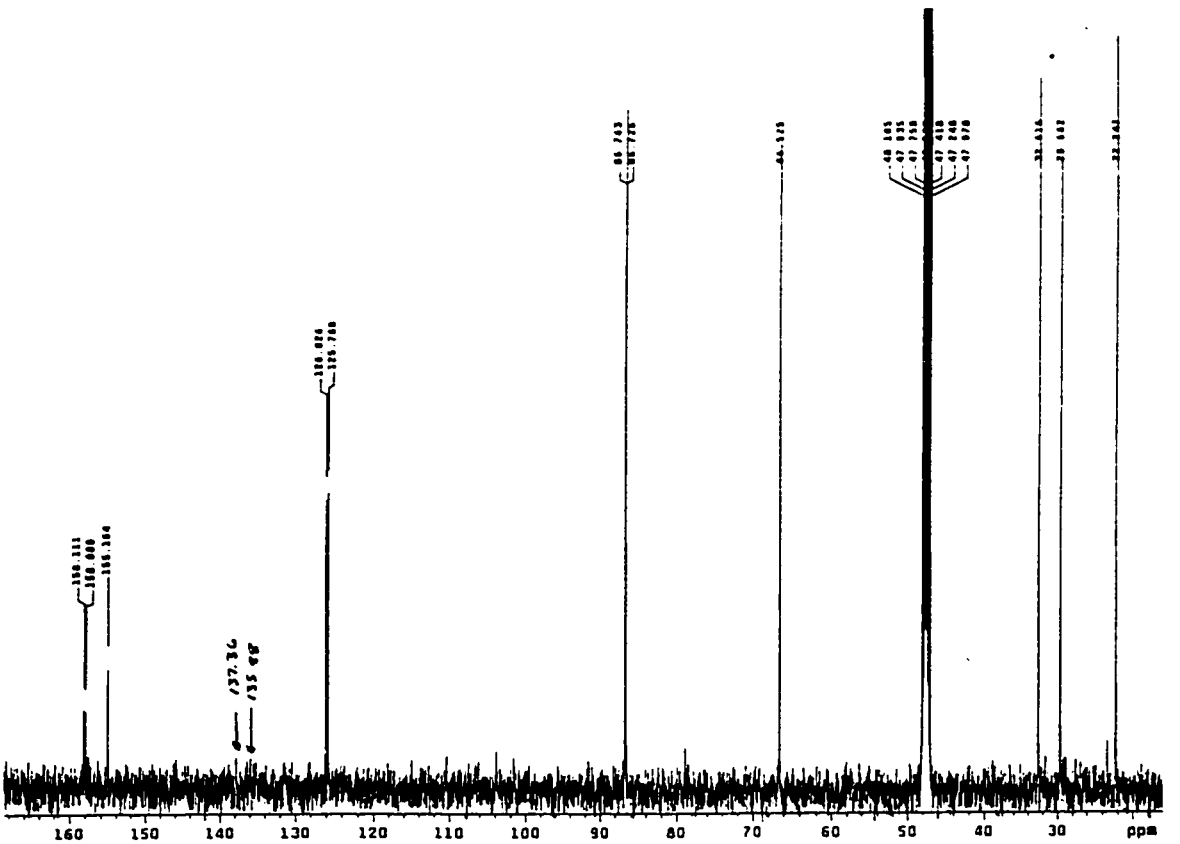
77

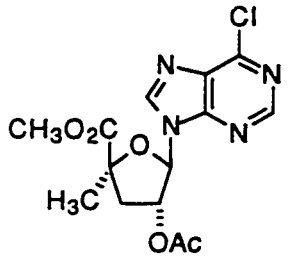



NH2
F
N
HO
N
O
O
H3C

78

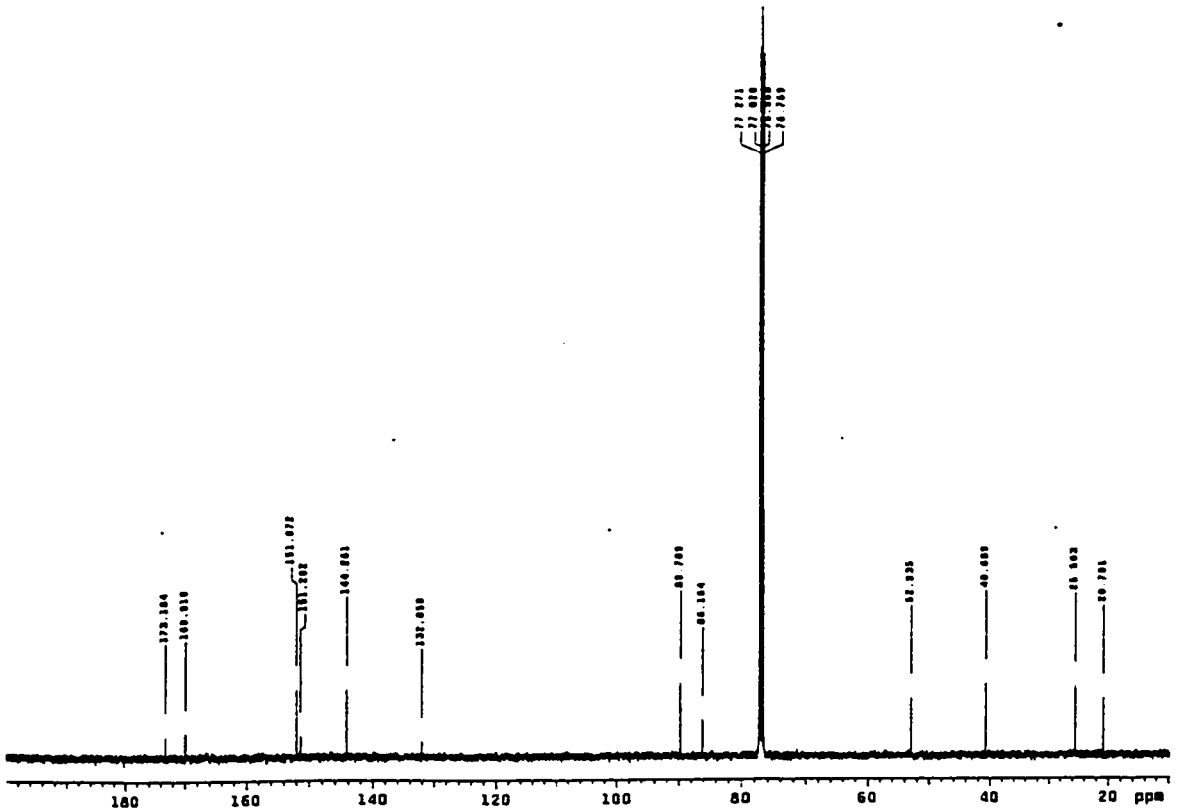
8
7
6
5
4
3
2
ppm

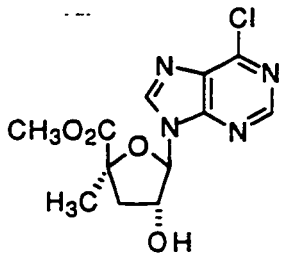

160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


Cl
N
N
N
N
O
CH3O2C
H3C
OAc

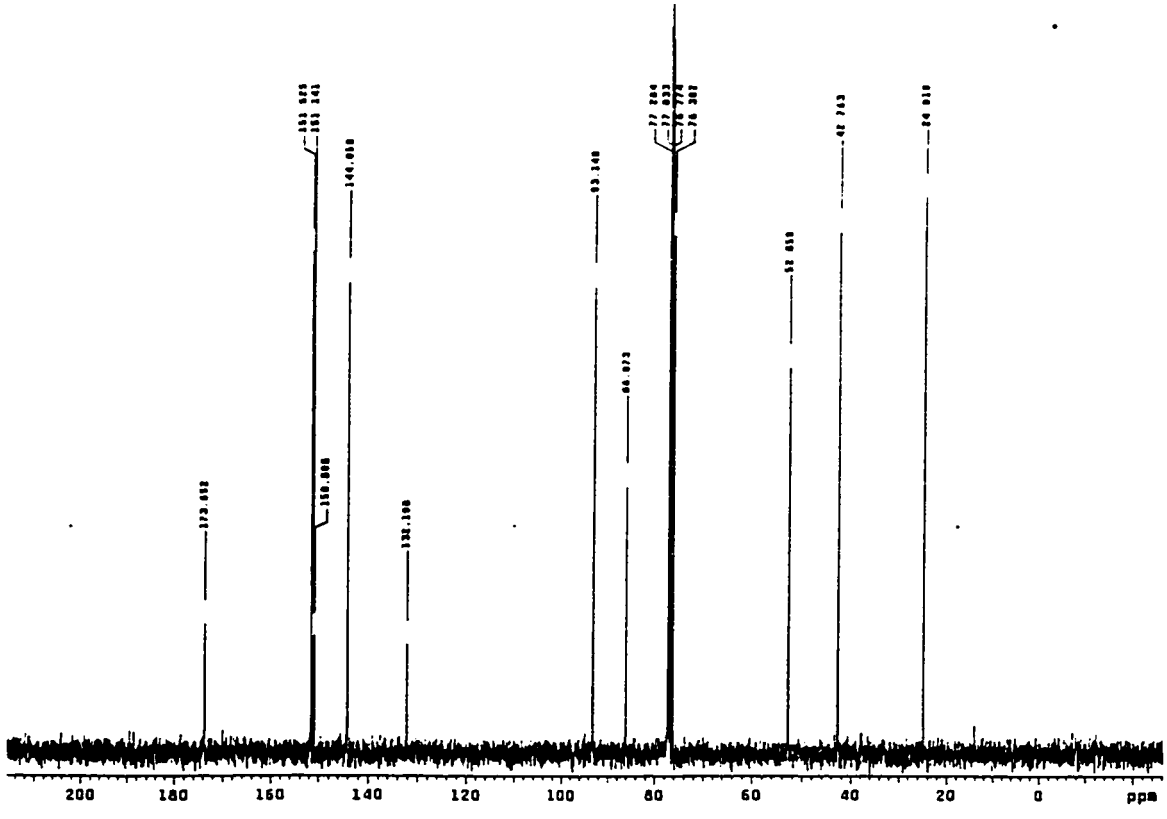
79

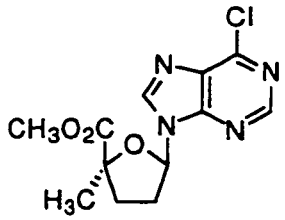
8
7
6
5
4
3
2
ppm


180
160
140
120
100
80
60
40
20
ppm



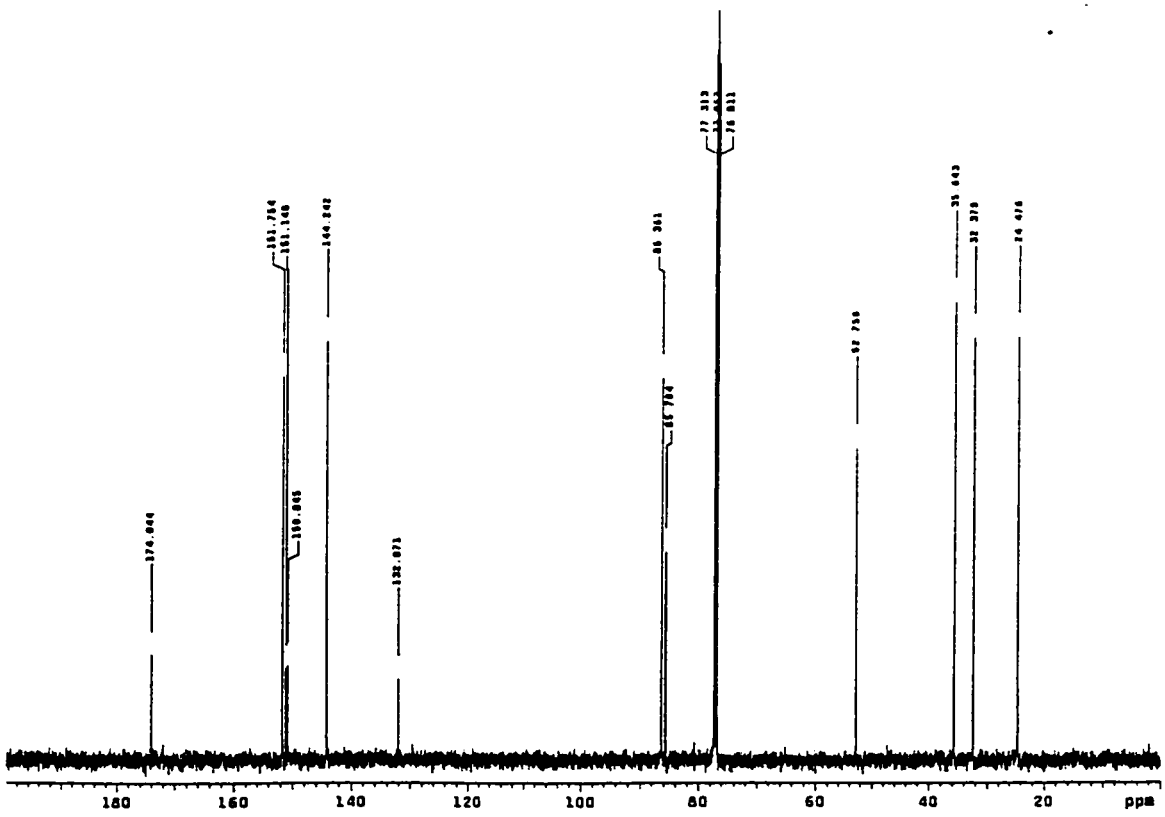
81

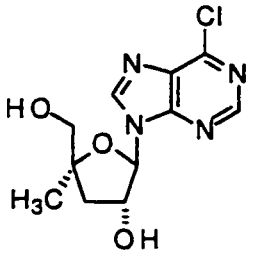



Cl
N
N
N
N
CH_3O_2C
O
H_3C

82

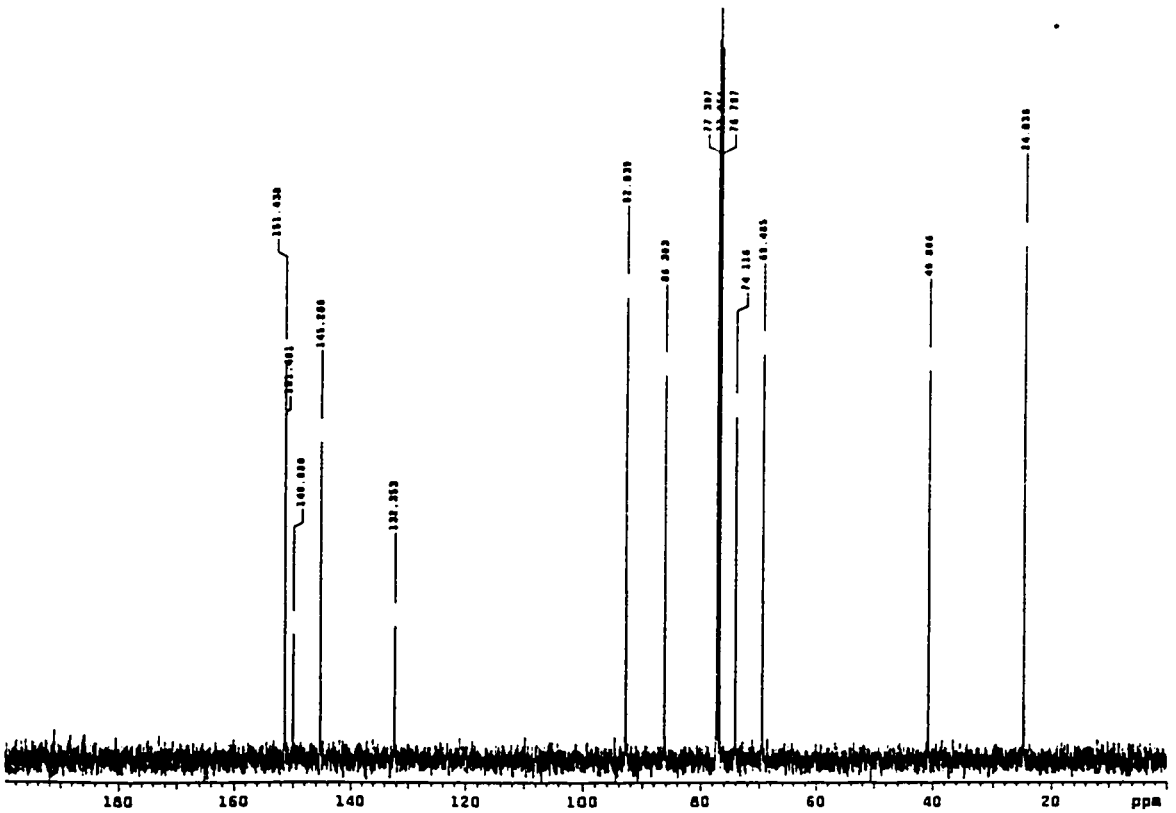
9
8
7
6
5
4
3
2
ppm

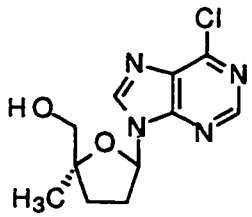

160
140
120
100
80
60
40
20
ppm


Cl
N
N
N
N
HO
O
H3C
OH

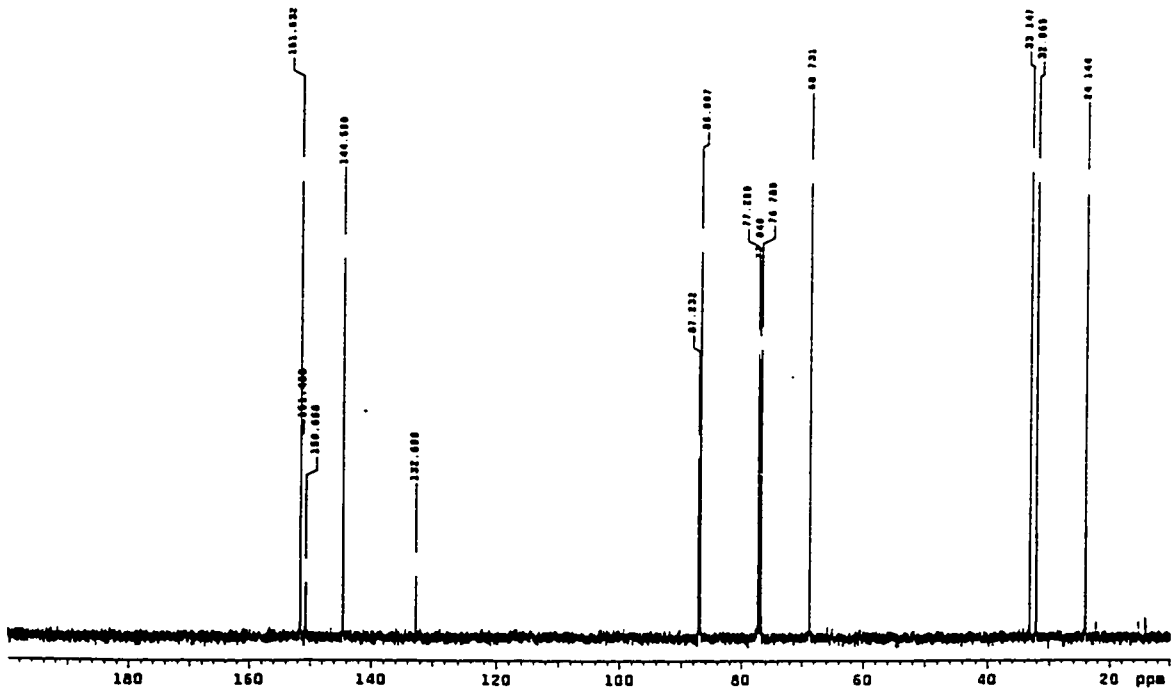
83

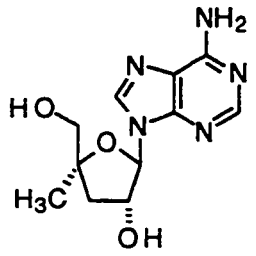
8
7
6
5
4
3
2
ppm


180
160
140
120
100
80
60
40
20
ppm



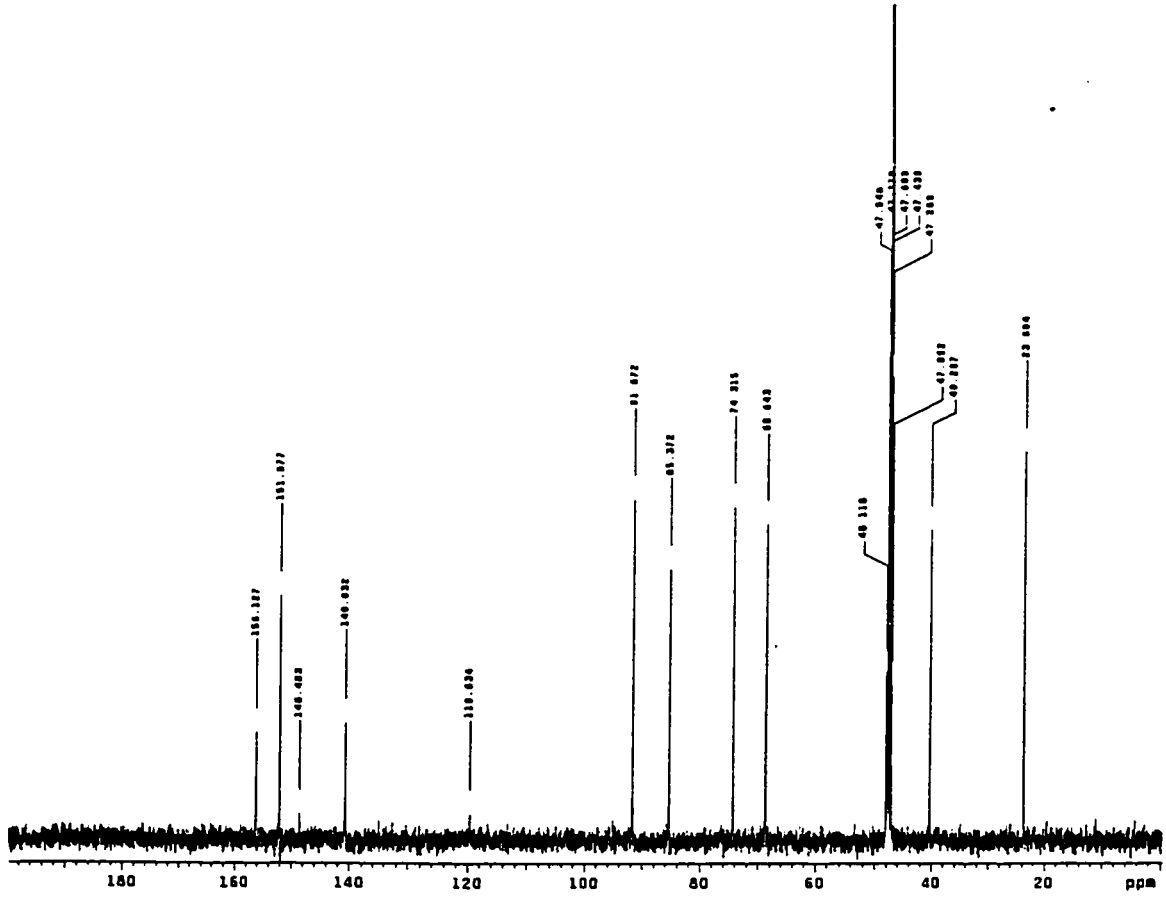
84

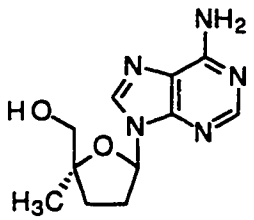



NH2
N
N
N
N
HO
O
H3C
OH

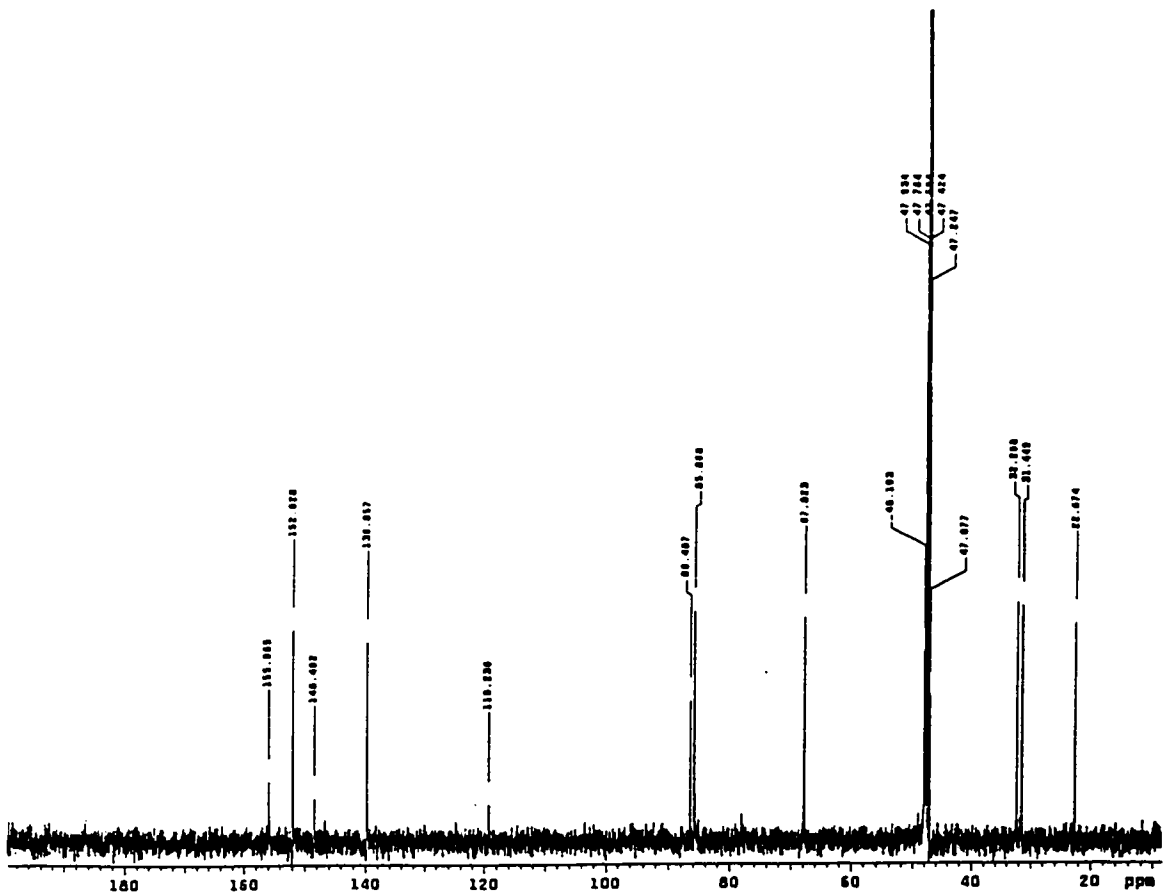
87

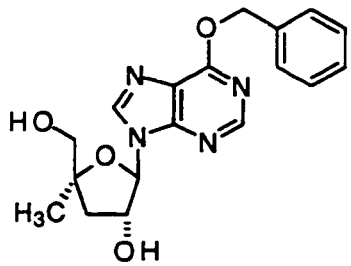
8
7
6
5
4
3
2
ppm


180
160
140
120
100
80
60
40
20
ppm

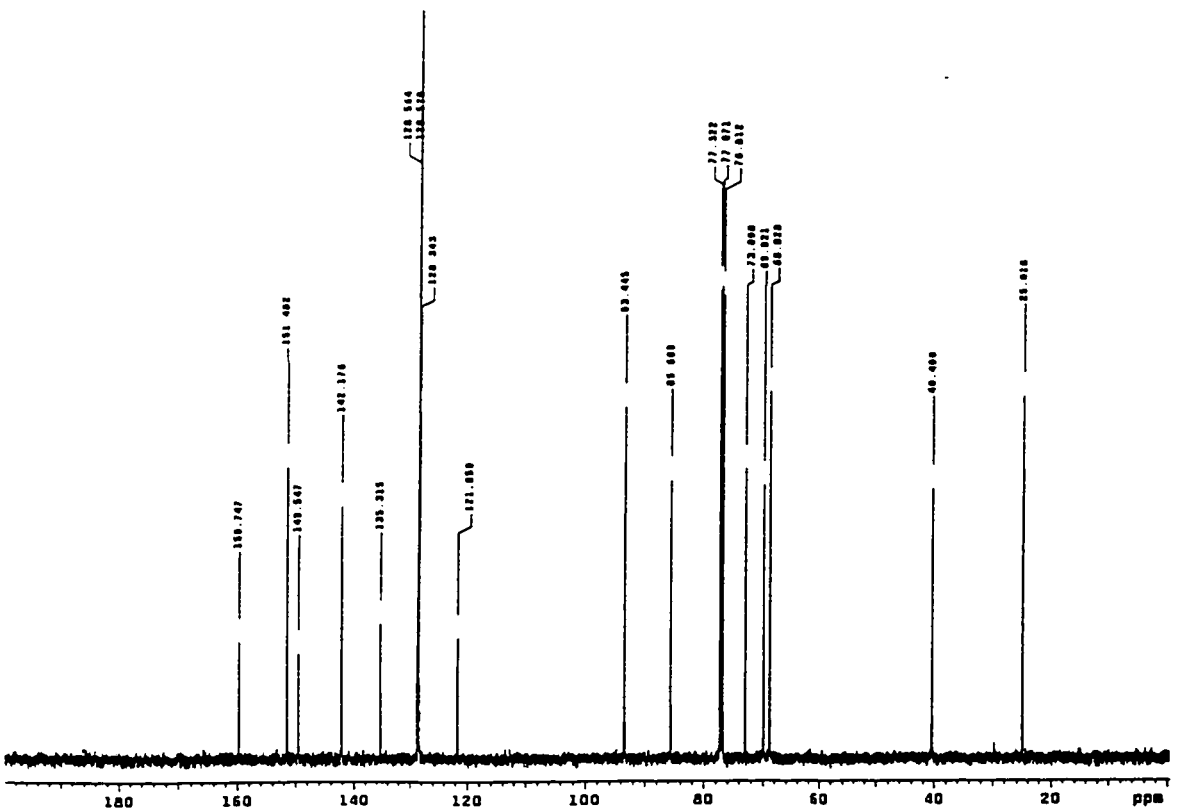


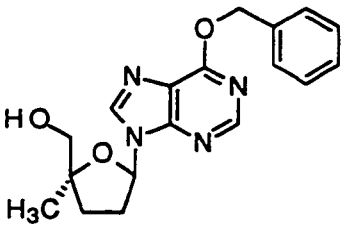
88



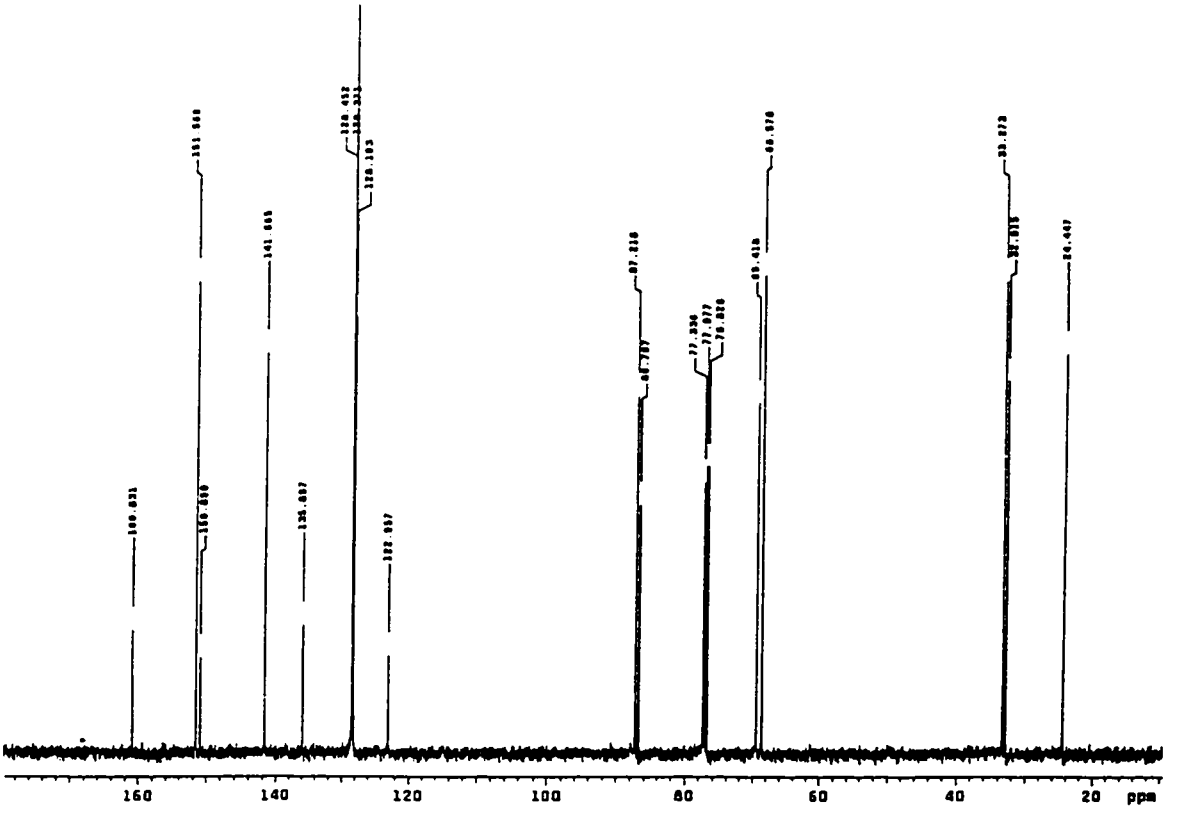


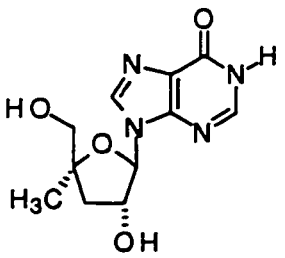
91





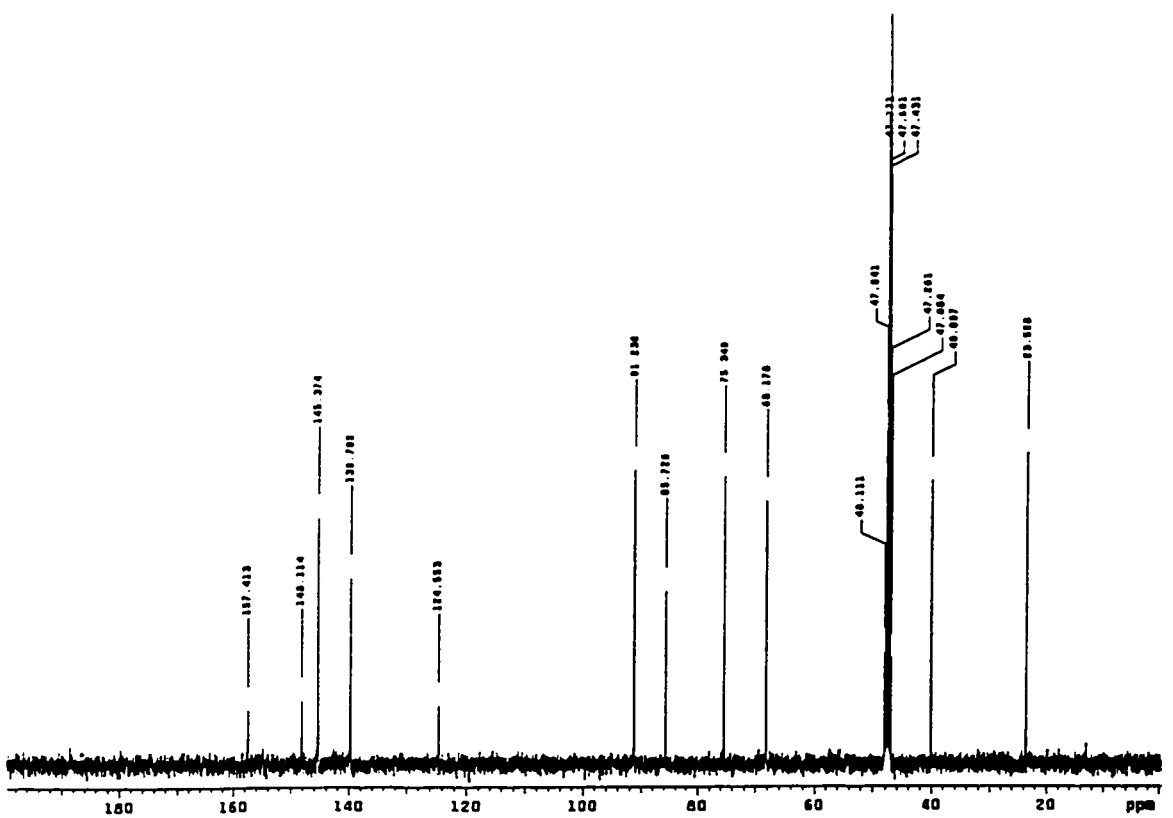
92

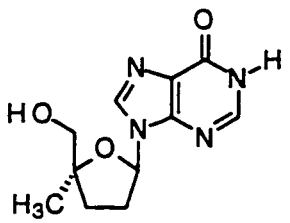



HO
N
N
N
N
H
O
O
H3C
OH

93

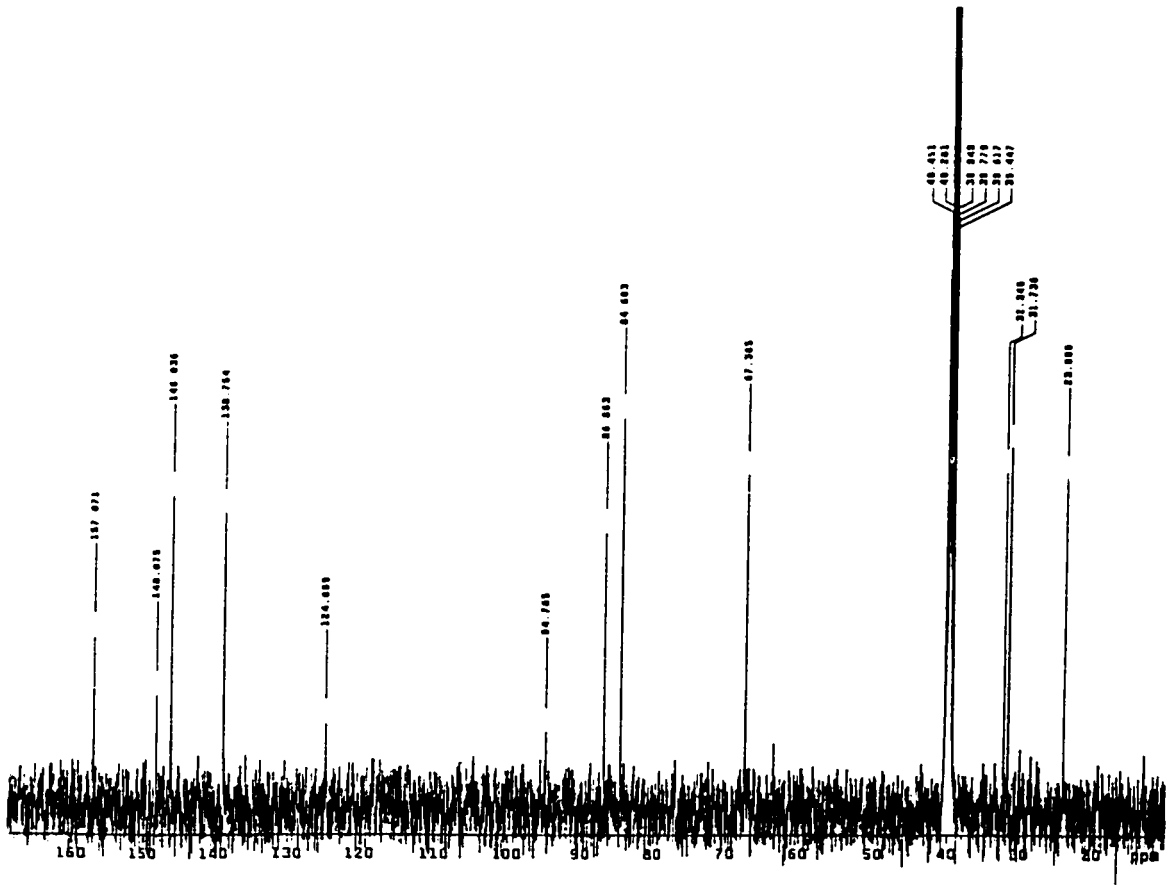
8
7
6
5
4
3
2
1
ppm

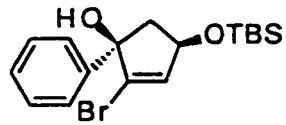

180
160
140
120
100
80
60
40
20
ppm


O
N
N
H
HO
N
N
O
H3C

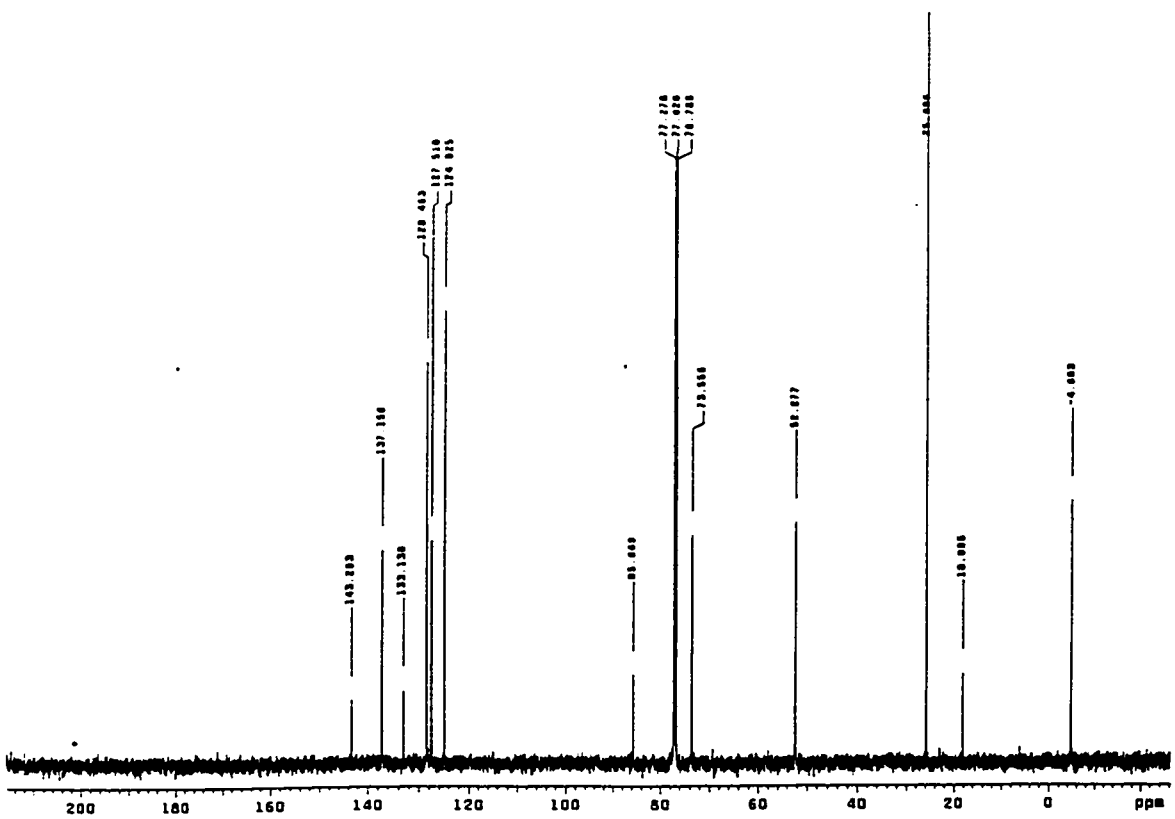
94

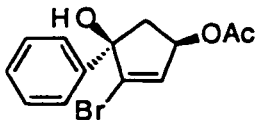
8
7
6
5
4
3
2
ppm


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

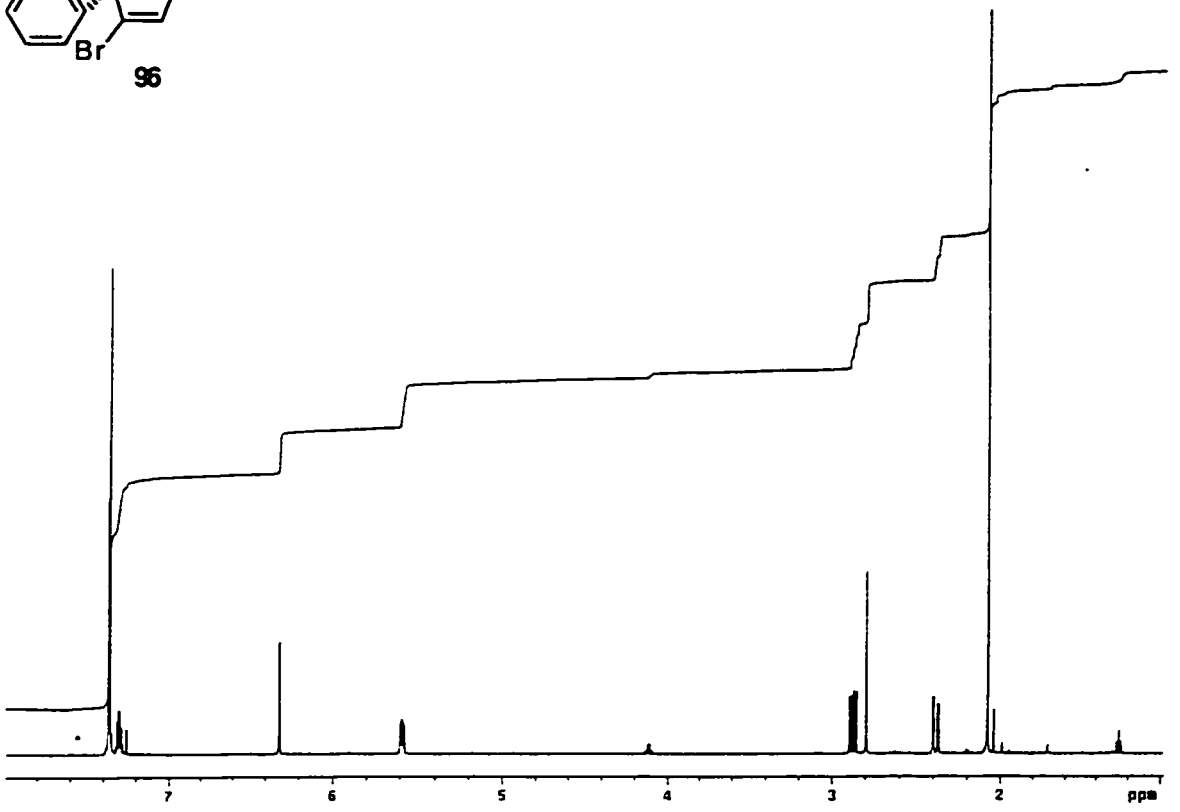


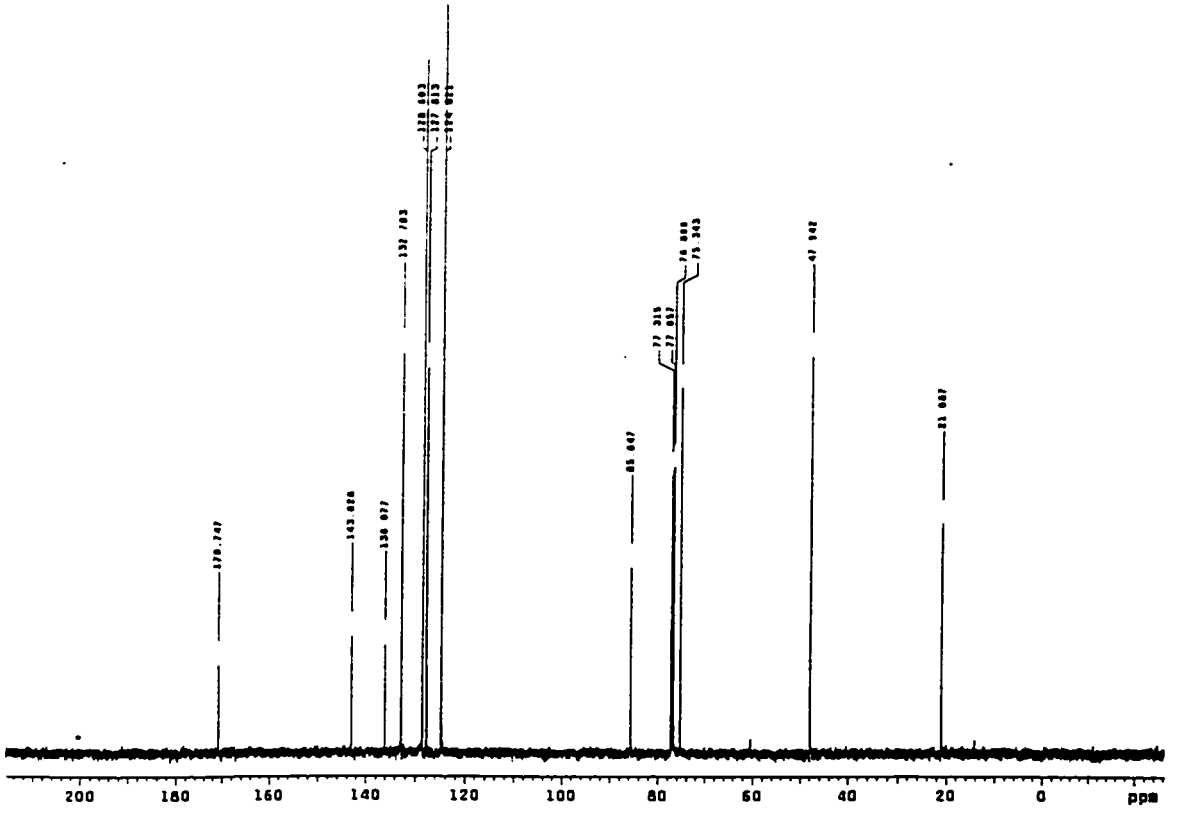
95a

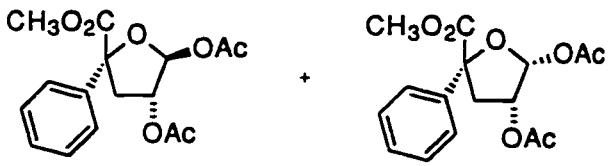




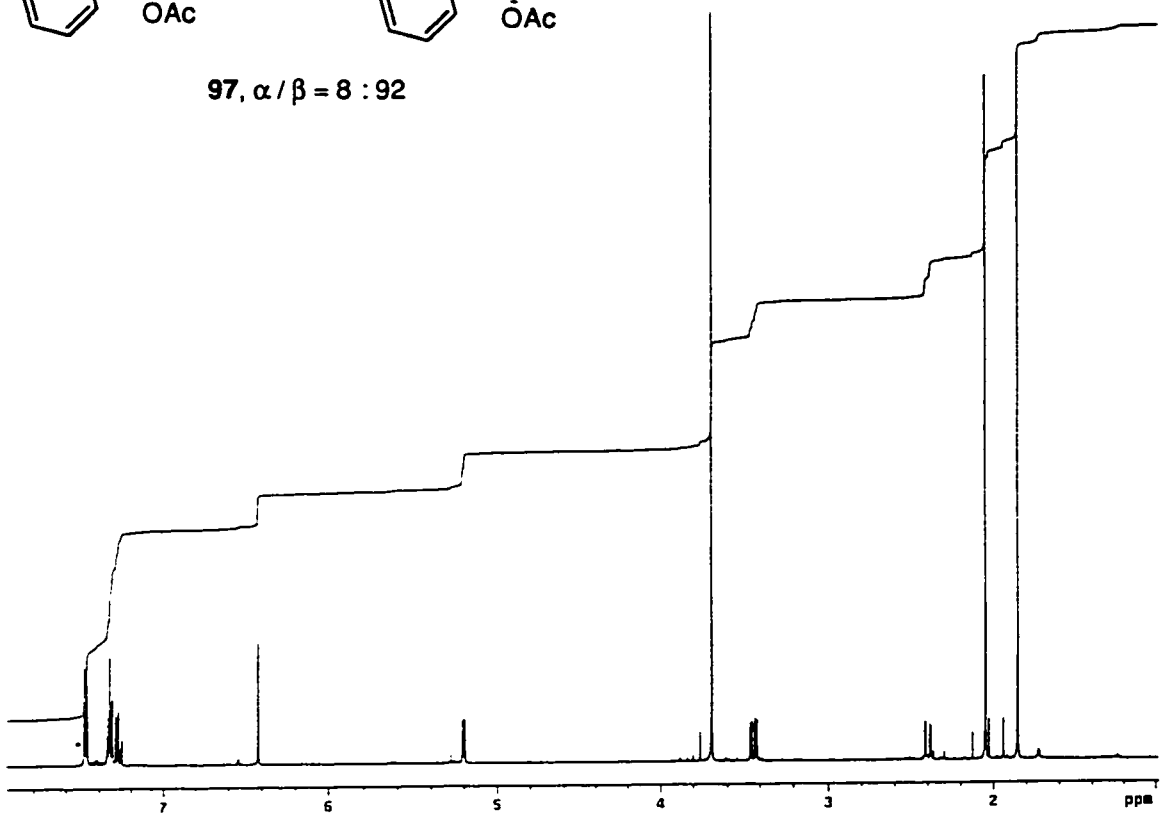
96

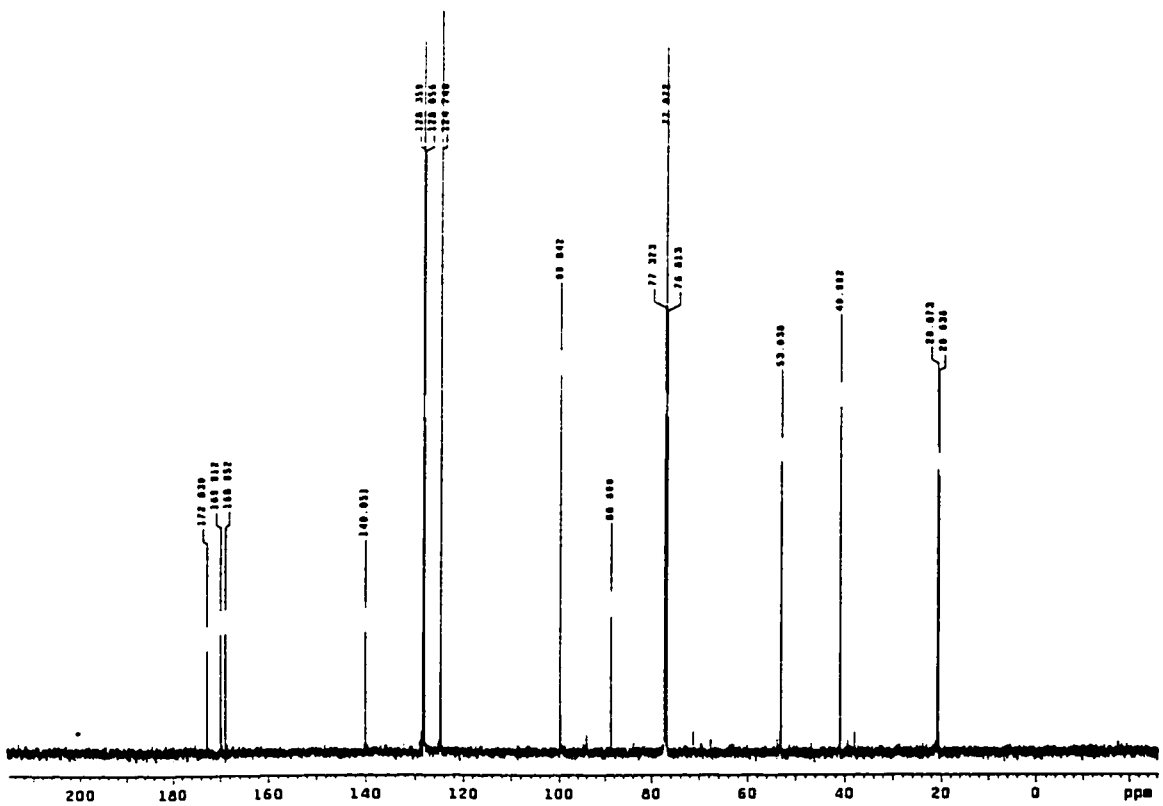


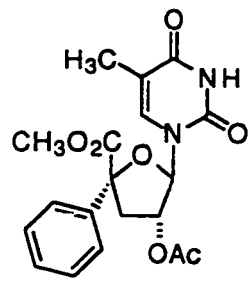




97, $\alpha / \beta = 8 : 92$

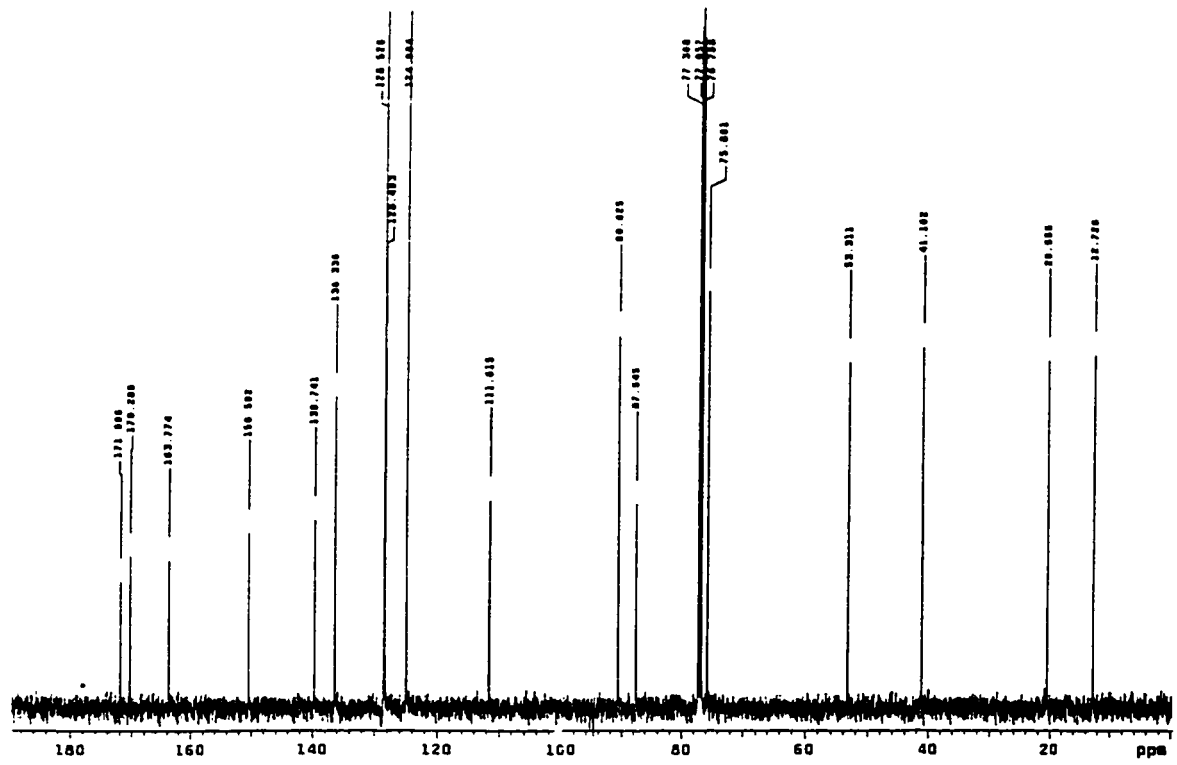


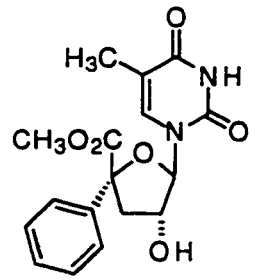



O
H3C
NH
CH3O2C
O
N
O
OAc

98

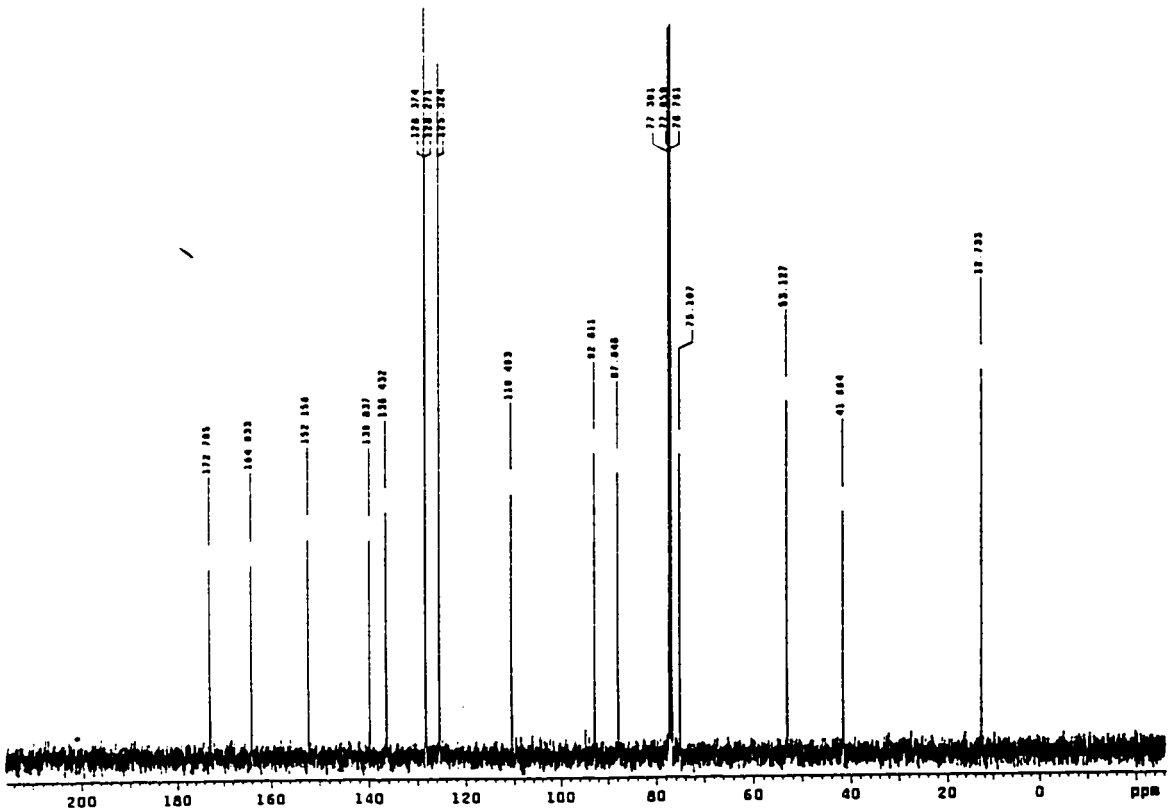
9
8
7
6
5
4
3
2
ppm

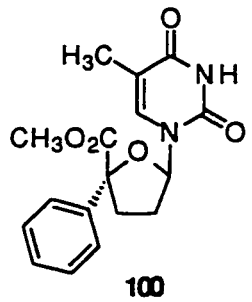

180
160
140
120
100
80
60
40
20
ppm


O
H3C
NH
N
O
CH3O2C
O
OH

99

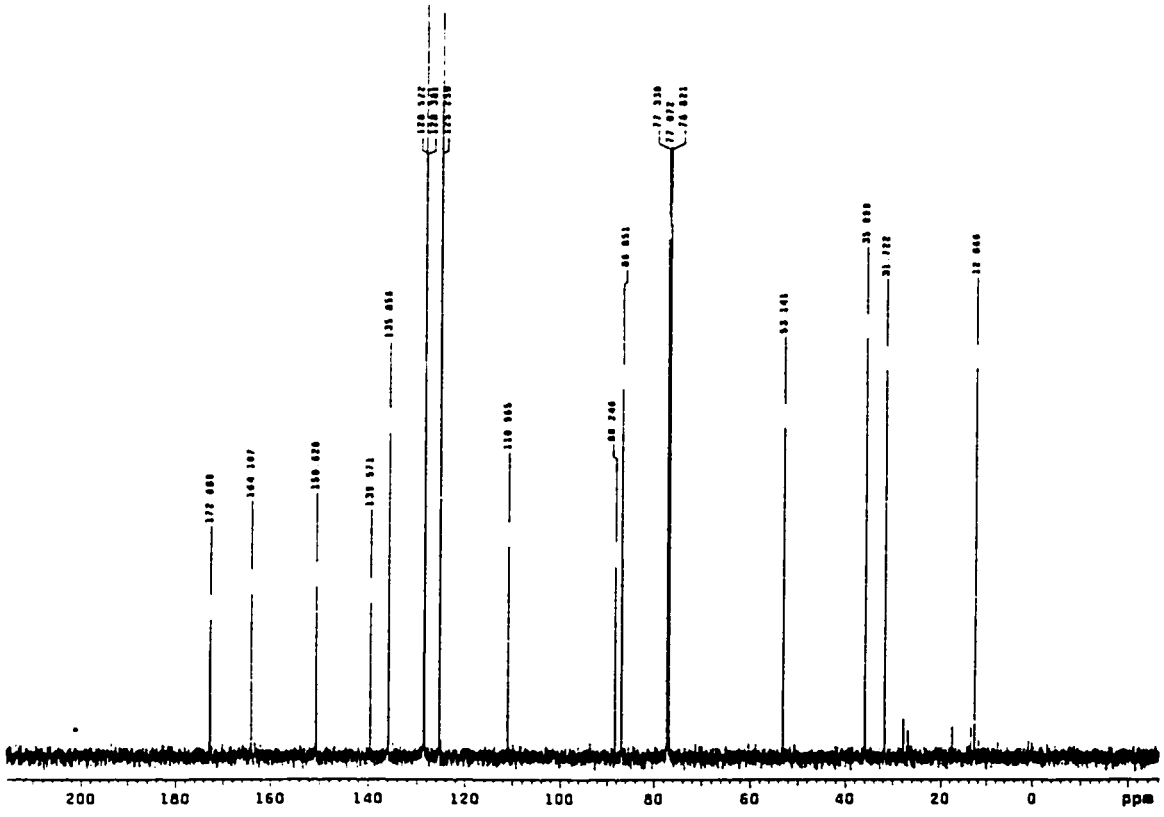
11
10
9
8
7
6
5
4
3
2
ppm

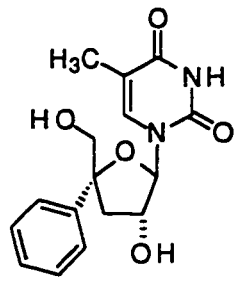

200
180
160
140
120
100
80
60
40
20
0
ppm


O
H3C
NH
CH3O2C
O
N
O

100

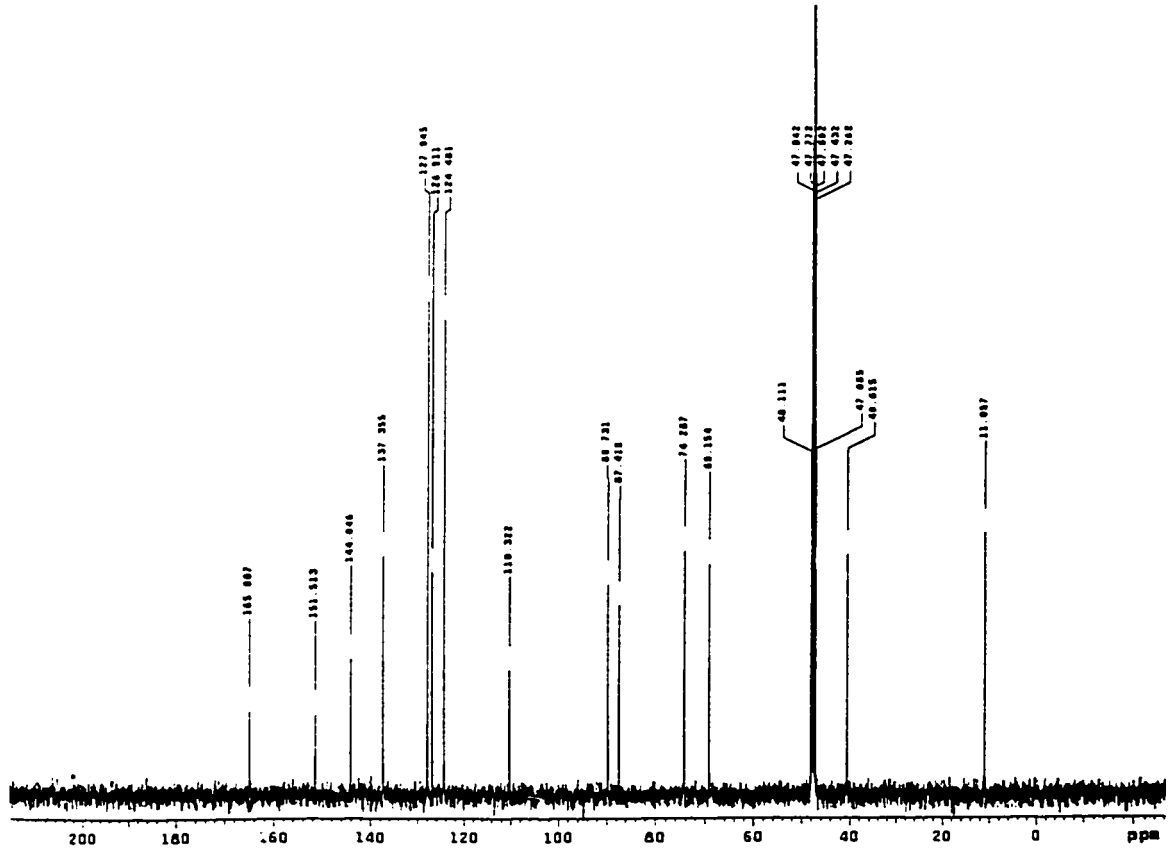
9
8
7
6
5
4
3
2
ppm

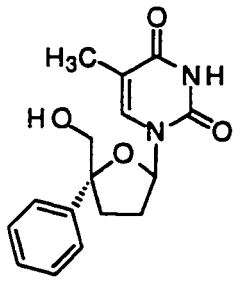

200
180
160
140
120
100
80
60
40
20
0
ppm


O
H3C
NH
HO
N
O
O
OH

101

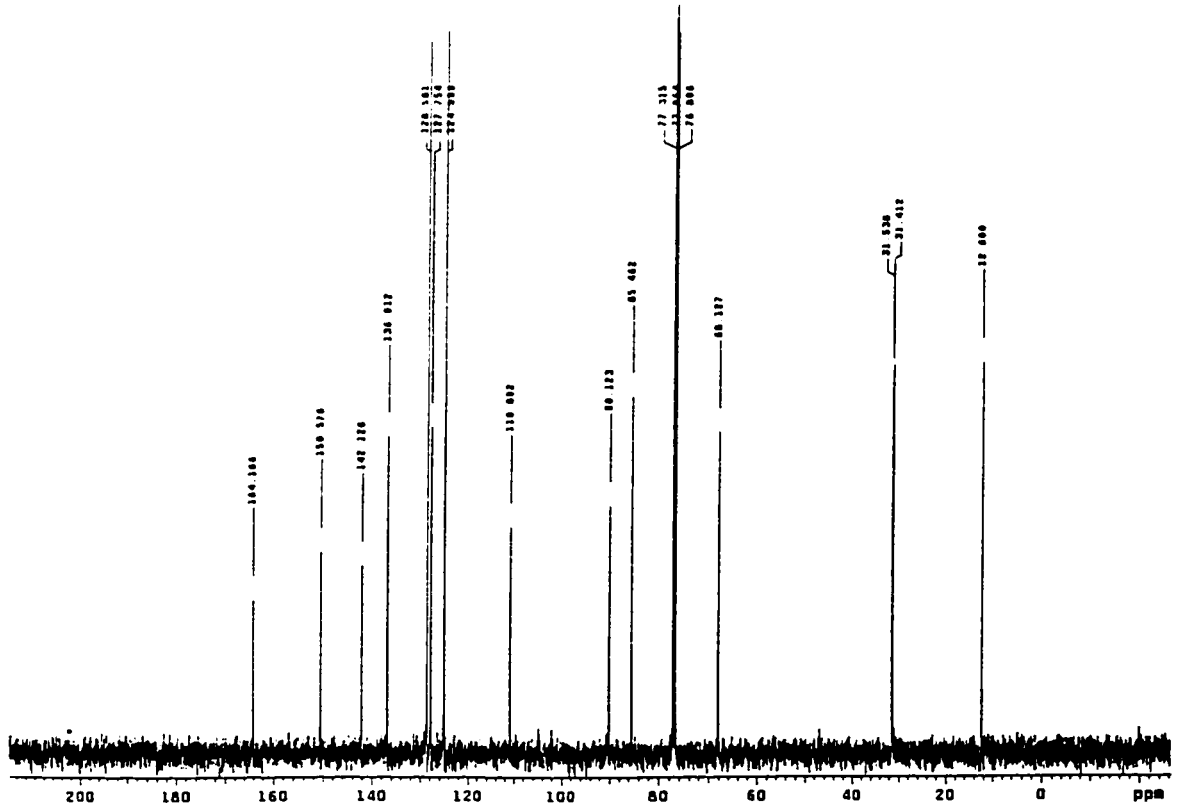
8
7
6
5
4
3
2
ppm

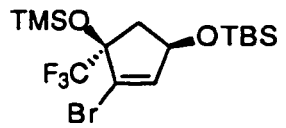

165.867
151.513
144.846
137.355
127.845
126.911
126.481
110.322
89.731
87.418
76.287
69.154
48.111
47.885
40.615
11.867
200
180
160
140
120
100
80
60
40
20
0
ppm


O
H3C
NH
HO
N
O
O

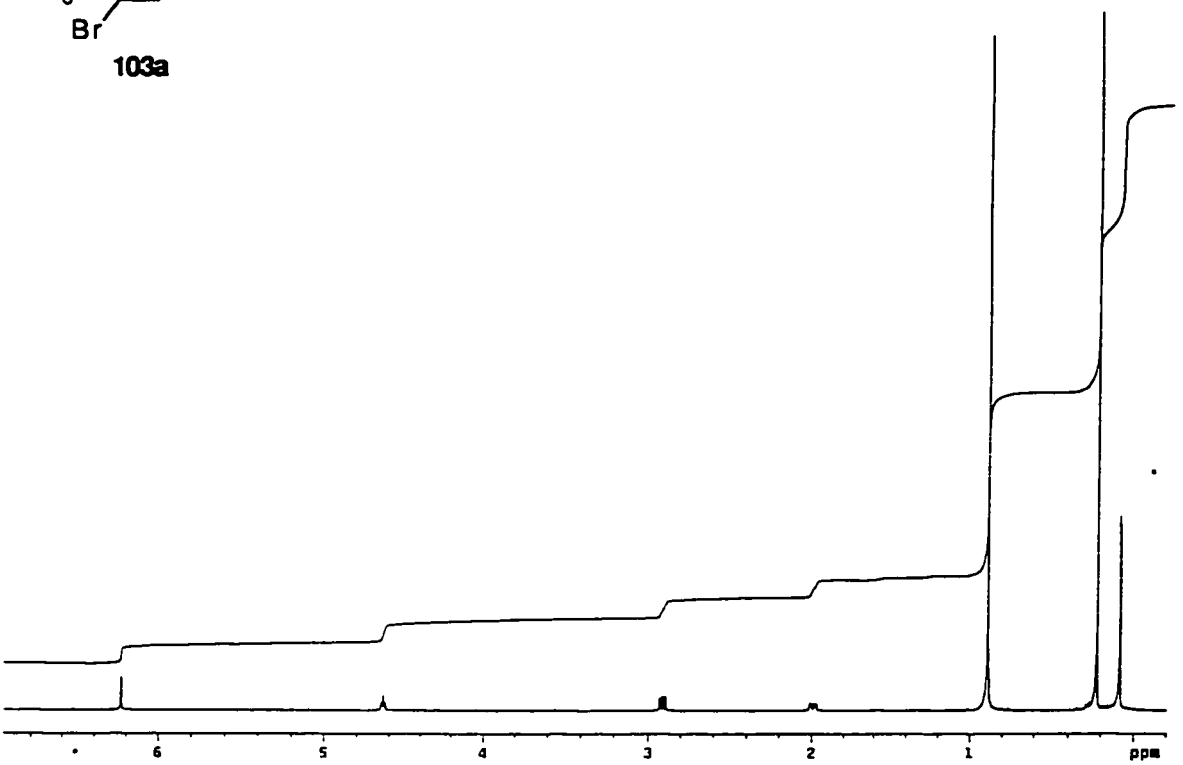
102

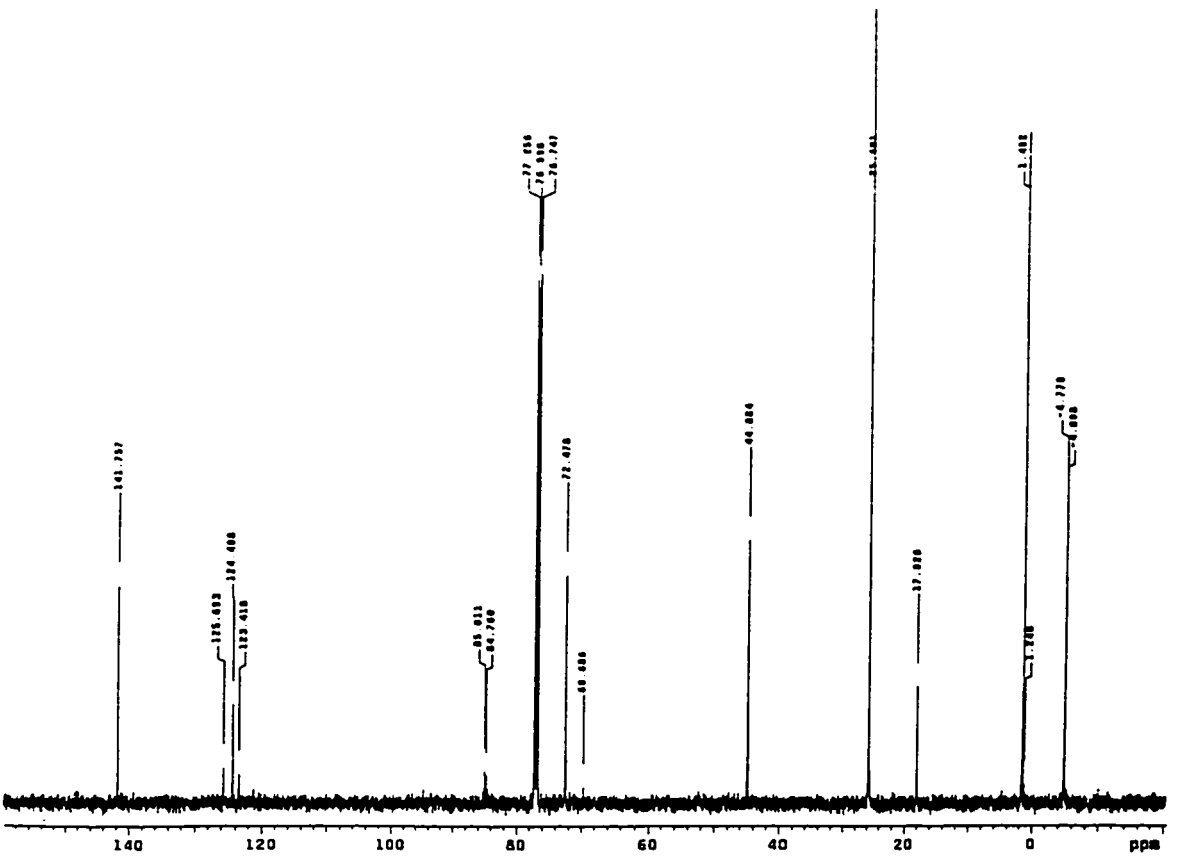
9
8
7
6
5
4
3
2
ppm

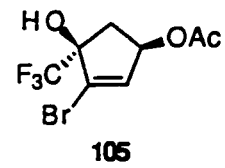

200
180
160
140
120
100
80
60
40
20
0
ppm



103a

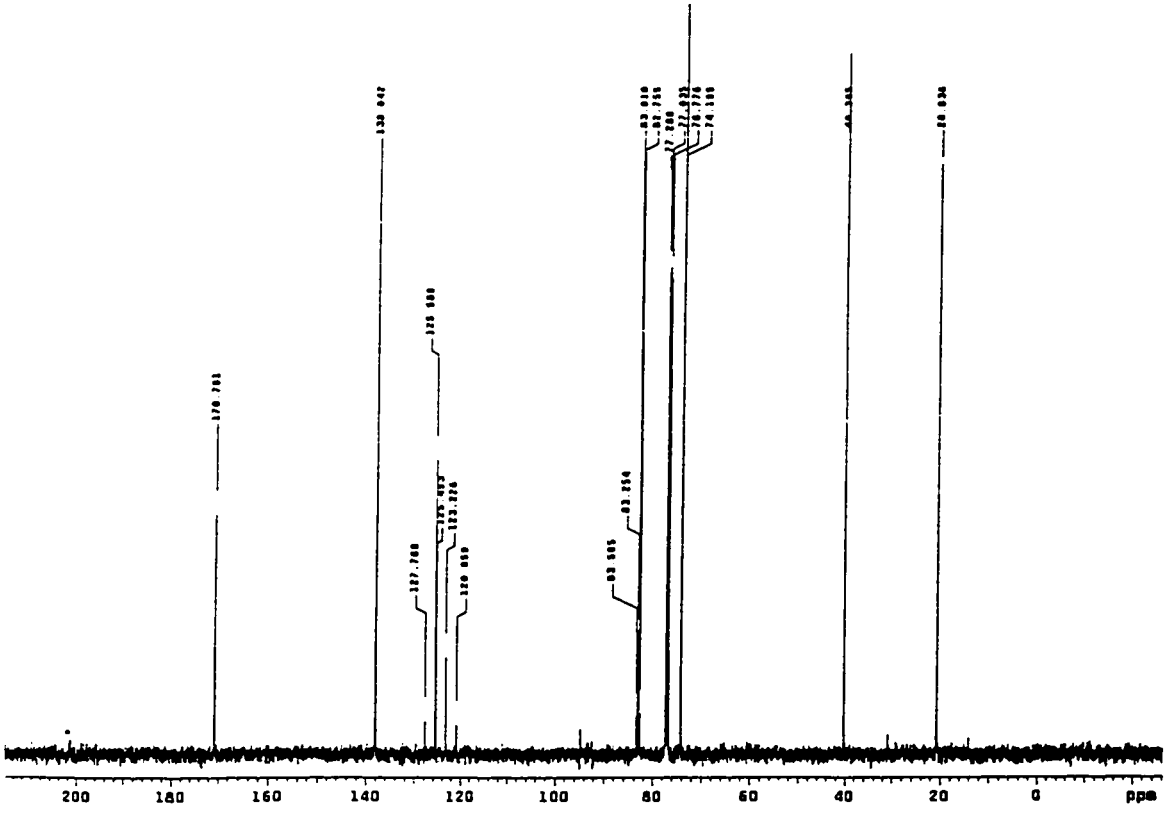


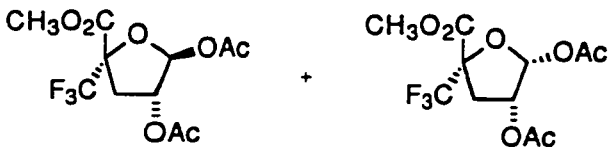



HO
OAc
F3C
Br

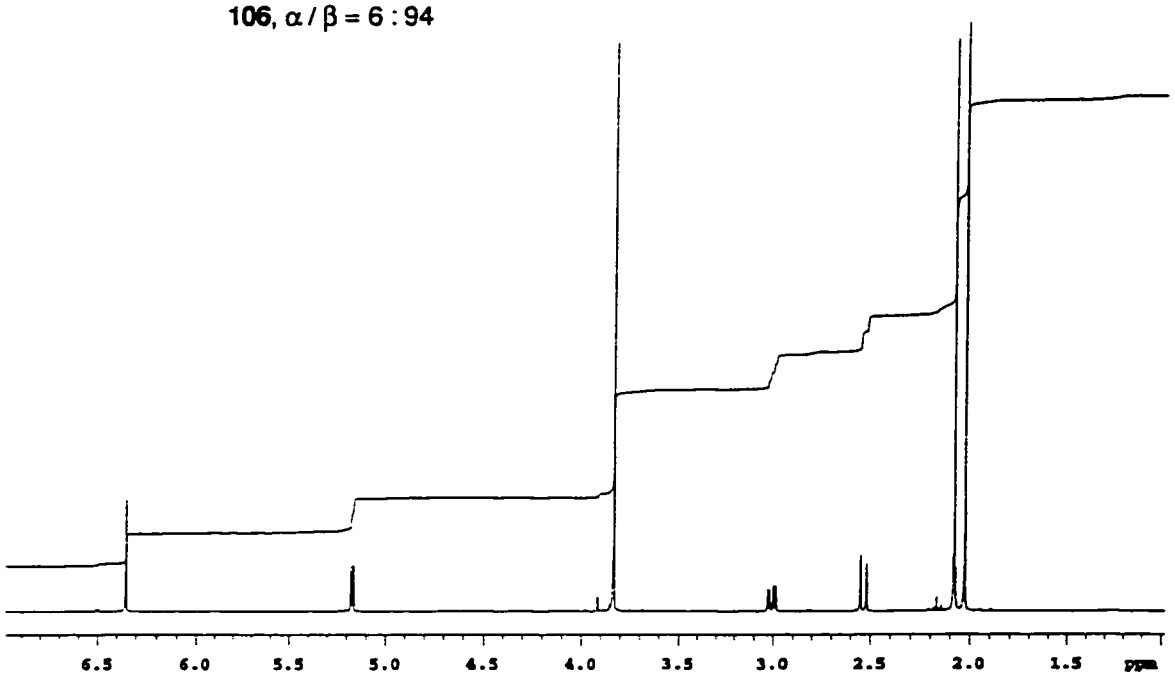
105

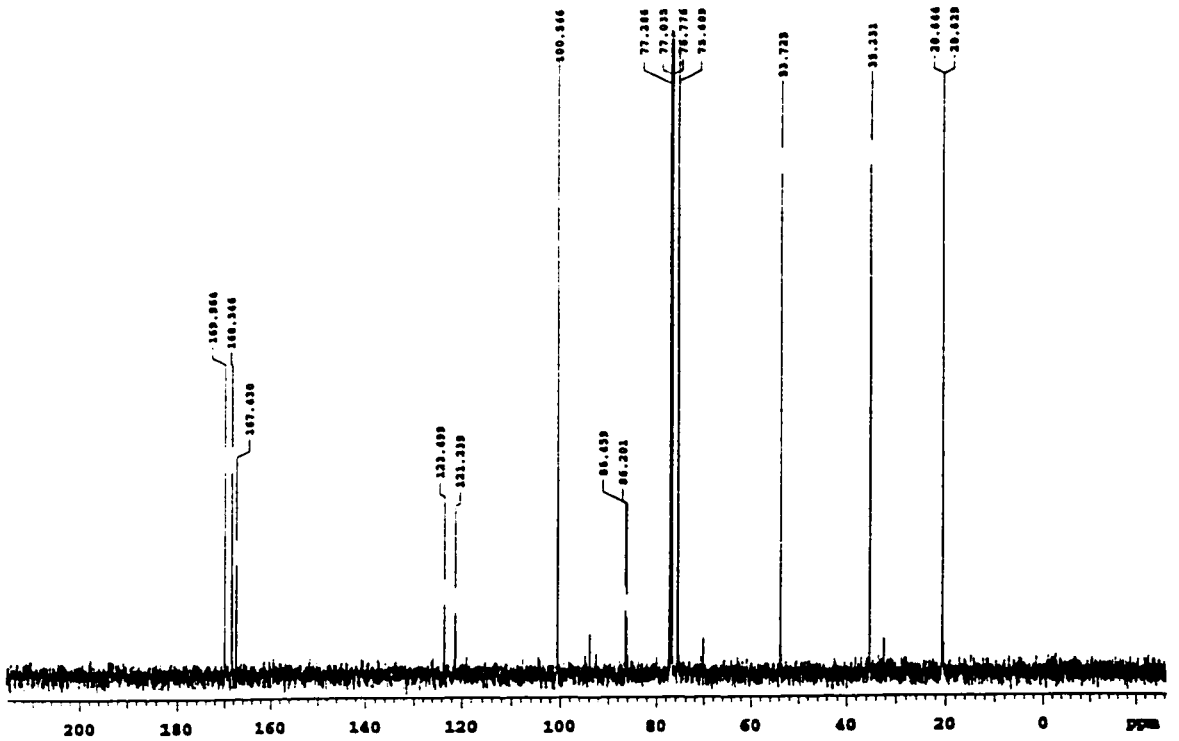
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

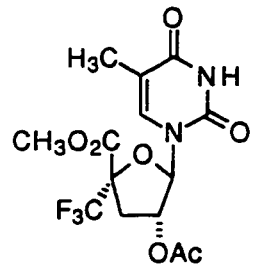

200
180
160
140
120
100
80
60
40
20
0
ppm



106, $\alpha / \beta = 6 : 94$

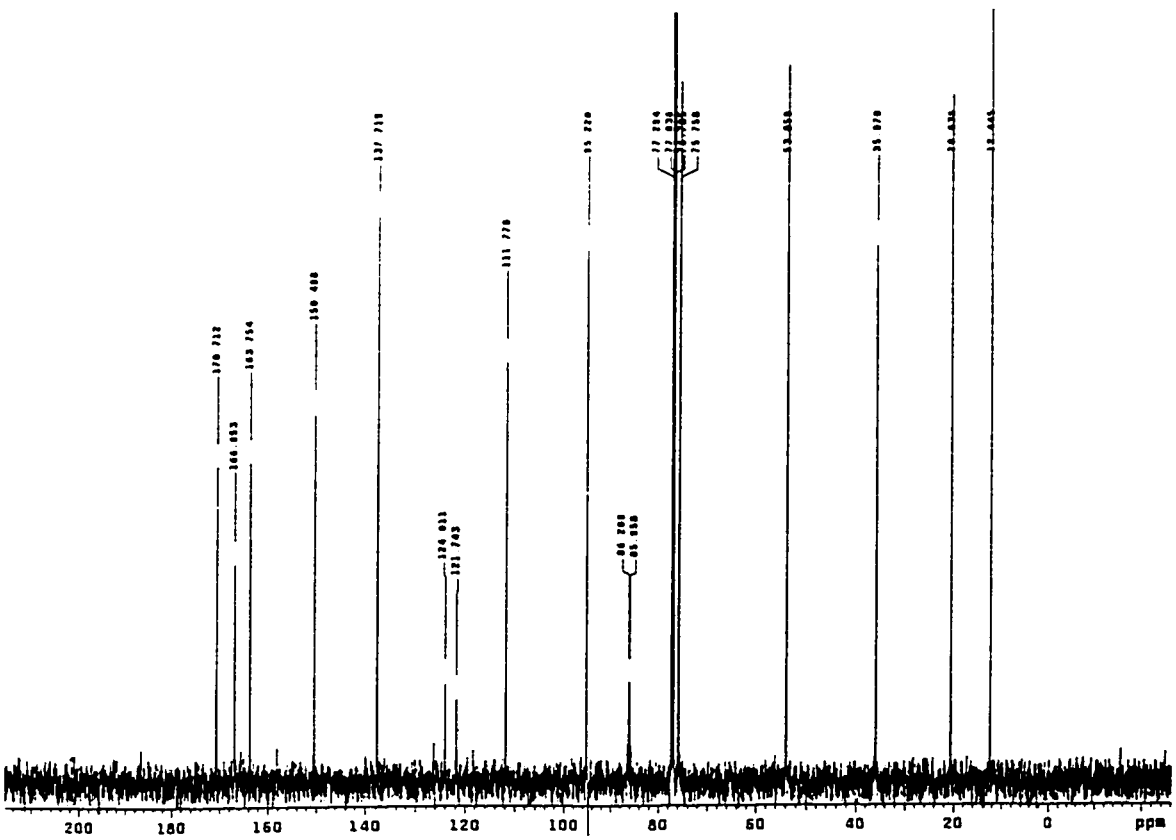


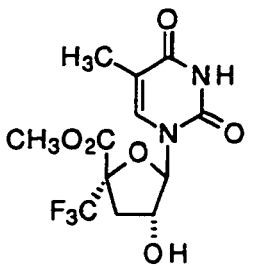



O
H3C
NH
CH3O2C
O
N
O
F3C
OAc

107

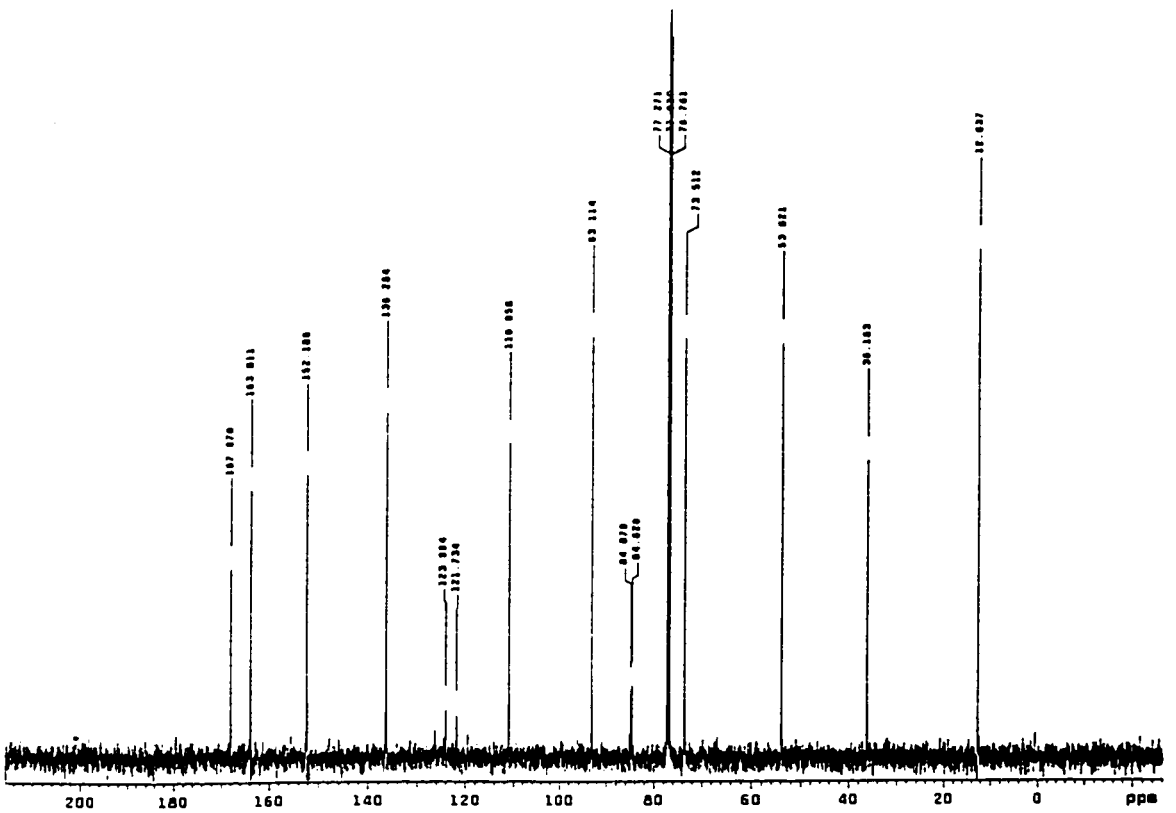
9
8
7
6
5
4
3
2
ppm

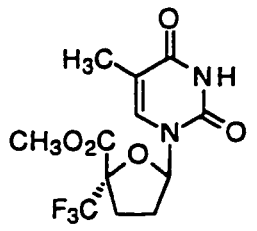

200
180
160
140
120
100
80
60
40
20
0
ppm


O
H3C
NH
CH3O2C
O
N
O
F3C
OH

108

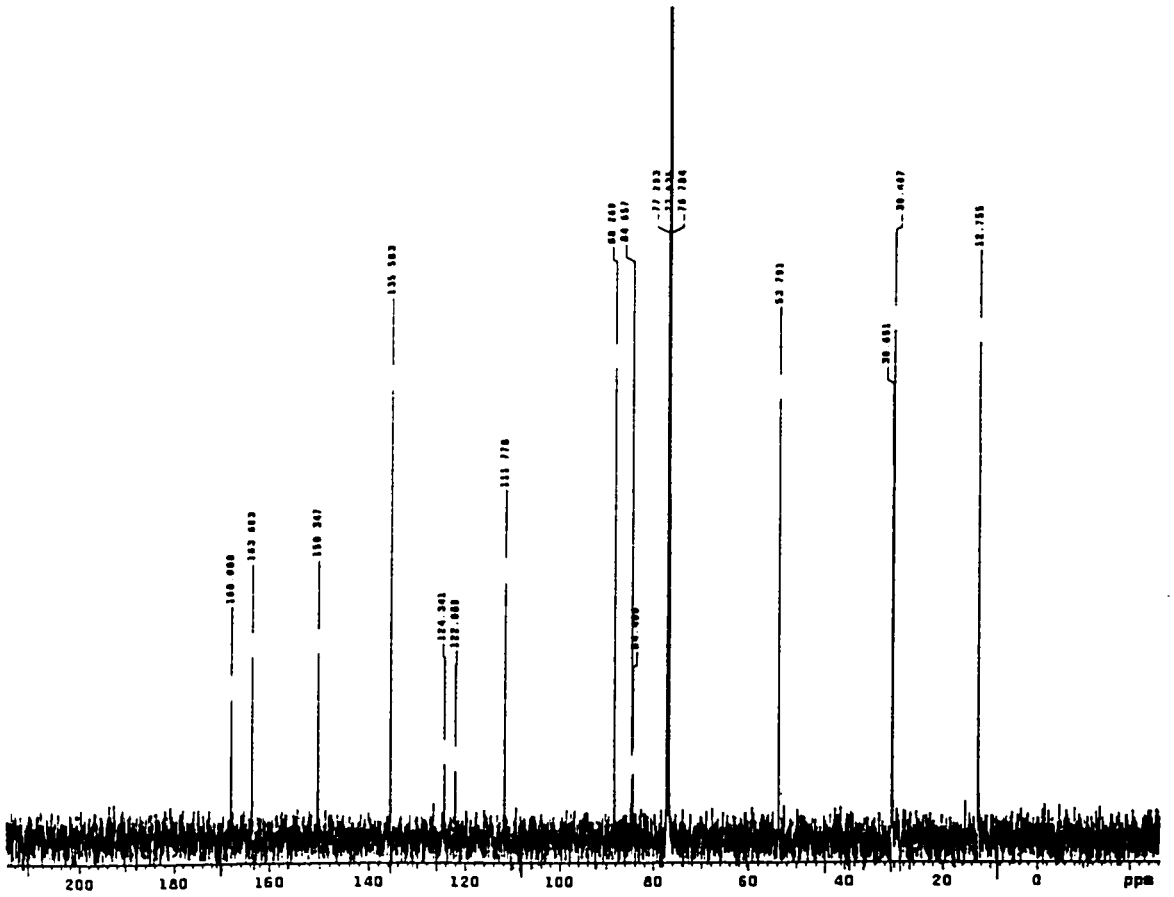
11
10
9
8
7
6
5
4
3
2
ppm

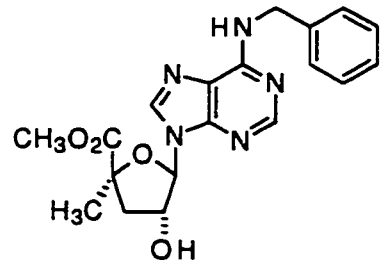

200
180
160
140
120
100
80
60
40
20
0
ppm


O
H3C
NH
CH3O2C
O
N
O
F3C

109

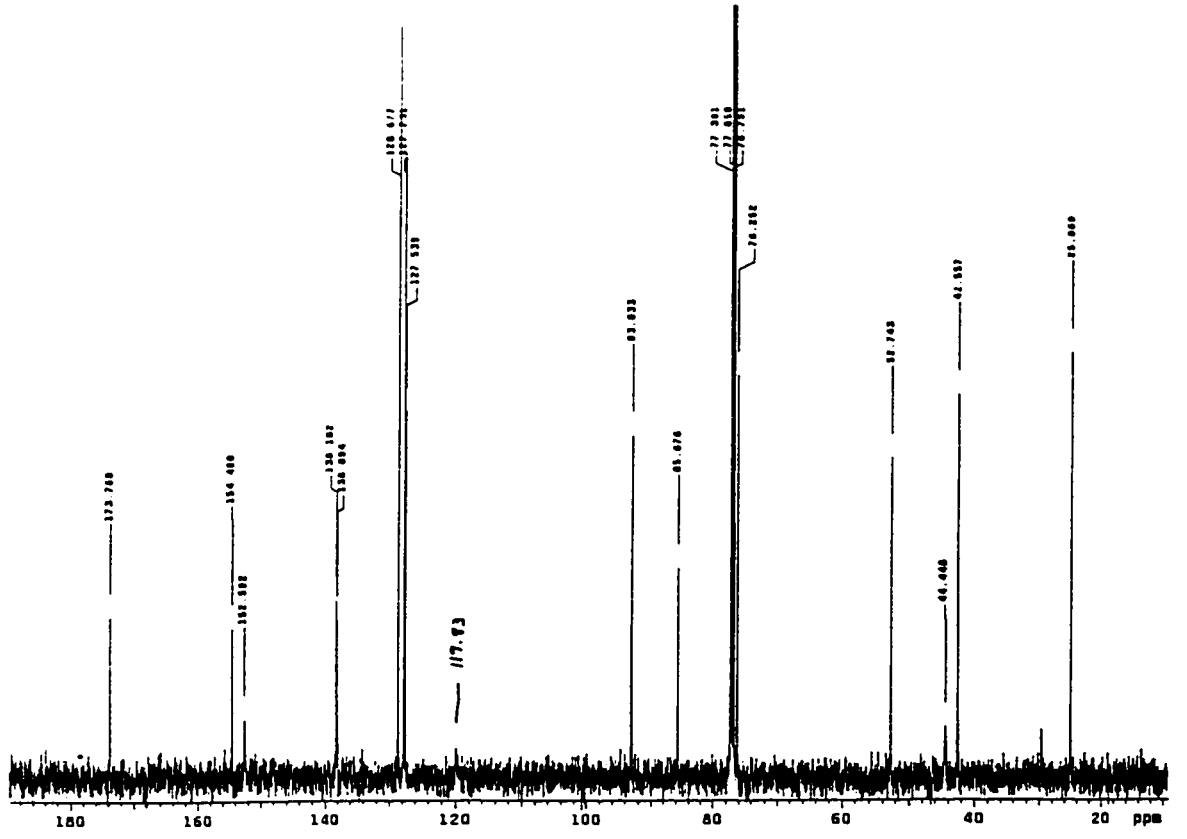
9
8
7
6
5
4
3
2
ppm

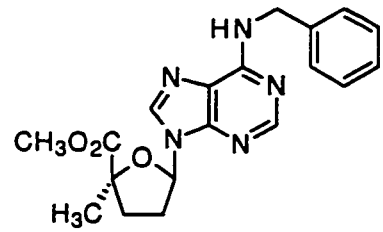

200
180
160
140
120
100
80
60
40
20
0
ppm


HN
N
N
N
N
CH3O2C
O
H3C
OH

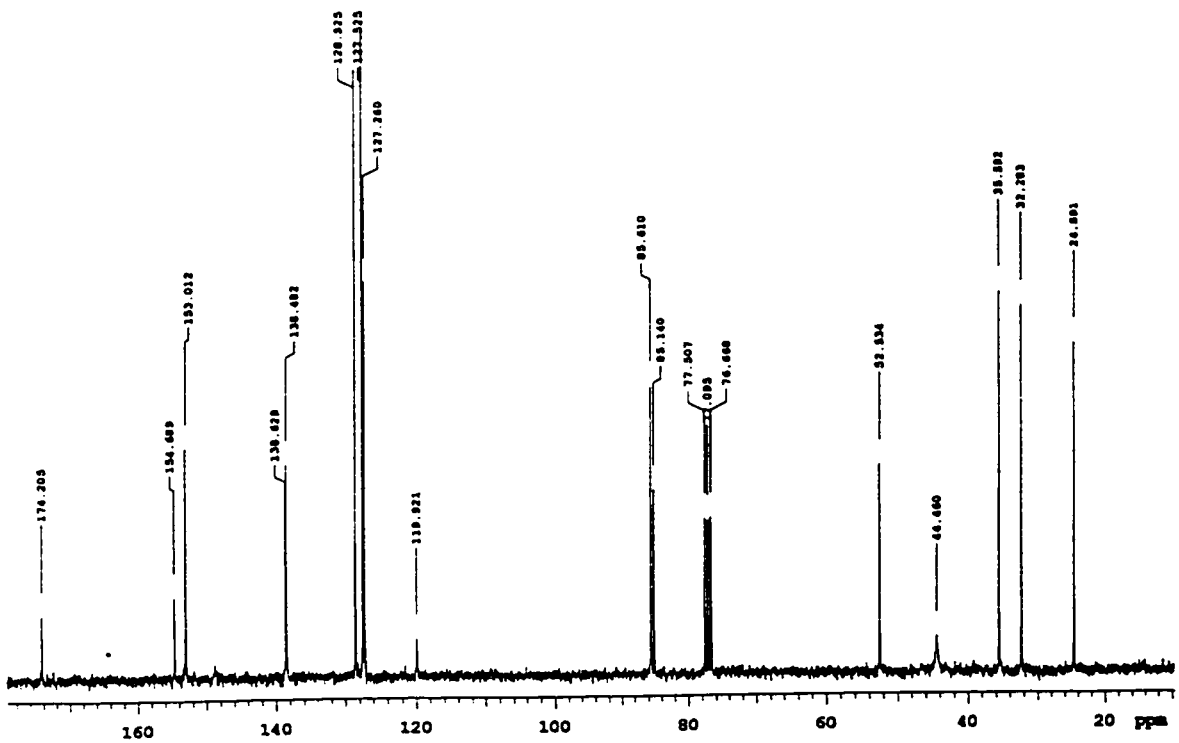
120

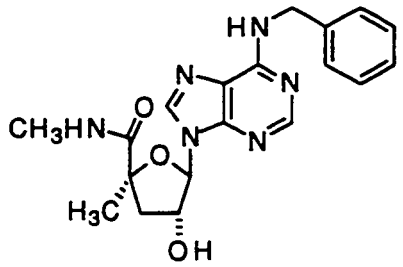
8
7
6
5
4
3
2
ppm


180
160
140
120
100
80
60
40
20
ppm



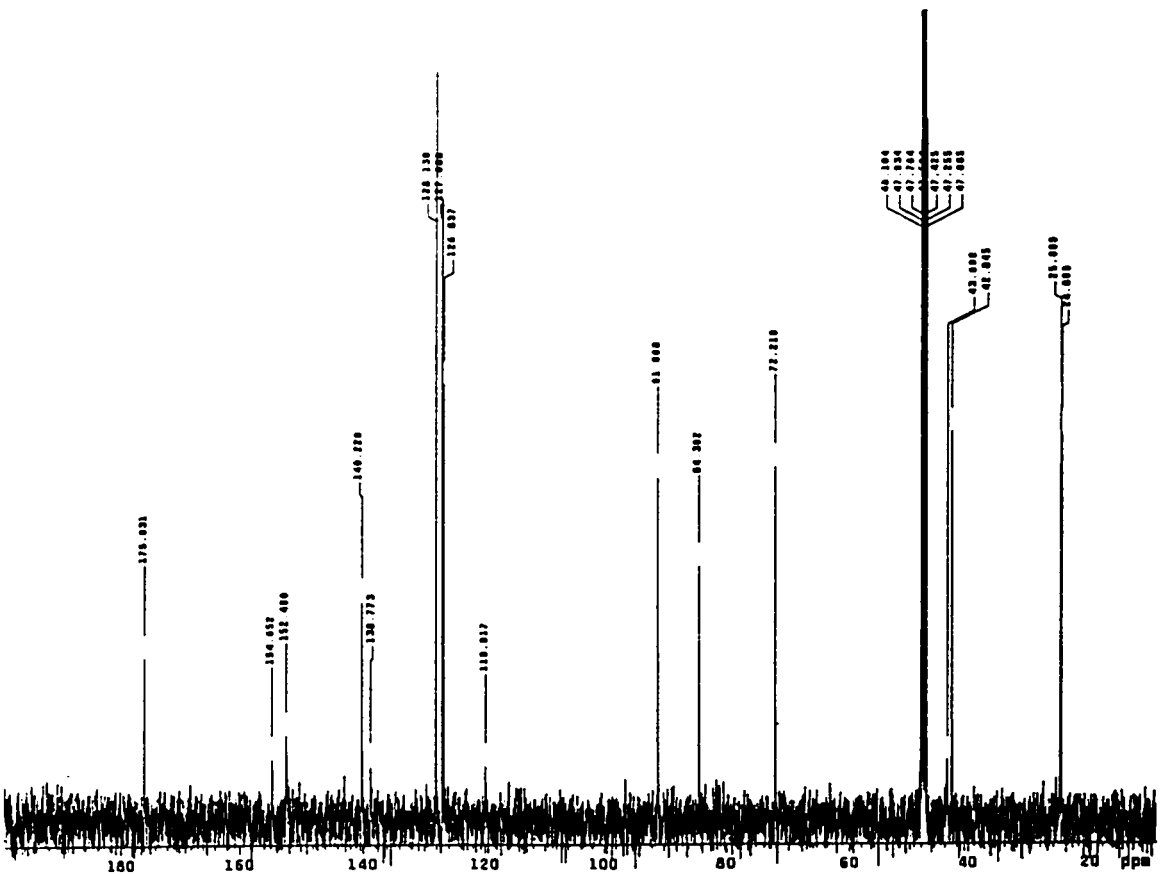
121

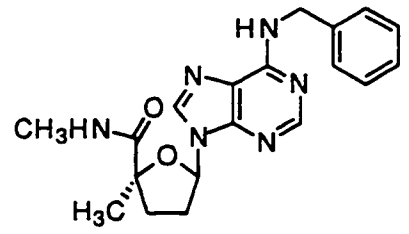



HN
N
N
N
N
O
CH3HN
O
H3C
OH

122

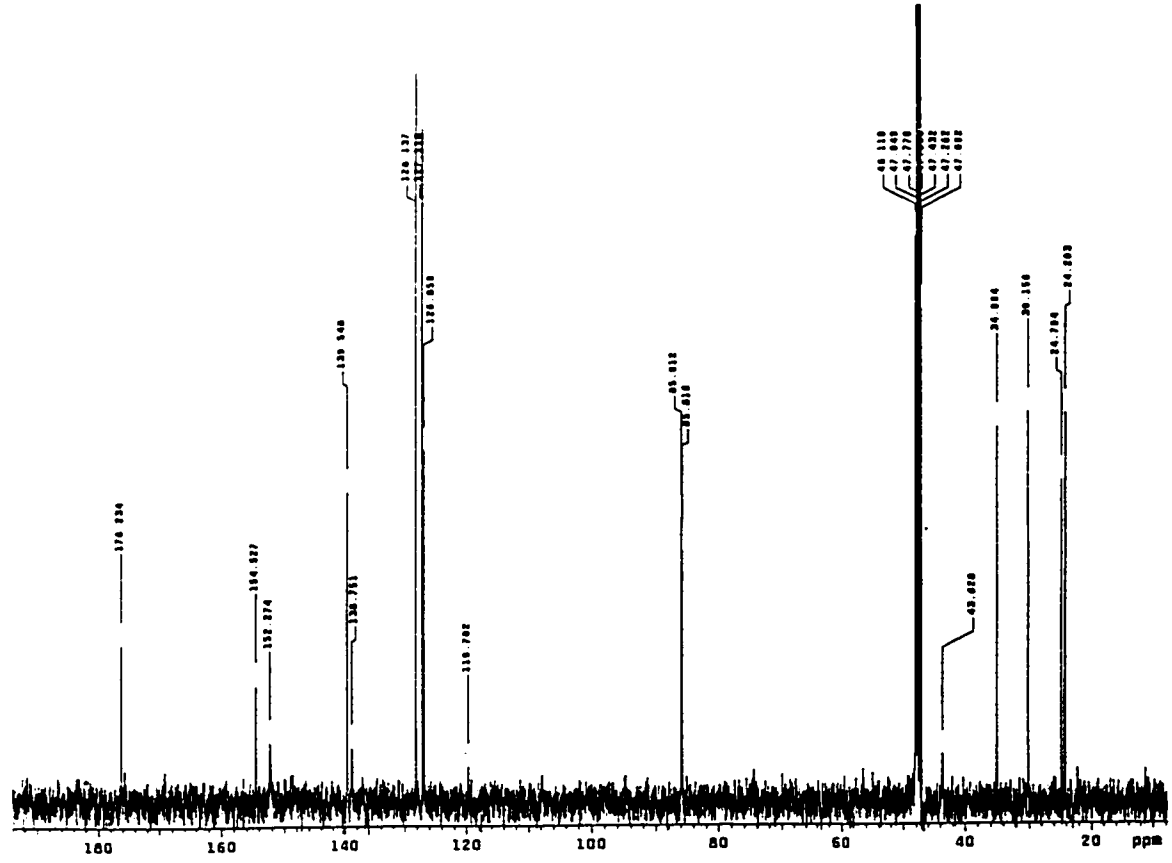
8
7
6
5
4
3
2
ppm


180
160
140
120
100
80
60
40
20
ppm


HN
N
N
N
N
O
CH3HN
O
H3C

123

8
7
6
5
4
3
2
ppm


180
160
140
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60
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ppm

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ABSTRACT

SYNTHESIS OF 3'-DEOXY- AND
2',3'-DIDEOXY-4'-*C*-ALKYL-D-NUCLEOSIDES:
POTENTIAL ANTIVIRAL AGENTS

by

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May 1998

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Novel methodology for the synthesis of 3'-deoxy- and 2',3'-dideoxy-4'-*C*-alkyl nucleosides has been developed. The target nucleosides are of interest as potential antiviral agents. Crucial features addressed by the methodology are: the ability to synthesize nucleosides analogs with a variety on 4'-*C*-alkyl substituents; exceptional stereocontrol over the C4' stereogenic center; and a semi-convergent synthesis, allowing the late stage *N*-glycosylation of heterocyclic bases. Both 4'-*C*-alkyl substituent variety and control of the C4' stereocenter are addressed by introducing the alkyl substituents and establishing the stereogenic center in a cyclopentene precursor. These alkyl substituted cyclopentenes are prepared by carbonyl alkylation of a biocatalitically derived enantiopure cyclopentenone. Employing the appropriate alkyl nucleophile in the alkylation of the cyclopentenone allows the introduction of a variety of alkyl substituents with exceptional stereocontrol. The five carbons of the alkyl substituted cyclopentene are then exposed as the five continuous carbons of a 4 -alkyl ribose analog by oxidative olefin cleavage.

The 4-alkyl ribose analogs prepared in the fashion described above were then used to glycosylate a variety of heterocyclic bases by a Vorbrüggen type coupling. Providing complete β-selectivity in the formation of the *N*-glycoside. Adjustment of the C5' oxidation

level then gives the 3'-deoxy-4'-*C*-alkyl nucleoside analogs. Deoxygenation at C2' by the method of Robins gave the 2',3'-dideoxy-4'-C-alkyl nucleoside analogs. Examples of target molecules prepared in this study include: 3'-deoxy- and 2',3'-dideoxy-4'-*C*-methyl analogs of uracil, 5-methyluracil, 5-fluorouracil, cytidine, 5-fluorocytidine, adenine and inosine; as well as, 3'-deoxy- and 2',3'-dideoxy-5-methyl-4'-*C*-phenyluridine.

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