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Dechalcogenative Allylic Selenosulfide And Disulfide Rearrangements For Cysteine Modification And Glycoligation

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DECHALCOGENATIVE ALLYLIC SELENOSULFIDE AND DISULFIDE REARRANGEMENTS FOR CYSTEINE MODIFICATION AND GLYCOLIGATION

by

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DISSERTATION

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Approved by:

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Advisor Date

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DEDICATION

To my beloved parents for their endless love and support

ACKNOWLEDGEMENTS

I owe my deepest gratitude to my advisor Professor David Crich for his endless patience, brilliant guidance, continuous encouragement and constant support throughout the years of my Ph.D study at University of Illinois at Chicago and at Wayne State University. Without his continuous help and guidance this dissertation would not have been possible.

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LIST OF ABBREVIATIONS

AA	Amino acid
Ac	Acetyl
ADDP	1,1'-Azo-dicarbonyldipiperidine
All	Allyl
Alloc	Allyloxycarbonyl
aq	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BSA	Bovine serum albumin
Bu	Butyl
Bz	Benzoyl
Calcd	Calculated
Cbz	Benzyloxycarbonyl
CDI	1,1'-Carbonyldiimidazole
Cys	Cysteine
DABCO	1,4-Diazobicyclo[2.2.2]octane
DBU	1,8-Diazobicyclo[5,4,0]undec-7-ene
DCM	Dichloromethane
DCC	*N,N'*-Dicyclohexylcarbodiimide
DIAD	Diisopropyl azodicarboxylate
DIC	*N,N'*-Diisopropylcarbodiimide

DIEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EI-HRMS	Electron impact high resolution mass spectroscopy
ESI-HRMS	Electrospray ionization high resolution mass spectroscopy
equiv.	Equivalent
Et	Ethyl
Fm	9-Fluorenylmethyl
Fmoc	9-Fluorenylmethoxycarbonyl
Gly	Glycine
h	Hour
HFIP	Hexa fluoro isopropanol
Hz	Hertz
im	Imidazole
i-Pr	Isopropyl
IR	Infrared
LAH	Lithium aluminum hydride
Me	Methyl
min	Minutes
mmol	Millimole
Mp	Melting point
MS	Molecular sieves

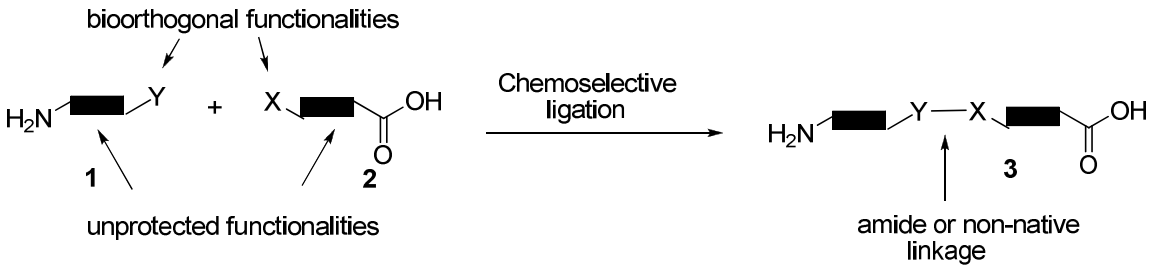
NCL	Native chemical ligation
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
p	para
PG	Protecting group
Ph	Phenyl
PMB	*p*-Methoxybenzyl
ppm	Parts per million
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
quant.	Quantitative
RP-HPLC	Reverse phase high performance liquid chromatography
r.t.	Room temperature
sat.	Saturated
SBL	Subtilisin *Bacillus lentus*
Se	Selenium
Ser	Serine
SPPS	Solid phase peptide synthesis
TBDPS	*tert*-Butyldiphenylsilyl
TBDMS	*tert*-Butyldimethylsilyl
temp.	Temperature
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
Tf	Trifluoromethanesulfonyl

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thr	Threonine
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPPS	Triphenylphosphine tris(sulfonate)
Ts	*p*-Toluenesulfonyl
UV/Vis	Ultraviolate-visible

CHAPTER I. Introduction

1.1 Chemoselective ligations

Nucleic acids, carbohydrates, proteins and lipids[1-2] are the four major classes of biological macromolecules. Among them carbohydrates and proteins play vital role and are critical components of living organisms. They mediate a vast number of fundamental biological pathways ranging from cellular operations to recognition events.[3-7] Therefore methods need to be developed for the conjugation of these molecules to each other and to other small molecules. The search for highly selective chemical reactions capable of proceeding within a physiological atmosphere led chemists to discover a set of technique called chemoselective ligation.[8] With the concept called "bioorthogonality", chemoselective ligation is labeld as the selective covalent coupling of two mutually and uniquely reactive functional groups in an aqueous environment (Scheme 1).[9-11]

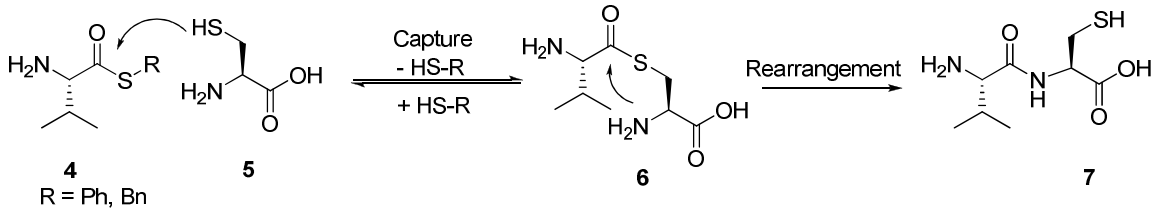


Scheme 1. Chemoselective ligation

Chemoselective ligations for the modification of macromolecules such as proteins and carbohydrates can be approached in two ways 1) acyl-transfer ligations and 2) non-native ligations.

1.1.1 Acyl-transfer ligations

In acyl-transfer ligations, a native amide bond is formed through a capture/rearrangement technique. In 1953 Wieland and co-workers were the first to synthesize amides by the intermolecular aminolysis of C-terminal thioesters with amines.[12] This capture/rearrangement technique was cleverly utilized to the synthesis of a dipeptide as shown in Scheme 2.

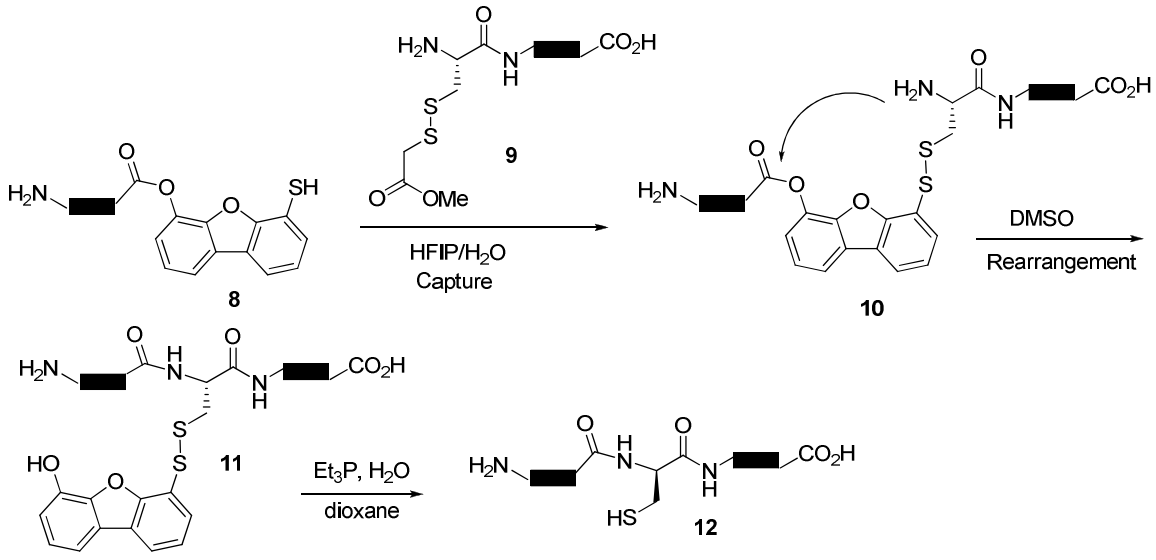


Scheme 2. Aminolysis of thioesters

Subsequent acyl transfer ligations, as described below, include prior thiol capture, pseudo proline ligation, native chemical ligation, and Staudinger ligation.

1.1.2 Prior thiol capture

Prior thiol capture, is one of the earliest ligation developed by Kemp et al.[13-15] Initially an auxiliary is attached to the N peptide through an ester linkage. The capture is mediated by the disulfide exchange between a Cys residue located at the N terminus of the C peptide and the free thiol of the auxiliary.[16] The intramolecular O→N transfer produces a native peptide bond as shown in Scheme 3.

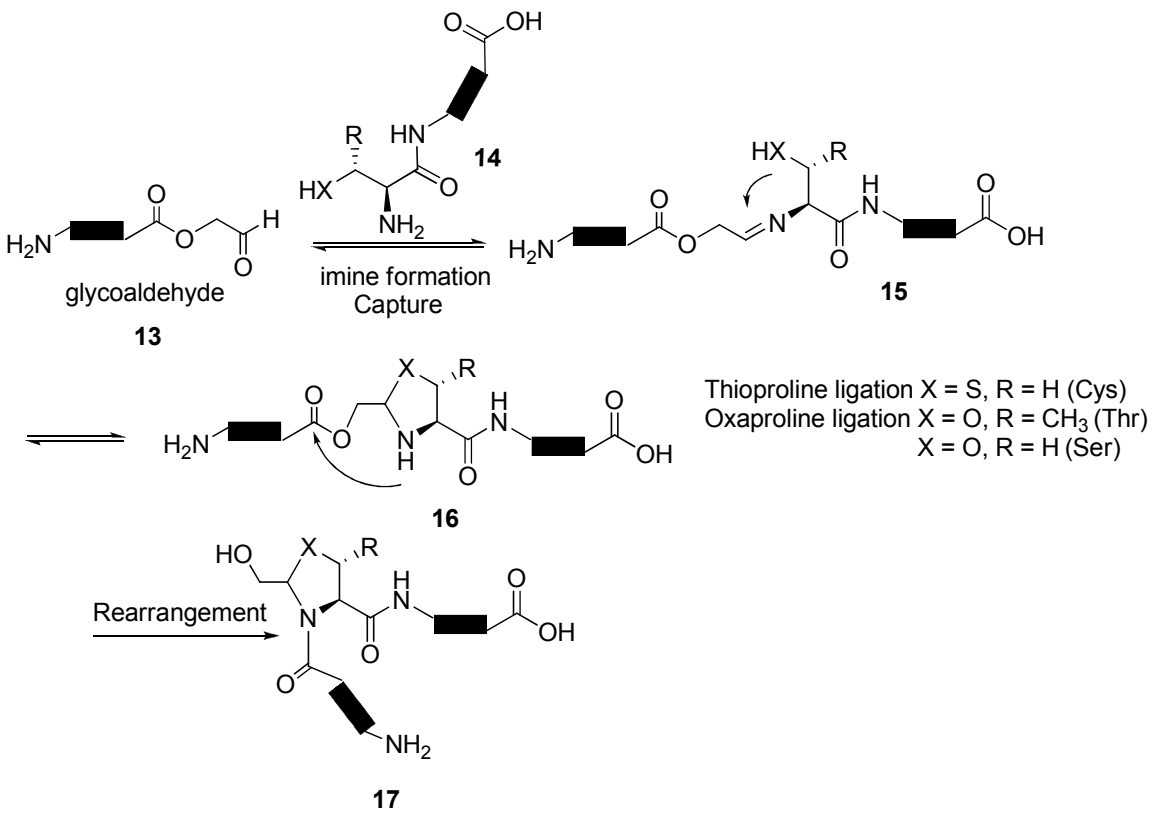


Scheme 3. Prior thiol capture

The prior thiol capture has been applied in the ligation of various unprotected peptides to yield polypeptides with up to 39 residues.[17]

1.1.3 Pseudo proline ligation

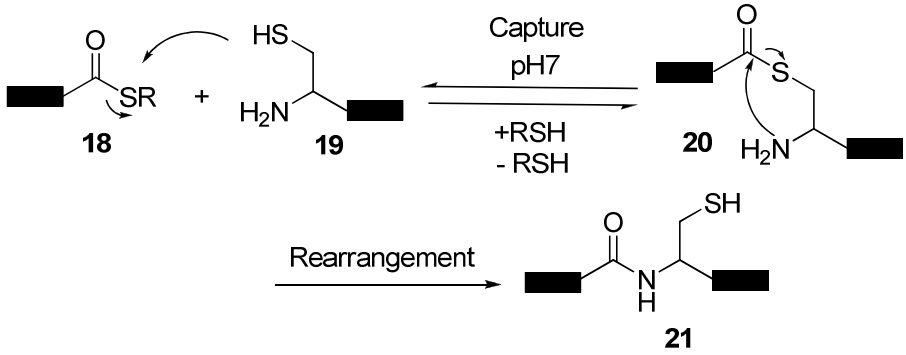
In pseudo proline ligation the capture step is the initial formation of an imine which transforms to an oxazolidine/thiazolidine in a reversible step. The irreversible O→N rearrangement delivers a pseudo proline at the ligation junction as shown in Scheme 4. This imine ligation reaction was successfully utilized in the assembly of proline rich peptide bactenecin 7 by Tom and Miao.[18-20]



Scheme 4. Pseudo proline ligation

1.1.4 Native chemical ligation

Native chemical ligation is one of the techniques in which a chemoselective transthioesterification of a peptide C-terminal thioester with an N-terminal Cys of another peptide forms a new thioester which spontaneously undergoes an S→N acyl transfer to form a native peptide bond (Scheme 5).

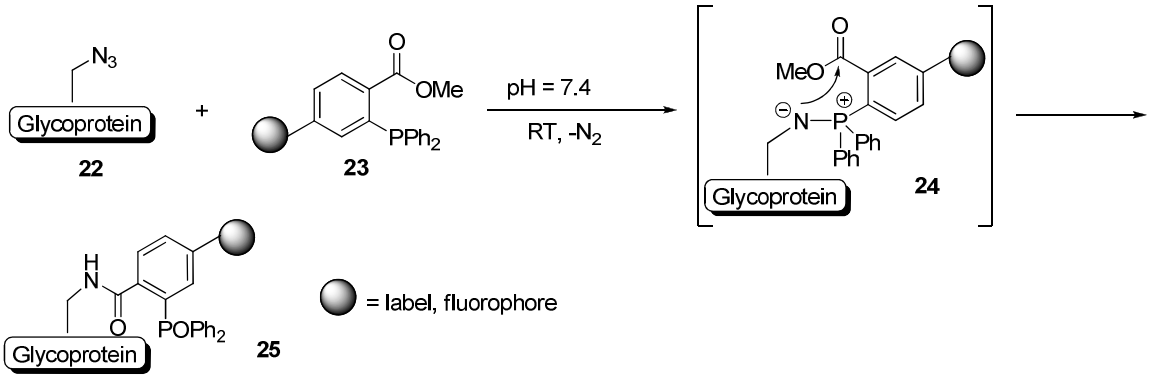


Scheme 5. Native chemical ligation

This capture/rearrangement strategy was elegantly used by Kent and coworkers in the synthesis of human interleukin 8 (IL-8) from two synthetic peptide fragments.[21] More recently native chemical ligation has been widely used in the synthesis of posttranslationally modified and unmodified proteins and in the conjugation of peptides with other macromolecules.[22-24]

1.1.5 Staundinger ligation

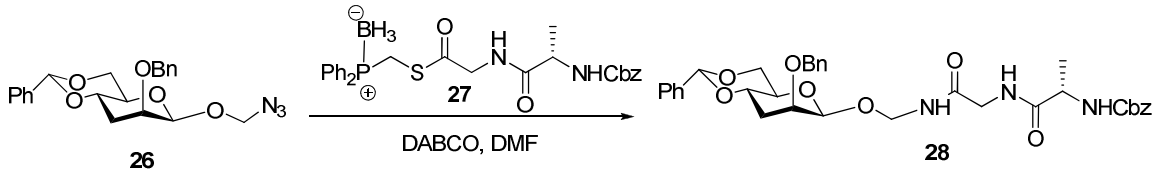
The reaction of phosphine with azide is known as the Staudinger reaction. Raines and Bertozzi independently developed this reaction to the formation of amide bonds. This chemoselective ligation technique for the site specific functionalization of biopolymers was introduced by Bertozzi and coworkers.[25-26] In its original variant, an iminophosphorane **24** undergoes an intramolecular nucleophilic attack with an ortho-substituted ester to form an amide **25** (Scheme 6).



Scheme 6. Staudinger ligation

The Staundinger ligation was applied to the selective labeling of sialic acid residues demonstrating the potential of its bioorthogonality.[25,27] Additionally this

ligation has been employed for site selective functionalization of proteins or their modifications and the immobilization of peptides and proteins.[10-11] More recently, Crich et al applied the traceless Staundinger ligation to synthesize a new class of glycoconjugates called amidomethyl glycosides by treating the azidothiomethyl glycosides with borane-protected phosphinothioesters as shown in Scheme 7.[28]



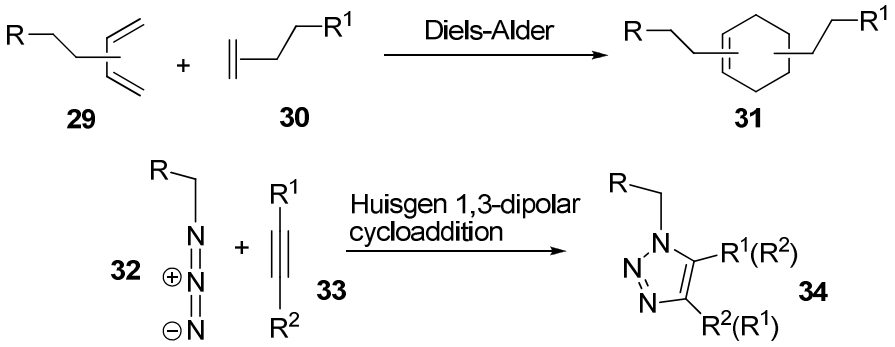
Scheme 7. Synthesis of amidomethyl glycosides through traceless Staudinger ligation

1.2 Non-native ligations

In non-native ligations linkage is achieved via the formation of bond not native to the naturally occurring biopolymers. For example, a bond is formed between two peptides through the reaction of a pair of mutually reactive functional groups. Typical non-native ligation methods include cycloadditions, oxime formation, thioesterification and thioetherification.

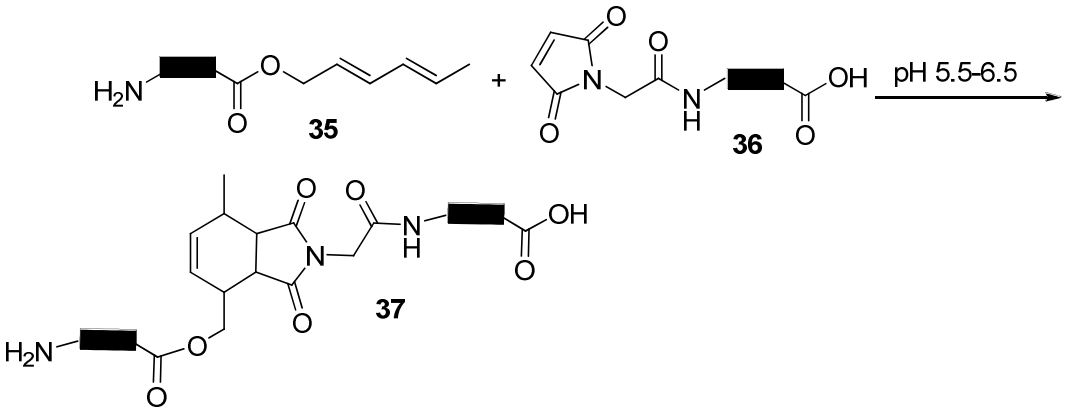
1.2.1 Cycloadditions

A number of cycloaddition reactions, including 1,3-dipolar cycloadditions and Diels-Alder reactions have been used as ideal chemoselective ligations since the reactants fuse together without generating any byproducts (Scheme 8).



Scheme 8. Cycloadditions as chemoselective ligations

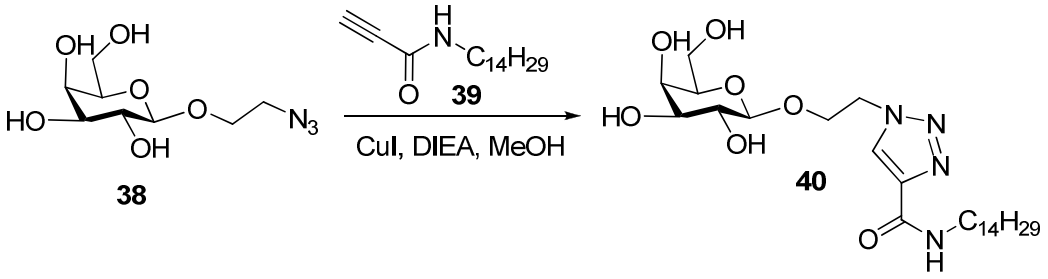
Recently Waldmann and co workers identified the [4+2] cycloaddition involving a maleimido group as a chemoselective reaction for the conjugation of peptides and functionalization of proteins as shown in scheme 9.[29] However, the determination of the stereoselectivity for this ligation product was not conclusive.



Scheme 9. Diels-Alder conjugation of peptides

The Huisgen dipolar cycloaddition of azides and alkynes is of great interest because azides are tolerant towards water, oxygen and the nucleophilic functional groups present in the living systems.[30-31] However, this cycloaddition is not highly bioorthogonal because higher temperatures are required to drive the reaction into the forward direction. Moreover it is not regioselective. These problems were independently addressed by Sharpless and Meldal groups.[32-33] It

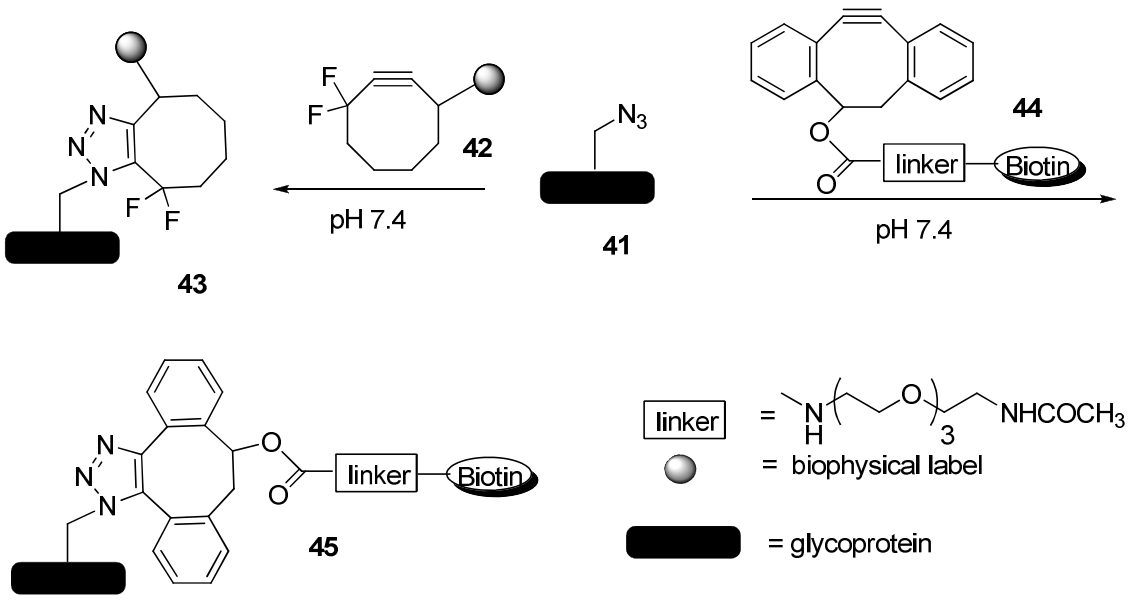
is believed that the addition of Cu-(I) salts allow the reaction to proceed at room temperature with improved regioselectivity involving a Cu-(I) acetylidene species via a stepwise process. This modification is known as the “click reaction”. It has found various applications in material and polymer science,[34] specific labeling of bioconjugates,[35] in monitoring enzyme activities and also in peptidomimetics.[36] The copper catalyzed cyclization has been applied to a range of carbohydrate modifications.[35] A representative example is shown in Scheme 10.



Scheme 10. Copper mediated Click reaction

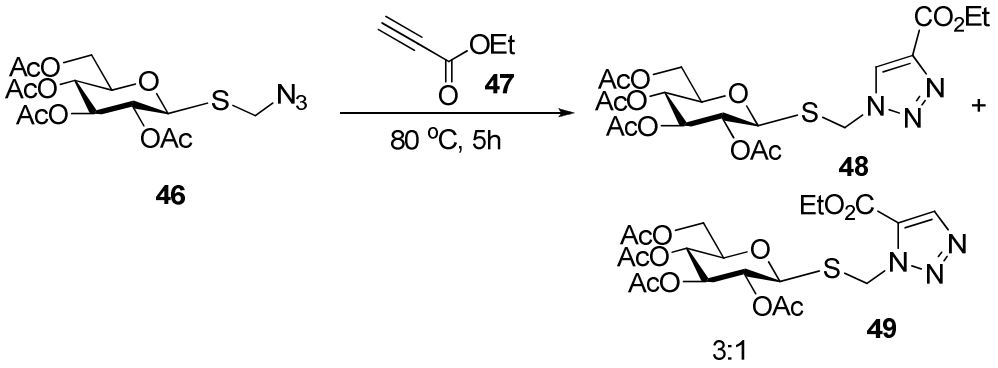
The 1,4-disubstituted 1,2,3-triazole units have been widely used to hold separate units together in complex glycosylated structures such as glycoconjugates, peptides and densely glycosylated molecular architectures including glycoclusters and glycodendrimers.[37-41] One of the major drawbacks of the Cu-(I)-catalyzed click coupling is the toxicity of copper, which limits its use in *in-vivo* applications. The toxicity issue was solved by Bertozzi et al who developed a strain-promoted cycloaddition in which the ring strain of the cyclic alkyne was used as a driving force to synthesize azido-functionalized glycoproteins (Scheme 11).[42] However the slow rate of this reaction limits its potential use and more recently, Boons et al developed an another version of this

strain promoted cycloaddition for visualizing metabolically labeled glycoconjugates of living cells.[43]



Scheme 11. Strain promoted cycloaddition of azido proteins

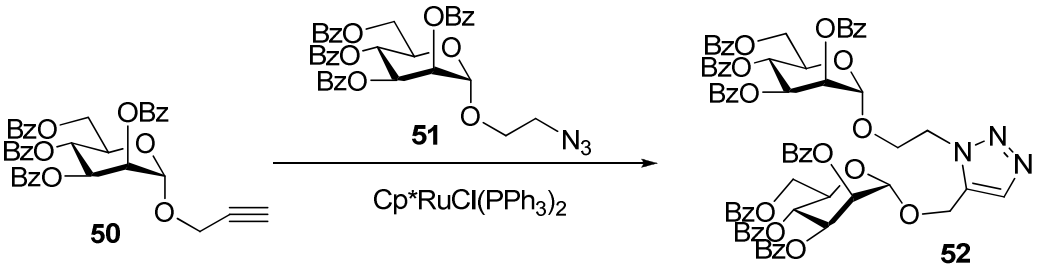
In 2004 Schmidt and coworkers reported a facile synthesis of glycosylthiomethyl-1,2,3-triazoles using the click approach (Scheme 12).[44]



Scheme 12. Synthesis of glycosylthiomethyl triazoles

Complementary to the copper catalyzed click reaction the Ru-catalyzed azide-alkyne 1,3-dipolar cycloaddition has provided ready access to the 1,5-disubstituted 1,2,3-triazoles.[45-47] More recently Crich and Yang have utilized the

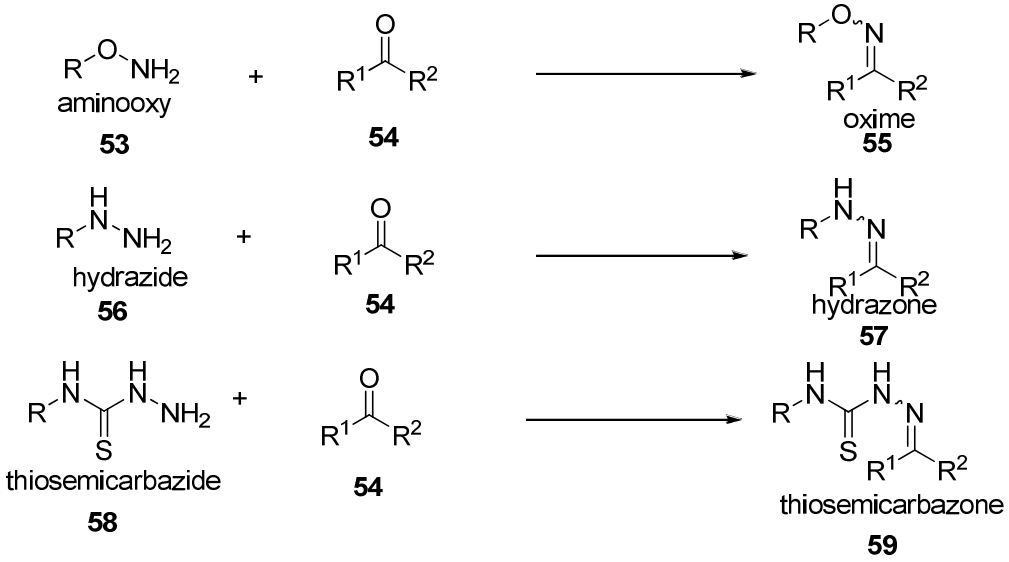
click approach to synthesize 1,2,3-triazole bridged dimeric oligosaccharides as shown in scheme 13.[28]



Scheme 13. 1,5-di substituted triazole bridged disaccharide

1.2.2 Oxime formation

Apart from the intramolecular electrophilic capture, several electrophile-nucleophile pairs can be coupled selectively with one another under more feasible conditions. For example, aldehydes and ketones react with aminooxy groups, hydrazides and thiosemicarbazides to form oximes, hydrazones and thiosemicarbazones respectively as shown in Scheme 14.



Scheme 14. Chemoselective ligations involving carbonyl electrophiles

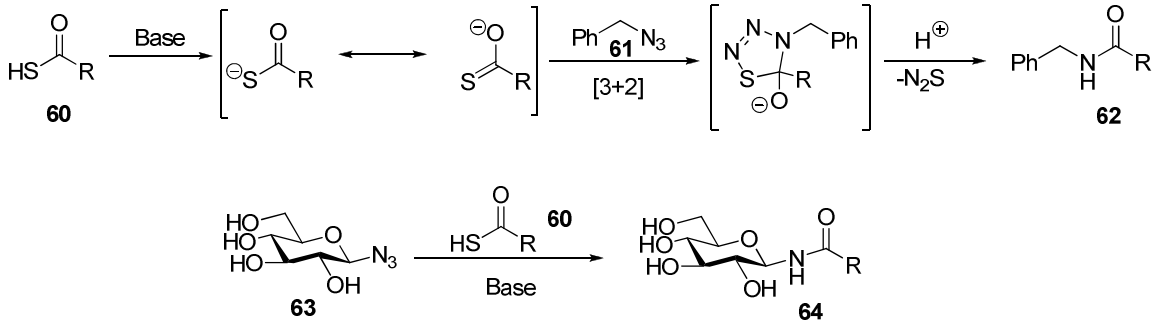
The enhanced nucleophilicity of the nitrogen atoms of the nucleophiles facilitate the reactions more favorable. The products are stable in pH 5-7 and have been extensively used in the formation of peptide conjugates,[48-52] *in vivo* protein labeling[53] and also in the generation of enzyme inhibitors.[54-55]

1.3 Thiol nucleophiles

The sulfhydryl group in cysteine has been used in reactions with a variety of electrophiles such as haloacetyl groups, maleimides, disulfides, sulfamidates and α,β-unsaturated esters because of its increased nucleophilicity. These reactions can be performed in water at neutral pH because these conditions are basic enough to supply a great amount of reactive thiolate species. More over, excellent selectivity can be reached in thiol-based ligations since thiolates are better nucleophiles compared to amines which are protonated at neutral pH. However the formation of thioether and disulfide bonds are not completely bioorthogonal chemoselective ligation reactions since many free thiol groups are present in the biological system and generally can only be used when competing sulfhydryl groups are not present.

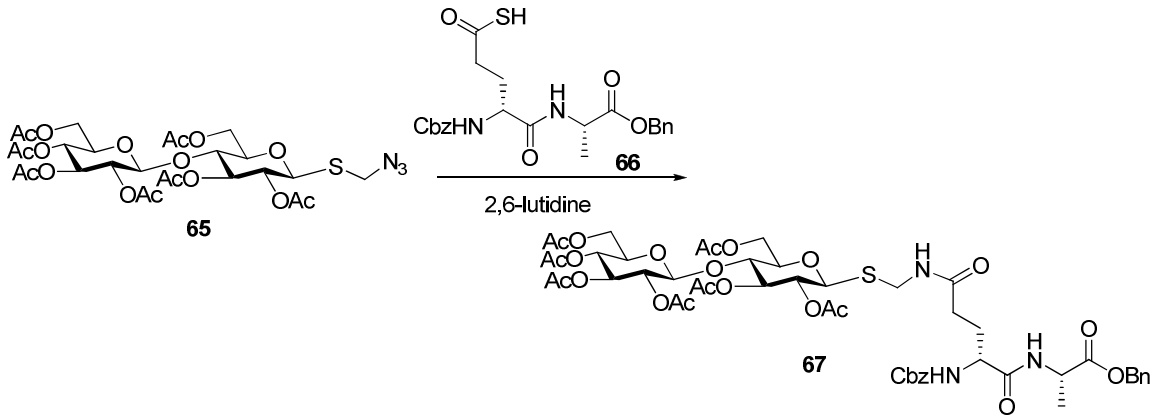
1.3.1 Thioesterification based chemoselective ligations

In 1980 Hosein Hakimelahi and Just described a reaction involving the formation of an amide bond between azides and thioacids.[56] The reaction proceeds via the formation of a thiatriazoline derivative through a [3+2] cycloaddition. Williams and coworkers applied this chemoselective ligation concept in the synthesis of β-glycosylamides as shown in scheme 15.[57-60]



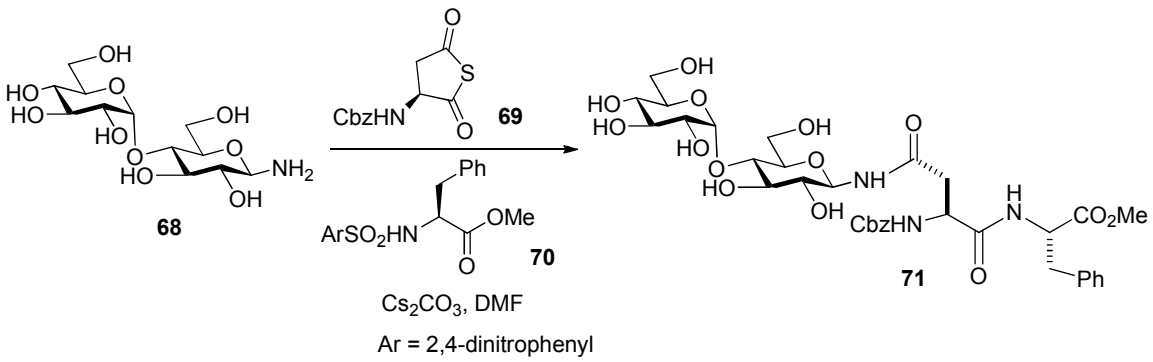
Scheme 15. Mechanism of thioacid/azide amidation and its application

In 2004 Schmidt et al applied this thioacid/azide amidation sequence in the synthesis of *S*-neoglycopeptides as shown in scheme 16.[61]



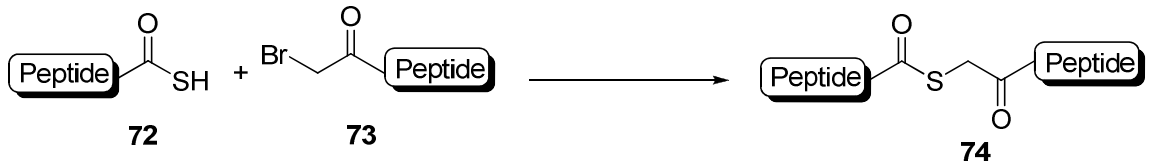
Scheme 16. Synthesis of *S*-neoglycopeptides

Furthermore, new chemoselective ligation reactions based on sulfonamide derivatives were developed utilizing the concept of the thioacid/azide reaction.[59-60] One of the recent reports which use the sulfonamide chemistry is the successful synthesis of glycosylated peptides by Crich et al (Scheme 17).



Scheme 17. Synthesis of a glycodipeptide through sulfonamide

The thioesterification ligation has also been used in the functionalization of proteins.[62] The 99-residue protein was synthesized by the ligation of C-terminal thiocarboxylic acid residue **72** with an *N*-terminal α-bromoacetamide residue **73** (Scheme 18).



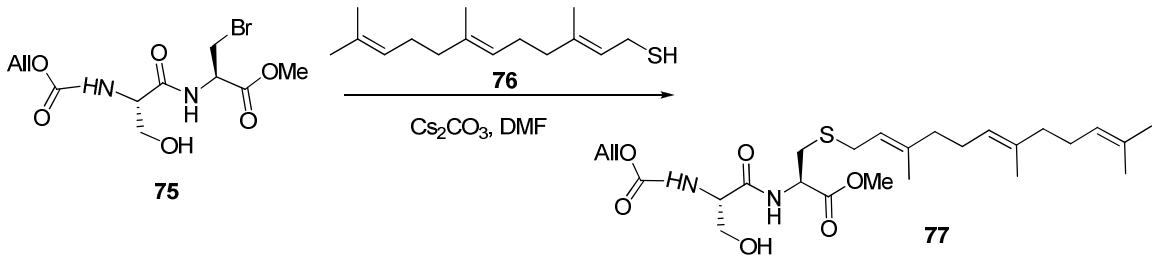
Scheme 18. Synthesis of a 99-residue protein, a modified HIV-1 protease

1.3.2 Thioetherification based chemoselective ligations

Thioetherification is extensively used in the lipidation of proteins where a lipid group is covalently attached to the peptide chain. Lipidated proteins play numerous roles in biological processes including signal transduction, cell adhesion and membrane localization.[63-65] *N*-Myristoylation, *S*-palmitoylation and *S*-isoprenylation are the three common types of lipid modifications in proteins.[66]

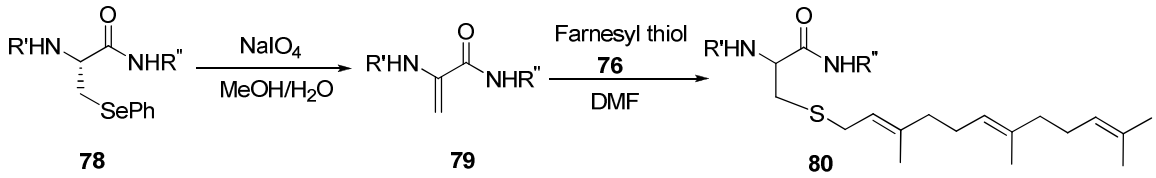
1.3.3 Synthesis of S-lipidated peptides

The synthesis of prenylated peptides in SPPS and in solution phase was successfully developed by different research groups. In 2005 Schmidt and coworkers have shown the efficient attachment of lipid groups to small peptides. This *S*-farnesylation and *S*-palmitoylation was accomplished by the S_N2 substitution of a bromide in bromoalanine containing peptide **75** with farnesyl thiol **76** (Scheme 19).[67]



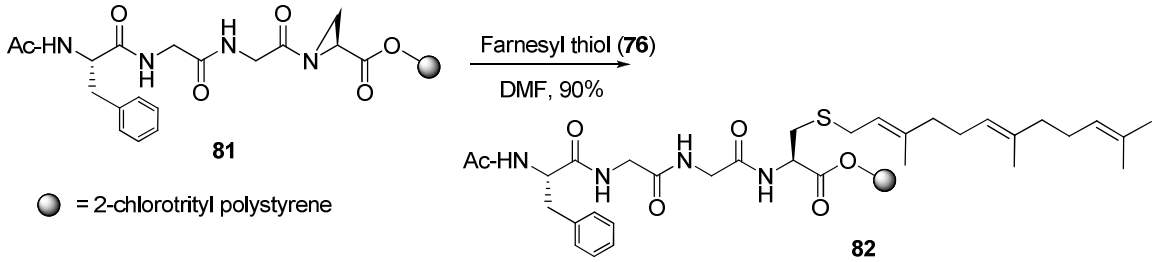
Scheme 19. Lipidation of small peptides

Another elegant approach to introduce the farnesyl groups into peptides was developed by van der Donk et al.[68] The conjugate addition of farnesyl thiol **76** to the dehydroalanine **79** resulted in the formation of farnesylated peptide **80** as shown in Scheme 20.



Scheme 20. Farnesylation of small peptides

The stereo control issue in the conjugate addition was addressed by using peptide containing aziridine-2-carboxylic acid by the same group on their subsequent work (Scheme 21)[69].

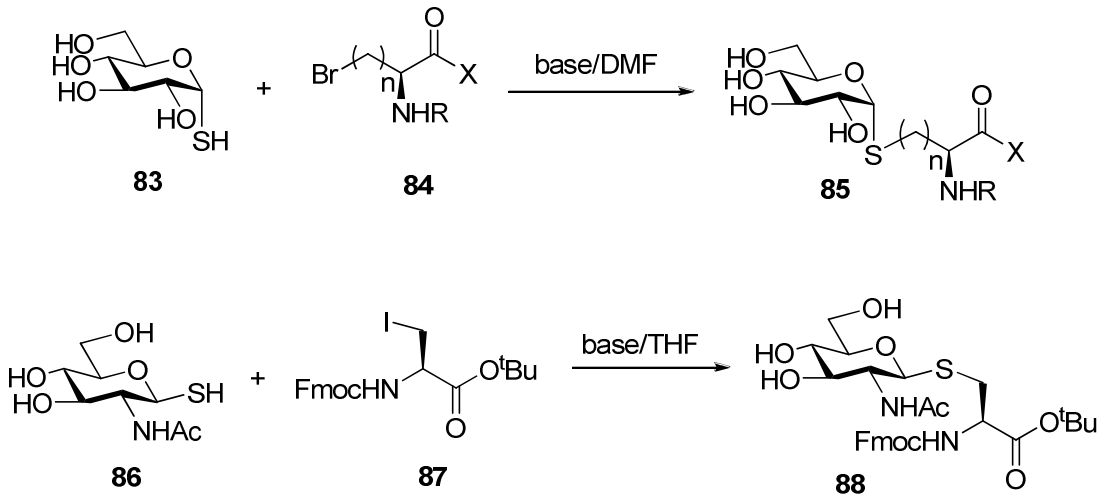


Scheme 21. Farnesylation without racemization

1.3.4 Synthesis of *S*-linked glycosyl amino acids and glycopeptides

1.3.4.1 Alkylation of anomeric thiol

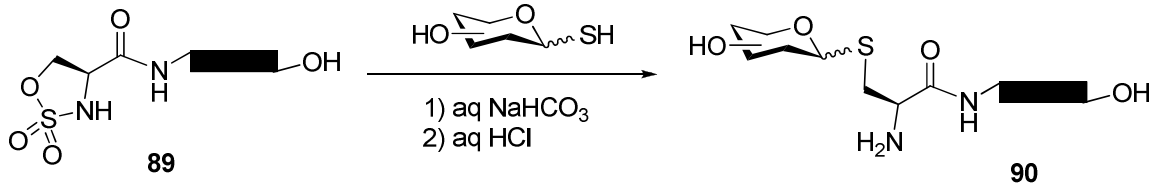
Several methods have been developed for the synthesis of *S*-linked glycopeptides since after the first identification of a natural *S*-glycosidic linkage on a peptide. *S*-linked glycopeptides show enhanced chemical and enzymatic stability compared to their native congeners. 1-Thio sugars have been alkylated with halo amino acids to afford the corresponding *S*-linked glycosylpeptides (Scheme 22).[70-75]



Scheme 22. Alkylation of anomeric thiol

The direct alkylation strategy is complicated by the competing elimination to form dehydroalanine derivatives. However, Halcomb et al have addressed this

problem by using cyclic sulfamidate containing amino acid incorporated into peptides. The chemeoselective ligation of 1-thiosugar affords the desired *S*-linked glycopeptides after the treatment with aqueous acid (Scheme 23). The acidic cleavage of the *N*-sulfate group limits its application for the synthesis of S-linked glycoconjugates containing oligosaccharides and peptides.

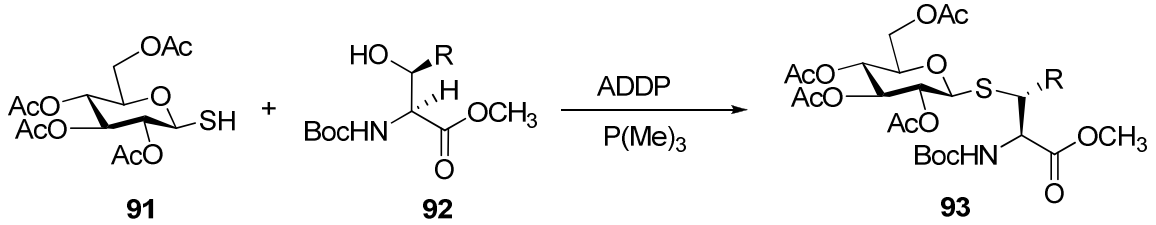


89 90

Scheme 23. Synthesis of S-linked glycopeptides

Mitsunobu conditions

Mitsunobu condensation has been applied in the synthesis of glycosylthio amino acids and peptides. The hydroxyl groups of *N*-Boc-serine methyl ester or *N*-Boc-threonine methyl ester were displaced by 1-thio glucosetetraacetate to provide the glycosylthio amino acids[76] (Scheme 24).



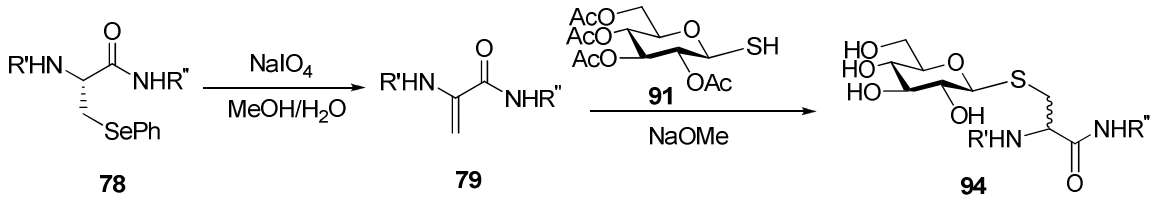
91 92 93

Scheme 24. Synthesis of glycosylthio amino acids by Mitsunobu condensation

1.3.5 Michael Additions

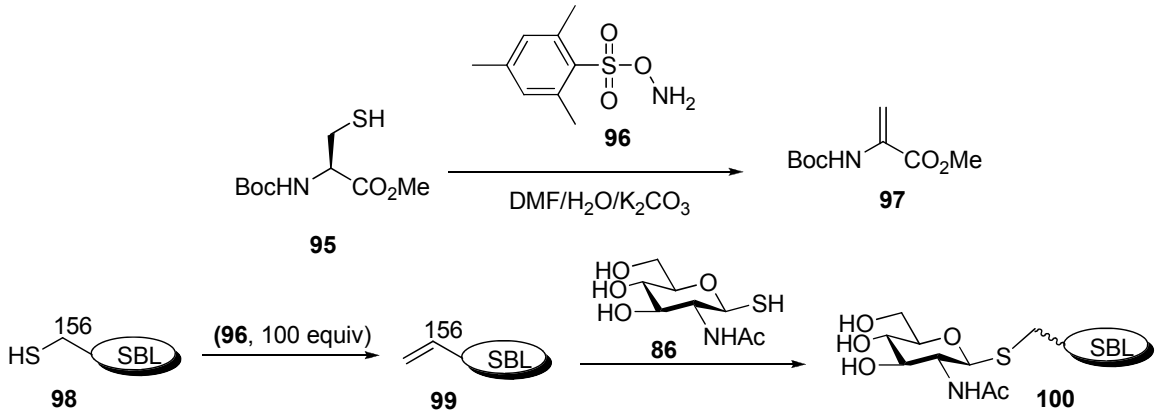
In 2001 van der Donk et al reported a convergent approach to the synthesis of *S*-linked glycopeptides by Michael addition of 1-thio sugars to Dha

containing peptides on both solution and solid phase (Scheme 25).[68] The synthesis of four tumor assisted carbohydrate antigens T_n, T, ST_n and 2,6-ST was successfully achieved by this methodology.[77]



Scheme 25. *S*-linked glycopeptides by Michael addition

Recently, Davis and co-workers used mesitylenesulfonylhydroxylamine as a reagent for the oxidative elimination of Cys to Dha. Furthermore, the selective functionalization of proteins and peptides were achieved by utilizing this methodology (Scheme 26).[78]

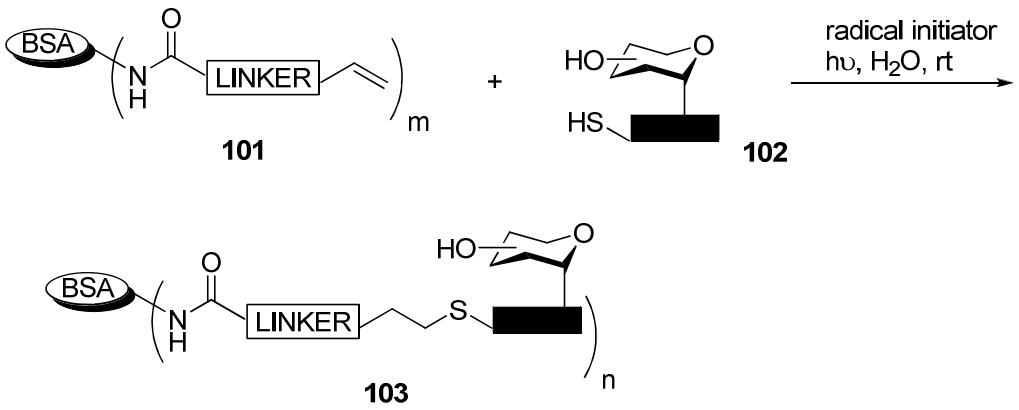


Scheme 26. Modification of proteins by transformation of Cys to Dha

1.4 Radical addition to form thioethers

The radical initiated addition of thiols to alkenes to form thioethers is a common bioconjugation technique, particularly applied in the conjugation of glycans. The reactions can be induced photochemically or by the addition of a radical initiator. This method tolerates various functioanal groups present in

proteins and peptides and can be applied to their functionalization. Kunz et al have applied this method for the synthesis of synthetic vaccines by conjugation of glycopeptides to bovine serum albumin (BSA) which has been previously functionalized with alkene end groups as shown in Scheme 27.[79]

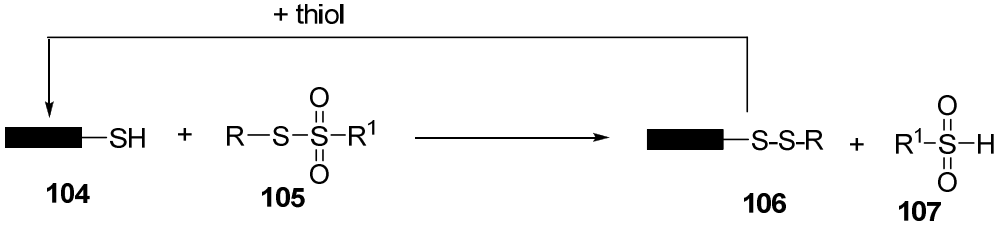


Scheme 27. Radical induced thioether formation

1.5 Synthesis of *S*-linked glycoprotein mimics

1.5.1 Ligation via disulfide linkage

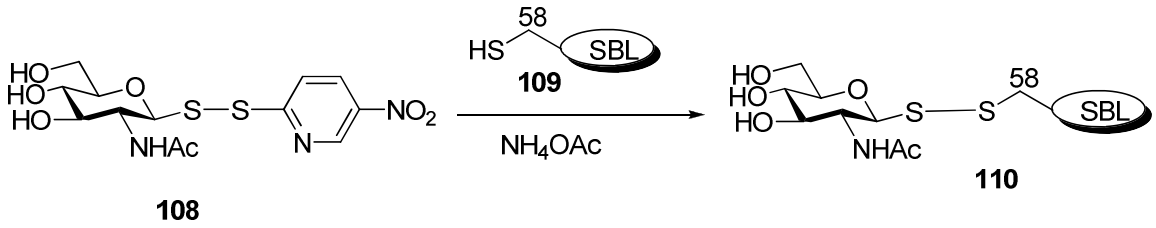
The formation of a mixed disulfide is also an established ligation method and its application has been successful in different disciples.[80-83] Disulfides, alkyl thiolsulfonates and thiopyridine mixed disulfides are the three types of available thiol modification reagents for protein mixed disulfides. A fundamental reaction involving protein thiol and alkyl alkanethiolsulfonates to form a mixed disulfide is shown in scheme 28.



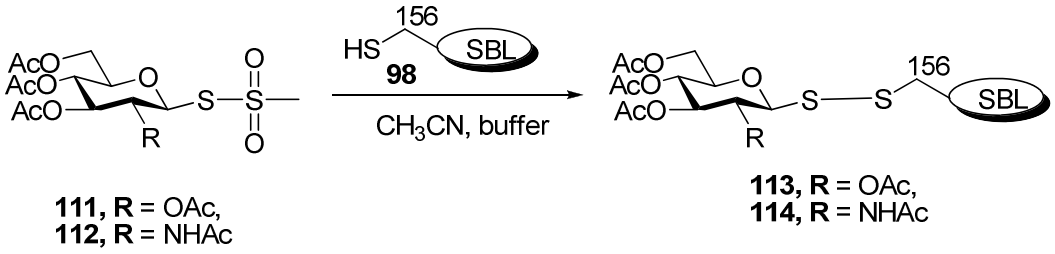
Scheme 28. Protein mixed disulfide via alkyl alkanethiosulfonates

Alkyl alkanethiolsulfonates had been used previously for the chemical synthesis of mixed disulfides[84-86] of simple organic compounds by Boldyrev et al[87] and Dunbar and Rogers.[88] A closely related aryl arenethiolsulfonate had been used by Field and Giles to block a sulfhydryl group of creatine kinase.[89]

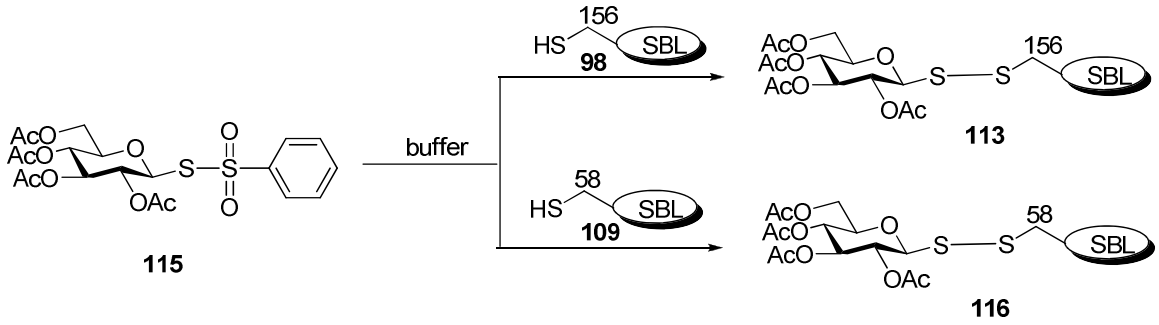
Boons and Davis reported a highly facile method for synthesizing disulfide linked glycoproteins and glycopeptides with thioglycoside precursors by means of sulfenyl transfer reagents such as 5-nitropyridine-2-sulfenyl thioglycosides,[83] glycosyl methanethiosulfonates and glycosyl penylthiosulfonates (Schemes 29-31).[90-92]



Scheme 29. Disulfide linked glycoprotein

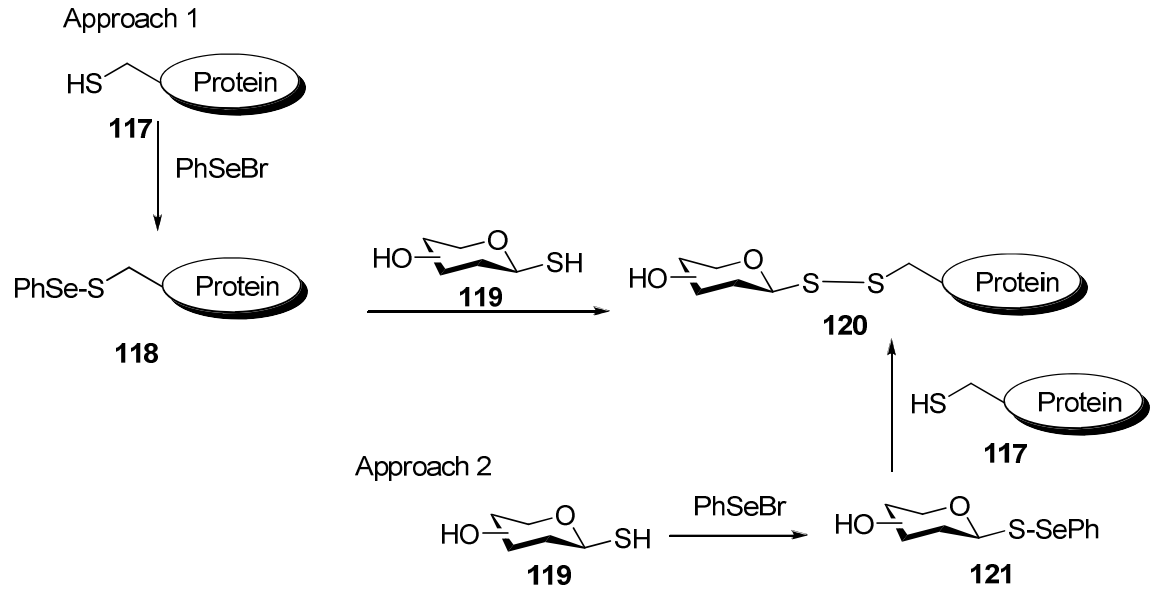


Scheme 30. Disulfide linked glycoproteins through methanethiosulfonates



Scheme 31. Disulfide linked glycoproteins through phenylthiosulfonates

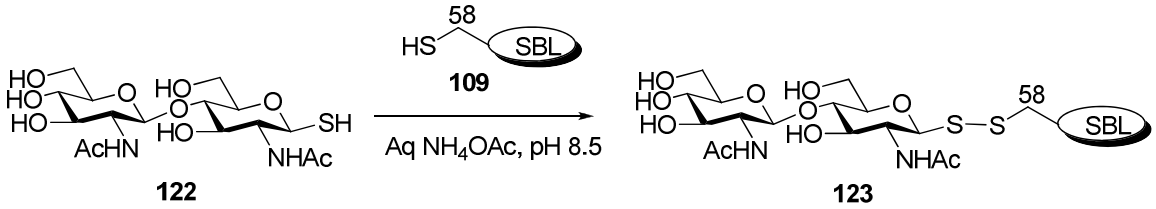
In an alternative approach to the disulfide ligation, selenylsulfide mediated protein glycoconjugation was approached by Davis et al.[93] In two different approaches this method allowed glycoconjugation with mono and oligosaccharides of upto seven saccharide units in size at single and multiple sites in a variety of proteins (Scheme 32).



Scheme 32. Selenylsulfide mediated protein glycoconjugation

The oxidative coupling of thiosugars to cysteine containing peptides and proteins for the synthesis of glycopeptides and glycoproteins was developed by

Boons et al (Scheme 33).[94] The homodimerization of the proteins is prevented by the use of excess thiosugars is the drawback to this method.



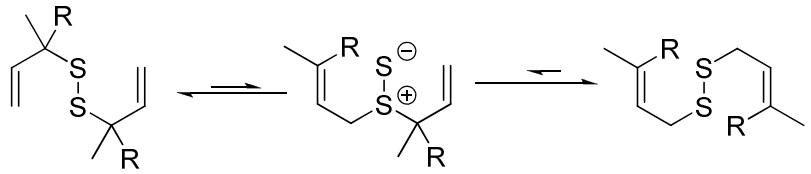
Scheme 33. Glycoproteins synthesis through cysteine oxidation

1.6 From Disulfides to thioether linked chemoselective ligations

1.6.1 Allylic disulfide rearrangement

Previous work by Moore and others showed that dialkyl or diaryl disulfides are unreactive with triphenylphosphine even under thermal conditions. However, the treatment of diallyl disulfide with triphenylphosphine in benzene at 80 °C gave diallylsulfide and triphenylphosphine sulfide.[95] A similar reaction was observed when diallyl disulfide was treated with cyclic phosphoramidites under the same conditions.[96]

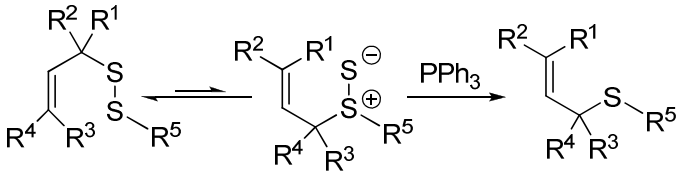
Hofle and Baldwin reported that α-substituted allylic disulfides **124** and **125** smoothly rearranged to the more stable isomer with double allylic inversion in benzene at room temperature (Scheme 34).[97]



Scheme 34. Rearrangement of diallyl disulfides

The diallyl disulfide rearrangement occurs through a double [2,3]-sigmatropic rearrangement proceeding via a thiosulfoxide intermediate which is closely related to the interconversion of allylic sulfoxides and sulfenates reported by Mislow.[98-99] Pseudo first order rate constants measured by Höfle and Baldwin for different substituted allylic disulfides were consistent with the earlier work of Moore and Trego. The rate constant values and the negative entropy of activation are consistent with a cyclic transition state which favors two consecutive [2,3]-sigmatropic processes and are also similar in magnitude with allylic sulfenate to sulfoxide rearrangement .

When no thiophile was involved, the mixed alkyl allyl disulfides were found to be stable at room temperature and even could be purified by distillation techniques. The disulfide and thiosulfoxide equilibrium strongly favors the allylic disulfides and is driven forward only by the addition of a thiophilic reagent (Scheme 35).

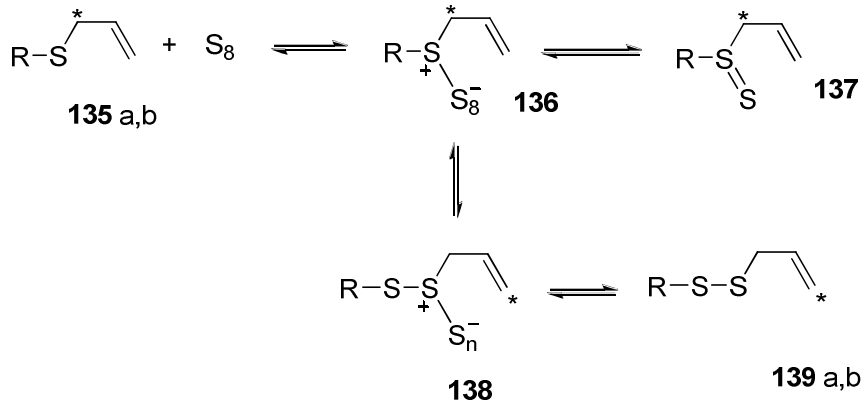


130: R^1, R^2 = Me, R^3, R^4 = H, R^5 = Me; k_{60} = 190 x 10^{-4} s^{-1}
131: R^2, R^5 = Me, R^1, R^3, R^4 = H; k_{60} = 140 x 10^{-4} s^{-1}
132: R^1, R^2 = H, R^3, R^4, R^5 = Me; k_{60} = 0.70 x 10^{-4} s^{-1}
133: R^1, R^2, R^3, R^4 = H, R^5 =$CH_2CH{=}CH_2$; k_{60} =8.90 x 10^{-4} s^{-1}
134: R^1, R^3, R^4 = H, R^5 = CH_3, R^2 = Ph ; spontaneous loss of S

Scheme 35. Pseudo first-order rate constants for phosphine mediated allylic rearrangement

The rate constant values for the phosphine promoted rearrangement measured by Baldwin et al led to the conclusion that increasing the bulk of R_3, R_4 and R_5 reduces the amount of thiosulfoxide whereas increasing the size of R_1 and R_2 favor this intermediate and enhance the rate of formation of allylic sulfide. It was also observed that increasing the polarity of the medium favors the formation of the thiosulfoxide intermediate. The rate dependency with the substitution pattern was also observed by Moore and Trego in their earlier work. The disulfides **133** and **134** spontaneously excised the sulfur atom from the thiosulfoxide intermediate even at room temperature.

The reverse direction of the reaction was described when allyl methyl sulfide (**135**a) or diallyl sulfide (**135**b) was heated with S_8 gave the corresponding disulfides **139**a and **139**b with complete allylic rearrangement (Scheme 36). However, dialkyl sulfides were apparently inert toward the reaction with elemental sulfur even at 90 °C for several days under identical conditions. It was believed that the reaction occurs through a series of equilibria involving dipolar polysulfides and thiosulfoxide intermediates as shown in scheme 36.

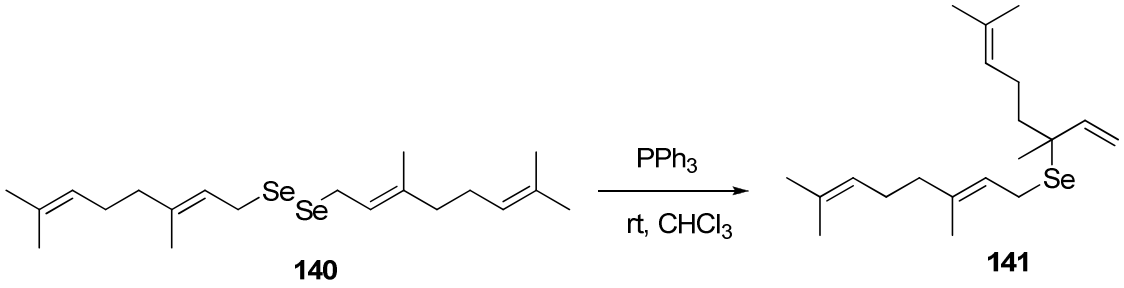


a; R = Me, b; R = Allyl

Scheme 36. Reaction of allyl methyl sulfide and diallyl sulfide with S_8

1.7 Allylic selenosulfide rearrangement

In 1972 Sharpless and Lauer reported that di(geranyl) diselenide (**140**), a diallyl diselenide transformed to geranyl linalyl selenide (**141**) on treatment with excess triphenylphosphine in chloroform indicating the selenium version of the disulfide reaction was faster than the original sulfur protocol (Scheme 37).[100] The reaction proceeded with a half life of 2.5 h. Subsequently, Guillemin et al successfully characterized a range of allylic diselenides and studied their reactions with tributylstannane, indicating such diselenides have moderate stability at room temperature.[101]

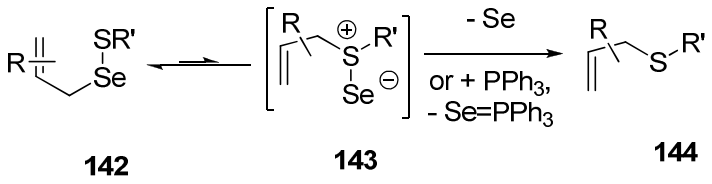


140 **141**

Scheme 37. Rearrangement of digeranyl diselenide to geranyl linalyl selenide

Taking these facts into account and also considering the practical advantages of the disulfide ligation and the disadvantages of its impermanence Crich et al developed a new chemical ligation technique in which one of the sulfur atoms in the allylic disulfide was replaced with a selenium atom.[102] In the allylic disulfide rearrangement reported by Hofle and Baldwin the equilibrium favors the allylic disulfide and the reaction is driven in the forward direction either by another rearrangement or a thiophilic reagent under heating. Crich et al

hypothesized that the allylic selenosulfide rearrangement might proceed through a selenosulfoxide intermediate in which the weaker Se–S bond would result in the formation of the rearranged sulfide at room temperature with or without the help of triphenylphosphine (Scheme 38).



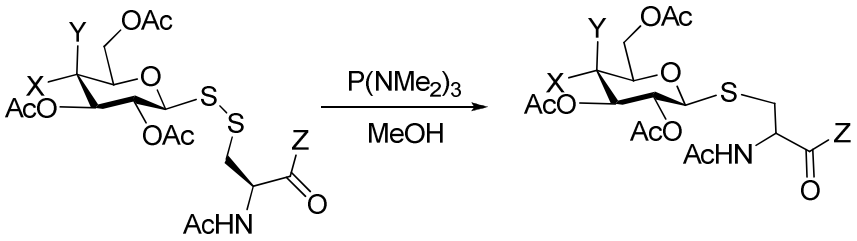
Scheme 38. Chemical ligation via *Se*-allyl selenosulfide

This hypothesis was validated and led to the development of new permanent chemical ligation method for thiols.[102] However, the tedious procedure for the synthesis of *Se*-allyl seleno Bunte salts and the slow addition of thiols to them required to obtain selenosulfides in the original proof of concept needed to be addressed. The further development of this novel selenosulfide ligation was as one of the outset of the work leading to this thesis. The results obtained in this area are described in Chapter II.

1.8 Thioether linked glycoproteins from disulfide bonds

The seminal work by Moore and Trego[95] and Baldwin[97] followed by the studies directed by Harpp et al[103] on the contraction of disulfide and peroxide linkages with P(III) reagents proved that a process for desulfurization from disulfide linkage to thioether derived anologues is possible. More recently, Davis and coworkers have applied this concept to practice by synthesizing thioether linked glycoconjugate from disulfide linked glycosyl peptides and proteins. This

strategy is compatible with uprotected sugar residues involving elimination-conjugate addition of thiol similar to Michael addition (Scheme 39).



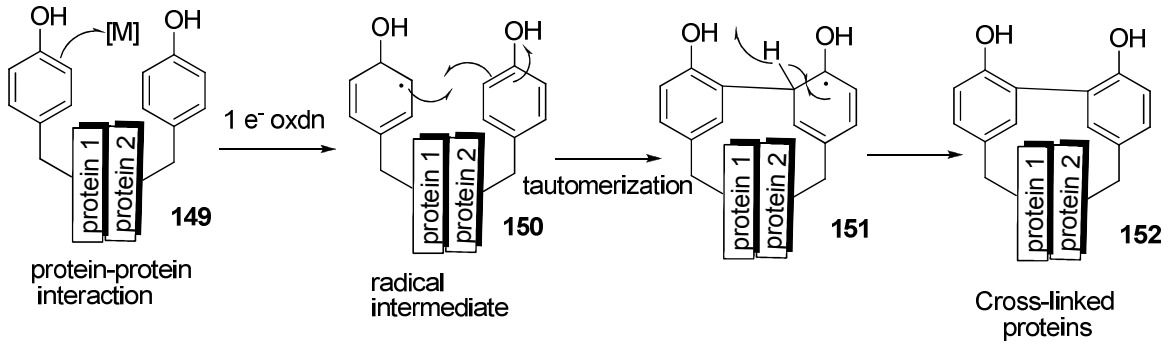
145, X = OAc, Y = H, Z = Ser(tBu)-Gly
146, X = H, Y = OAc, Z = Gly-Thr(tBu)-Gly

147, X = OAc, Y = H, Z = Ser(tBu)-Gly
148, X = H, Y = OAc, Z = Gly-Thr(tBu)-Gly

Scheme 39. Conversion of disulfide to thioether linked glycopeptides

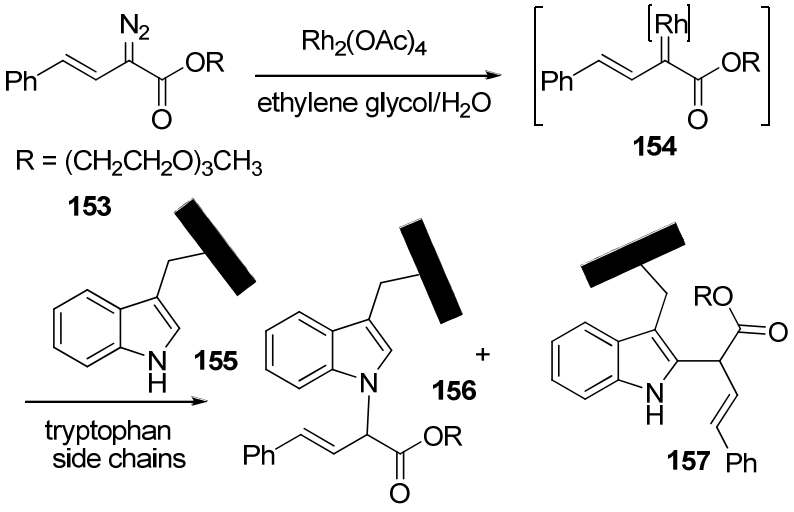
1.9 Transition metal based chemoselective ligations

Transition metal mediated reactions have the potential for selective bioconjugation techniques. Many transition metal catalyzed reactions can be optimized to proceed under mild reaction conditions with high chemeoselectivity and excellent functional group tolerance. An early example of transition metal catalyzed protein modification was developed by Kodadek et al.[104] This oxidative cross-linking method utilizes a high valent transition metal complex that initiates the reaction by abstraction of an electron from a tyrosine residue. The resulting tyrosyl radical then couples to nearby functional groups, joining the two residues through covalent linkages. In many cases the second reactive partner is also believed to be a tyrosine residue (Scheme 40).



Scheme 40. Transition metal catalyzed oxidative cross-linking

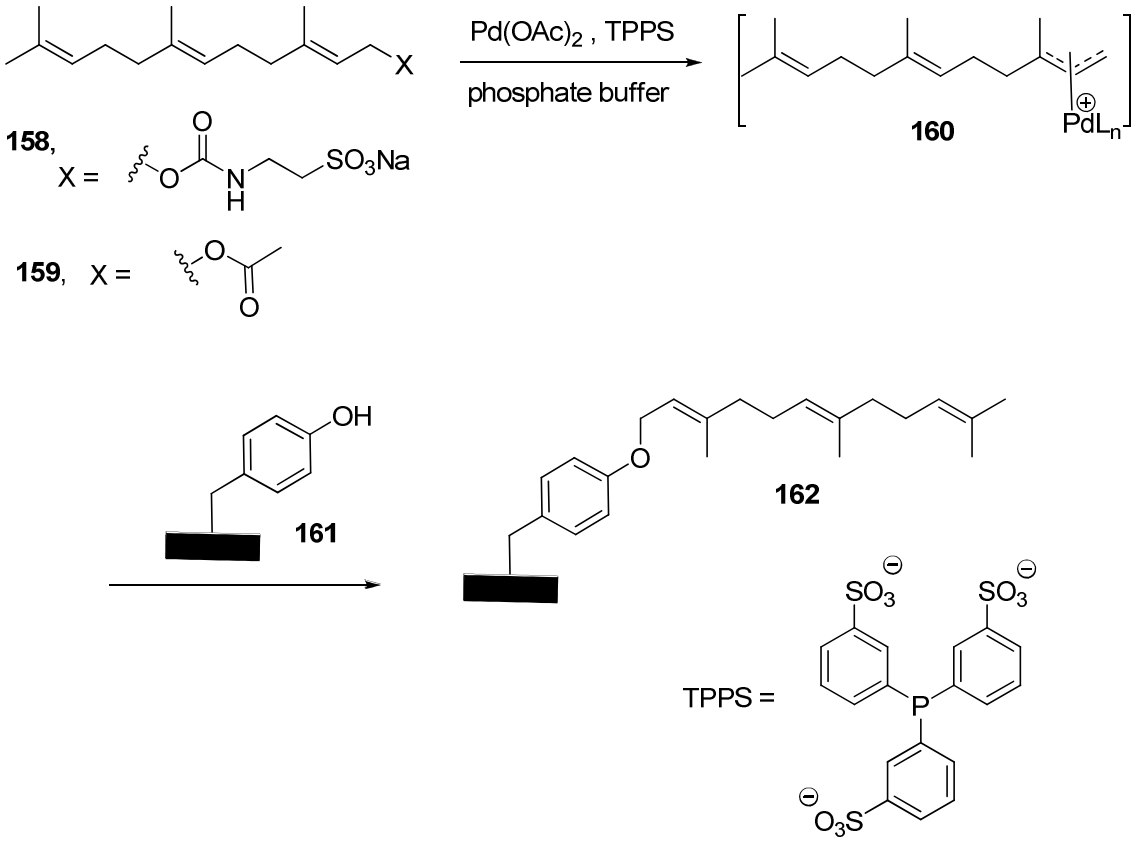
A number of catalytic systems have been developed to promote the oxidative cross-linking process. One of the first examples of using transition metals to covalently attach small molecules to natural amino acids was developed by Antos and Francis.[105-106] This method uses in situ generated rhodium carbenoids to selectively modify tryptophan side chains in aqueous medium (Scheme 41).



Scheme 41. Tryptophan modification with rhodium carbenoids

However, Crich and co-workers have later demonstrated that the rhodium carbenoid insertion reaction is not fully compatible with *S*-allylated peptides.[107]

Apart from the copper and ruthenium catalyzed formation of triazoles, palladium mediated cross coupling reactions such as Sonogashira, Stille, Heck and Suzuki-Miyuara have been broadly used to provide a wide regime of potential chemoselective ligation reactions. In 2006 Francis and co-workers have shown new tyrosine modification using π-allyl palladium complexes where hydrophobic moieties such as farnesyl groups were attached to a tyrosine residue of a protein as shown in Scheme 42.[108]

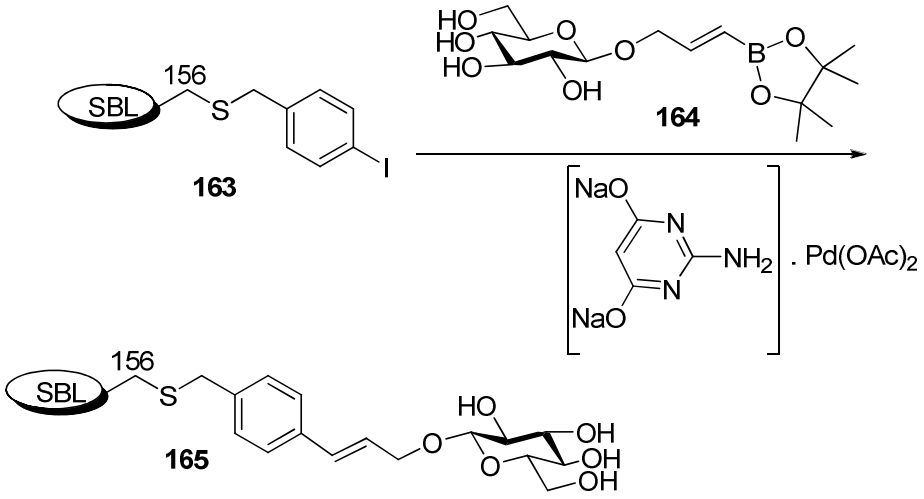


Scheme 42. Tyrosine modification with π-allyl palladium complexes

1.9.1 Metal mediated glycoconjugation

Transition metal mediated reactions have found wide applications in carbohydrate chemistry. Palladium mediated cross couplings and their

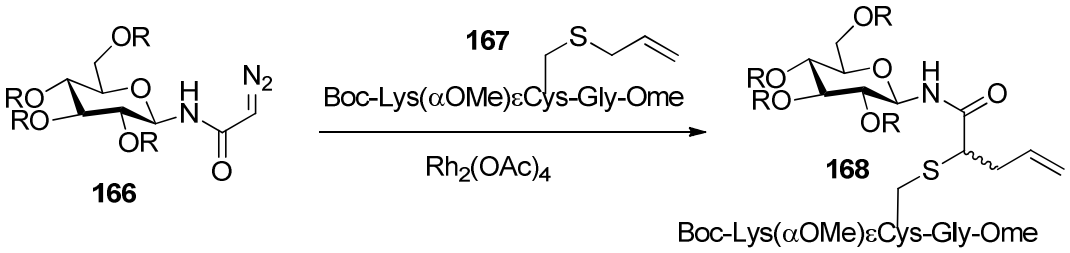
applications toward chemoselective ligations in carbohydrate chemistry were developed by various research groups. In 1998 Lowary et al developed carbon-linked glycopeptides through Sonogashira coupling of glycosyl acetylenes with aromatic iodides.[109] Palladium or nickel mediated synthesis of unsaturated aryl *C*-glycosides through a π-allyl methodology was reported by Sinou and co-workers.[110-111] More recently, Davis and co-workers have demonstrated the Pd-mediated Suzuki-Miyaura cross coupling for protein bioconjugation in aqueous media. An illustrative example showing the synthesis of a synthetic glycoprotein is shown in scheme 43.[112]



Scheme 43. Palladium mediated protein bio-conjugation

Metals like chromium, molybdenum, tungsten, cobalt and rhodium have also been utilized in glycoconjugation. The rhodium catalyzed cyclotrimerization reaction to synthesize an aryl *C*-glycoside which is structurally related to the papulacandin natural product was reported by McDonald et al.[113] Recently, Crich and coworkers have reported the rhodium catalyzed reaction for the ligation of diversely functionalized residues through a modified Kirmse-Doyle reaction.[107]

This methodology was further extended to the synthesis of thioether linked neoglycopeptides as shown in scheme 44.



Scheme 44. Kirmse-Doyle reaction mediated formation of thioether linked synthesis of neoglycopeptides

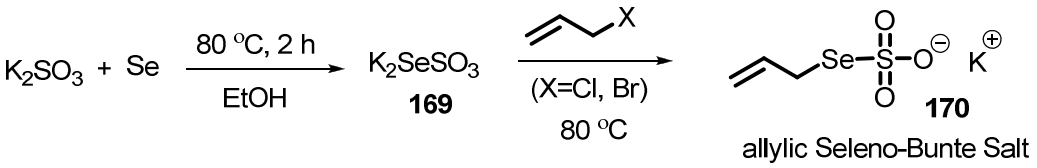
2.0 Goal of this thesis

The work described in this thesis was undertaken with a distinct goal in mind namely the development of new chemical ligation techniques for the permanent modification of thiols. Thus, as described in Chapter II, investigations were carried out on the further development of the selenosulfide ligation for the modification of cysteine thiols and cysteine containing small peptides. Chapter III deals with the investigations conducted while revisiting the allylic disulfide rearrangement for the primary thiol modifications with a view to designing phosphine free reagents to promote this rearrangement. Continuing this theme, Chapter IV describes the application of the newly invented silver mediated allylic desulfurative rearrangement to the chemoselective ligation of mono and disaccharides in the synthesis of β-(1,3)-glucan mimics.

CHAPTER II. Dechalcogenative Allylic Selenosulfide Rearrangement; Modification to Cysteine Thiols

2.1 Selenosulfides via selenocyanates

Despite the mild nature of the disulfide ligation and its established chemoselectivity for thiols the method finds only limited use because the disulfide linkage is susceptible to attack by thiols and reducing agents. Taking these problems into consideration recently, Crich and coworkers developed a new modification designed to provide a stable and permanent ligation as set out in Scheme 38.[102] This ligation proceeds with the formation of *Se*-allyl selenosulfides which on rearrangement lose the selenium atom to form the rearranged allyl sulfide. However, this chemistry has its own drawbacks, the most pertinent of which is the need to synthesize the *Se*-allyl seleno Bunte salts as precursors to the intermediate selenosulfides. The synthesis involves heating potassium sulfite to reflux with selenium powder in an ethanol/water mixture to give the potassium selenosulfite as shown in Scheme 45.

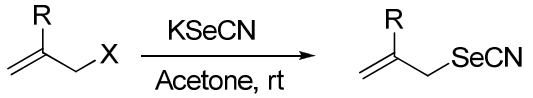


Scheme 45. Synthesis of Se-allyl seleno Bunte salt

The potassium selenosulfite was then heated with allyl halides to give the corresponding *Se*-allyl seleno Bunte salts as orange solids which are not stable and should immediately be converted to *Se*-allyl selenosulfides. The attempted purification of these Bunte salts led to rapid decomposition with selenium extrusion. The low yields observed for the selenosulfides indicate the

experimental difficulties and the stability associated with the intermediates, *Se*-allyl seleno Bunte salts. Moreover, selenosulfide formation could be achieved only by the slow addition of thiols to 10-15 equivalents of Bunte salts.

This inefficient protocol with the *Se*-allyl seleno Bunte salts prompted the search for an easier way to prepare the selenosulfides. The preparation and handling of allyl selenols is difficult, hence the idea of forming allyl selenosulfides from the reaction of allyl selenols with disulfides was not investigated.[101] However, it was anticipated that *Se*-allyl selenosulfides can be obtained in a simple way by the treatment of allyl selenocyanates with thiols. Earlier, Riague and Guillemin prepared several allylic selenocyanates and reported their purification.[101] Simple diaryl selenosulfides and diselenides also had been prepared by the reaction of phenyl selenocyanates and ary thiols as reported by Clark et al.[114] Thus, following the literature procedure, allyl selenocyanate and methallyl selenocyanate were prepared as shown in Scheme 46.[101]



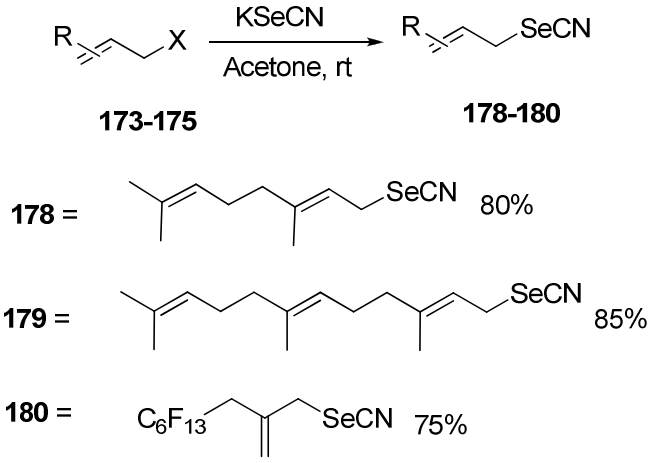
171: R = H, X = Br
172: R = Me, X = Cl

176: R = H: 70%
177: R = Me, 70%

Scheme 46. Synthesis of allyl and methallyl selenocyanates

Allylic thiocyanates undergo [2,3]-sigmatropic rearrangement to the corresponding allylic isothiocyanates within hours at room temperature, but it was found that these allylic selenocyanates could be stored for a long period.[115-116] Accordingly, various substituted allyl selenocyantes were prepared by treating

the corresponding allyl halides with potassium selenocyanate in acetone under N_2 atmosphere at ambient temperature (Scheme 47).



Scheme 47. Synthesis of various selenocyanates

The evaporation of acetone and work-up with ethylacetate and water leaves the selenocyanates in organic portion. Evaporation of the solvent leaves the crude selenocyanates. Unlike the Se-allyl seleno Bunte salts, the selenocyanates were very stable and did not excise selenium on storage. The allyl selenocyanates were obtained in higher yields compared to the *Se*-allyl seleno Bunte salts. A comparison of yields for the formation of *Se*-allyl seleno Bunte salts and selenocyantes is presented in Table 1.

Entry	Allyl halide	Se-allyl seleno Bunte salts	Yield	Selenocyanates	Yield
1	Br **171**	$SeSO_3^-K^+$ **170**	56	SeCN **176**	70

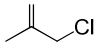
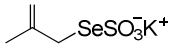
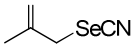
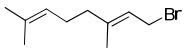
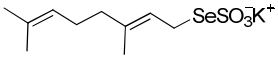
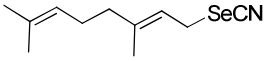
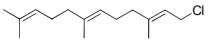
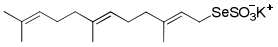
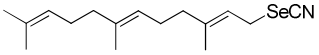
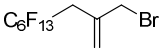
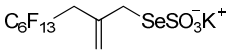
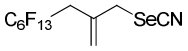
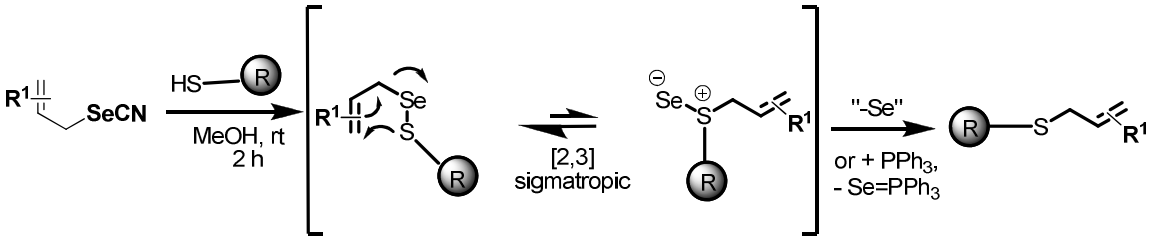
2	 **172**	 **177b**	58	 **177**	70
3	 **173**	 **178b**	40	 **178**	80
4	 **174**	 **179b**	35	 **179**	85
5	 **175**	 **180b**	28	 **180**	75

Table 1. Comparison of yields for the formation of *Se*-allyl seleno Bunte salts and selenocyanates

2.2 Selenosulfide ligation via allylic selenocyanates

2.2.1 Application to simple thiols cysteine thiols

A schematic representation of the reaction between allyl selenocyanates and thiols and the subsequent ligation is shown below.



Scheme 48. Chemical ligation via *Se*-allyl selenosulfides obtained from selenocyanates

The reaction of allyl selenocyanates with simple thiols was chosen for initial study. The reaction of allyl selenocyanate with primary aliphatic thiols produced the allylic selenosulfides which rearranged smoothly to allylic sulfides in methanol at room temperature without the help of triphenylphosphine, thereby establishing that the rearrangement and the subsequent loss of selenium could be performed at room temperature (Entries 1 and 2, Table 2). However the reaction of hexadecane-1-thiol (**201**) with geranyl selenocyanate required triphenylphosphine to give the rearranged linalyl sulfide **205** (Entry 3, Table 2).

Entry	Thiol	Selenocyanate	Product	Yield
1	$CH_3(CH_2)_{15}SH$ **181**	SeCN **176**	$CH_3(CH_2)_{15}S$ **184**	70
2	Ph SH **182**	SeCN **176**	Ph S **185**	70
3	$CH_3(CH_2)_7SH$ **183**	SeCN **178**	$S(CH_2)_7CH_3$ **186**	70

Table 2. Allylation of simple thiols with allyl selenocyanates

2.2.2 Application to cysteine thiols

Subsequently, the attachment of allyl and substituted allyl groups to cysteine derivatives was examined. Unlike the large quantity of *Se*-allyl seleno Bunte salts needed in the first generation method, equimolar amount of simple allyl and methallyl selenocyanates (Entries 1 and 2, Table 3) were sufficient to complete the reaction, proving the selenocyanate methodology could be a convenient way to introduce lipid units to cysteine and cysteine containing peptides. In contrast to the allyl and methallyl selenocyanates, geranyl selenocyanate required triphenylphosphine for the introduction of linanyl group to cysteine. The reaction of Boc-L-Cys-OEt (**208**) with geranyl selenocyanates **198** took place with the formation of a new stereogenic center, which was obtained as a 1:1 mixture of two diastereomers. (Entry 3, Table 3).

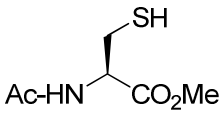
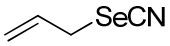
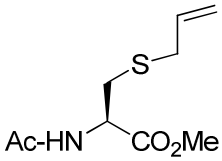
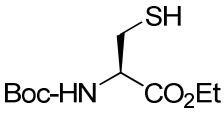
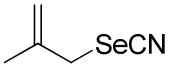
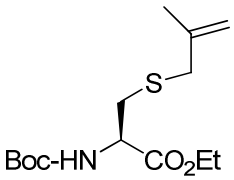
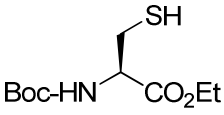
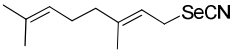
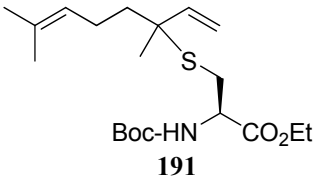
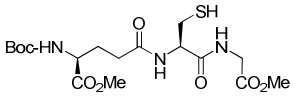
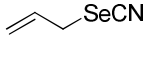
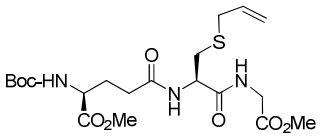
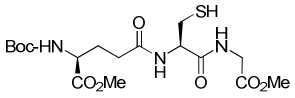
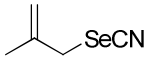
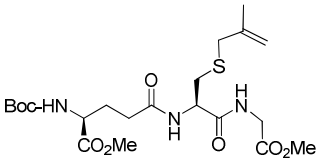
Entry	Thiol	Selenocyanate	Product	Yield
1	 **187**	 **176**	 **189**	80
2	 **188**	 **177**	 **190**	68
3	 **188**	 **178**	 **191**	66

Table 3. Allylation of cysteine thiols with allyl selenocyanates

2.2.3 Application to cysteine containing peptides

Functionalization of cysteine containing tripeptides like Boc-(α-OMe)-γ-L-Glu-L-Cys-Gly-OMe (**212**) and Boc-L-Cys-L-Ala-L-Trp-OMe (**213**) was explored with the selenocyanate methodology (Table 4). The transfer of allyl and methallyl groups to these peptides did not require phosphine. However, geranyl and farnesyl selenocyanates **198** and **199** needed triphenylphosphine to effect the rearrangement into linalyl sulfide and nerolidyl sulfide respectively. The observed difficulty in the latter rearrangements is caused by the transformation of stable prenyl system into less stable isoprenyl system (Table 4, Entry 3, 5 and 6). This result parallels that of Hofle and Baldwin who had earlier observed a similar behavior of allylic disulfides with the prenyl system undergoing the phosphine promoted rearrangement slowly. Nevertheless, it is noteworthy that the seleno sulfide rearrangement for cysteine functionalization is compatible with the indole nitrogen in tryptophan (Entry 4, 5 and 6, Table 4).

Entry	Thiol	Selenocyanate	Product	Yield
1	 **192**	 **176**	 **194**	75
2	 **192**	 **177**	 **195**	71

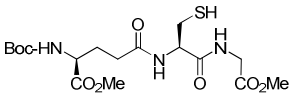
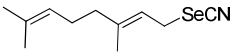
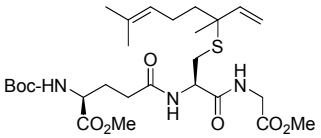
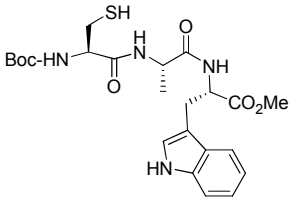
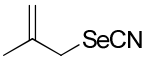
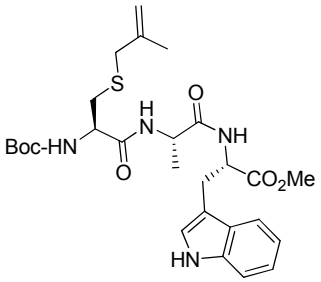
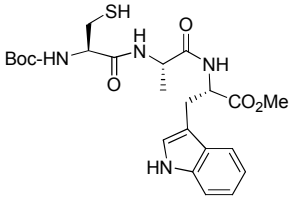
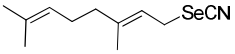
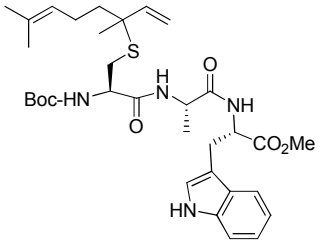
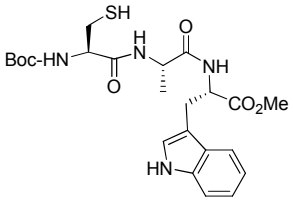
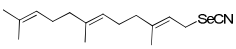
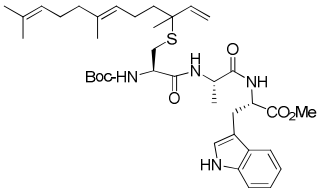
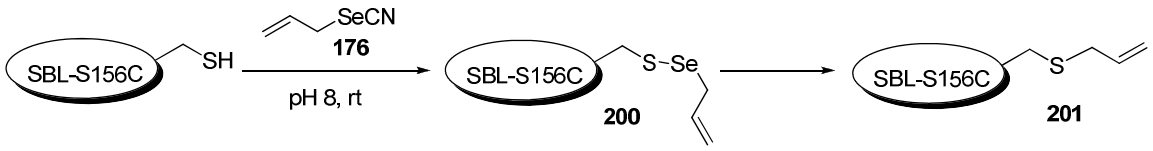
3	 **192**	 **178**	 **196**	
4	 **193**	 **177**	 **197**	
5	 **193**	 **178**	 **198**	
6	 **193**	 **179**	 **199**	

Table 4. Application to cysteine containing tripeptides

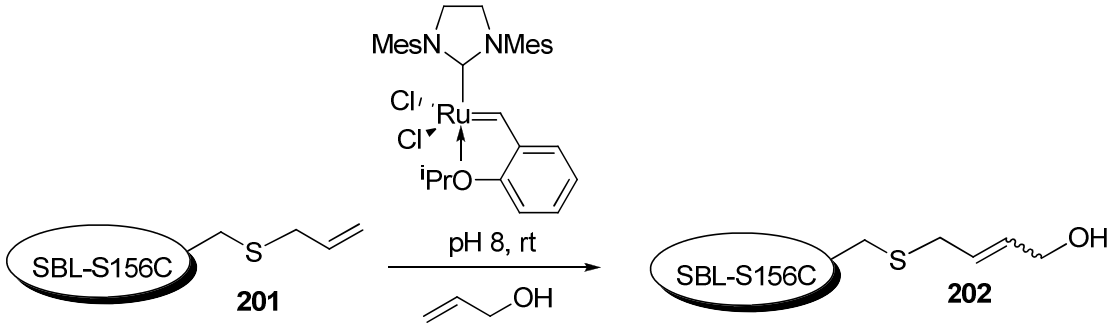
2.3 Application of selenocyanate methodology to the allylation of a protein

Pleasingly, Davis and coworkers have used this selenocyanate methodology to allylate a protein for its subsequent use in olefin metathesis.[117] In this application the allyl selenocyanate (**196**) was treated with a single-cysteine mutant of subtilisin from Bacillus lentus (SBL-S156C). The intermediate *Se*-allyl selenosulfide was formed and even was detected by ESI mass spectroscopy. The intermediate then smoothly rearranged to *S*-allyl cysteine **201** over a period of 2 h as shown in Scheme 49.



Scheme 49. Cysteine specific allylation via selenocyanate method

Davis et al have shown that the *S*-allyl cysteine **201** could be conveniently employed in olefin cross-metathesis (Scheme 50).

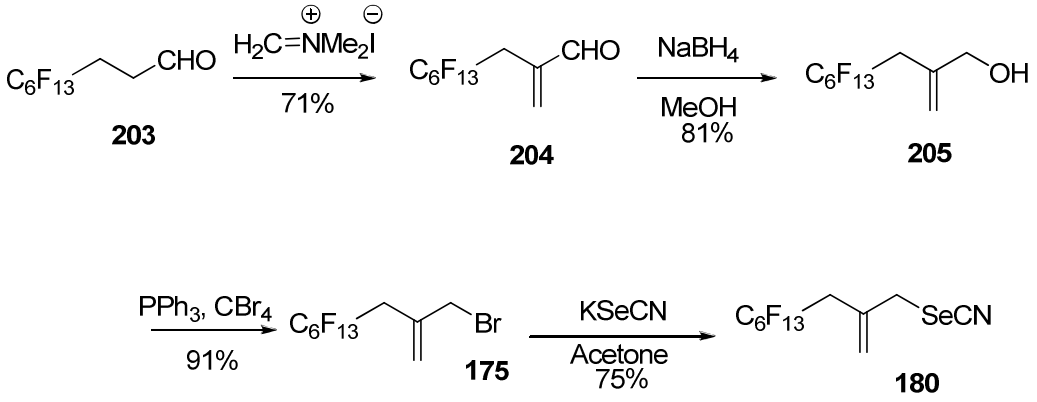


Scheme 50. Cross metathesis at *S*-allyl cysteine

2.4 Application to a fluorous system

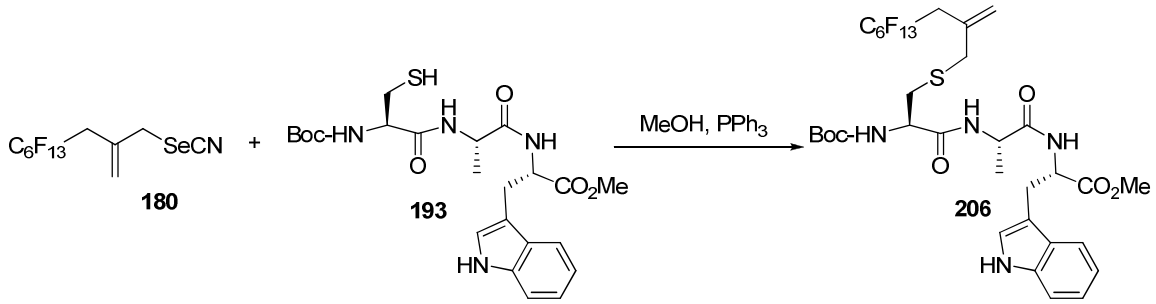
The selenocyanate methodology was further extended to the incorporation of a fluorous tag to a cysteine containing peptide. The fluorous tagged methallyl

selenocyanate **180** was synthesized according to Scheme 54. Thus, the commercially available fluorous aldehyde **203** was treated with a Mannich base to give the vinyl aldehyde **204**. This aldehyde was reduced with sodium borohydride in methanol to give the alcohol **205** in 81% yield. The allyl alcohol was converted to allyl bromide **175** by treatment with triphenylphosphine and carbontetrabromide. Finally the fluorous bromide thus obtained was treated with potassium selenocyanate in acetone at room temperature to give the corresponding fluorous selenocyanate **180** in 75% yield (Scheme 51).



Scheme 51. Synthesis of a fluorous selenocyanate

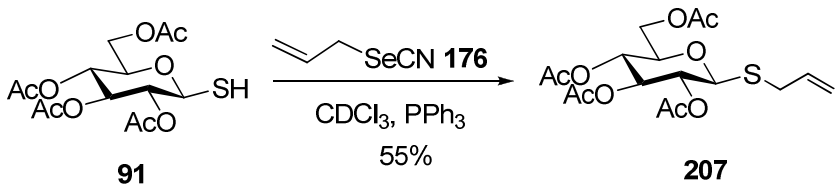
The fluorous substituted methallyl selenocyanate **180** when treated with Boc-L-Cys-L-Ala-L-Trp-OMe (**193**) formed the selenosulfide intermediate. Unlike the simple methallyl system, this fluorous methallyl selenocyanate required triphenylphosphine to yield the rearranged product **206** at room temperature as shown in Scheme 52.



Scheme 52. Allylation with a fluorous tag by the selenocyanate method

2.5 Application to carbohydrate chemistry

To test the ligation in carbohydrate based thiols, the simple allyl selenocyanate **196** was reacted with 1-thio-β-D-glucose tetraacetate (**90)** to give the corresponding seleno sulfide intermediate. The rearrangement of this anomeric selenosulfide proceeded slowly at room temperature over a period of days butwas accelerated by increasing the reaction temperature to 65 °C to give the product **230** as shown in Scheme 53. This rearrangement took place with complete retention of the anomeric stereochemistry, and serves to highlight the application to carbohydrate based thiols.



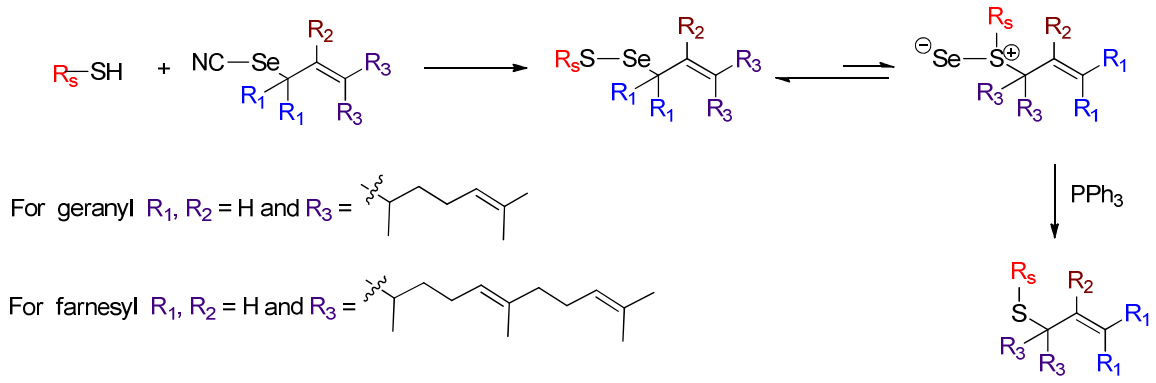
Scheme 53. Ligation reaction of anomeric thiol

2.6 Effect of various substituents on allylic selenosulfide rearrangement

2.6.1 Rearrangements requiring triphenylphosphine

The selenosulfide ligation proceeds through an unfavorable equilibrium with a selenosulfoxide via a reversible [2,3]-sigmatropic rearrangement. The triphenylphosphine removes the selenium atom from the transient selenosulfoxide to drive equilibrium in the forward direction as shown in Scheme 54, when selenium loss is not spontaneous.

Unlike the allyl and methallyl selenocyanates, the geranyl and farnesyl selenocyanates required triphenylphosphine for rearrangement into linalyl and nerolidyl groups (Scheme 54). The difficulty in the latter rearrangements reveals the fact that the substituents have a major role in this deselenative allylic rearrangement. This is in accordance with the work of Baldwin et al who studied the rate constants for rearrangements of the related various substituted allylic disulfides.[97] The phosphine mediated rearrangement of geranyl and farnesyl selenosulfides is shown in Scheme 54.

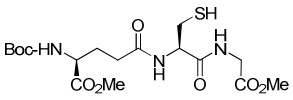
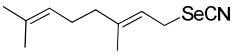
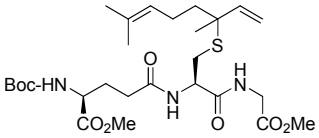
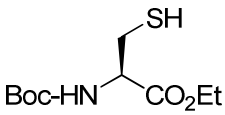
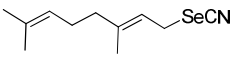
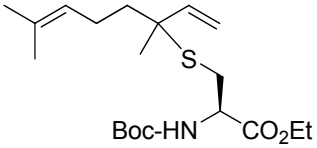
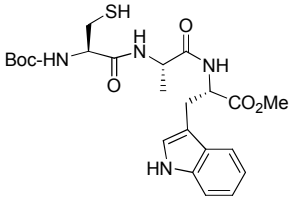
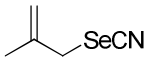
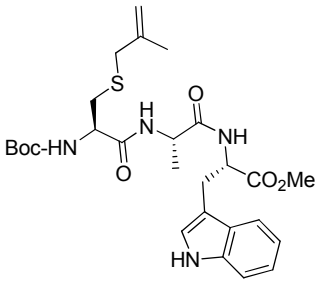


Scheme 54. Effect of substitution pattern on selenosulfide rearrangement

More recently, Liu et al have studied computationally the effect of the substitution pattern on the allylic disulfide rearrangement[118] and as the selenosulfides follows a parallel mechanism. Therefore, it is reasonable to extrapolate their conclusions to it. Thus, for the allylic disulfide rearrangements these workers computed that substituting two methyl groups for hydrogen at R_3 would increase the free energy barrier by 1.8 kcal/mol thereby slowing down the rearrangement 10 fold at room temperature[118]. This prediction is in line with the earlier experimental results of Baldwin et al who hypothesized that the increased bulk at R_3 reduces the concentration of thiosulfoxides in the equilibrium between alkyl allyl disulfides and thiosulfoxides.[97] In geranyl and farnesyl selenocyanates studied here, substitution at R_3 has a significant effect on the deselenative allylic rearrangement. Thus, by analogy, in this series, the prenyl type substituents at R_3 significantly increase the energy barrier to the rearrangement. In the simple allyl and methallyl selenocyanates where R_3 is hydrogen, the energy barrier is lower and the selenium atom is spontaneously excised from the selenosulfoxide intermediate.

The allylation of anomeric thiol proceeds slowly at room temperature but the reaction can be caused to take place at higher temperatures. This is best rationalized by the involvement of the sulfur atom in the anomeric thiol in an exoanomeric interaction. In agreement with the experimental work, Liu et al observed a higher energy barrier (23.2 kcal/mol) for a rearrangement involving an anomeric thiol derived allylic disulfide. In case of fluorous selenocyanate (Entry 7, Table 8), the relatively slow rearrangement is the result of the electron

withdrawing substituent disfavoring the formation of the selenosulfoxide intermediate shown in Scheme 39. The various selenosulfide rearrangements found to require triphenylphosphine are listed in Table 5.

Entry	Thiol	Selenocyanate	Product	Yield
1	 **192**	 **178**	 **196**	55
2	 **188**	 **178**	 **191**	66
3	 **193**	 **177**	 **197**	65

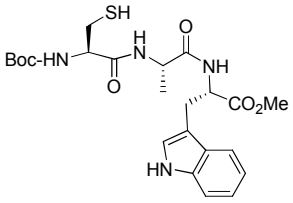
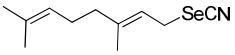
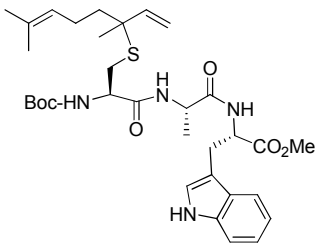
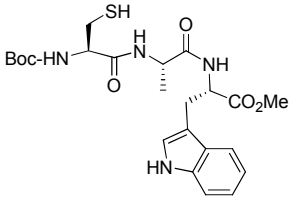
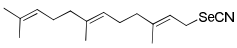
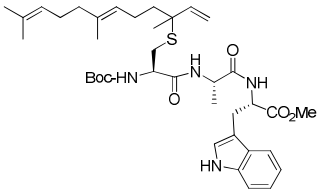
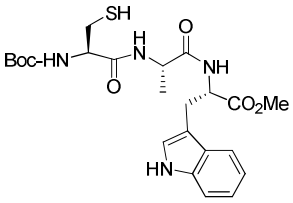
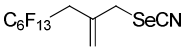
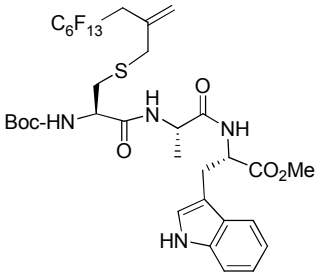
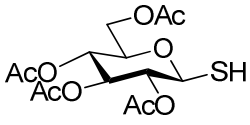
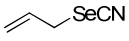
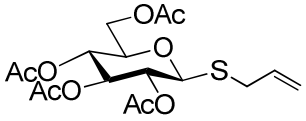
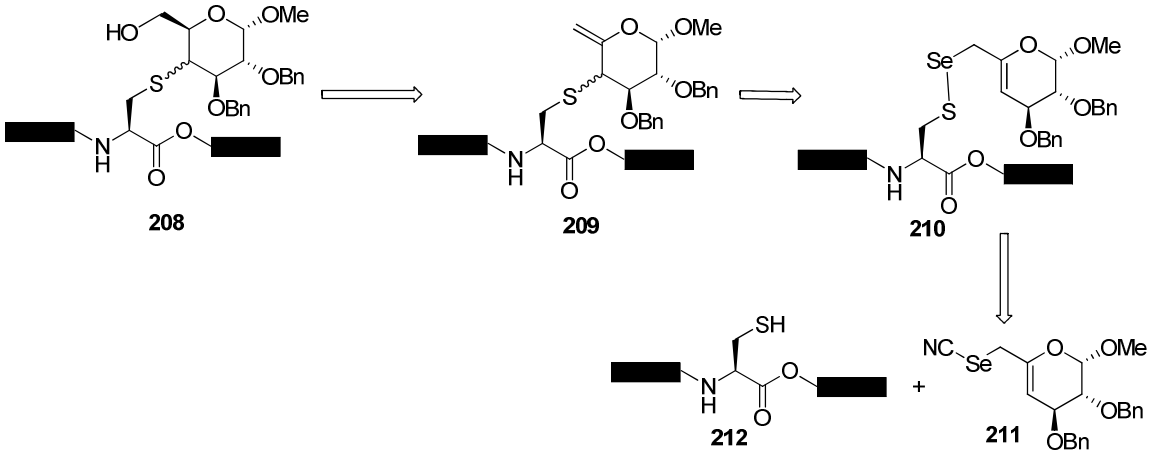
4	 **193**	 **178**	 **198**	
5	 **193**	 **179**	 **199**	
6	 **193**	 **180**	 **206**	
7	 **91**	 **176**	 **207**	

Table 5. Rearrangements required triphenylphosphine

2.7 Attempts toward the synthesis of *S*-linked glycoconjugates through selenocyanate methodology

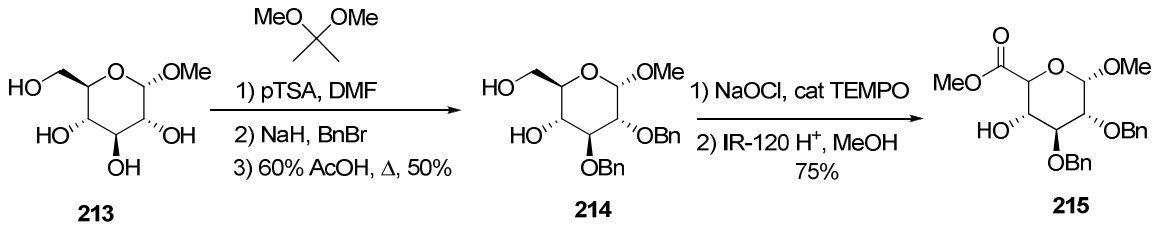
With a view to the formation of various glycoconjugates attention was next focused to the synthesis of cyclic selenocyanates based on a pyranose skeleton (Scheme 55).



Scheme 55. Schematic pathway for an *S*-glycoconjugate through selenocyanate

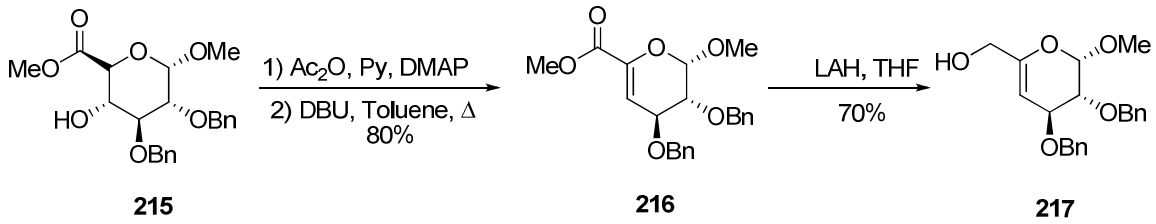
It was envisaged that the glycoconjugate **208** could be obtained from the rearranged product **209** derived from the coupling of the sugar allyl selenocyanate **211** with the cysteine containing peptide **212**. The synthesis of the sugar allyl selenocyanate donor **211** began with the isopropylidenation of the commercially available methyl α-D-glucopyranoside (**213**) using 2,2-dimethoxypropane and p-toluene-sulfonic acid, followed by benzylation with sodium hydride and benzyl bromide. Finally deacetylation in 60% aqueous acetic acid afforded the methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**214**) in 50% yield.[119] Regioselective oxidation of the primary 6-hydroxyl group with sodium

hypochlorite in the presence of catalytic amount of TEMPO[120] afforded the corresponding carboxylate, which was esterified in acidic methanol to give the methyl ester **215** in 75% yield (Scheme 56).



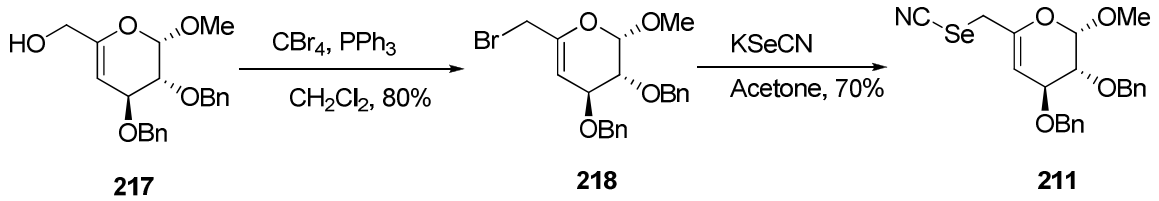
Scheme 56. Synthesis of methyl ester

Acetylation of **215**, with pyridine and acetic anhydride, followed by *β*-elimination with DBU gave the corresponding α,β-unsaturated ester **216** in good yield. A subsequent LAH reduction gave the allyl alcohol **217** as shown in Scheme 57.



Scheme 57. Synthesis of allyl alcohol

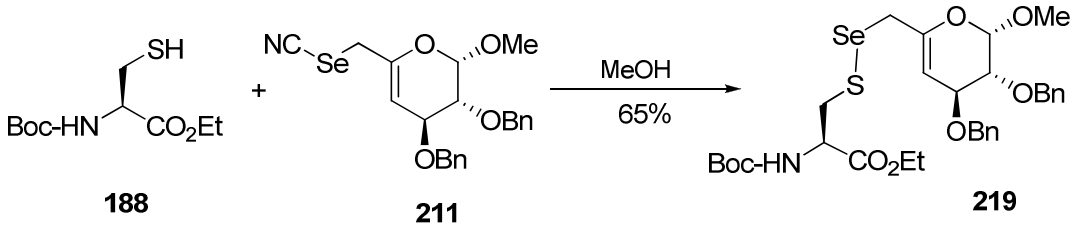
The allyl alcohol **217** was treated with carbon tetrabromide and triphenylphosphine[121-122] to give the allyl bromide[123] **218** in 80% yield. The allyl selenocyanate **211** was formed cleanly when the bromide was treated with potassium selenocyanate in acetone at room temperature (Scheme 58).



217 **218** **211**

Scheme 58. Synthesis of sugar selenocyanate

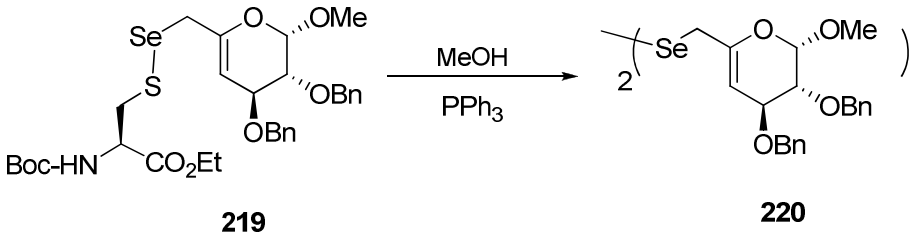
Initially the reaction of a simple cysteine thiol with this sugar selenocyanate **211** was chosen as a model reaction. When the selenocyanate was treated with *N*-Boc-L-Cys-OEt (**188**) in methanol the selenosulfide intermediate **219** was smoothly formed over a period of 2 h. The solvent was removed and the crude product was even purified over silica gel to give the sugar selenosulfide in 65% yield and its structure was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy and ESI mass spectroscopy (Scheme 59).



188 **211** **219**

Scheme 59. Synthesis of a selenosulfide

The sugar selenosulfide **219** did not extrude the selenium spontaneously unlike the simple allyl and methallyl selenosulfides. Therefore, triphenylphosphine was added to promote the rearrangement, unfortunately, the symmetrical diselenide **220** was obtained instead of the desired rearrangement (Scheme 60). Treatment of **219** with piperidine which was successful in driving the rearrangement of some allylic disulfides had no effect in this particular case.



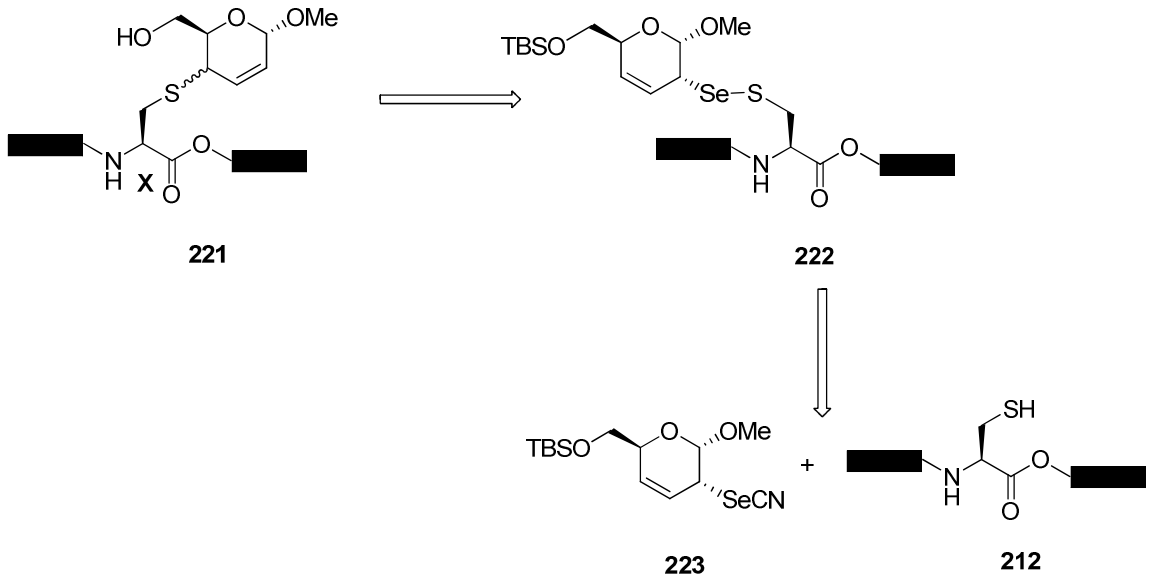
219 **220**

Scheme 60. Reaction of triphenylphosphine on selenosulfide

It would appear that the electron-rich nature of the enol ether double bond is sufficient to retard the rearrangement. The parallel can again be drawn with the computational studies of Liu et al who noted the effect of various substituents on the allylic disulfide rearrangement. Thus the electron rich enol ether with its unfavorable polarity increases the energy barrier to the 2,3-sigmatropic rearrangement which retards the formation of the selenosulfoxide intermediate. This being the case competing reactions encroach and the nucleophilic attack of triphenylphosphine on selenosulfide **219** produced the symmetrical diselenide **220** (Scheme 60).

2.8 Secondary selenocyanates

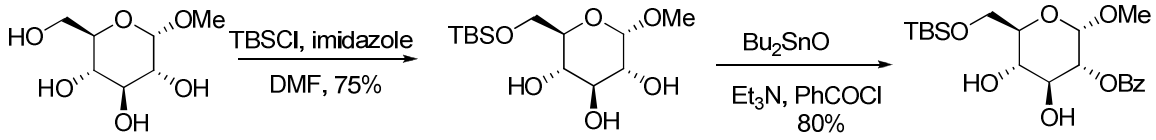
Bearing in mind the above synthesis, a second approach to the synthesis of the *S*-linked glycoconjugates that avoids the use of enol ethers was planned as shown in Scheme 61. Thus, the possibility that the secondary selenocyanate **213** and the cysteine containing peptide **212** would form a selenosulfide capable of undergoing the desired rearrangement was investigated.



221 **222** **223** **212**

Scheme 61. Alternate way for the S-linked glycoconjugates

The synthesis of the sugar selenocyanate started with the commercially available methyl α-D-glucopyranoside (**213**) which was treated with *tert*-butyldimethylsilyl chloride and imidazole in dry DMF to protect the primary hydroxyl group.[124] According to literature procedure, the triol **224** was treated with dibutyltin oxide to form the tin acetal.[125] The acetal was transformed to the corresponding ester regioselectively by treatment with benzoylchloride and triethylamine to afford the vicinal diol[125] **225** in 80% yield as shown in Scheme 62.

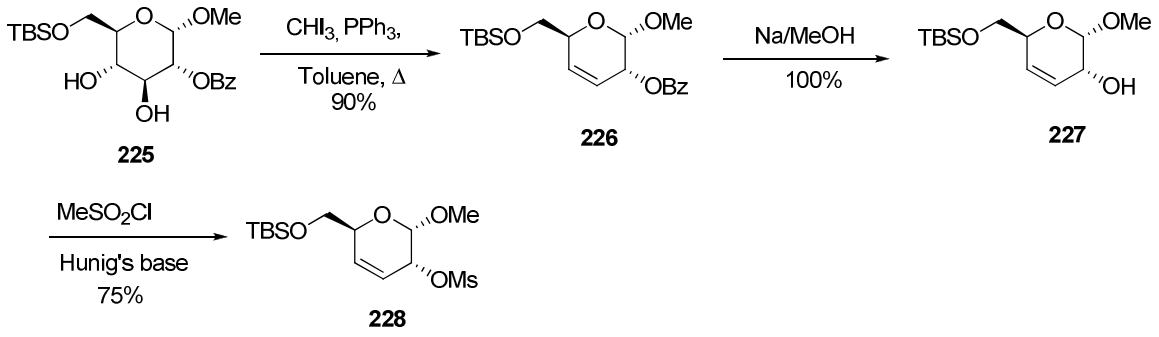


213 **224** **225**

Scheme 62. Synthesis of vicinal diol

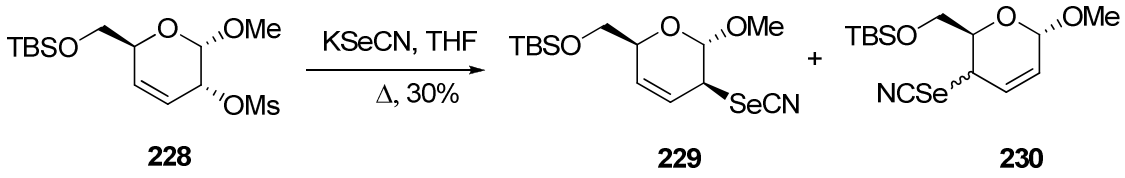
The vicinal diol **225** was refluxed in toluene with iodoform, triphenylphosphine and imidazole to give the olefin[125] **226** in 90% yield. The

treatment of **226** with catalytic sodium in dry methanol produced the allyl alcohol **227** quantitatively. The allyl alcohol **227** was treated with methanesulfonyl chloride and Hunig's base in dichloromethane to give the mesylate **228** as shown in Scheme 63.



Scheme 63. Synthesis of an allyl mesylate

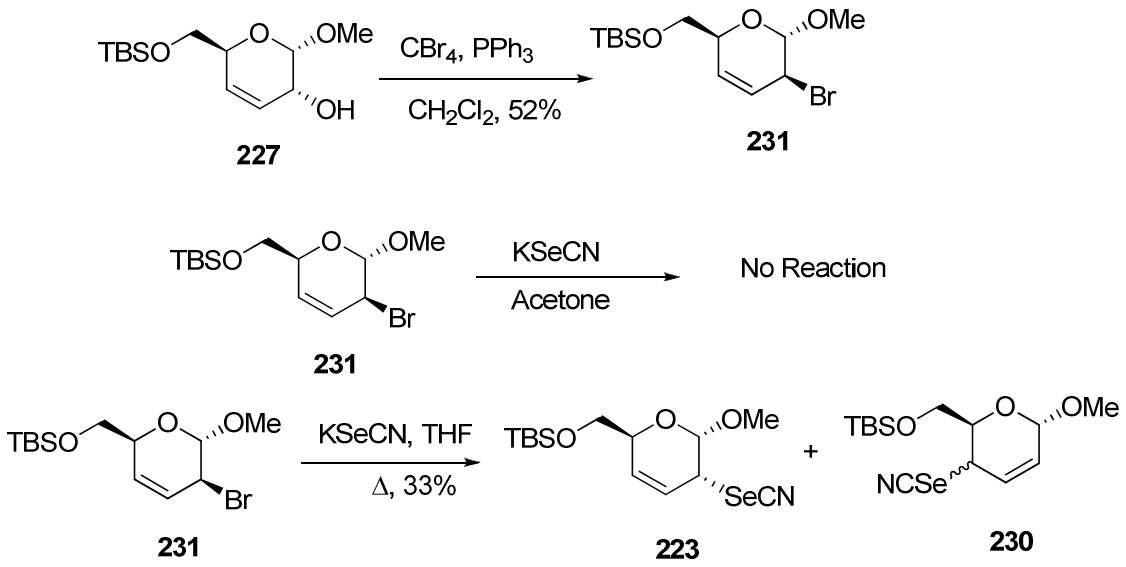
The initial attempts to synthesize the selenocyanate by the nucleophilic displacement of the mesylate **228** with potassium selenocyanate under ambient conditions were unsuccessful. However, the treatment of the mesylate with potassium selenocyanate in refluxing THF gave an inseparable mixture of selenocyanates **229** and **230** in poor yield (Scheme 64).



Scheme 64. Synthesis of a secondary selenocyante

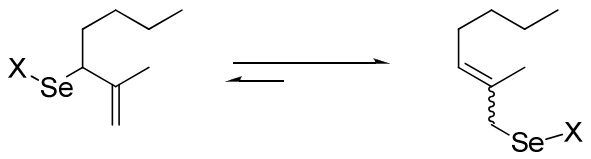
As the nucleophilic substitution of the secondary mesylate proved to be difficult, the displacement of the corresponding allyl bromide with KSeCN was attempted. The allyl alcohol **227** when treated with carbon tetrabromide and triphenylphosphine gave the corresponding bromide **231** in 52% yield. However

no product was observed when the allyl bromide **231** was treated with potassium selenocyanate at room temperature. When the reaction was carried out in refluxing THF, mixture of selenocyanates was formed as shown in Scheme 65.



Scheme 65. Reaction of a *sec*-bromide with KSeCN

The mixtures of secondary selenocyanates obtained in these reactions were in accordance with a result reported by Sharpless who attempted to prepare secondary selenocyanate **232** and selenide **233** but obtained only the rearranged primary isomers with selenium bound to the primary carbon.[100] This is attributed to the instability of the secondary selenides which were converted to the primary selenides via a rapid [1,3]-sigmatropic rearrangement (Scheme 66).



232: X = CN

233: X = SeC_7H_{15}

234: X = CN

235: X = SeC_7H_{15}

Scheme 66. Rearrangement of secondary selenocyanates and diselenides

2.9 Conclusion

Allylic selenocyanates were shown to bear important precursors for functionalization of thiols by the selenosulfide rearrangement. The tedious experimental procedure and instability associated with the *Se*-allyl seleno Bunte salts is avoided by use of the selenocyanates, which makes them an excellent alternative. However the attempted syntheses of *S*-linked glycoconjugates through the selenocyanate pathway revealed two major limitations. The incompatibility of electron-rich alkenes such as enol ethers and the instability of secondary and tertiary allylic selenocyanates. These limitations prompted further investigations on the allylic disulfide rearrangement which are described in the next chapter.

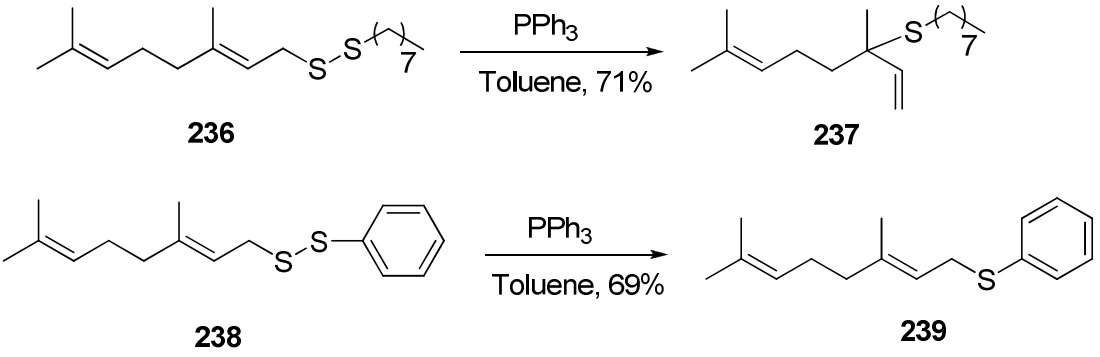
CHAPTER III. Desulfurative Allylic Disulfide Rearrangement

3.1 Background and significance

The deselenative allylic rearrangement of primary allyl selenosulfides was best employed for the introduction of tertiary allyl sulfides. However, the introduction of geranyl or farnesyl groups failed due to the instability associated with the secondary selenocyanates and the selenides. This prompted the revisitation of the allylic disulfide rearrangements. Ideally, the application of dechalcogenative allylic selenosulfide or disulfide rearrangements towards the functionalization of peptidyl thiols would be conducted in a phosphine free manner. Therefore, studies described in this chapter were directed toward two goals. Firstly, the synthesis of secondary and tertiary allylic disulfides for the introduction of primary thio ether groups and secondly the elaboration of a phosphine free desulfurative allylic rearrangement such as might be applicable for the application of this novel ligation to biologically relevant systems.

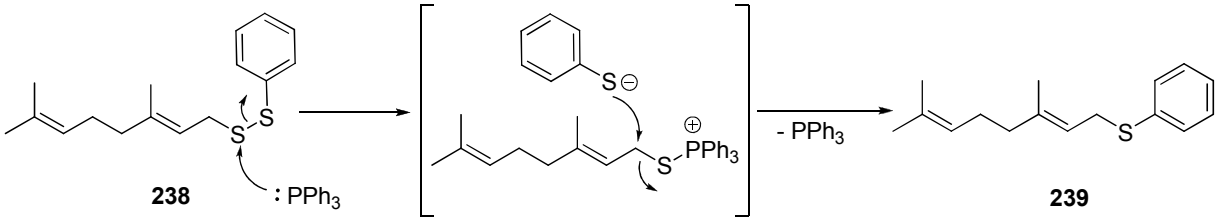
3.2 Drawbacks of triphenylphosphine

It was observed in the Crich laboratory, as exemplified in Scheme 69, the reaction of octyl geranyl disulfide **236** with triphenylphosphine proceeds in toluene at 110 °C by the desired rearrangement pathway to give the octyl linalyl sulfide **237**. However, the treatment of phenyl geranyl disulfide **238** with triphenylphosphine under the same conditions gave only phenyl geranyl sulfide **239** (Scheme 67).[126]



Scheme 67. Effect of triphenylphosphine

The second of these two reactions appeared to be a simple desulfurization rather than a dechalcogenative allylic disulfide rearrangement. The desulfurization reaction of organic disulfides with amino phosphines involving an Arbuzov type mechanism was proposed by Harpp et al[103] involving nucleophilic attack of phosphine on the disulfide as shown in Scheme 68. The attack of the thiolate anion on the phosphonium intermediate results in the formation of phenyl geranyl sulfide **239**.

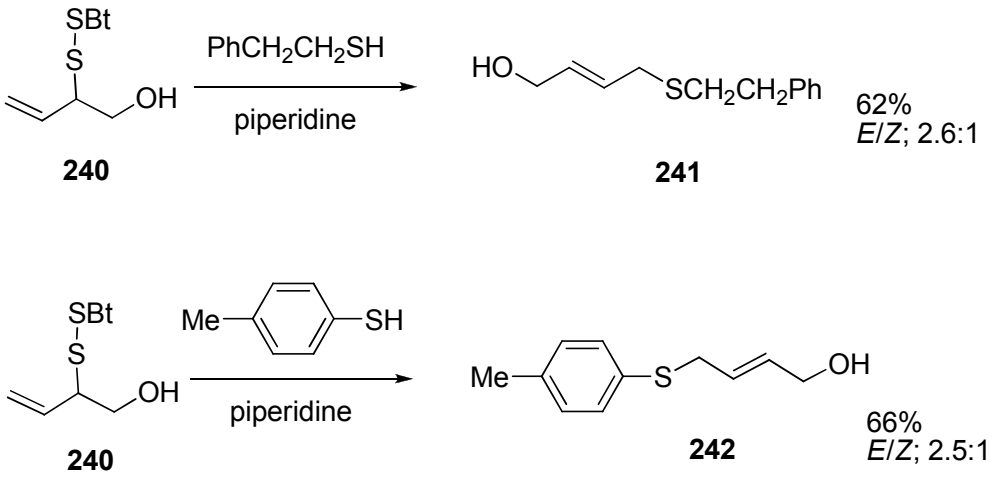


Scheme 68. Arbuzov type mechanism in the formation of phenyl geranyl sulfide

3.2.1 Use of other thiophilic reagents

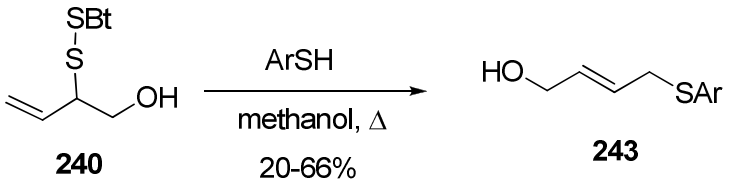
The use of morpholine or piperidine to drive the allylic sulfoxide/sulfenate rearrangement, and the reaction of molecular sulfur atom by allylic sulfides was known in the literature[99,127] and was extended by the Crich group to the

desulfurative allylic disulfide rearrangement. Thus, when the allyl disulfide derived from the disulfide **240** was treated with benzene ethanethiol the intermediated disulfide rearranged to the corresponding allyl sulfide **241** on treatment with 2 equiv piperidine at room temperature in methanol.[126] The rearrangement of allyl aryl disulfides to allyl aryl sulfides was also successful with piperidine (Scheme 69). However, in both the cases only moderate *E*/*Z* selectivity was obtained.



Scheme 69. Rearrangement with piperidine

It also was found in the Crich laboratory that the rearrangement of allyl aryl disulfides to allyl aryl sulfides could be accomplished in refluxing methanol without recourse to phosphines or any other external reagent to give exclusively *E* selective products.[126] For example, when the secondary allylic disulfide **240** was refluxed in methanol with various aromatic thiols, the rearranged aryl allyl sulfides were obtained as shown in Scheme 70.



240 **243**

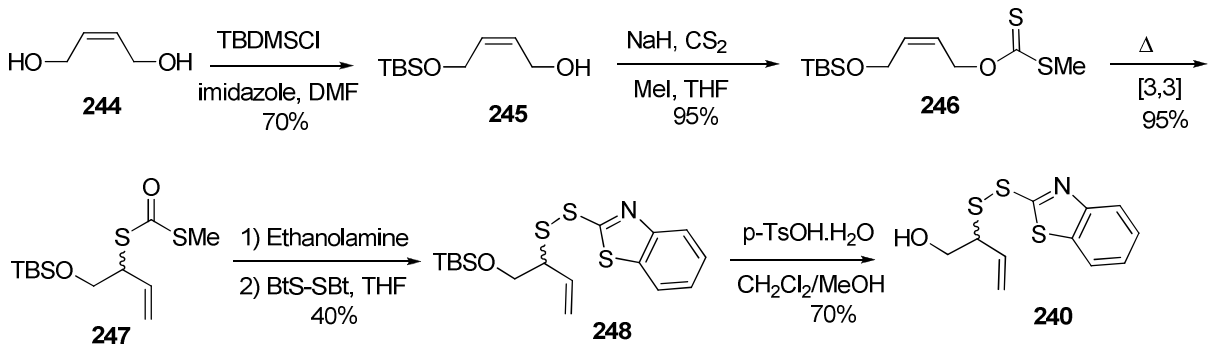
Scheme 70. Rearrangement with refluxing methanol

Unfortunately the refluxing conditions required to promote the desulfurative rearrangement without phosphine exclude application to peptidyl thiols and thiols containing polysaccharide units. Other methods, perhaps using metal catalysis, were therefore sought but first simple model systems had to be prepared.

3.3 Synthesis of secondary allylic disulfides

The allylic desulfurative rearrangement proceeds through a reversible [2,3]-sigmatropic rearrangement, in which the thiophilic reagent removes one atom of sulfur from the transient thiosulfoxide intermediate. As observed by Baldwin[97] and the recent computational studies by Liu et al[118] have shown that the disulfide rearrangement is principally dependent on the substituents on the allylic carbon to which sulfur is attached (Scheme 35). With a secondary or tertiary disulfide the rate constants for the desulfurative rearrangement at 60 °C in benzene are several orders of magnitude higher than rearrangements of primary disulfides. Recently, the synthesis of a secondary allylic disulfide was reported by Crich and Yang as shown in Scheme 71.[128] The synthesis began with the commercially available *cis*-but-2-ene-1,4-diol which was converted to mono silyl ether. The alcohol **244** was converted to allylic thiolcarbamate **247** in two steps and the obtained thiol carbamate was cleaved by the treatment with ethanolamine in THF. The crude thiol was treated with 2,2'-di(1,3-benzothiazolyl)

disulfide to give the allylic disulfide **248** in 40% for the two steps. The protecting group was then cleaved by the acidic hydrolysis to give the sulfenyl donor **240** in 70% yield (Scheme 71).

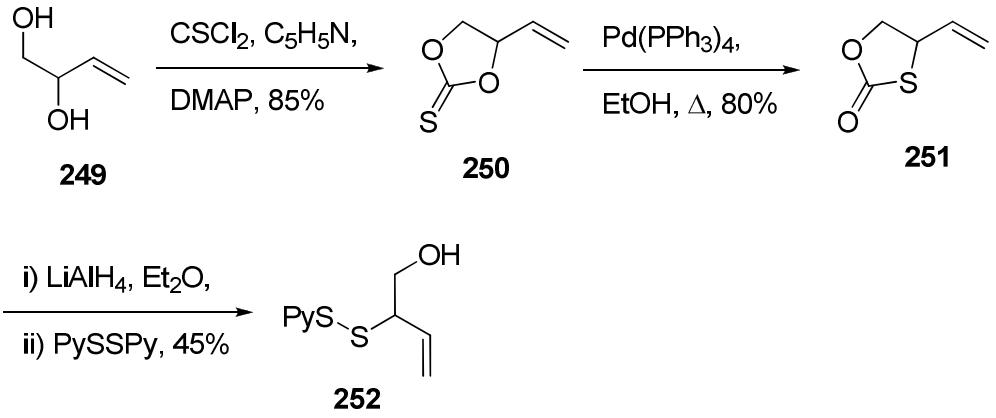


Scheme 71. Earlier method for the synthesis of a secondary allyl disulfide

3.3.1 Modified synthesis of a secondary allylic disulfide

A modified synthesis of pyridyl containing secondary allylic disulfide was planned for an efficient scale-up. The synthesis began with the commercially available 3,4-dihydroxybutene (**249**) which was readily converted to the cyclic thiocarbonate **250** with thiophosgene and pyridine in the presence of DMAP. The thiocarbonate **250** was subjected to the Newman-Kwart[129] rearrangement to give the thiolcarbonate **251** in excellent yield. The palladium catalyzed rearrangement was very efficient in ethanol as compared to the complex thermal processes.[130-133] After careful investigations it was observed that the thiol carbonate could be converted to the secondary disulfide in a two-step protocol. Thus the cyclic thiolcarbonate **251** was reduced with lithium aluminum hydride and the resulting mecapto alcohol was immediately converted to the corresponding pyridyl disulfide **252** by treatment with 2,2'-dipyridyl disulfide in 45% yield as shown in

Scheme 72. The low yield was attributed to the oxidation of the resulting mercapto thiol under basic conditions.

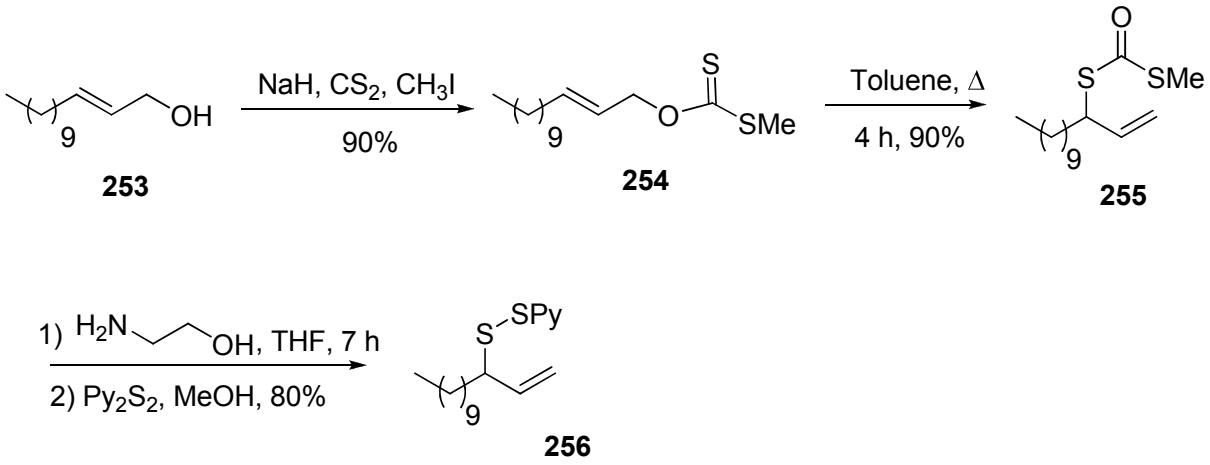


249 **250** **251** **252**

Scheme 72. Efficient synthesis of a secondary allyl disulfide

3.3.2 Synthesis of tridecenyl containing allylic disulfide

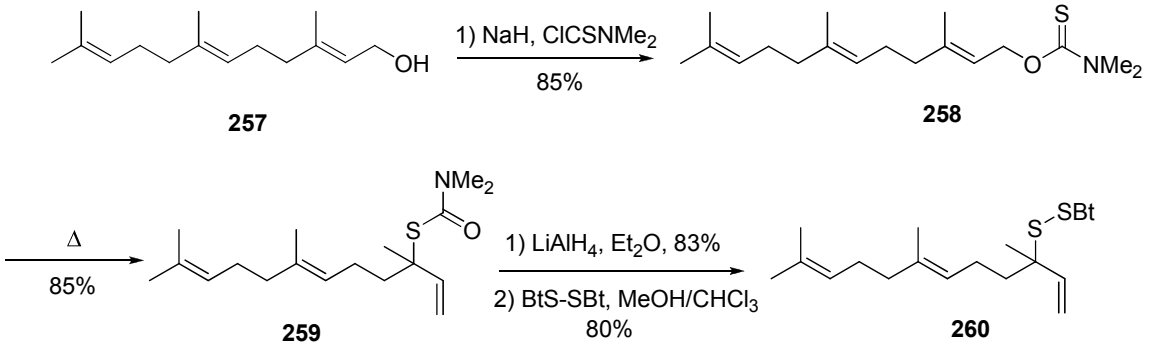
The synthesis of tridecene containing secondary allylic disulfide was accomplished according to the known procedure.[134] The trans-2-tridecen-1-ol (**253**) was converted to allylic xanthate **254** and advanced to dithiocarbonate **255** via a thermal [3,3]-sigmatropic rearrangement. The dithiocarbonate group in **255** was then cleaved using ethanolamine to afford the secondary thiol. The thiol was treated with dipyridyl disulfide in methanol at room temperature to give the secondary allylic disulfide **256** as a sulfenyl donor. The disulfide was further purified by column chromatography over silica gel in 80% yield (Scheme 73).



Scheme 73. Synthesis of a secondary allylic disulfide

3.4 Synthesis of a tertiary allyl disulfide

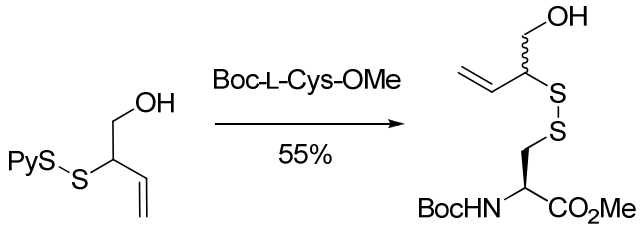
Similarly, the sulfenating agent **260** was synthesized from the commercially available *trans,trans*-farnesol (**257**) according to the known procedure.[134] The thiol carbamate **259** was reduced with lithium aluminum hydride in diethyl ether to give the tertiary thiol in 83% yield. The crude thiol was immediately treated with bis(benzothiazolyl)disulfide to the corresponding benzothiazolyl disulfide **260** to avoid the [1,3]-shift of the the tertiary thiol to the stable primary isomer under basic conditions as reported by Hackler et al (Scheme 74).[135]



Scheme 74. Synthesis of a tertiary allylic disulfide

3.5 Application of secondary and tertiary allylic disulfides

With the successful synthesis of secondary and tertiary allylic disulfides in hand, the search for a completely phosphine free system to promote the desulfurative rearrangement began. It was believed that polar solvents would accelerate the [2,3]-sigmatropic rearrangement by stabilizing the transient polar thiosulfoxide intermediate. This line of thinking was consistent with the work of Moore and Trego who observed earlier that the desulfurative rearrangement of 1,3-dimethylbut-2-enyl *tert*-butyl disulfide was faster in an ethanol/benzene combination compared to benzene alone.[95] Therefore, polar solvents were chosen for the applicability of secondary and tertiary allylic disulfides to the functionalization of simple thiols and cysteine containing peptides. With the view of finding a suitable thiophilic reagent and to test the desulfurative rearrangement at room temperature, a model disulfide was synthesized according to Scheme 75. The obtained secondary allyl disulfide **252** was treated with Boc-L-Cys-OMe in methanol to give the model disulfide **261** in 55% yield.

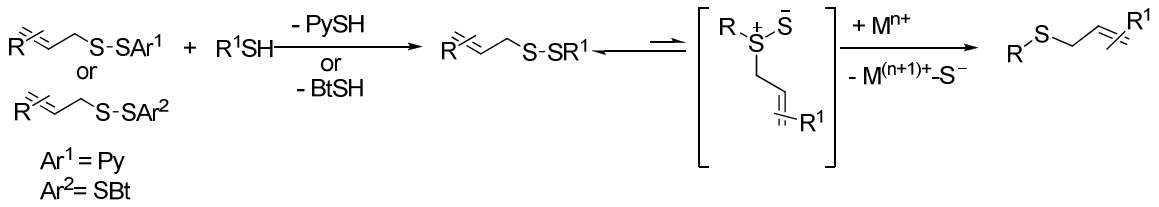


252 **261**

Scheme 75. Synthesis of a model disulfide

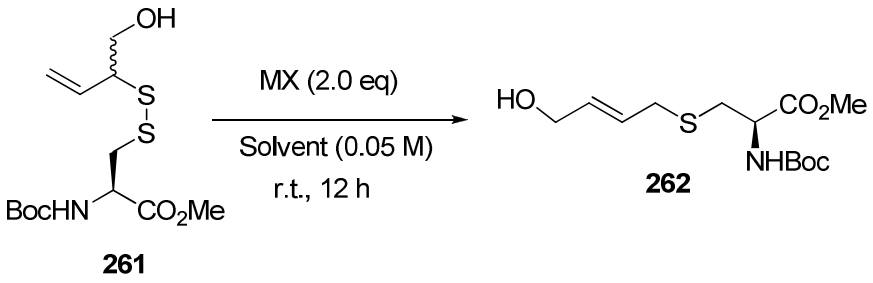
3.6 Phosphine free thiophilic reagent

It was hypothesized that thiophilic metallic salts would remove the sulfur atom from the thiosulfoxide intermediate because of their increased affinity towards sulfur atom as shown in Scheme 76.



Scheme 76. Metal mediated allylic desulfurative rearrangement

To test this hypothesis, various commercially available metallic salts were treated with the model allylic disulfide **261** in deuteriated methanol and deuteriated acetonitrile separately. The rearrangement was monitored by proton NMR spectroscopy (Scheme 77).



261 **262**

Scheme 77. Reaction of an allylic disulfide with metallic salts

3.6.1 Silver mediated allylic disulfide rearrangement

To this end various transition metallic salts were screened for the desulfurative allylic rearrangement (Table 6). Among the metal salts investigated, copper (I) chloride and silver nitrate promoted the desulfurative rearrangement smoothly at room temperature. However, silver nitrate furnished the best results

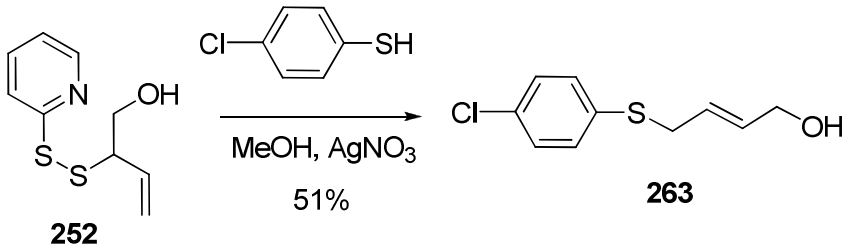
in methanol presumably because silver possesses a higher thiophilic character compared to copper and the other transition metals investigated. The rearrangement of the model disulfide **261** was performed in ethanol and dimethyl formamide with 2.2 equiv of silver nitrate separately and the rearranged products were observed in 68% and 70% respectively. This clearly demonstrates that the extrusion of sulfur from the thiosulfoxide is accelerated by silver and facilitated by polar solvents. More recently, Liu et al computationally supported the effect of polar solvents on the desulfurative [2,3]-rearrangement.[118]

MX	CD_3CN	CD_3OD
$CoCl_2$	<5%	<5%
$NiCl_2$	<5%	<5%
CuCl	25%	55%
$Fe(NH_4)_2(SO_4)_2$	<5%	<5%
$AgNO_3$	38%	72%

Table 6. Rearrangement of model disulfide with different metal salts

3.7 Synthesis of an allyl aryl sulfide

With the successful ligation of a cysteine thiol in hand, the silver mediated desulfurative allylic disulfide rearrangement was applied to a range of examples. Notably, when the disulfide formed from the reaction of secondary allyl disulfide **252** and 4-chloro thiophenol was treated with silver nitrate the corresponding allyl aryl sulfide **263** was obtained in 51% yield (Scheme 78) whereas under similar conditions triphenylphosphine did not effect any rearrangement but excised the sulfur atom from the disulfide.[126]



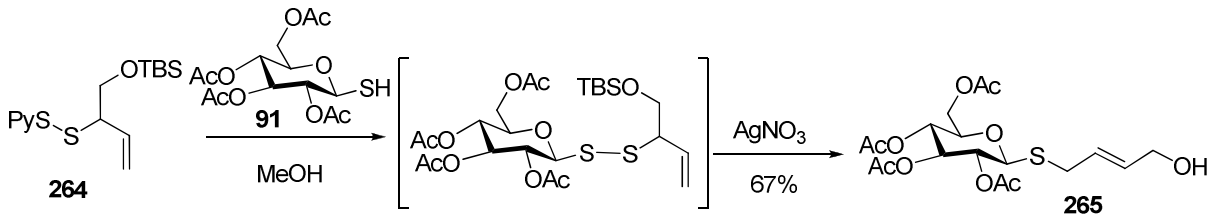
252 **263**

Scheme 78. silver nitrate mediated syntheis of an allyl aryl sulfide

3.8 Application to carbohydrate chemistry

3.8.1 Rearrangements involving anomeric thiol

The silver mediated desulfurative rearrangement was further applied to the synthesis of neoglycoconjugates and thio ether containing polysaccharides. The objective here was to investigate the scope of the desulfurative allylic disulfide rearrangement with silver nitrate. To start with, the desulfurative rearrangement of an electron deficient anomeric thiol was tested. When the silyl ether protected allylic disulfide **264** when treated with 1-thio glucose tetraacetate (**91**), the mixed disulfide was formed very cleanly in 3 h. The mixed disulfide when treated with silver nitrate rearranged to the corresponding thio ether **265** in 67% yield with the concomitant cleavage of the silyl ether group (Scheme 79). However under identical conditions, triphenylphosphine cleaved the disulfide bond without producing any significant amount of the rearranged product. The superiority of the silver-mediated reaction is therefore evident.



Scheme 79. Reaction with an anomeric thiol

The successful rearrangement involving the electron deficient anomeric thiol encouraged the use of silver mediated allylic desulfurative rearrangement to the lipidation of the anomeric thiol. The incorporation of tridecenyl and farnesyl groups on 1-thio glucose tetraacetate (**91**) was smoothly performed with silver nitrate at room temperature in methanol. The introduction of the farnesyl chain proceeded with a 1.5:1 ratio favoring the *E*-isomer (Table 7). The isolated yields of the rearranged products are compared with the triphenylphosphine mediated reactions and it is noteworthy to mention that the phosphine mediated rearrangement was again inferior as it needed reflux temperatures in benzene to furnish the rearrangement.

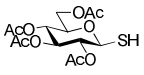
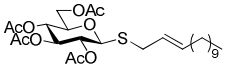
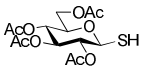
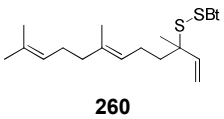
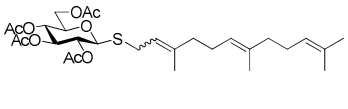
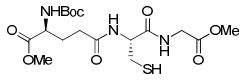
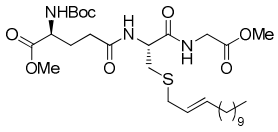
Entry	Thiol	Allylic Partner	Product	$AgNO_3$-Yield	PPh_3-Yield
1	 **91**	 **256**	 **266**	62%	73%
2	 **91**	 **260**	 **267**	50% *E/Z* = 1.5:1	66% *E/Z* = 1.8:1

Table 7. Lipidation of anomeric thiol

3.8.2 Application to cysteine functionalization

The silver mediated rearrangement was further applied to the functionalization of cysteine containing tripeptides and the yields were compared to the phosphine mediated yields (Table 8). In all the cases the silver mediated rearrangement proceeded smoothly to afford the products at room temperature. The incorporation of tridecenyl group to the cysteine tripeptide was smooth in methanol whereas more nucleophilic (4-dimethylaminophenyl)-diphenylphosphine was required to furnish the rearrangement in a mixture of methanol and THF[134] (Entry 1, Table 8). Similarly the rearrangement of tertiary allyllic disulfide produced the corresponding primary thio ether with a ratio of 1.5:1, favoring the *E*-isomer (Entry 2, Table 8).

Entry	Thiol	Allylic Partner	Product	$AgNO_3$-Yield	PPh_3-Yield
1	 **192**	 **256**	 **268**	62%	70%

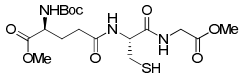
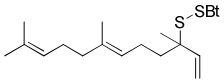
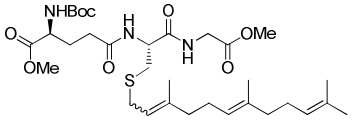
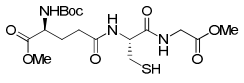
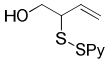
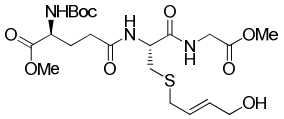
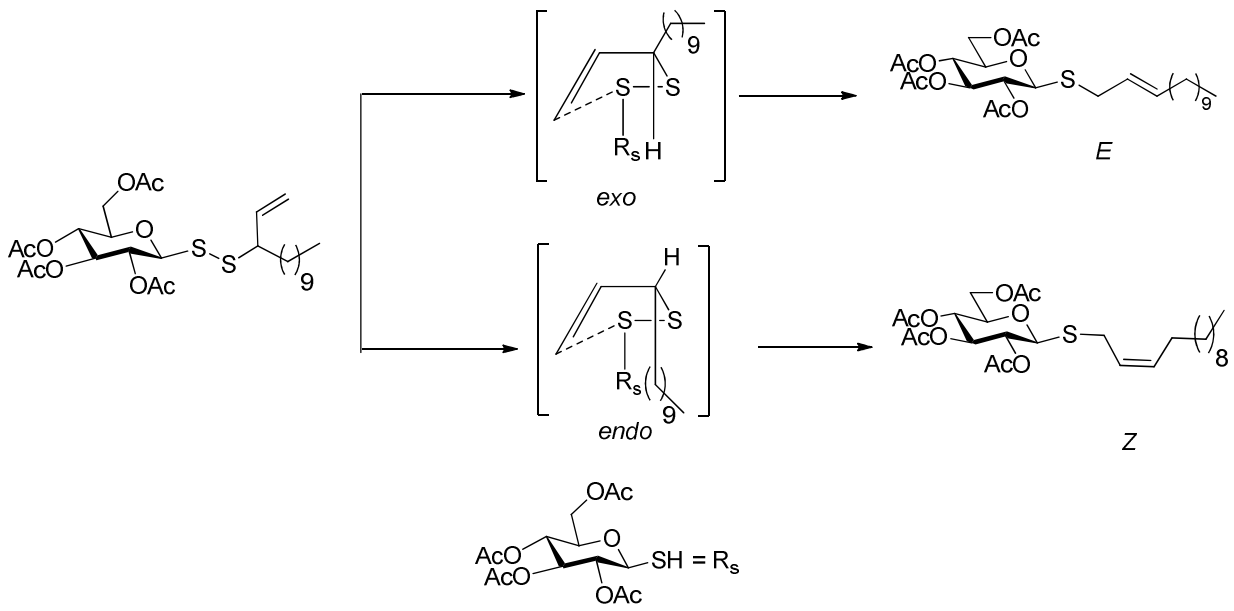
2	 **192**	 **260**	 **269**	60% *E/Z* = 1.5:1	70% *E/Z* = 1.7:1
3	 **192**	 **252**	 **270**	65%	37%

Table 8. Functionalization of cysteine tripeptides

3.9 Olefinic stereoselection

The silver promoted desulfurative rearrangement follows the phosphine pathway in its olefinic selectivity. The desulfurative rearrangement of the secondary allylic disulfides takes place with comparable *E*-selectivity to other [2,3]-simatropic rearrangements such as the Evans-Mislow rearrangement[99] or the [2,3]-Wittig rearrangement.[136] The transition state for this rearrangement is likely based on an envelope like conformation which is of either an endo and or an *exo* type. On examination it was found that the alkyl group prefers the *exo* orientation, leading to the preferential formation of *E*-products (Scheme 80). However, with the tertiary allylic disulfides *E/Z* mixtures of the rearranged products are formed favoring *E*-isomers.



Scheme 80. Mechanism for *E*-selectivity on [2,3]-sigmatropic rearrangement

3.9.1 Application to the synthesis of glycoconjugate

The applicability of the silver mediated allylic desulfurative rearrangement was further demonstrated in cysteine derivatization and to the synthesis of glycoconjugate in the absence of protecting groups. Thus, a secondary allylic disulfide **252** when treated with cysteine containing tripeptide (**271**), rearranged to the corresponding product **272** with excellent *E*-selectivity (Entry 1, Table 9). The conjugation of free sugar[128] **273** with the tripeptide L-glutathione (**271**) followed by the addition of silver nitrate was successfully achieved to give the glycoconjugate **274** in 65% yield (Entry 2, Table 9).

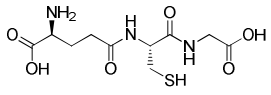
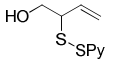
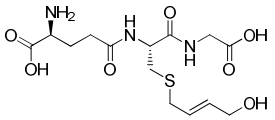
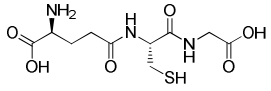
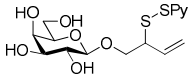
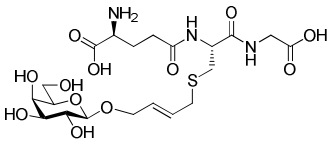
Entry	Thiol	Allylic Partner	Product	$AgNO_3$-Mediated Yield
1	 **271**	 **252**	 **272**	85%
2	 **271**	 **273**	 **274**	65%

Table 9. Silver mediated synthesis of neoglycoconjugates

4.0 Conclusion

The synthesis of secondary and tertiary allylic disulfides enabled the introduction of primary thio ether groups. To discharge the dechalcogenative allylic disulfide rearrangement from its phosphine dependency and to apply the desulfurative rearrangement to biologically relevant systems, a new variant has been designed. The strong thiophilicity of silver promotes the key desulfurization of transient thiosulfoxide in the desulfurative allylic rearrangement. The failure of triphenylphosphine to remove the sulfur from thiosulfoxide and the forcing conditions employed to the synthesis of allyl aryl sulfides was overcome in the silver mediated allylic desulfurative rearrangement. The silver mediated desulfurative rearrangement enabled the functionalization of cysteine peptides under mild conditions. The ambient reaction conditions required for the rearrangement of the allylic disulfide containing an electron deficient anomeric

thiol compared to the reflux conditions employed with triphenylphosphine make the silver mediated method a powerful tool for the lipidation of anomeric thiols. The silver mediated ligation of thiol containing oligosaccharide units for the synthesis of complex oligosaccharides would be discussed in the next chapter.

CHAPTER IV. Application of the Silver Mediated Desulfurative Allylic Rearrangement to the Synthesis of Glucan Mimics.

4.1 Background and biological significance of (1,3)-β-glucans

The research described in this chapter was focused mainly on the synthesis of complex oligosaccharide mimics making use of the silver mediated allylic rearrangement. It is becoming increasingly important that certain protein-carbohydrate interactions require long sequences of oligosaccharides for optimum binding. Dectin-1, a C-type lectin is a cell surface immune receptor for β-glucans and its binding is directed exclusively to 1,3-linked glucose oligomers with the minimum length required for detectable binding being a 10- or 11-mer. These bigger oligosaccharides are difficult to obtain from any naturally occurring biological sources in a homogeneous form. Therefore methods need to be developed for the synthesis of these complex oligosaccahrides under mild reaction conditions. It was envisaged that the silver mediated desulfurative rearrangement has the potential as a chemoselective ligation technique and could be used to stitch shorter oligosaccharide units to one another to form larger ensembles. Initial attention was focused to the synthesis of β-(1,3)-glucan mimics since poly-β-(1,3)-glucosides, or β-(1,3)-glucans have been extensively studied for their immunological and pharmacological effects, in particular because of their immunostimulating and antitumoral properties.[137-138] The β-(1,3)-glucans are found in nature as essential constituents of the cell wall in fungi[139] or and as major storage source in brown seaweed.[140] Recently, these polysaccharides have also been classified as biological response modifiers.[141-142] Derivatives of β-(1,3)-glucan have been used as enzyme inhibitors and as vehicles for drug

delivery.[143-149] Non-cellulosic β-glucans consist of a backbone of glucose residues usually joined by β-[1→3] linkages. The bacterial β-glucan, curdlan, which contains only β-[1→3] glucosidic linkages, is shown in Figure 1.

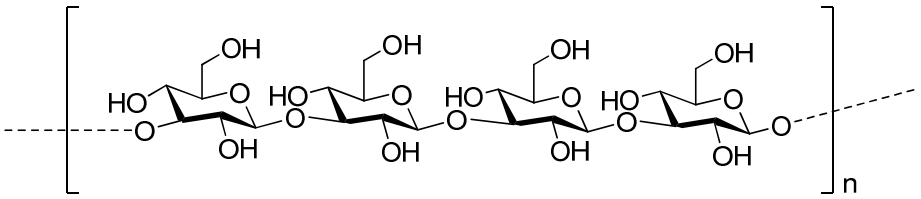


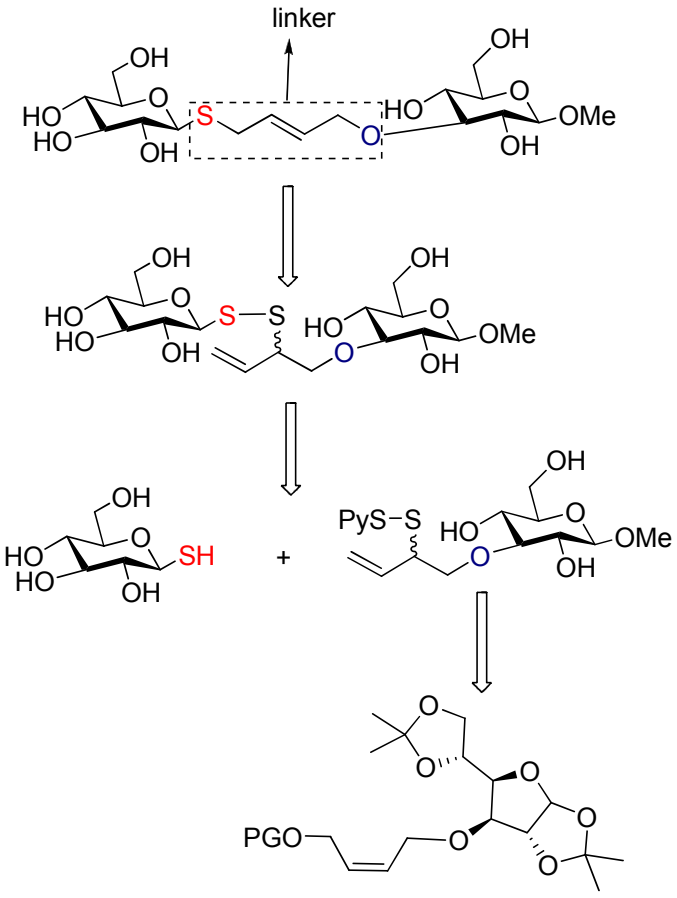
Figure 1. Curdlan, a β-(1,3)- glucan

β-(1,3)-glucans have been prepared both chemically and enzymatically by transglycosylation or by glycosynthases.[150-153]

4.2 Synthesis of glucan mimics

4.2.1 Synthesis of a glucan mimic disaccharide

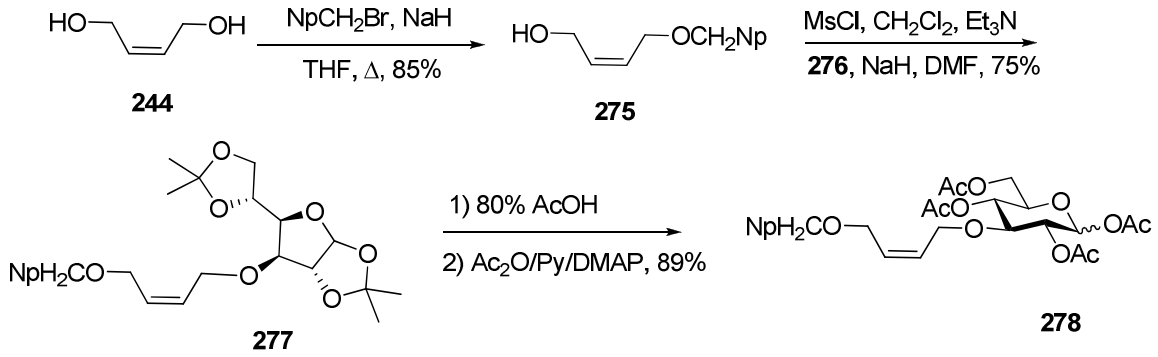
In the approach conceived toward the protecting group-free synthesis of glucan mimics it was envisaged that a short linker resulting from the desulfurative ligation could be used to link oligosaccharide unit with another. In a first approach to the problem, the synthesis of a disaccharide mimic having a β-[1→3]-glucosidic linkage was undertaken in which the linker unit could be derived by the silver promoted allylic disulfide rearrangemet as shown in the retrosynthetic analysis (Scheme 81).



Scheme 81. Retro synthetic scheme for a glucan mimic disaccharide

According to this retrosynthetic analysis, the target glucan mimic disaccharide would be derived from the silver mediated desulfurative allylic rearrangement of the disulfide. The allylic disulfide would be derived by the individual fragment coupling between the glucose thiol and the disulfide linked methyl glycoside. This disulfide containing allylic tether linked glycoside would be derived from a protected diacetone glucose moiety. It was envisioned that the orthogonally protected butenyl group would allow the later functionalization of the diacetone glucose ring to the desired disulfide linked donor. Reducing this analysis to practice, the synthesis of the disaccharide mimic began with the commercially available *cis*-butene-1,4-diol (**244**) which was treated with

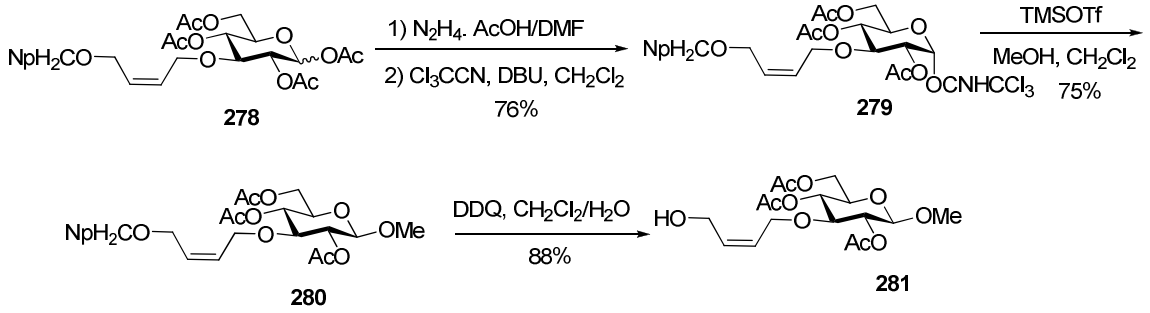
naphthylmethyl bromide in THF with sodium hydride to give the protected mono ether **275** in 85% yield. The alcohol was mesylated with methanesulfonyl chloride and Hunig's base in dichloromethane. The crude mesylate was directly advanced to the next step when it was treated with diacetone-D-glucose (**276**) in DMF with sodium hydride to give the compound **277** in 75% yield. The acetonide protecting groups in compound **277** were cleaved by heating the compound in aqueous acetic acid, after which the acetate groups were reinstalled by treating it with acetic anhydride and pyridine with a catalytic amount of DMAP to give **278** as shown in Scheme 82.



Scheme 82. Synthesis of a protected glucopyranoside with linker

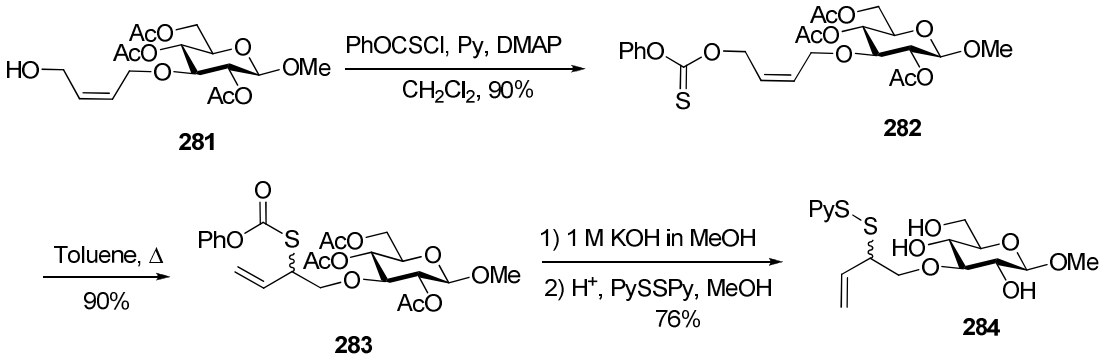
Subsequently, the anomeric acetate group was selectively cleaved with hydrazine acetate in DMF and the so-obtained hemiacetal was treated with trichloroacetonitrile and DBU in dichloromethane to give the trichloroacetimidate donor **279** in two steps with 68% yield. Attempted glycosylation of methanol with this donor in the presence of 4 Å molecular sieves was unsuccessful. However, glycosylation of methanol in the absence of molecular sieves at – 50 °C gave the β-methyl glycoside **280** in 75% yield. Oxidative cleavage of the naphthylmethyl

group with DDQ in dichloromethane and water at room temperature then gave the alcohol **281** in 88% yield (Scheme 83).



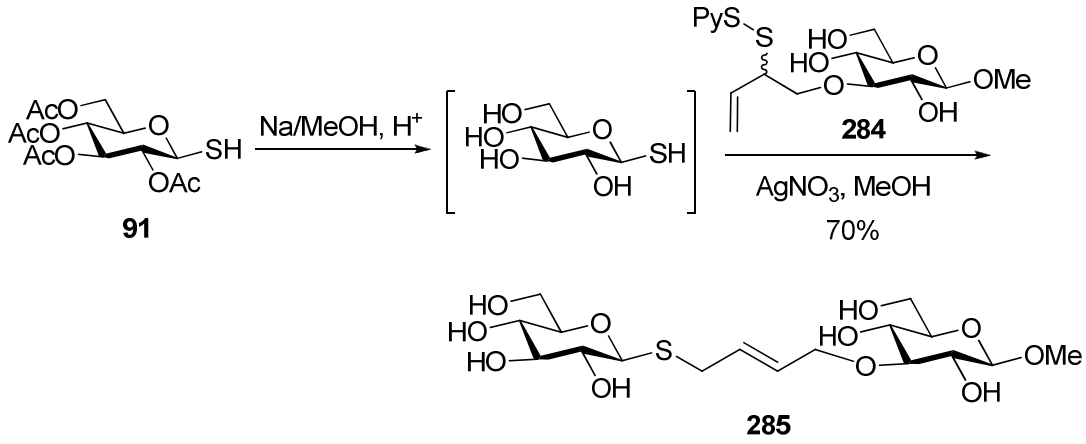
Scheme 83. Synthesis of the alcohol

The disulfide linker was attached to the methyl glucopyranoside **281** as shown in Scheme 84. Thus, alcohol **281** was treated with phenyl chlorothionocarbonate and pyridine in dichloromethane in the presence of DMAP to give the thionocarbonate **282** in 90% yield whose [3,3]-sigmatropic rearrangement proceeded smoothly in refluxing toluene to give the thiol carbonate **283** in 90% yield. The acetate groups and the thiol carbonate were hydrolyzed with 1 M KOH in methanol in one pot. The allyl thiolate was carefully acidified with Amberlyst resin and added to a solution containing 2,2`-dipyridyl disulfide in methanol. Evaporation of methanol and chromatographic purification yielded the allylic disulfide **284** in 76% yield over two steps as a mixture of two diastereoisomers.



Scheme 84. Synthesis of a sugar-based allyl pyridyl disulfide

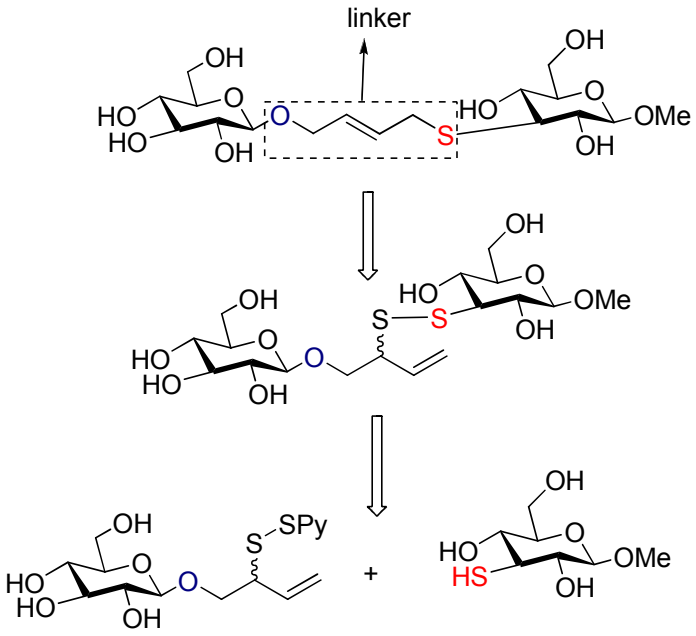
After the successful installation of the allylic disulfide linker sulfenyl transfer to an anomeric thiol and subsequent desulfurative rearrangement was attempted in methanol. The metal promoted synthesis of disaccharide mimic achieved in this manner is shown Scheme 85. Thus, saponification of the commercially available 1-thio glucose tetraacetate (**91**) with methanolic sodium followed by the treatment with acidic resin provided the glucose thiol. The crude glucose thiol was added to the allylic disulfide **284** to give the mixed disulfide with the liberation of the 2-pyridine thiol. When the mixed disulfide was treated with silver nitrate in methanol, the disulfide bearing anomeric thiol smoothly rearranged to give the disaccharide mimic **285** in 70% yield with *trans* olefinic configuration on the linker. The olefinic stereochemistry was unambiguously supported by proton NMR as the coupling constant found to be 16 Hz (Scheme 85).



Scheme 85. Synthesis of a glucan mimic disaccharide

4.3 Synthesis of an alternative disaccharide mimic

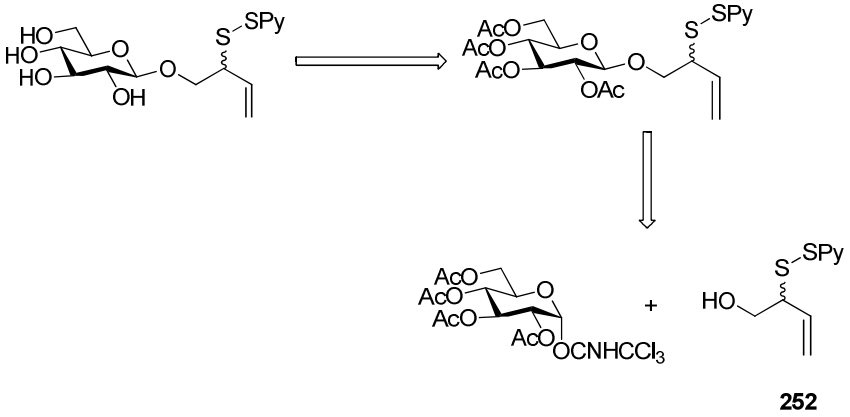
An alternative approach to the problem employs a carbohydrate in which the 3-OH has been replaced by a thiol group in which the anomeric position of the second reaction partner carries the sulfenyl transfer moiety as set out in the retrosynthesis below (Scheme 86).



Scheme 86. Alternative retrosynthetic scheme for a disaccharide mimic

4.3.1 Synthesis of the disulfide linked glycopyranoside

The shortest entry to an anomeric sulfenyl donor involves Lewis acid promoted glycosylation of the disulfide alcohol **252** with a glucose trichloroacetimidate donor (Scheme 87). However, Crich and Yang[128] had already investigated this approach in another context and found it to be challenging as a consequence of which it was not considered further here.

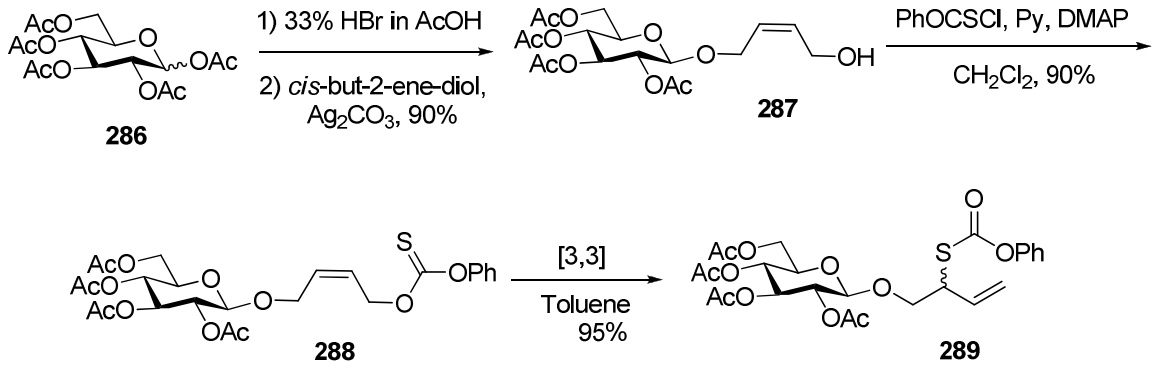


252

Scheme 87. First retrosynthetic scheme for the sulfenyl donor

Therefore, an alternate approach was employed to connect the linker to the anomeric carbon. Commercially available glucose pentaacetate (**286**) was treated with 33% HBr in acetic acid to give acetobromoglucose which was condensed with *cis*-but-2-ene-1,4-diol by the Koenigs-Knorr method[154] to give the β-D-glucoside **287** in 90% yield by the classical neighboring group participation mechanism. The stereochemistry of the coupling product was confirmed by the large $^{3}J_{H1,H2}$ coupling constant (7-8 Hz). The thiocarbonylation of the resulting glycosyl alcohol with CS_2 and NaH in DMF proceeded with a low yield. However, the treatment of the alcohol **287** with phenylchlorothionocarbonate and pyridine as a base with a catalytic DMAP gave the product in high yield. This

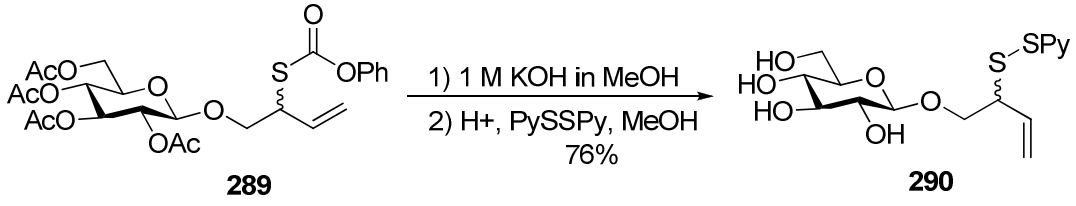
thionocarbonate **288** underwent a [3,3]-sigmatropic rearrangement in refluxing toluene afforded the allyl thiolcarbonate **289** as a mixture of stereoisomers (Scheme 88).



286 **287** **288** **289**

Scheme 88. Synthesis of glycosyl allylic thiolcarbonate

The one-pot hydrolysis of the thiolcarbonate **289** with the remaining acetoxy groups was performed with 1 M KOH in methanol. After acidification with Amberlyst resin, the resulting allylic thiol was immediately transferred to a solution of 2,2'-dipyridyl disulfide in methanol. The disulfide exchange reaction was monitored by TLC and was complete in several hours at room temperature. Evaporation of the solvent followed by purification of the disulfide by column chromatography gave the pure anomeric sulfenyl donor **290** in 76% yield (Scheme 89).

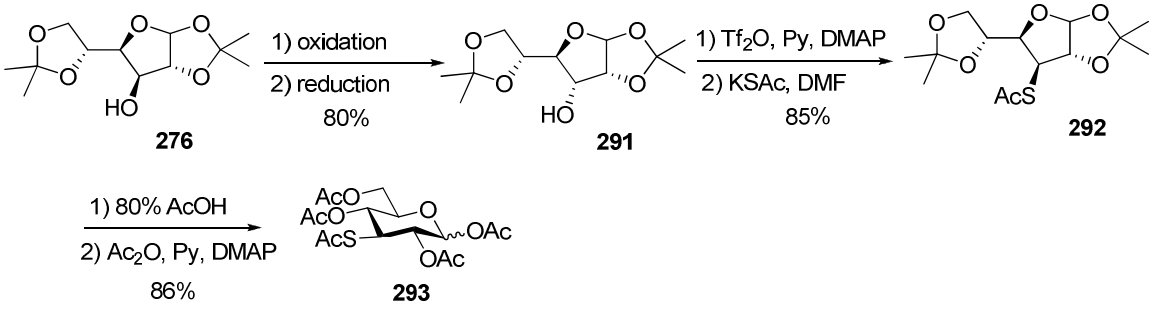


289 **290**

Scheme 89. Synthesis of a sulfenyl donor with linker on anomeric carbon

4.3.2 Synthesis of 3-thio methyl glycoside

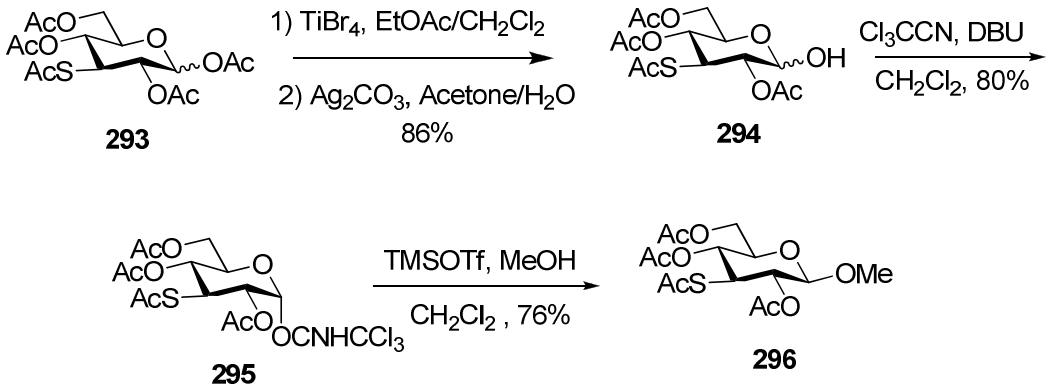
The synthesis of the thiol was accomplished in several steps. Thus, 1,2,4,6 tetra-*O*-acetyl-3-*S*-acetyl-3-deoxy glucopyranoside was prepared following the known literature procedure[155] beginning with commercially available diacetone-D-glucose **276** which was oxidized with pyridinium dichromate and acetic anhydride. The resulting ketone was reduced with sodium borohydride in aqueous ethanol to give the allose-configured alcohol **291** in 80% overall yield. This alcohol **291** was treated with triflic anhydride and pyridine in dichloromethane to give the corresponding triflate which was displaced with potassium thioacetate in DMF with a catalytic amount of 18-crown-6. Finally, the furanoside ring was cleaved with aqueous acetic acid and the acetoxy groups were installed by the treatment with acetic anhydride and pyridine with DMAP to give the pyranoside **293** in 86% yield (Scheme 90).



Scheme 90. Synthesis of 1,2,4,6 tetra-*O*-acetyl-3-*S*-acetyl-3-deoxy glucopyranoside

Initial attempts to hydrolyze the anomeric acetate in presence of the thio acetoxy group in compound **293** with hydrazine acetate were ineffective, just as attempts to convert the anomeric acetate to anomeric bromide with either HBr in acetic acid or with *N*-bromo succinimide in wet acetone were unsuccessful owing

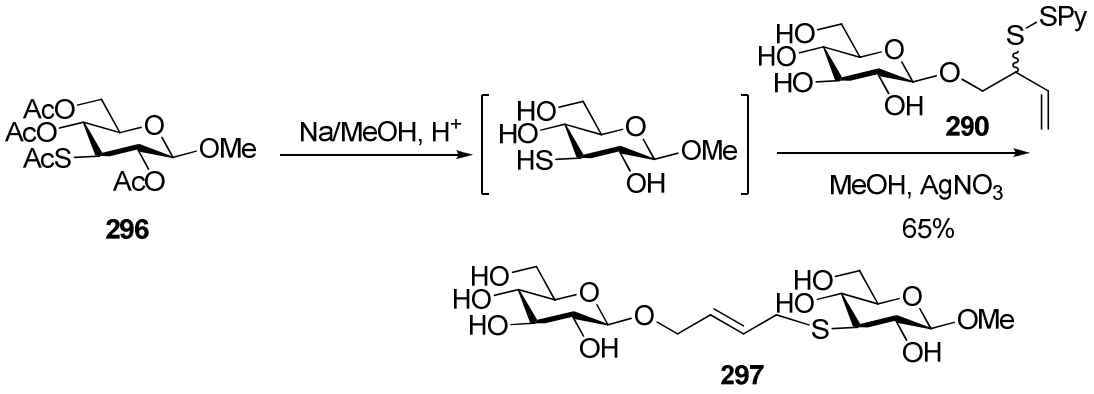
to the fact that the thio acetoxy group is more labile than the anomeric acetate. Eventually, titanium tetrabromide was used as an alternative brominating source to convert the anomeric acetate to the corresponding bromide in presence of a thio acetate group, based on the use of this reagent in a similar case reported by Elhalabi and Rice.[156] Pleasingly, titanium tetrabromide converted the anomeric acetate to the bromide after 96 h in a mixture of ethylacetate and dichloromethane without affecting the thioacetoxy group. The anomeric bromide was immediately taken to next step without any delay by stirring with silver carbonate in an acetone and water mixture at room temperature to give the alcohol **294** in 86% for two steps. The trichloroacetimidate group was introduced by treating the alcohol with trichloroacetonitrile in presence of DBU. Activation of this donor **295** with TMSOTf in the presence of methanol gave the methyl glycoside **296** in 76% yield as shown in Scheme 91.



Scheme 91. Synthesis of methyl glycoside

The methyl glycoside **296** was saponified under Zemplen conditions with metallic sodium in degassed methanol and the resulting thiolate solution was acidified and then added immediately to a solution of the allylic disulfide **290** in methanol. The mixed disulfide was formed in 3-4 h as observed by the mass

spectrometry and also by the yellow color of the reaction medium (due to the release of 2-pyridine thiol). Silver nitrate subsequently was added to the crude allylic disulfide obtained in this manner to furnish the rearranged product **297**. The more hindered thiol completely rearranged and afforded the allyl thio ether in 65% after 24 h. The olefinic configuration was once again found to be *trans* with the coupling constant between the olefinic protons being 15.5 Hz (Scheme 92).

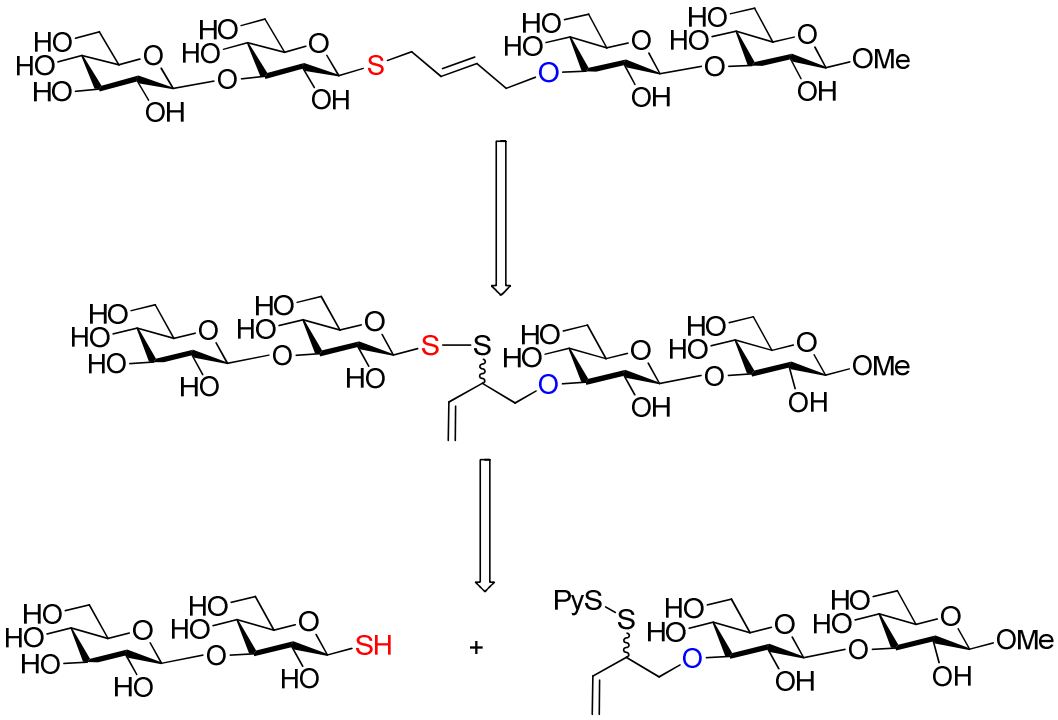


Scheme 92. Second silver mediated ligation for the synthesis of a disaccharide mimic

4.4 Silver mediated desulfurative ligation to the syntheses of tetrasaccharide mimics

4.4.1 First approach for a tetrasaccharide mimic

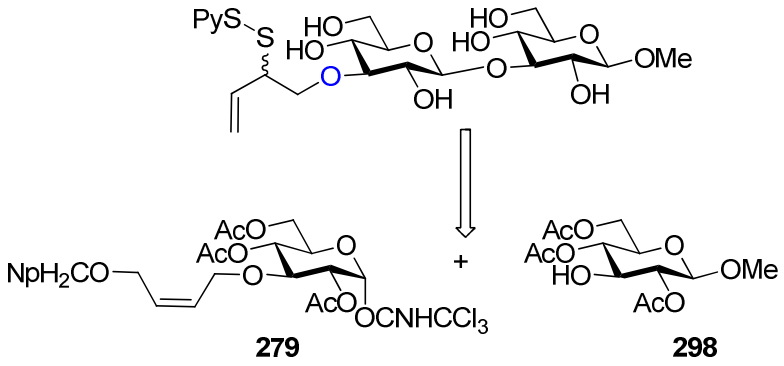
Having successfully demonstrated the synthesis of two disaccharide mimics, attention was turned to mimics of higher oligosaccharides, with special focus on tetrasaccharides obtained by ligating two laminaribiosyl units. Again, this chemistry could be approached from two different directions and attention was first focused on the use of an anomeric thiol as analyzed in Scheme 93.



Scheme 93. First retrosynthetic approach for a tetrasaccharide mimic

4.4.2 Synthesis of a laminaribiosyl disulfide as a sulfenyl donor

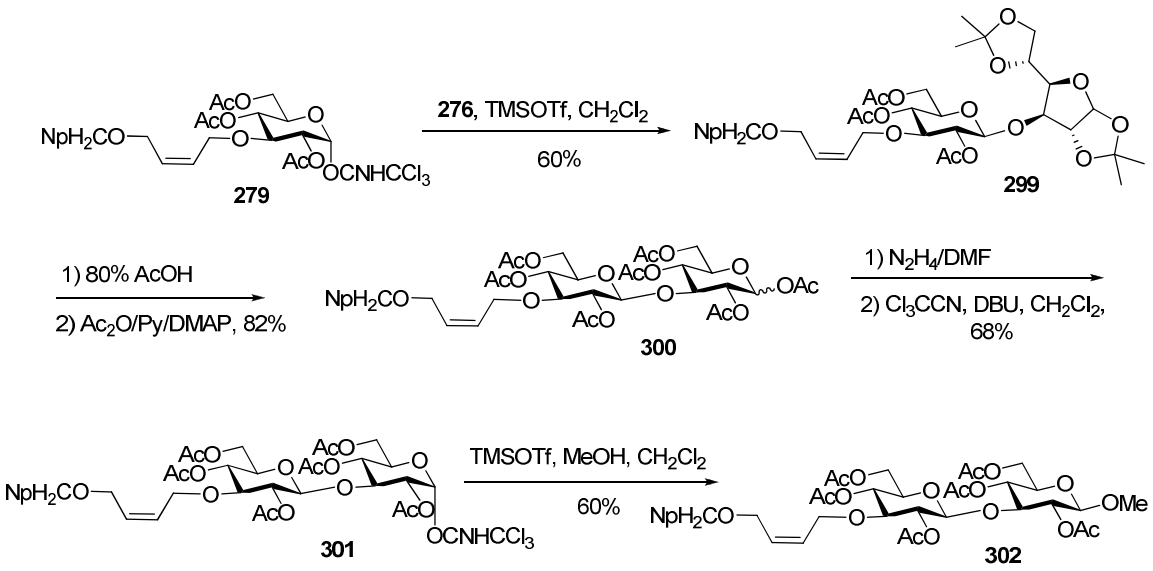
The initial idea for the laminaribiosyl sulfenyl donor is shown below (Scheme 94). However, the attempted glycosylation of the acceptor **298** with the trichloroacetimidate donor **279** produced no significant product.



279 **298**

Scheme 94. Attempted glycosylation to synthesize a disaccharide

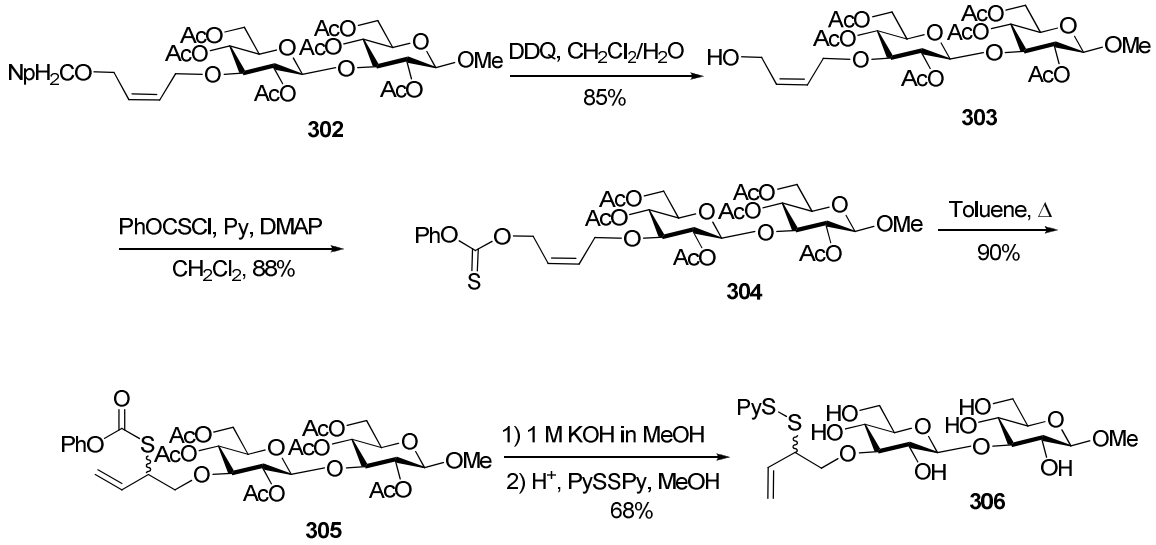
The hydrolyzed donor and the acceptor were completely recovered from the reaction mixture. It was considered that the combination of the strongly disarmed donor with the poorly nucleophilic acceptor alcohol was the reason for the failure of this glycosylation reaction. It was anticipated that the glycosylation of the less hindered dicetone-D-glucose acceptor **276** with this donor **279** and derivatization of the furanose ring to the pyranoside would solve this problem. Accordingly, the neighboring group assisted glycosylation of diacetone-D-glucose with the trichloroacetimidate donor **279** in the presence of TMSOTf in dichloromethane at room temperature gave the glycoside **299** stereoselectively in 60% yield. The acetonide groups in this glycoside were cleaved with aqueous acetic acid and the acetate groups were installed to give the protected laminaribioside **300** in 82% yield. The trichloroacetimidate donor was introduced after the facile cleavage of the anomeric acetate with hydrazine acetate and treatment of the alcohol with trichloroacetonitrile and DBU. The glycosylation with methanol at - 50 °C in presence of catalytic amount of TMSOTf produced the methyl glycoside **302** in 60% yield as shown in Scheme 95.



Scheme 95. Synthesis of a methyl laminaribioside

The oxidative cleavage of the naphthylmethyl group in **302** was performed with DDQ in dichloromethane and water to give the alcohol **303** in 85% yield. The disulfide linker was attached to the alcohol using a similar procedure employed for the monosaccharide. Thus, alcohol **303** was treated with phenylchlorothionocarbonate and pyridine as a base with a catalytic amount of DMAP in dichloromethane to give the thionocarbonate **304** in 88% yield. The [3,3]-sigmatropic rearrangement of the thionocarbonate gave the allylic thiolcarbonate **305** as a mixture of diastereomers in 90% yield. The global saponification of the allylic thiolcarbonate with the acetoxy groups with 1 M KOH in degassed methanol afforded the allylic thiol which was acidified and added immediately to a solution of 2,2'-dipyridyl disulfide in methanol, with monitoring of the progress of the reaction by TLC as well as by mass spectrometry. This disulfide linked laminaribioside **306** was purified by column chromatography over

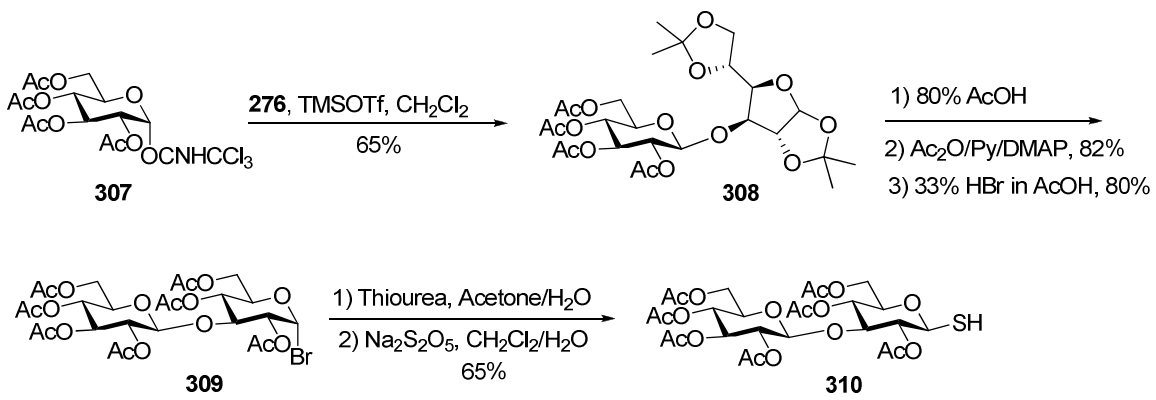
silica gel using methanol and dichloromethane as eluent to give the product in 68% isolated yield (Scheme 96).



Scheme 96. Synthesis of lalaminaribioside sulfenyl donor

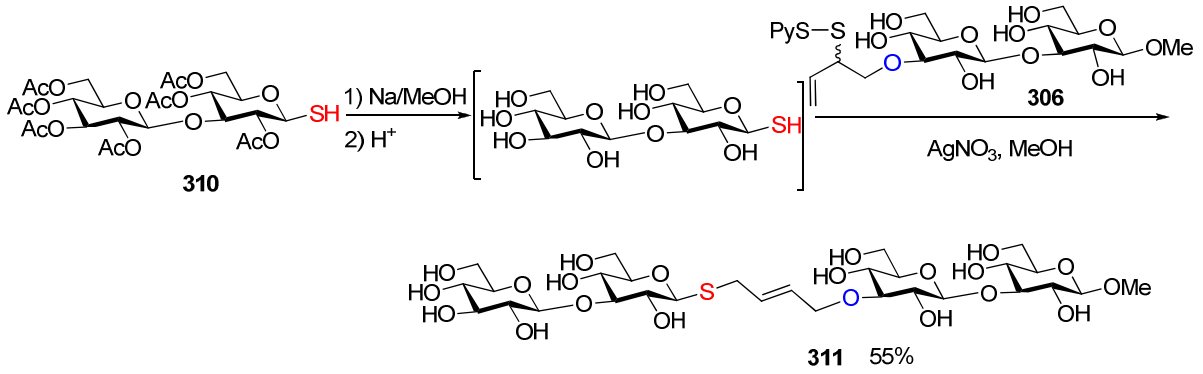
4.4.3 Synthesis of laminaribiosyl thiol

The synthesis of the peracetyl laminaribiosyl thiol **310** began with a known glycosylation reaction. Diacetone-D-glucose (**276**) was glycosylated with the known glucosyl trichloroacetimidate **307** donor in presence of TMSOTf in dichloromethane. The glycosylated product **308** was treated with aqueous acetic acid to remove the acid labile acetonide groups and acetoxy groups were installed with the treatment of acetic anhydride and pyridine to give the peracetyl glucopyranoside. This laminaribiosyl acetate was treated with 33% HBr in acetic acid to give the laminaribiosyl bromide **309** in 80% yield. Treatment with thiourea provided the laminaribiosyl isothiouronium bromide, which, on saponification with sodium meta-bisulfite, gave the protected laminaribiosyl thiol **310** in 65% yield as shown in Scheme 97.



Scheme 97. Synthesis of laminaribiosyl thiol

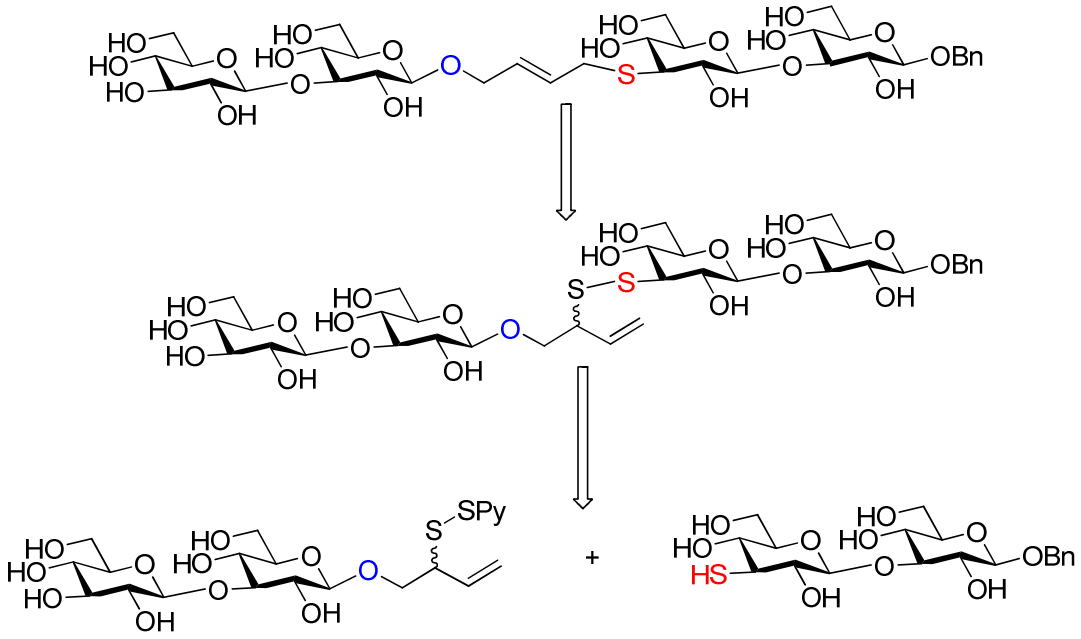
The unprotected laminaribiosyl sulfenyl donor and the laminaribioside thiol acceptor were ligated with silver nitrate to give the free tetrasaccharide **311** as shown in Scheme 98. The acetoxy protecting groups were removed from peracetyl laminaribiosyl thiol **310** by saponification with 2-3 equivalents of metallic sodium in degassed methanol and, after acidification, the deprotected thiol was immediately added to the sulfenyl donor **310** and the disulfide exchange reaction was monitored by mass spectrometry. After the completion of the disulfide exchange, 2.0 equivalents of silver nitrate were added to furnish the glycoligation product **311**. The progress of this glycoligation was monitored by mass spectrometry and also by the appearance of a black precipitate. The silver complex was removed by centrifugation and reaction mixture was purified by reverse phase chromatography to give the tetrasaccharide mimic in 55% yield over two steps (Scheme 98).



Scheme 98. Synthesis of a tetrasaccharide mimic

4.5 Synthesis of an alternative tetrasaccharide mimic

Attention was next focused on the alternative sequence employing an anomeric sulfenyl donor, according to the analysis to Scheme 99.



Scheme 99. Retrosynthetic plan for another tetrasaccharide mimic

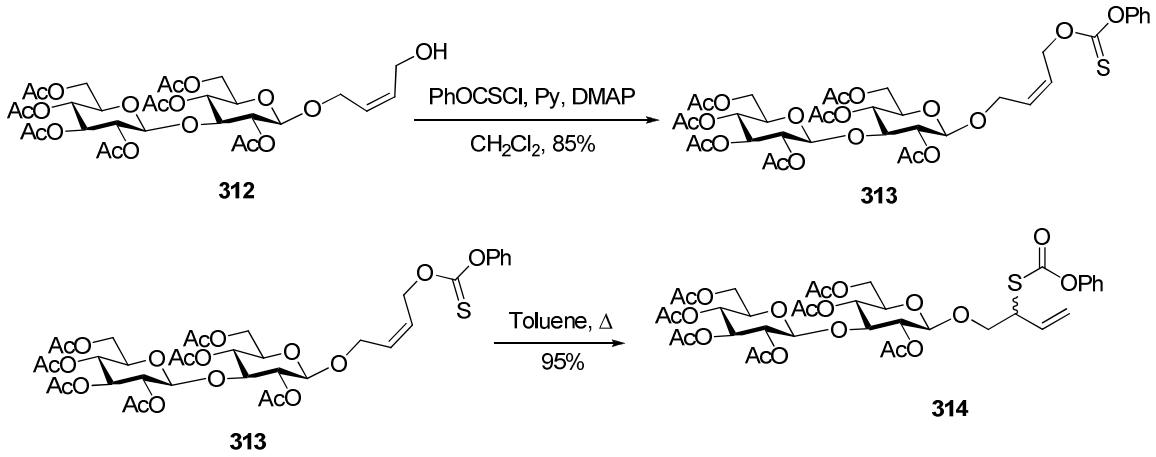
4.5.1 Synthesis of the laminaribiosyl donor

The installation of the disulfide linker began with the peracetyl laminaribiosyl bromide **309**, which was coupled with *cis*-butene 1,4-diol (**244**)

using the Koenigs-Knorr protocol[154] resulting in the β-glycoside **312** with its 8.0 Hz coupling for the newly introduced glycosidic bond, in 80% yield as shown in Scheme 100.

Scheme 100. Koenigs-Knorr synthesis of β-glycoside from laminaribiosyl bromide

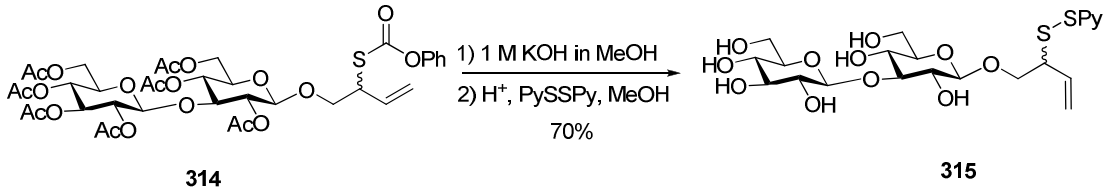
The alcohol **312** was functionalized as an allylic thiolcarbonate in two steps as shown in Scheme 101. In this sequence, the initial treatment of the alcohol with phenyl clorothionocarbonate and the thermal [3,3]-sigmatropic rearrangement of the thionocarbonate gave the allylic thiolcarbonate **314** in 95% yield as a mixture of isomers.



Scheme 101. Synthesis of peracetyl laminaribiosyl allylic thiolcarbonate

The protected thiolcarbonate **314** was saponified with powdered potassium hydroxide in methanol and the so-obtained thiol was transferred to the

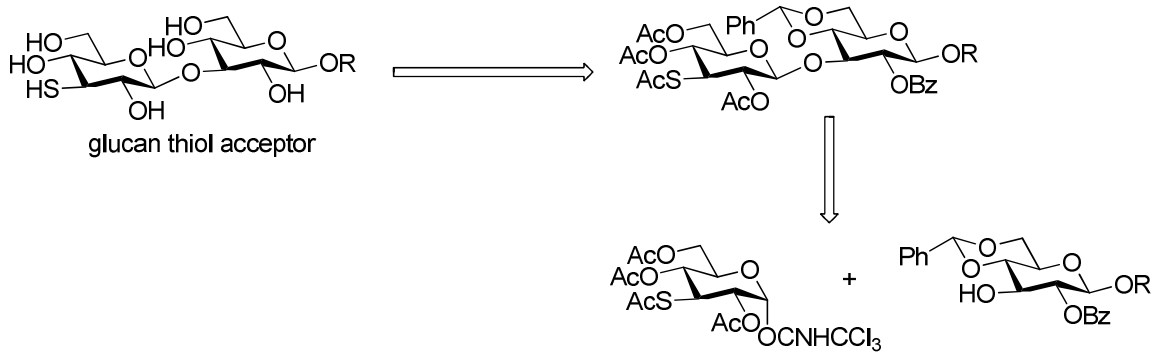
2,2'-dipyridyl disulfide in methanol without any isolation. Thus the synthesis of the laminaribiosyl sulfenyl donor **315** was accomplished in 70% yield (Scheme 102).



Scheme 102. Synthesis of laminaribiosyl allylic sulfenyl donor

4.5.2 Synthesis of the glucan thiol acceptor

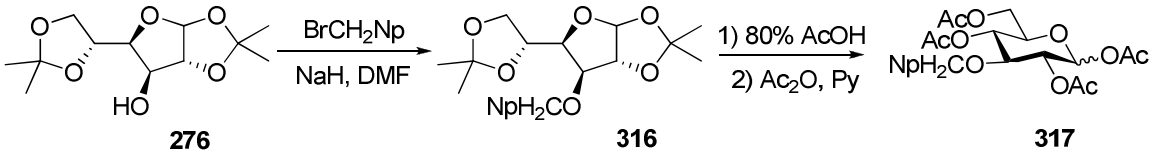
The synthesis of the laminaribio-3-thiol was planned as shown in the retro Scheme 103 and employed a benzylidene acetal group for the acceptor as several other groups had reported good success with 3-OH acceptors protected in this manner.



Scheme 103. Retrosynthetic scheme for the laminarabio-3-thiol

With the trichloroacetimidate donor **295** in hand, the synthesis of the benzylidene protected acceptor began with the commercially available diacetone-D-glucose (**276**). The synthesis of the benzyl glycoside was accomplished in several steps following the known literature protocol.[152] Naphthylmethyl protection of the diacetone glucose provided the ether **316** in 85% yield. The

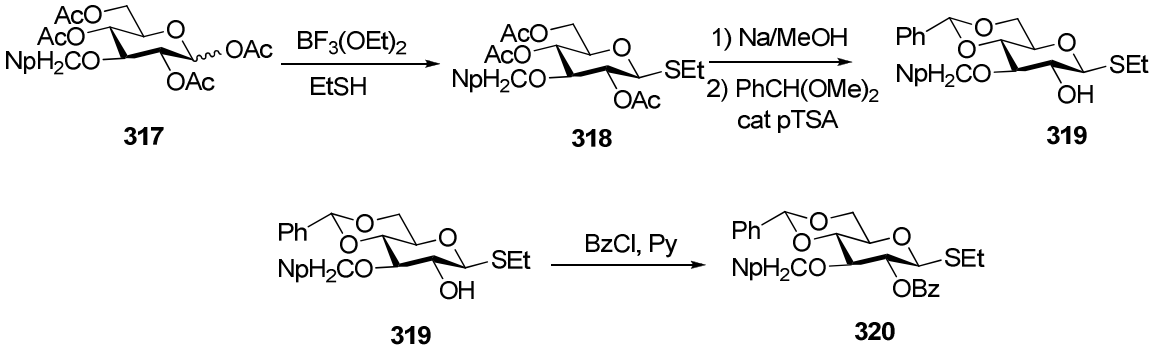
acetonide cleavage and the installation of the acetoxy groups gave the 3-*O*-naphthylmethyl protected glucopyranoside **317** in 80% yield as shown in Scheme 104.



276 **316** **317**

Scheme 104. Synthesis of a 3-*O*-ether linked glucopyranoside

The treatment of the glucopyranoside with ethanethiol under Lewis acidic condition provided the ethyl thio glucopyranoside donor **318** in 75% yield. Zemplen saponification of the donor **318** gave the triol which was treated with benzaldehyde dimethyl acetal in the presence of p-toluene sulfonic acid to give the alcohol **319** in 73% yield over two steps. This alcohol was treated with benzoyl chloride and pyridine in presence of DMAP to yield the thio glucopyranoside **320** in 70% yield (Scheme 105).



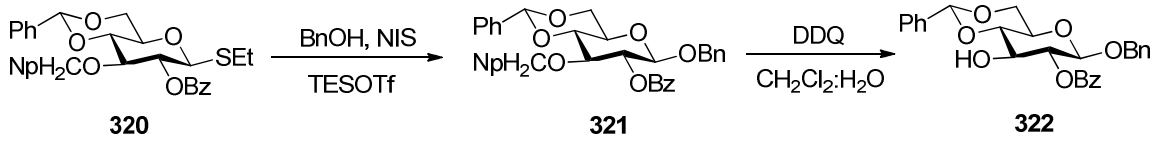
317 **318** **319**

319 **320**

Scheme 105. Synthesis of thio glucopyranoside

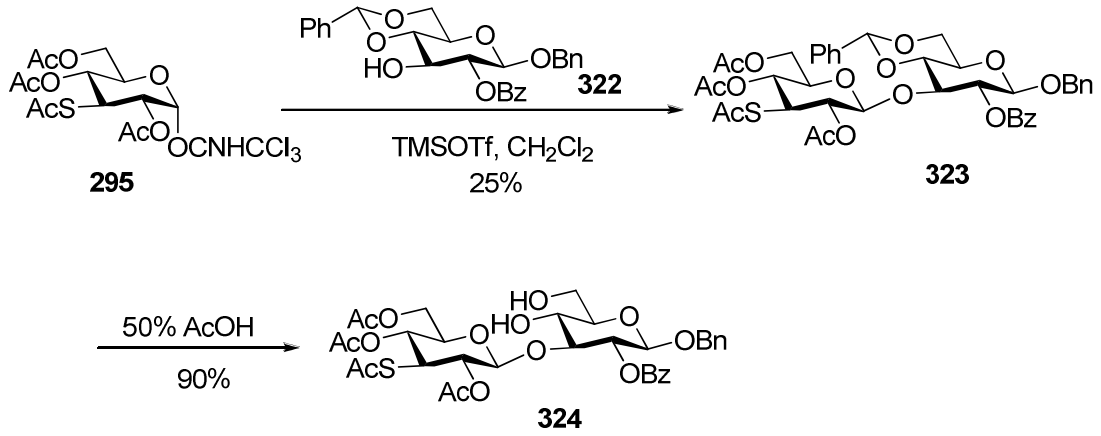
The thioglucopyranoside **320** was activated with TESOTf in the presence of benzyl alcohol and 4 Å molecular sieves to give the benzyl glucopyranoside

321 in 70% yield. The naphthylmethyl ether was then removed by DDQ oxidation to give the acceptor **322** in 65% yield as shown in Scheme 106.



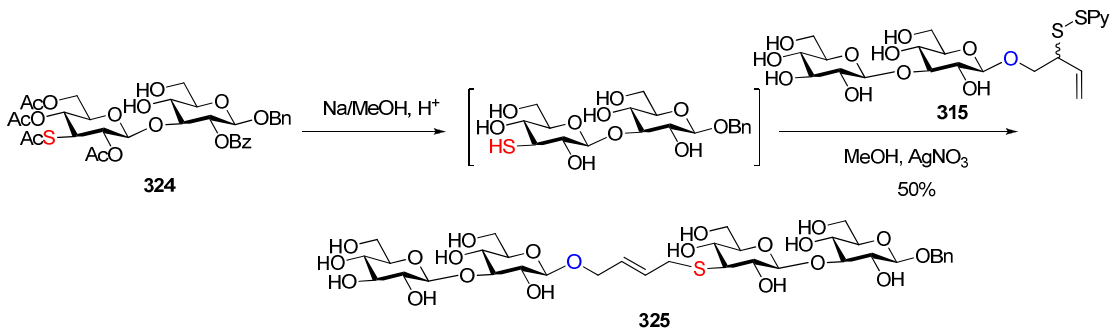
Scheme 106. Synthesis of the acceptor

Unfortunately, the glycosylation of the benzylidene protected acceptor with the trichloroacetimidate donor **295** yielded the disaccharide **323** only in 25% yield. Nevertheless, the benzylidene acetal in this disaccharide was cleaved by treatment with aqueous acetic acid to give the precursor **324** in 90% yield (Scheme 107).



Scheme 107. Synthesis of a glucan thiol acceptor

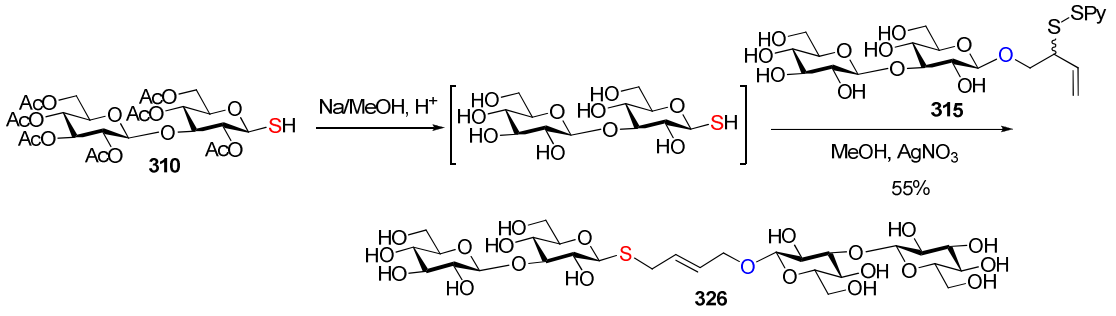
The protected thiol **324** was treated with sodium in methanol to give the thiol which was added to a solution of laminaribiosyl disulfide **315** in methanol without any isolation. After the formation of the new disulfide, silver nitrate was added and the progress of the reaction was monitored by mass spectrometry and the tetrasaccharide mimic **325** was isolated in 50% yield (Scheme 108).



Scheme 108. Synthesis of a second tetrasaccharide mimic

4.6 Synthesis of a head to head tetrasaccharide mimic

With the successful synthesis of two tetrasaccharide mimics, attention was focused on synthesizing the head to head tetrasaccharide mimic. Thus, the silver mediated glycoligation reaction was applied to the synthesis of a head to head tetrasaccharide mimic in which both the disulfide linker and the thiol were attached to their respective anomeric carbons. This head to head (1,3)-β-glucan mimic tetrasaccharide **326** was obtained by ligating the laminaribioside sulfenyl donor **315** with the laminaribioside thiol **310** as shown in Scheme 109.

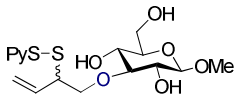
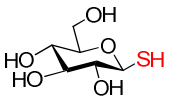
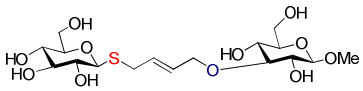
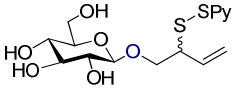
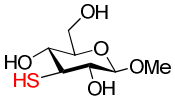
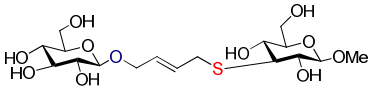
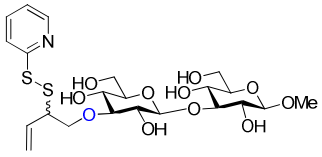
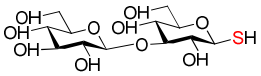
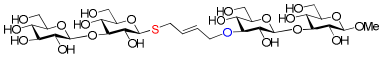
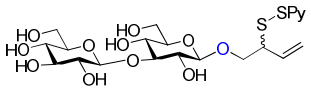
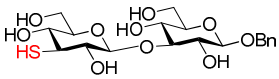
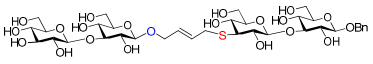


Scheme 109. Synthesis of a head to head tetrasaccharide mimic

4.7 Synthesis of a mixed disaccharide mimic

The silver mediated allylic desulfurative rearrangement was further demonstrated through the synthesis a mixed glucan disaccharide mimic. In this

sequence the sulfenyl donor **284** was treated with glucose 6-thiol, kindly provided by Ms Moume-Pymbock, in the Crich lab. The silver mediated desulfurative rearrangement was very effective and yielded the mixed disaccharide mimic **351** in 70% yield (Entry 7, Table 13). The silver mediated protecting group free syntheses of various glucan mimics achieved in the course of this study are summarized in Table 10.

Entry	Sulfenyl donor	In situ generated thiol acceptor	Product	Yield
1	 **284**		 **285**	70%
2	 **290**		 **297**	65%
3	 **306**		 **311**	55%
4	 **315**		 **325**	50%

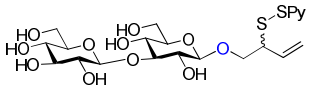
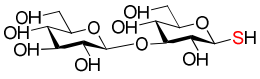
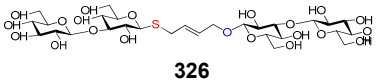
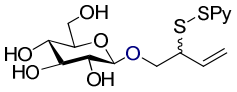
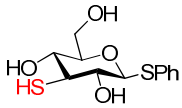
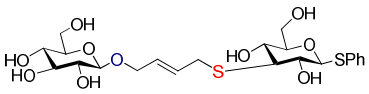
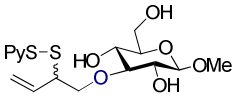
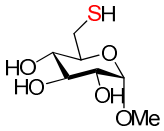
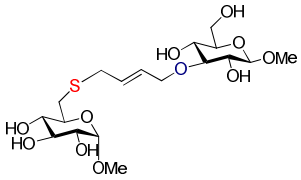
5	 **315**		 **326**	55%
6	 **290**		 **327**	70%
7	 **284**		 **328**	70%

Table 10. Silver mediated glycoligation to the synthesis of various glucan mimics

4.8 Conclusion

In summary, the desulfurative allylic rearrangement provides a new chemical ligation method. The silver mediated allylic desulfurative rearrangement has been employed as a powerful ligation method for the synthesis (1,3)-β glucan mimics. The synthesis of disaccharide and tetrasaccharide mimics was achieved in two different ways with comparable yields. However, for the synthesis of tetrasaccahride mimics, the approach involving the ligation of the laminaribiosyl thiol derived from **310** with the glucan disulfide donor **306** was more convenient than the rearrangement involving the glucan thiol derived from **324** with the laminaribiosyl disulfide donor **315** since the rearrangement was complete in the former.

CHAPTER V. Experimental Section

General: All solvents were dried and distilled by standard protocols. All reactions were conducted under an inert atmosphere of argon or nitrogen unless otherwise stated. All organic extracts were dried over sodium sulfate, and concentrated under aspirator vacuum. Chromatographic purifications were carried out over silica gel using Analogix fractional collectors. Unless otherwise stated optical rotations were recorded on an Autopol® III automatic polarimeter in $CHCl_3$ solution and ^{1}H and ^{13}C spectra were recorded in either $CDCl_3$ or CD_3OD solution. Mass spectra were recorded by the Research Resources Center at the University of Illinois at Chicago and Central Instrumentation Facility at Wayne State University. Reverse phase HPLC (RPHPLC) purification was performed with 215 and 254 nm UV detection, using a C-18 analytical and preparative columns (250 × 4.6) and (250 × 21.4), respectively. All runs used linear gradients of A in B (A: CH_3CN or MeOH and B: Water).

Experimental Section

1. General procedure for the synthesis of selenocyanates

To a stirred solution of allyl halide (1.0 mmol) in degassed acetone (10 mL) under an argon atmosphere, added potassium selenocyanate (1.2 mmol) in (10 mL) dropwise. The reaction mixture was stirred for 12 h. Solvents were evoparated and the reaction mixture is diluted with EtOAc and then washed with water. The organic part was washed with saturated NaCl solution, dried over sodium sulfate and evaporated to dryness. The crude selenocyanates were used directly without further purification.

2. General procedure for the coupling reaction of thiols with selenocyanates

To the freshly prepared selenocyanate (1.2 mmol) in degassed methanol (10 mL) under an argon atmosphere was added a solution of thiol (1.0 mmol) in methanol (5 mL) dropwise over 1 h at room temperature. The reaction mixture was stirred for 12 h and filtered through celite pad, washed with methanol (2 x 15 mL). The solvents were evoparated to dryness and purified by column chromatography to yield the rearranged product. PPh_3 (2.5 mmol) was used in some cases to complete the rearrangement.

3. General procedure for the acetonide removal from derivatives of 1,2;5,6-diisopropylideneglucofuranose derivatives and the subsequent installation of acetate groups.

The acetonide protected glucofuranoside (1.0 mmol) was dissolved in 80% acetic acid (10.0 mL) and heated with stirring to 95 °C for 8 h. After cooling the solvents were removed under reduced pressure, and the reaction mixture was azeotroped with toluene (2 X 30 mL). The crude product was dried under vacuo and dissolved in acetic anhydride (10.0 mmol), pyridine (10.0 mmol) and DMAP (0.1 mmol) and stirred at room temperature for 12 h. The solvents were evaporated under vacuum and the crude product was partitioned between ethyl acetate (30.0 mL) and water. The organic part was washed with brine (50 mL), dried, and evaporated to dryness.

4. General procedure for the preparation of glycosyl trichloroacetimidates. To a stirred solution of the anomeric acetate (1.0 mmol) in DMF (10.0 mL), NH_2NH_2.AcOH (1.5 mmol) was added, after which the reaction mixture was stirred at room temperature for 3-4 h before it was diluted with ethyl acetate (100 mL) and washed with brine (50 mL). The organic portion was separated and dried to give the hemiacetal, which was dissolved in dichloromethane (100 mL) and treated with trichloroacetonitrile (10.0 mmol), followed by DBU (0.1 mmol). The reaction mixture was stirred at room temperature for 12 h before the solvents were evaporated and the crude product was purified by column chromatography using ethyl acetate/hexanes as eluent.

5. General procedure for the glycosylation with trichloroacetaimidates.

The trichloroacetimidate (1.2 mmol), alcohol (1.0 mmol) and activated 4 A° molecular sieves were mixed in dichloromethane (10 mL) and stirred at room temperature for 0.5 h before TMSOTf (0.125 mmol) was added. Stirring was continued at room temperature for 12 h before triethylamine (0.2 mmol) was added and the reaction mixture was filtered. The solvents were evaporated and the crude product was purified by column chromatography using ethyl acetate/hexanes as eluent.

6. General procedure for the deprotection of naphthylmethyl groups.

The protected pyranoside (1.0 mmol) was dissolved in a mixture of ~9:1 dichloromethane and water (10 mL) and DDQ (1.3 mmol) was added. The reaction mixture was stirred at room temperature for 3-4 h until TLC showed the starting material has been consumed. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL). The

combined organic part was dried and evaporated to dryness. The crude product was purified by column chromatography using ethyl acetate/hexanes as eluent.

7. General procedure for the preparation of allylic thionocarbonates.

A solution of phenyl chlorothionocarbonate (2.0 mmol) in dichloromethane (2 mL) was added to a solution of the alcohol (1.0 mmol), pyridine (15.0 mmol) and DMAP (0.1 mmol) in dichloromethane (10.0 mL) and the resulting dark-yellow solution was stirred at room temperature for 4 h. The reaction mixture was poured into H_2O (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried, filtered, evaporated, and purified by column chromatography.

8. General procedure for the [3,3]-sigmatropic rearrangement of allylic thionocarbonates.

A solution of allylic thionocarbonate (1 mmol) in toluene (10.0 mL) was heated at reflux for 12 h. Evaporation of the solvent and chromatographic purification of the crude products using ethyl acetate/hexanes as eluent afforded the products.

9. General procedure for the conversion of allylic thiocarbonates to allylic pyridinsulfanyl disulfides.

The peracetyl glycosyl thiolcarbonate (1.0 mmol) was dissolved in MeOH (X mL) at 0 °C with stirring and 1 M KOH (6.0 mmol-12.0 mmol, 1.5 equiv per acetate group) was added dropwise. After 3-4 h, the pH of the reaction mixture was adjusted to 7 by careful addition of Amberlyst15 H^+ resin. The reaction mixture was then filtered, and the filtrate was washed with methanol (5 mL). The

combined filtrate was added to a solution of 2,2'-dipyridyl disulfide (1.25 mmol) in MeOH (2.0 mL) at room temperature for 4 h. The solvents were removed and the product was purifiifed by column chromatography using MeOH/dicloromethane as eluent.

10. General procedure for the silver nitrate promoted rearrangement of allylic disulfides.

A stirred solution of protected thiol in degassed methanol (0.5 M) was treated with metallic sodium (2-3 equiv) and stirred under a N_2 atmosphere for 4-6 h until the saponification was complete (monitored by ESI mass spectrometry and TLC). The reaction mixture was acidified with Amberlyst 15 resin and filtered. The resin was washed with methanol (3 X 5 mL). The combined washings and the filtrate were concentrated to a final volume of 1-2 mL and transferred to a stirred solution of disulfide (0.05 M) in methanol. The reaction mixture was stirred at room temperature under a nitrogen atmosphere until disulfide exchange was complete (ESI mass spectrometry). The reaction mixture was then treated with silver nitrate (2.0 equiv) and stirred in the dark for 16-24 h. After the completion of reaction (monitored by ESI mass spectrometry), NaCl (10 equiv) was added and the reaction mixture was stirred for 3-4 h. The reaction mixture was diluted with methanol and centrifuged to remove the black precipitate. The solvent was then concentrated to afford the crude product which was purified by column chromatography on silica gel to give the rearranged product.

Allyl hexadecyl sulfide (184).

Following the general procedure **2**, the title compound was obtained in 70% as colorless liquid. The selenosulfide intermediate did not require any triphenylphosphine for the [2,3]-sigmatropic rearrangement. The characterization data were in agreement with literature values. ^{1}H NMR (500 MHz, $CDCl_3$,): δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.25-1.31 (m, 24H), 1.36 (m, 2H), 1.56 (m, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 3.12 (d, *J* = 7.5 Hz, 2H), 5.07 (d, *J* = 10.0 Hz, 1H), 5.09 (d, *J* = 16.5 Hz, 1H), 5.79 (ddt, *J* = 10.0 Hz, *J* = 16.5 Hz, *J* = 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$,): δ 14.2, 22.7, 28.9, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 30.7, 32.0, 34.8, 116.7, 134.6, EIHRMS Calcd. For $C_{19}H_{38}S$ $[M]^+$ 298.2694, found: 298.2697.

Allyl phenethyl sulfide (185).

Following the general procedure **2**, the title compound was obtained in 70% as colorless liquid. The selenosulfide intermediate did not require any triphenylphosphine for the [2,3]-sigmatropic rearrangement. ^{1}H NMR (400 MHz, $CDCl_3$,): δ 2.71- 2.75 (m, 2H), 2.86-2.90 (m, 2H), 3.15 (d, *J* = 7.0 Hz, 2H), 5.09 (d, *J* = 16.6 Hz, 1H), 5.13 (d, *J* = 11.2 Hz, 1H), 5.72-5.82 (m, 1H), 7.20-7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 32.0, 34.8, 36.0, 117.0, 126.3, 128.3, 128.4 (2C), 128.5, 134.4, 140.6; EIHRMS Calcd for $C_{11}H_{14}S$ $[M+Na]^+$: 178.0816, found: 178.0831.

Linalyloctyl sulfide (186).

Following the general procedure **2**, the title compound was obtained in 70% yield as colorless oil. The selenosulfide intermediate required 2.5 equiv of triphenylphosphine for the completion of the [2,3]-sigmatropic rearrangement. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (t, *J* = 7 Hz, 3H), 1.25-1.28 (m, 8H), 1.32-1.34

(m, 5H), 1.57 (s, 3H), 1.55-1.61 (m, 4H), 1.67 (s, 3H), 1.92-2.10 (m, 2H), 2.29-2.37 (m, 2 H), 4.94 (d, *J* = 17.8 Hz, 1H), 5.05 (d, *J* = 9.5 Hz, 1H), 5.11-5.09 (m, 1H), 5.76-5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 17.6, 22.6, 23.1, 23.4, 25.6, 28.3, 29.1, 29.2, 29.3, 29.5, 31.8, 40.3, 49.7, 111.9, 124.0, 131.7, 143.7; EIHRMS Calcd. for $C_{18}H_{34}S_1$ [M]+•: 282.2381, found 282.2385.

***N*-Acetyl-*S*-allyl-L-cysteine methyl ester (189).**

Following the general procedure **2**, the title compound was obtained in 80% as colorless liquid. The selenosulfide intermediate did not require any triphenylphosphine for the [2,3]-sigmatropic rearrangement and the characterization data were in agreement with the literature values. ^{1}H NMR (400 MHz, $CDCl_3$,): δ 2.06 (s, 3H),2.87 (dd, *J* = 5.2 Hz, *J* = 14.0 Hz, 1H), 2.95 (dd, *J* = 4.8 Hz, *J* = 13.6 Hz, 1H), 3.11 (d, *J* = 6.0 Hz, 2H), 3.79 (s, 3H), 4.77-4.82 (m, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 5.13 (d, *J* = 2.0 Hz, 1H), 5.70-5.77 (m, 1H), 6.2 (br. d, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 23.1, 32.6, 35.1, 51.6, 52.6, 117.9, 133.5, 169.8, 171.4.

***N*-(*tert*-butoxycarbonyl)-*S*-(2-methylallyl)-L-cysteine ethyl ester (190)[126];** Following the general procedure **2**, the title compound was obtained in 68% as colorless liquid. The selenosulfide intermediate did not require any triphenylphosphine for the [2,3]-sigmatropic rearrangement**.** $[\alpha]^{27}_D$ +18.4 (c=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.29 (t, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 1.79 (s, 3H), 2.80 (dd, *J* = 5.5 Hz, *J* = 13.6 Hz, 1H), 2.89 (dd, *J* = 4.5 Hz, *J* = 13.8 Hz, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 3.11 (d, *J* = 13.5 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.47-4.49 (m, 1H), 4.84 (s, 1H), 4.87 (d, *J* = 1.5 Hz, 1H), 5.30 (d, *J* = 7.4 Hz,

1H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 14.1, 20.5, 28.2 (3C), 33.1, 39.8, 53.1, 61.6, 80.0, 114.3, 140.6, 155.1, 171.1; ESIHRMS Calcd for $C_{14}H_{25}NO_4S$ [M+Na]+: 326.1402, found: 326.1410.

***N*-(*tert*-butoxycarbonyl)-*S*-linalyl-L-cysteine ethyl ester (191);**

Following the general procedure **2**, the title compound was obtained in 66% yield as colorless oil. The selenosulfide intermediate required 2.5 equiv of triphenylphosphine for the completion of the [2,3]-sigmatropic rearrangement. $[\alpha]^{27}_D$ +6.4 (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.33 (d, *J* = 1.1 Hz, 3H), 1.45 (s, 9H), 1.57 (s, 3H), 1.55-1.60 (m, 2H), 1.66 (s, 3H), 1.92 -2.09 (m, 2H), 2.79 (d, *J* = 4.8 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.47-4.49 (m, 1H), 4.95 (d, *J* = 18.3 Hz, 1H), 5.04-5.09 (m, 1H), 5.08 (d, *J* = 10.9 Hz, 1H), 5.25 (d, *J* = 7.9 Hz, 1H), 5.70-5.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 17.6, 23.1, 23.3, 25.6, 28.3 (3C), 31.1, 40.2, 50.4, 53.0, 61.6, 79.9, 113.0, 123.7, 131.9, 142.9, 155.1, 170.9; ESIHRMS Calcd for $C_{20}H_{35}NO_4S$ $[M+Na]^+$: 408.2185, found: 408.2175.

***N*-(*tert*-Butoxycarbonyl)-*S*-allyl-glutathione dimethyl ester (194).**

Following the general procedure **2**, the title compound was obtained in 75% as colorless liquid. The selenosulfide intermediate did not require any triphenylphosphine for the [2,3]-sigmatropic rearrangement**.** $[\alpha]^{27}_D$ -31.1 (c=1, MeOH); ^{1}H NMR (400 MHz, MeOD,): δ 1.44 (s, 9H), 1.86-1.95 (m, 1H),2.11-2.17 (m, 1H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.68 (dd, *J* = 8.8 Hz, *J* = 13.9 Hz,1H), 2.94 (dd, *J* = 5.5 Hz, *J* = 13.9 Hz, 1H), 3.17 (d, *J* = 6.8 Hz, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 3.95 (s, 2H), 4.13-4.17 (m, 1H), 4.53-4.56 (m, 1H), 5.09 (d, *J* = 10 Hz, 1H), 5.16

(d, *J* =17.2 Hz, 1H), 5.75-5.82 (m, 1H); ^{13}C NMR (100 MHz, MeOD): δ 26.9, 27.2 (3C), 31.4, 31.8, 34.0, 40.4, 51.2, 51.3, 52.3, 53.0, 79.2, 116.4, 134.0, 156.6, 170.0, 171.9, 173.0, 173.3; ESIHRMS Calcd for $C_{20}H_{33}N_3O_8S$ $[M+Na]^+$: 498.1886, found: 498.1895.

***N*-(*tert*-Butoxycarbonyl)-*S*-(2-methylallyl) glutathione dimethyl ester (195).** Following the general procedure **2**, the title compound was obtained in 71% as colorless liquid. The selenosulfide intermediate did not require any triphenylphosphine for the [2,3]-sigmatropic rearrangement**.** $[\alpha]^{27}_D$ -39.1 (c=1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$,): δ 1.42 (s, 9H), 1.79 (s, 3H), 1.93-1.97 (m, 1H), 2.17-2.18 (m, 1H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.81 (d, *J* = 6.5 Hz, 2H), 3.14 (s, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 3.98 (dd, *J* = 5.4 Hz, *J* = 18.0 Hz, 1H), 4.06 (dd, *J* = 5.3 Hz, *J* = 18.1 Hz, 1H), 4.36 (m, 1H), 4.59 (q, *J* = 6.8 Hz, 1H), 4.86 (d, *J* = 1.3 Hz, 1H), 4.89 (s, 1H), 5.39 (d, *J* = 7.2 Hz, 1H), 6.86 (br s, 1H), 7.05 (br. s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 28.2 (3C), 28.7, 32.1, 32.5, 39.5, 41.2, 52.1, 52.4, 52.5, 52.6, 80.2, 114.5, 140.7, 155.7, 169.9, 170.6, 172.1, 172.8; ESIHRMS Calcd for $C_{21}H_{35}N_3O_8S$ $[M+Na]^+$: 512.2043, found: 512.2064.

***N*-(*tert*-Butoxycarbonyl)-*S*-linalyl glutathione dimethyl ester (196).**

Following the general procedure **2**, the title compound was obtained in 55% yield as colorless oil. The selenosulfide intermediate required 2.5 equiv of triphenylphosphine for the completion of the [2,3]-sigmatropic rearrangement. $[\alpha]^{27}_D$ -18.0 (c=1, MeOH); ^{1}H NMR (MeOD, 400 MHz): δ 1.37 (d, *J* = 3.6 Hz, 3H), 1.43 (s, 9H), 1.53-1.61 (m, 2H), 1.61 (s, 3H), 1.67 (s, 3H), 1.86-2.17 (m, 4H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.61-2.69 (m, 1H), 2.80-2.86 (m, 1H), 3.71 (s, 3H), 3.72

(s, 3H), 3.93 (s, 2H), 4.14-4.16 (m, 1H), 4.48-4.51 (m, 1H), 5.02 (d, *J* = 17.5 Hz, 1H), 5.08-5.12 (m, 1H), 5.10 (d, *J*= 10.5 Hz, 1H), 5.78-5.85 (m, 1H); ^{13}C NMR (MeOD, 100 MHz): δ = 16.3, 22.5, 22.8, 24.4, 27.0, 27.3 (3C), 30.0, 31.4, 40.2, 40.5, 50.2, 51.2, 51.3, 53.1, 53.3, 79.2, 112.1, 123.6, 131.3, 143.2, 156.7, 170.1, 171.9, 173.1, 173.2; ESIHRMS Calcd for $C_{27}H_{45}N_3O_8S$ $[M+Na]^+$: 594.2825, found: 594.2846.

***N*-(*tert*-butoxycarbonyl)-*S*-(2-methylallyl)-L-cysteinyl-L-alanyl-L-tryptophan methyl ester (197).**

Following the general procedure **2**, the title compound was obtained in 65% yield as colorless oil. The selenosulfide intermediate required 2.5 equiv of triphenylphosphine for the completion of the [2,3]-sigmatropic rearrangement. $[\alpha]^{27}_D$ +15.6 (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (d, *J* = 7.0 Hz, 3H), 1.47 (s, 9H), 1.78 (s, 3H), 2.69 (dd, *J* = 6.2 Hz, *J* = 13.8 Hz, 1H), 2.78 (dd, *J* = 5.8 Hz, *J* = 13.9 Hz, 1H), 3.04 (d, *J* = 13.5 Hz, 1H), 3.08 (d, *J* = 13.5 Hz, 1H), 3.27 (dd, *J* = 5.8 Hz, *J* = 14.8 Hz, 1H), 3.33 (dd, *J* = 5.3 Hz, *J* = 14.8 Hz, 1H), 3.69 (s, 3H), 4.09-4.21 (m, 1H), 4.44 (t, *J* = 7.2 Hz, 1H), 4.85-4.89 (m, 3H), 5.29 (br s, 1H), 6.72 (d, *J* = 6.1 Hz, 1H), 6.78 (d, *J* = 6.9 Hz, 1H), 6.97 (s, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 8.44 (br s,1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.8, 20.6, 27.4, 28.2 (3C), 33.3, 39.6, 48.8, 52.6, 52.8, 53.6, 80.7, 109.5, 111.3, 114.5, 118.4, 119.5, 122.1, 123.1, 127.4, 136.0, 140.7, 155.6, 170.4, 171.2, 171.9; ESIHRMS Calcd. for $C_{27}H_{38}N_4O_6S$ $[M+Na]^+$: 569.2410, found: 569.2407.

BocNH-L-Cys-(*S*-linalyl)-L-Ala-L-Trp-OMe (198).

Following the general procedure **2**, the title compound was obtained in 50% yield as colorless oil. The selenosulfide intermediate required 2.5 equiv of triphenylphosphine for the completion of the [2,3]-sigmatropic rearrangement. $[\alpha]^{27}_{D}$ +9.0 (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.47 (s, 9H), 1.56 (s, 3H), 1.67 (s, 3H), 1.73-1.75 (m, 2H), 1.91-2.05 (m, 2H), 2.56 - 2.65 (m, 1H), 2.74 - 2.82 (m, 1H), 3.26 (dd, *J* = 5.8 Hz, *J* = 14.8 Hz, 1H), 3.33 (dd, *J* = 5.3 Hz, *J* = 14.8 Hz, 1H), 3.68 (s, 3H), 4.10 - 4.23 (m, 1H), 4.39 - 4.46 (m, 1H), 4.83-4.88 (m, 1H), 4.96 (d, *J* = 17.6 Hz, 1H), 5.04 -5.08 (m, 1H), 5.09 (d, *J* = 11.0 Hz, 1H), 5.29 (m, 1H), 5.72-5.79 (m,1H), 6.75 (br s, 2H), 6.97 (s, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 8.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.6, 17.7, 23.1, 23.3, 25.6, 27.4, 28.3 (3C), 30.8, 40.1, 48.8, 50.9, 52.4, 52.7, 53.8, 80.7, 109.4, 111.3, 113.3, 118.4, 119.5, 122.0, 123.2, 123.6, 127.4, 132.0, 136.0, 142.9, 155.6, 170.3, 171.2, 171.9; ESIHRMS Calcd for $C_{33}H_{48}N_4O_6S$ $[M+Na]^+$: 651.3193, found: 651.3173.

BocNH-L-Cys-(*S*-nerolidyl)-L-Ala-L-Trp-OMe (199).

Following the general procedure **2**, the title compound was obtained in 40% yield as colorless oil. The selenosulfide intermediate required 2.5 equiv of triphenylphosphine for the completion of the [2,3]-sigmatropic rearrangement. $[\alpha]^{27}_{D}$ +9.9 (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz):δ 1.30 (d, *J* = 7.2 Hz, 3H), 1.34 (s, 3H), 1.47 (s, 9H), 1.58 (s, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.71-1.73 (m, 2H), 1.93-2.07 (m, 6H), 2.56- 2.65 (m, 1H), 2.74-2.82 (m, 1H), 3.26 (dd, *J* = 5.8 Hz, *J* = 14.8 Hz, 1H), 3.33 (dd, *J* = 5.3 Hz, *J* = 14.8 Hz, 1H), 3.68 (s, 3H), 4.10-

4.23 (m, 1H), 4.39 - 4.46 (m, 1H), 4.83 - 4.88 (m, 1H), 4.96 (d, *J* = 17.6 Hz, 1H), 5.06-5.09 (m, 2H), 5.10 (d, *J* = 11.0 Hz, 1H), 5.24 (m, 1H), 5.72-5.79 (m, 1H), 6.75 (br s, -NH, 2H), 6.97 (s, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 8.50 (br. s 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.9, 17.6, 23.0, 23.1, 23.3, 25.7, 26.6, 27.4, 28.3 (3C), 30.8, 39.6, 40.6, 48.8, 50.9, 52.4, 52.7, 53.8, 80.7, 109.5, 111.3, 113.4, 118.4, 119.5, 122.0, 123.2, 123.5, 124.2, 127.4, 131.4, 135.6, 136.0, 143.0, 155.6, 170.3, 171.2, 171.9; ESIHRMS Calcd for $C_{38}H_{56}N_4O_6S$ $[M+Na]^+$:719.3819, found: 719.3835.

4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-2-methylenenonanal (204).

To a stirred solution of 2H,2H,3H,3H perfluoro nan-1-al **203** (0.4 g, 1.06 mmol) and triethylamine (0.44 mL, 3.18 mmol) in CH_2Cl_2 (10 mL) was added N,N-dimethylmethyleneiminium iodide (0.4 g, 2.15 mmol) and the reaction mixture was stirred at room temperature for 15 h at room temperature. The reaction mixture was diluted with saturated $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (20 mL). The combined organic portion was washed with water followed by brine solution (20 mL) and dried over Na_2SO_4. It was concentrated and the residue was purified by column chromatography over silica gel using 5% EtOAc/hexanes as eluent to afford the title product as oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (s, 1H), 6.65 (s, 1H), 6.41 (s, 1H), 3.12 (t, *J* = 19.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1, 139.7, 138.7, 118.5, 116.0, 114.3, 112.4, 110.3, 108.5, 28.2.

4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-2-methylenenonan-1-ol (205).

To a stirred solution of $CeCl_3.7H_2O$ (385 mg, 1.03 mmol) in dry MeOH were added successively $NaBH_4$ (58 mg, 0.5 mmol) and a solution of aldehyde **204** (200 mg, 1.5 mmol) in MeOH (3 mL) at 0 °C. After 2 h, the reaction mixture was diluted with EtOAc (10 mL) and the solutions were filtered through a celite pad. To the filtrate, saturated $NaHCO_3$ solution (10 mL) and EtOAc (20 mL) were added and partitioned. The combined organic portion was washed with water followed by brine solution (10 mL) and dried over Na_2SO_4. It was concentrated and the residue was purified by column chromatography over silica gel using 5% EtOAc/hexanes as eluent to afford the title product as oil. 1H NMR (500 MHz, $CDCl_3$): ^{1}H NMR δ 5.43 (s, 1H), 5.20 (s, 1H), 4.17 (d, *J* = 5.5 Hz, 2H), 2.88 (t, J = 30.0 Hz, 2H), 1.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.3, 123.0, 118.5, 117.2, 115.7, 112.4, 110.5, 108.3, 65.7, 33.9, 33.8, 33.6.

2-(Bromomethyl)-4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononon-1-ene (175).

To a stirred solution of **205** (245 mg, 0.63 mmol) in CH_2Cl_2 (10 mL) was added triphenylphosphine (411 mg, 1.57 mmol) and carbontetrabromide (521 mg, 1.57 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and continued stirring for another 3 h under an argon atmosphere. The reaction mixture was diluted with saturated $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (20 mL). The combined organic portion was washed with water followed by brine solution (20 mL) and dried over Na_2SO_4. It was concentrated and the residue was purified by column chromatography over silica gel using EtOAc/hexanes as eluent to afford the title product as yellow oil. ^{1}HNMR (500 MHz, $CDCl_3$): δ 5.55 (s, 1H), 5.27 (s, 1H), 4.07 (s, 2H), 3.03 (t, *J* = 19.5 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.4, 123.5, 118.5, 117.2, 115.7, 112.4, 110.5, 108.3, 36.2 (2C), 34.4, 34.2, 31.6.

4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluoro-2-(selenocyanatomethyl)non-1-ene (180).

Following the general procedure **1**, the title compound was obtained as colorless oil in 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.53 (s, 1H), 5.35 (s, 1H), 3.78 (s, 2H), 3.03 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.1, 125.1, 100.6, 35.1 (2C), 34.9, 34.8 (2C), 34.6.

BocNH-L-Cys-*(S*-1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-ene-9-methylenyl)L-Ala-LTrp-OMe (206).

Following the general procedure **2**, the title compound was obtained in 65% yield as colorless oil. The selenosulfide intermediate required 2.5 equiv of triphenylphosphine for the completion of the [2,3]-sigmatropic rearrangement.Colorless oil; $[\alpha]^{19}_D$ + 19.6 (c=1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (d, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 2.64 (dd, *J* = 6.0 Hz, *J* = 13.5 Hz, 1H), 2.71 (dd, *J* = 5.5 Hz, *J* = 14.0 Hz, 1H), 2.94 (dt, *J* = 5.5 Hz, *J* = 19.5 Hz, 2H), 3.14 (d, *J* =14.0 Hz, 1H), 3.20 (d, *J* = 13.5 Hz, 1H), 3.27 (dd, *J* = 5.5 Hz, *J* = 15.0 Hz, 1H), 3.33 (dd, *J* = 5.0 Hz, *J* = 14.5 Hz, 1H), 3.67 (s, 3H), 4.18-4.19 (m, 1H), 4.45 (t, *J* = 7.5 Hz, 1H), 4.86-4.90 (m, 1H), 5.16 (s, 1H), 5.28 (s, 1H), 5.32 (br. d, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 6.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.95 (s, 1H), 7.09 (t, *J* = 8.5 Hz, 1H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 8.45 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.2, 27.4, 28.2 (3C), 32.9, 34.1, 38.4, 48.9, 52.3, 52.9, 53.7, 80.7, 108.5, 109.4, 110.2, 111.3,

112.6, 113.4, 115.7, 117.8, 118.3, 119.5, 122.1, 123.1, 127.5, 133.0, 136.1, 155.5, 170.3, 171.4, 172.0; ^{19}F NMR ($CDCl_3$, 282 MHz): δ -53.7, -50.5, -49.3, -40.2, -8.3; ESIHRMS Calcd for $C_{33}H_{37}F_{13}N_4O_6S_1$ $[M+H]^+$: 865.2299, found 865.2298.

_S_-Allyl 2,3,4,6-Tetra-_O_-acetyl-1-thio-β-D-glucopyranoside (207).

Following the general procedure **2**, the title compound was obtained in 55% yield as colorless oil. The selenosulfide intermediate was heated with 2.5 equiv of triphenylphosphine in MeOH to complete the [2,3]-sigmatropic rearrangement. $[\alpha]^{27}_D$ -15.7 (c=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$,): δ 2.01 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 3.22 (dd, *J* = 5.9 Hz, *J* = 13.5 Hz, 1H), 3.39 (dd, *J* = 8.6 Hz, *J* = 13.5 Hz, 1H), 3.63 - 3.67 (m, 1H), 4.13 (dd, *J* = 2.3 Hz, *J* = 12.3 Hz, 1H), 4.22 (dd, *J* = 5.1 Hz, *J* = 12.3 Hz, 1H), 4.48 (d, *J* = 10.1 Hz, 1H), 5.06 (t, *J* = 9.9 Hz, 1H), 5.07 (t, *J* = 9.8 Hz, 1H), 5.12-5.13 (m, 1H), 5.15 - 5.17 (m, 1H), 5.22 (t, *J* = 9.3 Hz, 1H), 5.76 - 5.8 (m, 1H); ^{13}C NMR(100 MHz, $CDCl_3$,): δ 20.5, 20.6, 20.7, 20.7, 32.8, 62.2, 68.3, 69.8, 73.8,75.7, 81.8, 118.0, 133.3, 169.4, 169.4, 170.2, 170.6. ESIHRMS Calcd for $C_{17}H_{24}O_9S$ $[M+Na]^+$: 427.1039 found 427.1050.

Methyl (methyl 2,3-di-_O_-benzyl-α-D-glucopyranoside-α-D-glucopyranosyl)uronate (215).

To a stirred solution of Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **214** (2.2 g, mmol) in a mixture of saturated solution of $NaHCO_3$ (25 mL) and THF (25 mL) was added KBr (75 mg) and TEMPO (75 mg). The reaction mixture was cooled to 0 °C and commercial bleach (60 mL) was added slowly over a period of

2 h. The reaction mixture was quenched with the addition of sodium thiosulfate solution (25 mL) and acidified with 1N HCl solution (40 mL). It was extracted with EtOAc (100 mL) and the organic portion was dried over Na_2SO_4 and evaporated to dryness. To a stirred solution of this crude acid in MeOH (40 mL) was added IR-120 H^+ resin (2.0 g) and the mixture was refluxed under N_2 atmosphere for 24 h. Solvents were evaporated and the residue was purified by column chromatography using EtOAc/hexanes as eluent to give the title product 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 10H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.68 – 4.65 (m, 2H), 4.17 (d, *J* = 9.5 Hz, 1H), 3.86 – 3.81 (m, 3H), 3.79 (s, 3H), 3.55 (dd, *J* = 9.0 Hz, J = 3.0 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 138.8, 138.2, 128.7, 128.7, 128.4, 128.2, 128.1, 128.0, 98.9, 80.6, 78.7, 75.7, 73.8, 72.0, 70.8, 56.1, 52.9.

Methyl (methyl 2,3-di-*O*-benzyl-4-deoxy-α-D-*erythreo*-glucopyranosyl)uronate (216).

To a stirred solution of **215** (1.65 g, 4.11 mmol) in CH_2Cl_2 (20 ml) was added DMAP (50 mg, 0.411 mmol) and pyridine (1.66 ml, 20.5 mmol). Acetyl chloride (0.65 g, 8.22 mmol) was added and the reaction was stirred at room temperature for 2 h. The reaction mixture was quenched with the addition of saturated NH_4Cl (25 ml) and diluted with CH_2Cl_2 (40 ml). The combined organic part was washed with water (50 ml) and dried over Na_2SO_4. The solvents were evaporated to dryness and the residue was dissolved in benzene (20 ml). DBU (3.12 g, 20.5 mmol) was added and the reaction was refluxed for 2 h under an

atmosphere of N_2. Solvents were removed under vacuum and the crude product was purified by column chromatography over silica gel using 40% EtOAc/hexanes as eluent to afford the title product. $[\alpha]^{27}_D$ 30.7 (c=1, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 10H), 6.15 (d, *J* = 3.0 Hz, 1H), 4.93 (d, *J* = 2.0 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.71 (s, 2H), 4.38 (dd, *J* = 7.5 Hz, J = 3.0 Hz, 1H), 3.81 (s, 3H), 3.81 – 3.79 (m, 2H), 3.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.8, 140.8, 138.2, 138.1, 128.7, 128.7, 128.4, 128.3, 128.2, 128.0, 128.0, 128.0, 111.0, 100.1, 76.2, 73.6, 73.4, 72.2, 57.1, 52.6.

Methyl 2,3-di-*O*-benzyl-4-deoxy-hex-4-enopyranoside (217).

To a stirred solution of **216** (1.2 g, 3.08 mmol) in THF (20 ml) was added LAH (293 mg, 7.71 mmol) and the reaction mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with the addition of saturated water (10 ml) and the addition of 1N NaOH (10 ml). The reaction mixture was diluted with EtOAc (30 ml) and filtered through a pad of silate. The combined organic portion was washed with water (30 ml) and dried over Na2SO4. The solvents were evaporated to dryness and the crude product was purified by column chromatography over silica gel using 60% EtOAc/hexanes as eluent to afford the title product. $[\alpha]^{27}_D$ 32.7 (c=1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 10H), 5.02 (d, *J* = 3.0 Hz, 1H), 4.85 (d, *J* = 2.5 Hz, 1H), 4.81 – 4.75 (m, 2H), 4.62 (s, 2H), 4.19 – 4.18 (m, 1H), 4.05 – 4.03 (m, 2H), 3.78 (dd, *J* = 6.5 Hz, *J* = 2.0 Hz, 1H), 3.52 (s, 3H). ^{13} C NMR (125 MHz, $CDCl_3$): δ 138.6, 138.3 (2C), 128.7, 128.6, 128.3, 128.1, 127.9, 127.9, 99.8, 76.1, 73.4, 73.3, 71.5, 62.5, 57.0

Methyl 2,3-di-*O*-benzyl-4,6-dideoxy-6-bromomethyl hex-4-enopyranoside (218).

To a stirred solution of alcohol **217** (760 mg, 2.13 mmol) in CH_2Cl_2 (30 mL) was added triphenylphosphine (670 mg, 2.56 mmol) and carbon tetrabromide (849 mg, 2.56 mmol) at – 78 °C. The reaction mixture was slowly allowed to reach to room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and water (30 ml). The organic portion was separated and dried over Na_2SO_4. The solvents were evaporated to dryness and the crude product was purified by column chromatography over neutral alumina using 30% EtOAc/hexanes as eluent to afford the title product. $[\alpha]^{27}_D$ 43.7 (c=1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 10H), 5.13 (d, *J* = 3.0 Hz, 1H), 4.88 (d, *J* = 2.5 Hz, 1H), 4.83 – 4.75 (m, 2H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.68 – 4.62 (m, 2H), 4.26 (dd, *J* = 7.5 Hz, *J* = 3.0 Hz, 1H), 3.85 (s, 2H), 3.78 (dd, *J* = 7.5 Hz, *J* = 2.5 Hz, 1H), 3.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8, 138.5, 138.3, 128.7, 128.7, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 102.2, 99.8, 76.5, 73.7, 73.4, 72.0, 57.0, 30.6.

Methyl 2,3-di-*O*-benzyl-4,6-dideoxy-6-selenocyanatomethyl hex-4-enopyranoside (211).

Following the general procedure **1**, the title product was obtained in 70% yield and was directly proceeded to the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 10H), 5.09 (d, *J* = 3.0 Hz, 1H), 4.87 (d, *J* = 2.0 Hz, 1H), 4.81 – 4.74 (m, 2H), 4.63 (s, 2H), 4.20 (dd, *J* = 6.5 Hz, *J* = 2.5 Hz, 1H), 3.76 (dd, *J* = 6.0 Hz, *J* = 2.5 Hz, 1H), 3.69 – 3.67 (m, 1H), 3.62 – 3.61

(m, 1H), 3.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.9, 138.4, 138.2, 128.7, 128.7, 128.6, 128.6, 128.3, 128.2, 128.0, 128.0, 128.0, 101.9, 100.2, 75.9, 73.4, 73.1, 71.7, 57.4, 30.8.

Methyl 3-[(3,4-bis(benzyloxy)-2-methoxy-3,4-dihydro-2-*H*-pyran-6-yl)methylselenylthio]-2-(*tert*-butoxycarbonylamino)propanoate (213).

To a stirred solution of crude selenocyanate **211**(180 mg, mmol) in MeOH (5.0 mL) was added Boc-L-Cys-OMe (100 mg, mmol) in MeOH (2.0 mL). The reaction was stirred at room temperature for 2 h. Solvents were evaporated and the crude selenosulfide was purified by column chromatography over silica gel using 50% EtOAc/hexanes as eluent to give the title product 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 10H), 5.33 (d, *J* = 8.0 Hz, 1H), 4.97 (d, *J* = 3.0 Hz, 1H), 4.83 (d, *J* = 2.5 Hz, 1H), 4.81 – 4.74 (m, 2H), 4.65 – 4.64 (m, 2H), 4.56 – 4.53 (m, 1H), 4.17 (dd, *J* = 6.5 Hz, *J* = 2.5 Hz, 1H), 3.78 – 3.74 (m, 1H), 3.73 (s, 3H), 3.54 (s, 3H), 3.50 – 3.46 (m, 3H), 3.29 – 3.22 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 148.7, 138.6, 138.4, 128.7, 128.6, 128.6, 128.3, 128.1, 127.9, 127.8, 100.2, 99.9, 76.1, 73.6, 73.3, 71.5, 57.2, 53.9, 52.7, 40.7, 34.3, 28.6.

1,2-bis[(3,4-bis(benzyloxy)-2-methoxy-3,4-dihydro-2-*H*-pyran-6-yl)methyl]diselane (220).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 20 H), 4.93 (d, *J* = 5.0 Hz, 2H), 4.78 (d, *J* = 4.0 Hz, 2H), 4.74 (d, *J* = 6.5 Hz, 4H), 4.59 (s, 4H), 4.15 (dd, *J* = 11.0 Hz, *J* = 5.0 Hz, 2H), 3.71 (dd, *J* = 12.0 Hz, 4.0 Hz, 2H), 3.54 (s, 4H), 3.50 (s, 6H).

Methyl 2-*O*-benzoyl-6-*O*-(tert-butyldiphenylsilyl)-3,4-dideoxy-α-D-hex-3-eno pyranoside (226).

Following the known literature procedure methyl 2-*O*-benzoyl-6-*O*-(tert-butyldiphenylsilyl)-α-D-glucopyranoside (**225**) was converted to the title product and the characterization data were in agreement with the literature data. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.69 – 7.68 (m, 4H), 7.58 – 7.55 (m, 2H), 7.46 – 7.38 (m, 8H), 6.04 (d, *J* = 10.5 Hz, 1H), 5.81 (d, *J* = 10.5 Hz, 1H), 5.53 (s, 1H), 5.21 (d, *J* = 4.0 Hz, 1H), 4.28 – 4.27 (m, 1H), 3.81 (dd, *J* = 9.5 Hz, *J* = 5.5 Hz, 1H), 3.74 (dd, *J* = 10.5 Hz, *J* = 6.0 Hz, 1H), 3.45 (s, 3H), 1.08 (s, 9H).

Methyl 6-*O*-(tert-butyldiphenylsilyl)-3,4-dideoxy-α-D-hex-3-eno pyranoside (227).

To a stirred solution of **226** (490 mg, 2.0 mmol) in MeOH (20.0 mL) was added a catalytic amount of metallic sodium. The reaction mixture was stirred at room temperature for 2 h and neutralized with Amberlyst 15 H^+ resin. Solvents were removed and the residue was purified by column chromatography over silica gel using 50% EtOAc/hexanes to give the title compound as colorless oil. $[\alpha]_D^{26}$ – 8.0 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.66 (m, 2H), 7.44 – 7.36 (m, 8H), 5.84 (d, *J* = 10.5 Hz, 1H), 5.74 (d, *J* = 10.5 Hz, 1H), 4.86 (d, *J* = 4.0 Hz, 1H), 4.19 – 4.12 (m, 2H), 3.74 (dd, *J* = 10.0 Hz, *J* = 5.5 Hz, 1H), 3.65 (dd, *J* = 10.0 Hz, *J* = 5.5 Hz, 1H), 3.49 (s, 3H), 2.19 (d, *J* = 11.0 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.7, 135.6, 129.7, 127.7, 127.7, 127.4, 98.0, 68.9, 66.1, 64.4, 55.9, 26.8, 19.3

Methyl 2-*O*-sulfonyl methyl-6-*O*-(tert-butyldiphenylsilyl)-3,4-dideoxy-α-D-hex-3-eno pyranoside (228).

To a stirred solution of alcohol **227** (190 mg, 0.48 mmol) in CH_2Cl_2 (10.0 mL) was added triethylamine (0.13 mL, 0.96 mmol) followed by methane sulfonylchloride (0.05 mL, 0.72 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (10.0 mL). The organic part was separated and evaporated to dryness to give the title product in 75% yield as colorless oil. $[\alpha]_D^{26}$ – 18.0 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.67 (m, 5H), 7.46 – 7.38 (m, 5H), 6.06 – 6.04 (m, 1H), 5.79 – 5.76 (m, 1H), 5.22 – 5.20 (m, 1H), 5.11 – 5.10 (m, 1H), 4.27 – 4.25 (m, 1H), 3.78 (dd, *J* = 10.5 Hz, *J* = 5.5 Hz, 1H), 3.73 (dd, *J* = 10.5 Hz, *J* = 5.5 Hz, 1H), 3.51 (s, 3H), 3.00 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 133.3, 133.2, 131.5, 129.9, 129.8, 127.8, 121.8, 96.0, 71.6, 69.5, 65.6, 56.1, 38.8, 26.8, 19.3

Methyl 2-deoxy-2-selenocyanato-6-*O*-(tert-butyldiphenylsilyl)-3,4-dideoxy-α-D-hex-3-eno pyranoside (229)..

To a stirred solution of **228** (130 mg, 0.27 mmol) in THF (5.0 mL) was added potassium selenocyanate (79 mg, 0.54 mmol). The reaction was refluxed for 12 h under an atmosphere of N_2. Solvents were evaporated and the reaction mixture was washed with EtOAc (10.0 mL) and water (10.0 mL). The organic portion was dried over Na_2SO_4 and evaporated to dryness to give the title compound as an inseparable mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 5H + 5H), 7.49 – 7.38 (m, 5H + 5H), 6.30 (dd, *J* = 10.0 Hz, *J* = 5.5 Hz, 1H),

6.10 (d, *J* = 10.5 Hz, 1H), 5.97 – 5.93 (m, 2H), 4.97 (d, *J* = 2.5 Hz, 1H), 4.31 – 4.30 (m, 1H), 4.25 – 4.22 (m, 2H), 4.01 (dd, *J* = 5.5 Hz, *J* = 2.5 Hz, 1H), 3.97 – 3.95 (m, 1H), 3.94 – 3.91 (m, 1H), 3.88 – 3.84 (m, 3H), 3.81 – 3.78 (m, 1H), 3.46 (s, 3H, one isomer), 3.37 (s, 3H, one isomer), 1.08 (s, 9H, one isomer), 1.07 (s, 9H, one isomer). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 135.5, 133.3, 132.3, 130.1, 130.1, 130.0, 129.8, 129.8, 129.6, 128.6, 128.2, 128.0, 127.9 (2C), 127.8 (2C), 127.8, 124.5, 121.7, 120.7, 100.4, 95.4, 95.0, 95.0, 71.5, 71.4, 70.2, 68.8, 68.7, 67.9, 65.7, 65.2, 62.8, 56.2, 56.0, 55.8, 55.8, 55.6, 50.3, 43.4, 42.9, 39.7, 38.8, 26.9, 26.8, 19.4, 19.2.

Methyl 2-deoxy-2-bromo-6-*O*-(tert-butyldiphenylsilyl)-3,4-dideoxy-α-D-hex-3-eno pyranoside (231)..

To a stirred solution of alcohol **227** (200 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) was added triphenylphosphine (158 mg, 0.60 mmol) and carbon tetrabromide (199 mg, 0.60 mmol) at –78 °C. The reaction mixture was slowly allowed to reach to room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 ml) and water (10 ml). The organic portion was separated and dried over Na_2SO_4. The solvents were evaporated to dryness and the crude product was purified by column chromatography over neutral alumina using 30% EtOAc/hexanes as eluent to afford the title product. $[\alpha]_D^{26}$ – 36.0 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 5H), 7.46 – 7.40 (m, 5H), 6.01 – 6.00 (m, 2H), 5.09 (s, 1H), 4.39 – 4.37 (m, 2H), 3.91 (dd, *J* = 10.5 Hz, *J* = 5.0 Hz, 1H), 3.80 (dd, *J* = 10.0 Hz, *J* = 6.5 Hz, 1H), 3.47 (s, 3H), 1.12 (s, 9H).^{13}C NMR (500 MHz, $CDCl_3$) δ

135.7, 135.7, 133.4, 133.4, 129.8, 127.8, 124.3, 100.7, 68.7, 65.7, 56.0, 42.7, 26.9, 19.4.

Methyl 2-deoxy-2-selenocyanato-6-*O*-(tert-butyldiphenylsilyl)-3,4-dideoxy-α-D-hex-3-eno pyranoside (229).

To a stirred solution of **231** (100 mg, 0.22 mmol) in THF (5.0 mL) was added potassium selenocyanate (38 mg, 0.26 mmol). The reaction was refluxed for 16 h under an atmosphere of N_2. Solvents were evaporated and the reaction mixture was washed with EtOAc (10.0 mL) and water (10.0 mL). The organic portion was dried over Na_2SO_4 and evaporated to dryness to give the title compound as an inseparable mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 5H + 5H), 7.49 – 7.38 (m, 5H + 5H), 6.30 (dd, *J* = 10.0 Hz, *J* = 5.5 Hz, 1H), 6.10 (d, *J* = 10.5 Hz, 1H), 5.97 – 5.93 (m, 2H), 4.97 (d, *J* = 2.5 Hz, 1H), 4.31 – 4.30 (m, 1H), 4.25 – 4.22 (m, 2H), 4.01 (dd, *J* = 5.5 Hz, *J* = 2.5 Hz, 1H), 3.97 – 3.95 (m, 1H), 3.94 – 3.91 (m, 1H), 3.88 – 3.84 (m, 3H), 3.81 – 3.78 (m, 1H), 3.46 (s, 3H, one isomer), 3.37 (s, 3H, one isomer), 1.08 (s, 9H, one isomer), 1.07 (s, 9H, one isomer). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 135.5, 132.8, 132.6, 132.4, 130.1, 130.0, 129.8, 129.8, 128.6, 128.2, 127.9, 127.8, 127.7, 120.6, 101.6, 101.6, 100.4, 95.4, 95.0, 68.9, 67.9, 65.6, 65.1, 55.6, 43.4, 42.9, 26.9, 26.8, 19.2.

Dithiocarbonic acid *O*-[4-(*tert*-butyl-dimethyl-silanyloxy)-but-2-enyl] ester *S*-methyl ester. (246).

To a solution of (*E*)-4-(*tert*-butyldimethylsiloxy)-but-2-en-1-ol **245** (2.02 g, 10.0 mmol) in THF (40 mL) was added NaH (520 mg, 13.0 mmol, 60% in mineral

oil) in portion at 0 °C. The solution was stirred for 45 minutes and carbon disulfide (1.5 mL, 25.0 mmol) was added. After 30 minutes, methyl iodide (0.94 mL, 15.0 mmol) was added slowly and the solution was stirred at room temperature for 45 minutes. The reaction was quenched with NH_4Cl and extracted with Et_2O. The organic layer was washed with water, brine and evaporated. Chromatographic purification (hexanes/CH_2Cl_2) afforded **246** (2.56 g, 87%) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 5.80 (m, 1H), 5.69 (m, 1H), 5.19 (d, *J* = 6.6 Hz, 2H), 4.30 (d, *J* = 5.6 Hz, 2H), 2.56 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.8, 135.2, 123.1, 69.8, 60.1, 26.2, 19.4, 18.6, -5.0; EIHRMS Calcd. for $C_{12}H_{24}O_2S_2SiNa$ $[M+Na]^+$ 315.08850, found 315.0870.

Dithiocarbonic acid *S*-[1-(*tert*-butyldimethylsiloxymethyl)-allyl]ester-*S*-methyl ester (247);

Following the general procedure **7**, and eluting with hexanes/CH_2Cl_2 from 95/5 to 80/20 afforded the title product **247** (552 mg, 94%) as yellow oil and the characterization data were in agreement with the literature. ^1H NMR (400 MHz, $CDCl_3$): δ 5.88 (ddd, *J* = 17.0, 10.4, 8.0 Hz, 1H), 5.32 (dt, *J* = 17.0, 1.0 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.32 (m, 1H), 3.78 (m, 2H), 2.41 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 134.9, 118.2, 65.5, 50.6, 26.1, 18.5, 13.3, -5.1, -5.2; EIHRMS Calcd. for $C_{12}H_{24}O_2S_2SiNa$ $[M+Na]^+$: 315.08850, found 315.0884.

2-[1-(*tert*-Butyl-dimethyl-silanyloxymethyl)-allyldisulfanyl]-benzothiazole (248).

To a solution of **247** (838 mg, 2.97 mmol) in THF (7.0 mL) was added ethanolamine (1 mL, 17.2 mmol) and the solution was stirred at room temperature for 4 h. A solution of 2,2'-dithiobis(benzothiazole) (1.9 g, 5.73 mmol) in chloroform (40 mL) was added over a period of 15 min and the reaction mixture was stirred for another 1 h. The reaction mixture was filtered over celite and washed with water extracted with CH_2Cl_2 (20.0 mL), dried over Na_2SO_4 and evaporated. Chromatographic purification (hexane/CH_2Cl_2 from 95/5 to 80/20) afforded the title product as colorless oil and the characterization data were in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.43 (m, 1H), 7.33 (m, 1H), 5.83 (ddd, *J* = 17.1, 10.3, 9.0 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 3.96 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.91 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.75 (dt, *J* = 9.0, 5.7 Hz, 1H), 0.92 (s, 9H), 0.089 (s, 3H), 0.086 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 155.4, 136.1, 133.7, 126.4, 124.7, 122.3, 121.3, 120.3, 64.8, 58.0, 26.1, 18.6, -5.1; EIHRMS Calcd for $C_{17}H_{25}NOS_3SiNa$ $[M+Na]^+$ 406.07655, found 406.0762.

2-(Benzothiazol-2-yldisulfanyl)-but-3-en-1-ol (240).

To a stirred solution of **248** (255 mg, 0.8 mmol) in MeOH/CH_2Cl_2 (2:8) was added PTSA (141 mg, 0.78 mmol) and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (20.0 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Chromatographic purification (hexanes/EA from 95/5 to 80/20) afforded the title product **240** (147 mg, 70%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.45 (m, 1H), 7.35 (m,

1H), 5.92 (m, 1H), 5.33 (d, *J* = 17.9 Hz, 1H), 5.29 (d, *J* = 10.7 Hz, 1H), 3.90 (m, 1H), 3.80-3.73 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 153.1, 136.1, 133.4, 126.8, 125.4, 122.1, 121.5, 120.0, 62.2, 57.3.

4-Vinyl-[1,3]dioxolane-2-thione (250).

To a stirred solution of but-3-ene-1,2-diol **249** (10.0 g, 113.5 mmol) in dichloromethane (200 mL) under a nitrogen atmosphere was added pyridine (19.7 g, 249.7 mmol) followed by DMAP (1.39 g, 11.35 mmol) at 0 ^{o}C. Thiophosgene (14.36 g, 124.8 mmol) dissolved in dichloromethane (100 mL) then was added dropwise over a period of 2 h. The reaction mixture was stirred at room temperature for 3 h and then diluted with 1.0 M HCl (100 mL). The organic part was separated and washed with sat NaCl (100 mL), dried over sodium sulfate and evaporated to dryness. The crude product was purified by column chromatography using EtOAc/hexanes as eluent to give 4-vinyl-[1,3]dioxolane-2-thione (**250**) as a dark yellow liquid. (12.5 g, 85%). IR (neat): 1709 cm^{-1}. ^{1}H NMR (500 MHz): 5.95 (ddd, *J* = 17.5, *J* = 10.0, *J* = 7.0 Hz, 1H), 5.56 (d, *J* = 17.0 Hz, 1H), 5.51 (d, *J* = 10.5 Hz, 1H), 5.34 (q, *J* = 8.0 Hz, 1H), 4.78 (t, *J* = 8.5 Hz, 1H), 4.36 (t, *J* = 8.5 Hz, 1H). ^{13}CNMR (125 MHz): δ 191.7, 131.2, 122.8, 82.7, 73.1. EI^{+}: calc. for $C_5H_6O_2S$ 130.0089, found 130.0064.

4-Vinyl-1,3-oxathiolan-2-one (251).

To a stirred solution of 4-vinyl-[1,3]dioxolane-2-thione (**250**) (5.08 g, 39.07 mmol) in degassed ethanol (150 mL) (0.26 M) was added $Pd(PPh_3)_4$ (904 mg, 0.78 mmol). The reaction mixture was stirred at 75 ^{o}C for 1 h after which the dark brown mixture was cooled to room temperature, and solvents were

evaporated and the product was purified by column chromatography using EtOAc/Hexanes as eluent to give 4-vinyl-1,3-oxathiolan-2-one (**251**) as a colorless oil. (4.0 g, 80%). IR (neat): 1738 cm^{-1}. ^{1}H-NMR (500 MHz): δ 5.89 (ddd, *J* = 17.0, *J* = 10.0, *J* = 7.0 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 4.62 - 4.55 (m, 2H), 4.24 - 4.19 (m, 1H). ^{13}C-NMR (125 MHz): δ 172.8, 133.2, 120.4, 72.7, 51.6. EI^{+}: calc. for $C_5H_6O_2S$ 130.0089, found 130.0089.

2-(Pyridin-2-yldisulfanyl)-but-3-en-1-ol (252).

To a stirred solution of 4-vinyl-1,3-oxathiolan-2-one (**251**) (2.0 g, 15.4 mmol) in dry ether (15 mL) cooled to 0 ^{o}C was added $LiAlH_4$ (584 mg, 15.4mmol). The reaction mixture was stirred at the same temperature for 30 min and then at room temperature for 2 h before ethyl acetate (5 mL) was added followed by the sequential addition of 1.0 M HCl (10.0 mL) and MeOH (10.0 mL). The reaction mixture was stirred at room temperature for 30 min and then filtered through a pad of Celite with washing of the filter pad with MeOH (10.0 mL) and 1.0 M HCl (5.0 mL). The filtrate and washings were transferred to a solution of 2,2'dipyridyl disulfide (3.0 g, 13.62 mmol) in MeOH (10.0 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1 h before the solvents were evaporated and the crude reaction mixture was dissolved in EtOAc (100.0 mL), and washed with sat bicarbonate solution (50 mL). The ethyl acetate portion was further washed with brine solution (50 mL), dried over sodium sulfate, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel using EtOAc/Toluene as eluent to give 2-(pyridin-2-yldisulfanyl)-but-3-en-1-ol (**252**) as a colorless liquid. (1.47 g, 45% for

two steps). ^{1}H-NMR (400 MHz): δ 8.48 (dd, *J* = 1.5 Hz, *J* = 4.8 Hz, 1H), 7.56 (m, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.14 (dd, *J* = 7.2 Hz, *J* = 4.8 Hz, 1H), 5.94 (m, 1H), 5.88 (m, 1H), 5.24 (dd, *J* = 16.5 Hz, *J* = 9.3 Hz, 2H), 3.79 (m, 1H), 3.62 (m, 2H). ^{13}C-NMR (125 MHz,): δ 159.2, 150.0, 137.1, 134.3, 122.2, 121.8, 118.6, 61.4, 56.6. ESIHRMS: calc. for $C_9H_{11}NOS_2Na$ [M+Na^+ 236.0180, found 236.0191.

(*E*)-*S*-Methyl *O*-tridec-2-enyl carbonodithioate (254).

To a solution of *trans*-2-tridecen-1-ol (1.0 g, 3.0 mmol) in benzene (15.0 mL) and THF (2.0 mL) was added NaH (775 mg, 5.4 mmol). Thereaction mixture was stirred at room temperature for 1 hour and CS_2 (0.56 mL, 9.0 mmol) was added. After 30 minutes, methyl iodide (0.35 mL, 5.40 mmol) was added slowly and the milky solution was stirred at room temperatue for 40 minutes. The reaction was quenched with AcOH (3 mL) and filtered through a pad of celite.. The precipitate was washed with Et_2O (2 x 30 mL) and the combined organic layers were evaporated. Chromatographic purification (hexanes/CH_2Cl_2 from 100/0 to 90/10) afforded the title product (1.0g, 80%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (m, 1H), 5.68 (m, 1H), 5.03 (d, *J* = 6.7 Hz, 2H), 2.56 (s, 3H), 2.07 (q, *J* = 6.9 Hz, 2H), 1.40-1.20 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H).

***S*-Methyl *S*-tridec-1-en-3-yl carbonodithioate (255).**

Following the general procedure **7** the title compound was obtained in 90% yield and the characterization data were in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (m, 1H), 5.24 (dt, *J* = 17.0, 1.0 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 4.16 (q, *J* = 7.6 Hz, 1H), 2.40 (s, 3H), 1.68-1.62 (m, 2H), 1.36-1.23 (m, 16H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3,

137.8, 116.8, 48.8, 34.3, 32.2, 29.9, 29.8, 29.7, 29.6, 29.5, 27.3, 23.0, 14.4, 13.3; EIHRMS: Calcd for $C_{15}H_{28}OS_2$ $[M]^+$ 288.15816, found 288.1589.

2-(2-(Tridec-1-en-3-yl)disulfanyl)pyridine (256).

Following the same procedure used for the conversion of compound **251** to Compound **252**, the title product was obtained in 80% yield for the two steps and the characterization data were in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.42 (d, *J* = 4.6 Hz, 1H), 7.71 (dd, *J* = 8.0 Hz, 1H), 7.61 (m, 1H), 7.05 (m, 1H), 5.62 (ddd, *J* = 16.9, 9.7, 9.5 Hz, 1H), 5.09-5.01 (m, 2H), 3.36 (m, 1H), 1.77 (m, 1H), 1.62 (m, 1H), 1.45-1.10 (m, 16H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 161.2, 149.5, 137.4, 137.0, 120.6, 120.0, 117.9, 55.3, 33.6, 32.2, 29.8, 29.7, 29.6, 29.55, 29.4, 27.6, 22.9, 14.4; ESIHRMS Calcd for $C_{18}H_{30}NS_2$ $[M+H]^+$ 324.18142, found 324.18121.

***O*-(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl dimethylcarbamothioate (258).**

To a stirred solution of DMF (8.0 mL) was added sodium hydride (1.12 g, 28 mmol) and *trans*, *trans*-farnesol **257** (5.01 mL, 20 mmol) in DMF (8.0 mL). The reaction mixture was stirred under an atmosphere of N_2 1 h. The reaction mixture was cooled to 0 ºC, and dimethylthiocarbamoyl chloride (3.46 g, 28 mmol) was added in DMF (6.0 mL). The mixture was heated to 60 ºC for 1 h, then cooled to room temperature and poured into 1% KOH (80.0 mL). The aqueous layer was extracted with ether (2 X 50 mL). The ethereal layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. Chromatographic purification afforded the title compound **258** (5.1 g, 85%) as slight yellow oil and the characterization data

were in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.41 (m, 1H), 5.10-5.04 (m, 2H), 4.96 (d, *J* = 7.0 Hz, 2H), 3.35 (s, 3H), 3.09 (s, 3H), 2.12-2.00 (m, 6H), 1.98-1.93 (m, 2H), 1.71 (s, 3H), 1.66 (s, 3H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5, 142.3, 135.6, 131.5, 124.5, 123.9, 118.8, 68.8, 42.9, 39.9, 39.7, 38.0, 26.9, 26.4, 25.9, 17.9, 16.9, 16.3;

ESIHRMS: Calcd for $C_{18}H_{32}NOS$ $[M+H]^+$ 310.21991, found 310.21930.

(*E*)-*S*-3,7,11-trimethyldodeca-1,6,10-trien-3-yl dimethylcarbamothioate (259). Following the general procedure **7**, and eluting with EtOAc/hexanes the title compound was obtained in 85% yield and the characterization data were in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.16 (d, *J* = 17.4 Hz, 1H), 5.13 (d, *J* = 10.6 Hz, 1H), 5.12-5.05 (m, 2H), 2.94 (s, 6H), 2.06-1.84 (m, 8H), 1.67 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 143.3, 135.6, 131.6, 124.6, 124.0, 113.6, 54.4, 40.4, 39.9, 36.7, 27.0, 26.0, 23.8, 23.5, 18.0, 16.3; ESIHRMS Calcd. for $C_{18}H_{32}NOS$ $[M+H]^+$ 310.2199, found 310.3193.

2-(1,5,9-Trimethyl-1-vinyl-deca-4,8-dienyldisulfanyl)-benzothiazole (260). Following the similar procedure used for the conversion of compound **251** to Compound **252**, the title product was obtained in 80% yield for the two steps and the characterization data were in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.41 (m, 1H), 7.31 (m, 1H), 5.84 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.14 (d, *J* = 17.3 Hz, 1H), 5.11 (d, *J* = 10.6 Hz, 1H), 5.12-5.05 (m, 2H), 2.10-1.96 (m, 6H), 1.83-1.78 (m, 2H), 1.68 (s, 3H), 1.59 (s, 6H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 155.0,

140.7, 136.2, 136.0, 131.7, 126.7, 124.7, 124.4, 123.4, 122.3, 121.2, 116.1, 58.1, 39.90, 39.86, 26.8, 26.0, 23.8, 22.8, 18.0, 16.3; ESIHRMS Calcd for $C_{22}H_{29}NS_3$ $[M]^+$ 403.1462, found 403.1447.

Methyl 2-*tert*-butoxycarbonylamino-3-(1-hydroxymethyl-allyldisulfanyl)-propionate (261).

To a stirred solution of 2-(pyridin-2-yldisulfanyl)-but-3-en-1-ol (**252**) (160 mg, 0.75 mmol) in methanol (6.0 mL) was added a solution of *N*-Boc-L-Cys-OMe (176 mg, 0.75 mmol) in methanol (1.5 mL). The reaction mixture was stirred at room temperature under N_2 atmosphere for 4 h before the solvents were removed and the crude product was purified by column chromatography on silica gel using EtOAc/hexanes as eluent to give methyl 2-*tert*-butoxycarbonylamino-3-(1-hydroxymethyl-allyldisulfanyl)-propionate (**261**) as a thick oil (139 mg, 55%). ^{1}H-NMR (500 MHz): δ 5.81 – 5.78 (m, 1H), 5.38 (d, *J* = 8.0 Hz, 1H), 5.35 – 5.26 (m, 2H), 4.64 – 4.62 (m, 1H), 3.94 (d, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 3.57 – 3.49 (m, 1H), 3.22 – 3.11 (m, 2H), 2.23 (br s, 1H), 1.42 (s, 9H), ^{13}C NMR (125 MHz): δ 171.7, 155.6, 134.8, 134.7, 119.7, 119.6, 80.9, 63.6, 57.2, 56.7, 53.5, 53.2, 42.0, 41.8, 28.8. ESIHRMS: calc. for $C_{13}H_{23}NO_5S_2Na$ $[M+Na]^+$ 360.0915, found 360.0933.

(*E*)-*N*-*tert*-Butoxycarbonyl-*S*-(4-hydroxybut-2-enyl)-L-cysteine methyl ester (262).

Following the general procedure (**10**) for the silver nitrate promoted rearrangement of allylic disulfides compound **262** was prepared in 72% yield as an oil. $[\alpha]^{23}_D$ 23.5 (*c* = 1.0); ^{1}H-NMR (500 MHz): δ 5.80 (dd, *J* = 15.0, *J* = 5.0 Hz,

1H), 5.68 (dd, *J* = 15.0, *J* = 6.0 Hz, 1H), 5.28 (d, *J* = 7.5 Hz, 1H), 4.51 (d, *J* = 8.0 Hz, 1H), 4.15 (d, *J* = 5.5 Hz, 2H), 3.78 (s, 3H), 3.17 (d, *J* = 7.0 Hz, 2H), 2.84 (dd, *J* = 14.0, *J* = 5.5 Hz, 2H), 1.90 (br s, 1H), 1.46 (s, 9H). ^{13}C-NMR (125 MHz): δ 172.0, 156.0, 133.3, 127.7, 80.7, 63.2, 53.6, 52.8, 34.3, 33.3, 28.5. ESIHRMS: calc. for $C_{13}H_{23}NO_5SNa$ $[M+Na]^+$ 328.1195, found 328.1183.

***(E)*-4-(4-Chlorophenylsulfanyl)but-2-en-1-ol (263).**

Following the general procedure (**10**) for the silver nitrate promoted rearrangement of allylic disulfides, compound **19** was prepared in 51% yield. ^{1}H NMR (500 MHz, C_6D_6) δ 6.94 – 6.87 (m, 5H), 5.47 – 5.41 (ddd, *J* = 15.0, *J* = 5.0, *J* = 1.3 Hz, 1H), 5.33 – 5.28 (ddd, *J* = 15.4, *J* = 5.0, *J* = 1.0 Hz, 1H), 3.60 (d, *J* = 4.5 Hz, 2H), 3.05 (dd, *J* = 7.0, *J* = 1.0 Hz, 2H) ^{13}C NMR (125 MHz) δ 135.2, 133.3, 132.1, 131.0, 129.0, 125.4, 62.4, 35.7

1-*tert*-Butyldimethylsilyloxy-2-(pyridin-2-yldisulfanyl)-but-3-ene (264).

To a stirred solution of 2-(pyridin-2-yldisulfanyl)-but-3-en-1-ol (**252**) (1.0 g, 4.69 mmol) in DMF (10.0 mL) under a nitrogen atmosphere was added imidazole (319 mg, 4.69 mmol) followed by *tert*-butyldimethylsilyl chloride (716 mg, 4.69 mmol) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL). The organic part was washed with saturated NaCl solution (50 mL), dried over sodium sulfate and evaporated to dryness. The crude product was purified by column chromatography on silica gel using EtOAc/Hexanes as eluent to give the title product (**264**) as oil. (1.20 g, 80%). ^{1}H-NMR (500 MHz): δ 8.44 (ddd, *J* = 5.0, *J* = 2.0, *J* = 1.0 Hz, 1H), 7.56 (m, 1H), 7.38 (d, *J* = 7.8 Hz, 1H),

7.14 (dd, *J* = 7.2, *J* = 4.8 Hz, 1H), 5.94 (m, 1H), 5.88 (m, 1H), 5.24 (dd, *J* = 16.5, *J* = 9.3 Hz, 2H), 3.79 (m, 1H), 3.62 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C-NMR (125 MHz): δ 161.2, 149.5, 137.1, 134.5, 120.6, 119.8, 119.2, 64.7, 57.1, 26.1, 18.6, -5.1. ESIHRMS: calc. for $C_{15}H_{25}NOS_2SiNa$ $[M+Na]^+$ 350.1045, found 350.1042.

(*E*)-*S*-4-Hydroxybut-2-enyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (265).

To a stirred solution of 1-*tert*-butyldimethylsilyloxy-2-(pyridin-2-yldisulfanyl)-but-3-ene (**264**) (115mg, 0.35mmol) in MeOH (2.0 mL) was added 1-thio-β-D-glucose tetraacetate **91** (100 mg, 0.29 mmol) under a nitrogen atmosphere. The yellow colored solution was stirred at room temperature for 1 h before the solvents were removed and the crude reaction mixture was purified by column chromatography on silica gel to give the mixed disulfide. The mixed disulfide (78 mg, 0.13 mmol) was dissolved in MeOH (2.0 mL) and silver nitrate (46 mg, 0.27 mmol) was added. The reaction mixture was stirred at room temperature under a N_2 atmosphere in the dark for 16 h before NaCl (75 mg, 1.3 mmol) was added and the solution was stirred for 3-4 h and then diluted with MeOH (10.0 mL) , centrifuged. The supernatant were evaporated to give the crude product which was purified by column chromatography on silica gel using EtOAc/Hexanes as eluent to give **265** (45 mg, 67%). $[\alpha]^{23}_D$ -49.5 (*c* = 1.0); ^{1}H NMR (500 MHz) δ 5.78 (ddd, *J* = 15.5, *J* = 5.0, *J* = 5.0 Hz, 1H), 5.71 (dddd, *J* = 15.5, *J* = 6.5, *J* = 6.5, *J* = 1.0 Hz, 1H), 5.22 (dd, *J* = 9.6, *J* = 9.5 Hz, 1H), 5.07 (dd, *J* = 9.6, *J* = 9.5 Hz, 1H), 5.06 (dd, *J* = 9.6, *J* = 9.5 Hz, 1H), 4.50 (d, *J* = 10.0

Hz,1H), 4.24 (dd, *J* = 12.0, *J* = 5.0 Hz, 1H), 4.18 - 4.10 (m, 2H), 4.15 (dd, *J* = 12.0, *J* = 2.0 Hz, 1H), 3.68 (ddd, *J* = 9.5, *J* = 5.0, *J* = 2.0, 1H), 3.38 (dd, *J* = 13.5, *J* = 7.5, 1H), 3.26 (ddd, *J* = 13.5, *J* = 6.0, *J* = 1.0 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.77 (br s, 1H). ^{13}C NMR (125 MHz) δ 170.9, 170.5, 169.7, 169.6, 133.0, 127.2, 82.2, 76.0, 74.1, 70.2, 68.6, 63.0, 62.4, 31.6, 20.9, 20.9, 20.8, 20.8 ESIHRMS: calc. for $C_{18}H_{26}O_{10}SNa$ $[M+Na]^+$ 457.1144, found 457.1138.

Tridec-2-enyl-(tetra-*O*-acetyl-1-thio-β-D-glucopyranoside) (266).

Following the general procedure (**10**) for the silver nitrate promoted rearrangement of allylic disulfides the title compound **266** was prepared in 62% yield with spectral data consistent with the literature. ^{1}H-NMR (500 MHz): δ 5.60-5.54 (m, 1H), 5.44-5.39 (m, 1H), 5.20 (d, *J* = 9.5 Hz, 1H), 5.10-5.05 (m, 2H), 4.47 (d, *J* = 10.0 Hz, 1H), 4.25 (dd, *J* = 11.0 Hz, *J* = 5.5 Hz, 1H), 4.13 (dd, *J* = 12.5 Hz, *J* = 2.5 Hz, 1H), 3.66 -3.63 (m, 1H), 3.55 (dd, *J* = 13.0 Hz, *J* = 8.0 Hz, 1H), 3.20 (dd, *J* = 12.5 Hz, *J* = 6.5 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03(s, 3H), 2.01(s, 3H), 1.4 (m, 3H), 1.27 (m, 15H), 0.88 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR (125 MHz): δ 170.8, 170.5, 169.6, 135.4, 124.7, 82.1, 75.9, 74.2, 70.2, 68.6, 62.5, 32.5, 32.4, 32.1, 29.8, 29.7, 29.6, 29.5, 22.9, 20.9, 20.9, 20.8, 20.8, 14.3.

3,7,11-Trimethyl-dodeca-2,6,10-trienyl-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (267).

To a stirred solution of 2-(1,5,9-trimethyl-1-vinyl-deca-4,8-dienyldisulfanyl)-benzothiazole (**260**) (78 mg, 0.19 mmol) in methanol (3.0 mL) was added triethylamine (27 µL, 0.19 mmol) followed by 1-thio-β-D-glucose tetraacetate (**91**)

(54 mg, 0.16 mmol). After1 h, silver nitrate (58 mg, 0.34 mmol) was added and the reaction mixture was stirred under a N_2 atmosphere in the dark for 48 h. After following the general work up procedure the crude product was purified by column chromatography to give the title product (**267**) in 50% yield with spectral data consistent with the literature. ^{1}H-NMR (500 MHz): δ 5.23-5.19 (m, 2x2H), 5.11-5.04 (m, 2x4H), 4.44 (dd, *J* = 10.0 Hz, *J* = 3.0 Hz, 1H), 4.27-4.23 (m, 1H), 4.15 (d, *J* = 11.0 Hz, 1H), 3.65-3.63 (m, 1H), 3.52-3.45 (m, 1H), 3.20-3.16 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03(s, 3H), 2.01(s, 3H), 1.68-1.67 (m, 6H), 1.61 (s, 8H). ^{13}C-NMR (125 MHz): δ 170.8, 170.5, 170.4, 169.6, 140.6, 135.7, 131.5, 124.5, 124.4, 123.8, 123.7, 119.9, 119.1, 82.7, 82.4, 76.1, 76.0, 74.2, 70.0, 78.6, 68.5, 62.5, 62.4, 39.9, 39.8, 31.8, 27.5, 26.9, 26.9, 26.8, 26.7, 25.9, 23.7, 20.9, 20.9, 20.8, 20.8, 17.9, 16.2, 16.1.

***N-tert*-Butoxycarbonyl-*S*-(tridec-2-enyl)glutathione dimethyl ester (268).** Following the general procedure (**10**) for the silver nitrate promoted rearrangement of allylic disulfides the title compound **268** was prepared in 61% yield with spectral data consistent with the literature. ^{1}H-NMR (500 MHz): δ 7.06 (br s, 1H), 6.77 (d, *J* = 6.0 Hz, 1H), 5.64-5.58 (m, 1H), 5.42-5.32 (m, 2H), 4.56 (d, *J* = 7.5 Hz, 1H), 4.39 (m, 1H), 4.13-3.98 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.15 (d, *J* = 7.5 Hz, 2H), 2.92-2.80 (m, 2H), 2.36-2.35 (m, 2H), 2.05-2.01 (m, 3H), 1.44 (s, 9H), 1.35-1.26 (m, 16H), 0.88 (t, *J* = 7.0 Hz, 3 H). ^{13}C-NMR (125 MHz): δ 173.1, 172.3, 170.9, 170.1, 155.9, 136.5, 135.3, 125.2, 124.3, 80.4, 68.2, 52.9, 52.7, 52.6, 52.5, 41.5, 34.5, 32.6, 32.5, 32.4, 32.3, 32.1, 29.8, 29.7, 29.5, 29.5, 29.4, 28.9, 28.5, 27.5, 25.8, 22.9, 14.4.

***N-tert*-Butoxycarbonyl-*S*-(3,7,11-trimethyldodeca-2,6,10-trienyl)glutathione dimethyl ester (269).**

To a stirred solution of 2-(1,5,9-trimethyl-1-vinyl-deca-4,8-dienyldisulfanyl)-benzothiazole (**260**) (120 mg, 0.30 mmol) in methanol (5.0 mL) was added triethylamine (38 µL, 0.27 mmol) followed by Boc-(α-OMe)-*γ*-L-Glu-L-Cys-Gly-OMe (**192**) (100 mg, 0.23 mmol). After 1 h, silver nitrate (78 mg, 0.46 mmol) was added and the reaction mixture was stirred under a N_2 atmosphere in the dark for 16 h. After following the general work up procedure the crude product was purified by column chromatography on silica gel to give the title product in 60% yield with spectral data consistent with the literature. ^{1}H-NMR (500 MHz): δ 7.04 (br s, 1H), 6.76 (br s, 1H), 5.30-5.24 (m, 2H), 5.11-5.08 (m, 2H), 4.59-4.57 (m, 1H), 4.41 (br s, 1H), 4.12-3.98 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.27-3.21 (m, 2H), 2.95-2.84 (m, 2H), 2.39-2.36 (m, 2H), 2.21-2.12 (m, 1H), 2.09-2.04 (m, 6H), 1.99-1.96 (m, 3H), 1.69 (s, 6H), 1.66 (s, 3H), 1.61 (s, 3H), 1.45 (s, 9H). ^{13}C-NMR (125 MHz): δ 173.1, 172.4, 170.9, 170.2, 155.9, 140.2, 135.8, 135.5, 131.5, 131.5, 124.5, 124.5, 123.9, 123.9, 123.8, 120.6, 119.8, 80.3, 53.0, 52.7, 52.6, 41.5, 39.9, 39.8, 33.2, 32.3, 32.0, 30.1, 30.0, 28.7, 28.5, 26.9, 26.9, 26.7, 26.6, 25.9, 23.6, 17.9, 16.4, 16.2.

***N-tert*-Butoxycarbonyl-*S*-(4-hydroxybut-2-enyl)glutathione dimethyl ester (270).**

Following the general procedure for the silver nitrate promoted rearrangement of allylic disulfides, a stirred solution of 2-(pyridin-2-yldisulfanyl)-but-3-en-1-ol (**252**) (70 mg, 0.25 mmol) in methanol (5.0 mL) was treated with

Boc-(α-OMe)-*γ*-L-Glu-L-Cys-Gly-OMe (**192**) (108 mg, 0.25 mmol). The reaction mixture was stirred under a N_2 atmosphere for 12 h before silver nitrate (85 mg, 0.50 mmol) was added and the mixture stirred in the dark for 16 h before the general work up procedure was applied. The crude product was purified by column chromatography on silica gel using $CHCl_3$/MeOH as eluent to give the title product (**17**) in 65% yield. $[\alpha]^{23}_D$ -2.0 (*c* 0.85); ^{1}H NMR (400 MHz) δ 7.16 (br s, 1H), 6.93 – 6.91 (d, *J* = 7.6 Hz, 1H), 5.87 – 5.80 (m, 1H), 5.72 -5.65 (m, 1H), 5.39 – 5.37 (d, *J* = 7.6 Hz, 1H), 4.64 – 4.59 (q, *J* = 7.2 Hz, 1H), 4.37 (brs, 1H), 4.12 (s, 2H), 4.03 – 4.02 (d, *J* = 5.6 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.27 (br s, 1H), 3.20 – 3.18 (d, *J* = 7.2, 2H), 2.90 – 2.86 (m, 1H), 2.80 – 2.76 (m, 1H), 2.37 – 2.33 (m, 2H), 2.17 – 2.14 (m, 1H), 1.94 – 1.91 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz) δ 173.1, 172.6, 170.9, 170.3, 156.1, 133.4, 128.4, 80.6, 63.1, 53.0, 52.9, 52.7, 41.5, 34.5, 33.0, 32.4, 29.0, 28.6. ESIHRMS: calc. for $C_{21}H_{35}N_3O_9SNa$ $[M+Na]^+$ 528.19920, found 528.2016.

(*E*)-*S*-(4-hydroxybut-2-enyl)-glutathione (272).

Glutathione (**271**) (29 mg, 0.09 mmol) was dissolved in 2 mL Tris buffer (0.2M, pH 8) and the resulting solution was treated with 2-(pyridin-2-yldisulfanyl)but-3-en-1-ol (**252**) (75 mg, 0.35 mmol) dissolved in 2.0 mL CH_3CN/THF (1:1). The reaction mixture was stirred at room temperature for 12 h after which excess disulfide and liberated pyridinethiol were removed by washing with t-butyl methyl ether (5 mL). The residue was dissolved in water (3 mL) and treated with silver nitrate (2.2 equiv). The yellow suspension was allowed to stir for 24 h and then treated with 3 mL of 5% dil HCl and centrifuged. The

supernatant was injected into a reversed-phase HPLC system for purification using a gradient of 100% A to 50% B developed over 50 min (A, 0.1% TFA/CH_3CN; B, 0.1% TFA/H_2O; column. Varian Microsorb C_{18} 250 x 21.4 mm; flow rate. 10 mL/min; UV detection. 215nm). Lyophillization of the fraction eluting at 19 min afforded the rearranged glutathione **272** in 85% yield as white foam. $[\alpha]^{23}_D$ -23.2 (*c* 0.8, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 5.80 – 5.74 (m, 1H), 5.69 – 5.64 (m, 1H), 4.53 (dd, *J* = 11.5, *J* = 6.0Hz, 1H), 4.06 (d, *J* = 5.0 Hz, 2H), 3.97 (d, *J* = 8.0 Hz, 2H), 3.61 (t, *J* = 8.5 Hz, 1H), 3.18 (d, *J* = 8.0 Hz, 2H), 2.99 (dd, *J* = 17.5, *J* = 6.0 Hz, 1H), 2.70 (dd, *J* = 17.0, *J* = 11.5 Hz, 1H), 2.57 – 2.50 (m, 2H), 2.48 – 2.03 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.9, 172.7, 172.4, 170.4, 132.8, 126.9, 61.8, 54.2, 53.2, 40.7, 33.2, 32.1, 31.7, 26.6 ESIHRMS: calc. for $C_{14}H_{23}N_3O_7SNa$ $[M+Na]^+$ 400.1154, found 400.1150.

(*E*)-*S*-[4-(β-D-Galactopyranosyloxy)but-2-enyl]glutathione (274).

Glutathione (11 mg, 0.03 mmol) was dissolved in 0.5 mL Tris buffer (0.2M, pH 8) to which 2-(2-pyridyldisulfanyl)-3-enyl β-D-galactopyranoside (**273**) (37.5 mg, 0.10 mmol) dissolved in 0.5 mL CH_3CN was added. The reaction mixture was stirred at room temperature for 16 h before the excess disulfide and liberated pyridine thiol were removed by washing with t-butyl methyl ether (5 mL). The residue was dissolved in water (3 mL) and treated with silver nitrate (2.2 eq). The yellow suspension was allowed to stir for 24 h and then was treated with 3 mL of 5% dil HCl and centrifuged. The supernatant was injected into a reversed-phase HPLC system for purification to give the product in 65% yield whose spectral data were consistent with the literature. ^1H NMR (500 MHz, D_2O) δ 5.69

– 5.66 (m, 2H), 4.43 (dd, *J* = 8.0, *J* = 5.5 Hz, 1H), 4.29 (d, *J* = 8.0 Hz, 1H), 4.27 (dd, *J* = 12.5, *J* = 4.0 Hz, 1H), 4.11 (dd, *J* = 12.0, *J* = 5.0 Hz, 1H), 3.88 (s, 2H), 3.83 – 3.78 (m, 2H), 3.67 – 3.59 (m, 2H), 3.55 – 3.49 (m, 2H), 3.39 (dd, *J* = 10.0, *J* = 8.0 Hz, 1H), 3.11 (d, *J* = 6.0 Hz, 1H), 2.88 (dd, *J* = 14.0, *J* = 5.5 Hz, 1H), 2.71 (dd, *J* = 14.0, *J* = 8.5 Hz, 1H), 2.46 – 2.41 (m, 2H), 2.09 – 2.41 (m, 2H). ^{13}C NMR (125 MHz, D_2O) δ 174.7, 173.2, 173.0 (2C), 130.6, 128.9, 101.8, 75.3, 72.9, 70.9, 69.5, 68.8, 61.1, 53.2, 53.1, 41.4, 32.9, 31.7, 31.2, 25.9.

(*Z*)-4-(2-Naphthylmethyloxy)but-2-ene-1-ol (275).

To a stirred solution of *cis*-1,4-but-2-ene-diol **244** (2.39 g, 27.1 mmol) in THF (10 mL) under an atmosphere of N_2 was added sodium hydride (0.38 g, 9.5 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. 2-(Bromomethyl)-naphthalene (2.0 g, 9.0 mmol) was added and the reaction was continued at room temperature for 2 h and heated at reflux for 6h. The reaction mixture was cooled to room temperature, diluted with saturated NH_4Cl solution (30 mL) and ethylacetate (20 mL). The organic portion was separated, dried over sodium sulfate and evaporated to dryness. The crude product was purified over silica gel using EtOAc/hexanes as eluent to give the title compound **275** as thick oil (1.76 g, 85%). ^{1}H NMR (500 MHz): δ 7.87 – 7.85 (m, 3H), 7.80 (s, 1H), 7.51 – 7.48 (m, 3H), 5.83 (dt, *J* = 11.0 Hz, *J* = 6.0 Hz, 1H), 5.78 (dt, *J* = 11.0 Hz, *J* = 6.0 Hz, 1H), 4.69 (s, 2H), 4.17 (d, *J* = 6.0 Hz, 2H), 4.13 (d, *J* = 6.5 Hz, 2H), 2.39 (br s, 1H). ^{13}C NMR (125 MHz): δ 135.6, 133.5, 133.3, 132.8, 128.5, 128.3, 128.1, 127.9, 126.9, 126.4, 126.2, 126.1, 72.8, 65.9, 58.8. ESIHRMS: calc. for $C_{15}H_{16}O_2Na$ $[M+Na]^+$ 251.1048, found 251.1055

1,2:5,6-Di-*O*-isopropylidene-3-*O*-4-(2-naphthylmethyloxy)but-2*Z*-enyl-α-D-glucofuranose (277).

To a stirred solution of (*Z*)-4-(2-naphthylmethyloxy)but-2-ene-1-ol **275** (1.76 g, 7.71 mmol) in dichloromethane (20 mL) under an atmosphere of N_2 was added triethylamine (1.60 mL, 11.56 mmol) followed by DMAP (94 mg, 0.77 mmol) at 0 °C. A solution of methanesulfonyl chloride (0.75 mL, 9.64 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred for 2 h and then diluted with saturated NaCl solution (20 mL). The organic portion was separated and the aqueous part was again washed with dichloromethane (15 mL). The combined organic part was dried over sodium sulfate and evaporated to dryness. The crude mesylate (2.36 g, ~ 100%) was used immediately without any purification. To a stirred solution of diacetone-D-glucose **276** (2.0 g, 7.7 mmol) in dimethylformamide (10.0 mL) was added sodium hydride (338 mg, 8.5 mmol) at 0 °C. The reaction was stirred at room temperature for 1 h followed by the addition of the crude mesylate (2.36 mmol, 7.7 mmol) in dimethylformamide (50 mL). The reaction is stirred at 60 °C for 12 h and diluted with water (100 mL) and ethylacetate (100 mL). The organic part was separated and washed with saturated NaCl solution (100 mL), dried over sodium sulfate and evaporated to dryness. The crude product was purified by column chromatography using EtOAc/hexanes as eluent to give the title product **277** as thick gum (2.61 g, 72%). $[\alpha]^{23}_{D}$ -2.0 (*c* 0.85); ^{1}H NMR (500 MHz): δ 7.86 – 7.84 (m, 3H), 7.80 (s, 1H), 7.51 – 7.47 (m, 3H), 5.87 (d, *J* = 4.0 Hz, 1H), 5.85 – 5.83 (m, 1H), 5.79 – 5.74 (m, 1H), 4.69 (s, 2H), 4.52 (d, *J* = 4.0 Hz, 1H), 4.32 – 4.28 (m, 1H), 4.26 –

4.22 (dd, *J* = 13.0 Hz, 6.5 Hz, 1H), 4.19 (d, *J* = 6.0 Hz, 1H), 4.17 – 4.15 (m, 2H), 4.13 – 4.11(m, 1H), 4.09 – 4.07 (m, 1H), 4.03 – 3.99 (m, 1H), 3.92 (d, *J* = 3.0 Hz, 1H) 1.51 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H) .^{13}C NMR (125 MHz): δ 135.8, 133.5, 133.3, 130.0, 129.3, 128.5, 128.1, 127.9, 126.7, 126.4, 126.2, 125.9, 112.0, 109.2, 105.5, 83.0, 81.8, 81.4, 72.7, 72.6, 67.6, 66.5, 66.0, 27.1, 27.0, 26.5, 25.6. ESIHRMS: calc. for $C_{27}H_{34}O_7Na$ $[M+Na]^+$ 493.2202, found 493.2216

1,2,4,6-tetra-*O*-acetyl-3-*O*-[(*Z*)-4-(2-naphthylmethyloxy)but-2-enyl]-D-α,β-glucopyranoside (278).

Following the general procedure **3**, and eluting with 50% EtOAc/hexanes the title compound was obtained in 89% yield. ^{1}H NMR (500 MHz): δ 7.84 - 7.83 (m, 3H), 7.78 (s, 1H) 7.50 – 7.46 (m, 3H), 6.29 (d, *J* = 3.5 Hz, 1H), 5.81 – 5.77 (m, 1H), 5.67 – 5.58 (m, 2H), 5.09 – 5.03 (m, 2H), 4.99 – 4.97 (m, 1H), 4.67 (s, 2H, major), 4.66 (s, 2H, minor), 4.25 – 4.13 (m,3H), 4.12 – 4.04 (m, 3H), 4.00 – 3.97 (m, 1H), 3.81 (t, *J* = 9.5 Hz, 1H), 3.64 – 3.62 (m, 1H), 3.58 – 3.54 (m, 1H), 2.12 – 1.97 (s, 12H major + 12H minor). ^{13}C NMR (125 MHz): δ 170.9, 169.7, 169.4, 169.2, 168.9, 135.7, 133.5, 133.2, 129.6, 129.4, 129.3, 129.2, 128.5, 128.5, 128.1, 128.0, 127.9, 126.7, 126.7, 126.4, 126.2, 125.9, 125.9, 92.1, 89.6, 79.7, 76.6, 73.2, 72.7, 71.6, 71.5, 70.4, 69.3, 69.1, 68.4, 67.8, 65.9, 65.8, 62.0, 61.9, 21.0, 20.9, 20.8, 20.7. ESIHRMS: calc. for $C_{29}H_{34}O_{11}Na$ $[M+Na]^+$ 581.1999, found 528.1998.

2,4,6-tri-*O*-acetyl-3-*O*-[(*Z*)-4-(2-naphthylmethyloxy)but-2-enyl]-α-D-glucopyranosyl trichloroacetimidate (279).

Following the general procedure **4,** and eluting with 40% EtOAc/hexanes the title compound was obtained in 76% yield. $[\alpha]^{23}_{D}$ 63.8 (*c* = 1); ^{1}H NMR (500 MHz): δ 8.67 (s, 1H), 7.85 – 7.82 (m, 3H), 7.78 (s, 1H), 7.50 – 7.46 (m, 3H), 6.5 (d, *J* = 3.5 Hz, 1H), 5.83 – 5.78 (m, 1H), 5.68 – 5.64 (m, 1H), 5.12 (t, *J* = 10.0 Hz, 1H), 5.01 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1H), 4.68 (d, *J* = 4.5 Hz, 2H), 4.27 – 4.18 (m, 3H), 4.13 – 4.07 (m, 4H), 3.92 (t, *J* = 10.0 Hz, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (125 MHz): δ 170.9, 169.9, 169.5, 160.8, 135.7, 133.5, 133.2, 129.6, 129.3, 128.5, 128.0, 127.9, 126.7, 126.4, 126.2, 125.9, 93.5, 91.1, 76.5, 72.7, 72.1, 70.7, 69.1, 68.5, 65.8, 61.9, 20.9, 20.9, 20.7. ESIHRMS: calc. for $C_{29}H_{32}Cl_3NO_{10}Na$ $[M+Na]^+$ 682.0989, found 682.0999.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-[(*Z*)-4-(2-napthylmethyloxy)but-2-enyl]-β-D-glucopyranoside (280).

Following the general procedure **5,** and eluting with 60% EtOAc/hexanes the title compound was obtained in 75% yield. $[\alpha]^{23}_{D}$ -14.5 (*c* =1); ^{1}H NMR (500 MHz): δ 7.85 -7.83 (m, 3H), 7.79 (s, 1H), 7.49 – 7.46 (m, 3H), 5.81 – 5.76 (m, 1H), 5.64 – 5.58 (m, 1H) 5.03 (t, *J* = 10.0 Hz, 1H), 4.94 (dd, *J* = 9.5 Hz, *J* = 8.0 Hz, 1H), 4.68 (s, 3H), 4.27 (d, *J* = 8.0 Hz, 1H), 4.20 (dd, *J* = 12.0 Hz, *J* = 5.0 Hz, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 4.11 (d, *J* = 3.0 Hz, 1H), 4.09 - 4.08 (m, 2H), 3.55 – 3.50 (m, 2H), 3.46 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (125 MHz): δ 171.0, 169.5, 169.4, 135.7, 133.5, 133.2, 129.4, 128.4, 128.1, 127.9, 126.7, 126.4, 126.2, 125.9, 101.9, 79.8, 72.7 (2C), 72.5, 72.2, 69.7, 67.3, 65.8, 62.5, 56.9, 21.1, 20.9 (2C). ESIHRMS: calc. for $C_{28}H_{34}O_{10}Na$ $[M+Na]^+$ 553.2050, found 528.2064.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-[(*Z*)-4-hydroxybut-2-enyl]-β-D-glucopyranoside (281).

Following the general procedure **6,** and eluting with 40% EtOAc/hexanes the title compound was obtained in 88% yield. $[\alpha]^{23}_{D}$ -25.4 (*c* = 1); ^{1}H NMR (500 MHz): δ 5.77 – 5.72 (m, 1H), 5.55 – 5.51 (m, 1H), 5.06 (t, *J* = 9.50 Hz, 1H), 4.98 – 4.95 (m, 1H), 4.34 (d, *J* = 8.0 Hz, 1H), 4.23 (dd, *J* = 12.0 Hz, *J* = 5.0 Hz, 1H), 4.15 – 4.11 (m, 5H), 3.62 – 3.58 (m, 2H), 3.48 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (125 MHz): δ 171.1, 169.8 (2C), 132.4, 127.9, 101.9, 79.8, 72.2 (2C), 69.3, 66.3, 62.5, 58.6, 57.1, 21.2, 21.1, 21.0. ESIHRMS: calc. for $C_{17}H_{26}O_{10}Na$ $[M+Na]^{+}$ 413.1424, found 413.1425.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-[(2-phenyloxycarbonylthioxy)but-3-enyl]-β-D-glucopyranoside (282).

Following the general procedure **7,** and eluting with 45% EtOAc/hexanes the title compound was obtained in 90% yield. $[\alpha]^{23}_{D}$ -11.5 (*c* = 1); ^{1}H NMR (500 MHz): δ 7.45 – 7.42 (m, 2H), 7.32 – 7.29 (m, 1H), 7.12 – 7.10 (m, 2H), 5.84 – 5.79 (m, 1H), 5.76 – 5.72 (m, 1H), 5.10- 5.06 (m, 3H), 5.01 – 4.97 (m, 1H), 4.35 (d, *J* = 7.50 Hz, 1H), 4.26 – 4.24 (m, 2H), 4.22 (d, *J* = 5.0 Hz, 1H), 4.13 (dd , *J* = 12.5 Hz, *J* = 2.5 Hz, 1H), 3.65 – 3.59 (m, 2H), 3.48 (s. 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H) ^{13}C NMR (125 MHz): δ 195.1, 171.0, 169.5, 169.5, 153.7, 131.9, 129.8, 126.9, 125.1, 122.1, 101.9, 80.0, 72.4, 72.2, 69.6, 69.5 (2C), 67.2 (2C), 62.4, 57.0, 21.2, 21.1, 21.0. ESIHRMS: calc. for $C_{24}H_{30}O_{11}SNa$ $[M+Na]^{+}$ 549.1407, found 549.1398.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-[(2-phenyloxycarbonylthioxy)but-3-enyl]-β-D-glucopyranoside (283).

Following the general procedure **8**, and eluting with 45% EtOAc/hexanes the title compound was obtained in 90% yield. ^{1}H NMR (500 MHz): δ 7.39 – 7.36 (m, 2H), 7.26 – 7.23 (m, 1H), 7.15 – 7.14 (m, 2H), 5.93 – 5.85 (m, 1H), 5.33 (d, *J* = 17.0 Hz, 1H), 5.19 (d, *J* = 10.5 Hz, 1H), 5.10 (t, *J* = 10.0 Hz, 1H), 5.03 – 4.99 (m, 1H), 4.33 (dd, *J* = 8.0 Hz, *J* = 3.0 Hz, 1H), 4.25 – 4.21 (m, 1H), 4.15 – 4.11 (m, 1H), 4.09 – 4.05 (m, 1H), 3.86 – 3.80 (m, 2H), 3.62 – 3.58 (m, 2H), 3.48 (s, 3H, major + minor), 2.12 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H X 3 minor). ^{13}C NMR (125 MHz): δ 171.0, 169.6, 169.5, 169.4 (2 C), 151.3, 134.1, 134.0, 129.7, 126.5, 121.5, 118.7 (2 C), 102.0, 81.0, 73.9, 73.8, 72.2 (2 C), 69.6, 69.5, 62.4, 57.0, 48.9 (2 C), 21.3, 21.2 (2 C), 21.1, 21.0. ESIHRMS: calc. for $C_{24}H_{30}O_{11}SNa$ $[M+Na]^+$ 549.1407, found 549.1385.

Methyl 3-*O*-[(2-pyridin-2-yldisulfanyl)but-3-enyl]-β-D-glucopyranoside (284). Following the general procedure **9,** and eluting with 5% MeOH/CH_2Cl_2 the title compound was obtained in 76% yield. ^{1}H NMR (500 MHz, CD_3OD): δ 8.37 – 8.36 (m, 1H), 7.93 – 7.91 (m, 1H), 7.81 – 7.78 (m, 1H), 7.22 – 7.19 (m, 1H), 5.87 – 5.79 (m, 1H), 5.24 – 5. 21 (m, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 4.17 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 4.13 – 4.09 (m, 1H), 4.07 – 4.06 (m, 1H), 4.04 – 4.01 (m, 1H), 3.88 -3.85 (m, 1H), 3.81 – 3.77 (m, 1H), 3.69 – 3.65 (m, 1H), 3.53 (s, 3H + 3H, two isomers), 3.32 (m, 5H), 3.28 – 3.19 (m, 3H). ^{13}C NMR (125 MHz): δ 160.7, 148.8, 137.8, 134.6, 134.5, 121.0, 120.3, 118.1, 104.2, 85.9, 76.7, 73.8,

73.7 (2C), 70.1, 70.0, 61.4, 56.2, 54.9. ESIHRMS: calc. for $C_{15}H_{21}NO_6S_2Na$ $[M+Na]^+$ 398.0708, found 398.0700.

Methyl 3-*O*-[4-(1-thio-β-D-glucopyranosyl)but-2*E*-enyl]-β-D-glucopyranoside (285).

Following the general procedure **10**, and eluting with 12% MeOH/CH_2Cl_2 the title compound was obtained in 70% yield. $[\alpha]^{23}_D$ -45.1 (*c* = 1); ^{1}H NMR (500 MHz, CD_3OD) δ 5.79 – 5.77 (m, 2H), 4.38 (d, *J* = 9.5 Hz, 1H), 4.35 – 4.34 (m, 2H), 4.19 – 4.18 (m, 1H), 3.89 – 3.86 (m, 2H), 3.70 – 3.63 (m, 2H), 3.53 (s, 3H), 3.50 – 3.46 (m, 1H), 3.32 – 3.31 (m, 3H), 3.29 – 3.27 (m, 2H), 3.26 – 3.22 (m, 4H). ^{13}C NMR (125 MHz) δ 130.3, 128.9, 104.2, 84.3, 83.9, 80.5, 78.5, 76.6, 73.9, 73.2, 72.7, 70.5, 70.1, 61.8, 61.5, 56.1, 30.9. ESIHRMS: calc. for $C_{17}H_{30}O_{11}SNa$ $[M+Na]^+$ 465.1401, found 465.1407.

2,4,6-Tri-*O*-acetyl-3-acetylsulfanyl-3-deoxy-α,β-D-glucopyranose (294).

To a stirred solution of 1,2,4,6-tetra-*O*-acetyl-3-*S*-acetyl-3-deoxy-D-glucopyranoside **293** (1.0 mmol) in a mixture of EtOAc and CH_2Cl_2 (20.0 mL + 10.0 mL) was added $TiBr_4$ (2.5 mmol). The reaction mixture was stirred at room temperature for 96 h and diluted with CH_2Cl_2 (30.0 mL). It was filtered through a pad of celite and the filtrate was washed with saturated $NaHCO_3$ (50.0 mL). The organic portion was dried over Na_2SO_4 and the residue was evaporated to dryness. The obtained crude bromide was dissolved in acetone/water mixture (20.0 mL) and was added Ag_2CO_3 (1.5 mmol). The reaction mixture was stirred at room temperature for 12 h and diluted with EtOAc (30.0 mL). It was filtered through a short celite pad and washed with saturated $NaHCO_3$ (50.0 mL). The

organic portion was dried over Na_2SO_4 and concentrated. The residue was further purified by column chromatography to give the title product **294** in 86% yield as oil. ^{1}H NMR (500 MHz): δ 5.39 (t, *J* = 4.0 Hz, 1H, major), 5.09 – 5.07 (m, 1H, major), 5.06 – 5.04 (m, 1H, minor), 4.95 – 4.92 (m, 1H, major), 4.84 (dd, *J* = 11.5 Hz, *J* = 8.0 Hz, 1H, minor), 4.73 (dd, *J* = 8.5 Hz, *J* = 8.0 Hz, 1H, minor), 4.28 – 4.25 (m, 1H, major), 4.23 – 4.15 (m, 2H, major), 4.12 – 4.11 (m, 1H, minor), 3.97 – 3.95 (m, 1H, minor), 3.85 – 3.83 (m, 1H, minor), 3.81 – 3.80 (m, 1H, major), 3.79 – 3.76 (m, 1H, minor), 2.32 (s, 3H, minor), 2.32 (s, 3H, major), 2.07 (s, 3H X 2), 2.06 (s, 3H X 2), 2.02 (s, 3H, major), 2.01 (s, 3H, minor). ^{13}C NMR (125 MHz): δ 193.7 (2C), 171.2, 171.1 (minor), 170.8 (minor), 170.3, 169.7, 169.6 (minor), 97.1 (minor), 89.9, 75.0, 72.4 (minor), 70.3, 68.7 (minor), 67.6, 62.6 (minor), 47.7 (minor), 44.4, 30.9, 30.9 (minor), 21.1 (2C), 20.9, 20.8 (2C), 20.7 (2C), 20.7. ESIHRMS: calc. for $C_{14}H_{20}O_9SNa$ $[M+Na]^+$ 387.0726, found 387.0724.

2,4,6-tri-*O*-acetyl-3-*S*-acetylsulfanyl-3-deoxy-α-D-glucopyranosyl trichloroacetimidate (295).

Following the general procedure **4**, and eluting with 45% EtOAc/hexanes the title compound was obtained in 80% yield. $[\alpha]^{23}_D$ 52.0 (*c* = 1); ^{1}H NMR (500 MHz): δ 8.66 (s, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 5.21 – 5.13 (m, 2H), 4.23 – 4.16 (m, 3H), 4.09 – 4.06 (m, 1H), 2.31 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (125 MHz): δ 193.2, 170.7, 169.8, 169.5, 161.0, 92.8, 91.0, 71.5, 68.9, 66.6, 61.9, 44.7, 30.9, 20.9, 20.7, 20.6. ESIHRMS: calc. for $C_{16}H_{20}Cl_3NO_9SNa$ $[M+Na]^+$ 529.9822, found 528.9799.

Methyl 2,4,6-tri-*O*-acetyl-3-*S*-acetylsulfanyl-3-deoxy-β-D-glucopyranoside (296). Following the general procedure **5**, and eluting with 60% EtOAc/hexanes the title compound was obtained in 76% yield. $[\alpha]^{23}_{D}$ -8.7 (*c* = 1); ^{1}H NMR (500 MHz): δ 5.06 (dd, *J* = 11.0 Hz, *J* = 9.5 Hz, 1H), 4.95 (dd, *J* = 11.0 Hz, *J* = 7.5 Hz, 1H), 4.45 (d, *J* = 7.5 Hz, 1H), 4.26 (dd, *J* = 12.0 Hz, *J* = 4.5 Hz, 1H), 4.12 (dd, *J* = 12.0 Hz, *J* = 3.0 Hz, 1H), 3.85 (t, *J* = 11.0 Hz, 1H), 3.76 – 3.73 (m, 1H), 3.50 (s, 3H), 2.33 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (125 MHz): δ 193.7, 170.9, 169.5 (2C), 103.2, 74.7, 70.3, 67.8, 62.5, 57.1, 47.9, 30.8, 20.9, 20.9, 20.8. ESIHRMS: calc. for $C_{15}H_{22}O_9SNa$ $[M+Na]^+$ 401.0882, found 401.0878.

Methyl 3-deoxy-3-[4-(β-D-glucopyranosyloxy)but-2*E*-enylsulfanyl]-β-D-glucopyranoside (297).

Following the general procedure **10**, and eluting with 12% MeOH/CH_2Cl_2 the title compound was obtained in 65% yield. $[\alpha]^{23}_{D}$ -2.0 (*c* 0.85); ^{1}H NMR (500 MHz, CD_3OD): δ 5.85 (dt, *J* = 15.0 Hz, *J* = 7.5 Hz, 1H), 5.75 (dt, *J* = 15.5 Hz, *J* = 6.5 Hz, 1H), 4.36 (d, *J* = 8.0 Hz, 1H), 4.32 (dd, *J* = 12.5 Hz, *J* = 5.0 Hz, 1H), 4.20 (d, *J* = 8.0 Hz, 1H), 4.17 (dd, *J* = 12.5 Hz, *J* = 6.5 Hz, 1H), 3.89 – 3.86 (m, 2H), 3.69 (dd, *J* = 12.0 Hz, *J* = 5.0 Hz, 1H), 3.66 (dd, *J* = 12.5 Hz, *J* = 5.5 Hz, 1H), 3.54 (s, 3H), 3.46 – 3.40 (m, 1H), 3.28 – 3.27 (m, 6H), 3.25 – 3.17 (m, 2H), 2.54 (t, *J* = 10.0 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 130.8, 128.7, 105.3, 101.5, 79.2, 76.8, 76.6, 73.9, 73.1, 70.5, 68.7, 68.6, 61.7, 61.6, 56.0, 54.6, 33.2. ESIHRMS: calc. for $C_{17}H_{30}O_{11}SNa$ $[M+Na]^+$ 465.1401, found 465.1407.

3-*O*-{2,4,6-Tri-*O*-acetyl-3-*O*-[(*Z*)-4-(2-naphthylmethyloxy)but-2-enyl]-β-D-glycopyranosyl}-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (299). Following the general procedure **5**, the acceptor **276** was glycosylated with the donor 2,4,6-tri-*O*-acetyl-3-*O*-[(*Z*)-4-(2-naphthylmethyloxy)but-2-enyl]-α-D-glucopyranosyl trichloroacetimidate **279** and after eluting with 70% EtOAc/hexanes the title compound was obtained in 60% yield. $[\alpha]^{23}_{D}$ -15.7 (*c* = 1); ^{1}H NMR (500 MHz) δ 7.86 – 7.83 (m, 3H), 7.79 (s, 1H), 7.51 – 7.46 (m, 3H), 5.84 (d, *J* = 3.5 Hz, 1H), 5.81 – 5.76 (m, 1H), 5.62 – 5.57 (m, 1H), 5.03 (t, *J* = 10.0 Hz, 1H), 4.92 (dd, *J* = 9.5 Hz, *J* = 7.5 Hz, 1H), 4.68 (s, 2H), 4.50 (d, *J* = 8.0 Hz, 1H), 4.42 (d, *J* = 4.0 Hz, 1H), 4.35 (dd, *J* = 12.0 Hz, *J* = 6.0 Hz, 1H), 4.27 (dd, *J* = 5.5 Hz, *J* = 3.0 Hz, 1H), 4.25 – 4.24 (m, 1H), 4.18 – 4.11 (m, 3H), 4.08 – 4.03 (m, 3H), 3.97 (dd, *J* = 9.0 Hz, *J* = 6.0 Hz, 1H), 3.53 – 3.49 (m, 2H), 2.08 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.50 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (125 MHz) δ170.9, 169.4, 168.9, 135.7, 133.5, 133.2, 129.5, 129.3, 128.5, 128.1, 127.9, 126.7, 126.5, 126.2, 125.9, 112.3, 108.8, 105.3, 99.6, 83.0, 81.2, 80.8, 79.7, 73.3, 72.7, 72.6, 69.5, 67.3, 66.4, 65.8, 62.4, 27.1, 26.8, 26.6, 25.5, 20.9. ESIHRMS: calc. for $C_{35}H_{47}NO_{17}SNa$ $[M+Na]^{+}$ 776.2742, found 776.2740.

2,2',4,4',6,6'-Hexa-*O*-acetyl-3'-*O*-[(*Z*)-4-(2-naphthylmethyloxy)but-2-enyl]-α-D-laminarabiosyl trichloroacetimidate (301).

Following the general procedure **3**, the acetonide groups were cleaved and the acetate groups were reinstalled to give compound **300** in 82% yield as a mixture. Follwing the general procedure **4**, and eluting with 70% EtOAc/hexanes

the title compound **301** was obtained 68% yield as yellow oil. $[\alpha]^{23}_{D}$ 28.0 (*c* = 1); ^{1}H NMR (500 MHz): δ 8.70 (s, 1H), 7.85 -7.82 (m, 3H), 7.77 (s, 1H), 7.50 – 7.45 (m, 3H), 6.46 (d, *J* = 4.0 Hz, 1H), 5.79 – 5.74 (m, 1H), 5.59 – 5.54 (m, 1H), 5.12 – 5.06 (m, 2H), 4.99 (t, *J* = 9.5 Hz, 1H), 4.89 – 4.85 (m, 1H), 4.66 (s, 2H), 4.54 (d, *J* = 8.5 Hz, 1H), 4.23 (dd, *J* = 12.0 Hz, *J* = 5.0 Hz, 1H), 4.19 (dd, *J* = 12.5 Hz, *J* = 4.5 Hz, 1H), 4.16 – 4.03 (m, 8H), 3.55 – 3.49 (m, 2H), 2.08 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (125 MHz): δ 170.9, 170.8, 169.7, 169.4, 169.3, 169.1, 160.8, 135.7, 133.5, 133.2, 129.5, 129.2, 128.5, 128.1, 127.9, 126.7, 126.5, 125.9, 101.4, 93.4, 79.8, 76.3, 72.7, 72.3, 72.1, 72.0, 70.5, 69.4, 67.5, 66.8, 65.9, 62.3, 61.8, 20.9, 20.9, 20.9, 20.9, 20.8, 20.8, 20.7. ESIHRMS: calc. for $C_{41}H_{48}Cl_3NO_{18}Na$ $[M+Na]^+$ 970.1835, found 970.1845.

Methyl 2,2',4,4',6,6'-hexa-*O*-acetyl-3'-*O*-[(*Z*)-4-(2-naphthylmethyloxy)but-2-enyl]-β-D-laminaribioside (302).

Following the general procedure **5**, and eluting with 75% EtOAc/hexanes the title compound was obtained in 60% yield. $[\alpha]^{23}_{D}$ -17.0 (*c* = 1); ^{1}H NMR (500 MHz): δ 7.85 -7.83 (m, 3H), 7.78 (s, 1H), 7.49 – 7.45 (m, 3H), 5.79 – 5.74 (m, 1H), 5.59 – 5.55 (m, 1H), 5.03 – 4.91 (m, 3H), 4.86 (t, *J* = 9.0 Hz, 1H), 4.66 (s, 2H), 4.46 (d, *J* = 8.5 Hz, 1H), 4.30 – 4.25 (m, 2H), 4.19 – 4.18 (m, 2H), 4.11 (d, *J* = 6.5 Hz, 2H), 4.07 (d, *J* = 6.0 Hz, 2H), 4.00 (dd, *J* = 12.0 Hz, *J* = 2.5 Hz, 1H), 3.85 (t, *J* = 9.0 Hz, 1H), 3.69 – 3.67 (m, 1H), 3.51 – 3.49 (m, 2H), 3.47 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz): δ 171.1, 170.9, 169.5, 169.4, 169.4, 169.0, 135.7, 133.5,

133.2, 129.5, 129.2, 128.5, 128.1, 127.9, 126.7, 126.4, 126.2, 125.9, 101.7, 101.4, 79.8, 78.8, 72.9, 72.7, 72.1, 72.1, 72.0, 69.3, 68.7, 66.8, 65.9, 62.4, 62.3, 56.8, 21.2, 21.0, 20.9, 20.9, 20.8, 20.7. ESIHRMS: calc. for $C_{40}H_{50}O_{18}Na$ $[M+Na]^+$ 841.2895, found 841.2870.

Methyl 2,2',4,4',6,6'-hexa-*O*-acetyl-3'-*O*-[(*Z*)-4-hydroxybut-2-enyl]-β-D-laminarabioside (303).

Following the general procedure **6**, and eluting with 90% EtOAc/hexanes the title product was obtained in 85% yield. $[\alpha]^{23}_D$ -37.0 (*c* = 1); ^{1}H NMR (500 MHz): δ 5.75 – 5.69 (m, 1H), 5.50 – 5.45 (m, 1H), 5.02 (t, *J* = 9.5 Hz, 1H), 4.97 – 4.90 (m, 2H), 4.86 (dd, *J* = 9.5 Hz, *J* = 8.5 Hz, 1H), 4.49 (d, *J* = 8.0 Hz, 1H), 4.31 – 4.28 (m, 2H), 4.20 – 4.16 (m, 2H), 4.14 – 4.09 (m, 4H), 4.02 (dd, *J* = 12.0 Hz, *J* = 2.5 Hz, 1H), 3.85 (t, *J* = 9.5 Hz, 1H), 3.67 – 3.64 (m, 1H), 3.59 – 3.52 (m, 2H), 3.45 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (125 MHz): δ 171.0, 170.8, 169.7, 169.6, 169.5, 169.1, 132.3, 127.7, 101.7, 101.4, 79.8, 78.9, 72.9, 72.1, 72.0, 71.7, 68.8, 68.6, 65.9, 62.4, 62.3, 58.5, 56.8, 21.2, 21.0, 21.0, 20.9, 20.9, 20.7. ESIHRMS: calc. for $C_{29}H_{42}O_{18}Na$ $[M+Na]^+$ 701.2269, found 701.2289.

Methyl 2,2',4,4',6,6'-hexa-*O*-acetyl-3'-*O*-[(*Z*)-4-(phenyloxythionocarbonyloxy)but-2-enyl]-β-D-laminaribioside (304).

Following the general procedure **7**, and eluting with 70% EtOAc/hexanes the title product was obtained in 90% yield. $[\alpha]^{23}_D$ -32.0 (*c* = 1); ^{1}H NMR (500 MHz): δ 7.43 – 7.40 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.09 – 7.07 (m, 2H), 5.80 – 5.75 (m, 1H), 5.71 – 5.66 (m, 1H), 5.05 – 5.02 (m, 3H), 4.97 – 4.87 (m, 3H), 4.48

(d, *J* = 8.0 Hz, 1H), 4.31 – 4.28 (m, 2H), 4.21 – 4.17 (m, 4H), 4.02 (dd, *J* = 12.5, *J* = 2.5 Hz, 1H), 3.86 (t, *J* = 9.5 Hz, 1H), 3.68 – 3.65 (m,1H), 2.12(s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (125 MHz) δ 195.1, 171.0, 170.8, 169.5, 169.4, 169.1, 153.6, 131.8, 129.8 (2C), 126.9, 125.1, 122.1 (2C), 101.7, 101.4, 80.4, 78.8, 77.0, 72.9, 72.1, 72.0, 71.9, 69.5, 69.2, 68.6, 66.8, 62.4, 62.2, 56.8, 21.1, 21.1, 21.0, 20.9 (2C), 20.7. ESIHRMS: calc. for $C_{36}H_{46}O_{19}SNa$ $[M+Na]^+$ 837.2252, found 837.2239.

Methyl 2,2',4,4',6,6'-hexa-*O*-acetyl-3'-*O*-[2-phenyloxycarbonylthioxy]but-3-enyl]-β-D-laminarabioside (305).

Following the general procedure **8**, and eluting with 70% EtOAc/hexanes the title product was obtained in 90% yield. ^{1}H NMR (500 MHz): δ 7.39 – 7.36 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.16 – 7.15 (m, 1H), 7.14 – 7.13 (m, 1H), 5.19 (dd, *J* = 10.0 Hz, *J* = 3.5 Hz, 1H), 4.10 – 5.05 (m, 1H), 4.99 – 4.91 (m, 3H), 4.49 (d, *J* = 8.5 Hz, 1H), 4.33 – 4.29 (m, 2H), 4.19 – 4.18 (m, 2H), 4.05 – 4.01 (m, 2H), 3.86 (t, *J* = 9.5 Hz, 1H), 382 – 3.77 (m, 2H), 3.47 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H x 3), 2.08 (s, 3H x 2), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (125 MHz): δ 171.0, 171.9, 169.5, 169.4 (2C), 169.1, 151.3, 133.9, 133.8, 129.7, 126.5, 121.5, 118.8, 118.7, 101.7, 101.4, 81.0, 80.8, 78.8, 73.5, 73.4, 72.9, 72.1, 72.1, 71.9, 71.7, 69.1, 68.9, 68.6, 62.4, 62.2, 56.8, 48.9, 48.7, 21.2, 21.1, 21.0 (2C), 20.9, 20.9, 20.9 (2C), 20.7 (2C). ESIHRMS: calc. for $C_{36}H_{46}O_{19}SNa$ $[M+Na]^+$ 837.2252, found 837.2224.

Methyl 3'-*O*-(2-pyridin-2-yldisulfanyl)but-3-enyl-β-D-laminaribioside (306). Following the general procedure **9**, and eluting with 10% MeOH/CH_2Cl_2 the title

product was obtained in 68% yield. ^{1}H NMR (500 MHz): δ 8.37 – 8.36 (m, 1H), 7.94 – 7.90 (m, 2H), 7.82 – 7.78 (m, 1H), 7.22 – 7.19 (m, 1H), 5.87 – 5.79 (m, 1H), 5.25 – 5.21 (m, 1H), 5.14 – 5.12 (m, 1H), 4.55 (dd, *J* = 7.5 Hz, *J* = 4.5 Hz, 1H), 4.23 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 4.12 (dd, *J* = 10.5 Hz, *J* = 6.0 Hz, 1H, minor), 4.08 – 4.07 (m, 1H), 4.03 (dd, *J* = 10.0 Hz, *J* = 6.0 Hz, 1H, minor), 3.90 – 3.86 (m, 2H), 3.80 (dd, *J* = 15.0 Hz, *J* = 6.5 Hz, 1H), 3.70 (dd, *J* = 11.5 Hz, *J* = 5.5 Hz, 1H), 3.65 - 361 (m, 1H), 3.54 (s, 3H major + 3H minor), 3.43 – 3.33 (m, 7H), 3.23 (t, *J* = 8.5 Hz, 1H). ^{13}C NMR (125 MHz): δ 160.7, 148.8, 137.8, 134.6, 134.5, 121.0, 120.3, 118.1, 104.1, 103.7, 86.9, 85.7, 85.6, 76.8, 76.4, 74.4, 74.3, 73.7, 73.2, 69.9, 69.8, 68.8, 61.4, 61.3, 56.2, 54.9, 54.8. ESIHRMS: calc. for $C_{22}H_{33}NO_{11}S_2Na$ $[M+Na]^+$ 574.1393, found 574.1385.

1-Bromo hepta-*O*-acetyl-α-D-laminarabiose (309).

Following the general experimental procedure **3**, the acetonide groups were cleaved and acetate groups were installed on the known glycoside **308**. The peracetyl laminaribioside (1.0 mmol) in CH_2Cl_2 (4.0 mL) was added 33% HBr in AcOH (15.0 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with CH_2Cl_2 (10.0 mL) and washed with saturated $NaHCO_3$ (10.0 mL). The combined organic portion was dried over Na_2SO_4 and evaporated to dryness. The crude bromide was purified by column chromatography over silica gel to give the title product as colorless liquid in 80% yield. ^{1}H NMR (500 MHz): δ 6.52 (d, *J* = 4.0 Hz, 1H), 5.17 – 5.06 (m, 3H), 4.90 (dd, *J* = 9.5 Hz, *J* = 8.5 Hz, 1H), 4.81 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1H), 4.69 (d, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 12.5 Hz, *J* = 4.5 Hz, 1H), 4.27 – 4.21

(m, 2H), 4.18 – 4.14 (m, 2H), 4.09 (dd, *J* = 12.3 Hz, *J* = 2.0 Hz, 1H), 3.76 – 3.73 (m, 1H), 2.19 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (100 MHz): δ 170.8, 170.7, 170.6, 169.7, 169.5, 169.3, 169.2, 100.9 (2C), 87.6, 73.1, 72.7, 72.6, 71.9, 71.6, 68.2, 66.8, 61.2, 61.3, 21.0, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5.

1-Thio-hepta-*O*-acetyl-β-D-laminaribiose (310).

To a stirred solution of 1-bromo hepta-*O*-acetyl-α-D-laminarabiose **309** (1.0 mmol) in acetone/water (5.0 mL) was added thiourea (1.5 mmol) and the reaction mixture was refluxed for 4-6 h. The reaction mixture was cooled to room temperature and solvents were evaporated. To a stirred solution of this residue in CH_2Cl_2/water (10.0 mL) was added sodium metabisulfite (2.0 mmol) and the reaction was refluxed under an atmosphere of N_2 for 2-4 h. The reaction mixture was diluted with CH_2Cl_2 (10.0 mL) and washed with saturated $NaHCO_3$ (10.0 mL). The combined organic portion was dried over Na_2SO_4 and evaporated to dryness. The crude thiol was purified by column chromatography over silica gel to give the title product as colorless liquid in 65% yield. $[\alpha]^{23}_D$ -18.2 (*c* = 1); ^{1}H NMR (500 MHz): δ 5.13 (t, *J* = 9.5 Hz, 1H), 5.06 (t, *J* = 9.5 Hz, 1H), 4.99 – 4.94 (m, 2H), 4.91 – 4.88 (m, 1H), 4.60 (d, *J* = 7.5 Hz, 1H), 4.42 – 4.36 (m, 2H), 4.19 - 4.12 (m, 2H), 4.03 (dd, *J* = 10.5, *J* = 2.0 Hz, 1H), 3.85 (t, *J* = 9.5 Hz, 1H), 3.70 – 3.66 (m, 2H), 2.29 (d, *J* = 10.5 Hz, 1H), 2.17 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.01(s, 3H), 2.00 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (125 MHz): δ 170.9, 170.7, 170.6, 169.6, 169.5, 169.5, 169.4, 101.1, 80.1, 79.0, 76.6, 75.3, 73.2,

71.9, 71.3, 68.2, 68.1, 62.5, 61.8, 21.3, 21.0, 20.8, 20.7, 20.7, 20.6, 20.5. ESIHRMS: calc. for $C_{26}H_{36}O_{17}SNa$ $[M+Na]^+$ 675.1571, found 675.1541.

Methyl 3-*O*-[4-(1-thio-β-D-laminarabiosyl)but-2*E*-enyl]-β-D-laminaribioside (311).

Following the general procedure 10, the title compound was obtained in 55% yield. $[\alpha]^{23}_D$ -15.0 (*c* 0.75); ^{1}H NMR (500 MHz, CD_3OD): δ 5.79 – 5.77 (m, 2H), 4.57 (d, *J* = 7.5 Hz, *J* = 4.0 Hz, 2H), 4.46 (d, J = 9.5 Hz, 1H), 4.36 – 4.35 (m, 2H), 4.24 (d, *J* = 7.5 Hz, 1H), 3.89 (dd, *J* = 7.0 Hz, *J* = 2.0 Hz, 4H), 3.72 – 3.67 (m, 2H), 3.66 – 3.62 (m, 3H), 3.58 – 3.53 (m, 2H), 3.54 (s, 3H), 3.52 – 3.47 (m, 2 H), 3.45 – 3.21 (m, 18H). ^{13}C NMR (125 MHz, CD_3OD): δ 130.3, 129.1, 104.1, 104.0, 103.7, 88.3, 86.9, 83.6, 83.3, 80.2, 76.9, 76.8, 76.6, 76.4, 74.6, 74.4, 73.2, 72.5, 72.4, 70.4, 70.0, 69.0, 68.9, 61.7, 61.4, 56.1, 30.8. ESIHRMS: calc. for $C_{29}H_{50}O_{21}SNa$ $[M+Na]^+$ 789.2463, found 789.2451.

(*Z*)-4-Hydroxybut-2-enyl hepta-*O*-acetyl-β-D-laminaribioside (312).

To a stirred solution of 1-bromo hepta-*O*-acetyl-α-D-laminarabioside **309** (1.0 mmol) in CH_2Cl_2 (10.0 mL) was added cis-butene-1,4-diol **244** (20.0 mmol), Ag_2CO_3 (1.5 mmol), $CaSO_4$ (1.0 g) and a catalytic amount of I_2. The reaction mixture was stirred at room temperature for 12 h without exposing the reaction mixture to light. The reaction mixture was diluted with CH_2Cl_2 (50.0 mL) and filtered through a pad of celite. The filtrate was washed with saturated $NaHCO_3$ (50.0 mL). The combined organic portion was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography over silica gel to give the title compound as colorless liquid in 80% yield. $[\alpha]^{23}_D$ -43.5 (*c* =

1.5); ^{1}H NMR (500 MHz): δ 5.84 – 5.79 (m, 1H), 5.60 – 5.55 (m, 1H), 5.11 (t, *J* = 9.5 Hz, 1H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.98 (t, *J* = 8.0 Hz, 1H), 4.93 (t, *J* = 10.0 Hz, 1H), 4.87 (t, *J* = 8.5 Hz, 1H), 4.57 (d, *J* = 8.0 Hz, 1H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.35 (dd, *J* = 12.5 Hz, *J* = 4.0 Hz, 1H), 4.31 (dd, *J* = 12.5 Hz, *J* = 5.5 Hz, 1H), 4.21 (dd, *J* = 13.0 Hz, *J* = 8.0 Hz, 1H), 4.17 (s, 2H), 4.16 (s, 2H), 4.02 (dd, *J* = 7.5 Hz, *J* = 2.5 Hz, 1H), 3.86 (t, *J* = 9.5 Hz, 1H), 3.67 – 3.64 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H x 2), 196 (s, 3H). ^{13}C NMR (125 MHz): δ 171.1, 170.7, 170.6, 169.6, 169.5, 169.4, 169.2, 133.6, 126.9, 101.2, 99.3, 79.1, 73.2, 72.8, 72.1, 71.9, 71.2, 68.6, 68.3, 64.0, 62.5, 61.9, 58.7, 21.1, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5. ESIHRMS: calc. for $C_{30}H_{42}O_{19}Na$ $[M+Na]^{+}$ 729.2218, found 729.2210.

(*Z*)-4-(Phenyloxythionocarbonyloxy)but-2-enyl hepta-*O*-acetyl-β-D-laminaribioside (313).

Following the general procedure **7,** and eluting with 75% EtOAc/hexanes the title compound was obtained in 85% yield. $[\alpha]^{23}_{D}$ -11.0 (*c* = 1); ^{1}H NMR (500 MHz): δ 7.43 (t, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.11 – 7.09 (m, 2H), 5.88 – 5.84 (m, 1H), 5.82 – 5.77 (m, 1H), 5.15 – 5.11 (m, 2H), 5.09 – 5.06 (m, 2H), 5.04 – 4.99 (m, 1H), 4.96 (t, *J* = 10.0 Hz, 1H), 4.89 (t, *J* = 9.5 Hz, 1H), 4.58 (d, *J* = 8.5 Hz, 1H), 4.44 (d, *J* = 8.5 Hz, 1H), 4.38 – 4.33 (m, 3H), 4.19 – 4.18 (m, 2H), 4.03 (dd, *J* = 12.5 Hz, *J* = 2.0 Hz, 1H), 3.87 (t, *J* = 9.5 Hz, 1H), 3.68 – 3.66 (m, 2H), 2.14 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz): δ 195.1, 170.9, 170.7, 170.6, 169.6, 169.5, 169.4, 169.1, 153.6, 130.9, 129.8, 126.9, 126.2, 122.1, 101.2, 99.6, 79.2,

73.2, 72.7, 72.2, 71.9, 71.3, 69.5, 68.4, 68.3, 64.4, 62.3, 61.9, 21.2., 21.0, 20.8, 20.8, 20.7, 20.7, 20.6 ESIHRMS: calc. for $C_{37}H_{46}O_{20}SNa$ $[M+Na]^+$ 865.2201, found 865.2190.

2-(Phenyloxycarbonylthioxy)but-3-enyl hepta-*O*-acetyl-β-D-laminaribioside (314).

Following the general procedure **8,** and eluting with 75% EtOAc/hexanes the title compound was obtained in 95% yield. ^{1}H NMR (500 MHz): δ 7.39 – 7.36 (m, 2H), 7.24 – 7.23 (m, 1H), 7.16 – 7.13 (m, 2H), 5.94 – 5.82 (m, 1H), 5.36 (dd, *J* = 17.0 Hz, *J* = 5.0 Hz, 1H), 5.22 (dd, *J* = 11.5 Hz, *J* = 10.5 Hz, 1H), 5.14 – 5.10 (m, 1H), 5.07 – 4.99 (m, 2H), 4.96 - 4.91 (m, 1H), 4.88 (t, *J* = 9.0 Hz, 1 H), 4.58 (dd, *J* = 8.0 Hz, *J* = 6.0 Hz, 1H), 4.43 (t, *J* = 8.0 Hz, 1H), 4.35 (dd, *J* = 12.5 Hz, *J* = 4.5 Hz, 1H), 4.20 – 4.16 (m, 3H), 4.14 – 4.09 (m, 1H), 4.07 – 4.02 (m, 1H), 3.89 – 3.85 (m, 1H), 3.74 (dd, *J* = 10.5 Hz, *J* = 6.5 Hz, 1H), 3.68 – 3.65 (m, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H X 2), 2.06 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H X 3), 1.97 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (125 MHz): δ 170.9, 170.7, 170.6, 169.6, 169.5, 169.4, 169.2, 169.0, 168.9, 151.3, 133.8, 133.5, 129.7, 126.5, 121.4, 119.1, 119.0, 101.5, 101.2 (2C), 100.7, 79.0, 78.9, 73.2, 72.7, 72.6, 72.2, 71.9, 71.7, 71.3, 70.3, 68.5, 68.4, 68.3, 62.3, 62.2, 61.9, 48.8, 48.0, 21.2, 21.1, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5. ESIHRMS: calc. for $C_{37}H_{46}O_{20}SNa$ $[M+Na]^+$ 865.2201, found 865.2220.

2-(Pyridin-2-yldisulfanyl)-3-enyl-β-D-laminaribioside (315).

Following the general procedure **9,** and eluting with MeOH/CH_2Cl_2 the title compound was obtained in 70% yield. ^{1}H NMR (500 MHz, CD_3OD): δ 8.36 (d, *J* =

7.0 Hz, 1H), 7.95 – 7.92 (m, 1H), 7.79 (t, *J* = 9.0 Hz, 1H), 7.20 (dd, *J* = 9.0 Hz, *J* = 6.0 Hz, 1H), 5.88 – 5.78 (m, 1H), 5.27 – 5.20 (m, 1H), 5.16 – 5.13 (m, 1H), 4.55 (d, *J* = 10.0 Hz, 1 H), 4.33 (dd, *J* = 15.0 Hz, *J* = 10 Hz, 1H), 4.16 – 4.09 (m, 1H), 3.89 – 3.86 (m, 3H), 3.85 – 3.80 (m, 1H), 3.78 – 3.77 (m, 1H), 3.69 – 3.61 (m, 2H), 3.56 – 3.51 (m, 1H), 3.42 – 3.36 (m, 4H), 3.33 – 3.25 (m, 6H). ^{13}C NMR (125 MHz): δ 160.6, 148.8, 137.9, 134.2, 134.1, 121.1, 120.4, 118.5, 118.3, 104.1, 102.9, 102.9, 86.7, 77.0, 76.6, 76.5, 74.3, 73.2, 70.4, 70.1, 68.8, 68.7, 61.4, 54.2, 54.1. ESIHRMS: calc. for $C_{21}H_{31}NO_{11}S_2Na$ $[M+Na]^+$ 560.1236, found 560.1220.

Benzyl 2-*O*-benzoyl–4,6-*O*-benzylidene-2',4',6'-tri-*O*-acetyl-3'-acetylsulfanyl-3'-deoxy-β-D-laminarabioside (323).

Following the general procedure **5**, benzyl 2-*O*-benzoyl–4,6-*O*-benzylidene-β-D-glucopyranoside (**322**) was glycosylated with 2,4,6-tri-*O*-acetyl-3-*S*-acetylsulfanyl-3-deoxy-α-D-glucopyranosyl trichloroacetimidate (**295**) donor and eluting with EtOAc/hexanes the title product was obtained in 25% yield. $[\alpha]^{23}_D$ -47.7 (*c* = 1); ^{1}H NMR (400 MHz): δ 7.99 – 7.97 (m, 2H), 7.64 – 7.60 (m, 1H), 7.51 – 7.45 (m, 4H), 7.35 – 7.33 (m, 3H), 7.21 – 7.16 (m, 1H), 7.14 – 7.12 (m, 4H), 5.57 (s, 1H), 5.35 (t, *J* = 10.0 Hz, 1H), 4.97 (t, *J* = 9.6 Hz, 1H), 4.90 (dd, *J* = 11.2 Hz, *J* = 7.2 Hz, 1H), 4.84 (d, *J* = 8.4 Hz, 1H), 4.64 – 4.58 (m, 3H), 4.38 (dd, *J* = 10.8 Hz, *J* = 4.8 Hz, 1H), 4.11 – 4.04 (m, 2H), 3.91 – 3.79 (m, 3H), 3.59 (t, *J* = 11.2 Hz, 1H), 3.52 – 3.46 (m, 2H), 2.21 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (125 MHz): δ 193.7, 169.4, 165.6, 137.4, 136.8, 133.5, 130.2, 130.0, 129.9, 129.3, 128.7, 128.6, 128.4, 128.1, 128.0, 126.3, 119.2, 102.1, 101.5, 99.8, 79.3, 79.1, 77.6, 77.3, 76.9, 74.4, 73.6, 70.6, 69.9, 68.8, 67.8,

66.8, 62.3, 47.9, 30.7, 20.9, 20.7, 20.2. ESIHRMS: calc. for $C_{41}H_{44}O_{15}SNa$ $[M+Na]^+$ 831.2299, found 831.2259.

Benzyl 2-*O*-benzoyl–2',4',6'-tri-*O*-acetyl-3'-acetylsulfanyl-3'-deoxy-β-D-laminaribioside (324).

The compound **323** was stirred in 50% aqeous AcOH (2.0 mL) at 50 °C for 4-6 h. Solvents were evaporated completely and purified by column chromatography to afford the title product in 90% yield. $[\alpha]^{23}_D$ -38.7 (*c* = 1); ^{1}H NMR (400 MHz): δ 7.99 – 7.97 (m, 2H), 7.64 – 7.61 (m, 1H), 7.51 – 7.47 (m, 2H), 7.19 – 7.14 (m, 1H), 7.12 – 7.11 (m, 4H), 5.25 (t, *J* = 11.0 Hz, 1H), 4.99 – 4.92 (m, 2H), 4.82 – 4.79 (m, 1H), 4.63 – 4.59 (m, 1H), 4.53 (d, *J* = 10.5 Hz, 2H), 4.17 – 4.08 (m, 2H), 3.99 – 3.94 (m, 1H), 3.83 – 3.75 (m, 4H), 3.73 – 3.71 (m, 1H), 3.67 – 3.62 (m, 2H), 3.41 – 3.36 (m, 1H), 2.23 (s, 3H), 2.07 (s, 3H X 2), 1.97 (s, 3H). ^{13}C NMR (125 MHz): δ 193.4, 170.7, 169.4, 169.3, 165.1, 137.0, 133.6, 130.0, 129.8, 128.7, 128.5, 128.0, 127.9, 102.7, 99.7, 85.7, 75.8, 74.8, 72.5, 70.7, 69.9, 69.5, 67.8, 63.1, 62.3, 47.9, 30.7, 20.8, 20.6, 20.1. ESIHRMS: calc. for $C_{34}H_{40}O_{15}SNa$ $[M+Na]^+$ 831.2299, found 831.2259.

Benzyl 3-deoxy-3-[4-(β-D-laminaribiosyloxy)but-2*E*-enylsulfanyl]-β-D-laminaribioside (325).

Following the general procedure 10, the title compound was obtained in 50% yield. $[\alpha]^{23}_D$ -16.0 (*c* 0.75); ^{1}H NMR (500 MHz, CD_3OD): δ 7.44 – 7.42 (m, 2H), 7.36 – 7.32 (m,2H), 7.29 – 7.27 (m, 1H), 5.88 – 5.83 (m, 1H), 5.76 – 5.71 (m, 1H), 4.94 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 8.5 Hz, 1H), 4.58 (t, *J* = 8.0 Hz, 1H), 4.47 – 4.41 (m, 2H), 4.31 (dd, *J* = 13.0 Hz, *J* = 5.0 Hz, 1H), 4.20 (dd, *J* =

13.0 Hz, *J* = 7.5 Hz, 1H), 3.93 – 3.87 (m, 5H), 3.74 – 3.26 (m, 3H), 2.59 (t, *J* = 10.0 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 137.7, 131.2, 128.6, 128.2, 128.1, 127.6, 105.3, 104.2, 101.6, 100.7, 86.9, 86.8, 79.4, 76.9, 76.5, 76.4, 76.2, 74.4, 73.8, 73.4, 73.3, 72.6, 70.6, 70.4, 69.0, 68.9, 68.7, 68.4, 63.2, 61.7, 61.5, 61.4, 53.9, 33.3. ESIHRMS: calc. for $C_{35}H_{54}O_{21}SNa$ $[M+Na]^+$ 865.2776, found 865.2768.

4-(1-Thio-β-D-laminarabiosyl)but-2*E*-enyl β-D-laminarabioside (326). Following the general procedure 10, the title compound was obtained in 55% yield. $[\alpha]^{23}_D$ -11.0 (*c* 0.75); ^{1}H NMR (500 MHz, CD_3OD): δ 5.86 – 5.80 (m, 1H), 5.77 – 5.71 (m, 1H), 4.59 (d, *J* = 11.0 Hz, *J* = 7.5 Hz, 2H), 4.44 – 4.41 (m, 2H), 4.33 (dd, *J* = 12.5 Hz, *J* = 4.5 Hz, 1H), 4.20 (dd, *J* = 12.0 Hz, *J* = 7.5 Hz, 1H), 3.91 – 3.89 (m, 4H), 3.75 – 3.62 (m, 5H), 3.59 – 3.55 (m, 2H), 3.53 – 3.18 (m, 20H). ^{13}C NMR (125 MHz, CD_3OD): δ 130.2, 128.8, 104.1 (2C), 103.9, 100.9, 88.6, 87.3, 83.1, 80.2, 76.9, 76.8, 76.5, 76.4, 74.4, 74.4, 73.2, 72.4, 70.4, 69.0, 68.9, 66.5, 61.7, 61.5, 30.6. ESIHRMS: calc. for $C_{28}H_{48}O_{21}SNa$ $[M+Na]^+$ 775.2306, found 775.2328.

Phenyl 3-deoxy-3-[4-(β-D-glucopyranosyloxy)but-2*E*-enylsulfanyl]-1-thio-β-D-glucopyranoside (327).

Following the general procedure 10, the title compound was obtained in 70% yield. $[\alpha]^{23}_D$ - 36.0 (*c* 0.75); ^{1}H NMR (400 MHz, CD_3OD): δ 7.57 – 7.54 (m, 2H), 7.32 – 7.23 (m, 3H), 5.86 – 5.79 (m, 1H), 5.74 – 5.67 (m, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 10.0 Hz, 1H), 4.30 (dd, *J* = 16.5 Hz, *J* = 7.0 Hz, 1H), 4.14 (dd, *J* = 16.0 Hz, *J* = 9.0 Hz, 1H), 3.87 (dd, *J* = 15.0 Hz, *J* = 2.0 Hz, 2H),

3.69 – 3.62 (m, 2H), 3.46 – 3.26 (m, 8H), 3.18 (t, *J* = 11.0 Hz, 1H), 2.58 (t, *J* = 11.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 133.9, 131.6, 130.8, 128.7, 127.1, 101.5, 89.6, 82.7, 76.8, 76.6, 73.9, 72.4, 70.5, 68.6, 68.5, 61.8, 61.6, 56.7, 33.6. ESIHRMS: calc. for $C_{22}H_{32}O_{10}S_2Na$ $[M+Na]^+$ 543.1335, found 543.1346.

Methyl 3-*O*-[4-(methyl α-D-glucopyranosid-6-sulfanyl)but-2*E*-enyl]-β-D-glucopyranoside (328).

Following the general procedure 10, the title compound was obtained in 70% yield. $[\alpha]^{23}_D$ - 26.0 (*c* 0.75); ^{1}H NMR (500 MHz, CD_3OD): δ 5.78 – 5.69 (m, 2H), 4.65 (d, *J* = 3.5 Hz, 1H), 4.36 – 4.35 (m, 1H), 4.19 – 4.18 (m, 1H), 3.86 (dd, *J* = 12.0 Hz, *J* = 2.5 Hz, 1H), 3.69 – 3.54 (m, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 3.44 – 3.37 (m, 1H), 3.32 – 3.31 (m, 2H), 3.29 – 3.19 (m, 6H), 2.94 (dd, *J* = 14.0 Hz, *J* = 2.0 Hz, 1H), 2.59 (dd, *J* = 14.6 Hz, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, CD_3OD): δ 130.2, 129.3, 104.2, 99.8, 84.5, 76.6, 73.9, 73.8, 73.5, 72.8, 72.4, 70.1, 61.5, 56.2, 54.4, 34.1, 32.1. ESIHRMS: calc. for $C_{18}H_{32}O_{11}SNa$ $[M+Na]^+$ 479.1563, found 479.1550.

CONCLUSIONS

The selenocyanates were shown to be excellent replacements for the seleno-Bunte salts employed in the original proof of concept experiments on the allylic selenosulfide rearrangement. The permanent modification of simple thiols, cysteine thiols and cysteine containing small peptides was achieved using the selenosulfide rearrangement. Primary allylic selenosulfides were obtained as intermediates by the treatment of allylic selenocyanates with thiols and the usefulness of this selenosulfide ligation has been demonstrated by application to the synthesis of tertiary allyl sulfides wherein cysteine thiols and cysteine containing small peptides were lipidated.

In response to the need to overcome the requirement for stoichiometric phosphine in the allylic disulfide rearrangement, a completely phosphine free system was developed employing silver nitrate as the desulfurization reagent. This silver mediated variant enabled the attachment of farnesyl-like primary thio ether groups to cysteine thiols and cysteine containing small peptides via nerolidyl disulfides. The advantages of this silver mediated desulfurative allylic rearrangement over the original triphenylphosphine mediated version were demonstrated by the lipidation of an electron deficient anomeric thiol under very mild reaction conditions and also by the synthesis of an allyl aryl sulfide. The protecting group free synthesis of a glycoconjugate further validated the silver mediated desulfurative rearrangement in aqueous media.

The utility of this metal mediated allylic desulfurative rearrangement as a chemoselective ligation for the synthesis of complex oligosaccharides was

investigated and established. The silver mediated allylic desulfurative rearrangement was applied successfully to the synthesis of various β-(1,3)-glucan mimics enabling the protecting group free synthesis of two distinct types of mimic of β-(1,3)-glucan disaccharides and tetrasaccharides.

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ABSTRACT

DECHALCOGENATIVE ALLYLIC SELENOSULFIDE AND DISULFIDE REARRANGEMENTS FOR CYSTEINE MODIFICATION AND GLYCOLIGATION

by

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Major: Chemistry

Degree: Doctor of Philosophy

This dissertation describes investigations directed at the development of methods for the selenosulfide and disulfide rearrangements for the permanent functionalization of thiols, and in particular of cysteine and carbohydrate based thiols. Emphasis is placed on the newly invented silver mediated allylic desulfurative rearrangement for the primary modification of thiols and the synthesis of complex oligosaccharide mimics.

Chapter one introduces the concept of chemoselective ligations for the modification of macromolecules like carbohydrates and proteins. It overviews the native and non-native ligation techniques for their modification of such entities with a attention focusing on thiol based ligation techniques. The later part of chapter one describes the need for a permanent ligation technique for the thiol modification and draws attention to a novel method called the selenosulfide ligation.

The second chapter describes studies focused on the further development of the selenosulfide rearrangement through selenocyanate methodology. The synthesis of various selenocyanates as convenient synthons for the selenosulfide ligation is described. The successful application of this selenosulfide methodology to the synthesis of tertiary allyl sulfides in which cysteine containing small peptides were modified with lipid units is highlighted.

In the studies covered in chapter three, with the view to introducing farnesyl-like primary thio ether groups to cysteine peptides and electron deficient anomeric thiols, the allylic disulfide rearrangement was reassessed with the further goal of identifying phosphine-free reagents for the desulfurative rearrangement. This led to the invention of silver mediated allylic desulfurative rearrangement, which enabled the attachment of lipid groups to cysteine peptides and an anomeric thiol under mild reaction conditions. The protecting group-free synthesis of a glycoconjugate was accomplished using this methodology.

In chapter four, extending the concept of this novel metal mediated allylic desulfurative rearrangement as a chemoselective ligation technique, for the synthesis of complex oligosaccharides is described with a focus to the synthesis of β-(1,3)-glucan surrogates.

In chapter five, the experimental procedures and characterization data for the synthesized compounds are documented.

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Patents:

1. Crich D, Karatholuvhu M**,** Krishnamurthy V, Brebion F, **Subramanian V,** Hutton T. Dechalcogenative methods for the preparation of allylic sulfides (**US Patent** 2008134058).

Papers:

1**.** Protecting Group-Free Glycoligation by the Desulfurative Rearrangement of Allylic Disulfides as a Means of Assembly of Oligosaccharide Mimetics: **Subramanian, V**.; Pymbock, M, M.; Hu,T.; Crich, D. (Manuscript in Preparation).

2. Silver-Mediated Allylic Disulfide Rearrangement for Conjugation of Thiols in Protic Media:
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Invited Publications: Subramanian,V. 1,3,5-Trimethyl-1,3,5-triazacyclohexane, Electronic Encyclopedia of Reagents for Organic Synthesis, ed. L. A. Paquette, John Wiley & Sons. Ltd.