SYNTHESIS OF SIX-MEMBERED RING HETEROANALOGUES OF THE GLYCOSIDASE INHIBITOR SALACINOL

by

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SYNTHESIS OF SIX-MEMBERED RING HETEROANALOGUES OF THE GLYCOSIDASE INHIBITOR SALACINOL

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ABSTRACT

The control of glycosidase enzyme inhibition is of great importance in processing carbohydrate containing biopolymers such as glycoproteins and glycolipids. These biopolymers are coated on the surfaces of cells and as such mediate cell-cell and cell-virus interactions. It is hoped that disrupting the enzymes responsible for their biosynthesis may alter these interactions.

The low affinity of carbohydrate-protein interactions has led to the evolution of non-carbohydrate mimics as natural inhibitors for these enzymes. Recently, the glucosidase inhibitors salacinol and kotalanol were isolated from *Salacia reticulata*, a plant known for its anti-diabetic properties. These molecules constitute a new class of glycosidase inhibitors in that they contain a unique thiosugar sulfonium ion with an internal sulfate providing the counterion. Hence, we designed six-membered heterocyclic ring analogues of salacinol as potential therapeutic agents, with the expectation that these molecules will mimic the shape and/or charge of the putative transition state in a glycosidase-mediated hydrolysis reaction.

The syntheses of target compounds 1,5-dideoxy-1,5 -[[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salt and its enantiomer 1,5-dideoxy-1,5 -[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salt, the corresponding selenium analogue and its enantiomer, as well as 1,5-dideoxy-1,5 -[[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt and the corresponding diastereoisomer 1,5-dideoxy-1,5 -[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt are described. Retrosynthetic

analysis showed that the target compounds could be obtained by alkylation of the protected anhydroxylitols or protected anhydroglucitols at the ring heteroatom. The alkylating agent used was a cyclic sulfate derivative, whereby selective attack of the sulfur or selenium atom at the least hindered primary center afforded the desired sulfonium or selenonium salt. Each salt was obtained as a mixture of diastereomers, differing in stereochemistry at the stereogenic sulfur or selenium atoms.

Proof of configuration and conformation of each compound was obtained by detailed NOE NMR experiments.

DEDICATION

This thesis is dedicated, with love, to my mother Lidia Szczepina

Aurora

Beneath and above the ground

above and beneath

eyes open and then close

the awakening begins

the land changes colour

mastered, manipulated by the sun

I reach out and pull myself up

the nerves tingle

they are alive and free

Monica Szczepina

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. B. Mario Pinto, for all his support, enthusiasm and encouragement. It was a privilege to work for him and to be a part of his group.

I am extremely grateful to Dr. Blair D. Johnston. His guidance and knowledge were invaluable. I would also like to thank him for providing me with 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranose.

I would like to thank Dr. Yue Yuan for performing the nuclear Overhauser enhancement difference experiments and the TOCSY experiments.

Thank-you to Dr. Ahmad Ghavami for providing me with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sulfate.

I thank also Dr. David McGillivray for measuring the high resolution mass spectra, Mr. M. K. Yang for performing the elemental analyses, Mrs. Marcy Tracey for running countless NMR spectra on both the 400 MHz and the 500 MHz spectrometers, and Dr. Alan Tracey for his help with the processing and manipulation of Varian NMR spectra.

I would like to thank my lab mates: it was a lot of fun!

Special thank-you to Cody Szczepina and Erica Louie, your friendships are a blessing.

Most importantly, I would like to thank my mother, Lidia Szczepina for her love, strength and courage.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	Optical rotation
Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
AIBN	2,2'-azobis(isobutyronitrile)
Anal.	Analysis
aq	Aqueous
Ar	Aromatic
Asn	Asparagine
ax	Axial
Bn	Benzyl
br	Broad
$(n\text{-Bu})_3SnH$	Tributyltin hydride
c	Concentration
Calcd	Calculated
COSY	Correlated spectroscopy
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dec.	Decomposition
DMF	*N,N*-dimethylformamide
DSS	2,2-dimethyl-2-silapentane-5-sulfonate

eq	Equatorial
equiv	Equivalent
EtOH	Ethanol
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3SiH	Triethyl silane
Et_3N	Triethyl amine
ER	Endoplasmic reticulum
Glc	Glucopyranose
GlcNAc	*N*-acetylglucosamine
h	Hours
HETCOR	Heteronuclear correlation
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HIV	Human immunodeficiency virus
HRMS	High resolution mass spectrometry
J	Coupling constant in Hz
lit.	Literature value
m	Multiplet
M	Molar
Man	Mannose
Me	Methyl
MeOH	Methanol
min	Minutes

mL	Milliliter
mmol	Millimole
mol	Mole
mp	Melting point
N	Normal
NaOAc	Sodium acetate
NaOMe	Sodium methoxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
p	*Para*
Ph	Phenyl
PTSA	Para-toluenesulphonic acid
pyr	Pyridine
R_f	Ratio-to-front
RP	Resolving power
s	Singlet
Ser	Serine
t	Triplet
TLC	Thin layer chromatography
Thr	Threonine
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TOCSY	Total correlation spectroscopy

CHAPTER 1: INTRODUCTION

1.1 General

At the molecular level, carbohydrates are classified as polyhydroxy-aldehydes and polyhydroxy-ketones or compounds that can be hydrolyzed to these substances.[1-3] They have the general formula $C_nH_{2n}O_n$.[1-3] Carbohydrates are vital to our existence and their functions are diverse. They serve as precursors for energy metabolism (e.g. glucose, starch), and provide the structural integrity in plants (e.g. cellulose) and in bacterial cell walls (e.g. as alternating polymers of *N*-acetylglucosamine and *N*-acetylmuramic acid cross-linked to peptides).[1-3] Furthermore, carbohydrates are also found as components of nucleic acids (e.g. D-ribose and 2-deoxy-D-ribose).[1-3]

In addition to these roles, carbohydrates are also involved in a variety of biological processes.[4-8] Glycoconjugates such as glycolipids and glycoproteins, whereby carbohydrates are attached to lipids and proteins, and the carbohydrate portions of these glycoconjugates, known as glycans, are vital to life.[4-8] Beyond their structural roles, glycans also serve to mediate cell adhesion as well as cellular signaling processes.[4-8] The inflammation response, for example, relies on the binding of selectins, which are expressed on endothelial cells following tissue damage, to carbohydrate ligands, specifically sialyl Lewis X, on circulating leukocytes.[4-8]

1.2 *N*-linked glycan biosynthesis

The linkage of the glycan to the protein may be either through a nitrogen or an oxygen and as such may be classified as either *N*-linked or *O*-linked glycoproteins.[4-8] In animal systems, the *N*-linkage is typically to an asparagine (Asn) amide nitrogen and the *O*-linkage is typically to a serine or threonine residue via *N*-acetylgalactosamine.[4-8] The requirement for glycosylation is the sequence Asn-X-Ser or Asn-X-Thr where X can be any amino acid except proline.[4-8] The *N*-linked biosynthetic pathway is depicted below (Figure 1). The biosynthesis begins in the ER with a $Glc_3Man_9GlcNAc_2$ precursor which is transferred during translation to the nascent polypeptide.[4-8] The ensuing *N*-linked glycan undergoes initial trimming in the rough ER and processing in the Golgi apparatus by various glycosidases and glycosyltransferases.[4-8] Finally the glycoprotein is shuttled to its final destination, the plasma membrane.[4-8] It is hoped that inhibiting an enzyme involved in the synthesis, trimming and maturation of these glycoconjugates may affect a cell's ability to recognize and interact with other cells or viruses. This forms the basis of the therapeutic strategy employed for the treatment of various diseases including cancer and HIV infections.

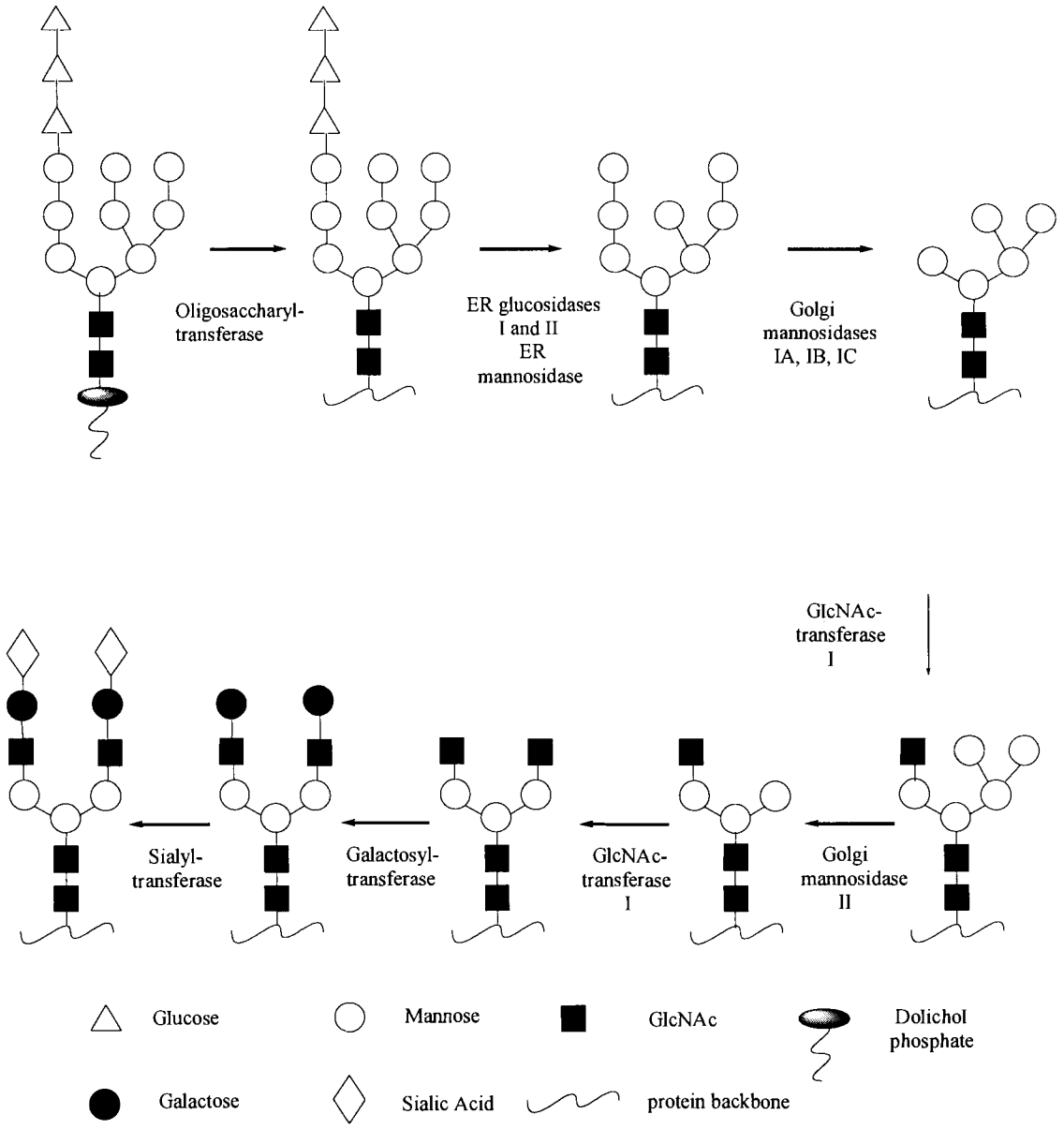
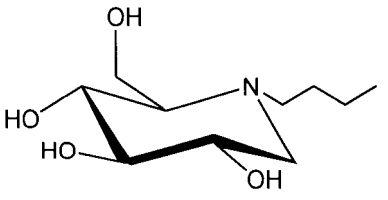


Figure 1. *N*-linked oligosaccharide biosynthetic pathway.

1.3 Naturally occurring glycosidase inhibitors and derivatives

The α-glucosidase inhibitor *N*-butyldeoxynojirimycin (*N*-BuDNJ) **1.1** (Figure 2) has been shown to be a potent inhibitor of HIV replication.[9-11] HIV infectivity begins with the interaction of viral envelope glycoprotein gp160, consisting of gp41 and gp120, with plasma membrane receptors CD4 on the T4 lymphocyte.[9-11] *N*-BuDNJ **1.1** is believed to alter the gp120 *N*-linked glycans, thereby preventing correct folding of the viral envelope proteins.[9-11] This does not affect the binding of the virus to the target cell, but rather it prevents the conformational change required to release gp120 and to expose gp41, which is believed to be required for entry of the virus into the host cell.[9-11]



1.1

Figure 2. Structure of *N*-butyldeoxynojirimycin 1.1.

The naturally occurring indolizidine alkaloid swainsonine **1.2** (Figure 3) was isolated from the Australian legume *Swainsona canascens*.[12] It is the cause of locoism, a neurological disorder characterized by the accumulation of glycoproteins in the lymph

nodes, in livestock fed with spotted locoweed, *Astragalus lentiginosus*.[13] Swainsonine **1.2** is able to reduce tumor cell metastasis.[5] Metastasis involves a series of cell adhesion events typically believed to be mediated by the interaction of terminal sialic acid residues of *N*-linked glycans with selectins.[5] Swainsonine **1.2** is a Golgi α-mannosidase II inhibitor.[5] This results in the generation of increased hybrid type *N*-linked glycans.[5] These glycans contain a significantly lower quantity of terminal sialyl groups and as such reduce cell-cell adhesion which is required for metastasis.

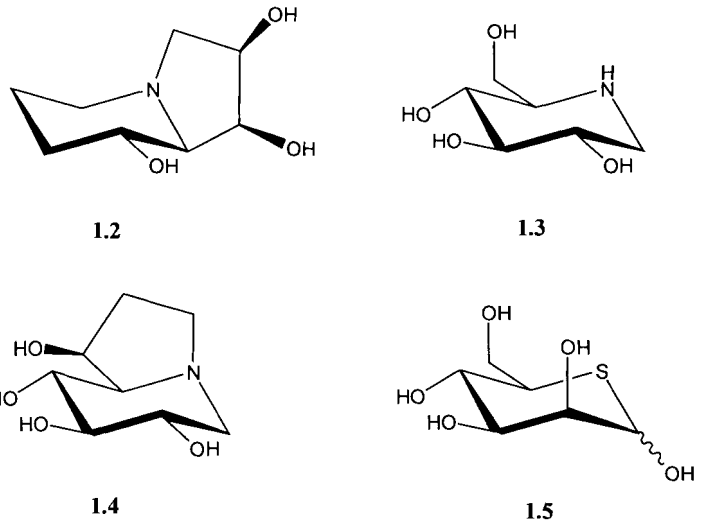


Figure 3. Examples of naturally occurring glycosidase inhibitors.

Other examples of naturally occurring glycosidase inhibitors that have attracted attention as potential therapeutic targets include: 1-deoxynojirimycin **1.3**, castanospermine **1.4**, and 5-thio-D-mannose **1.5** (Figure 3).[10,12,14] 1-Deoxynojirimycin **1.3** is found in the root bark of the mulberry tree, *Morus bombycis*, and is a potent inhibitor

of α-glucosidase I and II.[10] The seed of the Australian chesnut tree, *Castanospermum australe*, produces castanospermine **1.4**, which inhibits both α-glucosidase I and II.[12] Castanospermine **1.4**, is such a potent inhibitor of intestinal glycosidases that it is toxic to animals as it causes severe gastrointestinal problems such as diarrhea.[12] The first naturally occurring 5-thiosugar, 5-thio-D-mannose **1.5**, was isolated from the marine sponge *Clathria pyramida*, which is found off the coast of New South Wales.[14] It is able to inhibit the growth of both gram positive bacteria, such as *Bacillus subtilis*, and gram negative bacteria, such as *Escherichia coli*.[14]

1.4 Mechanisms of glycosidase mediated hydrolysis

The control of glycosidase enzyme inhibition is important in processing carbohydrate containing biopolymers such as glucans and xylans.[15] To understand the process of glycosidase inhibition, the mechanism of a glycosidase-mediated hydrolysis reaction must be considered. Two mechanisms have been proposed which account for the inversion or net retention at the anomeric center on hydrolysis of the glycosidic linkage (Figures 4 and 5).

The double displacement retaining mechanism involves general acid/general base catalysis with formation of an enzyme-glycosyl intermediate, which is subsequently hydrolyzed.[16-18] Typically the catalytic carbonyl residues are separated by approximately 5 Å.[16-18] The single displacement inverting mechanism similarly involves general acid/general base catalysis but without formation of an intermediate. In this case, the catalytic residues are separated by 9-10 Å.[16-18] The greater distance between active site residues in inverting glycosidases relative to retaining glycosidases is believed to be due to the presence of a water molecule catalyzing the initial cleavage of the glycosidic bond.[16] In retaining glycosidases, the initial cleavage is mediated by a carboxylate and hence the active site is less crowded.

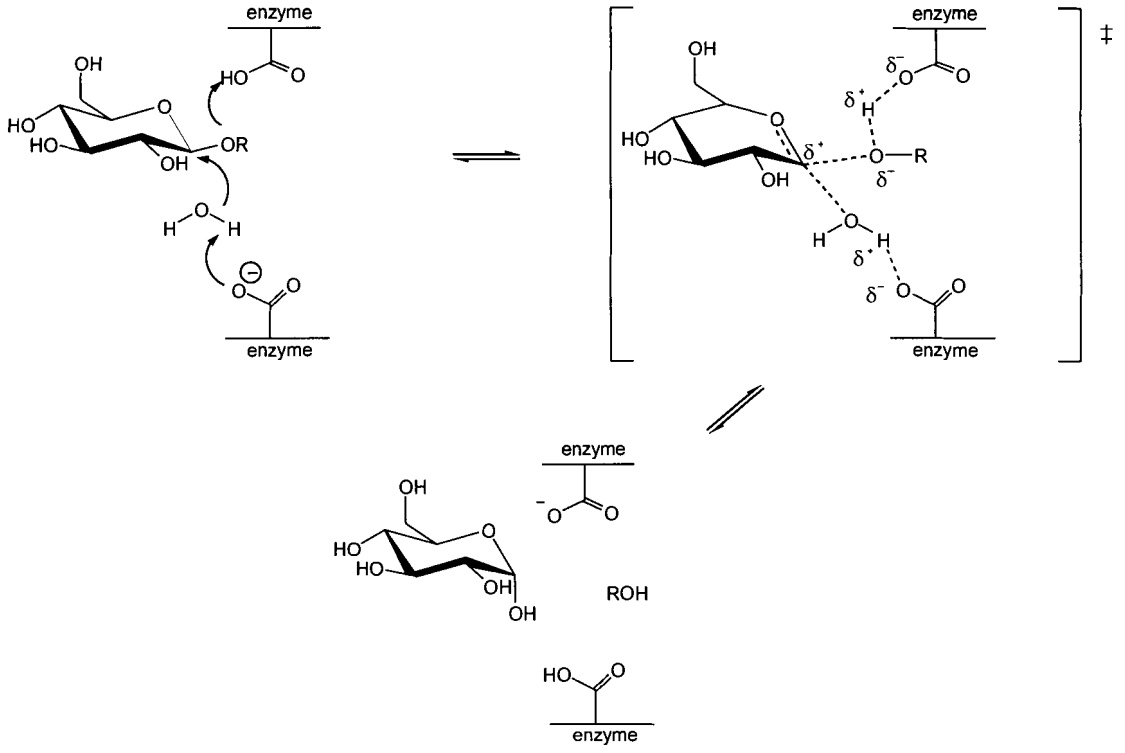


Figure 4. Glycosidase-catalyzed hydrolysis with inversion at the anomeric center.

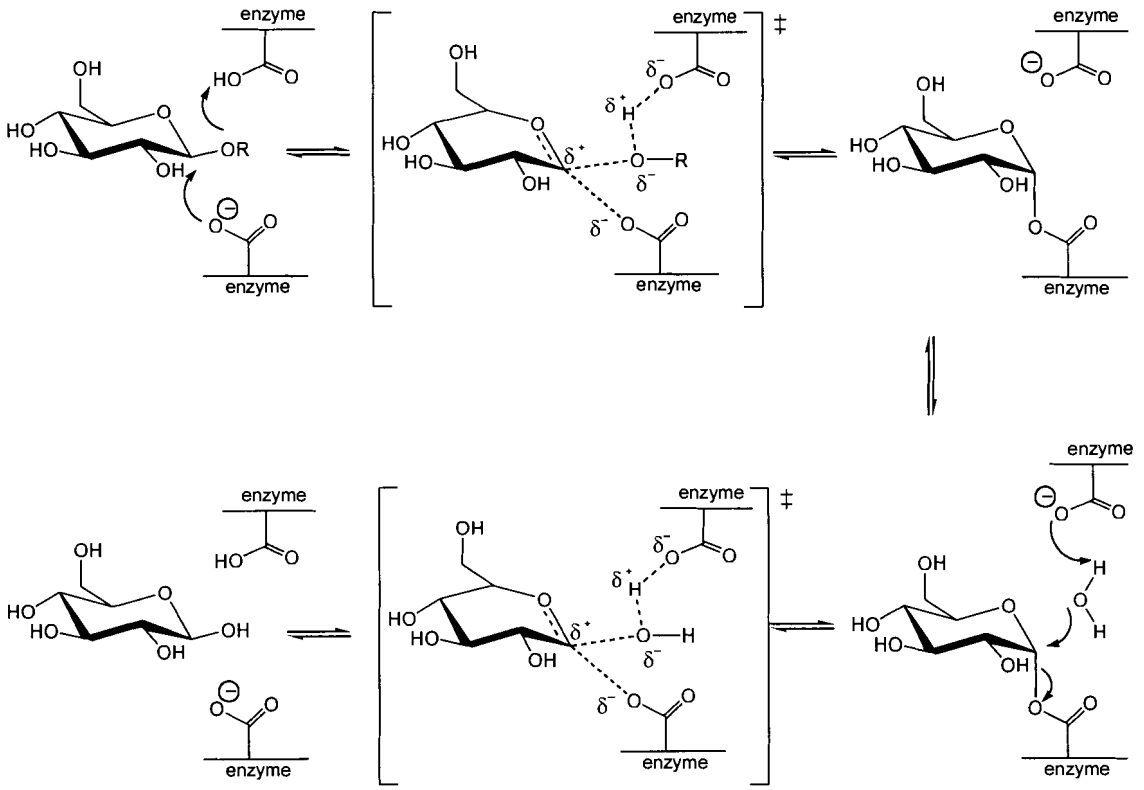


Figure 5. Glycosidase-catalyzed hydrolysis with net retention at the anomeric center.

Both mechanisms involve the formation of an oxacarbenium ion-like transition state, as shown in Figure 6. The positive charge is delocalized between the anomeric carbon and the endocyclic oxygen and the partial double bond character that ensues distorts the ring. It is the mimicry of this putative transition state that is the rationale behind designing inhibitors for glycosidases.[12] Since an enzyme lowers the activation energy by stabilizing the transition state, inhibitors which are transition-state analogues can be expected to show strong binding with large inhibition constants K_i.[12]

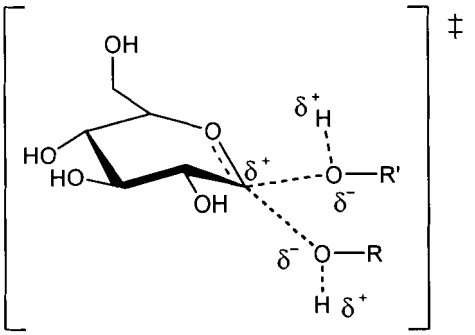
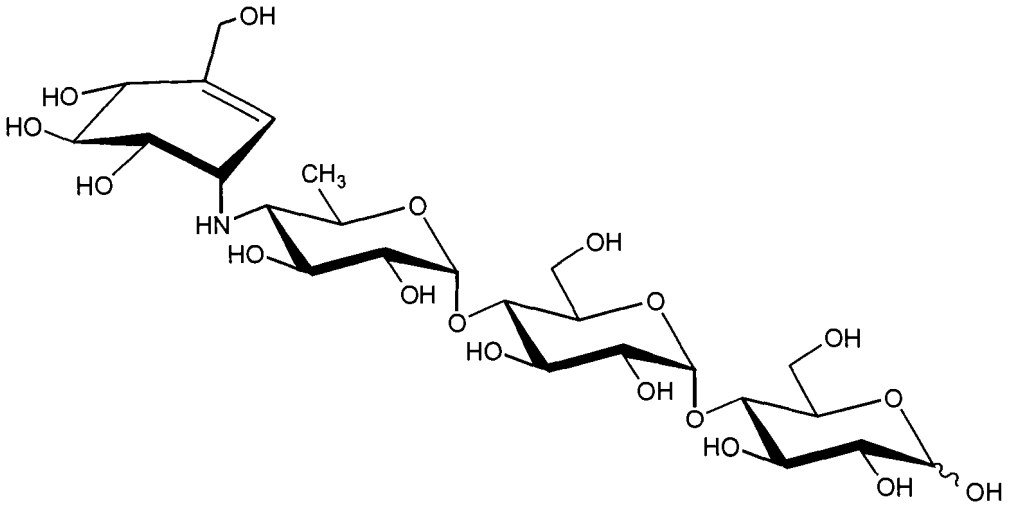


Figure 6. Proposed oxacarbenium ion-like transition state for a glycosidase reaction.

1.5 Nitrogen and sulfur containing glycosidase inhibitors

The low affinity of carbohydrate-protein interactions has led to the search for non-carbohydrate mimics as inhibitors for these enzymes.[15] For example, the naturally occurring glycosidase inhibitor acarbose **1.6** (Figure 7) is used in the treatment of type II diabetes.[19] It has the highest affinity for the carbohydrate processing enzyme glucoamylase from *Aspergillus niger* ($K_i = 1.1 \times 10^{-12}$ M).[19]

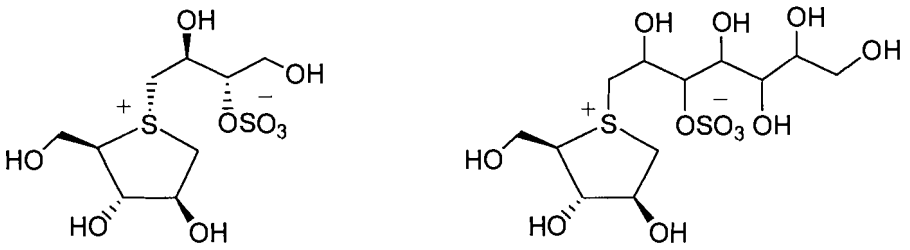


1.6

Figure 7. Structure of acarbose 1.6.

The high affinity is postulated to be the result of the interaction between the positive charge on the nitrogen and active site carboxylate residues as well as the resemblance of the half chair on the pseudo-sugar to the distorted ring conformation in the TS for glycosidase-catalyzed hydrolysis.

The concept of a positively charged center on the inhibitor interacting with active site carboxylate residues was validated by the isolation of glucosidase inhibitors salacinol **1.7** and kotalanol **1.8** from *Salacia reticulata*, a plant native to Sri Lanka known for its antidiabetic properties (Figure 8).[20,21] These constitute a new class of glycosidase inhibitors in that they contain a thiosugar sulfonium ion with an internal sulfate providing the counterion.[20-24]



1.7 **1.8**

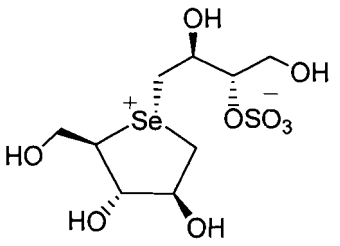
Figure 8. Structures of salacinol 1.7 and kotalanol 1.8.

1.6 Glycosidase inhibitors and the treatment of type II diabetes

In type II diabetes, insulin secretion from the pancreas may be normal but the entry of insulin into cells is compromised due to a shortage of insulin receptors on target cells.[15,25] It is the binding of insulin to these insulin receptors which makes the plasma membrane of muscle and fat cells permeable to glucose.[25] If this event does not occur due to a shortage of insulin receptors, blood glucose levels are high.[25] The inhibition of α–glucosidases such as sucrase and maltase glucoamylase (which break down oligosaccharides into glucose) in the intestinal membrane are targets for glucosidase inhibitors such as acarbose **1.6**, salacinol **1.7**, and kotalanol **1.8**.[19] This inhibition results in a slowing of glucose absorption into the blood and a lowering of post meal hyperglycemia.[15] Hence, there is interest in salacinol and kotalanol since these may potentially have fewer side effects than other existing oral anti-diabetic compounds.[20-22] Side effects with acarbose include flatulence and diarrhea.[20-22]

1.7 Selenium containing glycosidase inhibitors

Prompted by this new class of glycosidase inhibitors, and by the scarcity of carbohydrates containing selenium in the ring, efforts were extended in our laboratory to synthesize and investigate the biological effects of the selenium analogue of salacinol, blintol **1.9** (Figure 9). [26-28] Blintol **1.9** was found to be a better inhibitor of glucoamylase (0.72 mM) than salacinol (1.7 mM) and more significantly, a more potent low μM inhibitor of intestinal maltase glucoamylase (unpublished work).



1.9

Figure 9. Structure of blintol 1.9.

1.8 Overview of thesis

In order to expand the repertoire of molecules of this class that could serve as glycosidase inhibitors, we proposed to synthesize the hitherto unknown six-membered heterocyclic ring analogues of salacinol (X= S, Se; R= CH_2OH, H) as potential inhibitors of glucosidases and xylosidases or xylanases, respectively (Figure 10). Xylans consist of a backbone of β-(1→4)-linked xylopyranose residues. As xylans are the second most widely distributed polysaccharides in the biosphere on a mass basis,[29] there is considerable interest in the inhibition of enzymes which degrade these substrates, particularly to the wood industry.

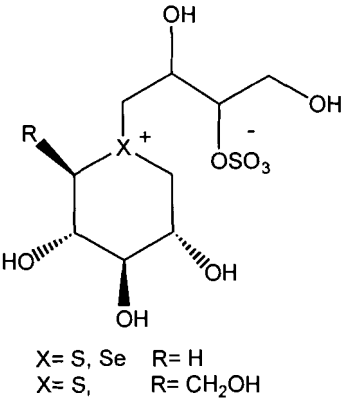
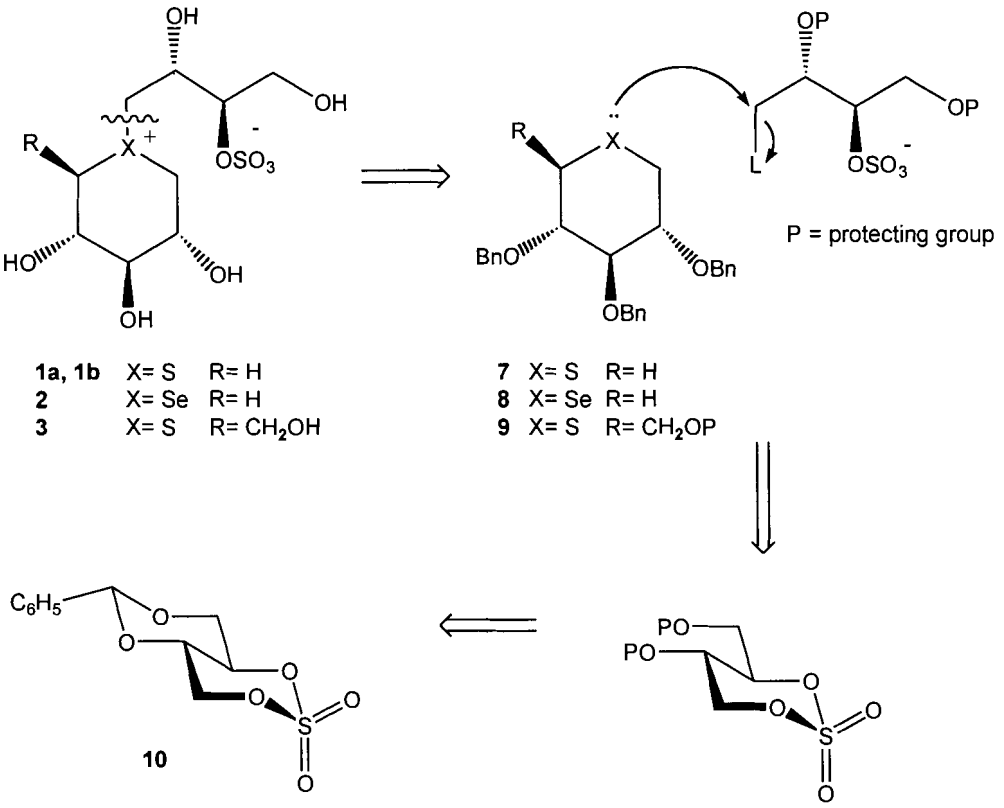


Figure 10. Proposed target molecules.

CHAPTER 2. RESULTS AND DISCUSSION

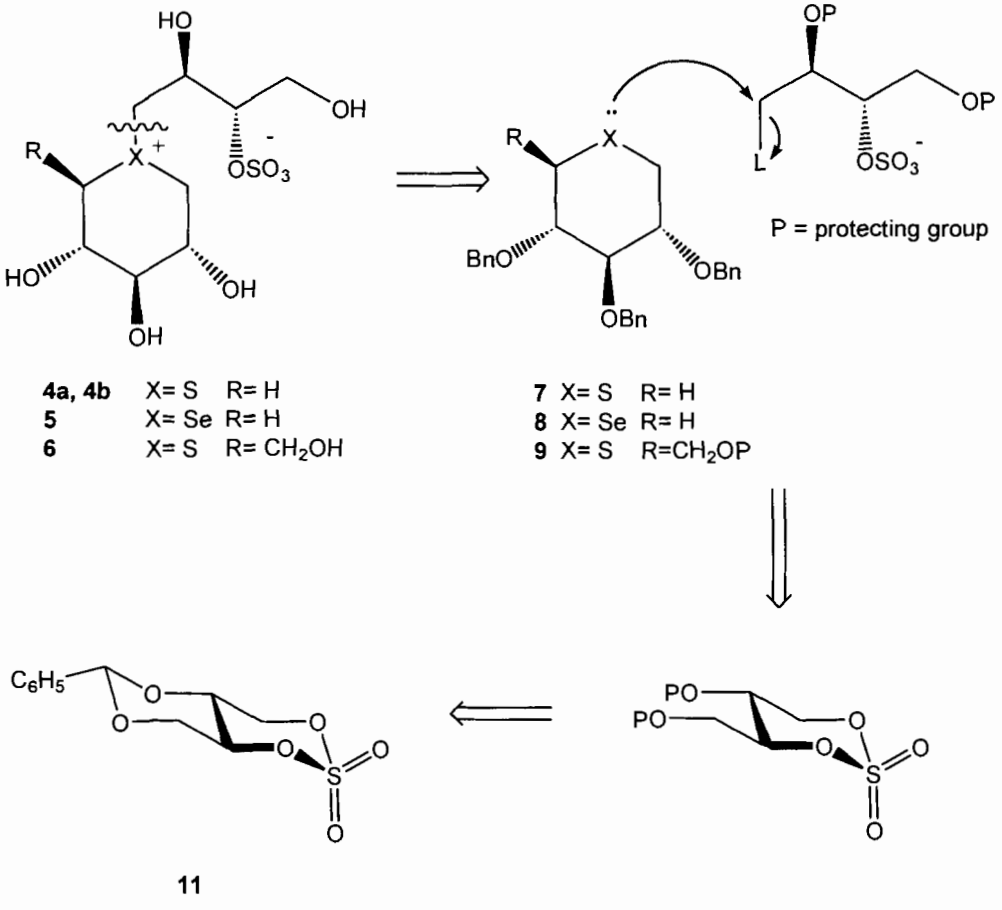
2.1 Retrosynthetic analysis

Retrosynthetic analysis indicated that the target compounds: 1,5-dideoxy-1,5 -[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salts **1a** and **1b**, the corresponding selenium analogue **2**, as well as 1,5-dideoxy-1,5 -[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt **3** could be synthesized by alkylation of the protected anhydroxylitols **7**, **8**, and anhydroglucitol **9**,



Scheme 1. Retrosynthetic analysis for target compounds 1a, 1b, 2, and 3.

respectively, at the ring heteroatom (Scheme 1). Analogously, 1,5-dideoxy-1,5 -[[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salts **4a** and **4b** the corresponding selenium analogue **5**, as well as 1,5-dideoxy-1,5 -[[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt **6** could be obtained by reacting the aforementioned protected anhydroxylitols with the appropriate alkylating agent (Scheme 2). The alkylating agent could be either an open chain



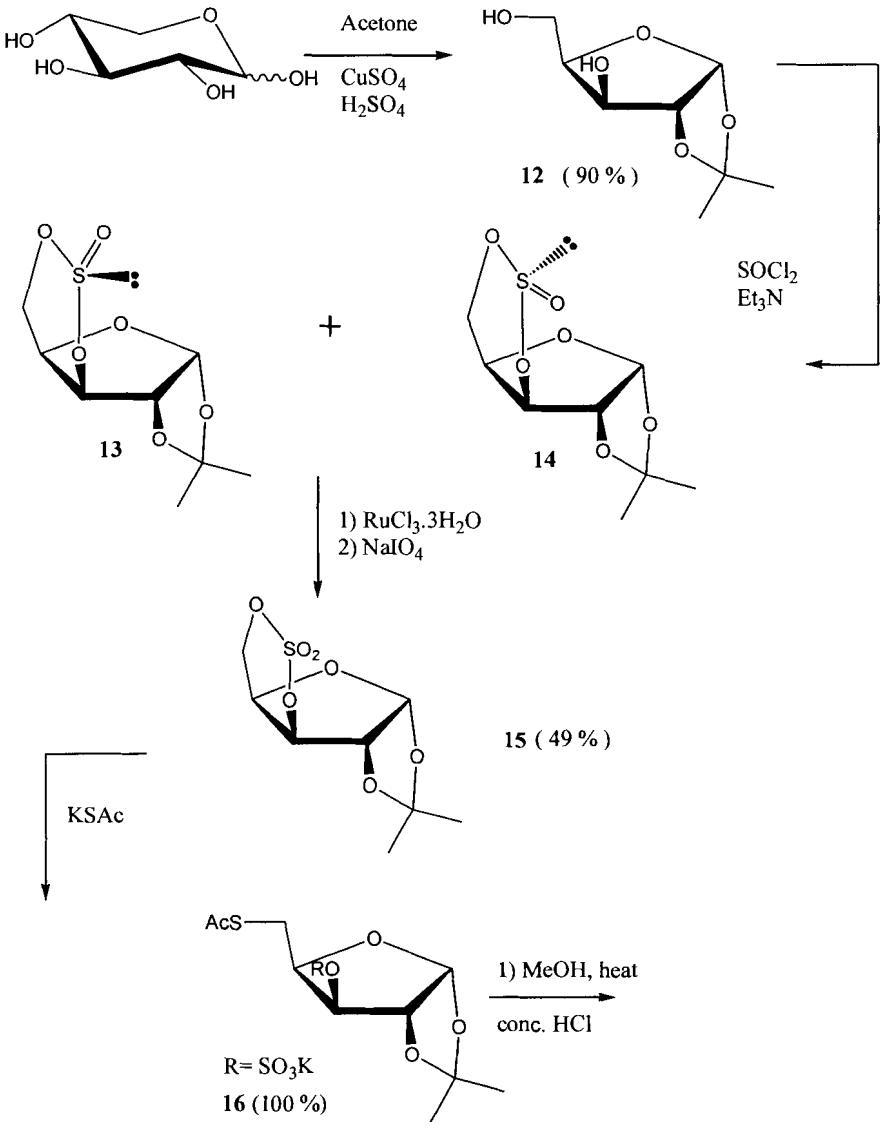
Scheme 2. Retrosynthetic analysis for compounds 4a, 4b, 5, and 6.

electrophile or a cyclic sulfate derivative **10** or **11**, whereby selective attack of the sulfur or selenium atom at the least hindered primary center should afford the desired sulfonium or selenonium ion.

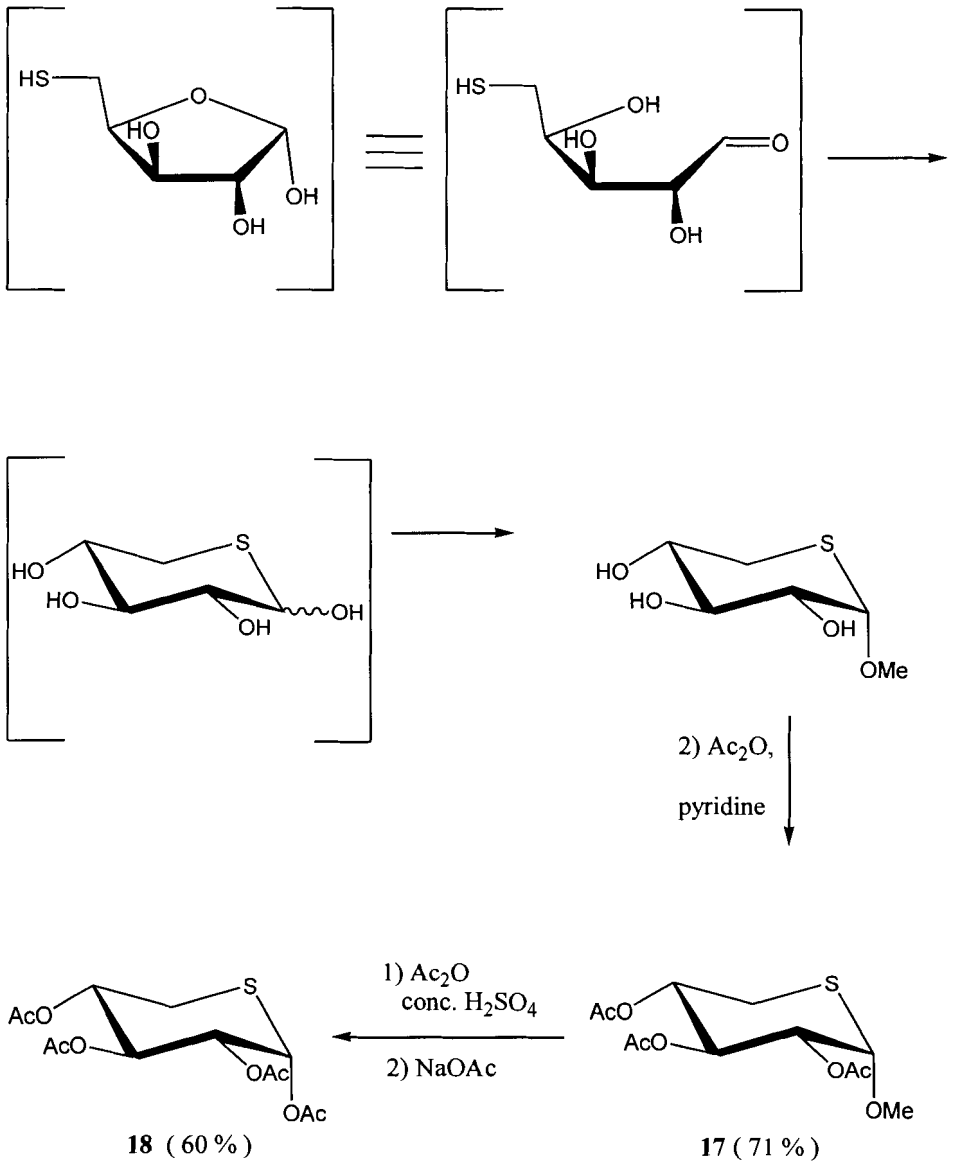
We chose to use the protected 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sufate **10** and protected 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sufate **11** as electrophiles as this has been used previously and with success in the synthesis of salacinol **1.7**, blintol **1.9**, and its derivatives.[23,24] The cyclic sulfates undergo ring opening up on attack by the thioether or the selenoether nucleophile at the least hindered primary carbon center.

2.2 Synthesis of 2,3,4-tri-*O*-benzyl-1,5-anhydro-5-thioxylitol 7.

The synthesis of 2,3,4-tri-*O*-benzyl-1,5-anhydro-5-thioxylitol **7**, as devised by E. Bozo *et al.*,[30] began with acid catalyzed isopropylidenation of D-xylose (see Scheme 3).



Scheme 3. Synthesis of 1,2,3,4-Tetra-*O*-acetyl-5-thio-α-D-xylopyranose 18.



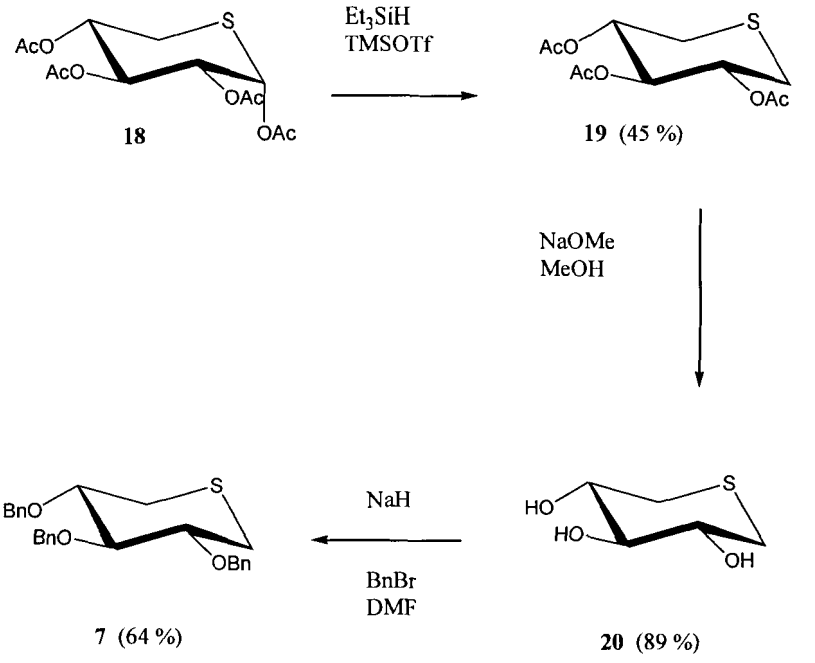
Scheme 3 (Continued). Synthesis of 1,2,3,4-Tetra-*O*-acetyl-5-thio-α-D-xylopyranose 18.

The D-xylose was initially converted to the kinetically favoured furanose form with isopropylidene groups O-1/O-2 and O-3/O-5. The isopropylidene group protecting O-3 and O-5 is more sensitive to acid hydrolysis and hence, only **12**, with the five membered

ring acetal at O-1 and O-2, remained. Compound **12** was then converted to the diastereomeric cyclic sulfites **13** and **14** with thionyl chloride in quantitative yield. The mixture of **13** and **14** was then oxidized to the corresponding cyclic sulfate **15** with $RuCl_3.3H_2O$ and $NaIO_4$. The periodate oxidized the black RuO_2 to the yellow RuO_4 which, in turn, oxidized the sulfites. The addition of KSAc to **15** resulted in the sulfate ring opening to give **16** in quantitative yield. The thioester attacks at the least hindered carbon i.e. C5. The protecting groups were removed by refluxing a methanolic solution in the presence of acid to give initially, the hemiacetal, followed by cyclization by the thiol (a more reactive nucleophile than the alcohol) to give the thiopyranose, then glycosylation by MeOH and finally, acetylation to give exclusively the *alpha* isomer **17**. The axial preference of the methoxy group is attributed to the "endo anomeric effect" whereby the lone pair on the sulfur interacts with the σ^* antibonding orbitals of the $C_{anomeric}$ -OMe bond.[31] This results in electron delocalization which is favourable and hence the methoxy group prefers an axial arrangement. Acetolysis of **17** then afforded the tetra-*O*-acetyl-D-xylopyranose **18**.

At this point, compound **18** was reduced at the anomeric carbon with TMSOTf and Et_3SiH according to the method of Jeffery et al.,[32] to give compound **19** (Scheme 4). The reaction proceeds via a thiacarbenium ion, then presumably an acetoxonium ion intermediate which forms between O1 and O2, thus directing the addition of the hydride to the equatorial position only. This step results in the removal of chirality since a meso compound is formed as evidenced by a mirror plane which passes through the sulfur atom and C3. The thio-xylitol **19** was then deprotected via methanolysis to give **20**. Finally, compound **20** was reprotected via benzylation to give **7**. The reason for re-protection is

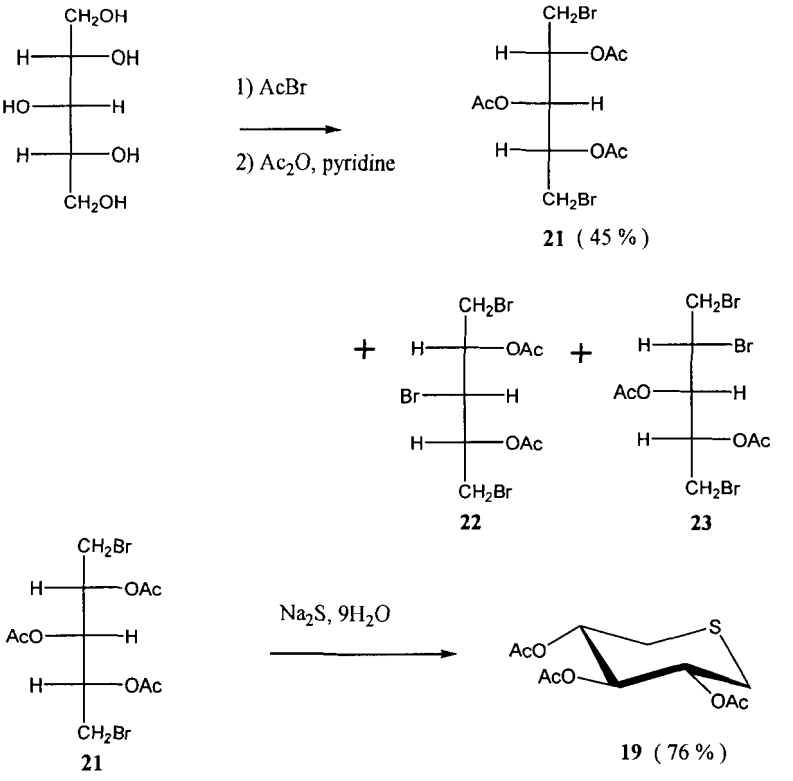
that the three benzyl groups are more electron donating than the three acetyl groups and hence, they increase the overall reactivity of the thioether.



Scheme 4. Synthesis of 2,3,4-tri-*O*-benzyl-1,5-anhydro-5-thioxylitol 7.

2.3 Alternative synthesis of 2,3,4-tri-*O*-benzyl-1,5-anhydro-5-thioxylitol 7

Since the above synthesis produced a meso compound, we thought that we could begin with xylitol as a way to reduce the number of synthetic steps (Scheme 5). Thus, as described by Crombez-Robert et al.,[33] this synthetic route began with the bromination and subsequent acetylation of xylitol to give the α, ω-dibromodideoxylitol, **21**, and minor products **22** and **23**. In the second step, compound **21** was reacted with binucleophilic sodium sulfide nonahydrate to generate the anhydrothioheterocyclic product **19**, according to the method of Halila et al.[34] At this point, this product was deprotected and benzylated as in Scheme 4 to generate the desired compound **7**.

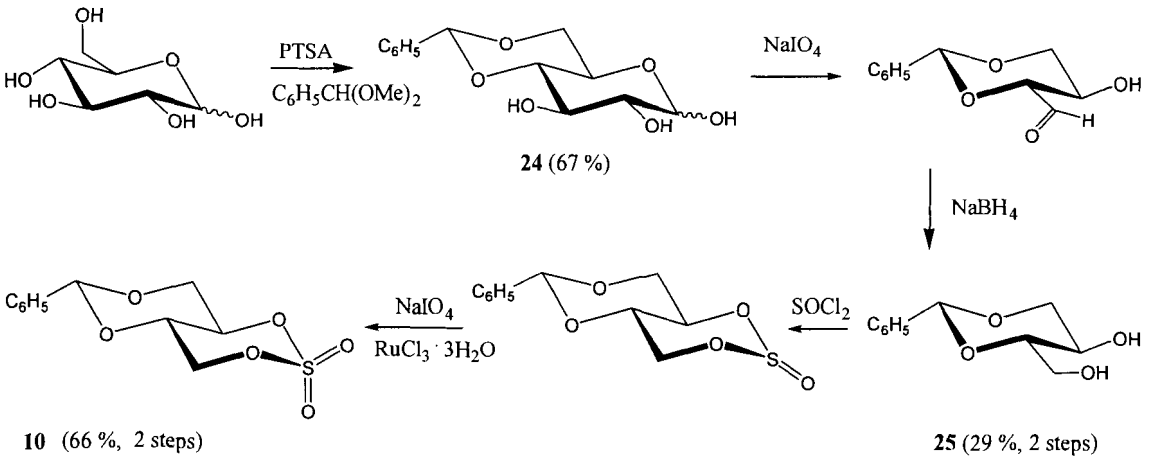


Scheme 5. Synthesis of 1,5-Anhydro-2,3,4-tri-*O*-acetyl-5-thioxylitol 19.

2.4 Synthesis of 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sulfate 10

The synthetic route to 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sulfate **10** is shown below in (Scheme 6). The synthesis began with the treatment of D-glucose with benzaldehyde dimethyl acetal to afford compound **24**, D-glucose with a six- membered benzylidene acetal at O-4 and O-6. This acetal was then subjected to periodate cleavage to generate the aldehyde followed immediately by sodium borohydride reduction. At this point, the diol was converted to the diastereomeric sulfites (1:1 ratio) with thionyl

chloride, and the mixture was then oxidized with $NaIO_4$ and $RuCl_3.3H_2O$ to give the corresponding D-cyclic sulfate **10**.

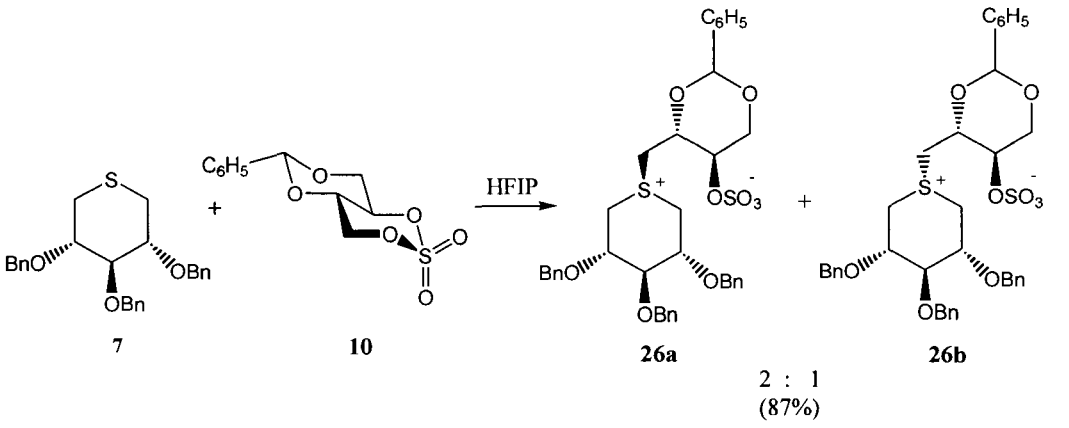


Scheme 6. Synthesis of D-cyclic sulfate 10.

2.5 Synthesis of target compounds: Sulfonium salts 1a, 1b, 4a, and 4b.

Having obtained the protected 5-thioxylitol **7**, and the D-cyclic sulfate **10**, the stage was set for the critical coupling reaction. Thus, compound **7** was reacted with D-cyclic sulfate **10** in acetone. The reaction was initially performed at 80°C but this resulted in the decomposition of the cyclic sulfate. On decreasing the temperature to 65°C, no reaction was observed until the volume was reduced considerably to obtain an approximate concentration of 0.8-1 mol/L of starting materials. At this point, two spots were observed on TLC that were more polar than the starting materials. The two components were separated and characterized by NMR techniques. Isolation of the products gave a mixture of **26a** and **26b** in approximately 37% yield. On changing the solvent to 1,1,1,3,3,3-hexafluoro-2-propanol, the yield improved to 87% (Scheme 7).

The ratio of **26a** (erythritol side chain cis to C-3 benzyloxy) to **26b** (erythritol side chain trans to C-3 benzyloxy) was 2:1. The two components were separated, isolated, and characterized by NMR techniques.

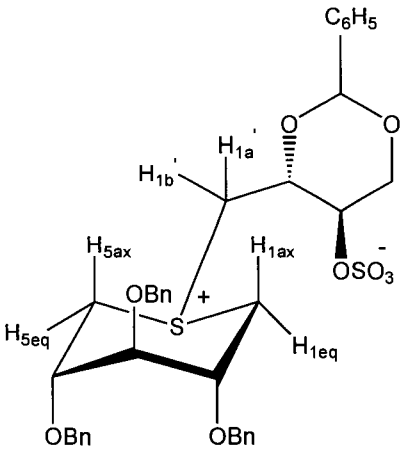


Scheme 7. Synthesis of protected sulfonium salts 26a and 26b.

Initially, a 1D ^{1}H NMR spectrum was recorded which revealed that the two compounds had the same number of hydrogen atoms. A COSY spectrum of both compounds was also obtained. This permitted the assignment of the protons on the thio-xylitol moiety and on the erythritol side chain in both compounds. Firstly, it was found that all the protons on the thioxylitol ring were shifted downfield relative to the parent thioxylitol **7**. This was not surprising since the positive sulfonium center is expected to be electron withdrawing. Furthermore, it was expected that the three benzyloxy groups at C-2, C-3 and C-4 would favour the sterically less hindered equatorial positions. However, analysis of the coupling constants showed that $J_{2,3} \approx J_{3,4} \approx 3.8$ Hz. These values are much smaller than those ($J_{2,3} \approx J_{3,4} \approx 8.9$ Hz) observed for axial-axial vicinal coupling constants in the precursor **7**. Thus, we reasoned that these compounds preferred a $^1C_4$ conformation,

placing the three benzyloxy groups in axial positions and accounting for the small coupling constants. This conformational preference can be explained by the fact that the axial substituents at C-2 and C-4 provide stabilizing gauche electrostatic interactions of the polar benzyloxy groups with the sulfonium ion center.[35] The group at C-3 can also provide stabilizing electrostatic interactions.[35] The similarity of the spectra of the two compounds suggested that the compounds differed in stereochemistry only at the stereogenic sulfur atom.

The stereochemistry at the stereogenic sulfonium center was thus established by means of a NOESY experiment. A correlation between the axial/equatorial protons of C-1 and C-5 and H-1a' and H-1b' is expected if the erythritol side chain is in an equatorial position. However, if the erythritol side chain is in an axial position then one would



26a

Figure 12. Structure of 26a.

expect to see a correlation between H-1a'/H-1b' and the equatorial protons of C-1 and C-5 only. Indeed, the NOESY spectrum for one diastereomer showed H-1b' correlations to

H-1ax/H-1eq/H-5ax as well as H-1a' and correlations to H-5eq/H-5ax (Figure 11). This isomer was thus assigned to structure **26a** with the erythritol side chain occupying the equatorial position (Figure 12). The absolute configuration at sulfur was thus established as *S*.

The NOESY spectrum for the other diastereomer showed a correlation between H-1a' and the isochronous signal assigned to H-1ax/H-1eq, as well as a correlation between H-1b' and H-5eq. No correlation with H-5ax was observed (Figure 13). This isomer was thus assigned to structure **26b**, the diastereomer with the erythritol side chain in an axial position (Figure 14). The absolute configuration at sulfur was thus established as *R*.

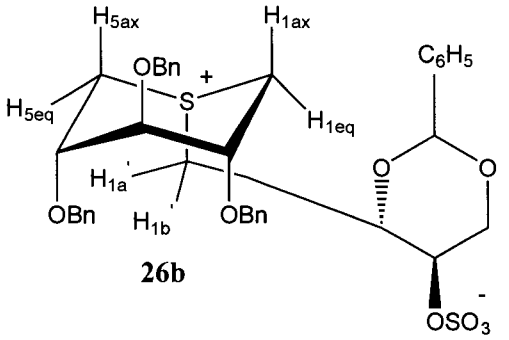


Figure 14. Structure of 26b.

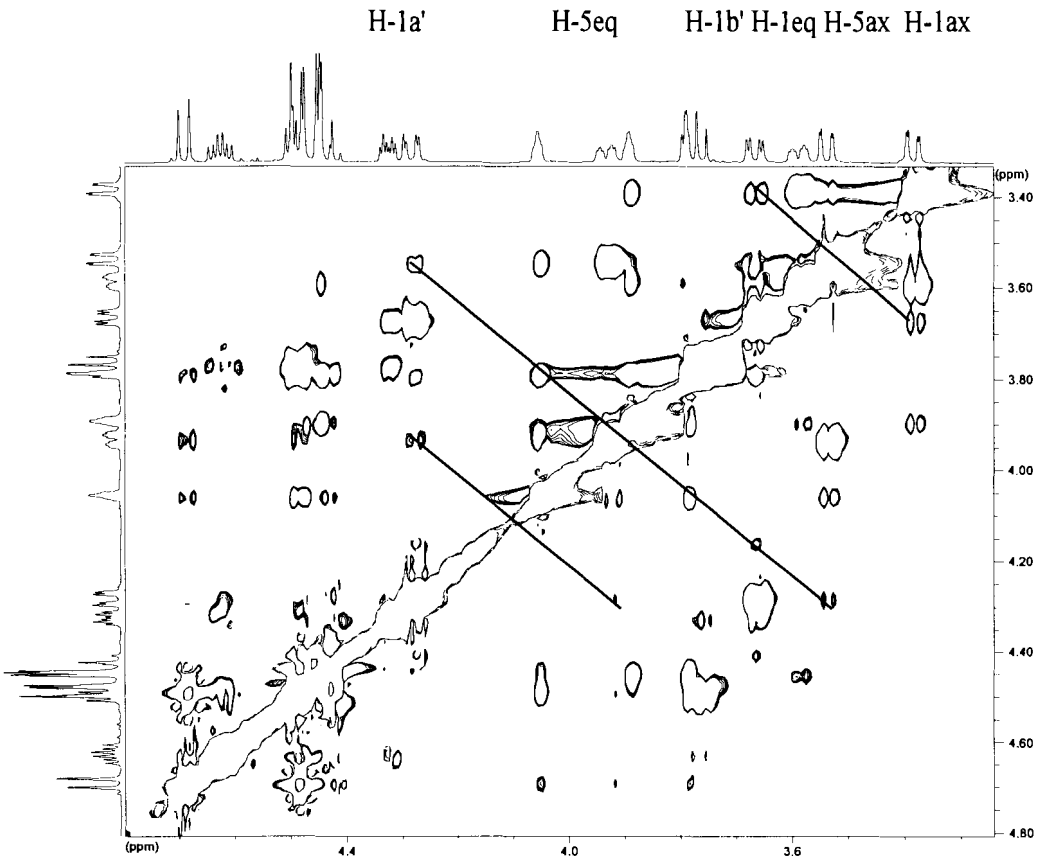


Figure 11. NOESY Spectrum of compound 26a showing relevant NOEs.

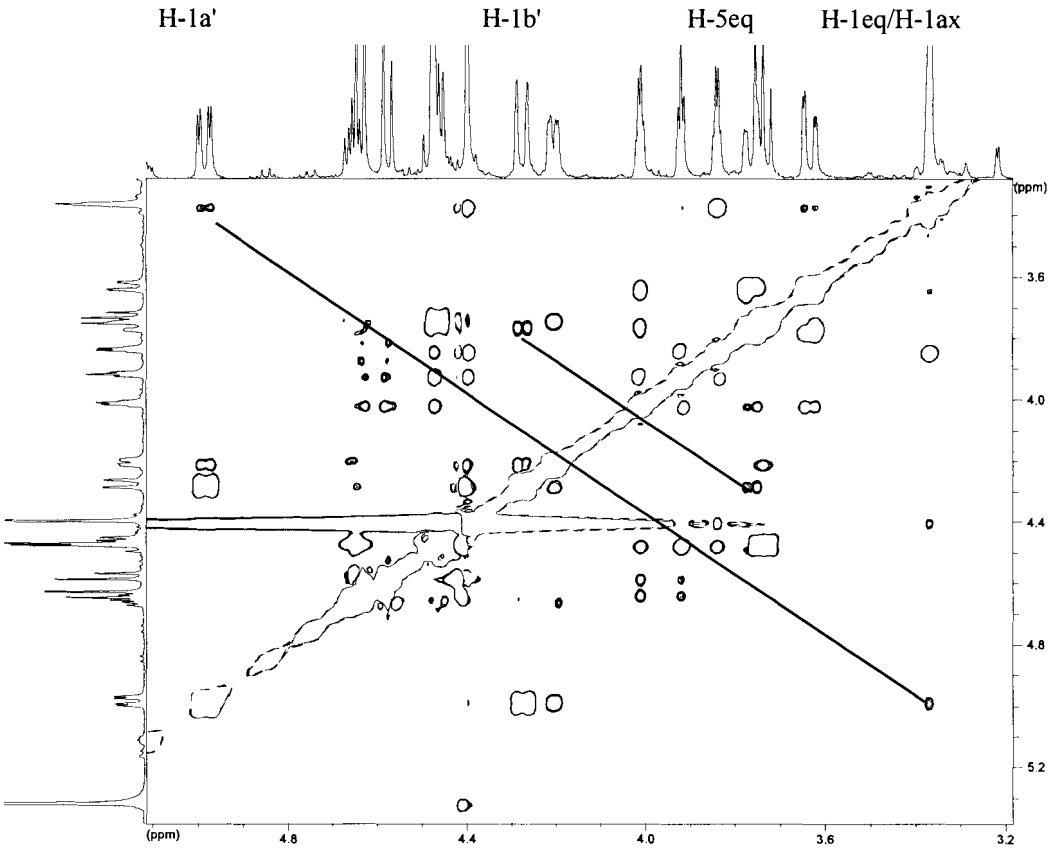
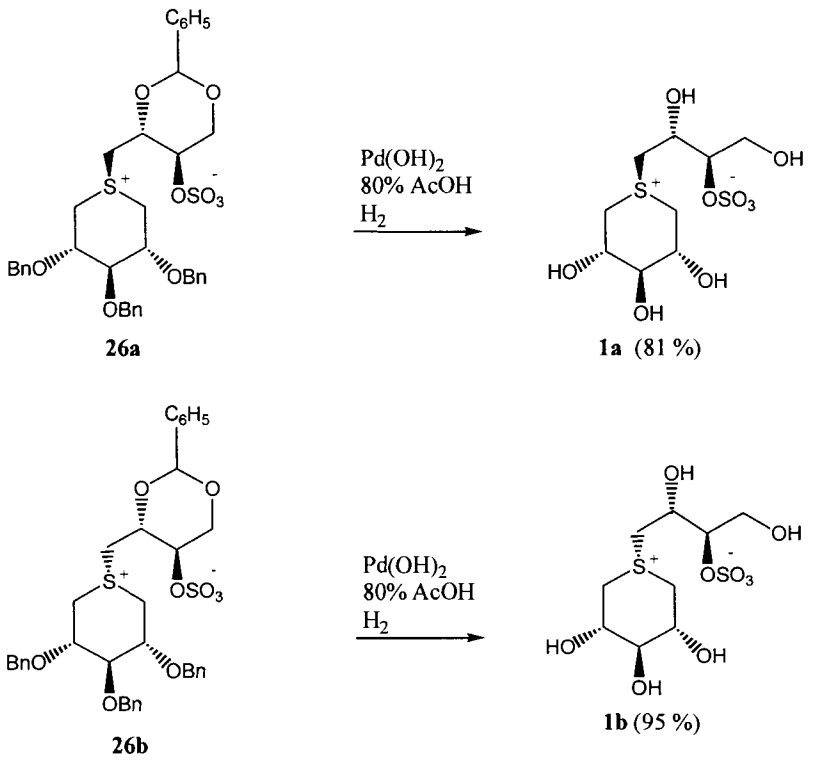


Figure 13. NOESY Spectrum of compound 26b showing relevant NOEs.

Since the two diastereomers were isolated and characterized we reasoned that the barrier to inversion at the sulfonium-ion center (which would result in the interconversion of **26a** and **26b**) is high, as also supported by the work of Brinkmann and Uzar.[40]

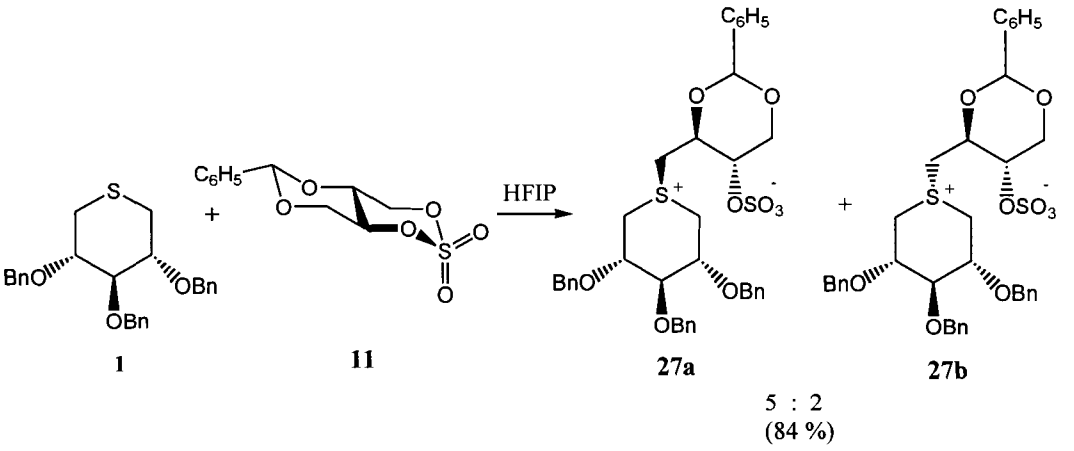
The formation of compounds **26a** and **26b** can explained by realizing that alkylation of the meso thioxylitol **7** can occur at two sites, since the sulfur atom of a sulfonium ion is a stereogenic center. On reacting with the D-cyclic sulfate **10**, two diastereoisomers are formed. The major compound, **26a**, places the benzylidene-protected erythritol side chain trans to the C-2 benzyloxy group and C-4 benzyloxy group and cis to the C-3 benzyloxy group. The preponderant conformation of compound **26a** is one in which the benzylidene-protected erythritol side chain occupies an equatorial arrangement. The minor compound, **26b**, places the benzylidene-protected erythritol side chain cis to both the C-2 and C-4 benzyloxy groups and trans to the C-3 benzyloxy group. The preponderant conformation of compound **26b** is one that places the benzylidene-protected erythritol side chain in an axial arrangement.

At this point, both diastereomers **26a** and **26b** were deprotected by hydrogenolysis (Scheme 8). Each compound gave one spot on TLC (7:3:1 EtOAc/MeOH/H_2O). The compounds were isolated and characterized by NMR techniques and found to be the desired target molecules 1,5-dideoxy-1,5 -[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salts **1a** and **1b** obtained in 81% and 95% yield, respectively.



Scheme 8. Deprotection of 26a and 26b to give the target molecules 1a and 1b.

2:5 ratio (84% yield) (Scheme 9). The major diastereoisomer **27a**, in which the erythritol side chain is cis to the C-3 benzyloxy group, was separated from the minor

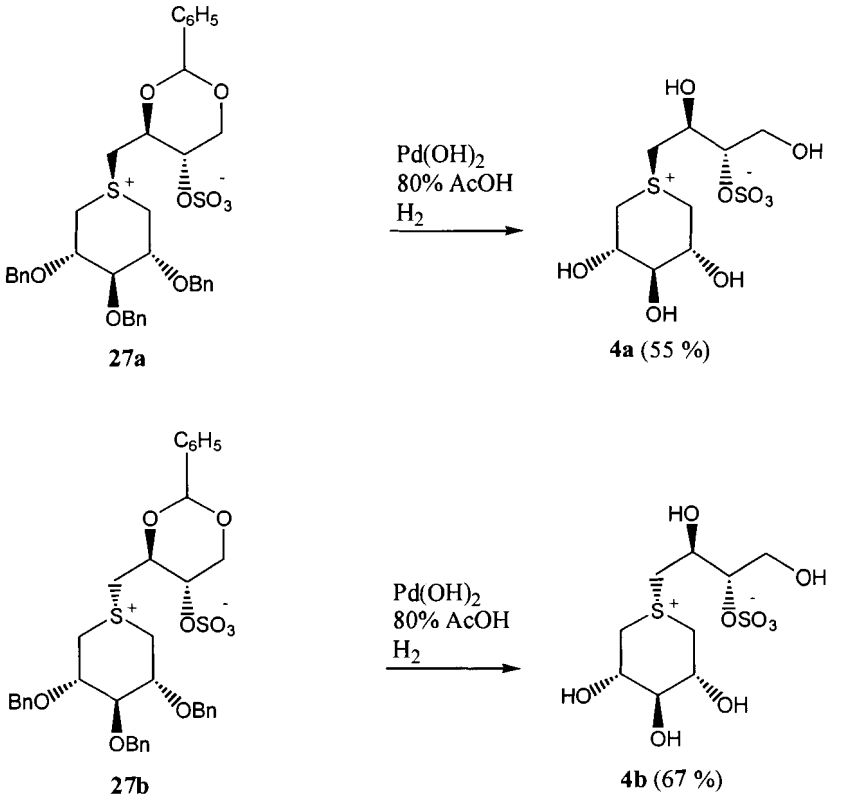


Scheme 9. Synthesis of 27a and 27b.

diastereoisomer **27b**, with the erythritol side chain trans to the C-3 benzyloxy group. These were isolated and characterized.

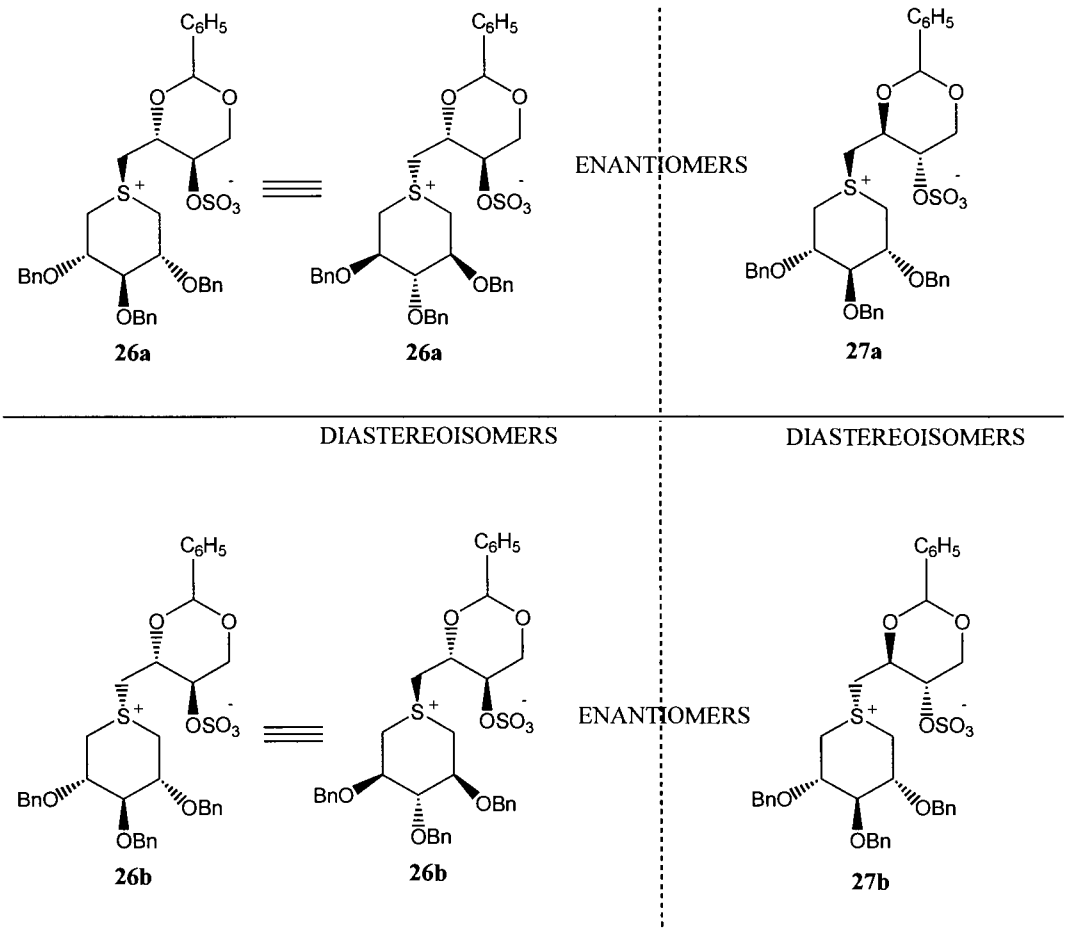
When meso thioxylitol **7** is reacted with the enantiomeric cyclic sulfate, namely the L-cyclic sulfate **11**, two diastereoisomers are formed again consisting of cis/trans isomers. The major compound, **27a**, presents the erythritol side chain in an equatorial position, as before, with the minor compound **27b** presenting an axial erythritol side chain. Compound **26a** is enantiomeric to compound **27a** and compound **26b** is enantiomeric to compound **27b** by virtue of the fact that the starting materials are enantiomeric, namely the D- and L- cyclic sulfates **10** and **11**.

At this point, both diastereomers **27a** and **27b** were deprotected via hydrogenolysis. Each compound gave one spot on TLC (7:3:1 EtOAc/MeOH/H_2O). The compounds were isolated and characterized by NMR techniques and found to be the desired target molecules 1,5-dideoxy-1,5 -[[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salts **4a** and **4b**, as shown in Scheme 10.



Scheme 10. Deprotection of 27a and 27b to give the target molecules 4a and 4b.

It was found that the NMR spectrum of compound **26a** was identical to that of compound **27a**; also the NMR spectrum of compound **26b** was identical to that of compound **27b**. This is not surprising since compounds **26a** and **27a** are enantiomers, as are compounds **26b** and **27b**. Hence **26a** and **26b** are diastereoisomers as are compounds **27a** and **27b** (Scheme 11).



Scheme 11. Stereochemical relationships between the different isomers of 26 and 27.

It is interesting to note that alkylation at the sulfur atom occurs to give the minor compounds **26b** and **27b**. Since the benzylidene-protected erythritol side chain is expected to occupy the equatorial position of the thio-ether ring based on steric hindrance, the formation of any axial product is surprising.

2.6 Configurational and conformational analysis of sulfonium salts 1a, 1b, 4a, and 4b.

Configurational analysis on compounds **1a** and **1b** was undertaken to show conclusive proof of configuration at the sulfonium center. 1D- Transient nuclear Overhauser enhancement difference experiments confirmed that there is no configurational inversion at the sulfonium center upon removal of the benzyl and benzylidene protecting groups. Thus, the major isomer **1a**, upon irradiation of the H-1a'/H-4b' multiplet showed no NOEs with the ring axial protons (Figure 15b). Irradiation of H-1ax/H-5ax showed NOE effects on the H-1eq/H-5eq/H-3 multiplet and H-2/H-4 only (Figure 15c). No NOEs with the erythritol side chain were observed. These experiments provide evidence for the erythritol side chain being present on the face opposite H-1ax, namely being up and axial. This confirmed the S configuration at the sulfonium center, as was previously assigned for the protected precursor **26a**. The minor isomer **1b**, showed, upon irradiation of the H-1b'/ H-4b' multiplet, NOE effects on the H-1ax/H-5ax protons (Figure 16b). Irradiation of the H-1ax/H-5ax triplet, showed NOE effects on the H-1b'/H-4b' multiplet as well as to the H-2/H-4/H-1a'/H-4a' multiplet, in addition to NOE effects on the ring protons (Figure 16c). These experiments provide evidence for the erythritol side chain being present on the same face as H-1ax, namely being down and equatorial. This confirmed the R configuration at the sulfonium center, as was previously assigned for the protected precursor **26b**. The configurations and conformations are depicted in Figure 17.

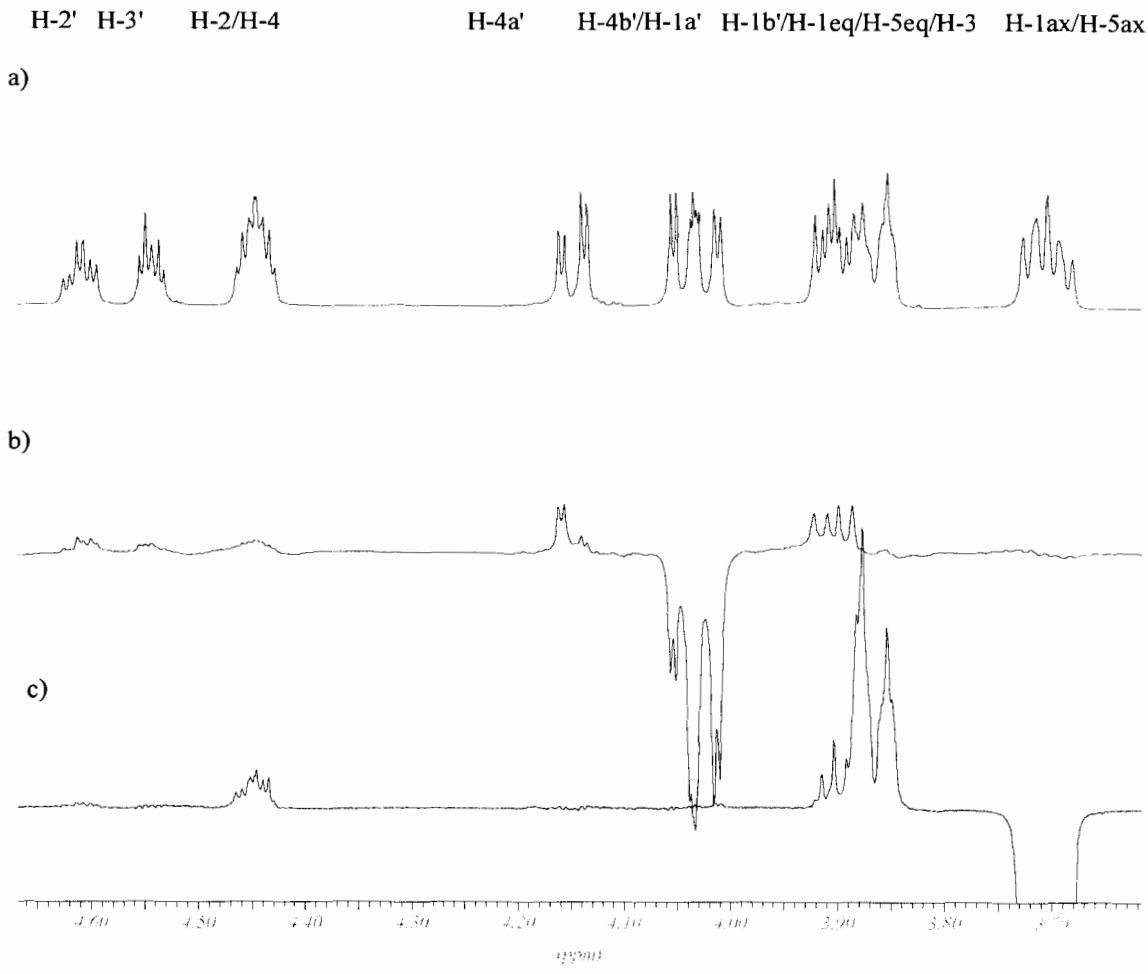


Figure 15. a) 1D NMR spectrum, b) 1D- transient NOE difference spectrum on irradiation of H-4b'/H-1a', and c) 1D- transient NOE difference spectrum on irradiation of H-1ax/H-5ax for compound 1a.

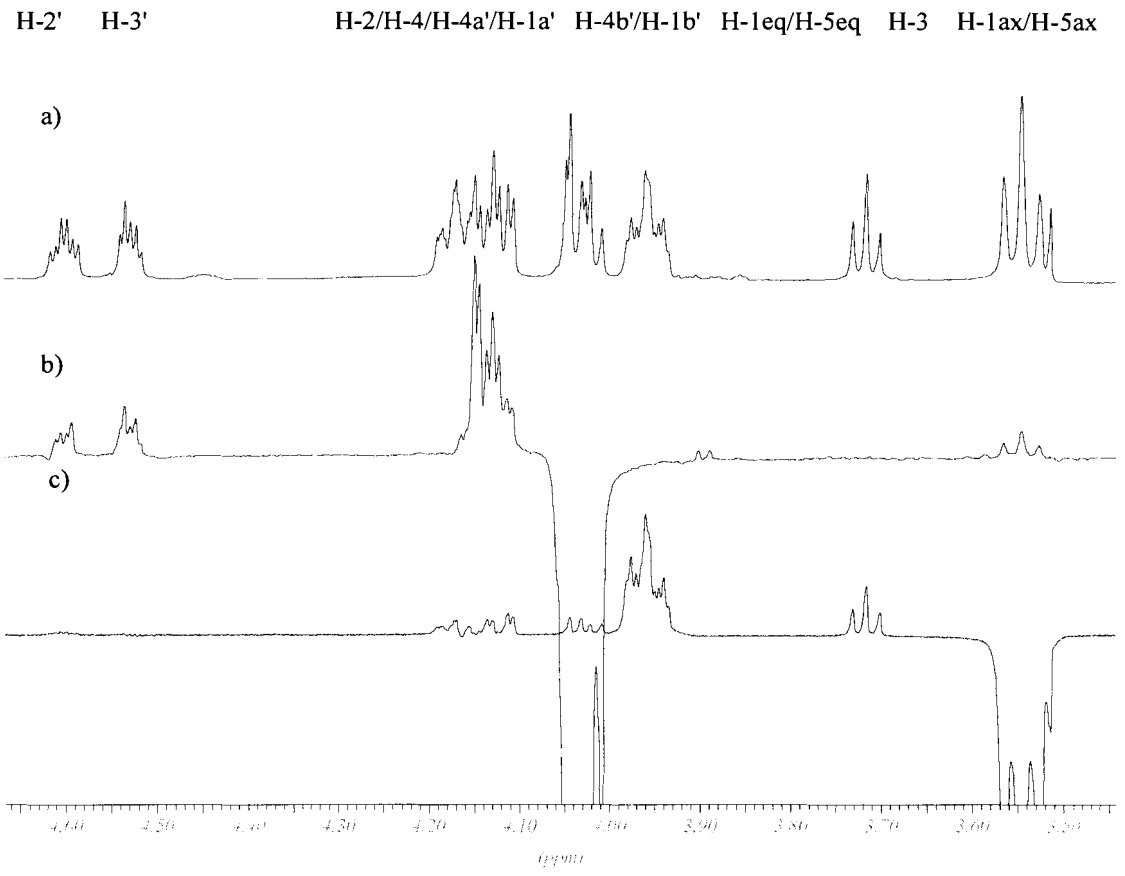


Figure 16. a) 1D NMR spectrum, b) 1D- transient NOE difference spectrum on irradiation of H-4b'/H-1b', and c) 1D- transient NOE difference spectrum on irradiation of H-1ax/H-5ax for compound 1b.

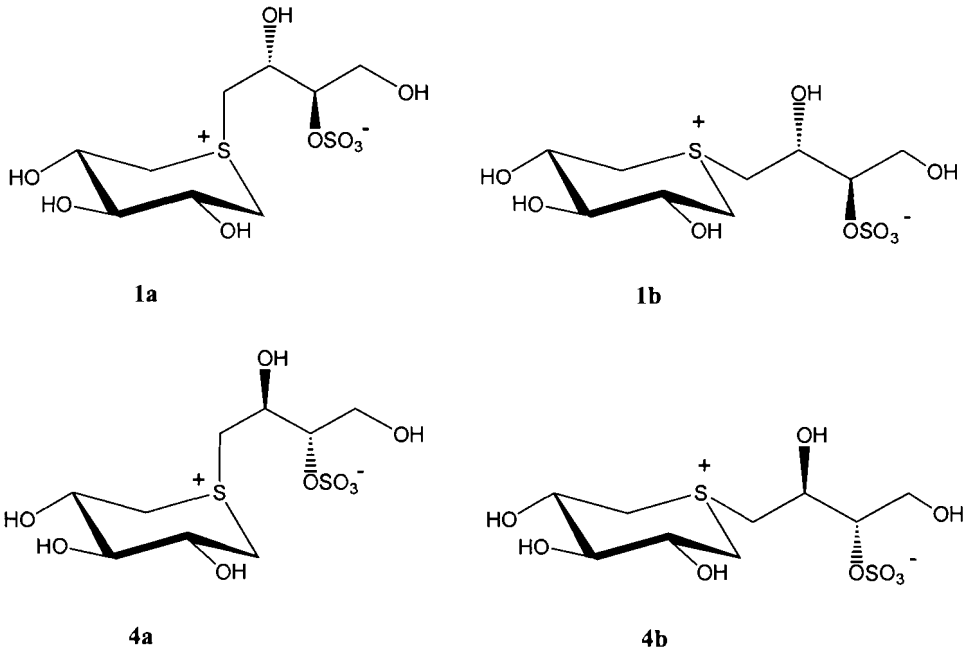
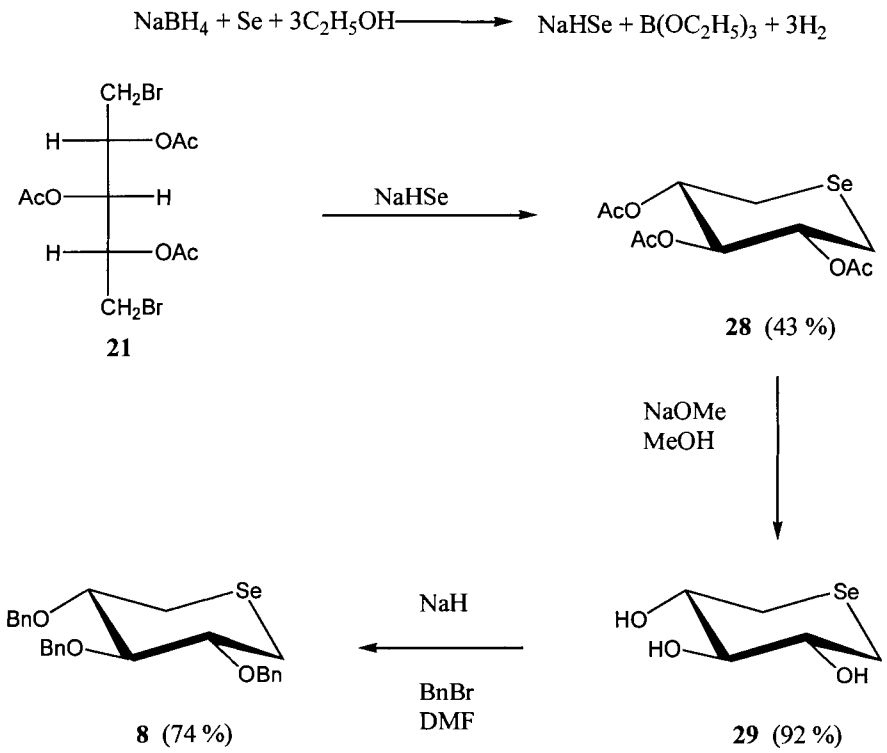


Figure 17. Conformation and configuration of target compounds 1a, 1b, 4a, and 4b.

Several interesting results were obtained upon removal of the protecting groups. Not surprisingly, one observes, on deprotection of compound **26a**, that compound **1a** is enantiomeric to the deprotected product from compound **27a**, namely **4a**. The analogous situation holds for the diastereoisomer of **26a**, namely, **26b**; that is compound **26b** is enantiomeric to compound **27b**, and compound **1b** is the enantiomer of compound **4b**. Conformational analysis of compounds **1a**, **1b**, **4a**, **4b**, reveals that all reverted to the $^4C_1$ conformation as evidenced by the coupling constants: $J_{2,3} \approx J_{3,4} \approx$ 8-9 Hz. This is indicative of axial-axial vicinal coupling and places all three hydroxyl substituents, from the xylitol moiety, in an equatorial arrangement (Figure 17). This differs from the protected precursors, **26a**, **26b**, **27a**, **27b**, in which there is predominantly a $^1C_4$ conformation with all three benzyloxy substitutents favouring an axial arrangement. The apparent differences in steric or electrostatic interactions between the two series of compounds is not readily obvious. However, it is clear that the steric interactions in **1a**, **1b**, **4a**, and **4b**, outweigh the stabilizing interactions.

2.7 Synthesis of 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol 8

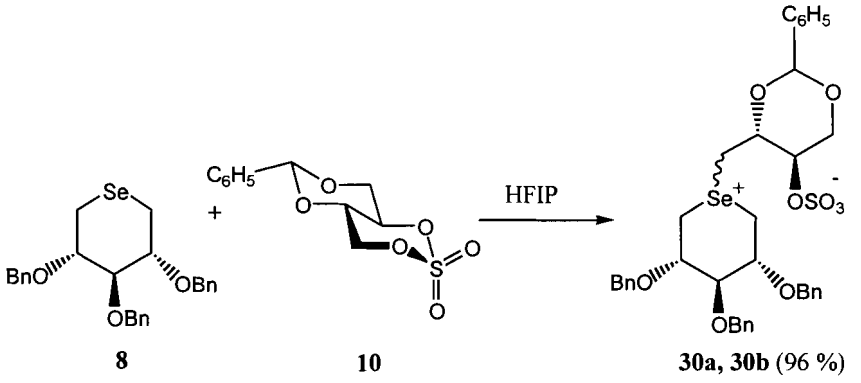
The synthesis of 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **8** began as shown in Scheme 12 with the preparation of sodium hydrogen selenide according to Klayman et al.,[36] and this was used immediately by adding the α, ω-dibromodideoxylitol, **21** to the ethanol suspension to give 1,5-anhydro-2,3,4-tri-*O*-acetyl-5-selenoxylitol **28**. At this point, compound **28** was treated identically to the sulfur analogue to generate the 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **8**.



Scheme 12. Synthesis of 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol 8.

2.8 Synthesis of target compounds: selenonium salts 2 and 5.

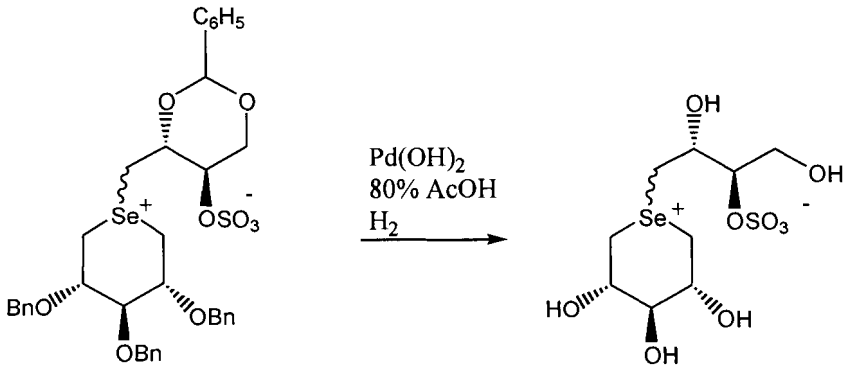
The selenium analogue, 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **8**, was coupled to the D-cyclic sulfate **10** in 1,1,1,3,3,3-hexafluoro-2-propanol solvent and afforded an inseparable mixture of two compounds, **30a** and **30b** in a 4:1 ratio in 96% yield (Scheme 13). These two compounds are diastereoisomers at the stereogenic selenium center. Alkylation can occur on selenium to give, as with sulfur, the benzylidene protected erythritol side chain either cis to the C-3 benzyloxy group or trans to the C-3 benzyloxy group. It was found that the major product, **30a**, in the 5-selenoxylitol analogues was that in which the benzylidene-protected erythritol side chain occupied an axial arrangement or more specifically was cis to the C-2 and C-4 benzyloxy



Scheme 13. Synthesis of protected selenonium salts 30a and 30b.

groups and trans to the one benzyloxy group at C-3. The minor product, **30b**, was that in which the benzylidene protected erythritol side chain was trans to the C-2 and C-4 benzyloxy groups and cis to the C-3 benzyloxy group. There was greater preference for placing the erythritol side chain axial in the 5-selenoxylitol series (80 %) whereas in the 5-thioxylitol series there was greater preference for placing the erythritol side chain equatorial (71 %). This could be because the C-2, C-3 and C-4 benzyl substituents in 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **8** are further from the selenium center than in 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol **7** and as a result the electrophile encounters less steric interactions on C-Se bond formation versus C-S bond formation. The predominant conformation observed in 5-selenoxylitol was, as with the 5-thioxylitol series, that which placed all three benzyloxy groups in an axial arrangement, thus favouring a $^1C_4$ conformation, as evidenced by the coupling constants.

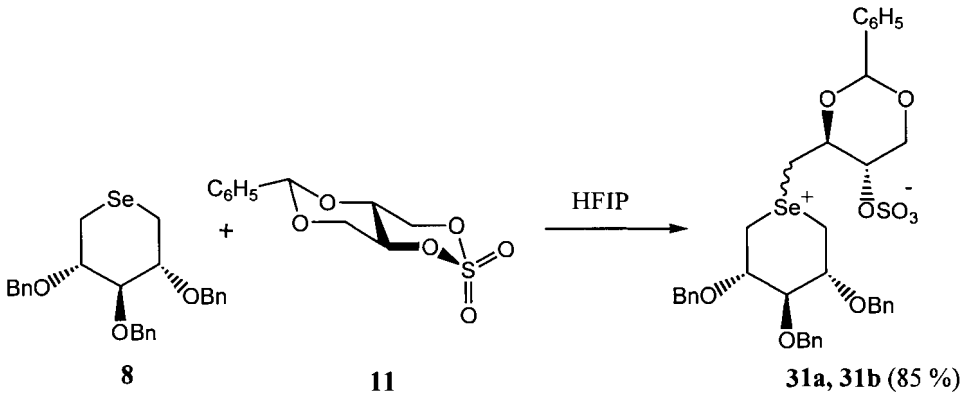
The mixture consisting of compounds **30a** and **30b** was then deprotected via hydrogenolysis to give mostly one diastereoisomer, **2**, in 39 % yield (Scheme 14). The low yield was due to catalyst poisoning, and the reaction not proceeding to completion. This major compound was characterized by NMR techniques and found to be the desired 1,5-dideoxy-1,5-[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episelenoniumylidene]-xylitol inner salt **2**.



30a, 30b **2** (39 %)

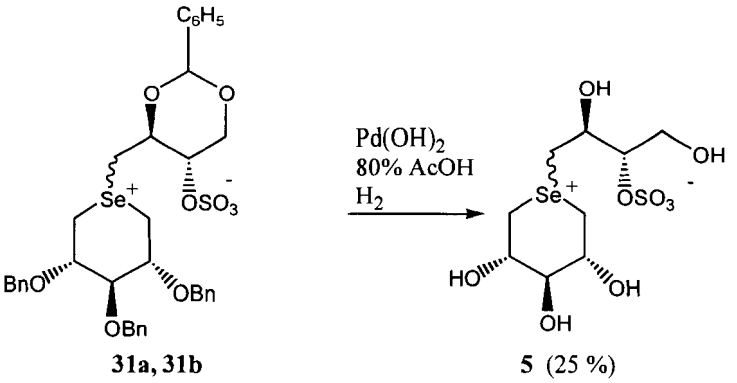
Scheme 14. Deprotection of a mixture of 30a and 30b to give the target molecule 2.

This study was concluded by reacting the seleno-ether **8** with the L-cyclic sulfate **11**. This afforded an inseparable mixture of two compounds, **31a** and **31b** (Scheme 15), which are diastereoisomers at the stereogenic selenium center, in a 23:7 ratio.



Scheme 15. Synthesis of protected selenonium salts 31a and 31b.

The mixture consisting of **31a** and **31b** was then deprotected by hydrogenolysis to afford mostly one diastereoisomer, **5**, in 25% yield (Scheme 16). The major compound was characterized by NMR techniques and found to be the desired 1,5-dideoxy-1,5-[[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episelenoniumylidene]-xylitol inner salt **5**, the enantiomer of 1,5-dideoxy-1,5-[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episelenoniumylidene]-xylitol inner salt **2**.



31a, 31b **5** (25 %)

Scheme 16. Deprotection of a mixture of 31a and 31b to give the target molecule 5.

Comparison of enantiomeric **2** and **5** with the corresponding thio analogue **1b** revealed very little differences in the ^{1}H and ^{13}C NMR spectra. There was a slight upfield shift observed for atoms close to the selenium center relative to the sulfur center. This is to be expected as the carbon-sulfur bond is shorter than the carbon-selenium bond, and the electron withdrawing effect of the positively charged center decreases with distance. As with the 5-thioxylitol series, on deprotection, the molecule favoured a $^{4}C_{1}$ conformation in which all three hydroxyl groups on the selenoxylitol moiety occupied an equatorial arrangement.

The stereochemistry at the stereogenic selenonium center for the enantiomers **30a** and **31a** was established by means of NOESY experiments. The NOESY spectrum is shown in Figure 19. The major isomer was found to be that in which the erythritol side chain occupied the axial position and was cis to the C-2 and C-4 benzyloxy groups and trans to the C-3 benzyloxy group. This was evidenced by correlations between H-1b' and H-5eq as well as correlations between H-1a' and H-1eq. An axial preference would imply correlations between H-1a'/H-1b' and H-5eq and H-1a'/H-1b' and H-1eq only, since free rotation about the C-1'-selenium bond would not permit the H-1a' and H-1b' protons to interact with the axial C-1 and C-5 protons as these are on the other side of the selenoether ring. Therefore, NOEs would not be expected between H-1a'/H-1b' and H-1ax/H-1eq. On the other hand, an equatorial preference would imply correlations between H-1a'/H-1b' to H-1ax and H-5ax as well as possibly to H-1eq and H-5eq. On this basis, the enantiomeric selenonium salts were assigned the absolute configurations shown in Figure 18. Thus, for compound **30a** the absolute configuration at the selenium center is R whereas for the enantiomeric **31a**, the absolute configuration at the selenium center is S. In both cases, the erythritol side chain is cis to the benzyloxy groups at C-2 and C-4 and trans to the C-3 benzyloxy group.

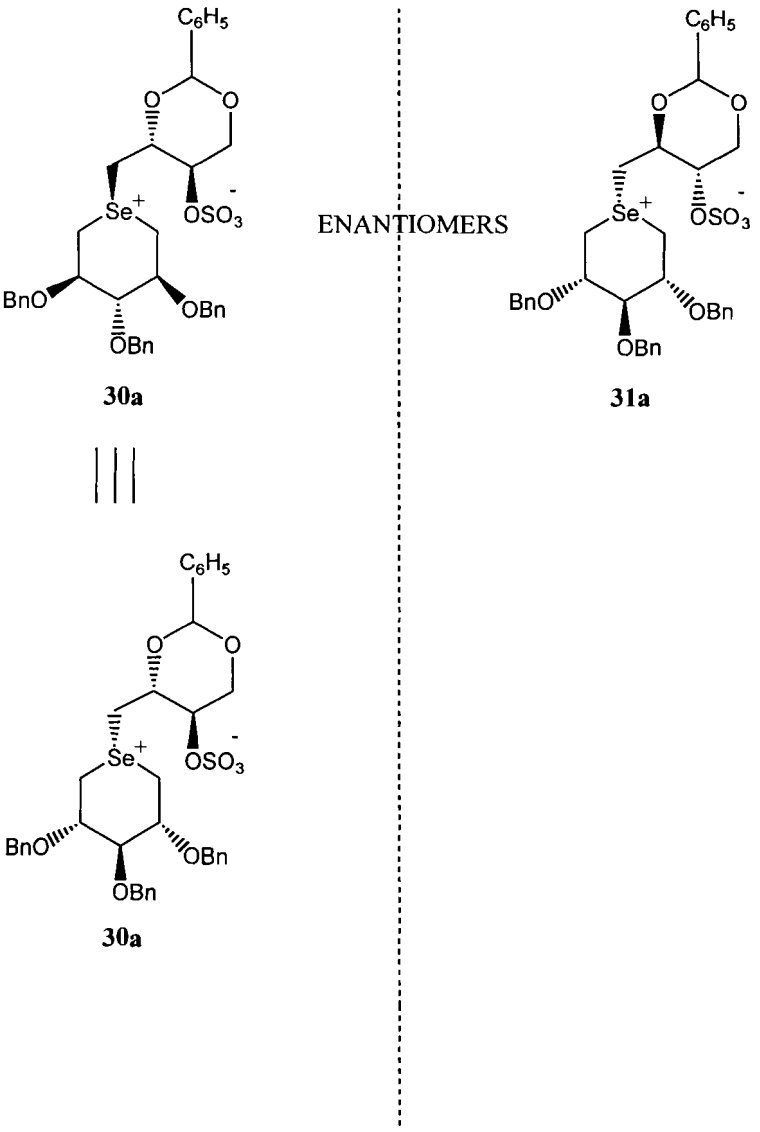


Figure 18. Structures of enantiomers 30a and 31a.

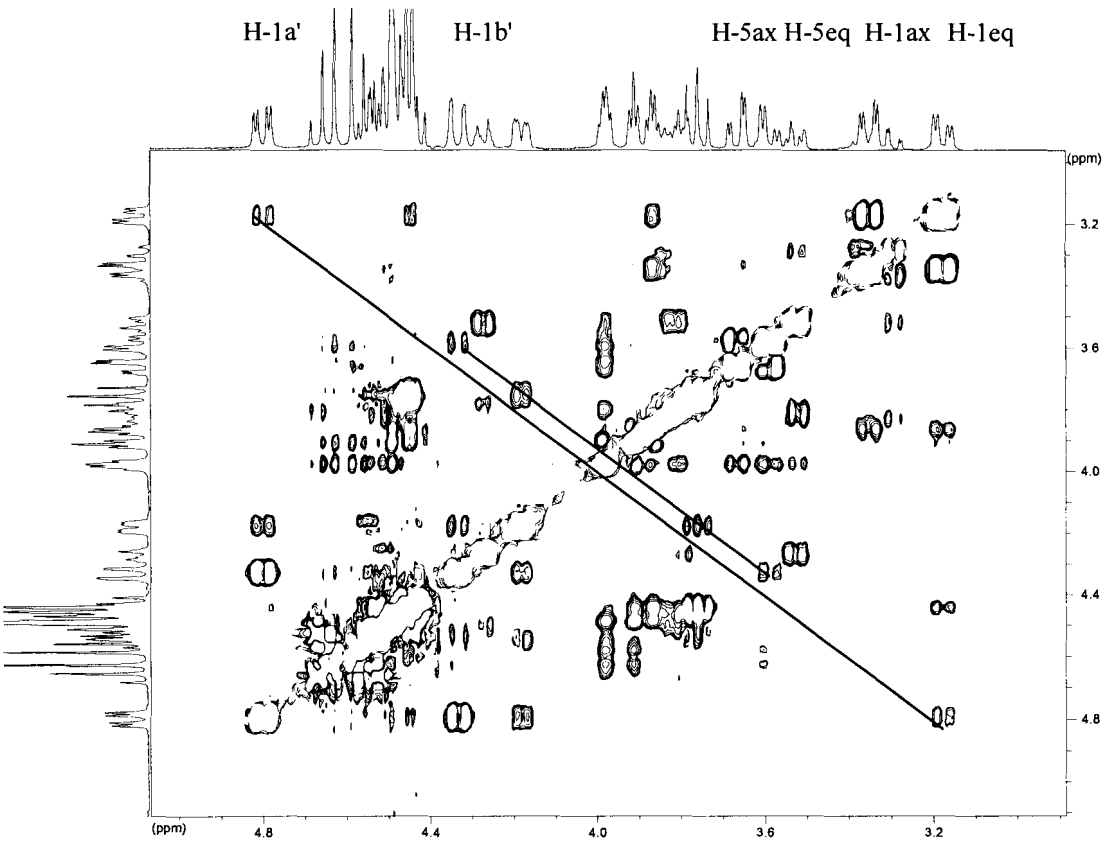


Figure 19. NOESY spectrum of compounds 30a and 30b showing relevant NOEs.

2.9 Configurational and conformational analysis of selenonium salts 2 and 5.

Configurational analysis of enantiomeric compounds **2** and **5** was undertaken to show conclusive proof of configuration at the selenonium center. 1D- Transient nuclear Overhauser enhancement difference experiments confirmed that there is no configurational inversion at the selenonium center upon removal of the benzyl and benzylidene protecting groups. Thus, the major isomer **2**, showed, upon irradiation of the H-1ax/H-5ax multiplet, NOEs with H-3, H-1eq/H-5eq as well as to the multiplet consisting of H-2/H-4 and to H-1a'/H-1b'/H-4a' (Figure 20b). Irradiation of H-1eq/H-5eq showed NOE effects on H-1ax/H-5ax and on H-2/H-4 only (Figure 20c). No NOEs with the erythritol side chain were observed. These experiments proved that the erythritol side chain is on the same side of the seleno-ether ring as H-1ax, and confirmed the R configuration at the selenonium center, as was previously assigned for the protected precursor **30a**. The conformations and configurations are shown in Figure 21.

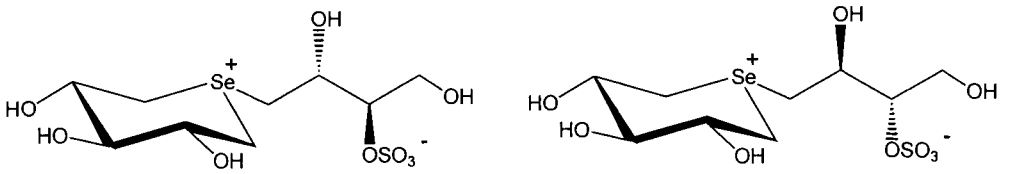


Figure 21. Conformation and configuration of target compounds 2 and 5.

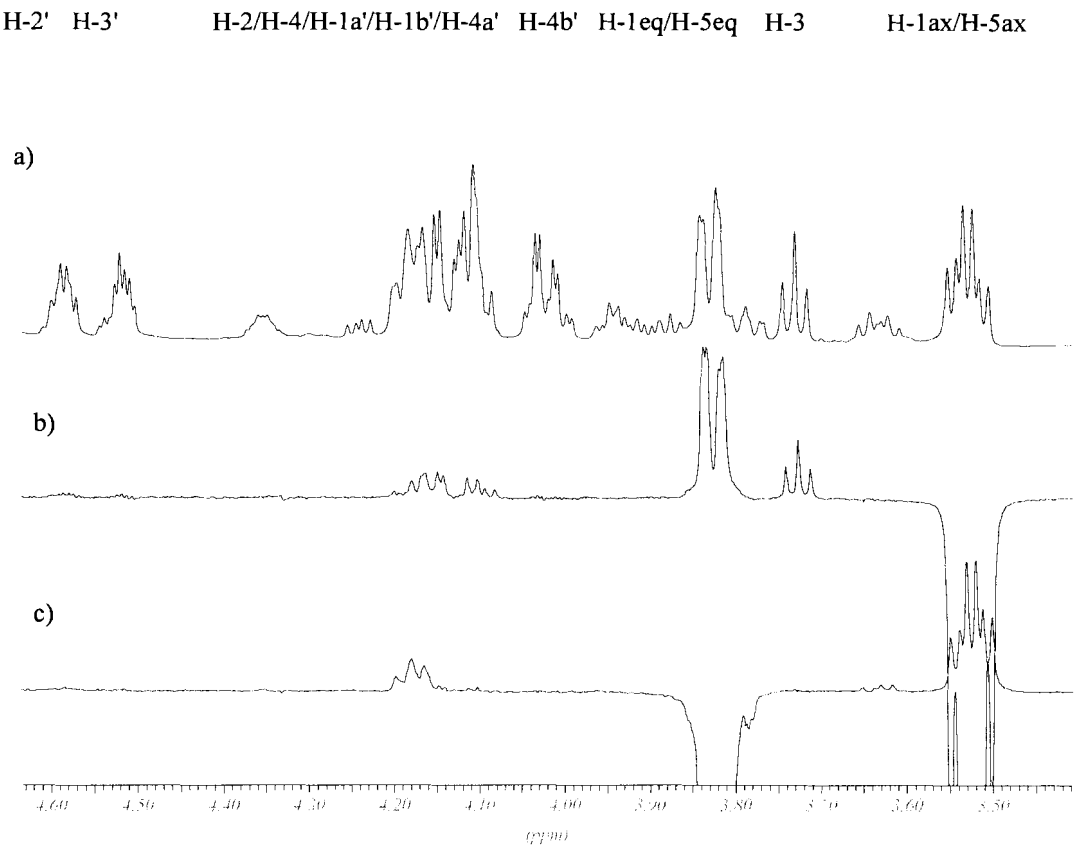
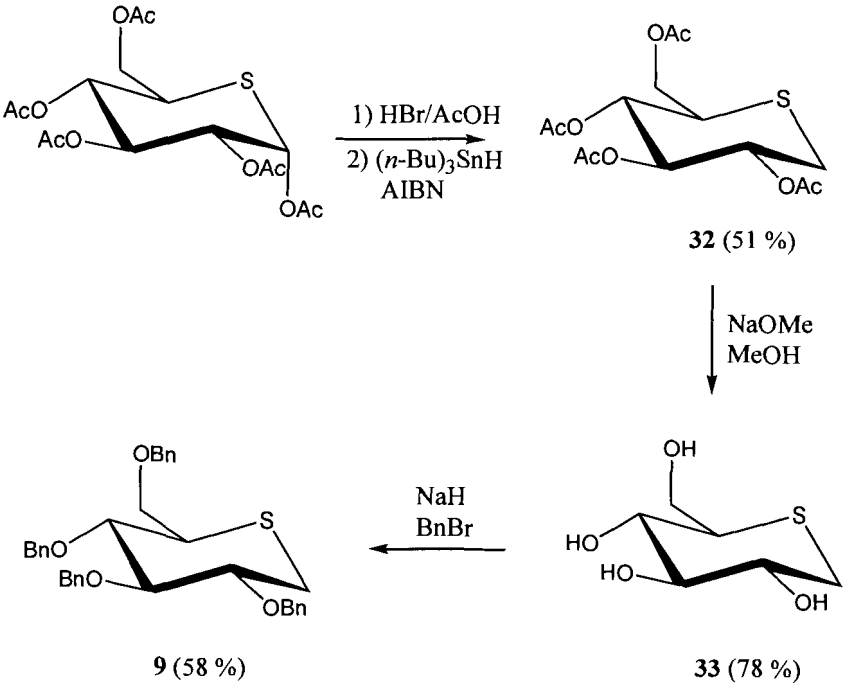


Figure 20. a) 1D NMR spectrum, b) 1D- transient NOE difference experiment on irradiation of H-1ax/H-5ax, and c) 1D- transient NOE difference experiment on irradiation of H-1eq/H-5eq for compound 2.

2.10 Synthesis of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol 9

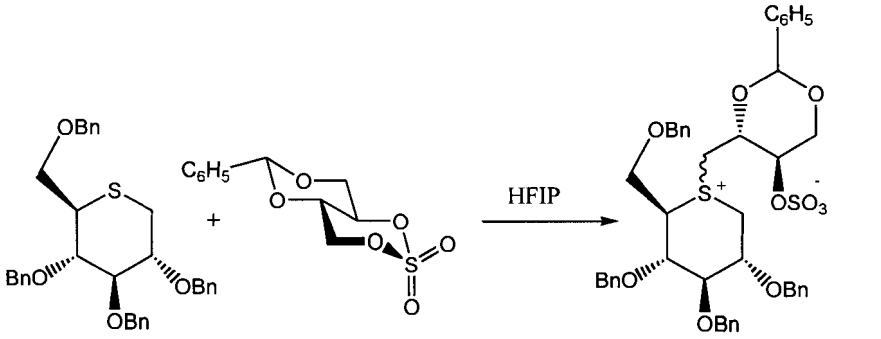
Entry into the 5-thio-D-glucitol analogues began with peracetylated 5-thio-D-glucose as shown in Scheme 17. As described previously,[35] activation to α– and β–glycosyl bromides by treatment with HBr in AcOH was followed by reduction with (n-Bu)$_3$SnH to give 1,5-anhydro-2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucitol **32** in 51% yield. Methanolysis then removed the acetate protecting groups in 78% yield. Reprotection with benzyl ethers was then carried out in 58% yield to generate the 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **9** moiety required for the critical coupling reaction.



Scheme 17. Synthesis of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol 9.

2.11 Synthesis of target compounds 3 and 6

Treatment of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **9** with the D-cyclic sulfate **10** afforded an inseparable mixture of compounds **34a** and **34b** in 70% yield in an approximate 2:1 ratio (Scheme 18).



9 **10** **34a, 34b** (70 %)

Scheme 18. Synthesis of protected sulfonium salts 34a and 34b.

As with the xylitol series, the protected glucitol derivative **34a** displayed an unusual $^1C_4$ conformation, as indicated by the coupling constants. This places the three benzyloxy groups at C-2, C-3 and C-4 as well as the benzyloxy methyl group at C-5 in an axial arrangement.

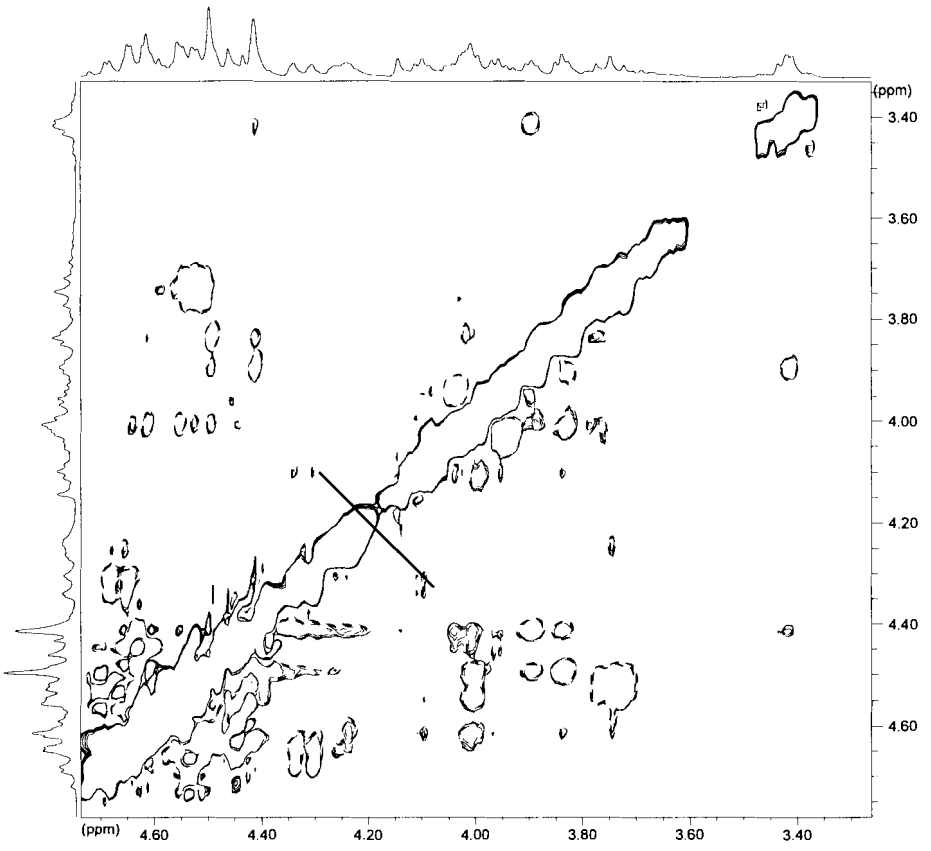
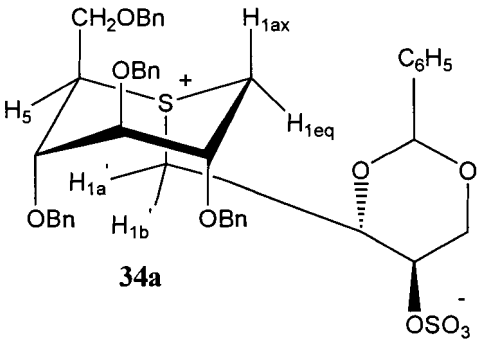


Figure 22. NOESY spectrum of a mixture of 34a and 34b showing relevant NOEs.

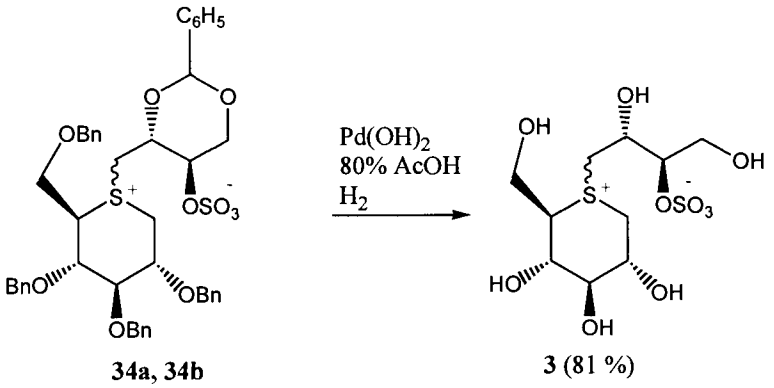
The stereochemistry at the stereogenic sulfonium center for the major isomer **34a** was established by means of a NOESY experiment. The NOESY spectrum is shown in Figure 22. A strong NOE correlation was observed between the H-1b' proton and the H-5 proton, thus confirming that the benzylidene-protected erythritol side chain was on the same side as H-5. NOEs to H-1ax and to H-6a/H-6b were not observed. Thus, the absolute configuration at the sulfonium center was S (Figure 23). This is not surprising because it is expected that the top face of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **9** is shielded because that is the side from which the C-5 benzyloxymethyl group protrudes. As a result, the electrophile, **10**, will prefer to orient from the opposite face, on the same side as the C-2 and C-4 benzyl ethers.



34a

Figure 23. Structure showing the absolute configuration of compound 34a.

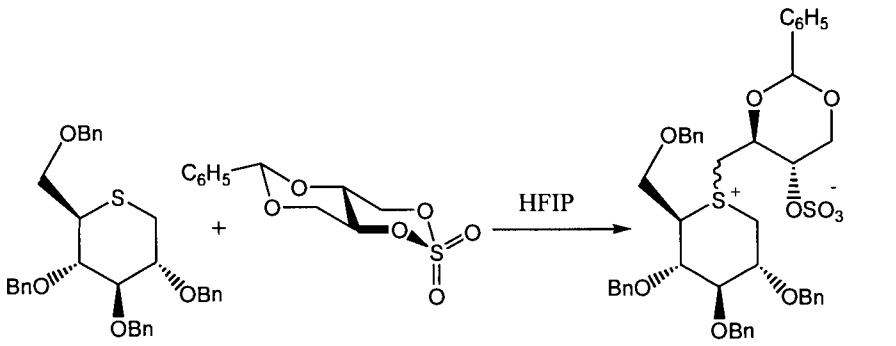
The mixture consisting of compounds **34a** and **34b** was then subjected to hydrogenolysis to give primarily 1,5-dideoxy-1,5 -[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt **3** in 81% yield (Scheme 19).



34a, 34b **3** (81 %)

Scheme 19. Deprotection of a mixture of 34a and 34b to give the target molecule 3.

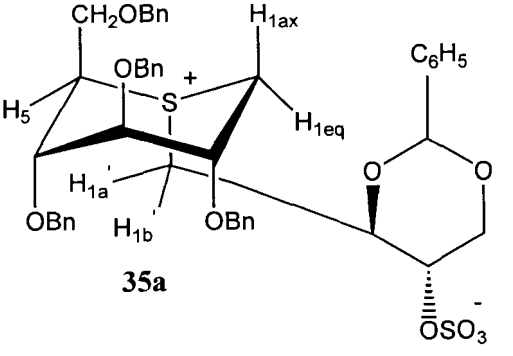
Treatment of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **9** with the L-cyclic sulfate **11** afforded an inseparable mixture of compounds **35a** and **35b** in 68% yield in an approximate 3:1 ratio (Scheme 20). Whereas the meso 1,5-anhydro-2,3,4,-tri-*O*-benzyl-5-thioxylitol, and the meso 1,5-anhydro-2,3,4,-tri-*O*-benzyl-5-selenoxylitol generated enantiomers on reacting with enantiomeric L- and D- cyclic sulfates, this was not the case for the chiral 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol. In this case, compounds **34a** and **35a** are not enantiomers.



9 **11** **35a, 35b** (68 %)

Scheme 20. Synthesis of protected sulfonium salts 35a and 35b.

The stereochemistry at the stereogenic sulfonium center for the major isomer **35a** was established by means of a NOESY experiment. A strong NOE correlation was observed between the H-1a' proton and H-5. In addition, there was also an NOE correlation between H-2' and H-5. The NOESY spectrum is shown in Figure 24. This confirmed that the benzylidene protected erythritol side chain was on the same side as H-5. NOEs to H-1ax and to H-6a/H-6b were not observed. Thus, the absolute configuration at the sulfonium center was S (Figure 25). This is in agreement with diastereoisomer **34a**, in which the electrophile is oriented, and thus attacked on the least hindered side of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **9**.



35a

Figure 25. Structure showing the absolute configuration of compound 35a.

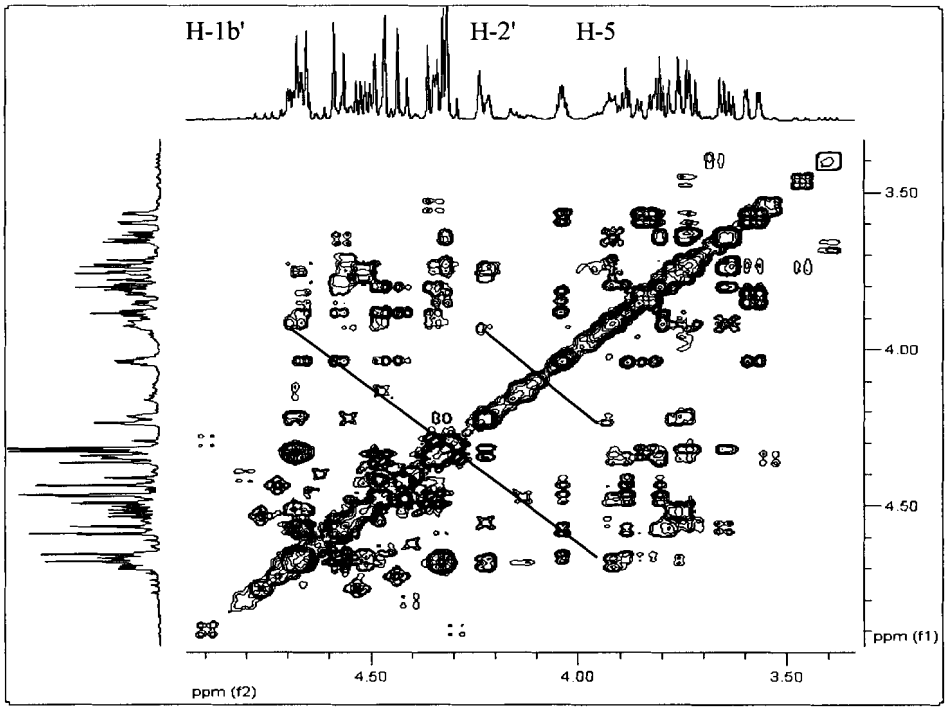
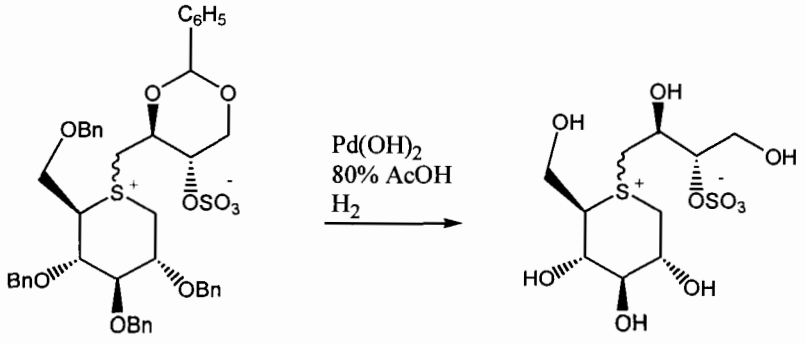


Figure 24. NOESY spectrum of a mixture of 35a and 35b showing relevant NOEs.

The mixture containing **35a** and **35b** was then subjected to hydrogenolysis to give primarily 1,5-dideoxy-1,5-[[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt **6** in 67 % yield (Scheme 21).



35a, 35b **6** (67 %)

Scheme 21. Deprotection of a mixture of 35a and 35b to give the target molecule 6.

2.12 Configurational and conformational analysis of sulfonium salts 3 and 6.

Configurational analysis of diastereomeric compounds **3** and **6** was undertaken to show conclusive proof of configuration at the sulfonium center. 1D- Transient nuclear Overhauser enhancement difference experiments confirmed that there is no configurational inversion at the sulfonium center upon removal of the benzyl and benzylidene protecting groups. Compound **3** showed, upon irradiation of H-1ax, NOEs with H-1eq, H-3, H-5 and importantly with H-1b' (Figure 26b). This was evidence for the erythritol side chain being on the same side of the thio-ether ring as H-1ax, that is, the side chain was down and equatorial. The 1D ^{1}H NMR spectrum is shown in Figure 26a and the 1D TOCSY spectrum for the thio-ether ring spin system is shown in Figure 26c. This confirmed the S configuration at the sulfonium center, as was previously assigned for the protected precursor **34a**. Compound **6**, showed, upon irradiation of the H-1ax triplet, NOEs with H-1b' as well as to H-5 and H-1eq (Figure 27c). This was evidence for the erythritol side chain being on the same side of the thio-ether ring as H-1ax, that is the side chain was down and equatorial. The 1D TOCSY NMR spectrum for the erythritol spin system is shown in Figure 27a and that for the thio-ether ring spin system is shown in Figure 27b. This confirmed the S configuration at the sulfonium center, as was previously assigned for the protected precursor **35a**. The configurations are shown in Figure 28.

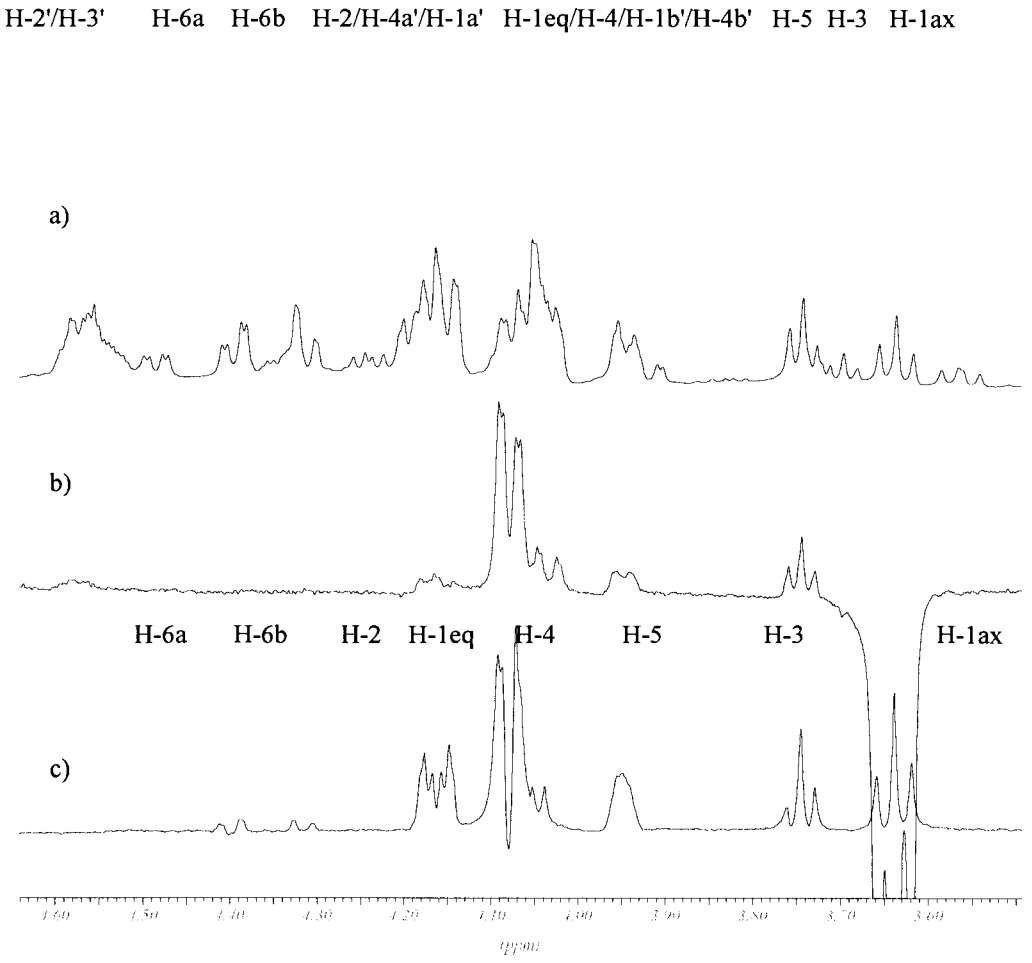


Figure 26. a) 1D ^{1}H NMR spectrum, b) 1D- transient NOE difference experiment on irradiation of H-1ax and c) 1D TOCSY spectrum on irradiation of H-1ax, for compound 3.

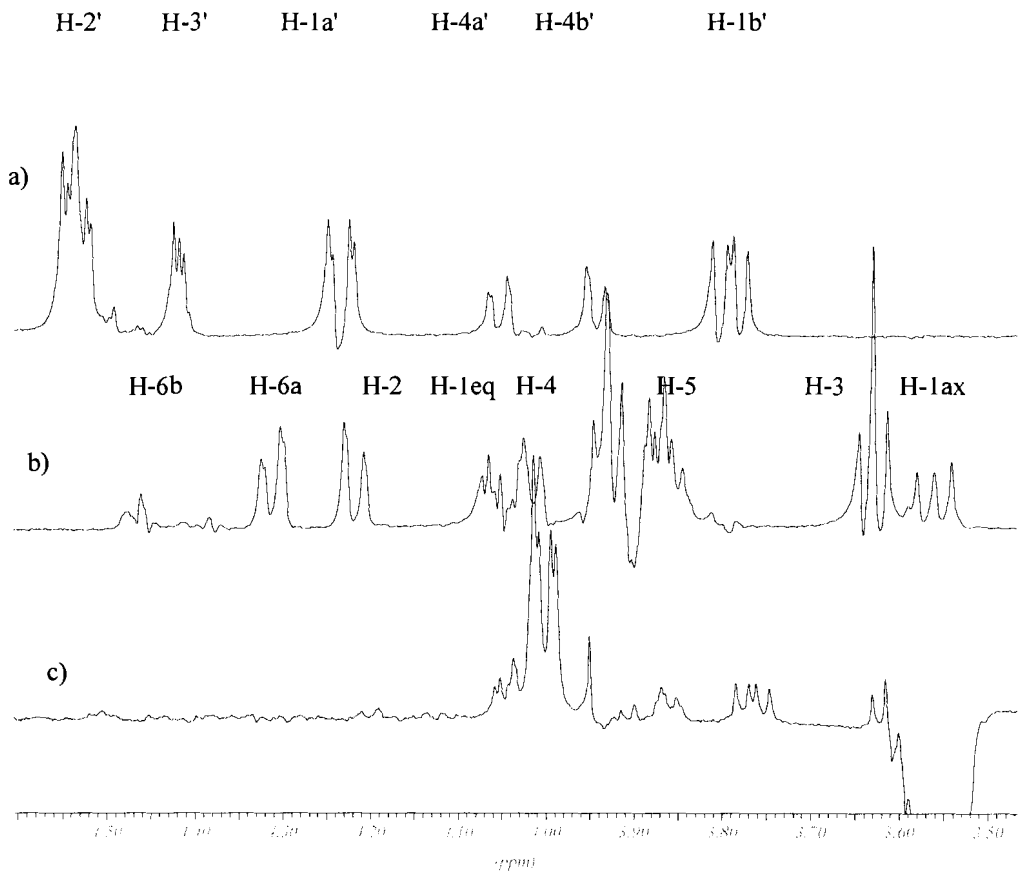
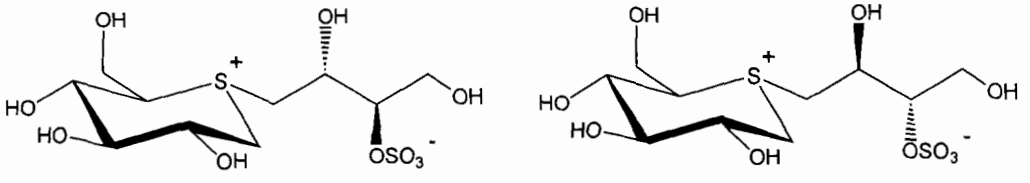


Figure 27. a) 1D TOCSY spectrum on irradiation of H-5, b) 1D TOCSY spectrum on irradiation of H-2', and c) 1D- transient NOE difference experiment on irradiation of H-1ax for compound 6.

Upon removal of the protecting groups, compounds **3** and **6** adopted a $^4C_1$ conformation, as indicated by the inter-proton coupling constants. This places all of the ring substituents in an equatorial orientation. The analogous situation was observed for the xylitol series. The conformation and configuration of compounds **3** and **6** are shown in Figure 28.



3 6

Figure 28. Conformation and configuration of target compounds 3 and 6.

CHAPTER 3. CONCLUSIONS

The syntheses of target compounds: 1,5-dideoxy-1,5-[(*S*)-[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salt **1a** and its enantiomer 1,5-dideoxy-1,5-[(*R*)-[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salt **4a**, as well as their configurational isomers, the enantiomers 1,5-dideoxy-1,5-[(*R*)-[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salt **1b** and 1,5-dideoxy-1,5-[(*S*)-[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-xylitol inner salt **4b** have been achieved. The program was extended to include the syntheses of the corresponding selenium analogue **2** and its enantiomer **5**, as well as 1,5-dideoxy-1,5 -[(*S*)-[(2*S*, 3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt **3** and the corresponding diastereoisomer 1,5-dideoxy-1,5 -[(*S*)-[(2*R*, 3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-glucitol inner salt **6**.

The stereochemistry at the stereogenic chalcogen centers was established by means of 2D-NMR NOESY experiments, as well as 1D- transient NOE difference experiments. This permitted the assignment of the absolute configurations of target compounds **1a**, **1b**, **2**, **3**, **4a**, **4b**, **5**, and **6**. The absolute configuration for the protected precursors was also assigned and found to be in agreement with the aforementioned target compounds.

Structure elucidation revealed that the conformations of the protected precursors were $^{1}C_{4}$. This placed the *O*-benzyl groups in an axial arrangement. Removal of the

protecting groups in the target compounds placed the hydroxyl groups in the preferred equatorial orientation, thus resulting in a $^4C_1$ conformation.

CHAPTER 4. EXPERIMENTAL

General Methods

Optical rotations were measured at 23°C. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with Merck silica gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light and/or sprayed with a solution containing 1% $Ce(SO_4)_2$ and 1.5% molybdic acid in 10% aq H_2SO_4 and heated. Compounds were purified by flash chromatography on Kieselgel 60 (230-400 mesh). Rexyn 101 was obtained from Fischer. ^1H and ^{13}C NMR spectra were recorded on: Bruker AMX-400 NMR spectrometer at 400.13 MHz, Bruker AMX-600 NMR spectrometer at 600.13 MHz and Varian INOVA 500 NMR spectrometer at 499.97 MHz and for ^1H and ^{13}C. Chemical shifts are given in ppm downfield from TMS for those measured in $CDCl_3$, CD_3OD and CD_2Cl_2 and from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for those spectra measured in D_2O. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. Assignments were fully supported by two-dimensional $^1H,^1H$ (COSY), $^1H,^1H$ (NOESY) and $^1H,^{13}C$ (HETCOR) experiments using standard Bruker or Varian pulse programs. Processing of the spectra was performed with standard UXNMR (Bruker) and WINNMR software or MestReC software. Zero filling of the acquired data (512 t_1 values and 2K data points in t_2) led to a final data matrix of 1K x 1K (F_1 x F_2) data points.

The 1D- transient NOE experiments were performed by inverting the signal of interest with a 80 ms Gaussian selective pulse which was constructed from 1024 steps. Spectra were collected in difference mode by alternating the phase of the receiver gain

during on- and off-resonance. The digitized signal was stored in a 32 K data set using a sweep width of 10.00 ppm, an acquisition time of 2.72 s, 128 scans, and 8 dummy scans. Processing of the spectra was accomplished by zero filling to 64 K followed by an exponential multiplication using a line width of 1 Hz.

High resolution mass spectra were liquid secondary ion mass spectrometry (LSIMS), run on a Kratos Concept double focussing mass spectrometer at 10 000 RP, using a glycerin matrix or, in the case of compound **26a**, with *meta*-NO_2-benzyl alcohol as the matrix. Solvents were distilled before use and were dried, as necessary. Solvents were evaporated under reduced pressure and below 50°C.

1,2-*O*-Isopropylidene-α-D-xylofuranose (12). To D-xylose (30.92 g, 205.9 mmol) in acetone (600 mL) were added $CuSO_4$ (40.1 g, 250 mmol) and H_2SO_4 (3 mL) and this was stirred at rt overnight. The mixture was filtered and the filtrate was treated with NH_4OH (10 mL). The mixture was filtered again and then concentrated. To the residue was added MeOH (240 mL) and the mixture was brought to pH 3 with 0.12M HCl (130 mL). The reaction was quenched after 1 h with $NaHCO_3$ (1 equiv) to pH 8 and filtered. At this point EtOH (200 mL) was added and the mixture was concentrated. Toluene (200 mL) was then added and the mixture was concentrated. The residue was dissolved in CH_2Cl_2 (200 mL) and dried over $MgSO_4$. Removal of the solvent afforded a yellow syrup (35.4 g, 90%); ^{1}H NMR ($CDCl_3$): δ 5.96 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 4.50 (1H, d, H-2), 4.31 (1H, br d, $J_{3,4}$ = 2.4 Hz, H-3), 4.17-4.10 (2H, m, H-4 and H-5a), 4.03 (1H, br dd, $J_{5a,5b}$ = 13.9 Hz, $J_{4,5b}$ = 3.7 Hz, H-5b), 1.46 (3H, s, CH_3), 1.29 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ

111.77 ($C(CH_3)_2$), 104.78 (C-1), 85.54 (C-2), 78.90 (C-3), 76.60 (C-4), 60.89 (C-5), 26.70 (CH_3), 26.12 (CH_3).

1,2,*O*-Isopropylidene-α-D-xylofuranose-3,5-cyclic sulfites (13 and 14). To 1,2-*O*-isopropylidene-α-D-xylofuranose **12** (34.4 g, 181 mmol) in CH_2Cl_2 (264 mL) and Et_3N (62 mL) at -30°C was added $SOCl_2$ (14 mL). The mixture was stirred at -30°C for 15 min. At this point H_2O (7 mL) was added and stirring was continued at rt. The mixture was washed with 6% $NaHCO_3$ (200 mL) and H_2O (500 mL) and concentrated to give a brown syrup (47.7 g, 100%); Two spots on TLC [hexanes/EtOAc, 3:1] were observed, R_f = 0.3 and R_f = 0.17.

1,2-*O*-Isopropylidene-α-D-xylofuranose-3,5-*O*-cyclic sulfate (15). To a stirred solution of 1,2,*O*-isopropylidene-α-D-xylofuranose-3,5-cyclic sulfites **13** and **14** (47.7 g, 202 mmol) in EtOAc (240 mL) and CH_3CN (240 mL) at 0°C were added, $RuCl_3.3H_2O$ (0.02 g, 0.08 mmol) then, slowly $NaIO_4$ (95.9 g, 448 mmol) in H_2O (960 mL). The mixture was stirred at rt for 30 min, then filtered. The solid was washed with EtOAc (3 x 80 mL), and the filtrate was washed with 6% aq. $NaHCO_3$ and then water. The organic phase was placed in the fridge overnight and the solid was removed by filtration. The filtrate was concentrated and the residue was purified by flash chromatography [hexanes] to give a solid. This was recrystallized from acetone/hexane to give compound **7** as white crystals (24.7 g, 49%): mp 165-170°C, lit.[30] mp 151-155°C; $[\alpha]_D$ +22.1 (*c* 1.2, acetone) (lit.[30] +21 (*c* 1, acetone)); ^1H NMR ($CDCl_3$): δ 6.02 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 5.15 (1H, d, $J_{3,4}$ = 2.1 Hz, H-3), 4.94 (1H, dd, $J_{5a,5b}$ = 12.8 Hz, $J_{4,5a}$ = 2.1 Hz, H-5a), 4.80 (1H, d, H-5b), 4.69 (1H, d, H-2), 4.23 (1H, br s, H-4), 1.48 (3H, s, CH_3), 1.52 (3H, s, CH_3). ^{13}C NMR

($CDCl_3$): δ 113.09 ($C(CH_3)_2$), 104.72 (C-1), 86.46 (C-3), 82.79 (C-2), 72.34 (C-5), 69.26 (C-4), 26.51 and 26.08 (2 Me).

5-S-Acetyl-1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose-3-*O*-sulfonic acid potassium salt (16). To 1,2-*O*-isopropylidene-α-D-xylofuranose-3,5-*O*-cyclic sulfate **15** (1.96 g, 7.77 mmol) in CH_3CN (20 mL) was added KSAc (1.04 g, 9.11 mmol) and this was kept stirring at rt for 3 h. The mixture was concentrated, and the residue was dissolved in acetone (10 mL) and Et_2O (10 mL). The solids were removed by filtration and the filtrate was concentrated to give a beige solid (2.90 g, 100%); ^1H NMR ($CDCl_3$): δ 5.89 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 4.89 (1H, br d, H-2), 4.71 (1H, br d, $J_{3,4}$ = 2.7 Hz, H-3), 4.21 (1H, br m, H-4), 3.25 (1H, dd, $J_{5a,5b}$ = 14.5 Hz, $J_{4,5a}$ = 4.6 Hz, H-5a), 3.11 (1H, br dd, $J_{4,5b}$= 8.9 Hz H-5b), 2.32 (3H, s, SAc), 1.27 (3H, s, CH_3), 1.22 (3H, s, CH_3).

Methyl-2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranoside (17). To a stirred solution of 5-S-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-xylofuranose-3-*O*-sulfonic acid potassium salt **16** (2.70 g, 7.37 mmol) in MeOH (30 mL) was added conc. HCl (3 mL). The mixture was refluxed for 4 h, at which point no more changes were detected on TLC. The mixture was cooled, neutralized with $NaHCO_3$ (3.3 g, 39 mmol), and EtOH (10 mL) and toluene (10 mL) were added. This was concentrated and to the residue was added pyridine (9 mL) and Ac_2O (7 mL) and this was allowed to stir overnight. The mixture was concentrated, EtOAc was added, and this was washed with 6% aq. $NaHCO_3$ and water. The organic phase was dried with $MgSO_4$. After removal of the solvent, the product was purified by flash chromatography [hexanes/EtOAc, 2:1] to give the title compound as a golden syrup (1.6 g, 71%); ^1H NMR ($CDCl_3$): δ 5.45 (1H, t, $J_{2,3} = J_{3,4}$ = 10.0 Hz, H-3), 5.11 (1H, dd, $J_{1,2}$ = 2.8 Hz, H-2), 5.05 (1H, ddd, H-4), 4.58 (1H, br d, H-

1), 3.38 (3H, s, OMe), 2.79 (1H, dd, $J_{5ax,5eq}$ = 13.0 Hz, $J_{4,5ax}$ = 11.2 Hz, H-5ax), 2.59 (1H, ddd, $J_{4,5eq}$ = 4.6 Hz, H-5eq), 2.05-1.97 (4 Ac).

1,2,3,4-Tetra-*O*-acetyl-5-thio-α-D-xylopyranose (18). To a stirred solution of methyl-2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranoside **17** (1.6 g, 5.22 mmol) at 0°C was added Ac_2O (6 mL) and conc. H_2SO_4 (0.2 mL). After stirring for 1 h, NaOAc (0.353 g, 4.31 mmol) was added. The mixture was brought to pH 6 with ice cold 6% aq. $NaHCO_3$. The mixture was then extracted with CH_2Cl_2 after 3 h when no more changes were visible on TLC, washed with water, and concentrated to give a solid. Recrystallization from Et_2O/hexanes gave **18** as fine white crytals (1.05 g, 60% yield): mp 93-97°C (lit.[30] mp 98-100°C); $[\alpha]_D$ +213 (*c* 1.3, $CHCl_3$) (lit.[30] +204 (*c* 0.5, $CHCl_3$)); ^{1}H NMR ($CDCl_3$): δ 6.05 (1H, d, $J_{1eq,2}$ = 2.6 Hz , H-1), 5.41 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, H-3), 5.18 (1H, dd, H-2), 5.08 (1H, m, H-4), 2.97 (1H, dd, $J_{5ax,5eq}$ = 13.1 Hz, $J_{4,5ax}$ = 11.3 Hz, H-5ax), 2.78 (1H, ddd, $J_{4,5eq}$ = 4.5 Hz, H-5eq). ^{13}C NMR ($CDCl_3$): δ 169.80, 169.73, 169.62, 169.08 (4C, Ac), 73.25, 72.49, 70.87, 69.9 (4C, C-1, C-2, C-3, C-4), 26.06 (C-5), 20.89, 20.77, 20.59, 20.51 (4 CH_3).

1,5-Anhydro-2,3,4-tri-*O*-acetyl-5-thioxylitol (19). To a stirred solution of 2,3,5-tri-*O*-acetyl-1,5-dibromo-1,5-dideoxy-xylitol **21** (5.08 g, 12.6 mmol) in DMSO (100 mL) was added $Na_2S.9H_2O$ (5.04 g, 21.0 mmol) in DMSO (100 mL). The mixture was stirred overnight and this was followed by extraction with Et_2O (5 x 100 mL) and washing with H_2O (2 x 100 mL). The ether was removed to give white crystals (2.63 g, 76%); mp 115-122 °C; ^{1}H NMR ($CDCl_3$): δ 4.99 (3H, m, H-2, H-3 and H-4), 2.80 (2H, br dd, H-5eq and H-1eq), 2.57 (2H, br m, H-5ax and H-1ax), 2.01 (3H, s, OAc), 1.99 (6H, s, OAc); ^{13}C NMR ($CDCl_3$): δ 172.89 and 169.77 (3 C=O), 73.80 (C-3), 72.83 (2C, C-2 and C-4),

30.68 (2C, C-1 and C-5), 20.79 (2 OAc), 20.62 (OAc). Anal. Calcd for $C_{11}H_{16}O_6S$: C, 47.82; H, 5.84. Found: C, 48.01; H, 5.95.

1,5-Anhydro-2,3,4-tri-*O*-acetyl-5-thioxylitol (19). To a stirred solution of 1,2,3,4-tetra-*O*-acetyl-5-thio-α-D-xylopyranose **18** (0.84 g, 2.5 mmol) in CH_3CN (10 mL) were added Et_3SiH (1.20 mL, 7.5 mmol) and TMSOTf (1.0 mL, 5.5 mmol). The mixture was stirred for 21 h. The mixture was washed with H_2O (50 mL) then with 6% aq $NaHCO_3$ (50 mL). This was followed by extraction with CH_2Cl_2 (2 x 50 mL). The organic phase was concentrated and the residue was chromatographed [hexanes/EtOAc, 1:1] to give **19** as a white solid (0.311 g, 45%).

1,5-Anhydro-5-thioxylitol (20). A mixture of 1,5-anhydro-2,3,4-tri-*O*-acetyl-5-thioxylitol **19** (0.125 g, 0.453 mmol), 1M NaOMe in MeOH (0.6 mL, 0.6 mmol) in dry MeOH (10 mL) was kept stirring under N_2 overnight. The mixture was acidified with excess Rexyn 101. The resin was removed by filtration and the organic phase was concentrated to give **20** as a solid (59.6 mg, 88%); mp 137-140°C ; ^{1}H NMR (D_2O): δ 3.65 (2H, m, $J_{1eq,2} = J_{4,5eq}$ = 4.5 Hz, $J_{1ax,2} = J_{4,5ax}$ = 10.9 Hz, H-2 and H-4), 3.15 (1H, t, $J_{2,3} = J_{3,4}$ = 9.1 Hz, H-3), 2.66 (2H, m, H-5eq and H-1eq), 2.56 (2H, dd, $J_{5ax,5eq} = J_{1ax,1eq}$ = 13.6 Hz , H-5ax and H-1ax); ^{13}C NMR (D_2O): δ 81.20 (C-3), 75.75 (2C, C-2 and C-4), 34.86 (2C, C-1 and C-5). Anal. Calcd for $C_5H_{10}O_3S$: C, 39.99; H, 6.71. Found: C, 39.68; H, 6.91.

1,5-Anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol (7). A mixture of 1,5-anhydro-5-thioxylitol **20** (0.520 g, 3.47 mmol) and 60% NaH (0.744 g, 5 equiv) in DMF (50 mL) was stirred in an ice-bath for 1 h. A solution of BnBr (1.4 mL, 4 equiv) was added and the solution was stirred at rt overnight. The mixture was quenched with MeOH (8 mL).

At this point H_2O (100 mL) was added and this was extracted with Et_2O (3 x 150 mL). The organic solution was dried with Na_2SO_4 and concentrated. The product was purified by flash chromatography [hexanes/EtOAc, 20:1] to give **7** as a white solid (0.928 g, 64%); mp 46-49°C; ^{1}H NMR ($CDCl_3$): δ 7.36-7.24 (15H, m, Ar), 4.83 (2H, s, CH_2Ph), 4.69 (2H, d, $J_{A,B}$ = 11.4 Hz, CH_2Ph), 4.65 (2H, d, $J_{A,B}$ = 11.6 Hz, CH_2Ph), 3.63 (2H, m, $J_{1eq,2} = J_{4,5eq}$ = 4.2 Hz, $J_{1ax,2} = J_{4,5ax}$ = 11.0 Hz, H-4 and H-2), 3.31 (1H, t, $J_{2,3} = J_{3,4}$ = 8.9 Hz, H-3), 2.72 (2H, m, H-5eq and H-1eq), 2.47 (2H, dd, $J_{5ax,5eq} = J_{1ax,1eq}$ = 13.4 Hz, H-5ax and H-1ax); ^{13}C NMR ($CDCl_3$): δ 138.9, 138.37 ($3C_{ipso}$), 128.42-127.51 (15C, Ar), 86.76 (C-3), 82.26 (2C, C-2 and C-4), 76.33 (*C*H_2Ph), 73.02 (2 *C*H_2Ph), 31.49 (2C, C-1 and C-5). Anal. Calcd for $C_{26}H_{28}O_3S$: C, 74.25; H, 6.71. Found: C, 74.16; H, 6.91.

2,3,5-Tri-*O*-acetyl-1,5-dibromo-1,5-dideoxy-xylitol (21). To a solution of xylitol (3.18 g, 20.9 mmol) was added AcBr (4.6 mL, 62.2 mmol) and the mixture was stirred overnight. The mixture was concentrated, Ac_2O (15 mL) and pyridine (20 mL) were added, and this was allowed to stir overnight. The solvents were evaporated and the residue was purified by flash chromatography [hexanes/EtOAc, 5:2] to give compound **21** as white crystals (2.28 g, 40%): mp 62-65°C (lit.[11] mp 63-65°C) and minor products **22** and **23**; **21**: ^{1}H NMR ($CDCl_3$): δ 5.57 (1H, t, $J_{2,3} = J_{3,4}$ = 5.0 Hz, H-3), 5.18 (2H, dd, H-2 and H-4), 3.44 (4H, m, H-1', H-1, H-5, H-5'), 2.09 (3H, s, Ac), 2.10 (6H, s, Ac). **22** : ^{1}H NMR ($CDCl_3$): δ 5.24 (2H, dd, H-2 and H-4), 4.44 (1H, t, $J_{2,3} = J_{3,4}$ = 6.3 Hz, H-3), 3.66 (4H, d, H-1', H-1, H-5, H-5'), 2.15 (6H, s, Ac). **23**: ^{1}H NMR ($CDCl_3$): δ 5.57 (1H, m, H-2), 5.52 (1H, dd, H-3), 4.27 (1H, m, H-4), 3.72 (2H, dd, H-5, H-5'), 3.39 (2H, m, H-1, H-1').

4,6-*O*-Benzylidene-D-glucopyranose (24). To a solution of D-glucose (21.57 g, 120 mmol) in DMF (80 mL) were added *p*-toluenesulphonic acid (130 mg) and benzaldehyde dimethyl acetal (22 mL, 1.2 equiv). This was allowed to spin on a rotary evaporator under reduced pressure at 40-45°C. After two hours further portions of *p*-toluenesulphonic acid (100 mg) and benzaldehyde dimethyl acetal (2 mL, 13 mmol) were added and the reaction was continued for a total of 6 h. The reaction was quenched with Et_3N (4 mL). The solution was concentrated and the product was purified by flash chromatography [EtOAc + 0.1% Et_3N] to give **24** as a white solid (21.7 g, 67%). A portion was recrystallized from EtOAc: mp 183-185°C (lit.[36] mp 186-187°C); $[\alpha]_D$ -4 (*c* 1.6, MeOH) (lit.[36] $[\alpha]_D^{20}$ -5 (*c* 2.6, MeOH)); α isomer: ^{1}H NMR (C_5D_5N): δ 7.47-7.31 (5H, m, ArH), 5.87 (1H, br s, H-1), 5.78 (1H, s, C*H*Ph), 4.79 (1H, t, $J_{2,3} = J_{3,4} = 9.2$ Hz, H-3), 4.69 (1H, ddd, $J_{5,6eq} = 4.9$ Hz, $J_{5,6ax} = J_{4,5} = 9.9$ Hz, H-5), 4.48 (1H, dd, $J_{6ax,6eq} = 10.1$ Hz, H-6eq), 4.26 (1H, dd, $J_{1,2} = 3.7$ Hz, H-2), 4.02 (1H, t, H-4), 3.96 (1H, dd, H-6ax); β isomer: ^{1}H NMR (C_5D_5N): δ 7.47-7.31 (5H, m, ArH), 5.83 (1H, s, C*H*Ph), 5.37 (1H, d, $J_{1,2} = 7.6$ Hz, H-1), 4.49 (1H, dd, $J_{6ax,6eq} = 10.2$ Hz, H-6eq), 4.40 (1H, t, $J_{2,3} = J_{3,4} = 9.1$ Hz, H-3), 4.21 (1H, dd, H-2), 3.98 (1H, t, H-4), 3.97 (1H, t, H-6ax), 3.83 (1H, ddd, $J_{5,6eq} = 4.9$ Hz, $J_{5,6ax} = J_{4,5} = 9.9$ Hz, H-5).

2,4-*O*-Benzylidene-D-erythritol (25). To a stirring solution of $NaIO_4$ (58.2 g, 2.5 equiv) in H_2O (150 mL) were added bromocresol green and sufficient $NaHCO_3$ to make the solution basic. To this was added 4,6-*O*-benzylidene-D-glucoppyranose **24** (29.3 g, 109 mmol) dissolved in MeOH (50 mL) dropwise over a period of 4 h. A further portion of $NaIO_4$ (10 g, 47 mmol) was added and the mixture was kept stirring overnight. At this point, TLC showed no more starting material and the reaction was quenched with

glycerol. The solids were removed by filtration and the solution was used immediately in the next step. To the solution was added $NaBH_4$ (8.32 g, 220 mmol) in portions while stirring at rt. Reaction was quenched after 2 hours by adding AcOH (8 mL). The residue was extracted with CH_2Cl_2 (3 x 100 mL). The product was purified by flash chromatography [EtOAc + 0.1% Et_3N] and recrystallized from EtOAc to give **25** as white crystals (6.22 g, 27% for 2 steps); mp 129-133°C (lit.[39] mp 135-136°C); $[\alpha]_D$ -41.6 (*c* 1.1, MeOH) (lit.[39] $[\alpha]_D$ -43.0 (*c* 2.0, MeOH)); ^1H NMR ($CDCl_3$): δ 7.47-7.31 (5H, m, ArH), 5.51 (1H, s, C*H*Ph), 4.29 (1H, dd, $J_{4ax,4eq}$ = 10.6 Hz, $J_{3,4eq}$ = 5.4 Hz, H-4eq), 3.91 (3H, m, $J_{2,3}$ = 9.8 Hz, $J_{1a,1b}$ = 11.8 Hz, $J_{1a,2}$ = 4.4 Hz, $J_{1b,2}$ = 4.2 Hz, H-3, H-1a, H-1b), 3.68 (1H, ddd, H-2), 3.61 (1H, t, $J_{3,4ax}$ = 10.4 Hz, H-4ax).

2,4-*O*-Benzylidene-D-erythritol-1,3-cyclic sulfate (10). To 2,4-*O*-benzylidene-D-erythritol **25** (0.528 g, 2.5 mmol) dissolved in CH_2Cl_2 (10 mL) was added Et_3N (6 mL). While stirring under N_2 at 0°C, $SOCl_2$ (0.30 mL, 4.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 1 h. The reaction was complete after 2.5 h. At this point the organic phase was washed with H_2O (3 x 50 mL), ice cold 1N HCl (5 x 50 mL), $NaHCO_3$ (50 mL) and NaCl (50 mL). The organic phase was dried with Na_2SO_4, concentrated and used immediately in the next step. The residue was dissolved in CH_3CN (10 mL) and to this was added CCl_4 (10 mL). This was followed by the addition of $NaIO_4$ (1.05 g), $RuCl_3.3H_2O$ (49 mg) and H_2O (25 mL) . This was kept stirring vigorously for 1.5 h. The mixture was then extracted with Et_2O (4 x 50 mL) and washed with H_2O (3 x 50 mL) then brine (50 mL). The organic phase was dried with Na_2SO_4 and concentrated. The product was purified by flash chromatography [hexanes/EtOAc, 2:1 + 0.1% Et_3N] to give **10** as a white solid (0.454 g, 66% for 2 steps): mp 139-144°C (dec) (lit.[24] mp 115-

125°C (dec)); $[\alpha]_D$ +4.3 (*c* 1.4, $CHCl_3$) (lit.[24] $[\alpha]_D$ +4 (*c* 1.0, $CHCl_3$)); ^1H NMR (CD_2Cl_2): δ 7.48-7.37 (5H, m, ArH), 5.64 (1H, s, C*H*Ph), 4.86 (1H, ddd, $J_{2,3}$ = 9.9 Hz, H-3), 4.76 (1H, t, $J_{1ax,2}$ = 10.7 Hz, H-1ax), 4.65 (1H, dd, $J_{1ax,1eq}$ = 10.5 Hz, $J_{1eq,2}$ = 5.0 Hz, H-1eq), 4.44 (1H, dd, $J_{4ax,4eq}$ = 10.5 Hz, $J_{3,4eq}$ = 5.0 Hz, H-4eq), 4.25 (1H, m, H-2), 3.97 (1H, t, $J_{4ax,3}$ = 10.4 Hz, H-4ax).

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[(*S*)-[(2*R*, 3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-episulfoniumylidene]-xylitol inner salt (26a) and 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-[(*R*)-[(2*R*, 3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-episulfoniumylidene]-xylitol inner salt (26b). To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sulfate **10** (0.565 g, 2.08 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol **7** (0.677 g, 1.61 mmol) and anhydrous K_2CO_3 (70 mg). The mixture was stirred in a sealed tube in a 70°C oil bath overnight, after which an extra 40 mg of anhydrous K_2CO_3 was added. The solvents were removed and the residue was chromatographed [$CHCl_3$/MeOH, 10:1] to give **26a** and **26b** in a 2:1 ratio (0.975 g, 87%). Major isomer **26a**: mp 186-189°C; $[\alpha]_D$ +2.1 (*c* 1.2, CH_2Cl_2); ^1H NMR (CD_2Cl_2): δ 7.09-6.77 (20H, m, Ar), 5.55 (1H, s, C*H*Ph), 4.68 (1H, d, CH_2Ph), 4.62 (1H, m, $J_{3',4a'}$ = 5.3 Hz, H-3'), 4.55-4.40 (6H, m, H-4a', CH_2Ph), 4.33 (1H, ddd, $J_{1a',2'} = J_{1b',2'}$ = 3.4 Hz, $J_{2',3'}$ = 9.4 Hz, H-2'), 4.26 (1H, dd, $J_{1a',1b'}$ = 13.5 Hz, $J_{1a',2'}$ = 3.1 Hz, H-1a'), 4.05 (1H, br m, H-4), 3.96-3.87 (2H, m, H-2, H-5eq), 3.81-3.74 (2H, m, $J_{2,3} = J_{3,4}$ = 3.6 Hz, H-3, H-4b'), 3.69 (1H, dd, H-1b'), 3.64 (1H, dd, $J_{5ax,5eq}$ = 12.7 Hz, $J_{4,5ax}$ = 1.8 Hz, H-5ax), 3.60 (1H, ddd, H-1eq), 3.39 (1H, dd, $J_{1ax,1eq}$ = 12.7 Hz, $J_{1ax,2}$ = 1.9 Hz H-1ax); ^{13}C NMR (CD_2Cl_2): δ 137.35, 136.96, 136.92, 136.85, ($4C_{ipso}$), 129.84-126.54 (20C, Ar), 102.07 (*C*HPh), 76.75 (C-2'), 73.68, 72.17, 72.00

(3*C*H_2Ph), 71.72 (C-4), 71.61 (C-2), 70.94 (C-3), 69.51 (C-4'), 66.88 (C-3'), 46.00 (C-1'), 42.08 (C-1) 39.24 (C-5). HRMS Calcd for $C_{37}H_{40}O_9S_2$ (M + H): 693.2192. Found: 693.2209. Anal. Calcd for $C_{37}H_{40}O_9S_2$: C, 64.14; H, 5.82. Found: C, 64.39; H, 5.94. Minor isomer **26b**: mp 169-172°C; $[\alpha]_D$ -49.1 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.45-7.15 (20H, m, Ar), 5.52 (1H, s, C*H*Ph), 4.99 (1H, dd, $J_{1a',1b'}$ = 14.2 Hz, $J_{1a',2'}$ = 3.6 Hz H-1a'), 4.65 (1H, m, $J_{3',4a'}$ = 5.3 Hz, H-3'), 4.59 (2H, t, CH_2Ph), 4.51-4.44 (3H, m, H-4a', CH_2Ph), 4.40 (2H, s, CH_2Ph), 4.27 (1H, br d, H-1b'), 4.21 (1H, dd, H-2'), 4.02 (1H, br dd, H-4), 3.92 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 4.0 Hz, H-3), 3.84 (1H, m, $J_{1ax,2}$ = 6.6 Hz, H-2), 3.80-3.71 (2H, m, H-4b', H-5eq), 3.64 (1H, dd, $J_{5ax,5eq}$ = 15.1 Hz, $J_{4,5ax}$ = 2.6 Hz, H-5ax), 3.38 (2H, br s, H-1ax, H-1eq); ^{13}C NMR (CD_2Cl_2): δ 137.38, 137.11, 137.00, 136.80 (4C_{ipso}), 129.80 – 126.48 (20C, Ar), 102.19 (*C*HPh), 77.44 (C-2'), 73.59, 72.64, 72.10 (3*C*H_2Ph), 70.99 (C-2), 70.72 (C-4), 70.31 (C-3), 69.51 (C-4'), 65.73 (C-3'), 43.31 (C-1'), 33.41 (C-5), 32.90 (C-1). Anal. Calcd for $C_{37}H_{40}O_9S_2$: C, 64.14; H, 5.82. Found: C, 63.84: H, 5.96.

1,5-Dideoxy-1,5-[(*S*)-[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene]-xylitol inner salt (1a). To compound **26a** (0.33 g, 0.48 mmol) dissolved in 80% AcOH (12 mL) was added $Pd(OH)_2$ (0.2 g). The mixture was stirred under 110 psi H_2 for 48 h and then filtered through Celite with MeOH. The solvent was evaporated and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1]. Compound **1a** was obtained as a syrup (0.13 g , 81%); $[\alpha]_D$ -21.8 (*c* 1.1, H_2O); ^{1}H NMR (D_2O): δ 4.42 (1H, ddd, H-2'), 4.34 (1H, ddd, $J_{2',3'}$ = 7.6 Hz, H-3'), 4.25 (2H, m, $J_{4,5eq}$ = $J_{1eq,2}$ = 1.7 Hz, $J_{2,3}$ = $J_{3,4}$ = $J_{4,5ax}$ = $J_{1ax,2}$ = 8.3 Hz, H-2, H-4), 3.96 (1H, dd, $J_{4b',4a'}$ = 12.8 Hz, $J_{3',4a'}$ = 3.4 Hz, H-4a'), 3.84 (2H, ddd, $J_{1a',1b'}$ = 13.6 Hz,

$J_{1a',2'}$ = 3.5 Hz, $J_{3',4b'}$ = 3.0 Hz, H-4b', H-1a'), 3.75-3.62 (4H, m, $J_{1b',2'}$ = 7.4 Hz, H-1b', H-1eq, H-3, H-5eq), 3.50 (2H, m, $J_{5ax,5eq}$ = 13.7 Hz, $J_{1ax,1eq}$ = 13.6 Hz, H-1ax, H-5ax); ^{13}C NMR (D_2O): δ 82.29 (C-3'), 74.05 (C-3), 69.09, 69.05 (2C, C-2 and C-4), 67.97 (C-2'), 62.01 (C-4'), 45.44 (C-1'), 41.25 and 41.01 (2C, C-1 and C-5). HRMS Calcd for $C_9H_{19}O_9S_2$ (M + H): 335.0470. Found: 335.0454. Anal. Calcd for $C_9H_{18}O_9S_2$: C, 32.33; H, 5.43. Found: C, 32.03; H, 5.59.

1,5-Dideoxy-1,5-[(*R*)-[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene]-xylitol inner salt (1b). To compound **26b** (0.249 g, 0.36 mmol) dissolved in 80% AcOH (15 mL) was added $Pd(OH)_2$ (0.5 g). The mixture was stirred under 110 psi H_2 for 48 h and then filtered through Celite with MeOH. The solvent was removed and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1] to give the title compound as a syrup (0.13 g, 95%); $[\alpha]_D$ -16.2 (*c* 0.9, H_2O). ^{1}H NMR (D_2O): δ 4.41 (1H, ddd, H-2'), 4.32 (1H, m, $J_{2',3'}$ = 7.5 Hz, H-3'), 4.00-3.90 (4H, m, $J_{1a',1b'}$ = 13.6 Hz, $J_{1a',2'}$ = 3.7 Hz, $J_{4b',4a'}$ = 12.7 Hz, $J_{3',4a'}$ = 3.4 Hz, H-2, H-4, H-4a', H-1a'), 3.86-3.79 (2H, m, $J_{1b',2'}$ = 7.2 Hz, $J_{3',4b'}$ = 2.9 Hz, H-1b', H-4b'), 3.75 (2H, m, $J_{1eq,2}$ = $J_{4,5eq}$ = 3.4 Hz, H-5eq, H-1eq), 3.51 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.35 (2H, t, $J_{5ax,5eq}$ = $J_{4,5ax}$ = $J_{1ax,1eq}$ = $J_{1ax,2}$ = 11.7 Hz, H-1ax, H-5ax); ^{13}C NMR (D_2O): δ 82.33 (C-3'), 78.10 (C-3), 69.85 and 69.81 (2C, C-2 and C-4), 69.09 (C-2'), 62.04 (C-4'), 50.39 (C-1'), 43.24 and 43.14 (2C, C-1 and C-5). HRMS Calcd for $C_9H_{19}O_9S_2$ (M + H): 335.0470. Found: 335.0478. Anal. Calcd for $C_9H_{18}O_9S_2$: C, 32.33; H, 5.43. Found: C, 31.88; H, 5.21.

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[(*R*)-[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-episulfoniumylidene]-xylitol inner salt (27a) and 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-[(*S*)-[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-

episulfoniumylidene]-xylitol inner salt (27b). To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sulfate **11** (0.265 g, 0.97 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol **7** (0.328 g, 0.78 mmol) and anhydrous K_2CO_3 (24 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 5 days. The solvent was evaporated and the residue was purified by column chromatography [$CHCl_3$/MeOH, 10:1] to give **27a** and **27b** as a white solid in a 5:2 ratio (0.465 g, 86%). Major isomer **27a**: mp 175-180°C; $[\alpha]_D$ -3.7 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.44-7.11 (20H, m, Ar), 5.54 (1H, s, C*H*Ph), 4.75 (1H, d, CH_2Ph), 4.65 (1H, m, $J_{3',4a'}$ = 5.3 Hz, H-3'), 4.55-4.43 (6H, m, H-4a', CH_2Ph), 4.38 (1H, dd, $J_{1a',1b'}$ = 13.8 Hz, $J_{1a',2'}$ = 2.2 Hz, H-1a'), 4.30 (1H, br ddd, $J_{2',3'}$ = 9.8 Hz, H-2'), 4.06 (1H, br s, H-4), 4.00 (1H, ddd, $J_{4,5eq}$ = $J_{1eq,5eq}$ = 3.2 Hz, H-5eq), 3.87 (1H, br s, H-2), 3.81 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 3.7 Hz, H-3), 3.77 (1H, t, $J_{4a',4b'}$ = $J_{3',4b'}$ = 10.6 Hz, H-4b'), 3.52 (1H, m, $J_{1eq,2}$ = 3.2 Hz, H-1eq), 3.48 (1H, dd, $J_{1b',2'}$ = 3.8 Hz, H-1b'), 3.44 (1H, dd, $J_{5ax,5eq}$ = 12.8 Hz, $J_{4,5ax}$ = 1.7 Hz, H-5ax) 3.31 (1H, dd, $J_{1ax,1eq}$ = 12.5 Hz, $J_{1ax,2}$ = 1.8 Hz, H-1ax); ^{13}C NMR (CD_2Cl_2): δ 137.34, 137.03, 136.98, 136.92, (4C_{ipso}), 129.80-126.53 (20C, Ar), 101.98 (*C*HPh), 76.69 (C-2'), 73.59, 72.11, 71.97 (3*C*H_2Ph), 71.79 (C-4), 71.68 (C-2), 71.00 (C-3), 69.50 (C-4'), 67.04 (C-3'), 45.77 (C-1'), 41.73 (C-1) 39.32 (C-5). Anal. Calcd for $C_{37}H_{40}O_9S_2$: C, 64.14; H, 5.82; Found: C, 63.81; H, 5.68. Minor isomer **27b**: mp 163-170°C; $[\alpha]_D$ +41.8 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.45-7.05 (20H, m, Ar), 5.52 (1H, s, C*H*Ph), 4.99 (1H, dd, $J_{1a',2'}$ = 3.8 Hz, H-1a'), 4.65 (1H, m, $J_{3',4a'}$ = 5.3 Hz, H-3'), 4.59 (2H, t, CH_2Ph), 4.47 (3H, m, H-4a', CH_2Ph), 4.40 (2H, s, CH_2Ph), 4.28 (1H, br d, $J_{1a',1b'}$ = 14.3 Hz, H-1b'), 4.21 (1H, dd, $J_{2',3'}$ = 9.7 Hz, H-2'), 4.02 (1H, br dd, H-4), 3.93 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 3.8 Hz, H-3), 3.84 (1H, dd, $J_{1ax,2}$ = 6.6Hz, H-2), 3.81-3.71 (2H, m, H-

4b', H-5eq), 3.63 (1H, dd, $J_{5ax,5eq}$ = 15.3 Hz, $J_{4,5ax}$ = 2.4 Hz, H-5ax), 3.37 (2H, br s, H-1ax, H-1eq); ^{13}C NMR (CD_2Cl_2): δ 137.39, 137.04, 136.95, 136.76 ($4C_{ipso}$), 129.81 – 126.47 (20C, Ar), 102.21 (*C*HPh), 77.50 (C-2'), 73.61, 72.66, 72.11 ($3CH_2Ph$), 70.89 (C-2), 70.60 (C-4), 70.12 (C-3), 69.53 (C-4'), 65.68 (C-3'), 43.35 (C-1'), 33.33 (C-5), 32.80 (C-1). Anal. Calcd for $C_{37}H_{40}O_9S_2$: C, 64.14; H, 5.82. Found: C, 64.42; H, 5.75.

1,5-Dideoxy-1,5-[(*R*)-[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene]-xylitol inner salt (4a). To compound **27a** (0.304 g, 0.44 mmol) dissolved in 80% AcOH (10 mL) was added Pd/C (0.5 g). The mixture was stirred under 120 psi H_2 for 96 h. The mixture was filtered through Celite with MeOH, and the solvent removed. The residue was then redissolved in 80% AcOH (10 ml). To the solution was added $Pd(OH)_2$ (0.2 g) and stirring under 120 psi H_2 was continued for 48h. The mixture was filtered through Celite with MeOH, the solvent evaporated, and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1] to give the title compound as a syrup (0.08 g, 55%); $[\alpha]_D$ +21.7 (*c* 0.8, H_2O). ^{1}H NMR (D_2O): δ 4.42 (1H, ddd, H-2'), 4.34 (1H, ddd, $J_{2',3'}$ = 7.7 Hz, H-3'), 4.25 (2H, m, $J_{4,5eq} = J_{1eq,2}$ = 1.7 Hz, $J_{2,3} = J_{1ax,2} = J_{3,4} = J_{4,5ax}$ = 8.3 Hz, H-2, H-4), 3.95 (1H, dd, $J_{4b',4a'}$ = 12.8 Hz, $J_{3',4a'}$ = 3.2 Hz, H-4a'), 3.84 (2H, ddd, $J_{1a',1b'}$ = 13.5 Hz, $J_{1a',2'}$ = 3.4 Hz, $J_{3',4b'}$ = 2.8 Hz, H-4b', H-1a'), 3.74-3.64 (4H, m, $J_{1b',2'}$ = 7.4 Hz, H-1b', H-1eq, H-3, H-5eq), 3.50 (2H, m, $J_{1ax,1eq}$ = 13.6 Hz, $J_{5ax,5eq}$ = 14.0 Hz, H-1ax, H-5ax); ^{13}C NMR (D_2O): δ 82.44 (C-3'), 74.18 (C-3), 69.23 and 69.20 (2C, C-2 and C-4), 68.12 (C-2'), 62.16 (C-4'), 45.60 (C-1'), 41.40 and 41.16 (2C, C-1 and C-5). HRMS Calcd for $C_9H_{18}O_9S_2Na$ (M + Na): 357.0290. Found: 357.0284.

1,5-Dideoxy-1,5-[(*S*)-[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene]-xylitol inner salt (4b). To compound **27b** (0.240 g, 0.35 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.3 g). The mixture was stirred under 130 psi H_2 for 48 h. The mixture was filtered through Celite with MeOH, the solvent was removed, and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1] to give the title compound as a syrup (0.08 g, 67%); $[\alpha]_D$ +19.5 (*c* 0.7, H_2O). ^1H NMR (D_2O): δ 4.41 (1H, ddd, H-2'), 4.32 (1H, ddd, $J_{2',3'}$ = 7.5 Hz, H-3'), 4.00-3.90 (4H, m, $J_{1a',1b'}$ = 13.5 Hz, $J_{1a',2'}$ = 3.7 Hz, $J_{4b',4a'}$ = 12.7 Hz, $J_{3',4a'}$ = 3.3 Hz, H-2, H-4, H-4a', H-1a'), 3.86-3.79 (2H, m, $J_{3',4b'}$ = 3.0 Hz, $J_{1b',2'}$ = 7.2 Hz, H-1b', H-4b'), 3.75 (2H, m, $J_{1eq,2} = J_{4,5eq}$ = 3.5 Hz, H-5eq, H-1eq), 3.50 (1H, t, $J_{2,3} = J_{3,4}$ = 9.0 Hz, H-3), 3.35 (2H, t, $J_{5ax,5eq} = J_{4,5ax} = J_{1ax,1eq} = J_{1ax,2}$ = 11.7 Hz, H-1ax, H-5ax); ^{13}C NMR (D_2O): δ 82.47 (C-3'), 78.24 (C-3), 69.99 and 69.95 (2C, C-2 and C-4), 67.85 (C-2'), 62.18 (C-4'), 50.53 (C-1'), 43.38 and 43.28 (2C, C-1 and C-5). HRMS Calcd for $C_9H_{19}O_9S_2$ (M + H): 335.0470. Found: 335.0477.

1,5-Anhydro-2,3,4-tri-*O*-acetyl-5-selenoxylitol (28). To a stirring solution of selenium (1.48 g, 18.7 mmol) in anhydrous EtOH (40 mL) at 0°C was added $NaBH_4$ (0.9 g, 23.8 mmol). This produced an almost colorless solution. The ice bath was removed and 2,3,5-tri-*O*-acetyl-1,5-dibromo-1,5-dideoxy-xylitol **21** (4.87 g, 12.0 mmol) was added and allowed to stir at rt overnight. To the mixture was added H_2O (200 mL) which was extracted with Et_2O (5 x 100 mL). The solids were removed by filtration. The residue was concentrated and the product was purified by flash chromatography [hexanes/EtOAc, 1:1] to give **28** as yellow crystals (2.22 g, 57%): mp 106-111°C; ^1H NMR ($CDCl_3$): δ 5.11 (2H, ddd, $J_{1eq,2} = J_{4,5eq}$ = 4.5 Hz, $J_{1ax,2} = J_{4,5ax}$ = 10.8 Hz, H-2, H-4), 4.96 (1H, t,

$J_{2,3} = J_{3,4}$ = 9.7 Hz, H-3), 2.74 (2H, dd, H-1eq, H-5eq), 2.67 (2H, t, $J_{5ax,5eq} = J_{1ax,1eq}$ = 12.0 Hz, H-1ax, H-5ax), 2.00 (3H, s, OAc), 1.99 (6H, s, OAc); ^{13}C NMR ($CDCl_3$): δ 169.79 and 169.65 (3C=O), 73.98 (C-3), 73.78 (2C, C-2 and C-4), 21.02 (2 OAc), 20.80 (2C, C-1 and C-5), 20.56 (OAc). Anal. Calcd for $C_{11}H_{16}O_6Se$: C, 40.88; H, 4.99. Found: C, 40.76; H, 5.02.

1,5-Anhydro-5-selenoxylitol (29). A mixture of 1,5-anhydro-2,3,4-tri-*O*-acetyl-5-selenoxylitol **28** (2.22 g, 6.87 mmol) and 1M NaOMe in MeOH (10 mL, 10 mmol) in dry MeOH (60 mL) was kept stirring under a N_2 atmosphere overnight. The mixture was acidified with excess Rexyn 101. The resin was removed by filtration and the organic phase was concentrated to give **29** as tan crystals (1.19 g, 88%); mp 98-105°C; ^{1}H NMR (D_2O): δ 3.75 (2H, m, $J_{1eq,2} = J_{4,5eq}$ = 4.6 Hz, $J_{1ax,2} = J_{4,5ax}$ = 10.8 Hz, H-2, H-4), 3.11 (1H, t, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 2.66 (2H, t, $J_{5ax,5eq} = J_{1ax,1eq}$ = 11.8 Hz, H-5ax, H-1ax), 2.60 (2H, dd, H-1eq, H-5eq); ^{13}C NMR (D_2O): δ 81.40 (C-3), 76.62 (2C, C-2 and C-4), 25.65 (2C, C-1 and C-5). Anal. Calcd for $C_5H_{10}O_3Se$: C, 30.47; H, 5.11. Found: C, 30.29; H, 5.21.

1,5-Anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol (8). To 1,5-anhydro-5-selenoxylitol **29** (0.289 g, 1.47 mmol) in dry DMF (20 mL) was added 60% NaH (0.516 g, 6 equiv) while stirring in an ice bath. The ice bath was removed and BnBr (0.9 mL, 4 equiv) was added. This was kept stirring under N_2 overnight. The reaction was then quenched with MeOH (5 mL). At this point H_2O (100 mL) was added and this was extracted with Et_2O (3 x 50 mL). The organic solution was dried with Na_2SO_4 and concentrated. The product was purified by flash chromatography [hexanes/EtOAc, 20:1] to give the title compound **8** as a white solid (0.505 g, 74%); mp 56-60°C; ^{1}H NMR ($CDCl_3$): δ 7.32-7.24 (15H, m,

ArH), 4.81 (2H, s, CH_2Ph), 4.70 (2H, d, $J_{A,B}$ = 11.6 Hz, CH_2Ph), 4.66 (2H, d, $J_{A,B}$ = 11.5 Hz, CH_2Ph), 3.73 (2H, m, $J_{1eq,2} = J_{4,5eq}$ = 4.2 Hz, $J_{1ax,2} = J_{4,5ax}$ = 11.2 Hz, H-2, H-4), 3.27 (1H, t, $J_{2,3} = J_{3,4}$ = 8.9 Hz, H-3), 2.69 (2H, dd, $J_{5ax,5eq} = J_{1ax,1eq}$ = 12.0 Hz, H-5eq, H-1eq), 2.58 (2H, t, H-5ax, H-1ax); ^{13}C NMR ($CDCl_3$): 138.89 (C_{ipso}), 138.44 ($2C_{ipso}$), 128.39-127.46 (15C, Ar), 86.98 (C-3), 83.17 (2C, C-2 and C-4), 76.34 (*C*H_2Ph), 72.97 (2 *C*H_2Ph), 22.11 (2C, C-1 and C-5). Anal. Calcd for $C_{26}H_{28}O_3Se$: C, 66.80; H, 6.04. Found: C, 66.88; H, 6.22.

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[(*R*)-[(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-episelenoniumylidene]-xylitol inner salt (30a). To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sufate **10** (0.272 g, 1.00 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-seleno-xylitol **8** (0.362 g, 0.78 mmol) and anhydrous K_2CO_3 (50 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 48 h. The solvent was concentrated and the residue was purified by column chromatography [$CHCl_3$/MeOH, 10:1] to give an inseparable mixture of **30a** and **30b** in a 4:1 ratio (0.20 g, 96%). $[\alpha]_D$ -45.7 (*c* 1.1, CH_2Cl_2); Major isomer **30a** : ^{1}H NMR (CD_2Cl_2): δ 7.49-7.09 (20H, m, Ar), 5.54 (1H, s, C*H*Ph), 4.82 (1H, dd, $J_{1a',1b'}$ = 12.7 Hz, $J_{1'a,2'}$ = 3.8 Hz, H-1a'), 4.68 – 4.40 (8H, m, H-3', H-4a', CH_2Ph), 4.30 (1H, br d, H-1b'), 4.18 (1H, br dd, $J_{2',3'}$ = 9.3 Hz, H-2'), 3.97 (1H, dd, H-4), 3.91 (1H, t, $J_{2,3} = J_{3,4}$ = 4.1 Hz, H-3), 3.86 (1H, dd, H-2), 3.82 – 3.61 (2H, m, $J_{4a',4b'} = J_{3',4b'}$ = 10.4 Hz, $J_{5eq,5ax}$ = 13.4 Hz, $J_{4,5eq}$ = 2.8 Hz, H-5eq, H-4b'), 3.56 (1H, m, $J_{4,5ax}$ = 4.3 Hz, H-5ax), 3.36 (1H, dd, $J_{1eq,2}$ = 3.1 Hz, H-1eq), 3.18 (1H, dd, $J_{1eq,1ax}$ = 13.5 Hz, $J_{1ax,2}$ = 4.2 Hz, H-1ax); ^{13}C NMR (CD_2Cl_2): δ 137.39, 137.29, 137.13, 137.09 ($4C_{ipso}$), 129.74 – 126.49 (20C, Ar), 102.04 (*C*HPh), 77.47 (C-2'), 73.37, 72.83 (2 *C*H_2Ph), 72.48 (C-3), 72.25 (*C*H_2Ph), 72.16 (C-2),

72.08 (C-4), 69.51 (C-4'), 67.41 (C-3'), 43.37 (C-1'), 30.73 (C-5), 30.17 (C-1). Anal. Calcd for $C_{37}H_{40}O_9SSe$: C, 59.99; H, 5.45. Found: C, 59.73; H, 5.36.

1,5-Dideoxy-1,5-[(*R*)-[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episelenoniumylidene]-xylitol inner salt (2). To the mixture of compounds **30a** and **30b** (0.295 g, 0.40 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.29 g). The mixture was stirred under 120 psi H_2 for 5 days. TLC revealed one major product and two minor products. The mixture was filtered through Celite, concentrated, and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1] to give the major product, compound **2** as a syrup (0.06 g, 39%); $[\alpha]_D$ -16.6 (*c* 0.9, H_2O). ^1H NMR (D_2O): δ 4.39 (1H, m, H-2'), 4.31 (1H, m, $J_{2',3'}$ = 7.1 Hz, H-3'), 4.02-3.87 (5H, m, $J_{1b',1a'}$ = 13.7 Hz, $J_{1b',2'}$ = 6.6 Hz, $J_{1a',2'}$ = 4.3 Hz, $J_{3',4a'}$ = 3.4 Hz, H-2, H-4, H-1a', H-1b', H-4a'), 3.82 (1H, dd, $J_{4b',4a'}$ = 12.7 Hz, H-4b'), 3.63 (2H, dd, $J_{1eq,2}$ = $J_{4,5eq}$= 2.7 Hz, H-1eq, H-5eq), 3.52 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 8.6 Hz, H-3), 3.34 (2H, ddd, $J_{5ax,5eq}$ = $J_{4,5ax}$ = 11.4 Hz, $J_{1ax,1eq}$ = $J_{1ax,2}$ = 11.3 Hz, H-1ax, H-5ax); ^{13}C NMR (D_2O): δ 83.03 (C-3'), 78.42 (C-3), 70.67 and 70.64 (2C, C-2 and C-4), 68.02 (C-2'), 62.30 (C-4'), 50.20 (C-1'), 39.29 and 39.11 (2C, C-1 and C-5). HRMS Calcd for $C_9H_{19}O_9SSe$ (M + H): 382.9915. Found: 382.9916. Anal. Calcd for $C_9H_{18}O_9SSe$: C, 28.35 ; H, 4.76. Found: C, 28.44; H, 4.71.

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[(*S*)-[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-episelenoniumylidene]-xylitol inner salts (31a). To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sufate **11** (0.226 g, 0.83 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **8** (0.308 g, 0.66 mmol) and anhydrous K_2CO_3 (20 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 72 h. The solvent was removed and the residue was purified by

column chromatography [$CHCl_3$/MeOH, 10:1] to give an inseparable 23:7 mixture of **31a** and **31b** as a white solid (0.42 g, 85%). Major isomer **31a** : $[\alpha]_D$ -44.0 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.44-7.11 (20H, m, Ar), 5.54 (1H, s, C*H*Ph), 4.81 (1H, dd, $J_{1a',1b'}$ = 12.7 Hz, $J_{1a',2'}$ = 3.7 Hz, H-1a'), 4.71 – 4.40 (8H, m, H-3', H-4a', CH_2Ph), 4.35 (1H, br d, H-1b'), 4.17 (1H, br dd, $J_{2',3'}$ = 9.2 Hz, H-2'), 3.98 (1H, dd, H-4), 3.92 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 4.0 Hz, H-3), 3.86 (1H, dd, H-2), 3.76 (1H, t, $J_{4a',4b'}$ = $J_{3',4b'}$ = 10.4 Hz, H-4b'), 3.65 (1H, dd, $J_{4,5eq}$ = 3.0 Hz, H-5eq), 3.60 (1H, dd, $J_{4,5ax}$ = 4.3 Hz, $J_{5ax,5eq}$ = 13.7 Hz, H-5ax), 3.31 (1H, dd, $J_{1eq,2}$ = 3.1 Hz, H-1eq), 3.17 (1H, dd, $J_{1eq,1ax}$ = 13.5 Hz, $J_{1ax,2}$ = 3.8 Hz, H-1ax); δ 137.39, 137.20, 137.08, 137.01 ($4C_{ipso}$), 129.76 – 126.46 (20C, Ar), 102.05 (*C*HPh), 77.54 (C-2'), 73.44, 72.64 (2*C*H_2Ph), 72.54 (C-3), 72.19 (*C*H_2Ph), 72.13 (C-2), 71.91 (C-4), 69.53 (C-4'), 67.34 (C-3'), 43.60 (C-1'), 30.68 (C-5), 30.03 (C-1). Anal. Calcd for $C_{37}H_{40}O_9SSe$: C, 59.99; H, 5.45. Found: C, 59.85; H, 5.58.

1,5-Dideoxy-1,5-[(*S*)-[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episelenoniumylidene]-xylitol inner salt (5). To a mixture of compounds **31a** and **31b** (0.406 g, 0.55 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.50 g). The mixture was stirred under 120 psi H_2 for 8 days. TLC revealed one major product and two minor products. The mixture was filtered through Celite with MeOH, the solvent was removed, and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1]. Compound **5** was obtained as a syrup (0.05g, 25%); $[\alpha]_D$ +14.1 (*c* 0.4, H_2O). ^{1}H NMR (D_2O): δ 4.41 (1H, m, $J_{1a',2'}$ = 4.0 Hz, H-2'), 4.33 (1H, m, $J_{2',3'}$ = 7.1 Hz, H-3'), 4.04-3.88 (5H, m, $J_{1b',1a'}$ = 13.7 Hz, $J_{1b',2'}$ = 6.6 Hz, $J_{3',4a'}$ = 3.2 Hz, H-2, H-4, H-1a', H-1b', H-4a'), 3.84 (1H, dd, $J_{4b',4a'}$ = 12.7 Hz, $J_{3',4b'}$ = 3.0 Hz, H-4b'), 3.65 (2H, dd, $J_{1eq,2}$ = $J_{4,5eq}$= 2.5 Hz, H-1eq, H-5eq), 3.55 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 8.6 Hz, H-3), 3.36 (2H, ddd, $J_{5ax,5eq}$ =

$J_{4,5ax}$ = 11.7 Hz, $J_{1ax,1eq} = J_{1ax,2}$ = 11.1 Hz, H-1ax, H-5ax); ^{13}C NMR (D_2O): δ 83.06 (C-3'), 78.42 (C-3), 70.69 and 70.65 (2C, C-2 and C-4), 68.06 (C-2'), 62.33 (C-4'), 50.19 (C-1'), 39.31 and 39.11 (2C, C-1 and C-5). HRMS Calcd for $C_9H_{18}O_9SSeNa$ (M + Na): 404.9734. Found: 404.9735. Anal. Calcd for $C_9H_{18}O_9SSe$: C, 28.35; H, 4.76. Found: C, 28.56; H, 4.54.

1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucitol (32). To a solution of 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranoside (1.01 g, 2.48 mmol) in dry CH_2Cl_2 (10 mL) was added, while stirring at 0°C, 33% HBr/HOAc (2.7 mL, 15.7 mmol). The ice bath was removed and the reaction mixture allowed to stir at rt for 7 h before being stored in the freezer overnight. The organic phase was diluted with CH_2Cl_2 (50 mL), and washed with ice cold water (2 x 50 mL), sat. $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried with Na_2SO_4 and concentrated down. The residue was dissolved in dry toluene (40 mL) and AIBN (0.17 g) and (*n*-Bu)$_3$SnH (1.2 mL, 4.5 mmol) in dry toluene (30 mL) were added over 5 h via a dropping funnel. The mixture was allowed to reflux overnight. The organic phase was concentrated and the product was purified by flash chromatography [EtOAc/hexanes 1:1] to give a white solid which was recrystallized from EtOAc/hexanes (0.442 g, 51%); mp 85-89°C (lit.[35] mp 100-102°C); $[\alpha]_D$ = +36.5 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.14 (1H, m, H-4), 5.00 (2H, m, H-3, H-2), 4.21 (1H, dd, $J_{5,6a}$ = 5.8 Hz, $J_{6b,6a}$ = 11.9 Hz, H-6a), 4.09 (1H, dd, $J_{5,6b}$ = 3.4 Hz, H-6b), 3.13 (1H, ddd, $J_{4,5}$ = 9.1 Hz, H-5), 2.85 (1H, dd, $J_{1ax,1eq}$ = 13.4 Hz, $J_{1eq,2}$ = 3.8 Hz, H-1eq), 2.63 (1H, m, H-1ax), 2.03 (3H, s, OAc), 1.99 (3H, s, OAc), 1.98 (3H, s, OAc), 1.97 (3H, s, OAc).

1,5-Anhydro-5-thio-D-glucitol (33). To a solution of 1,5-anhydro-2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucitol **32** (0.310 g, 0.89 mmol) in dry MeOH (20 mL) was added 1M

NaOMe/MeOH (4 mL, 4 equiv). This was kept stirring under N_2 overnight. The solution was acidified with excess Rexyn 101. Rexyn 101 was removed by filtration and the organic phase was concentrated. The product was purified by flash chromatography [$CHCl_3$/MeOH 5:2] to give **33** as a white solid (0.125 g, 78%); mp 110-115°C; $[\alpha]_D$ = +27.4 (*c* 1.2, MeOH); ^{1}H NMR (D_2O): δ 3.90 (1H, dd, $J_{5,6a}$ = 3.2 Hz, $J_{6b,6a}$ = 11.9 Hz, H-6a), 3.75 (1H, dd, $J_{5,6b}$ = 6.4 Hz, H-6b), 3.64 (1H, m, H-2), 3.48 (1H, dd, $J_{4,5}$ = 10.2 Hz, H-4), 3.19 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.1 Hz, H-3), 2.88 (1H, m, H-5), 2.71 (1H, dd, $J_{1eq,2}$ = 4.6 Hz, $J_{1eq,1ax}$ = 13.3 Hz, H-1eq), 2.62 (1H, dd, $J_{1ax,2}$ = 11.0 Hz, H-1ax).

1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol (9). To a stirring solution of 1,5-anhydro-5-thio-D-glucitol **33** (0.194 g, 1.08 mmol) in dry DMF (60 mL) was added NaH (0.5 g, 12.5 mmol) and then BnBr (0.7 mL, 5.9 mmol). This was kept stirring overnight. Excess NaH was destroyed by the addition of MeOH. The organic phase was concentrated under reduced pressure. To the residue was added H_2O (200 mL) and this was extracted with CH_2Cl_2 (5 x 100 mL). The organic phase was dried with Na_2SO_4 and concentrated. The product was purified by flash chromatography [hexanes/EtOAc 20:1] to give a syrup which was recrystallized from EtOAc/hexanes to give the title compound as a white solid (0.276 g, 58%); mp 56-59°C; $[\alpha]_D$ = +15.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.34-7.12 (20H, m, ArH), 4.94 (1H, d, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.86 (1H, d, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.81 (1H, d, $J_{A,B}$ = 10.7 Hz, CH_2Ph), 4.70 (2H, s, CH_2Ph), 4.53 (1H, d, $J_{A,B}$ = 10.8 Hz, CH_2Ph), 4.51 (2H, s, CH_2Ph), 3.73 (4H, m, $J_{6a,6b}$ = 12.2 Hz, $J_{4,5}$ = 10.4 Hz, H-2, H-4, H-6a, H-6b), 3.40 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.1 Hz, H-3), 2.95 (1H, ddd, $J_{5,6b}$ = 3.0 Hz, $J_{5,6a}$ = 5.4 Hz, H-5), 2.79 (1H, dd, $J_{1eq,2}$ = 4.3 Hz, $J_{1eq,1ax}$ = 13.4 Hz, H-1eq), 2.56 (1H, dd, $J_{1ax,2}$ = 11.1 Hz, H-1ax).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[(*S*)-[(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-episulfoniumylidene]-D-glucitol inner salts (34a) and (34b).

To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic-sulfate **2** (0.115 g, 0.42 mmol), 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **8** (0.174 g, 0.32 mmol) and anhydrous K_2CO_3 (30 mg). The mixture was stirred in a sealed tube in a 70°C oil bath for 5 days. The solvent was removed and the residue was purified by column chromatography [$CHCl_3$/MeOH, 10:1] to give an inseparable mixture of **34a** and **34b** as a white solid in a 2:1 ratio (0.182 g, 70%); $[\alpha]_D$ = +2.1 (*c* 1.3, CH_2Cl_2). Major isomer **34a**: ^{1}H NMR (CH_2Cl_2): δ 7.44-7.06 (25H, m, Ar), 5.48 (1H, s, C*H*Ph), 4.70 (1H, dd, $J_{1b',1a'}$ = 14.0 Hz, $J_{1a',2'}$ = 4.2 Hz, H-1a'), 4.67- 4.57 (3H, m, $J_{A,B}$ = 11.6 Hz, $J_{A,B}$ = 11.5 Hz, H-3', CH_2Ph), 4.58-4.42 (5H, m, $J_{3',4a'}$ = 5.5 Hz, $J_{A,B}$ = 11.4 Hz, $J_{A,B}$ = 11.5 Hz, $J_{A,B}$ = 11.5 Hz, $J_{A,B}$ = 11.7 Hz, H-4a', CH_2Ph), 4.40 (2H, s, CH_2Ph), 4.32 (1H, br dd, $J_{1b',2'}$ = 2.0 Hz, H-1b') 4.22 (1H, m, $J_{2',3'}$ = 9.6 Hz, H-2') 4.09 (1H, t, $J_{4,5}$ = $J_{5,6a}$ = 5.1 Hz, H-5), 4.06-4.00 (2H, m, $J_{6b,6a}$ = 10.4 Hz, H-6b, H-4), 3.98 (2H, m, H-6a, H-2), 3.85 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 4.6 Hz, H-3), 3.75 (1H, t, $J_{4b',4a'}$ = $J_{3',4b'}$ = 10.5 Hz, H-4b'), 3.39 (1H, m, $J_{1ax,2}$ = 4.6 Hz, H-1ax), 3.31 (1H, dd, $J_{1ax,1eq}$ = 14.8 Hz, $J_{1eq,2}$ = 3.1 Hz, H-1eq); ^{13}C NMR (CD_2Cl_2): δ 137.54, 137.44, 137.35, 137.17, 136.85 (5C_{ipso}), 129.80 – 126.54 (20C, Ar), 101.95 (*C*HPh), 77.23 (C-2'), 76.87 (C-3), 74.48, 74.13, 73.99 (3*C*H_2Ph), 73.66 (C-4), 73.49 (C-2), 72.35 (*C*H_2Ph), 69.59 (C-4'), 66.63 (C-3'), 65.33 (C-6), 53.46 (C-5), 45.38 (C-1'), 34.69 (C-1). Anal. Calcd for $C_{45}H_{48}O_{10}S_2$: C, 66.48 ; H, 5.96. Found: C, 66.36; H, 6.08.

1,5-Dideoxy-1,5-[(*S*)-[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene]-D-glucitol inner salt (3).

To a mixture of compounds **34a** and **34b** (0.1639 g, 0.20 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.17 g). The mixture was stirred under 120 psi H_2 for 48 h. The mixture was filtered through Celite with MeOH, the solvent was removed, and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1]. Compound **3** was obtained as a syrup (0.06 g, 81%); $[\alpha]_D$ = -20.4 (*c* 0.8, H_2O). ^1H NMR (D_2O): δ 4.33 (2H, m, $J_{2',3'}$ = 6.9 Hz, H-2', H-3'), 4.21 (1H, dd, $J_{6a,6b}$ = 13.2 Hz, $J_{5,6a}$ = 3.7 Hz, H-6a) 4.12 (1H, dd, $J_{5,6b}$ = 2.6 Hz, H-6b), 4.04-3.81 (7H, m, $J_{4a',4b'}$ = 12.7 Hz, $J_{3',4a'}$ = 3.3 Hz, $J_{3',4b'}$ = 2.9 Hz, H-1eq, H-2, H-4, H-1a', H-1b', H-4a', H-4b'), 3.76 (1H, m, $J_{4,5}$ = 10.7 Hz, H-5), 3.55 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.1 Hz, H-3), 3.45 (1H, t, $J_{1ax,1eq}$ = $J_{1ax,2}$ = 11.5 Hz, H-1ax); ^{13}C NMR (D_2O): δ 83.03 (C-3'), 78.58 (C-3), 70.91 and 69.64 (2C, C-2 and C-4), 67.04 (C-2'), 62.11 (C-4'), 60.88 (C-5), 58.63 (C-6), 49.01 (C-1'), 41.76 (C-1). HRMS. Calcd for $C_{10}H_{21}O_{10}S_2$ (M + H): 365.0576 Found: 365.0574.

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[(*S*)-[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy) butyl]-episulfoniumylidene]-D-glucitol inner salts (35a) and (35b) . To 1,1,1,3,3,3-hexafluoro-2-propanol (0.5 mL) were added 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic-sufate **11** (0.148 g, 0.54 mmol), 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **9** (0.240 g, 0.44 mmol) and anhydrous K_2CO_3 (33 mg). The mixture was stirred in a sealed tube in a 69-70°C oil bath for 84 h. The solvent was evaporated and the residue was purified by column chromatography [$CHCl_3$/MeOH, 10:1] to give an inseparable 3:1 mixture of **35a** and **35b** as a white solid (0.25g, 68%); $[\alpha]_D$ = +48.8 (*c* 1.6, CH_2Cl_2). ^1H NMR (CD_2Cl_2): δ 7.48-7.04 (25H, m, Ar), 5.54 (1H, s, C*H*Ph), 4.71-

4.64 (3H, m, $J_{1b',1a'}$ = 14.0 Hz, $J_{1a',2'}$ = 3.4 Hz, $J_{A,B}$ = 11.5 Hz, CH_2Ph, H-1a'), 4.60- 4.41 (5H, m, $J_{3',4a'}$ = 5.5 Hz, $J_{A,B}$ = 11.6 Hz, $J_{A,B}$ = 11.9 Hz, $J_{A,B}$ = 11.7 Hz, H-4a', CH_2Ph), 4.37-4.29 (4H, m, $J_{1b',2'}$ = 2.2 Hz, $J_{A,B}$ = 12.0 Hz, $J_{A,B}$ = 12.0 Hz, $J_{A,B}$ = 11.4 Hz, H-1b', CH_2Ph), 4.23 (1H, ddd, $J_{2',3'}$ = 9.9 Hz, H-2'), 4.04 (1H, m, H-2), 3.93 (1H, m, H-5), 3.89 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 4.2 Hz, H-3), 3.84 (1H, dd, $J_{1ax,2}$ = 4.5 Hz, H-1ax), 3.81 (1H, t, $J_{4,5}$ = 4.3 Hz, H-4), 3.79-3.71 (2H, m, $J_{3',4b'}$ = $J_{4b',4a'}$ = 10.4 Hz, $J_{5,6b}$ = 7.4 Hz, H-4b', H-6b), 3.65 (1H, dd, $J_{6b,6a}$ = 11.1 Hz, $J_{5,6a}$ = 5.1 Hz, H-6a), 3.58 (1H, dd, $J_{1ax,1eq}$ = 14.9 Hz, $J_{1eq,2}$ = 2.7 Hz, H-1eq); ^{13}C NMR (CD_2Cl_2): δ 137.18, 137.07, 137.00, 136.85, 136.75 ($5C_{ipso}$), 129.71-126.65 (25C, Ar), 102.11 (*C*HPh), 77.10 (C-2'), 73.84 (C-3), 73.70, 73.51, 73.40 (3*C*H_2Ph), 73.16 (C-4), 72.52, (C-2), 71.85 (*C*H_2Ph), 69.50 (C-4'), 65.89 (C-6), 65.80 (C-3'), 52.36 (C-5), 44.94 (C-1'), 32.49 (C-1). Anal. Calcd for $C_{45}H_{48}O_{10}S_2$: C, 66.48; H, 5.95. Found: C, 66.19; H, 6.07.

1,5-Dideoxy-1,5-[(*S*)-[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene]-D-glucitol inner salt (6).

To a mixture of compounds **35a** and **35b** (0.180 g, 0.22 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.20 g). This was stirred under 120 psi H_2 for 6 days. The mixture was filtered through Celite with MeOH, the solvent was removed and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 7:3:1]. Compound **6** was obtained as a syrup (0.05g , 67%); $[\alpha]_D$ = +10.3 (*c* 0.6, H_2O). ^{1}H NMR (D_2O): δ 4.41 (1H, ddd, $J_{2',3}$ = 7.9 Hz, H-2'), 4.27 (1H, m, H-3'), 4.22 (1H, dd, $J_{6a,6b}$ = 12.9 Hz, $J_{5,6b}$ = 3.9 Hz, H-6b), 4.14 (2H, m, $J_{1a',2'}$ = 3.8 Hz, $J_{1a',1b'}$ = 13.4 Hz, $J_{5,6a}$ = 2.9 Hz, H-1a', H-6a), 3.97 (1H, dd, $J_{4a',4b'}$ = 12.7 Hz, $J_{3',4a'}$ = 3.8 Hz, H-4a'), 3.90 (1H, t, $J_{4,5}$ = 8.2 Hz, H-4), 3.86 (2H, m, $J_{3',4b'}$ = 3.4 Hz, $J_{1eq,2}$ = 3.1 Hz, H-4b', H-1eq), 3.79 (1H, t, H-2), 3.75 (1H, ddd, H-

5), 3.70 (1H, dd, $J_{1b',2'}$ = 8.5 Hz, $J_{1b',1a'}$ = 14.0 Hz, H-1b'), 3.52 (1H, t, $J_{2,3} = J_{3,4}$ = 8.5 Hz, H-3), 3.47 (1H, t, $J_{1ax,1eq} = J_{1ax,2}$ = 11.3 Hz, H-1ax); ^{13}C NMR (D_2O): δ 83.15 (C-3'), 78.57 (C-3), 70.96 and 69.69 (2C, C-2 and C-4), 68.54 (C-2'), 62.11 (C-4'), 61.20 (C-5), 58.69 (C-6), 49.41 (C-1'), 43.62 (C-1). HRMS Calcd for $C_{10}H_{21}O_{10}S_2$ (M + H): 365.0576. Found: 365.0577.

CHAPTER 5: REFERENCES

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