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Synthesis of Alkylated Deoxynojirimycin and 1,5-Dideoxy-1,5-iminoxylitol Analogues: Polar Side-Chain Modification, Sulfonium and Selenonium Heteroatom Variants, Conformational Analysis, and Evaluation as Glycosidase Inhibitors

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Abstract: The syntheses of *N*-alkylated deoxynojirimycin and 1,5-dideoxy-1,5-iminoxylitol derivatives having either a D- or an L-erythritol-3-sulfate functionalized *N*-substituent are reported. The alkylating agent used was a cyclic sulfate derivative, whereby selective attack of the nitrogen atom at the least hindered primary center afforded the desired ammonium salt. In aqueous solution, these salts were configurationally labile at the ammonium center. Sulfonium and/or selenonium analogues of the ammonium salts were prepared by analogous reactions. The chalcogen salts were obtained as mixtures of diastereomers, separable in some cases, differing only in the stereochemistry at the configurationally stable sulfur or selenium atoms. Proof of configuration and conformation of each compound was obtained by detailed NMR experiments. The compounds are six-membered ring analogues of salacinol, a known sulfonium-salt glucosidase inhibitor. Evaluation of the target compounds for enzyme inhibition of the glucosidase enzyme glucoamylase G2 indicated that these compounds were either inactive or, at best, only weak inhibitors of maltose hydrolysis.

Introduction

Metabolic processing of oligosaccharides involves a variety of glycosidase enzymes that catalyze the hydrolytic cleavage of glycosidic linkages. Inhibition of these enzymes affords various opportunities to manipulate the rates of glycosidase reactions, either for enzymology studies or for therapeutic purposes.[1−4] Known inhibitors include certain carbohydrate mimics that act as substrate surrogates for glycosidase enzymes.[5] An example is the naturally occurring glycosidase inhibitor acarbose **1**. This oligosaccharide contains the pseudo-sugar valienamine at the nonreducing end and has extremely high affinity for glucoamylase, a carbohydrate processing enzyme from *Aspergillus niger* ($K_i = 1.1 \times 10^{-12}$ M).[6] This strong binding is postulated to originate from electrostatic interactions of the positively charged, protonated nitrogen atom with carboxylate residues in the enzyme active-site. In addition, the half-chair conformation of the pseudo-sugar resembles the distorted pyranose ring conformation that is transiently attained during the generally accepted mechanism for glycosidase-catalyzed hydrolysis.[10]

A large number of glycosidase inhibitors are based on simpler amino anhydroalditol derivatives having the nitrogen atom as the ring heteroatom in either five-or six-membered ring structures. Prototypical examples are deoxynojirimycin (**2**) and its *N*-alkylated analogues.[7] Two derivatives of deoxynojirimycin, namely miglitol (**3**) and *N*-butyldeoxynojirimycin (**4**), are currently in use as drugs for the treatment of Type II diabetes

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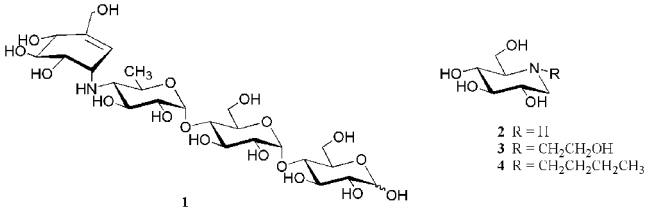
and Gaucher's disease, respectively. Both drugs act by inhibition of glycosidase enzymes.



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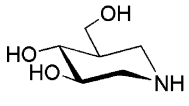
2 R = H
3 R = CH_2CH_2OH
4 R = $CH_2CH_2CH_2CH_3$

In the case of Type II diabetes, which generally develops in adults, insulin secretion from the pancreas may be normal but the entry of glucose into cells is compromised due to a shortage of insulin receptors on target cells.[8] Blood glucose levels are abnormally high, and deleterious effects ensue. Treatment with miglitol (**3**) before a meal inhibits α-glucosidases such as sucrase, maltase, and maltose glucoamylase in the intestinal tract and attenuates the spike in blood glucose levels that follows ingestion of food, thus leading to a more controlled metabolism of carbohydrates.

Gaucher's disease is an inherited metabolic defect that results in accumulation of glycosphingolipids due to the lack of a glycosidase enzyme necessary for their degradation. Oral treatment with *N*-butyldeoxynojirimycin (**4**) causes inhibition of glycolipid synthesis through slowing of Glucosidase I and II enzymes in the trimming pathways of oligosaccharide synthesis as well as inhibition of a specific glycosyl transferase involved in glycosphingolipid synthesis.[9] This limits the buildup of unwanted glycolipids to manageable levels and avoids or decreases the necessity of administering exogenous cerebrocidease enzymes by intravenous methods.

It has often been postulated that nitrogenous glycosidase inhibitors bind to their target enzymes at least partially due to electrostatic interaction of their protonated ammonium salts with active site carboxylate residues. This is similar to the stabilizing interactions of these negatively charged carboxylate groups with the transient charges that develop in the accepted transition state for glycoside hydrolysis.[10] Partial breakage of the glycosidic bond leads to incremental positive charge development at both the ring oxygen and the anomeric carbon of the glycoside. Replacement of either of these two atoms by a protonated nitrogen center therefore mimics the charge at these centers in the transition state. Most glycosidase inhibitors result from replacement of the ring oxygen of sugars with an amine, while nitrogenous compounds that a mimic positive charge at the anomeric carbon are found in the form of 1-azasugar analogues such as isofagomine (**5**).[11]

Recently, in the case of an isofagomine derivative bound in the active site of an endocellulase, direct crystallographic evidence has been presented to support a protonated imino center in the bound inhibitor, although the conformation of the six-membered heterocycle was unchanged from the free ligand.[12] Other studies have shown that a variety of distortions in the conformation of iminosugar inhibitors occur upon binding.[13,14] It is unclear at present whether a strong correlation exists between the strength of inhibition and the extent to which the bound conformation of the inhibitor matches the conformation of the transition state for glycoside hydrolysis. A consensus has emerged, however, that the binding of iminosugar inhibitors is usually enthalpically driven with a major exothermic contribution arising from protonation of the amine by an active site carboxylic acid.[14]



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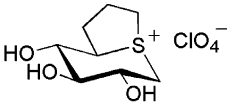

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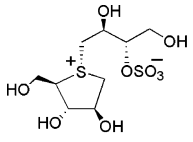
We have begun a program to investigate the synthesis and properties of sulfonium analogues of known amine glycosidase inhibitors and have reported the synthesis of a sulfonium analogue (**6**) of castanospermine.[15] These studies were initiated under the premise that sulfonium salts should be permanently charged mimics of the protonated ammonium salts that are presumed to be the enzyme-bound form of amine glycosidase inhibitors. Indeed, compound **6** was shown by NMR studies to bind to glucoamylase G2 with a high energy $^{1,4}B$ conformation, and modeling studies provided evidence for electrostatic interaction of the sulfonium center with an active site carboxylate residue.[16] Concurrent with these studies, the importance of electrostatic binding interactions was reinforced by the isolation of sulfonium ion glucosidase inhibitors salacinol (**7**)[17] and kotalanol (**8**)[18] from *Salacia reticulata*, a plant native to Sri Lanka and known for its antidiabetic properties. These compounds constitute a new class of glycosidase inhibitors in that they contain a thiosugar sulfonium ion with an internal sulfate providing the counterion. Presumably the sulfonium center can act in the same way as the protonated ammonium center of the nitrogenous glycosidase inhibitors when binding in the active site of glycosidase enzymes. We have synthesized several salacinol analogues by either varying the stereochemistry at one or more chiral centers or by replacing the sulfonium locus by an ammonium or selenonium center.[19−22] Some of these



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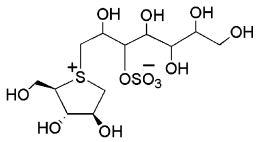

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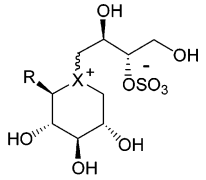
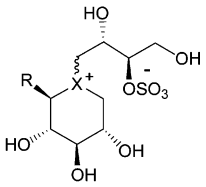
derivatives are active glucosidase inhibitors that show interesting selectivity for glucosidase enzymes from various sources.

The variance in inhibitory power for alkylated deoxynojirimycin and 1,5-dideoxy-1,5-iminoxylitol derivatives with different side chains has been investigated previously.[23−25] These studies were limited to simple alkyl or aromatic derivatives for the most part, and there seems to have been little investigation of the effect of including more polar substituents in the alkyl group. To expand the repertoire of molecules of this class that could serve as glycosidase inhibitors, we proposed to synthesize *N*-alkylated 1,5-dideoxy-1,5-iminoxylitol (**9a**) and deoxynojirimycin (**10a**) having the same L-erythritol-derived, sulfated side chain as salacinol. The advantage of having an internal sulfate counterion for the ammonium salt was deemed to be worth pursuing in order to investigate whether such a structural modification would lead to increased in vivo stability and/or membrane permeability. In addition, the internal sulfate salt and polar side chain may provide cationic inhibitors that bind to glycosidase enzymes without deprotonating the catalytic active-site carboxylic acid and provide additional insight into the structural features that are important for inhibition. We report herein the syntheses of **9a** and **10a** as well as the corresponding sulfonium and selenonium analogues **11a**, **12a**, and **13a**. We report also the syntheses of the corresponding enantiomers or diastereomers **9b**−**13b** resulting from incorporation of a side chain derived from D-erythritol. The compounds were evaluated as inhibitors of glucoamylase G2.



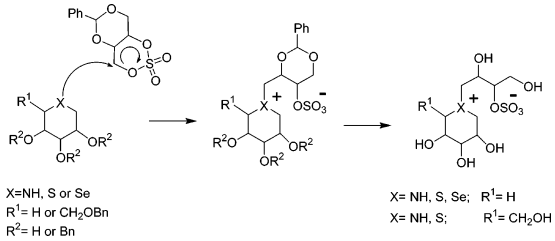


9a	X = NH	R = H		**9b**	X = NH	R = H
10a	X = NH	R = CH_2OH		**10b**	X = NH	R = CH_2OH
11a	X = S	R= H		**11b**	X = S	R= H
12a	X = S	R= CH_2OH		**12b**	X = S	R= CH_2OH
13a	X = Se	R= H		**13b**	X = Se	R= H

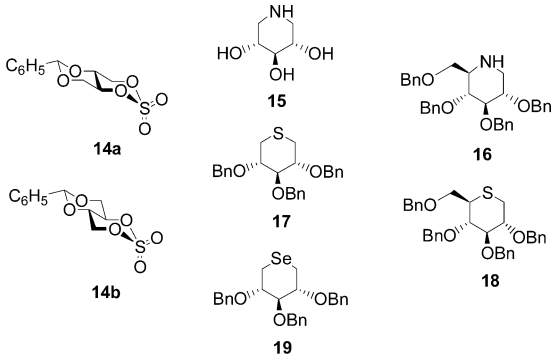
Results and Discussion

Each target compound was synthesized in two stereoisomeric forms (a or b) by using either of the enantiomeric forms of the cyclic sulfate **14a** or **14b** as the source of the sulfated alkyl side chain. In the case of compounds **9**, **11**, and **13**, these stereoisomers are enantiomers, while compounds **10** and **12** were prepared as either of two diastereomers. For the enantiomeric sulfonium salts **11a** and **11b**, *R*/*S* isomers at the stereogenic sulfonium ion center were separated and characterized independently. Similar isomers for the sulfonium salts **12** and selenonium salt **13** were not separable by chromatography, and the products were characterized as mixtures. In the case of the ammonium salts **9** and **10**, inversion at the nitrogen center, via the free amine, was sufficiently fast in solution at room

Scheme 1



temperature that stereoisomers at the ammonium center were not observed.



The general synthetic strategy (Scheme 1) involved alkylation of the piperidine (**15** and **16**), tetrahydrothiapyran (**17** and **18**), or tetrahydroselenapyran (**19**) heterocycles with either the 2,4-*O*-benzylidene-L-1,3-cyclic sulfate (**14a**),[19] derived from L-glucose, or its enantiomer (**14b**),[19] obtained from D-glucose. In general, the reactions with the less-expensive **14b** were examined first. These methods are analogous to those that we used previously to synthesize the five-membered ring analogues, salacinol and its nitrogen or selenium congeners.[19−22]

1. Preparation of Starting Materials. In preliminary experiments investigating the reactivity of the cyclic sulfate **14b**, we found that, for complex amine nucleophiles having only secondary alcohols as additional functional groups, protection of hydroxyl groups was unnecessary but that any primary alcohol functional groups may be alkylated in competition with amines.

Accordingly, the unprotected anhydroxylitol imine (**15**) was prepared by the literature method,[25] while deoxynojirimycin was prepared as its tetra-*O*-benzyl derivative (**16**).[23] The tetrahydrothiapyran derivative **17** was prepared (Scheme 2) by deacetylation and benzylation of the known triacetate **20**.[26] The benzylated tetrahydrothiapyran **18** was similarly prepared from the known anhydro-5-thio-D-glucitol tetraacetate (**21**)[15] by protecting group interchange. Compound **20** was obtained, in turn, either by reduction of tetra-*O*-acetyl-5-thio-D-xylopyranose (**22**)[27] or, more conveniently, from reaction of acetylated 1,5-dibromoxylitol (**23**) with sodium sulfide.[26] The selenium heterocyle **24** was prepared by substituting $NaSeB(OEt)_3$ (obtained in situ[28] by reduction of Se with NaBH4/EtOH) for sodium sulfide in the reaction with acetylated 1,5-dibromoxylitol (**23**) (Scheme 2). Subsequent exchange of the acetates for benzyl

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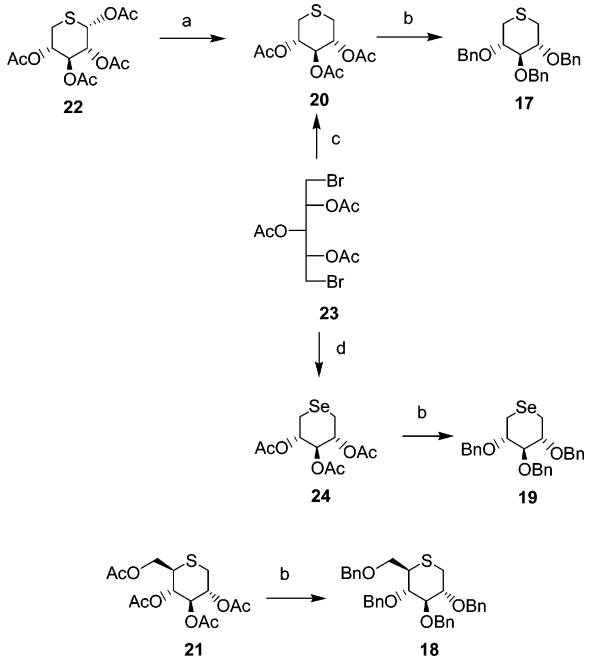
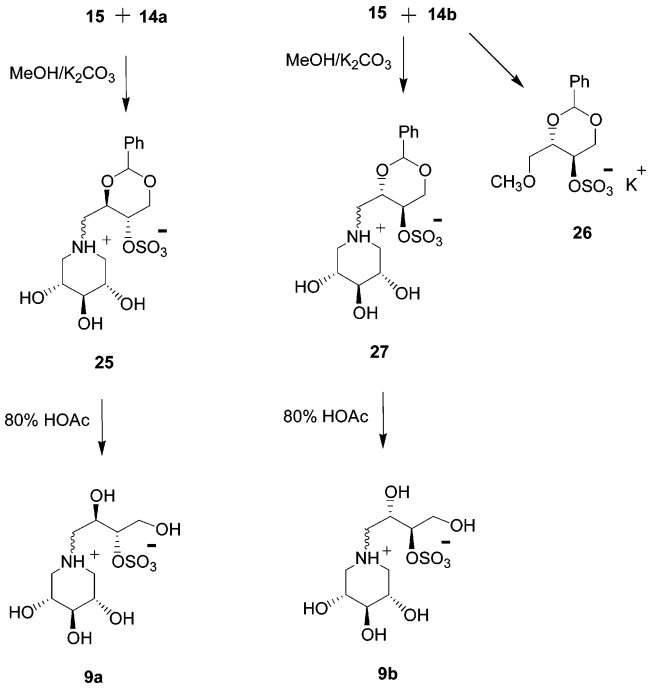
Scheme 2



a. Et_3SiH, HOAc
b. i) NaOMe/MeOH; ii) BnBr/NaH/DMF
c. Na_2S/DMF
d. $NaSeB(OEt)_3$/EtOH

Scheme 3



protecting groups gave the desired tetrahydroselenapyran derivative **19**, whose preparation was recently reported by an unrelated method.[29]

2. Target Ammonium Compounds. Compound **15** was reacted with the D-cyclic sulfate **14b** in MeOH containing K_2CO_3 (Scheme 3). Isolation of the more polar product gave the ammonium salt **27** in 43% yield. An abundant side product (**26**) resulting from opening of the cyclic sulfate by the methanol solvent could be isolated from the early chromatographic fractions. A similar reaction with the L-cyclic sulfate **14a** gave somewhat less of this side product, and the desired coupled product **25** was obtained in slightly higher yield (56%). The ^{1}H NMR spectra of compounds **25** and **27** exhibited sharp resonances for methylene groups α to the amine in D_2O (made basic with K_2CO_3), but neutral or acidic D_2O solutions gave downfield shifts and much broader resonances for these methylene resonances. We attribute these observations to exchange, at an intermediate rate relative to the chemical-shift NMR time scale, of the conjugate-acid *R*/*S* ammonium salts, with nitrogen inversion taking place via the free amines that exist in equilibrium with their conjugate acids at acidic pH.

Removal of the benzylidene protecting groups by hydrolysis in aqueous acetic acid gave the target compounds **9a** (73%) and **9b** (72%) after purification by chromatography on silica gel. These ammonium salts gave severely exchange-broadened NMR spectra and were more productively characterized by adding base to the NMR samples to produce the conjugate amine bases. Prolonged treatment with strong base should be avoided, however, due to the possibility of sulfate ester hydrolysis, as noted below. As expected for enantiomers, the NMR data for **9a** and **9b** were virtually identical, although small differences in chemical shifts between different samples for both identical and enantiomeric compounds were noted. These differences were attributed to the concentration and temperature dependence of the NMR chemical shifts between samples. The tendency of zwitterionic compounds to exist as aggregates in solution is the likely origin of these effects.

The coupled products **28** and **29**, derived from the benzyl-protected deoxynojirimycin, were obtained by reaction of compound **16** with the cyclic sulfates **14a** and **14b** in acetone/K_2CO_3 in yields of 80% and 65%, respectively (Scheme 4). The ^{1}H NMR resonances for compounds **28** and **29** were extremely broad in $CDCl_3$ but sharpened in CD_3OD (made basic with NaOD), thus indicating that the coupled products were obtained as an equilibrating mixture of the desired ammonium salts with the corresponding conjugate bases. Simultaneous removal of both the benzyl and benzylidene protecting groups was achieved by hydrogenolysis in aqueous acetic acid to give the target compounds **10a** and **10b**.

Analysis by ^{1}H NMR spectroscopy indicated that these products were contaminated by KOAc. Nevertheless, other than a resonance at δ 1.8 in the spectrum that was attributed to the acetate impurity, the target compounds were essentially pure and all resonances in both the ^{1}H and ^{13}C spectra were assigned by two-dimensional techniques. Prolonged storage of the NMR sample of compound **10b** in D_2O/NaOD at pH > 10 produced a slow loss of the 3′-sulfate group as evidenced by an upfield shift of the H-3′ resonance. After 2 days at ambient temperature the sulfate ester had been completely hydrolyzed to yield cleanly the tertiary amine compound **30** and inorganic sulfate salts.

The ^{1}H NMR data for all of the amine compounds in D_2O (pH > 8) indicated that the predominant conformation of the piperidine ring was $^4C_1$ (carbohydrate numbering) and that this conformational preference did not appear to change upon protonation (pH < 3). Similar conclusions were reached in a previous conformational study of alkylated deoxynojirimycin derivatives.[24]

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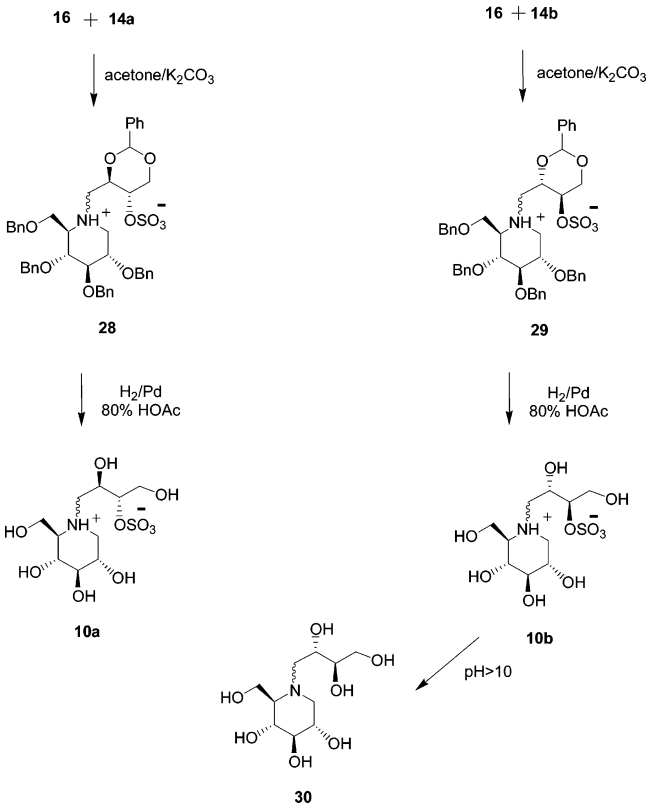
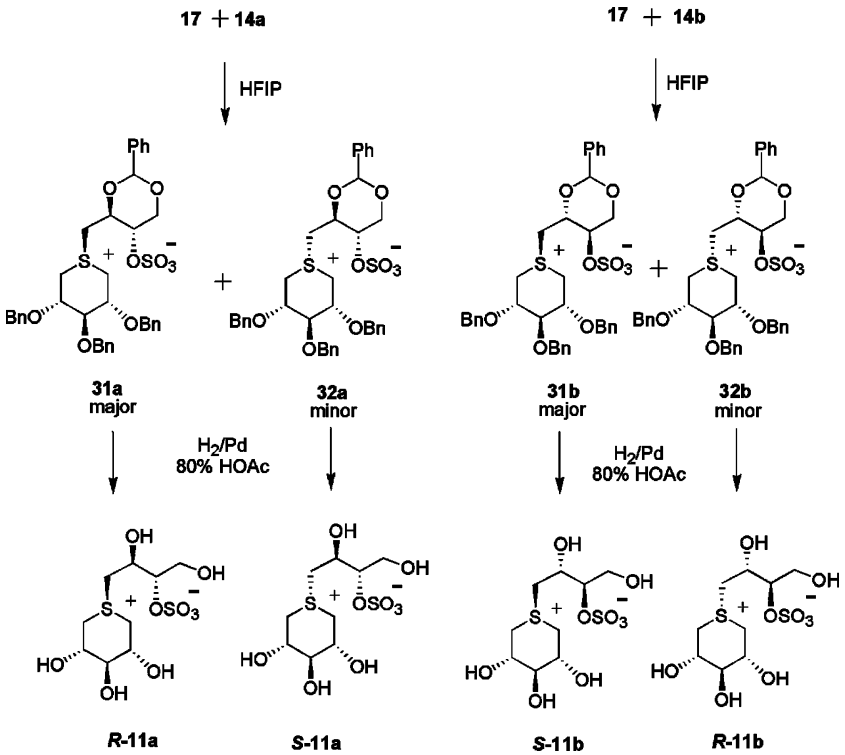
Scheme 4



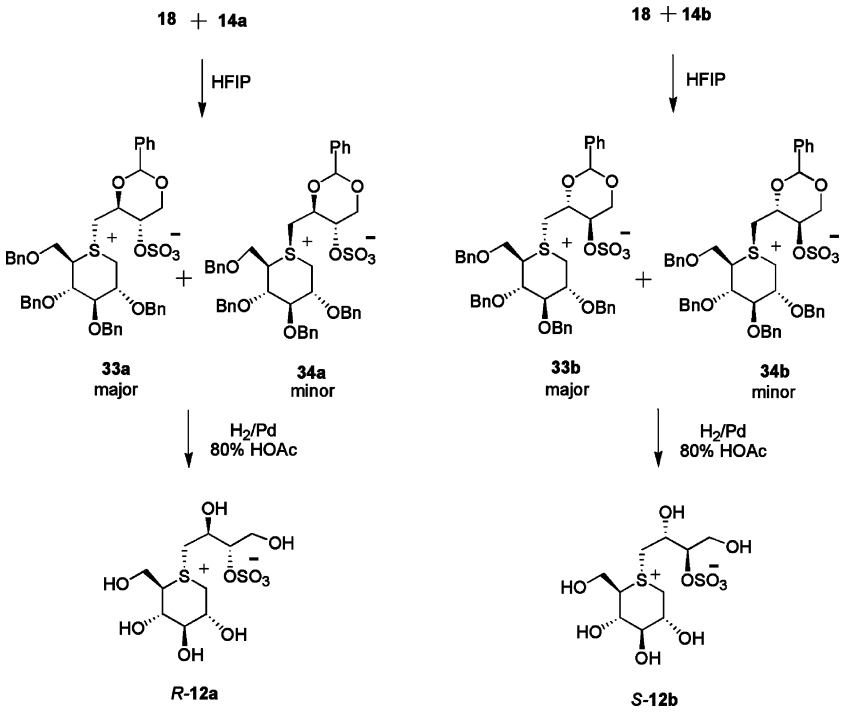
3. Target Sulfonium Compounds. The syntheses of sulfonium salts **11** and **12** (Schemes 5 and 6) were achieved in a fashion similar to those of the ammonium salts. Thus, compound **17** was initially reacted with the D-cyclic sulfate **14b** in acetone at 65 °C. Slow formation of two more-polar products was observed by TLC analysis. Isolation of the mixture of products gave **31b** and **32b** in approximately 37% yield. On changing the solvent to 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), the yield improved to 87%. The dramatically beneficial effect of HFIP solvent on the yields for sulfonium salt formation has been noted previously.[19b] The ratio of the major product **31b** to the minor product **32b** was 2:1. Pure samples of the two components were obtained by chromatography and characterized separately by NMR techniques.

Initially, 1D ^{1}H NMR spectra were obtained which revealed that the two compounds were isomers, having the same number of hydrogen atoms. The similarity of the spectra of the two compounds suggested that the compounds differed in stereochemistry only at the stereogenic sulfur atom. COSY spectra permitted the assignment of the proton signals for the tetrahydrothiapyran ring and for the erythritol side chain in both compounds. Notably, it was found that all of the ring proton signals were shifted downfield relative to the parent tetrahydrothiapyran **17**. This was anticipated, since the positive sulfonium center is electron withdrawing. Furthermore, although it was initially expected that the three benzyloxy groups at C-2, C-3, and C-4 would favor the sterically less-hindered equatorial positions, analysis of vicinal coupling constants showed that $J_{2,3}$ and $J_{3,4} = 3.5-3.9$ Hz. These values are much smaller than those ($J_{2,3} \approx J_{3,4} \approx 8.9$ Hz) observed for the axial−axial vicinal coupling constants in the precursor **17**. Thus, we reasoned that compounds **31b** and **32b** preferred a $^1C_4$ conformation, placing the three benzyloxy groups in axial positions and accounting for the small vicinal 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; the group at C-3 can also provide stabilizing electrostatic interactions.[15] The results are reminiscent of our previous work with the sulfonium ion **6**.[15]

Scheme 5



Scheme 6



The configuration at the sulfonium center was next established by means of a NOESY experiment. The NOESY spectrum for the major diastereomer showed H-1b′ correlations to H-1ax/H-1eq/H-5ax as well as H-1a′ and correlations to H-5eq/H-5ax. This isomer was thus assigned to structure **31b** with the erythritol side chain occupying the equatorial orientation (Figure 1). The absolute configuration at sulfur was thus established as being *R*.

The NOESY spectrum for the minor 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. This isomer was thus assigned to structure **32b**, the diastereomer with the erythritol side chain in an axial orientation (Figure 1). The absolute configuration at sulfur was thus established as being *S*. Each of the diastereomers **31b** and **32b** was deprotected by hydrogenolysis to give sulfonium salts *R*-**11b** and *S*-**11b**, which were obtained in 81% and 95% yields, respectively. Vicinal coupling constants indicated that deprotection was accompanied in both cases by a change in the preponderant ring conformation from $^1C_4$ to $^4C_1$ (*R*-**11b** $J_{2,3} \approx J_{3,4} \approx 7.2$ Hz, *S*-**11b** $J_{2,3} \approx J_{3,4} \approx 9.0$ Hz) (Figure 1). Transient one-dimensional nuclear Overhauser enhancement (NOE) difference experiments confirmed that there was no configurational inversion at the sulfonium center upon removal of the benzyl and benzylidene protecting groups. Thus, the major isomer *R*-**11b**, upon irradiation of the H-4′b/H-1′a multiplet, showed no NOE with the ring axial protons (Figure 2). Irradiation of H-1ax/H-5ax showed NOEs on the H-1eq/H-5eq/H-3 and H-2/H-4 multiplets only. No NOEs with the erythritol side chain protons were observed. These experiments provide evidence for the erythritol side chain occupying the axial position at sulfur, on the β-face and opposite to H-1ax, and confirm the *R* configuration at the sulfonium center for the major isomer *R*-**11b**, as was previously assigned for the protected precursor **31b**.

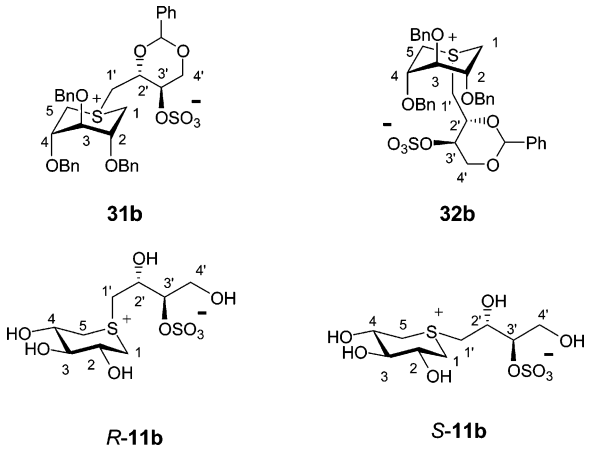


Figure 1. Preferred conformations of **31b**, **32b**, *R*-**11b**, and *S*-**11b**.

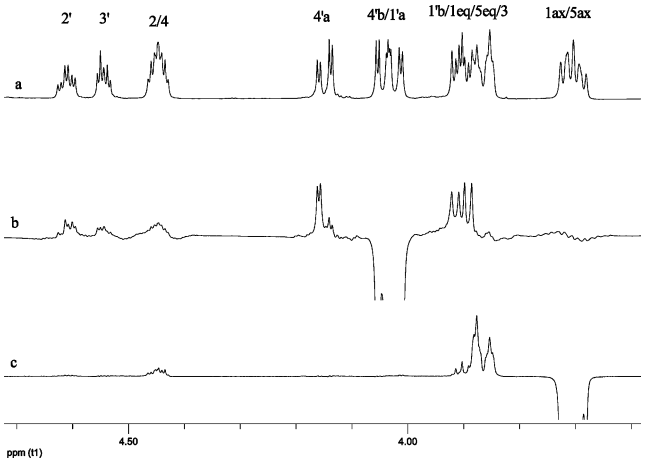


Figure 2. One-dimensional transient NOE difference spectra of *R*-**11b** in D_2O. (a) ^1H NMR spectrum (b) with selective irradiation of the H-4′b/H-1′a multiplet and (c) with selective irradiation of the H-1ax/H-5ax multiplet.

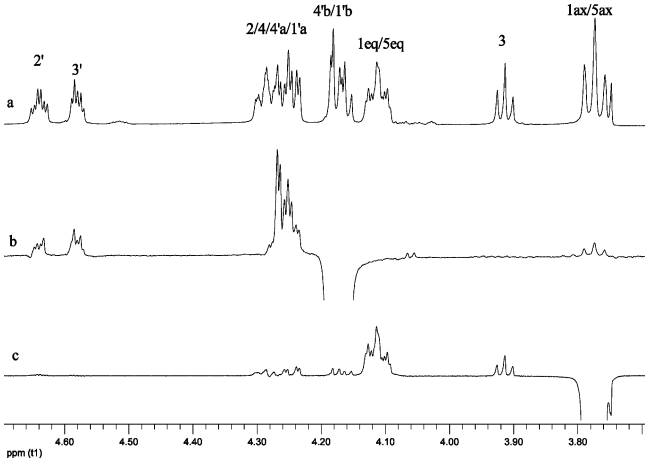
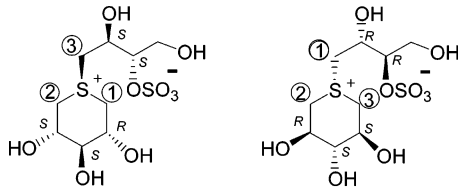


Figure 3. One-dimensional transient NOE difference spectra of compound *S*-**11b** in D_2O. (a) ^1H NMR spectrum (b) with selective irradiation of the H-4′b/H-1′b multiplet and (c) with selective irradiation of the H-1ax/H-5ax multiplet.



***R*-11a** ***R*-11b**

Figure 4. Cahn−Ingold−Prelog *R*/*S* descriptors for the sulfonium centers in the enantiomeric pair **11a**/**11b**.

The minor isomer *S*-**11b** showed, upon irradiation of the H-4′b/H-1′b multiplet, NOE with the H-1ax/H-5ax protons (Figure 3). Irradiation of the H-1ax/H-5ax multiplet showed NOEs with the H-4′b/H-1′b multiplet as well as to the H-2/H-4/H-4′a/H-1′a multiplet, in addition to NOEs to the ring protons. These experiments provide evidence for the erythritol side chain being present on the same face as H-1ax, occupying the α-equatorial position at sulfur, thus confirming the *S* configuration of the minor isomer *S*-**11b** at the sulfonium center, as was previously assigned for the protected precursor **32b**.

The synthesis of the sulfonium salts from the L-cyclic sulfate **14a** was examined next (Scheme 5). Compound **17** was reacted with **14a** at 70 °C in HFIP solvent to give two products **31a** and **32a** in a 5:2 ratio (84% yield). The major diastereoisomer **31a**, in which the erythritol side chain is cis to the C-3 benzyloxy group, was separated from the minor diastereoisomer **32a**, with the erythritol side chain trans to the C-3 benzyloxy group. The ^1H NMR spectra were virtually identical to those of the enantiomers **31b** and **32b** except for small variations due to concentration, as noted above. Each of the diastereomers **31a** and **32a** was deprotected via hydrogenolysis to give the target compounds *R*-**11a** and *S*-**11a**, respectively. It is noteworthy that, for pairs of enantiomers (for example, *R*-**11a**/*R*-**11b**), the stereochemical descriptors for the configurations at the sulfonium centers are invariant in these compounds because of sequence rule changes in priority between the side chain and the ring substituents (see Figure 4).

Entry into the 5-thio-D-glucitol analogues began by treatment of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **18** with the D-cyclic sulfate **14b.** The reaction afforded an inseparable mixture of compounds **33b** and **34b** with an approximate 2:1 isomer ratio in 70% yield (Scheme 6). As in the xylitol series, the protected glucitol derivative **33b** displayed an unusual $^1C_4$ conformational preference, as indicated by the coupling constants. This places the three benzyloxy groups at C-2, C-3, and C-4 as well as the benzyloxymethyl group at C-5 in an axial orientation.

The stereochemistry at the stereogenic sulfonium center for the major isomer **33b** was established by means of a NOESY experiment. A strong NOESY correlation was observed between the H-1b′ proton and the H-5 proton, thus confirming that the benzylidene-protected erythritol side chain was cis to H-5. NOEs to H-1ax and to H-6a/H-6b were not observed. Thus, the absolute configuration at the sulfonium center in the major isomer was *S*. Alkylation of the sulfur must occur preferentially from the α-face of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **18** due to shielding of the *β*-face by the adjacent C-5 benzyloxymethyl group.

The mixture consisting of compounds **33b** 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]-*S*-episulfonium-ylidene]-D-glucitol inner salt *S*-**12b** in 81% yield (Scheme 6).

Treatment of 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **(18)** with the L-cyclic sulfate **14a** afforded an inseparable mixture of compounds **33a** and **34a** with an approximate 3:1 isomer ratio in 68% yield (Scheme 6). Whereas the achiral anhydro xylitol compound **17** generated enantiomers upon reaction with the enantiomeric D- and L-cyclic sulfates, this was not the case for the chiral compound **18**. For this reaction, the products **33a** and **33b** are diastereomers rather than enantiomers.

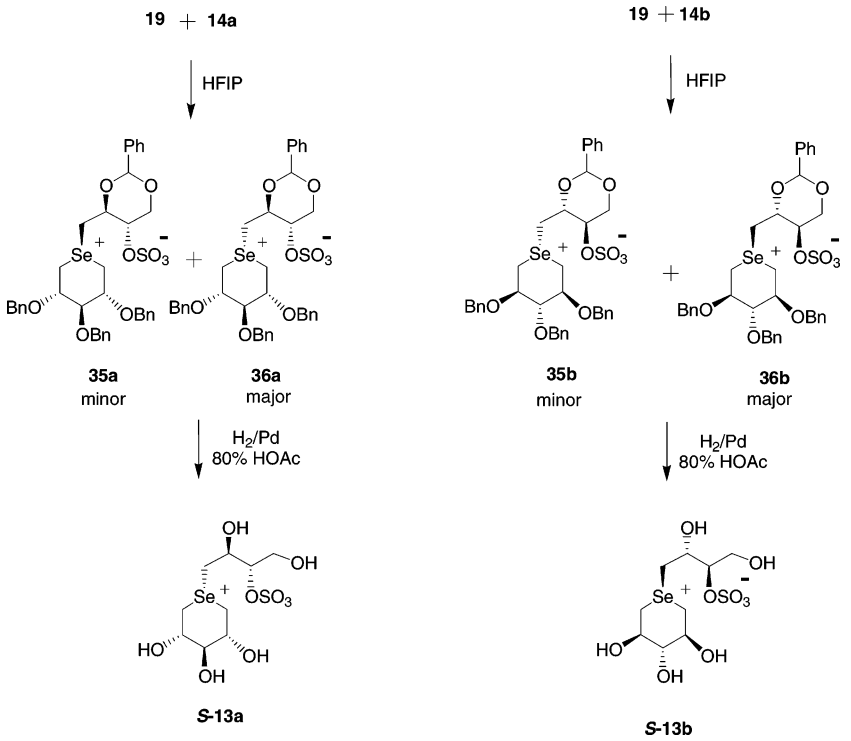
The stereochemistry at the stereogenic sulfonium center for the major isomer **33a** was again established by means of a NOESY experiment. A strong NOE correlation was observed between the H-1′a proton and H-5. In addition, there was also an NOE correlation between H-2′ and H-5, confirming that the benzylidene-protected 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 for compound **33a** was *R*, that is, the same stereochemistry at sulfur previously found for the diastereoisomer **33b**. (Note: The change in *R*/*S* descriptor for the sulfonium center between **33a** and **33b** derives only from changes in priority between the side chain and the ring substituents and does not imply a change in stereochemistry at sulfur in this case.) Therefore, independent of the configuration (**14a** or **14b)** of the cyclic sulfate reagent, in both cases, alkylation at sulfur occurred preferentially from the least-hindered α-face of compound **18**.

The mixture containing **33a** and **34a** was then subjected to hydrogenolysis to give primarily 1,5-dideoxy-1,5-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-*R*-episulfonium-ylidene]-D-glucitol inner salt *R*-**12a** in 67% yield (Scheme 6).

Upon removal of the protecting groups, compounds *R*-**12a** and *S*-**12b** adopted a $^4C_1$ conformation, as indicated by the vicinal proton coupling constants. This places all of the ring substituents in an equatorial orientation, as observed for the xylitol series.

4. Target Selenonium Compounds. The tetrahydroselenapyran **19** was coupled to the D-cyclic sulfate **14b** in HFIP solvent and afforded an inseparable mixture of two compounds, **35b** and **36b**, in a 1:4 ratio in 96% yield (Scheme 7). These two compounds are diastereoisomers at the stereogenic selenium

Scheme 7



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 by comparison of the NMR data to those of the sulfonium analogues **31b**/**32b**, and by analysis of the NOESY spectrum (see below), that the major product, **36b**, was that in which the benzylidene-protected erythritol side chain was trans to the benzyloxy group at C-3. The minor product, **35b**, was that in which the benzylidene-protected erythritol side chain was cis to the C-3 benzyloxy group. Curiously, the ratio was opposite to the results obtained with the tetrahydrothiapyran products **31b** and **32b** for which the major isomer was the cis isomer. The predominant conformations observed in both compounds **35b** and **36b** were, as with the corresponding thio analogues, those which placed all three benzyloxy groups in an axial arrangement, thus favoring $^1C_4$ conformations, as evidenced by the coupling constants. The major isomer **36b** in its preferred $^1C_4$ conformation places the selenonium alkyl group in the axial position. The longer C−Se bonds in compounds **35b**/**36b** compared to the thio analogues must result in less severe gauche steric interactions between the selenonium alkyl group and C-2 and C-4.

The mixture consisting of compounds **35b** and **36b** was then deprotected via hydrogenolysis to give mostly one diastereoisomer of **13b**, in 39% yield (Scheme 7). The low yield was due to catalyst poisoning by decomposition products and the reaction could not be brought to completion. This major compound was characterized by NMR techniques and found to be 1,5-dideoxy-1,5-[[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-*S*-episelenoniumylidene]-xylitol inner salt *S*-**13b**.

Reaction of the selenoether **19** with the L-cyclic sulfate **14a** concluded the synthetic study. The product was an inseparable mixture of two diastereoisomers at the stereogenic selenium center, **35a** and **36a**, in a 1:3 ratio. (Scheme 7).

The configuration at the stereogenic selenonium centers for the enantiomers **36a** and **36b** was confirmed by means of NOESY experiments performed on the mixtures of the compounds containing their minor diastereomers. The major isomer in each case was found to be that in which the erythritol side chain occupied the axial position in the preferred $^1C_4$ conformation. This was evidenced by correlations between H-1b′ and H-5eq as well as correlations between H-1′a and H-1eq. An axial preference would imply correlations between H-1′a/H-1′b and H-5eq, and H-1′a/H-1′b and H-1eq only, since free rotation about the C-1′-Se bond would not permit the H-1′a and H-1′b protons to interact with the axial C-1 and C-5 protons as these are on the opposite side of the selenoether ring. Therefore, NOEs would not be expected between H-1′a/H-1′b and H-1ax/H-1eq. On the other hand, an equatorial preference would imply correlations between H-1′a/H-1′b to H-1ax and H-5ax as well as possibly to H-1eq and H-5eq. Thus, for compound **36b** the absolute configuration at the selenium center is *S* and that for the enantiomeric **36a** is also *S* (see previous discussion on stereochemical descriptors for **11a**/**11b**). 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.

The mixture consisting of **35a** and **36a** was then deprotected by hydrogenolysis to afford mostly one diastereoisomer of **13a** in 25% yield (Scheme 7). 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]-*S*-episelenoniumylidene]xylitol inner salt *S*-**13a**, the enantiomer of compound *S*-**13b**.

5. Glucoamylase Inhibition Studies. Compounds **9a**, **9b**, **10a**, **10b**, *S*-**11a**, *R*-**11a**, *S*-**11b**, *R*-**11b**, **12a**, **12b**, **13a**, and **13b** were tested for inhibition of glucoamylase G2 from *Aspergillus niger* with maltose as a substrate. The rate of the hydrolysis reaction was measured by assaying for glucose concentration

using a linked glucose oxidase method. The tested compounds were either inactive or, at best, only weak inhibitors of maltose hydrolysis (compounds **9b** and **12a** were the only compounds exhibiting inhibitory activity and were estimated to have K_i values in excess of 70 mM). It would appear that the five-membered ring of salacinol (**7**) is a necessary and key structural determinant of sulfonium sulfate glycosidase inhibitors and their analogues[19a,19c,21] for this particular enzyme. It is curious, however, that the nitrogen analogues (**10a** and **10b**) were inactive given the known inhibitory activities of *N*-alkylated deoxynojirimycin derivatives for this enzyme.

Experimental Section

General. 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 the following: 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 for ^1H. 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 $^1H,^{13}C$ (HMQC) experiments using standard Bruker or Varian pulse programs. Processing of the spectra was performed with standard UXNMR and WINNMR software (Bruker) or MestReC software (Varian).

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 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. NOESY spectra were obtained with a mixing time of 500 or 800 ms.

MALDI mass spectra were obtained on a PerSeptive Biosystems, Voyager DE time-of-flight spectrometer for samples dispersed in a 2,5-dihydroxybenzoic acid matrix. High-resolution mass spectra were liquid secondary ion mass spectrometry (LSIMS) run on a Kratos Concept double focusing mass spectrometer at 10 000 RP, using a glycerin matrix or, in the case of compound **31a**, 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.

1,5-Anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol (17). (a) Acetate Methanolysis: A mixture of 1,5-anhydro-2,3,4-tri-*O*-acetyl-5-thioxylitol **20** (0.125 g, 0.453 mmol) and 1 M NaOMe in MeOH (0.6 mL, 0.6 mmol) in dry MeOH (10 mL) was stirred under N_2 overnight. The mixture was neutralized with excess Rexyn 101. The resin was removed by filtration, and the organic phase was concentrated to give 1,5-anhydro-5-thioxylitol as a solid (59.6 mg, 88%). Mp 137−140 °C. ^1H 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.

(b) Benzylation: A mixture of 1,5-anhydro-5-thioxylitol (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), H_2O (100 mL) was added, and the solution was extracted with Et_2O (3 × 150 mL). The organic solution was dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography [hexanes/EtOAc, 20:1] to give **17** as a white solid (0.928 g, 64%). Mp 46−49 °C. ^1H NMR ($CDCl_3$): δ 7.36−7.24 (15H, m, Ar), 4.83 (2H, s, C*H*$_2$Ph), 4.69 (2H, d, $J_{A,B} = 11.4$ Hz, C*H*$_2$-Ph), 4.65 (2H, d, $J_{A,B} = 11.6$ Hz, C*H*$_2$Ph), 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$_2$Ph), 73.02 (2 *C*H$_2$Ph), 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.

1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol (18). (a) Acetate Methanolysis: To a solution of 1,5-anhydro-2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucitol **21** (0.310 g, 0.89 mmol) in dry MeOH (20 mL) was added 1 M NaOMe/MeOH (4 mL, 4 equiv), and the mixture was stirred under N_2 overnight. The mixture was neutralized with excess Rexyn 101 ion-exchange resin, the resin was removed by filtration, and the organic phase was concentrated. The residue was purified by flash chromatography [$CHCl_3$/MeOH, 5:2] to give 1,5-anhydro-5-thio-D-glucitol as a white solid (0.125 g, 78%). Mp 110−115 °C; $[\alpha]_D = +27.4$ (*c* 1.2, MeOH). ^1H 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).

(b) Benzylation: To a stirred solution of 1,5-anhydro-5-thio-D-glucitol (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), and the mixture was stirred 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 × 100 mL). The organic phase was dried over Na_2SO_4 and concentrated. The product was purified by flash chromatography [hexanes/EtOAc, 20:1] to give a syrup that was recrystallized from EtOAc/hexanes to give compound **18** as a white solid (0.276 g, 58%). Mp 56−59 °C; $[\alpha]_D = +15.1$ (*c* 1.1, $CHCl_3$). The ^1H NMR spectrum was consistent with the literature data.[30]

1,5-Anhydro-2,3,4-tri-*O*-acetyl-5-selenoxylitol (24). To a stirred suspension 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). An almost colorless solution resulted. The ice bath was removed, 2,3,5-tri-*O*-acetyl-1,5-dibromo-1,5-dideoxy-xylitol **23** (4.87 g, 12.0 mmol) was added, and the mixture was stirred at rt overnight. H_2O (200 mL) was added, and the mixture was extracted with Et_2O (5 × 100 mL). The solids were removed by filtration, the solution was concentrated, and the residue was purified by flash chromatography [hexanes/EtOAc, 1:1] to give **24** 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-2,3,4-tri-*O*-benzyl-5-selenoxylitol (19). (a) Acetate Methanolysis: A mixture of 1,5-anhydro-2,3,4-tri-*O*-acetyl-5-selenoxy-

(30) Hashimoto, H.; Masashi, K.; Yuasa, H. *Carbohydr. Res.* **1996**, *282*, 207−222.

litol **24** (2.22 g, 6.87 mmol) and 1 M NaOMe in MeOH (10 mL, 10 mmol) in dry MeOH (60 mL) was stirred under an N_2 atmosphere overnight. The mixture was netralized with excess Rexyn 101, the resin was removed by filtration, and the organic phase was concentrated to give 1,5-anhydroselenoxylitol 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.

(b) Benzylation: To 1,5-anhydro-5-selenoxylitol **24** (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. The mixture was stirred under N_2 overnight. The reaction was then quenched with MeOH (5 mL), H_2O (100 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The organic solution was dried over Na_2SO_4 and concentrated. The product was purified by flash chromatography [hexanes/EtOAc, 20:1] to give the title compound **19** 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_2-Ph), 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.

1,5-Dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]xylitol (27). 1,5-Dideoxy-1,5-iminoxylitol **15** (0.161 g, 1.21 mmol) and 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic sulfate **14b** (0.360 g, 1.32 mmol) were dissolved in reagent grade MeOH (2 mL). Anhydrous K_2CO_3 (0.015 g, 0.11 mmol) was added, and the mixture was stirred in a sealed tube at 65 °C for 3.5 h, at which point TLC showed that the cyclic sulfate had been consumed. The solvent was removed, and the residue was purified by column chromatography (EtOAc/MeOH/H_2O, 8:2:1) to give the product **27** as a yellow oil (0.209 g, 43%): $[\alpha]_D$ −50 (*c* 0.48, H_2O); NMR data in Tables 1 and 3 (Supporting Information).

1,5-Dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]xylitol (9b). Aqueous 60% HOAc (25 mL) was added to compound **27** (0.209 g, 0.515 mmol), and the mixture was stirred while warming in an open flask for 20 h at 70 °C. The mixture was cooled and concentrated, and the crude product was purified by column chromatography (EtOAc/MeOH/H_2O, 6:4:1) to give compound **9b** (0.118 g, 72%) as a colorless, hard foam: $[\alpha]_D$ −9 (*c* 0.57, H_2O); NMR data in Tables 2 and 4 (Supporting Information); MALDI MS *m*/*e* 339.99 (M^+ + Na), 238.12 (M^+ + H − SO_3).

1,5-Dideoxy-1,5-[[*N*-(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]xylitol (25). 1,5-Didexy-1,5-iminoxylitol **15** (0.158 g, 1.19 mmol) and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate **14a** (0.347 g, 1.27 mmol) were dissolved in reagent grade MeOH (2 mL). Anhydrous K_2CO_3 (0.018 g, 0.15 mmol) was added, and the mixture was stirred in a sealed tube at 65 °C for 4 h. The solvent was removed, and the residue was purified by column chromatography (EtOAc/MeOH/H_2O, 8:2:1) to give the product **25** as a yellow oil (0.273 g, 56%). $[\alpha]_D$ +55 (*c* 0.65, H_2O); ^{1}H and ^{13}C NMR data were virtually identical with those of the enantiomer **27** (see Tables 1 and 3 (Supporting Information)); MALDI MS *m*/*e* 428.09 (M^+ + Na), 406.11 (M^+ + H), 326.15 (M^+ + H − SO_3).

1,5-Dideoxy-1,5-[[*N*-(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]xylitol (9a). Aqueous 60% HOAc (25 mL) was added to compound **25** (0.273 g, 0.673 mmol), and the mixture was stirred while warming in an open flask for 14 h at 75 °C. The mixture was cooled and concentrated, and the crude product was purified by column chromatography (EtOAc/MeOH/H_2O, 6:4:1) to give compound **9a** (0.156 g, 73%) as a colorless, hard foam. $[\alpha]_D$ +11 (*c* 0.56, H_2O); ^{1}H and ^{13}C NMR data were virtually identical to those of the enantiomer **9b** (see Tables 2 and 4 (Supporting Information)); MALDI MS *m*/*e* 399.99 (M^+ + Na), 318.28 (M^+ +H), 238.12 (M^+ + H − SO_3).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]-D-glucitol (29). Tri-*O*-benzyldeoxynojirimycin **16** (0.241 g, 0.460 mmol) and 2,4-*O*-benzylidene-D-erythritol-1,3-cyclic sulfate **14b** (0.143 g, 0.525 mmol) were dissolved in reagent grade acetone (2 mL). Anhydrous K_2CO_3 (0.020 g, 0.15 mmol) was added, and the mixture was stirred in a sealed tube at 70 °C for 20 h. The solvent was removed, and the residue was purified by column chromatography ($CHCl_3$/MeOH, 5:1) to give the product **29** as a colorless gum (0.240 g, 65%). $[\alpha]_D$ −5.4 (*c* 0.9, $CHCl_3$); NMR data in Tables 1 and 3 (Supporting Information).

1,5-Dideoxy-1,5-[[*N*-(2*R*,*RS*)-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]-D-glucitol (10b). Compound **29** (0.209 g, 0.263 mmol) was dissolved in 80% aqueous acetic acid (20 mL) and the solution was stirred with 10% Pd/C catalyst (0.42 g) under 1 atm of H_2 for 20 h. The catalyst was removed by filtration through a small plug of silica gel and washed with water (50 mL). The filtrate was evaporated, and the gummy residue was freed of acetic acid by dissolving in water and reconcentrating (2 × 50 mL). The crude product was purified by column chromatography (EtOAc/MeOH/H_2O, 6:3:1) to give compound **10b** (0.096 g, containing 0.56 equiv or 13 wt % of KOAc by ^{1}H NMR, 91% after correcting for acetate content). NMR data in Tables 2 and 4 (Supporting Information).

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[[*N*-(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]-D-glucitol (28). Tri-*O*-benzyldeoxynojirimycin **16** (0.223 g, 0.426 mmol) and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate **14a** (0.123 g, 0.4535 mmol) were dissolved in reagent grade acetone (2 mL). Anhydrous K_2CO_3 (0.020 g, 0.15 mmol) was added, and the mixture was stirred in a sealed tube at 70 °C for 20 h. The solvent was removed, and the residue was purified by column chromatography ($CHCl_3$/MeOH, 5:1) to give the product **28** as a colorless amorphous solid (0.271 g, 80%): $[\alpha]_D$ +36 (*c* 0.8, $CHCl_3$); NMR data in Tables 1 and 3 (Supporting Information).

1,5-Dideoxy-1,5-[[*N*-(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium]-D-glucitol (10a). Compound **28** (0.205 g, 0.263 mmol) was dissolved in 80% aqueous acetic acid (20 mL), and the solution was stirred with 10% Pd/C catalyst (0.41 g) under 1 atm of H_2 for 20 h. The catalyst was removed by filtration through a small plug of silica gel and washed with water (50 mL). The filtrate was evaporated, and the gummy residue was freed of acetic acid by dissolving in water and reconcentrating (2 × 50 mL). The crude product was purified by column chromatography (EtOAc/MeOH/H_2O, 6:3:1) to give compound **10a** (0.094 g, containing 0.77 equiv or 18 wt % of KOAc by ^{1}H NMR, 89% after correcting for acetate content). See Tables 2 and 4 for ^{1}H and ^{13}C NMR data (Supporting Information).

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]xylitol Inner Salt (31b) and 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]xylitol Inner Salt (32b). 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 **14b** (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 were added. The solvents were removed, and the residue was chromatographed [$CHCl_3$/MeOH, 10:1] to give **31b** and **32b** in a 2:1 ratio (0.975 g, 87%).

Major isomer **31b**: Mp 186−189 °C; $[\alpha]_D$ +2.1 (*c* 1.2, CH_2Cl_2); NMR data in Tables 1 and 3 (Supporting Information). 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 **32b**: mp 169−172 °C; $[\alpha]_D$ −49.1 (*c* 0.8, CH_2Cl_2);

NMR data in Tables 1 and 3 (Supporting Information); 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-[[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]xylitol Inner Salt (*R*-11b). To compound **31b** (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 H_2 (110 psi) 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 *R*-**11b** was obtained as a syrup (0.13 g, 81%); $[\alpha]_D$ −21.8 (*c* 1.1, H_2O); NMR data in Tables 2 and 4 (Supporting Information). 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-[[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]xylitol Inner Salt (*S*-11b). Compound **32b** (0.249 g, 0.36 mmol) was deprotected by hydrogenolysis using the procedure described above for *R*-**11b** to give the title compound as a syrup (0.13 g, 95%); $[\alpha]_D$ −16.2 (*c* 0.9, H_2O); NMR data in Tables 2 and 4 (Supporting Information). 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-[[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]xylitol Inner Salt (31a) and 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]xylitol Inner Salt (32a). 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 **14a** (0.265 g, 0.97 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-thioxylitol **17** (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 **31a** and **32a** in a 5:2 ratio as a white solid (0.465 g, 86%). Pure samples were obtained by rechromatography.

Major isomer **31a**: Mp 175−180 °C; $[\alpha]_D$ −3.7 (*c* 0.9, CH_2Cl_2); ^1H and ^{13}C NMR data were virtually identical to those of the enantiomer **31b**. 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 **32a**: Mp 163−170 °C; $[\alpha]_D$ +41.8 (*c* 1.1, CH_2Cl_2); ^1H and ^{13}C NMR data were virtually identical to those of the enantiomer **32b**. 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-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]xylitol Inner Salt (*R*-11a). To compound **31a** (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 of H_2 for 96 h. The mixture was filtered through Celite with MeOH, and the solvent was removed. The residue was then redissolved in 80% AcOH (10 mL). To the solution was added $Pd(OH)_2$ (0.2 g) and the solution was stirred under 120 psi of H_2 for 48 h. The mixture was filtered through Celite with MeOH, the solvent was 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). ^1H and ^{13}C NMR data were virtually identical to those of the enantiomer *R*-**11b** (see Tables 1 and 3 (Supporting Information)). HRMS Calcd for $C_9H_{18}O_9S_2Na$ (M + Na): 357.0290. Found: 357.0284.

1,5-Dideoxy-1,5-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]xylitol Inner Salt (*S*-11a). Compound **32a** (0.240 g, 0.35 mmol) was deprotected by hydrogenolysis using the procedure described above for *S*-**11b** to give the title compound as a syrup (0.08 g, 67%); $[\alpha]_D$ +19.5 (*c* 0.7, H_2O). ^1H and ^{13}C NMR data were virtually identical to those of the enantiomer *S*-**11b** (see Tables 2 and 4 (Supporting Information)). HRMS Calcd for $C_9H_{19}O_9S_2$ (M + H): 335.0470. Found: 335.0477.

2,3,4,6-Tetra-*O*-benzyl-1,5-dideoxy-1,5-[[(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*/*R*)-episulfoniumylidene]-D-glucitol Inner Salts (33b 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 **14b** (0.115 g, 0.42 mmol), 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **18** (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 **33b** and **34b** in a 2:1 ratio as a white solid (0.182 g, 70%); $[\alpha]_D$ = +2.1 (*c* 1.3, CH_2Cl_2). Major isomer **33b**: See Tables 1 and 2 (Supporting Information) for ^1H and ^{13}C NMR data. 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-[[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]-D-glucitol Inner Salt (12b). To a mixture of compounds **33b** 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 of 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 **12b** was obtained as a syrup (0.06 g, 81%); $[\alpha]_D$ = −20.4 (*c* 0.8, H_2O). See Tables 2 and 4 (Supporting Information) for ^1H and ^{13}C NMR data. 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-[[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*/*S*)-episulfoniumylidene]-D-glucitol Inner Salts (33a and 34a). 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 **14a** (0.148 g, 0.54 mmol), 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-5-thio-D-glucitol **18** (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 **33a** and **34a** as a white solid (0.25 g, 68%); $[\alpha]_D$ = +48.8 (*c* 1.6, CH_2Cl_2). Major isomer **33a**: See Tables 1 and 2 (Supporting Information) for ^1H and ^{13}C NMR data. 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-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]-D-glucitol Inner Salt (12a). To a mixture of compounds **33a** and **34a** (0.180 g, 0.22 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.20 g), and the mixture was stirred under 120 psi of 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 **12a** was obtained as a syrup (0.05 g, 67%); $[\alpha]_D$ = +10.3 (*c* 0.6, H_2O). See Tables 2 and 4 (Supporting Information) for ^1H and ^{13}C NMR data. HRMS Calcd for $C_{10}H_{21}O_{10}S_2$ (M + H): 365.0576. Found: 365.0577.

2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[[(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(S/*R*)-episelenoniumylidene]xylitol Inner Salt (35b and 36b). 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 **14b** (0.272 g, 1.00 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **19** (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 **35b** and **36b** in a 1:4 ratio (0.20 g, 96%). $[\alpha]_D$ −45.7 (*c* 1.1, CH_2Cl_2). For the major isomer 3**6b**: See Tables 1 and 2 (Supporting Information) for ^1H and ^{13}C NMR data. 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-[[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episelenoniumylidene]xylitol Inner Salt (13b). To the mixture of compounds **35b** and **36b** (0.295 g, 0.40 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.29 g), and the mixture was stirred under 120 psi of H_2 for 5 days. TLC revealed one major product and two minor products. The mixture was filtered through Celite and concentrated, and the residue was purified by column chromatography [EtOAc/

MeOH/H_2O, 7:3:1] to give the major product, compound **13b** as a syrup (0.06 g, 39%); $[\alpha]_D$ −16.6 (*c* 0.9, H_2O). See Tables 2 and 4 (Supporting Information) for ^1H and ^{13}C NMR data. 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-[[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*/*R*)-episelenoniumylidene]xylitol Inner Salts (35a and 36a). 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 **14a** (0.226 g, 0.83 mmol), 1,5-anhydro-2,3,4-tri-*O*-benzyl-5-selenoxylitol **19** (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 1:3 mixture of **35a** and **36a** as a white solid (0.42 g, 85%). $[\alpha]_D$ −44.0 (*c* 0.9, CH_2Cl_2). For the major isomer **36a**, the ^1H and ^{13}C NMR data were virtually identical to those of the enantiomeric compound **36b** (see Tables 1 and 2 (Supporting Information)) except for small chemical shift differences due to concentation effects. 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-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episelenoniumylidene]xylitol Inner Salt (13a). To a mixture of compounds **35a** and **36a** (0.406 g, 0.55 mmol) dissolved in 80% AcOH (10 mL) was added $Pd(OH)_2$ (0.50 g), and the mixture was stirred under 120 psi of 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 **13a** was obtained as a syrup (0.05 g, 25%); $[\alpha]_D$ +14.1 (*c* 0.4, H_2O). For compound **13a**, the ^1H and ^{13}C NMR data were virtually identical to the enantiomeric compound **13b** (see Tables 1 and 2 (Supporting Information)) except for small chemical shift differences due to concentration effects. 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.

Enzyme Inhibition Assays. Glucoamylase G2 from *Aspergillus niger* was purified from a commercial enzyme (Novo Nordisk, Bagsvaerd, Denmark) as described.[31,32] The initial rates of glucoamylase G2 catalyzed hydrolysis were tested with 1.2 mM maltose as substrate, in 0.1 M sodium acetate, pH 4.5, at 45 °C. The enzyme concentration was 8×10^{-7} M, and seven inhibitor concentrations in the range 0.2−4.2 mM were tested. The glucose release was analyzed in aliquots removed at appropriate time intervals, using a glucose oxidase assay adapted to microtiter plate reading,[33] and with a total reaction volume for the enzyme reactions of 150 or 300 μL. The K_i values were calculated assuming competitive inhibition, from $1/\nu = (1/V_{max}) + [(K_m)/(V_{max}[S]K_i)][I]$ where ν is the rate measured in the presence and absence of inhibitor, [I] and [S] are the concentrations of inhibitor and substrate, K_m = 1.6 mM, and k_{cat} = 11.3 s^{-1} (k_{cat} is the catalytic constant), using ENZFITTER.[34]

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Supporting Information Available: NMR data tables consisting of assigned chemical shifts and coupling constants for isomers of compounds **9**, **10**, **11**, **12**, and **13** and their protected precursors as well as selected NMR spectra illustrating typical ^1H and ^{13}C resonances (61 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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