Synthesis and Conformational Analysis of a Sulfonium-Ion Analogue of the Glycosidase Inhibitor Castanospermine

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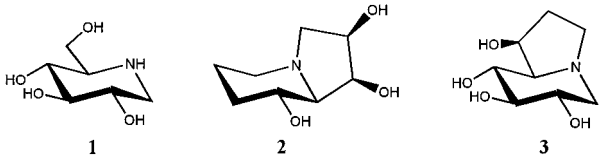
Abstract: The synthesis of a bridgehead sulfonium salt analogue (**7**) of the indolizidine alkaloid castanospermine has been achieved by a multistep procedure starting from 5-thio-D-glucopyranose pentaacetate. The compound was intended to test the theory that glycosidase inhibitory activity of the indolizidine alkaloids might be due to electrostatic stabilization of a positively charged species in the enzyme active site and that a sulfonium salt carrying a permanent positive charge might be advantageous. The structure of the bicylic sulfonium salt (**7**) [3(*R*),4(*S*),5(*R*),6(*S*)-3,4,5-trihydroxy-*cis*-1-thioniabicyclo[4.3.0]nonane perchlorate] was confirmed by X-ray crystallography. Analysis of the ^{1}H NMR spectrum of compound **7** indicated that a similar conformation was adopted in solution. This conformational preference, with hydroxyl groups in the more sterically hindered axial orientations, has been attributed to the dominance of stabilizing electrostatic interactions between the oxygen atoms and the sulfonium center.

Introduction

Carbohydrates play critical roles in many biological processes.[1] For example, the carbohydrate structures on glycoproteins mediate a variety of host-microorganism interactions and are also involved in host intercellular communication. The maturation of glycoproteins involves the trimming of nascent glycoproteins by glucosidase and mannosidase enzymes to provide the core structure that is necessary for the construction of more complex glycoforms through the action of glycosyl transferase enzymes.[2] Inhibition of these enzymes by natural or synthetic inhibitors provides a means of studying this important post-translational modification of protein structure and function, and can in some cases lead to therapeutic strategies. The best-known inhibitors of glycosidase enzymes are analogues of carbohydrates in which one or more of the oxygen atoms have been replaced by nitrogen.[3] Monocyclic amines such as 1-deoxynojirimycin (**1**) or bicyclic derivatives such as swainsonine (**2**) or castanospermine (**3**) are postulated to bind to glycosidase enzymes by mimicry of the shape and charge of the oxacarbenium ion intermediate for the hydrolysis reaction.[4] This



requires that the nitrogen atom be protonated in the enzyme active site and that the interaction with the enzyme be dominated by stabilizing electrostatic interactions with active site carboxylate residues. An alternative means of providing an inhibitor with the required charge-state would be to include in the structure an atom that carries a permanent positive charge at a suitable position. One obvious strategy would be to make this atom a positively charged sulfur, because sulfonium salts are known to be quite stable, as opposed to their highly unstable oxonium ion counterparts. We, therefore, designed the castanospermine analogue **7** in which the bridgehead nitrogen atom is replaced by a sulfonium ion. Our reasoning was further inspired by the pioneering work of the late B. Belleau who synthesized sulfonium-ion analogues of the morphinans, levorphanol and isolevorphanol, and showed that they were agonists or antagonists of morphine for the opiate receptor.[5a−d] More recently, the use of sulfonium salts as enzyme inhibitors has been elegantly demonstrated in the field of sterol biosynthesis. The cyclase enzyme that mediates the cyclization of the open-chain oxidosqualene precursor to sterols is inhibited by sulfonium salt

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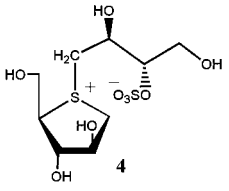
mimics, either preformed or generated in situ, of the carbocation intermediates.[5e−f]

Recently, a new class of glycosidase inhibitor with an intriguing inner-salt sulfonium-sulfate structure has been isolated from the roots and stems of the plant *Salacia reticulata.* Extracts of this plant have been traditionally used in the Ayurdevic method of Indian medicine as a treatment for diabetes. The most active ingredients of these extracts appear to be the sulfonium salts salacinol[6] (**4**) and kotalanol[7] (**5**) both of which have an anhydro alditol structure in common with well-known imino-alditol inhibitors such as 1,4-dideoxy-1,4-imino-D-arabinitol (**6**).



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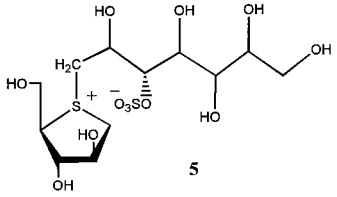

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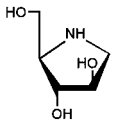

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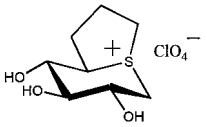
The inhibition of glycosidase enzymes by compounds **4** and **5** rivals, or in some cases exceeds, the most potent aminosugar inhibitors, such as acarbose.[8] It appears that the potential for glycosidase inhibition by sulfonium salts has not been neglected by nature, and thus, it is our contention that the synthesis of sulfur analogues of the known nitrogen-based glycosidase inhibitors may lead to glycosidase inhibitors with increased potency and utility.

We have previously synthesized disaccharides in which the ring oxygen atom of the nonreducing monosaccharide unit has been replaced by sulfur and the interglycosidic atom is either oxygen, sulfur, selenium, or nitrogen.[9] These compounds are weak-to-moderate inhibitors of glycosidase enzymes. They appear to act as non-hydrolyzable substrate mimics that are competitive inhibitors of the glycosidase enzymes. It is of interest, therefore, to question whether the presence of a sulfonium salt in 5-thioglucose derivatives would result in increased inhibitory potencies. We report herein the synthesis of the bicyclic compound **7** as a sulfonium-ion analogue of castanospermine. Compound **7** lacks the hydroxyl group at C-7



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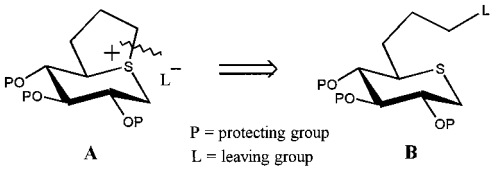
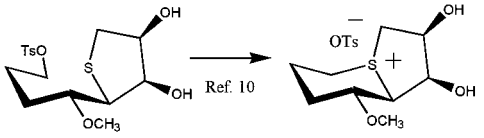
Scheme 1

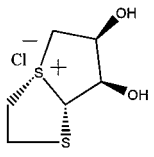


A P = protecting group L = leaving group **B**

that is present in castanospermine but should still serve as a suitable model with which to test the theory. Related work has been the subject of recent reports from other groups. Izquierdo and co-workers[10] have reported an intramolecular displacement of the tosylate group by the sulfur atom of the thiolane derivative **8** to yield the swainsonine analogue **9.** The five-membered ring sulfonium salts **10**[11] and **11**[12] have also been prepared and tested for their inhibition of glycosidase enzymes.



8 **9**



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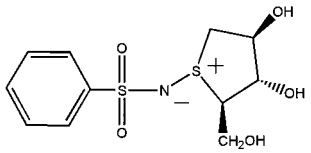

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Results and Discussion

The most direct method for the synthesis of a bicyclic sulfonium salts such as **A** is the intramolecular displacement of a suitable side-chain-leaving group by a cyclic thioether (Scheme 1). This retrosynthetic analysis led to the extended-chain, 1,5-anhydro-5-thio-D-glucitol derivative **B** as the key intermediate.

Scheme 2 outlines the synthesis of the bromo derivative **32** corresponding to **B.** Two methods were developed. Initially, 5-thioglucose pentaacetate (**12**)[13] was reacted with ethanethiol and boron trifluoride etherate to give an α/β mixture of ethylthio glycosides. Both isomers were obtained as pure crystalline compounds after separation by chromatography. The pure α-isomer, **13**α was used for the following steps because the β-isomer, **13**β, or the mixture of **13**α/**13**β proved to be less suitable for some of the subsequent transformations. First, the acetates were removed from **13**α by methanolysis to give **14**, which was reacted with benzaldehyde dimethyl acetal to yield the benzylidene derivative **15**. Benzyl ether-protecting groups were then introduced at the 2- and 3-positions to produce compound **16**. The benzylidene acetal was subjected to selective reductive cleavage with $Me_3N{:}BH_3$ and $AlCl_3$[14] to yield the 2,3,4 tri-*O*-benzyl derivative **17**. Swern oxidation[15] of the 6-OH group then yielded the aldehyde **18**. This sensitive intermediate was

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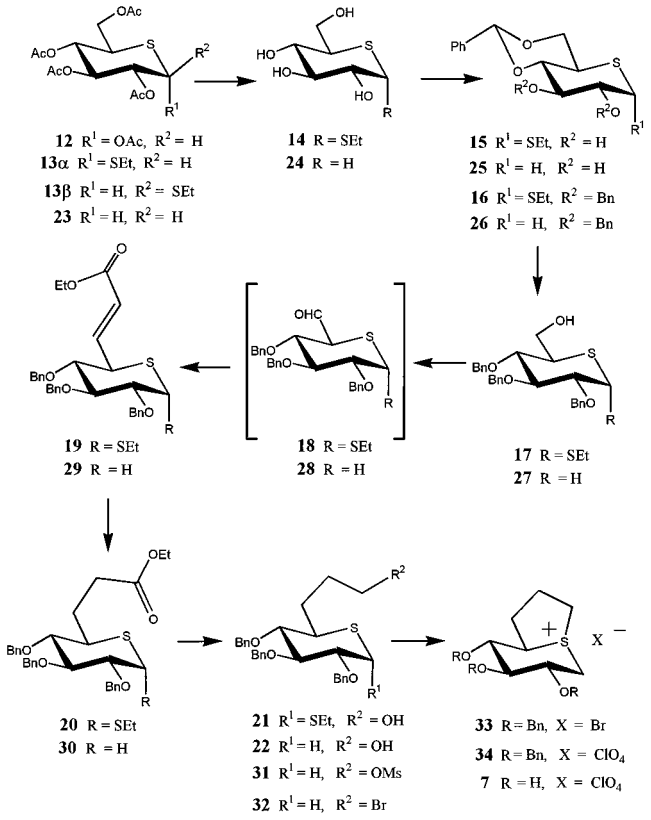
Scheme 2



not isolated but was immediately reacted in situ with carboethoxymethylene triphenylphosphorane to give the *gluco*-octenouronate derivative **19** by Wittig chain extension.[16]

The α,*β*-unsaturated ester was reduced in two steps: first, with $NaBH_4/CoCl_2$[17] to give the saturated ester **20** and then, with $LiAlH_4$ to give the primary alcohol **21**. At this stage, the thioglycoside was removed by radical reduction using *n*-Bu_3SnH/AIBN[18] to yield the 1-deoxy derivative **22**. Alternatively, the same series of reactions was applied to the known tetraacetate **23**[18] of 1,5-anhydro-5-thio-D-glucitol to yield compound **22** in seven steps (**23**→**24**→**25**→**26**→**27**→**28**→**29**→**30**→**22**), with similar overall yield. The second route avoided the separation of α- and *β*-isomers of **13** and was judged to be more convenient for the large-scale synthesis. The alcohol **22** was mesylated to give the sulfonate ester **31,** which was displaced by a bromide ion to yield the key intermediate **32**. Compound **32** (or for that matter, compound **31**) might be expected to undergo spontaneous cyclization to yield the desired bicyclic sulfonium salt, but both compounds were unexpectedly stable under ambient conditions. Nevertheless, after storage as a neat amorphous solid for several months at room temperature, the bromide **32** yielded a small amount of a more polar compound, as indicated by TLC analysis. This product was isolated by column chromatography and was shown to be the bicyclic sulfonium salt **33**, but this compound quickly equilibrated in $CDCl_3$ solution over 1 day to give a mixture of **33** and the open-chain sulfide **32** (ratio **32**:**33** > 10:1 by NMR). Evidently, the bromide counterion in the sulfonium salt **33** opens the five-membered ring by nucleophilic attack at C-9 to regenerate **32**. A nonnucleophilic counterion was, therefore, proposed as a prerequisite for sulfonium-ion stability in this case. Treatment of the bromide **32** with $AgClO_4$ gave the sulfonium salt **34** as a stable amorphous gum. No decomposition of compound **34** was noted even after long-term storage at ambient temperature. The benzyl groups were removed uneventfully by catalytic hydrogenolysis of **34** using H_2/Pd/C. The presence of the sulfur atom in **34** as a sulfonium salt evidently prevented the poisoning of the catalyst, which would be expected for a sulfide. The target sulfonium salt **7** was isolated in a near quantitative yield as an amorphous solid, and a crystalline sample was obtained by slow evaporation of a MeOH/EtOAc solution.

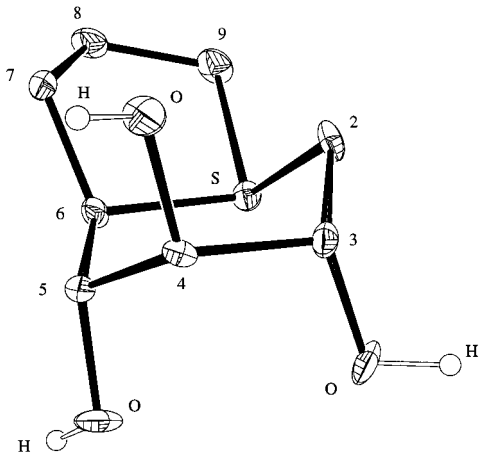


Figure 1. Crystal and molecular structure of the sulfonium cation of compound **7** (graphical output from NRCVAX Crystal Structure System: Gabe, E. J.; LePage, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384).

Analysis of compounds **34** and **7** by ^1H and ^{13}C NMR spectroscopy initially provided some doubt as to the true identity of these compounds. Both bicyclic derivatives were initially expected to favor the $^5C_2$ conformation for the six-membered ring, thus placing all three of the oxygen substituents, as well as C-7 (heterocyclic numbering), of the fused five-membered ring in the less sterically hindered, equatorial positions. However, the vicinal ^1H NMR coupling constants for compounds **34** and **7** could not be reconciled with this assumption. Both of the compounds showed $J_{3,4}$, $J_{4,5}$, and $J_{5,6}$ values of 3−4 Hz, which are much smaller than the 8−10 Hz that one would predict for the axial-axial, vicinal coupling constants in 1,5-anhydro-D-glucitol derivatives. In addition, although formation of the sulfonium salt **34** had resulted in the expected downfield shifts in the ^{13}C spectrum for the carbons α to the sufonium center[19] (i.e., C-2 and C-6 in **34**), the remaining six-membered-ring carbon resonances were observed to shift upfield by approximately 10 ppm. These trends were maintained after deprotection to yield **7,** thus indicating that the anomalous shifts for **34** could not be attributed to the shielding effects of the bulky benzyl-protecting groups. The 10-ppm upfield shifts in the resonances for the carbons that are *β* and *γ* to the sulfur atom in **34** and **7** as compared to the corresponding resonances for **32** are much larger than would be expected[19] for conversion of a sulfide to a sulfonium salt.

Furthermore, the observed ^1H and ^{13}C NMR chemical shift differences between the sulfonium salt **7** and the sulfide **32** were quite different from the literature values[10] for the related sulfonium salt **9** and its sulfide precursor **8**. Proof of the structure of compound **7** was, therefore, obtained by X-ray crystallography. This structure (Figure 1) indicated that compound **7** was, indeed, the desired sulfonium salt derivative but that the

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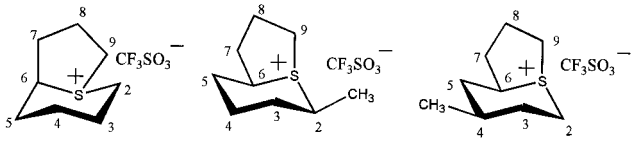
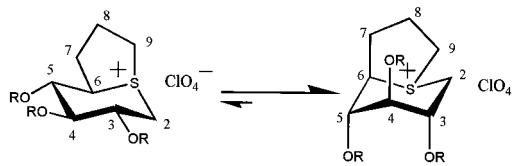
six-membered ring adopted a $^2C_5$ conformation, with all three hydroxyl groups and the C-7 substituent in axial orientations. If this conformation is also present in solution, then the unexpectedly small ^{1}H NMR coupling constants in compounds **34** and **7** are but typical values for coupling between equatorial-equatorial vicinal protons. Accordingly, the upfield ^{13}C NMR chemical shifts for C-3, C-4, and C-5 in compounds **34** and **7** must be due to the effects of steric compression on carbons bearing 1,3 diaxial substituents. The unexpected conformations for **34** and **7**, thus, explained the NMR data, and the X-ray structure ensured that no configurational ambiguity remained. We were, therefore, forced to conclude that the NMR data presented by Izquierdo et al.[10] for compound **9** are in error and that the data reported may actually be those of the tosylate precursor, sulfide **8**. The equilibration of sulfonium salts with their sulfide precursors, as we have observed for compound **33**, may have caused the confusion in this case.

The conformational preference of the sulfonium salt **7** is of some interest because the question of why such a seemingly high-energy conformation would predominate both in solution and in the solid state is less clear. A literature report[20] concerning the conformational preferences of the parent bicyclo [4.3.0] sulfonium salt **35** and some of its methyl-substituted derivatives, **36** and **37**, provides results that are pertinent to the present case. The unsubstituted sulfonium salt **35** was found to be exclusively cis-fused, with a preferred conformation in which the six-membered ring is in a normal chair conformation and C-7 of the five-membered ring occupies the axial position with respect to the six-membered ring. This conformation matches the



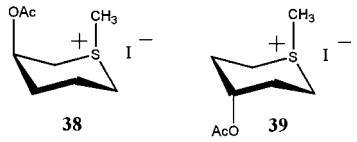
35 conformation **C** **36** conformation **D** **37** conformation **D**

preferred conformations determined for compounds **34** and **7** in the present work. The reasons advanced by Cerè et al.[20] for the overwhelming preference for conformation C, with an axial C-7, over the alternative conformation D, with an equatorial C-7, are speculative. In fact, conformation D does not seem to display any steric interactions that are significantly different from those in conformation C. Indeed, it was found that placing one or more methyl groups at the C-2 or C-4 positions cis to the fused five-membered ring resulted in a change in the preferred conformation of **36** or **37** from a C-type to a D-type. In the D-type conformations, both the C-7 and the methyl group at either C-2 or C-4 assume positions that are equatorial relative to the six-membered ring.



conformation **D** **34** R = Bn **7** R = H conformation **C**

The C-type conformation of compound **7** exhibits an unfavorable 1,3 diaxial OH−OH interaction and a 1,3 diaxial CH_2−OH interaction that would be relieved by assuming a D-type conformation. The driving force that favors conformation C must, therefore, be substantial. We attribute the stabilization of compounds **34** and **7** in conformations with the polar substituents in axial positions to the stabilizing electrostatic interactions of the oxygen atoms with the positive sulfonium ion center. In the C-type conformations for compounds **34** and **7**, the axial substituents at the 3- and 6-positions provide two gauche electrostatic interactions of the polar groups with the sulfonium center. The axial oxygen substituent at C-4 can also provide stabilizing electrostatic interactions. In the alternative D-type conformation, the electrostatic attraction would be much less important because the polar groups would then be anti to the sulfonium center. For the C-type conformation, the stabilizing gauche electrostatic interactions must be of sufficient magnitude to offset the nonbonded interactions. This explanation could account for the observed diaxial conformations in the solid state of S-methyl thianium ions **38**[21] and **39**[22] with polar acetoxy substituents at the 3- or 4-position, respectively. It is noteworthy



38 **39**

that Eliel and co-workers[23] have found that, although the $\Delta G°$ value for the equilibrium of 3-methylthiotetrahydropyran (**40**) is −1.21 kcal mol^{-1} in CH_2Cl_2 (in favor of the equatorial isomer), the corresponding $\Delta G°$ value for the methylated analogue (**41**) is +0.55 kcal mol^{-1}. The stabilizing gauche

40 X = SMe

41 X = S^+Me_2

O−C−C−S^+ interaction in **41** can be estimated by evaluating the nonbonded interactions in the axial conformer. The latter can be estimated, in turn, from the *A* value of Me_2S^+ (−1.09 kcal mol^{-1})[23] and the ratio of the conformational free energies for the axial−equatorial equilibria in 3-Me-tetrahydropyran (1.43 kcal mol^{-1})[24] and methylcyclohexane (1.80 kcal mol^{-1}).[25] This procedure yields a value for the O−C−C−S^+ interaction in **41** of 1.42 kcal mol^{-1}. We conclude, therefore, that conformation C of **7** or **34** is favored by O_3−C−C−S^+ and O_5−C−C−S^+ stabilizing interactions, worth ≈2.84 kcal mol^{-1}, with an additional contribution from the O_4−C−C−C−S^+ electrostatic interaction.

It is also of relevance that S-adenosyl methionine (SAM) **42** has been found to prefer overwhelmingly a conformation in which the sulfonium center is gauche to the ring oxygen of the ribofuranose moiety.[26] This is not the case for the related neutral species, S-adenosyl homocysteine **43** (SAH). The authors of this study have speculated that this preferred conformation for SAM places the S-methyl group in an exposed position that may have some significance in enzyme-catalyzed methyl-

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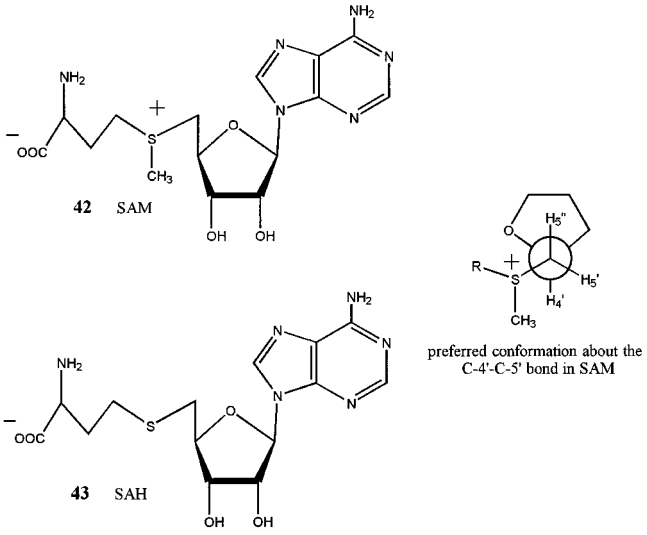

transfer reactions involving SAM. We would add that this conformation is likely to be preferred because of electrostatic attraction between the sulfonium salt and the ring oxygen. Such interactions may have more biological importance than has previously been recognized.

Conclusions

The preparation of compound **7**, a bicyclic sulfonium analogue of the glycosidase inhibitor castanospermine, has been achieved. The ring opening reaction of the sulfonium salt **33** described above raises the possibility that compound **7** might function as an irreversible inhibitor by covalent modification of active-site nucleophilic residues. The conformation of compound **7**, both in the solid state and in solution, reflects the dominance of electrostatic effects over steric effects. The activity of this compound as a glycosidase inhibitor will be the subject of future investigations. The relevance of the preferred conformation of compound **7** to both the conformations and the mechanism-of-action of related amino-sugar glucosidase inhibitors such as castanospermine is also of interest and will be the subject of further investigations in this laboratory.

Experimental Section

Chromatographic and spectroscopic techniques have been described previously.[9] Optical rotations were measured at the specified temperature using a Rudolph Research Autopol II polarimeter. ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.6 MHz, respectively. All assignments were confirmed with the aid of two-dimensional ^{1}H,^{1}H (COSYDFTP) or ^{1}H,^{13}C (INVBTP) experiments using standard Bruker pulse programs. Crystallographic data for compound **7** $C_8H_{15}O_7SCl$: Colorless plates, fw = 290.72, monoclinic, $P2_1$, $Z = 6$, $a = 11.7546(6)$, $b = 8.5384(5)$, $c = 17.847(1)$ Å, $\beta = 105.94(1)°$, $T = -100$ °C, $R = 0.038$ (calculated on F, $I > 3.00\sigma(I)$), GOF = 1.28. The data were collected on a Rigaku/ADSC CCD area detector in two sets of scans ($\varphi = 0.0-190.0°$, $\chi = -90°$; and $\omega = -18.0-23.0$, $\chi = -90°$), using 0.50° oscillations with 58.0-s exposures. The crystal-to-detector distance was 40.51 mm with a detector swing angle of −5.54°. The structure was solved by direct methods[27] and expanded using Fourier techniques.[28] The structure was found to contain three salt moieties in the asymmetric unit. All non-hydrogen atoms were refined anisotropically, and all hydroxyl hydrogens were refined isotropically. All other hydrogens were included in calculated positions. The absolute configuration was assigned on the basis of the lowest residuals from a parallel refinement of both enantiomers. All calculations were performed using the teXsan[29] crystallographic software package of Molecular Structure Corp.

Ethyl 2,3,4,6-Tetra-*O*-acetyl-1,5-dithio-α- and *β*-D-glucopyranoside (13α and 13*β*). Boron trifluoride diethyl etherate (28 mL, 0.10 mol) was added dropwise to a stirred solution of 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranoside[13] (11.46 g, 28.20 mmol) and ethanethiol (6.0 mL, 81 mmol) in CH_2Cl_2 (70 mL) under N_2 at 0 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by slowly pouring the mixture into an excess of saturated aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted using CH_2Cl_2 (2 × 150 mL). The combined extracts were dried, filtered, and concentrated. The mixture was separated by column chromatography (hexanes:EtOAc, 2:1); each isomer was crystallized from Et_2O:hexanes to yield **13**α (5.15 g, 45%) and **13***β* (3.25 g, 28%). **13**α: mp 116 °C; $[\alpha]^{19}_D$ +275 (*c* 1.05, $CHCl_3$); R_f 0.36 (hexanes:EtOAc, 2:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.37 (dd, 1H, $J_{2,3} = 10.0$, $J_{3,4} = 9.5$ Hz, H-3), 5.25 (dd, 1H, $J_{4,5} = 10.5$ Hz, H-4), 5.23 (dd, 1H, $J_{1,2} = 4.5$ Hz, H-2), 4.50 (d, 1H, H-1), 4.41 (dd, 1H, $J_{6a,6b} = 12.0$, $J_{5,6a} = 5.0$ Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b} = 3.5$ Hz, H-6b), 3.69 (ddd, 1H, H-5), 2.72−2.59 (m, 2H, SC*H*$_2$-CH_3), 2.08, 2.07, 2.02, 2.00 (4s, each 3H, 4 × COC*H*$_3$), 1.24 (t, 3H, $J = 7.5$ Hz, SCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.49, 169.87, 169.51(2C) (4 × *C*OCH$_3$), 74.69 (C-2), 72.40 (C-4), 71.37 (C-3), 61.25 (C-6), 49.13 (C-1), 39.46 (C-5), 25.81 (S*C*H$_2$CH$_3$), 20.73, 20.59, 20.51 (2C) (4 × CO*C*H$_3$), 14.02 (SCH_2CH_3). Anal. Calcd for $C_{16}H_{24}O_8S_2$: C, 47.04; H, 5.92. Found: C, 47.20; H, 5.96. **13***β*: mp 102 °C; $[\alpha]^{19}_D$ −2.0 (*c* 1.02, $CHCl_3$); R_f 0.29 (hexanes:EtOAc, 2:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 5.25 (dd, 1H, $J_{4,5} = 10.5$, $J_{3,4} = 9.5$ Hz, H-4), 5.16 (dd, 1H, $J_{1,2} = 10.5$, $J_{2,3} = 9.5$ Hz, H-2), 5.03 (dd, 1H, H-3), 4.23 (dd, 1H, $J_{6a,6b} = 12.0$, $J_{5,6a} = 6.0$ Hz, H-6a), 4.10 (dd, 1H, $J_{5,6b} = 3.5$ Hz, H-6b), 3.81 (d, 1H, H-1), 3.26 (ddd, 1H, H-5), 2.78−2.62 (m, 2H, SC*H*$_2$-CH_3), 2.06, 2.05, 2.00, 1.98 (4s, each 3H, 4 × COC*H*$_3$), 1.24 (t, 3H, $J = 7.5$ Hz, SCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.45, 169.66, 169.36, 169.31 (4 × *C*OCH$_3$), 74.62 (C-3), 73.22 (C-2), 71.99 (C-4), 61.37 (C-6), 47.82 (C-1), 44.50 (C-5), 24.93 (S*C*H$_2$CH$_3$), 20.58, 20.52 (2C), 20.47 (4 × CO*C*H$_3$), 14.52 (SCH_2CH_3). Anal. Calcd for $C_{16}H_{24}O_8S_2$: C, 47.04; H, 5.92. Found: C, 47.33; H, 5.83.

Ethyl 1,5-dithio-α-D-glucopyranoside (14). Compound **13**α (4.75 g, 11.6 mmol) was dissolved in a NaOMe/MeOH solution (0.05 M, 50 mL). The mixture was stirred for 0.5 h at room temperature and then neutralized by stirring with Rexyn 101 H^+ ion-exchange resin. The resin was removed by filtration, and the filtrate was evaporated to dryness. The crude product was obtained in quantitative yield and was used directly in the next step. An analytically pure sample was obtained by crystallization from EtOH:Et_2O to yield compound **14** as a colorless crystalline solid: mp 131−132 °C; $[\alpha]^{19}_D$ +398 (*c* 0.85, EtOH); R_f 0.68 (EtOAc:MeOH:H_2O, 7:2:1); ^{1}H NMR (400.13 MHz, D_2O) δ 4.26 (d, 1H, $J_{1,2} = 4.5$ Hz, H-1), 3.99 (dd, 1H, $J_{2,3} = 9.5$ Hz, H-2), 3.89 (dd, 1H, $J_{6a,6b} = 12.0$, $J_{5,6a} = 5.0$ Hz, H-6a), 3.85 (dd, 1H, $J_{5,6b} = 4.0$ Hz, H-6b), 3.54 (dd, 1H, $J_{4,5} = 10.0$, $J_{3,4} = 9.5$ Hz, H-4), 3.45 (dd, 1H, H-3), 3.23 (ddd, 1H, H-5), 2.78−2.62 (m, 2H, SC*H*$_2$CH$_3$), 1.22 (t, 3H, $J = 7.5$ Hz, SCH_2CH_3); ^{13}C NMR (100.6 MHz, D_2O) δ 77.54 (C-3), 77.37 (C-2), 76.39 (C-4), 62.74 (C-6), 54.67 (C-1), 46.91 (C-5), 28.59 (S*C*H$_2$CH$_3$), 16.26 (SCH_2CH_3). Anal. Calcd for $C_8H_{16}O_4S_2$: C, 39.98; H, 6.71. Found: C, 40.13; H, 6.86.

Ethyl 4,6-*O*-Benzylidene-1,5-dithio-α-D-glucopyranoside (15). To a solution of compound **14** (2.79 g, 11.61 mmol) and *p*-toluenesulfonic acid (300 mg, 1.58 mmol) in acetonitrile (50 mL) was added benzaldehyde dimethyl acetal (5.3 mL, 35.3 mmol) and the resulting mixture was stirred for 20 h at room temperature. Saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was concentrated to a small volume. The aqueous residue was partitioned between water (50 mL) and CH_2Cl_2 (250 mL). The aqueous phase was further extracted using CH_2Cl_2 (50 mL) and the combined extracts were dried, filtered,

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and concentrated. The residue was purified by column chromatography (hexanes:EtOAc, 1:1), followed by crystallization from EtOAc:hexanes to give **15** (3.26 g, 86%): mp 172−173 °C; $[\alpha]^{19}_{D}$ +357 (*c* 1.01, $CHCl_3$); R_f 0.33 (hexanes:EtOAc, 1:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.53−7.37 (m, 5H, Ph), 5.60 (s, 1H, PhC*H*), 4.25 (dd, 1H, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 5.0 Hz, H-6a), 4.19 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 4.08 (dd, 1H, $J_{2,3}$ = 9.0 Hz, H-2), 3.79 (dd, 1H, $J_{5,6b}$ = 11.0 Hz, H-6b), 3.77 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.73 (dd, 1H, H-3), 3.57 (ddd, 1H, $J_{4,5}$ = 9.0 Hz, H-5), 3.05 and 2.98 (2 brs, each 1H, OH-2 and OH-3), 2.74 (q, 2H, *J* = 7.5 Hz, SC*H*$_2$CH$_3$), 1.31 (t, 3H, SCH$_2$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.37, 129.32, 128.37, 126.33 (Ph), 102.05 (Ph*C*H), 83.94 (C-4), 75.17 (C-2), 73.14 (C-3), 68.12 (C-6), 53.41 (C-1), 36.34 (C-5), 26.81 (S*C*H$_2$CH$_3$), 14.20 (SCH$_2$*C*H$_3$). Anal. Calcd for $C_{15}H_{20}O_4S_2$: C, 54.85; H, 6.14. Found: C, 54.87; H, 6.14.

Ethyl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-1,5-dithio-α-D-glucopyranoside (16). To an ice-cold suspension of sodium hydride (1.9 g, 47.5 mmol) in DMF (70 mL) was added dropwise a solution of compound **15** (3.6 g, 11.0 mmol) in DMF (20 mL). The mixture was stirred for 10 min, after which benzyl bromide (5.5 mL, 46.2 mmol) was added. The resulting mixture was stirred for an additional 2 h and then quenched with methanol (10 mL), followed by water (10 mL). The mixture was concentrated, and the residue was partitioned between water (100 mL) and Et_2O (300 mL). The aqueous phase was extracted using additional Et_2O (50 mL) and the combined organic layers were dried, filtered, and concentrated. The residue was purified by column chromatography (toluene:EtOAc, 15:1), followed by crystallization from EtOAc:hexanes to give **16** (5.14 g, 92%): mp 108−109 °C; $[\alpha]^{19}_{D}$ +137 (*c* 1.03, CHCl3); R_f 0.55 (hexanes:EtOAc, 4:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.56−7.23 (m, 15H, Ph), 5.67 (s, 1H, PhC*H*), 4.84 and 4.81 (2d, each 1H, $J_{a,b}$ = 12.0 Hz, C*H*$_2$Ph) 4.78 and 4.73 (2d, each 1H, $J_{a,b}$ = 11.5 Hz, C*H*$_2$Ph), 4.28 (dd, 1H, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 4.5 Hz, H-6a), 4.26 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 4.04 (dd, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 3.93 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.5 Hz, H-4), 3.87 (dd, 1H, H-3), 3.81 (dd, 1H, $J_{5,6b}$ = 11.0 Hz, H-6b), 3.66 (ddd, 1H, H-5), 2.78−2.65 (m, 2H, SC*H*$_2$CH$_3$), 1.30 (t, 3H, *J* = 7.5 Hz, SCH$_2$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.8−126.05 (18C, Ph), 101.45 (Ph*C*H), 84.99 (C-4), 82.98 (C-2), 80.55 (C-3), 76.40 (*C*H$_2$Ph), 72.51 (*C*H$_2$Ph), 68.27 (C-6), 51.05 (C-1), 36.47 (C-5), 25.70 (S*C*H$_2$CH$_3$), 14.14 (SCH$_2$*C*H$_3$). Anal. Calcd for $C_{29}H_{32}O_4S_2$: C, 68.47; H, 6.34. Found: C, 68.65; H, 6.53.

Ethyl 2,3,4-Tri-*O*-benzyl-1,5-dithio-α-D-glucopyranoside (17). A solution of $AlCl_3$ (3.90 g, 29.2 mmol) in Et_2O (20 mL) was added dropwise to a stirred mixture of compound **16** (5.00 g, 9.83 mmol), Me_3N:BH_3 (1.4 g, 19.2 mmol), and molecular sieves (2 g) in CH_2Cl_2 (60 mL) and Et_2O (20 mL) at 0 °C. After 30 min at 0 °C, the mixture was filtered through a pad of Celite, the solids were washed with CH_2Cl_2, and the combined filtrate and washings were stirred with 1 M aqueous H_2SO_4 (20 mL) for 30 min. The organic layer was separated, washed with aqueous $NaHCO_3$ solution, dried, filtered, and concentrated. The residue was purified by column chromatography (hexanes: EtOAc, 4:1), followed by crystallization from Et_2O:hexanes to give **17** (4.3 g, 86%): mp 70−71 °C; $[\alpha]^{19}_{D}$ +186 (*c* 1.03, $CHCl_3$); R_f 0.24 (hexanes:EtOAc, 4:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.43−7.25 (m, 15H, Ph), 4.95 and 4.77 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.95 and 4.71 (2d, each 1H, $J_{a,b}$ = 11.0 Hz, C*H*$_2$Ph), 4.76 and 4.67 (2d, each 1H, $J_{a,b}$ = 11.5 Hz, C*H*$_2$Ph), 4.22 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 4.02 (dd, 1H, $J_{2,3}$ = 9.0 Hz, H-2), 3.92 (dd, 1H, $J_{6a,6b}$ = 11.5, $J_{5,6a}$ = 4.0 Hz, H-6a), 3.83 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.77 (dd, 1H, $J_{5,6a}$ = 4.0 Hz, H-6a), 3.73 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 3.41 (ddd, 1H, H-5), 2.75−2.62 (m, 2H, SC*H*$_2$CH$_3$), 1.67 (bs, 1H, 6-OH), 1.27 (t, 3H, *J* = 7.5 Hz, SCH$_2$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.77−127.53 (18C Ph), 83.92 (C-2), 83.80 (C-3), 82.60 (C-4), 76.18 (*C*H$_2$Ph), 75.57 (*C*H$_2$Ph), 72.24 (*C*H$_2$Ph), 62.03 (C-6), 50.11 (C-1), 43.73 (C-5), 25.52 (S*C*H$_2$CH$_3$), 14.16 (SCH$_2$*C*H$_3$). Anal. Calcd for $C_{29}H_{34}O_4S_2$: C, 68.20; H, 6.71. Found: C, 67.84; H, 6.62.

(*E*)-Ethyl (Ethyl 2,3,4-Tri-*O*-benzyl-6,7-dideoxy-1,5-dithio-α-D-*gluco*-oct-6-enopyranosid)-uronate (19). A solution of DMSO (1.36 mL, 19.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 2 min to a solution of oxalyl chloride (1.10 mL, 12.6 mmol) in CH_2Cl_2 (40 mL) at −78 °C. The resulting mixture was stirred for 5 min and then a solution of compound **17** (4.45 g, 8.71 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 2 min. The mixture was stirred for 15 min at −78 °C, then Et_3N (6 mL, 43 mmol) was added in one portion, and the mixture was warmed to room temperature. The crude solution of the aldehyde **18** was treated with (carboethoxymethylene)-triphenylphosphorane (3.60 g, 10.3 mmol) and the resulting mixture was stirred for 1 h at room temperature. The solvent was removed by rotary evaporation, and the residue was dissolved in Et_2O (75 mL). Insoluble material was removed by filtration and washed with Et_2O (50 mL). The combined washings and filtrate were concentrated, and the residue was purified by column chromatography (hexanes:EtOAc, 6:1), followed by crystallization from Et_2O:hexanes to give **19** (3.68 g, 73%): mp. 83−85 °C; $[\alpha]^{19}_{D}$ +149 (*c* 1.05, $CHCl_3$); R_f 0.32 (hexanes:EtOAc, 6:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.42−7.22 (m, 15H, Ph), 6.90 (dd, 1H, $J_{6,7}$ = 16.0, $J_{5,6}$ = 9.0 Hz, H-6), 6.08 (dd, 1H, $J_{5,7}$ = 1.0 Hz, H-7), 4.91 and 4.75 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.80 and 4.58 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.75 and 4.68 (2d, each 1H, $J_{a,b}$ = 11.5 Hz, C*H*$_2$Ph), 4.23−4.17 (m, 2H, OC*H*$_2$CH$_3$), 4.19 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 4.06 (ddd, 1H, $J_{4,5}$ = 10.0, $J_{5,6}$ = 9.0 Hz, H-5), 4.04 (dd, 1H, $J_{2,3}$ = 9.0 Hz, H-2), 3.81 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.58 (dd, 1H, H-4), 2.76−2.62 (m, 2H, SC*H*$_2$CH$_3$), 1.29 (t, 3H, J 7.0 Hz, OCH2C*H*$_3$), 1.27 (t, 3H, *J* = 7.5 Hz, SCH$_2$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.61 (*C*═O), 142.93 (C-6), 138.64−127.53 (18C, Ph), 125.22 (C-7), 85.08 (C-4), 83.69 (C-2), 83.03 (C-3), 76.32 (*C*H$_2$Ph), 75.63 (*C*H$_2$Ph), 72.24 (*C*H$_2$Ph), 60.48 (O*C*H$_2$CH$_3$), 50.61 (C-1), 42.75 (C-5), 25.51 (S*C*H$_2$CH$_3$), 14.20 and 14.12 (OCH$_2$*C*H$_3$ and SCH$_2$*C*H$_3$). Anal. Calcd for $C_{33}H_{38}O_5S_2$: C, 68.48; H, 6.62. Found: C, 68.70; H, 6.77.

Ethyl 2,3,4-Tri-*O*-benzyl-6,7-dideoxy-1,5-dithio-α-D-*gluco*-octopyranoside (21). To a solution of compound **19** (3.68 g, 6.36 mmol) and $CoCl_2$:$(H_2O)_6$ (1.80 g, 7.57 mmol) in a mixture of EtOH (90 mL) and THF (30 mL) at 0 °C was added $NaBH_4$ (0.580 g, 15.3 mmol) in portions. The mixture was stirred at room temperature for 3 h and then poured into water (100 mL). The mixture was concentrated to a small volume and extracted with Et_2O (2 × 150 mL). The combined organic layers were dried, filtered, and concentrated to give the saturated ester derivative **20**. Compound **20** was dissolved in Et_2O (20 mL), and the solution was added dropwise to a mixture of $LiAlH_4$ (0.400 g, 10.5 mmol) in Et_2O (200 mL) at 0 °C. The mixture was stirred for 30 min and then quenched by dropwise addition of MeOH (3 mL), followed by water (5 mL). The mixture was washed with aqueous 1 M HCl (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), was dried, filtered, and concentrated. The residue was purified by column chromatography (hexanes:EtOAc, 3:1), followed by crystallization from Et_2O:hexanes to give **21** (2.61 g, 76%): mp 88−90 °C; $[\alpha]^{19}_{D}$ +166 (*c* 1.05, $CHCl_3$); R_f 0.39 (hexanes:EtOAc, 2:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.42−7.24 (m, 15H, Ph), 4.94 and 4.62 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.92 and 4.66 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.75 and 4.66 (2d, each 1H, $J_{a,b}$ = 11.5 Hz, C*H*$_2$Ph), 4.18 (d, 1H, $J_{1,2}$ = 4.5 Hz, H-1), 4.03 (dd, 1H, $J_{2,3}$ = 9.0 Hz, H-2), 3.79 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 3.65−3.54 (m, 2H, H-8a, H8b), 3.44 (dd, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 3.26 (ddd, 1H, $J_{5,6a}$ = 10.0, $J_{5,6b}$ = 3.5 Hz, H-5), 2.75−2.60 (m, 2H, SC*H*$_2$CH$_3$), 2.09 (m, 1H, H-6a), 1.77−1.67 (m, 1H, H-7a), 1.63−1.53 (m, 1H, H-7b), 1.48−1.39 (m, 1H, H-6b), 1.26 (t, 3H, *J* = 7.5 Hz, SCH$_2$C*H*$_3$), 1.21 (t, 1H, $J_{8,OH}$ = 5.5 Hz, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.85−127.49 (18C, Ph), 85.71 (C-4), 84.15 (C-2), 83.83 (C-3), 76.23 (*C*H$_2$Ph), 75.77 (*C*H$_2$Ph), 72.10 (*C*H$_2$Ph), 62.55 (C-8), 49.79 (C-1), 41.36 (C-5), 30.04 (C-7), 25.64 (C-6), 25.41 (S*C*H$_2$CH$_3$), 14.25 (SCH$_2$*C*H$_3$). Anal. Calcd for $C_{31}H_{38}0_4S_2$: C, 69.11; H, 7.11. Found: C, 68.91; H, 7.13.

1,5-Anhydro-6,7-dideoxy-2,3,4-tri-*O*-benzyl-5-thio-D-*gluco*-octitol (22). (a) From compound **21**: A solution of (*n*-Bu)$_3$SnH (0.43 mL, 1.6 mmol) and AIBN (8.0 mg, 0.15 mmol) in toluene (2 mL) was added over 6 h to a refluxing solution of compound **21** (427 mg, 0.792 mmol) in toluene (10 mL). After the addition was complete, the mixture was refluxed for an additional 15 min and then concentrated to a small volume and purified by column chromatography (toluene→toluene: EtOAc, 1:1). Crystallization from Et_2O:hexanes yielded **22** (337 mg, 89%): mp 95−97 °C; $[\alpha]^{19}_{D}$ +2.8 (*c* 1.06, $CHCl_3$); R_f 0.28 (hexanes: EtOAc, 2:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.36−7.24 (m, 15H, Ph), 4.95 and 4.81 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.95 and 4.63 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.71 (s, 2H, C*H*$_2$Ph), 3.77−

3.67 (m, 1H, H-2), 3.65−3.55 (m, 2H, H-8a, H-8b), 3.46−3.47 (m, 2H, H-3, H-4), 2.78 (dd, 1H, $J_{1eq,1ax}$ 13.5, $J_{1eq,2}$ = 4.5 Hz, H-1eq), 2.73 (ddd, 1H, $J_{4,5}$ = 9.5, $J_{5,6a}$ = 3.0, $J_{5,6b}$ = 9.5 Hz, H-5), 2.52 (dd, 1H, $J_{1ax,2}$ = 11.0 Hz, H-1ax), 2.17−2.08 (m, 1H, H-6a), 1.78−1.67 (m, 1H, H-7a), 1.64−1.53 (m, 1H, H-7b), 1.44−1.34 (m, 1H, H-6b), 1.22 (bs 1H, 8-OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.86−127.51 (18C, Ph), 85.65 and 87.81 (C-3 and C-4), 82.74 (C-2), 76.19 (*C*H_2Ph), 75.97 (*C*H_2Ph), 72.82 (*C*H_2Ph), 62.67 (C-8), 46.78 (C-5), 30.71 (C-1), 30.05 (C-7), 26.80 (C-6). Anal. Calcd for $C_{29}H_{34}O_4S$: C, 72.77; H, 7.16. Found: C, 72.92; H, 7.27. (b) From compound **23**: application of the sequence. (i) Methanolysis of acetates to give **24**, (ii) 4,6-O-benzylidene formation to give **25**, (iii) benzylation to give **26**, (iv) regioselective benzylidene reductive cleavage to give **27**, (v) oxidation of the 6-OH to an aldehyde **28** and then Wittig chain extension to give **29**, (vi) $NaBH_4/CoCl_2$ reduction of the double bond to give **30**, and (vii) reduction of the ester with $LiALH_4$ to give **22** was carried out exactly as described for the thioglycoside series (**13**α→**14**→**15**→**16**→**17**→**18**→**19**→**20**→**21**). The modified sequence proceeded uneventfully to give compound **22** in an overall yield of 26%. Compound **22** prepared by this route was identical in all respects to that obtained above.

1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucitol (23). A solution of 1,2,3,4,6-penta-*O*-acetyl-5-thio-α-D-glucopyranoside[13] (3.90 g, 9.60 mmoL) in CH_2Cl_2 (40 mL) was cooled with stirring in an ice-bath while 35 wt % HBr/HOAc solution (7.0 mL, 40 mmol) was added dropwise. The cooling bath was removed and the mixture was stirred at room temperature for 4h. After dilution with CH_2Cl_2 (100 mL), the solution was washed with ice/water (2 × 30 mL), cold saturated aqueous $NaHCO_3$ (2 × 50 mL), and aqueous NaCl (50 mL). The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated give an α/β mixture of glycosyl bromides as a syrup. This was dissolved in toluene (120 mL) and a portion of the toluene (≈20 mL) was removed by distillation to ensure dryness. A solution of $(n\text{-Bu})_3SnH$ (4.3 g, 15 mmoL) and AIBN (0.51 g, 3.1 mmoL) in toluene (100 mL) was added dropwise over 4 h to the refluxing mixture through the condensor. Reflux was continued for a further 16 h. The mixture was cooled and concentrated to a syrup. Purification by column chromatography (hexanes:EtOAc, 3:2) yielded **23** as a crystalline solid (3.39 g, 97%): mp 103−105 °C, lit.[18] mp 100−102 °C.

1,5-Anhydro-8-bromo-6,7,8-trideoxy-2,3,4-tri-*O*-benzyl-5-thio-D-*gluco*-octitol (32). To an ice-cold solution of compound **22** (500 mg, 1.04 mmol) in pyridine (10 mL) was added methanesulfonyl chloride (0.12 mL, 1.6 mmol) in one portion. The mixture was stirred for 30 min at room temperature, after which small portions of ice were added and the resulting mixture was stirred for an additional 10 min. The solvent was evaporated, and the aqueous residue was partitioned between CH_2Cl_2 (200 mL) and aqueous 1 M HCl (50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL), dried, filtered, and concentrated to dryness to give the crude mesylate derivative **31**. This was dissolved in THF (15 mL) and reacted with LiBr (360 mg, 4.15 mmol) at reflux for 1 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 (200 mL) and water (50 mL). The organic phase was dried, filtered, and concentrated. The residue was purified by column chromatography (hexanes:EtOAc, 12:1) to give **32** as a white solid (546 mg, 97%): mp 63−65 °C; $[\alpha]^{24}_D$ +4.1 (*c* 1.22, $CHCl_3$); R_f 0.32 (hexanes:EtOAc, 15:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.39−7.22 (m, 15H, Ph), 4.95 and 4.79 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.93 and 4.63 (2d, each 1H, $J_{a,b}$ = 10.5 Hz, C*H*$_2$Ph), 4.69 (s, 2H, C*H*$_2$Ph), 3.74−3.67 (m, 1H, H-2), 3.43−3.32 (m, 4H, H-3, H-4, H-8a, H-8b), 2.76 (dd, 1H, $J_{1eq,1ax}$ = 13.4, $J_{1eq,2}$ = 4.3 Hz, H-1eq), 2.73−2.66 (m, 1H H-5), 2.51 (dd, 1H, $J_{1ax,2}$ = 11.0 Hz, H-1ax), 2.29−2.19 (m, 1H, H-6a), 2.08−1.97 (m, 1H, H-7a), 1.94−1.83 (m, 1H, H-6b), 1.47−1.37 (m, 1H, H-7b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.77−127.49 (18C, Ph), 87.68 and 85.40 (C-3 and C-4), 82.58 (C-2), 76.15 (*C*H_2Ph), 75.98 (*C*H_2Ph), 72.76 (*C*H_2Ph), 46.26 (C-5), 33.38 (C-8), 30.65 (C-1), 30.06 (C-7), 29.14 (C-6). Anal. Calcd for $C_{29}H_{33}O_3SBr$: C, 64.32; H, 6.14. Found: C, 64.16; H, 6.20.

3(*R*),4(*S*),5(*R*),6(*S*)-3,4,5-Tribenzyloxy-*cis*-1-thioniabicyclo[4.3.0]-nonane Perchlorate (34). A solution of compound **32** (546 mg, 1.01 mmol) in acetonitrile (5 mL) was treated with $AgClO_4$ (420 mg, 2.03 mmol) for 24 h at room temperature. The solvent was removed, and the residue was partitioned between CH_2Cl_2 (200 mL) and water (50 mL). The organic phase was dried, filtered, concentrated, and purified by column chromatography (CH_2Cl_2:MeOH 35:1) to yield compound **34** as a colorless foam (434 mg, 77%): $[\alpha]^{24}_D$ +3.3 (*c* 1.20, $CHCl_3$); R_f 0.6 (EtOAc:MeOH:H_2O, 10:2:1); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.38−7.17 (m, 15H, Ph), 4.68 and 4.56 (2d, each 1H, $J_{a,b}$ = 11.5 Hz, C*H*$_2$Ph), 4.60 and 4.54 (2d, each 1H, $J_{a,b}$ = 11.7 Hz, C*H*$_2$Ph), 4.49 and 4.44 (2d, each 1H, C*H*$_2$Ph), 4.21−4.17 (m, 1H, H-6), 4.13−3.99 (m, 1H, H-3), 3.98 (dd, 1H, $J_{4,5}$ = $J_{5,6}$ = 3.2 Hz, H-5), 3.87 (ddd, J_{9a9b} = 12.0, $J_{8b,9a}$ = 8.0, $J_{8a,9a}$ = 3.5 Hz, H-9a), 3.79 (dd, 1H, $J_{3,4}$ = 3.9 Hz, H-4), 3.78 (dd, 1H, $J_{2a,2b}$ = 13.0, $J_{2a,3}$ = 6.5 Hz, H-2a), 3.49−3.39 (m, 1H, H-9b), 3.34 (dd, 1H, $J_{2b,3}$ = 2.0 Hz, H-2b), 2.53−2.31 (m, 3H, H-7a, H-7b, H-8a), 2.22−2.09 (m, 1H, H-8b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.74−128.10 (18C, Ph), 74.38 (C-4), 73.14 (C-5), 73.00 (*C*H_2Ph), 72.44 (*C*H_2Ph), 71.62 (*C*H_2Ph), 71.36 (C-3), 56.83 (C-6), 43.26 (C-9), 34.17 (C-2), 31.02(C-7), 27.28 (C-8). Anal. Calcd for $C_{29}H_{33}ClO_7S$: C, 62.08; H, 5.93. Found: C, 61.92; H, 6.00.

3(*R*),4(*S*),5(*R*),6(*S*)-3,4,5-Trihydroxy-*cis*-1-thioniabicyclo[4.3.0]-nonane Perchlorate (7). To a solution of compound **34** in glacial acetic acid (15 mL) was added palladium hydroxide catalyst (20% Pd/C, Degussa type E101NE/W, 188 mg), and the mixture was stirred at room temperature in a bomb that was pressurized with H_2 to 52 psi. After 21 h, the catalyst was removed by filtration through Celite with the aid of EtOH (80 mL). The filtrate was concentrated on a rotary evaporator and then evaporated again with water (20 mL) to remove the remaining acetic acid. This yielded compound **7** as a pale-yellow syrup (132 mg, 94%), which was essentially pure by ^{1}H NMR analysis. An analytically pure sample was obtained by crystallization from MeOH:EtOAc as colorless leaflets: mp 79−80 °C; $[\alpha]^{24}_D$ +35 (*c* 0.56, MeOH); ^{1}H NMR (400.13 MHz, CD_3OD) δ 4.21 (ddd, 1H, $J_{2a,3}$ = $J_{2b,3}$ = $J_{3,4}$ = 3.7 Hz, H-3), 4.17 (dd, 1H, $J_{4,5}$ = $J_{5,6}$ = 4.1 Hz, H-5), 3.95 (ddd, 1H, $J_{6,7a}$ = 10.4, $J_{6,7b}$ = 5.9 Hz, H-6), 3.86 (dd, 1H, H-4), 3.73 (ddd, $J_{9a,9b}$ = 12.7, $J_{8a,9a}$ = 8.5, $J_{8b,9a}$ = 3.6 Hz, H-9a), 3.54 (d, 2H, H-2a, H-2b), 3.51−3.43 (m, 1H, H-9b), 2.80−2.68 (m, 1H, H-7a), 2.53−2.41 (m, 2H, H-7b, H-8a), 2.18−2.05 (m, 1H, H-8b); ^{13}C NMR (100.6 MHz, CD_3OD) δ 70.75 (C-4), 69.96 (C-5), 68.73 (C-3), 61.17 (C-6), 44.13 (C-9), 38.63 (C-2), 32.309 (C-7), 27.99 (C-8). Anal. Calcd for $C_8H_{15}ClO_7S$: C, 33.05; H, 5.20. Found: C, 33.25; H, 5.12.

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Supporting Information Available: Views of the three cations in the asymmetric unit, text and tables giving additional crystallographic details and tables listing atomic coordinates, anisotropic displacement parameters, distances, angles, possible hydrogen bonds, nonbonded contacts, and structure factors. This material is available free of charge via the Internet at http://pubs.acs.org.

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