A New Class of Glycosidase Inhibitor: Synthesis of Salacinol and Its Stereoisomers†

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Salacinol (**4**) is one of the active principles in the aqueous extracts of *Salacia reticulata* that are traditionally used in Sri Lanka and India for the treatment of diabetes. The syntheses of salacinol (**4**), the enantiomer of salacinol (**5**), and a diastereomer (**7**) are described. The synthetic strategy relies on the selective nucleophilic attack of 2,3,5-tri-*O*-benzyl-1,4-anhydro-4-thio-D- or L-arabinitol at C-1 of 2,4-*O*-benzylidene D- or L-erythritol-1,3-cyclic sulfate. The work serves to resolve the ambiguity about the exact structure of salacinol and establishes conclusively the structure of the natural product.

Introduction

Glycosidase enzymes with diverse functional specificity play important roles in the biochemical processing of biopolymers containing carbohydrates.[1] One important class of these enzymes is responsible for the liberation of glucose from its higher oligomers or polymers. Disruption in the function and regulation of these enzymes can lead to disease states such as diabetes. In the treatment of Type II noninsulin dependent diabetes (NIDD) management of blood glucose levels is critical. One strategy for treating NIDD is to delay digestion of ingested carbohydrates, thereby lowering postprandial blood glucose concentration. This can be achieved by administering drugs which inhibit the activity of enzymes, such as the glucosidases, which mediate the hydrolysis of complex starches to oligosaccharides in the small intestine. For example, the carbohydrate analogue acarbose, which is currently used for the oral treatment of diabetes,[2,3] reversibly inhibits the function of pancreatic α-amylase and membrane-bound intestinal α-glucoside hydrolase enzymes. In patients suffering from Type II diabetes, such enzyme inhibition results in delayed glucose absorption into the blood and a smoothing or lowering of postprandial hyperglycemia, resulting in improved glycemic control.

Inhibition of glycosidase enzymes involved in carbohydrate processing of glycoproteins has also been effective in the treatment of some nondiabetic disorders such as cancer.[4] While normal cells display characteristic oligosaccharide structures, tumor cells display very complex structures that are usually restricted to embryonic tissues.[4] It is believed that these complex structures provide signal stimuli for rapid proliferation and metastasis of tumor cells. A possible strategy for the therapeutic use of glycosidase inhibitors is to take advantage of the different rates of normal vs cancer cell growth to inhibit assembly of complex oligosaccharide structures. For example, the indolizidine alkaloid swainsonine (**1**), an inhibitor of Golgi α-mannosidase II, reportedly reduces tumor cell metastasis, enhances cellular immune responces, and slows tumor cell growth in mice.[5] Swainsonine treatment has led to significant reduction of tumor mass in human patients with advanced malignancies, and is a promising drug therapy for patients suffering from breast, liver, lung and other malignancies.[6,7] Therefore, natural or synthetic inhibitors of glycosidase enzymes have potential as new therapeutic agents. Known glycosidase inhibitors such as the indolizidine alkaloids swainsonine (**1**) and castanospermine (**2**) are known to carry a positive charge at physiological pH.[8] It is believed that the mechanism of action of such inhibitors may be at least partially explained by the establishment of stabilizing electrostatic interactions between the inhibitor and a carboxylate residue in the enzyme active site.[8] Recently, we reported the synthesis of the sulfonium salt (**3**) which might function as a mimic of castanospermine (**2**).[9] We reasoned that **3**, which bears a permanent positive charge, would provide the necessary electrostatic stabilization to bind competitively to glycosidases. The feasibility of such an approach has been recently validated by the report of the isolation of the glycosidase inhibitor salacinol (**4**) from the roots and stems of *Salacia*

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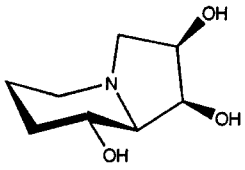
Chart 1



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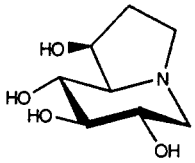

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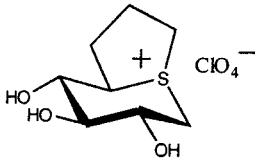

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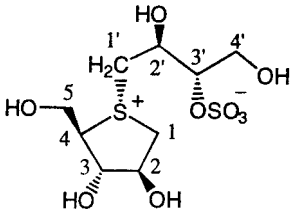
Chart 2



4

reticulata Wight, (known as "Kothalahimbutu" in Singhalese).[10] This sulfonium salt was found to be one of the active principles in the aqueous extracts of *S. reticulata* (a woody climbing plant) that are traditionally used in Sri Lanka for the treatment of diabetes. Traditionally, Ayurvedic medicine advised that a person suffering from diabetes should drink water left overnight in a mug carved from Kothalahimbutu wood. The initial structural assignment of salacinol (**4**) revealed an intriguing inner-salt structure composed of a 1,4-anhydro-4-thio-arabinitol alkylated at sulfur by a 1-deoxy-erythritol-3-sulfate moiety. The relative configuration of the chiral centers was elucidated by X-ray crystallography, and the structure was formulated as an anhydro-4-thio-L-arabinitol unit linked to a D-erythritol unit (**5**).[10] Subsequently, the same group isolated another glucosidase inhibitor from *S. reticulata* with a related sulfonium-salt structure, namely kotalanol (**6**), which showed more potent inhibitory activity against sucrase than salacinol (**4**).[11] The configurations of the stereogenic centers in the longer heptitol side chain or at the sulfur atom were not determined, but degradation led to the release of 1,4-anhydro-4-thio-D-arabinitol. This apparently led to a revision of the structure of salacinol (**4**) to reflect the probable close biosynthetic relationship of the two inhibitors, and salacinol (**4**) was then assigned to be the enantiomer of the original structure **5**. The recent report by Yuasa et al.[12] on the synthesis of salacinol (**4**) prompts us to report our own findings.[13] To unequivocally establish the absolute configuration of salacinol (**4**) and to further investigate the inhibition of glycosidase enzymes by this new class of inhibitor, we now report the synthesis of salacinol (**4**) and its enantiomeric structure **5**. In addition, the diastereomeric sulfonium-salt (**7**) was synthesized in order to assess structure−activity relationships.

Results and Discussion

Retrosynthetic analysis indicated that salacinol (**4**) or its analogues (**A**) could be obtained by alkylation of anhydro-alditol derivatives at the ring heteroatom (Scheme 1). This strategy was chosen in order to provide flexibility for the synthesis of analogues having other heteroatoms such as nitrogen or selenium in the ring, and different configurations of the sugar rings. The alkylating agent could either be an open-chain electrophile (**C**) or a cyclic sulfate derivative such as **D** or **E**, whereby selective attack of the thioether at the least hindered primary center should afford the desired sulfonium ions. We have investigated the latter approach and have found that the opening of appropriately protected cyclic sulfate derivatives by thioether nucleophiles proceeds smoothly to give the desired compounds.

The thio-arabinitols **8**[14] and **9**[15] were synthesized from D-glucose and D-xylose, respectively. The 2,4-*O*-benzylidene-L- (**10**) and D- (**13**) erythritol-1,3-cyclic sulfates were synthesized from L- and D-glucose, respectively, in a manner similar to that described for the corresponding 2,4-*O*-ethylidene derivative (Scheme 2).[16]

The target compounds were prepared by opening of the cyclic sulfates by nucleophilic attack of the sulfur atom in the five-membered rings. Initially, reactions were carried out at room temperature in methanol, but the reaction rates were too slow. Increasing the temperature resulted in competing nucleophilic attack of methanol and formation of methyl ethers. Dry acetone was found to be a more suitable solvent. The addition of K_2CO_3 was necessary to prevent decomposition due to the hydrolysis reactions of the cyclic sulfates. Yuasa et al.[12] have also noted the decomposition of the related cyclic sulfates in DMF when the temperature was increased to 60−70 °C.[12] Thus, compound **14** was synthesized by alkylation of the protected thio-arabinitol (**8**) with the cyclic sulfate (**10**) (1.2 equiv) in dry acetone containing K_2CO_3, to give the protected compound **14** in 33% yield. Compound **14** exhibited the expected downfield shifts due to sulfonium ion formation for H-1 and H-4 and for C-1 and C-4 in the NMR spectra when compared to those of the precursor sulfide **8**. Sulfonium salt formation also resulted in broadening of the ^{1}H resonances of the arabinitol ring such that $J_{1a,2}$, $J_{2,3}$, and $J_{3,4}$ were no longer resolved. Compound **15** was similarly prepared in 40% yield from the enantiomeric thioether (**9**) and the cyclic sulfate (**13**). Comparison of the ^{1}H and ^{13}C NMR spectra for com-

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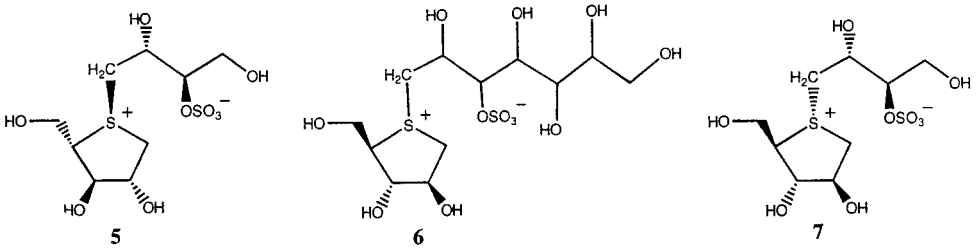
Chart 3



Scheme 1

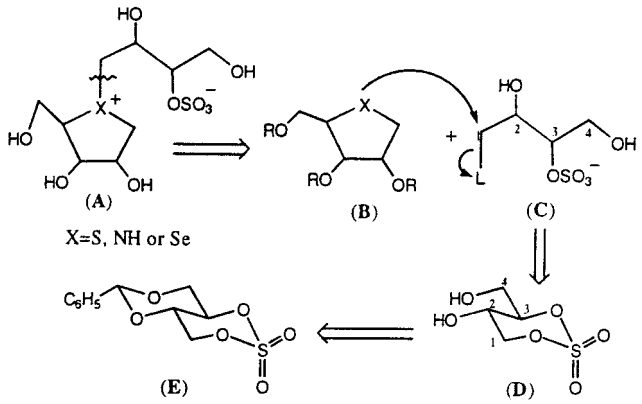
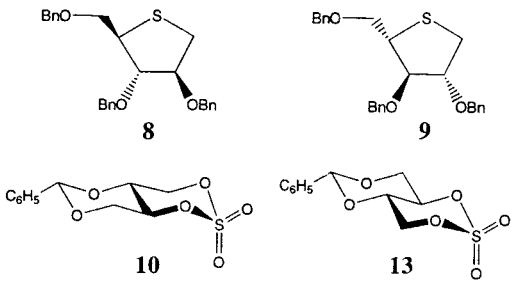


Chart 4



pounds **14** and **4** with those of compounds **15** and **5**, respectively, showed small chemical shift differences between the enantiomeric pairs (±0.1 ppm for ^{1}H NMR spectra and ± 1 ppm for ^{13}C NMR spectra), but the coupling constants were identical. We attribute the chemical shift discrepancies to concentration or temperature differences between samples. Deprotection of the coupled products **14** and **15** by hydrogenolysis over a Pd/C catalyst gave compounds **4** (67%) and **5** (80%), respectively, each exhibiting ^{1}H and ^{13}C NMR spectra that were in complete accord with those reported for salacinol (**4**) (Scheme 3).[10]

The stereochemistry at the stereogenic sulfonium center in **4** and **5** was established by means of a NOESY experiment. A correlation between H-1′ and H-4 for each isomer confirmed the trans relationship between the erythritol side chain and the C-4 substituent on the anhydroarabinitol moiety. Optical rotations for the two enantiomers indicated that the value for the dextrorotatory isomer **4** ([α]$_D$ +2.1°) most closely matched the literature value reported for the naturally occurring compound, salacinol ([α]$_D$ +4.9°).[10] Since the X-ray crystal structure of the naturally occurring salacinol, with [α]$_D$ +4.9°, had indicated a trans relative configuration between the anhydro-4-thio-arabinitol unit and the erythritol unit,[10] it is clear that the authentic structure of salacinol is represented by structure (**4**), namely an anhydro-4-thio-D-arabinitol unit linked to an L-erythritol unit, and not the enantiomeric structure (**5**). The diasteromeric compound **7** was similarly obtained by the reaction of compound **8** with the cyclic sulfate (**13**) to produce **16** in 79% yield. Deprotection, as before, gave compound **7** in 59% yield (Scheme 4), which exhibited distinctly different NMR spectra and optical rotation from salacinol (**4**). The stereochemistry at the stereogenic sulfur center in **7** was confirmed by means of a NOESY experiment, as described above. These results constitute additional evidence that salacinol (**4**) is the sulfonium salt composed of 1-deoxy-L-erythritol-3-sulfate and 1,4-anhydro-4-thio-D-arabinitol.

To reduce the number of synthetic steps, the coupling reactions were attempted with partially protected or unprotected thio-arabinitols. Thus, the partially protected compound **17** was reacted with the cyclic sulfate (**10**) in acetone containing K_2CO_3, to give compound **18** in 32% yield. Deprotection yielded salacinol (**4**) in 36% yield (Scheme 5). 1,4-Anhydro-4-thio-D-arabinitol itself was not soluble in acetone, and the reaction in methanol produced several products.

The glucosidase inhibitory properties of compounds **4**, **5**, and **7** are under investigation, as are the syntheses of other analogues of this new class of glycosidase inhibitors.

Experimental Section

General. Optical rotations were measured at 23 °C. ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.6 MHz. 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. MALDI-TOF mass spectra were obtained for samples dispersed in a 2,5-dihydroxybenzoic acid matrix using a PerSeptive Biosystems Voyager-DE instrument. Column chromatography was performed with Merck Silica gel 60 (230−400 mesh). High-resolution mass spectra were LSIMS (Fab), run on a Kratos Concept H double focusing mass spectrometer at 10000 RP.

2,4-*O*-Benzylidene-D-erythritol (11). Compound (**11**) was prepared from 4,6-*O*-benzylidene-D-glucose according to standard procedures.[17,18] Compound (**11**) has been reported by MacDonald et al.,[18] without NMR characterization which is therefore dealt with here. Mp 138−139 °C, lit.[18] mp 135−136 °C; [α]$_D$ −44° (*c* 1.0, MeOH) (lit.[18] −43° (*c* 2.0, MeOH)); ^{1}H NMR (CD$_3$OD): δ 7.53−7.28 (5H, m, Ar), 5.53 (1H, s, C*H*Ph), 4.20 (1H, m, H-4$_{eq}$), 3.92 (1H, dd, $J_{1a,1b}$ = 12.1, $J_{1a,2}$ = 1.7 Hz, H-1a), 3.74 (1H, dd, $J_{1b,2}$ =5.7 Hz, H-1b), 3.67−3.55 (3H, m, H-3, H-2, H-4$_{ax}$); ^{13}C NMR (CD$_3$OD): δ 139.52 (C$_{ipso}$), 129.77 (C$_{para}$), 128.99 (2C) and 127.49 (2C) (C$_{ortho}$ and C$_{meta}$), 102.36 (*C*HPh), 84.22 (C-3), 72.21 (C-4), 62.76 (C-1), 62.59 (C-2); MALDI-TOF MS: *m/e* 211 (M$^+$ + H), 233 (M$^+$ + Na). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.96; H, 6.55.

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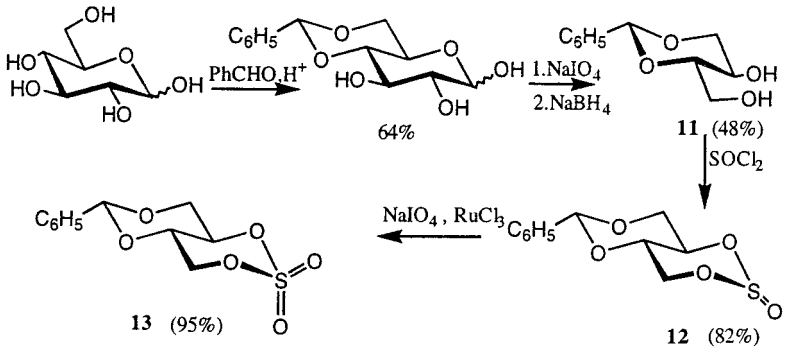
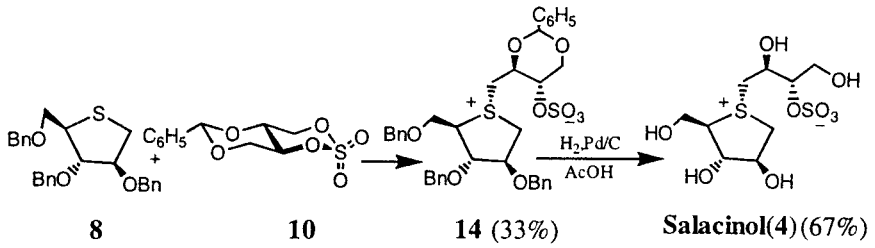
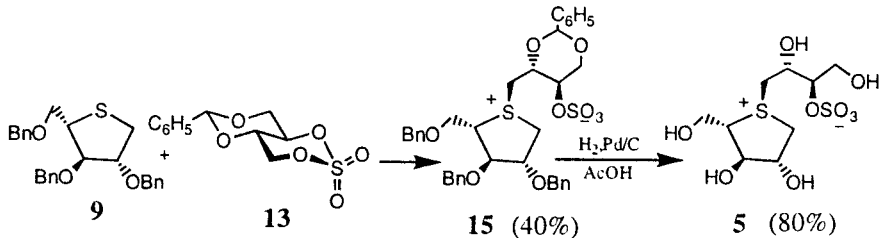
Scheme 2

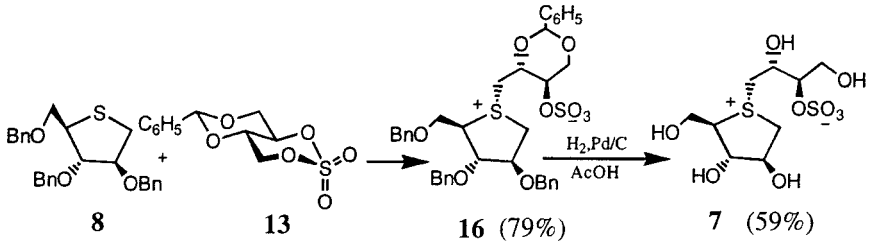


Scheme 3





Scheme 4



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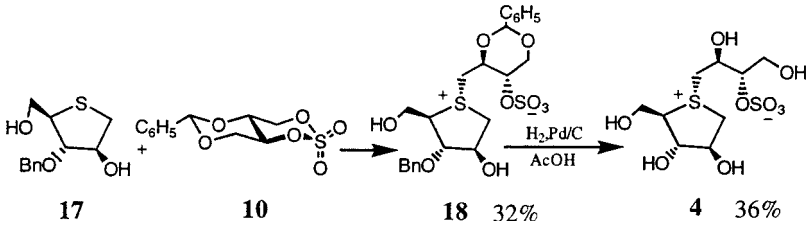

2,4-*O*-Benzylidene-D-erythritol-1,3-cyclic Sulfite (12). A solution of the diol (**11**) (4.5 g, 21 mmol) and Et_3N (11 mL, 4 equiv) in dry CH_2Cl_2 (90 mL) was added dropwise to a solution of $SOCl_2$ (2.4 mL, 1.5 equiv) in dry CH_2Cl_2 (60 mL), with stirring in an ice-bath under an N_2 atmosphere. Stirring was continued at 0 °C, until TLC (hexanes/EtOAc, 4:1) showed complete disappearance of the starting material. The mixture was diluted with CH_2Cl_2 (150 mL) and washed with H_2O (150 mL) and brine (150 mL). The organic solution was dried (Na_2SO_4) and concentrated on a rotary evaporator. The product was purified by flash chromatography [hexanes/EtOAc, 4:1 + 0.1% Et_3N] to give **12** as a 1:1 mixture of two diastereomers (4.5 g, 82%). The less polar isomer was selectively recrystallized from EtOAc/hexanes. Mp 137−139 °C; $[\alpha]_D$ +32° (*c* 1.0, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.48−7.36 (5H, m, Ar), 5.68 (1H, s, C*H*Ph), 5.04 (1H, ddd, $J_{3,4ax}$ = 10.4, $J_{2,3}$ = 9.5, $J_{3,4eq}$ = 5.0 Hz, H-3), 4.80 (1H, dd, $J_{1ax,2} = J_{1ax,1eq}$ = 10.4 Hz, H-1ax), 4.24 (1H, dd, $J_{4eq,4ax}$ = 10.5 Hz, H-4eq), 4.18 (1H, ddd, $J_{1eq,2}$ = 4.8 Hz, H-2), 4.06 (1H, dd, H-1eq), 3.89 (1H, dd, H-4ax); ^{13}C NMR (CD_2Cl_2): δ 137.14 (C_{ipso}), 129.74 (C_{para}), 128.65 (2C) and 126.50 (2C) (C_{ortho} and C_{meta}), 102.72 (*C*HPh), 73.56 (C-2), 68.16 (C-4), 63.90 (C-3), 60.18 (C-1). Anal. Calcd for $C_{11}H_{12}O_5S$: C, 51.55; H, 4.72. Found: C, 51.80; H, 4.66.

2,4-*O*-Benzylidene-D-erythritol-1,3-cyclic Sulfate (13).

The cyclic sulfite (**12**) (3.5 g, 14 mmol) was dissolved in a mixture of MeCN (50 mL) and CCl_4 (50 mL), and $NaIO_4$ (4.1 g, 1.5 equiv) and $RuCl_3 \cdot H_2O$ (50 mg) were added followed by H_2O (50 mL). The mixture was stirred vigorously at room temperature until TLC (hexanes/EtOAc, 4:1) showed complete disappearance of the starting material. The mixture was diluted with Et_2O (200 mL) and washed with H_2O (200 mL) and brine (200 mL). The organic solution was dried (Na_2SO_4) and concentrated on a rotary evaporator. The product was purified by flash chromatography [hexanes/EtOAc, 4:1 + 0.1% Et_3N] to yield a white solid (3.5 g, 95%). A portion of the product was recrystallized from EtOAc/hexanes. Mp 115−125 °C (dec); $[\alpha]_D$ +4° (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_2Cl_2): δ 7.48−7.37 (5H, m, Ar), 5.65 (1H, s, C*H*Ph), 4.86 (1H, ddd, $J_{2,3} = J_{3,4ax} = 10.0$, $J_{3,4eq} = 5.0$ Hz, H-3), 4.76 (1H, dd, $J_{1ax,2} = 10.7$, $J_{1ax,1eq} = 10.5$ Hz, H-1ax), 4.65 (1H, dd, $J_{1eq,2} = 5.0$ Hz, H-1eq), 4.44 (1H, dd, $J_{4eq,4ax} = 10.5$ Hz, H-4eq), 4.25 (1H, ddd, H-2), 3.97 (1H, dd, H-4ax); ^{13}C NMR (CD_2Cl_2): δ 136.32 (C_{ipso}), 130.03 (C_{para}), 128.74 (2C) and 126.52 (2C) (C_{ortho} and C_{meta}), 102.98 (*C*HPh), 75.74 (C-3), 73.19 (C-1), 71.68 (C-2), 67.64 (C-4); MALDI-TOF MS: *m/e* 273 (M^+ + H), Anal. Calcd for $C_{11}H_{12}O_6S$: C, 48.53; H, 4.44. Found: C, 48.43; H, 4.39.

1,4-Anhydro-2,3,5-tri-*O*-benzyl-4-thio-D-arabinitol (8). A mixture of 1,4-anhydro-3-*O*-benzyl-4-thio-D-arabinitol (**17**)[14] (1.0 g, 4.2 mmol) and 60% NaH (0.85 g, 5 equiv) in DMF (20 mL) was stirred in an ice-bath for 1 h. A solution of benzyl bromide (1.9 mL, 3.8 equiv) in DMF (5 mL) was added, and the solution was stirred at room temperature for 3 h. The mixture was added to ice−water (150 mL) and extracted with Et_2O (150 mL). The organic solution was dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography [hexanes/EtOAc, 4:1] to give a syrup (1.6 g, 90%). $[\alpha]_D$ +5° (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38−7.23 (15H, m, Ar), 4.61 (2H, s, CH_2Ph), 4.53 and 4.48 (2H, 2d, $J_{A,B} = 12.1$ Hz, CH_2Ph), 4.51 and 4.47 (2H, 2d, $J_{A,B} = 11.9$ Hz, CH_2Ph), 4.19 (1H, ddd, $J_{1b,2} = 4.6$ Hz, H-2), 4.11 (1H, dd, $J_{2,3} = 3.8$, $J_{3,4} = 3.6$ Hz, H-3), 3.69 (1H, dd, $J_{5a,5b} = 8.8$, $J_{4,5a} = 7.6$ Hz, H-5a), 3.57 (1H, ddd, $J_{4,5b} = 6.3$ Hz, H-4), 3.50 (1H, dd, H-5b), 3.08 (1H, dd, $J_{1a,1b} = 11.4$, $J_{1a,2} = 5.1$ Hz, H-1a), 2.90 (1H, dd, H-1b). ^{13}C NMR ($CDCl_3$): δ 138.16, 138.06, 137.88 ($3C_{ipso}$), 128.40−127.59 ($15C_{Ar}$), 85.08 (C-3), 85.04 (C-2), 73.01 (*C*H_2-Ph), 72.34 (C-5), 71.85, 71.50 (2CH_2Ph), 48.99 (C-4), 33.10 (C-1). Anal. Calcd for $C_{26}H_{28}O_3S$: C, 74.25; H, 6.71. Found: C, 74.18; H, 6.53.

General Procedure for the Synthesis of the Protected Sulfonium Sulfates (14, 15, 16). The thiosugar (3 mmol) and the cyclic sulfate (1.2 equiv) were dissolved in dry acetone (0.5 mL), and anhydrous K_2CO_3 (7 mg) was added. The mixture was stirred in a sealed tube in an oil-bath (75 °C) overnight. The solvent was removed under reduced pressure, and the product was purified by column chromatography.

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[[(2*S*,3*S*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (14). Column chromatography [$CHCl_3$/MeOH, 10:1 + 0.1% Et_3N] of the crude product gave an amorphous solid (33%). $[\alpha]_D$ −11.9° (*c* 1.7, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.49−7.12 (20H, m, Ar), 5.54 (1H, s, C*H*Ph), 4.59 (1H, ddd, $J_{2',3'} = 9.6$, $J_{3',4'ax} = 10.7$, $J_{3',4'eq} = 5.4$ Hz, H-3′), 4.54 (2H, s, CH_2Ph), 4.51 (1H, br d, H-2), 4.50 (1H, dd, $J_{4'eq,4'ax} = 10.7$ Hz, H-4′eq), 4.48 and 4.37 (2H, 2d, $J_{A,B} = 11.7$ Hz, CH_2-Ph), 4.38 (1H, dd, $J_{1'a,1'b} = 13.6$, $J_{1'a,2'} = 2.7$ Hz, H-1′a), 4.35 (1H, br s, H-3), 4.29 (1H, ddd, $J_{1a',2'} = 3.4$ Hz, H-2′), 4.25 and 4.15 (2H, 2d, $J_{A,B} = 11.9$ Hz, CH_2Ph), 4.06 (1H, br-*d*, $J_{1a,1b} = 13.3$, H-1a), 4.00 (1H, dd, H-1′b), 3.98 (1H, br dd, H-4), 3.77 (1H, dd, H-4′ax), 3.74 (1H, dd, $J_{1b,2} = 3.8$ Hz, H-1b), 3.62 (1H, dd, $J_{5a,5b} = 9.9$, $J_{4,5a} = 8.7$ Hz, H-5a), 3.53 (1H, dd, $J_{4,5b} = 7.2$ Hz, H-5b); ^{13}C NMR (CD_2Cl_2): δ 137.34, 137.24, 136.56, 136.39 ($4C_{ipso}$), 129.73−126.62 ($20C_{Ar}$), 101.95 (*C*HPh), 83.75 (C-3), 82.82 (C-2), 76.80 (C-2′), 73.73, 72.84, 72.52 (3CH_2Ph), 69.54 (C-4′), 67.01 (C-5), 66.48 (C-3′), 65.27 (C-4), 49.67 (C-1′), 48.28 (C-1); MALDI-TOF MS: *m/e* 693 (M^+ + H). Anal. Calcd for $C_{37}H_{40}O_9S_2$: C, 64.14; H, 5.82. Found: C, 63.88; H, 5.83.

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[[(2*R*,3*R*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-episulfoniumylidene]-L-arabinitol Inner Salt (15). Column chromatography [$CHCl_3$/MeOH, 10:1 + 0.1% Et_3N] of the crude product gave an amorphous solid (40%). $[\alpha]_D$ +14.3° (*c* 1.4, CH_2Cl_2). Anal. Calcd for $C_{37}H_{40}O_9S_2$: C, 64.14; H, 5.82. Found: C, 64.13; H, 5.74.

2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[[(2*R*,3*R*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (16). Column chromatography [$CHCl_3$/MeOH, 10:1 + 0.1% Et_3N] of the crude product gave an amorphous solid (79%). $[\alpha]_D$ −46.9° (*c* 0.65, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ 7.43−7.10 (20H, m, Ar), 5.49 (1H, s, C*H*Ph), 4.59 and 4.51 (2H, 2d, $J_{A,B} = 11.8$ Hz, CH_2Ph), 4.54 and 4.42 (2H, 2d, $J_{A,B} = 11.7$ Hz, CH_2Ph), 4.56 (1H, ddd, $J_{2',3'} = J_{3',4'ax} = 9.7$, $J_{3',4'eq} = 4.2$ Hz H-3′), 4.50 (1H, dd, H-4′eq), 4.45 (1H, m, H-2), 4.44 (1H, dd, H-1′a), 4.41 (1H, m, H-3), 4.40 and 4.36 (2H, 2d, $J_{A,B} = 11.7$ Hz, CH_2Ph), 4.27 (1H, ddd, $J_{1'a,2'} = J_{1'b,2'} = 3.5$ Hz, H-2′), 4.24 (1H, br dd, H-4), 3.96 (1H, dd, $J_{5a,5b} = 9.7$, $J_{4,5a} = 6.2$ Hz, H-5a), 3.90 (1H, dd, $J_{1'b,1'a} = 13.3$ Hz, H-1′b), 3.82 (1H, dd, $J_{4,5b} = 9.7$ Hz, H-5b), 3.76 (1H, dd, $J_{4'ax,4'eq} = 10.2$ Hz, H-4′ax), 3.73 (1H, br d, H-1a), 3.51 (1H, dd, $J_{1b,1a} = 13.2$, $J_{1b,2} = 3.9$ Hz, H-1b); ^{13}C NMR (CD_2Cl_2): δ 137.62, 137.27, 136.48, 136.29 ($4C_{ipso}$), 129.80−126.56 ($20C_{Ar}$), 102.16 (*C*HPh), 84.25 (C-3), 82.56 (C-2), 77.07 (C-2′), 74.02, 72.74 (3CH_2Ph), 69.75 (C-4′), 67.19 (C-5), 66.82 (C-3′), 65.76 (C-4), 50.41 (C-1′), 49.60 (C-1); MALDI-TOF MS: *m/e* 693 (M^+ + H). Anal. Calcd for $C_{37}H_{40}O_9S_2$: C, 64.14; H, 5.82. Found: C, 64.16; H, 5.73.

3-*O*-Benzyl-1,4-dideoxy-1,4-[[(2*S*,3*S*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (18). Column chromatography [$CHCl_3$/MeOH, 10:1 + 0.1% Et_3N] of the crude product gave an amorphous solid (32%); ^{1}H NMR (CD_2Cl_2): δ 7.49−7.26 (10H, m, Ar), 6.22 (1H, d, $J_{2,OH} = 4.4$ Hz, 2-OH), 5.54 (1H, s, C*H*Ph), 4.96 (1H, br s, H-2), 4.65 and 4.56 (2H, 2d, $J_{A,B} = 11.6$ Hz, CH_2Ph), 4.64 (1H, br m, 5-OH), 4.52 (1H, ddd, $J_{2',3'} = 9.6$ Hz, H-3′), 4.46 (1H, dd, $J_{4'eq,4'ax} = 10.6$, $J_{3',4'eq} = 5.4$ Hz, H-4′eq), 4.32 (1H, br s, H-3), 4.30 (1H, br d, H-1a), 4.28 (1H, ddd, H-2′), 4.12 (1H, dd, $J_{1'a,2'} = 2.6$ Hz, H-1′a), 4.10 (1H, dd, H-4), 4.01 (1H, dd, $J_{1'b,1'a} = 13.5$, $J_{1'b,2'} = 3.5$ Hz, H-1′b), 3.92−3.78 (2H, m, H-5a, H-5b), 3.78 (1H, dd, $J_{3',4'ax} = 10.1$ Hz, H-4′ax), 3.67 (1H, dd, $J_{1b,1a} = 13.4$, $J_{1b,2} = 3.9$ Hz, H-1b); ^{13}C NMR (CD_2Cl_2): δ 136.92, 136.73 ($2C_{ipso}$), 129.97−126.61 ($10C_{Ar}$), 102.32 (*C*HPh), 88.45 (C-3), 76.61 (C-2′), 76.22 (C-2), 72.96 (*C*H_2Ph), 71.24 (C-4), 69.27 (C-4′), 66.96 (C-3′), 60.51 (C-5), 52.43 (C-1), 48.30 (C-1′); MALDI-TOF MS: *m/e* 513 (M^+ + H). Anal. Calcd for $C_{23}H_{28}O_9S_2$: C, 53.89; H, 5.51. Found: C, 53.64; H, 5.34.

General Procedure for the Deprotection of the Protected Sulfonium Sulfates. The protected compound (120 mg, 0.17 mmol) was dissolved in AcOH/H_2O, 4:1 (3 mL) and stirred with Pd−C (80 mg) under H_2 (52 psi). After 60 h the reaction mixture was filtered through a pad of Celite, which was subsequently washed with MeOH. The combined filtrates were concentrated, and the residue was purified by column chromatography.

1,4-Dideoxy-1,4-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (4). Column chromatography [$CHCl_3$/MeOH/H_2O, 7:3:1] of the crude product gave an amorphous solid (67%). $[\alpha]_D$ +2.1° (*c* 0.48, MeOH) (lit.[10] $[\alpha]^{28}_D$ +4.9° (*c* 0.35, MeOH)); ^{1}H NMR (pyridine-d_5): δ 5.25 (1H, ddd, $J_{2',3'} = 7.4$, $J_{3',4'b} = 3.8$, $J_{3',4'a} = 3.6$ Hz, H-3′), 5.14−5.09 (2H, m, H-3, H-2), 5.00 (1H, m, H-2′), 4.78 (1H, dd, $J_{1'a,1'b} = 13.0$, $J_{1'a,2'} = 4.9$ Hz, H-1′a), 4.70 (1H, m, H-4), 4.63 (1H, dd, $J_{1'b,2'} = 4.0$ Hz, H-1′b), 4.61 (1H, dd, $J_{4'a,4'b} = 11.8$ Hz, H-4′a), 4.54 (1H, dd, $J_{5a,5b} = 11.6$, $J_{4,5a} = 6.5$ Hz, H-5a), 4.51 (1H, dd, $J_{4,5b} = 7.5$ Hz, H-5b), 4.37 (1H, dd, H-4′b), 4.32 (2H, br-s, H-1a, H-1b); ^{13}C NMR (pyridine-d_5): δ 79.14 (C-3′), 79.06 (C-3), 78.18 (C-2), 72.30 (C-4), 67.44 (C-2′), 62.05 (C-4′), 59.98 (C-5), 52.46 (C-1′), 50.35 (C-1). HRMS Calcd for $C_9H_{18}O_9S_2$ (M + H): 335.0471. Found: 335.0481.

1,4-Dideoxy-1,4-[[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-L-arabinitol Inner Salt (5). Column chromatography [$CHCl_3$/MeOH/H_2O, 7:3:1] of the crude product gave an amorphous solid (80%). $[\alpha]_D$ −1.6° (*c* 0.6, MeOH); HRMS Calcd for $C_9H_{18}O_9S_2$ (M + H): 335.0471. Found: 335.0466.

1,4-Dideoxy-1,4-[[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)-butyl]-episulfoniumylidene]-D-arabinitol Inner Salt (7). Column chromatography [$CHCl_3$:MeOH:H_2O, 7:3:1] of the

crude product gave an amorphous solid (59%). $[\alpha]_D$ −35.6° (*c* 0.86, MeOH); ^{1}H NMR (pyridine-d_5): δ5.19 (1H, ddd, $J_{2',3'}$ = 7.8, $J_{3',4'a} = J_{3',4'b} = 3.7$ Hz, H-3′), 5.17−5.12 (2H, m, H-2, H-3), 5.00 (1H, ddd, $J_{1'a,2'} = 5.1$, $J_{1'b,2'} = 4.0$ Hz, H-2′), 4.83 (1H, dd, $J_{1'a,1'b} = 13.0$ Hz, H-1′a), 4.78 (1H, ddd, $J_{3,4} = 2.0$ Hz, H-4), 4.65 (1H, dd, $J_{4'a,4'b} = 11.9$ Hz, H-4′a), 4.65 (1H, dd, $J_{5a,5b} = 11.5$, $J_{4,5a} = 5.0$ Hz, H-5a), 4.60 (1H, dd, $J_{4,5b} = 6.4$ Hz, H-5b), 4.53 (1H, dd, H-1′b), 4.40 (1H, dd, H-4′b), 4.29 (1H, dd, $J_{1a,1b} = 12.7$, $J_{1a,2} = 3.9$ Hz, H-1a), 4.17 (1H, dd, $J_{1b,2} = 2.6$ Hz, H-1b); ^{13}C NMR (pyridine-d_5): δ 79.46 (C-3′), 79.38 (C-3), 78.94 (C-2), 71.94 (C-4), 67.52 (C-2′), 62.02 (C-4′), 60.26 (C-5), 52.64 (C-1′), 51.01 (C-1). HRMS Calcd for $C_9H_{18}O_9S_2$ (M + H): 335.0471. Found: 335.0486.

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