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Synthesis and glycosidase inhibitory activities of chain-modified analogues of the glycosidase inhibitors salacinol and blintol

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Abstract—The synthesis of chain-modified analogues of the naturally-occurring glycosidase inhibitor, salacinol, and its selenium analogue, blintol is described. The modification consists of a frame shift of the sulfate moiety by one carbon atom in the zwitterionic structures as well as an extension of the acyclic chain to five carbons. The target molecules were synthesized by alkylation of 1,4-anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio (or seleno)-D-arabinitol at the ring heteroatom by 2,3,5-tri-*O*-*p*-methoxybenzyl D- or L-xylitol-1,4-cyclic sulfate, followed by deprotection with trifluoroacetic acid. Two of the four compounds inhibit recombinant human maltase glucoamylase, one of the key intestinal enzymes involved in the breakdown of glucose oligosaccharides in the small intestine, with K_i values of 20 ± 4 and 53 ± 5 μM.

Keywords: Glycosidase inhibitors; Salacinol analogues; Blintol analogues; Chain-modified analogues; 5-Carbon extended analogues; Sulfonium salt; Selenonium salt; Cyclic sulfate; Human maltase glucoamylase (MGA)

1. Introduction

Glycosidases are involved in several metabolic pathways and specific reversible inhibitors of these enzymes can have therapeutic utility in the treatment of diabetes,[1] cancer,[2] and viral infections.[3] One important class of these enzymes is responsible for the liberation of glucose from its higher oligomers. Disruption in the function and regulation of these enzymes can lead to disease states such as diabetes. In the treatment of Type II non-insulin dependent diabetes (NIDD) management of blood glucose levels is critical.[4] This can be achieved by administering drugs which inhibit the activity of glucosidases that mediate the hydrolysis of complex starches to oligosaccharides in the small intestine. An attractive approach to potent glucosidase inhibitors is to create compounds that mimic the oxacarbenium-ion transition state of the enzyme-catalyzed reaction.[5] Many of the natural and synthetic azasugars are believed to mimic the transition state in either charge or shape.[6]

Recently, a new class of glycosidase inhibitors with an intriguing inner salt, sulfonium-sulfate was isolated from *Salacia reticulata*.[7] Extracts of this plant have been traditionally used in the Indian Ayurvedic system of medicine for the treatment of diabetes.[8] The active components of these extracts are found to be the sulfonium salts salacinol (**1**) and kotalanol (**2**) (Chart 1). It is believed that the inhibition of glycosidases by **1** and **2** is in fact due to their ability to mimic the shape and/or charge of the transition state involved in the enzymatic reactions. We and others previously reported the synthesis of salacinol and its stereoisomers.[9,10] We have also reported the synthesis of blintol (**3**), the selenium analogue of salacinol, as a potential glycosidase inhibitor.[11] Indeed both salacinol (**1**) and blintol (**3**) have been

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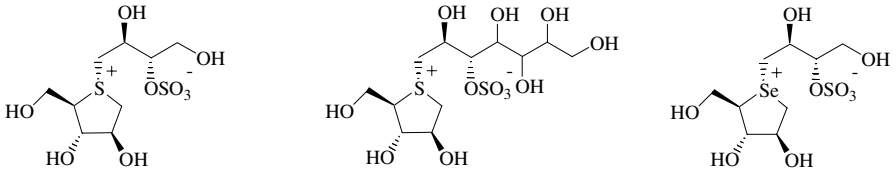
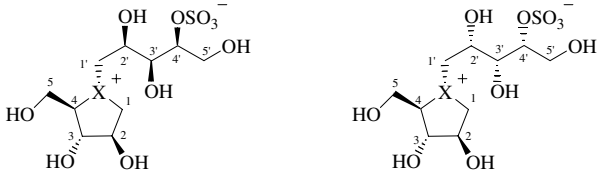


1 **2** **3**

Chart 1.

shown to be very effective in controlling blood glucose levels in rats after a carbohydrate meal, thus providing lead candidates for the treatment of Type 2 diabetes.[12]

As part of a program aimed at the synthesis of new glycosidase inhibitors, we have focused recently on the synthesis of chain-modified analogues of salacinol (**1**) and blintol (**3**) that vary in the length of the polyhydroxylated, sulfated chain. We have synthesized several 5-carbon and 6-carbon chain analogues in which the sulfate moiety is located at C-3′ as in salacinol and blintol.[13–15] These compounds were synthesized by a strategy that involved cyclic sulfate derivatives of different monosaccharides or alditols. We have also reported the mapping of the active site of recombinant human maltase glucoamylase using these synthetic analogues[15].



4. X = S

5. X = Se

6. X = S

7. X = Se

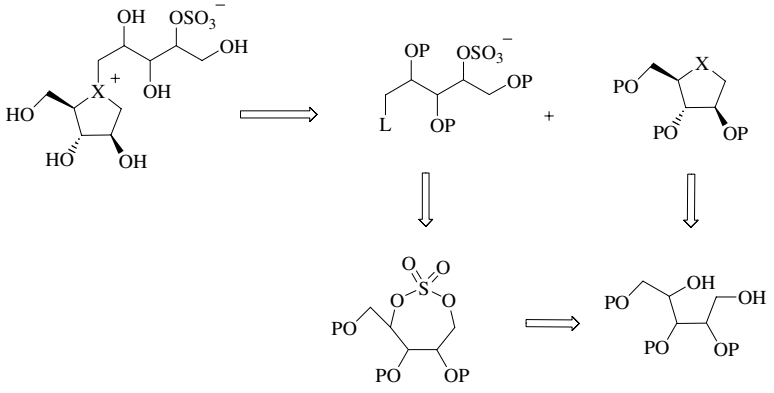
Chart 2.

We now report on the effect of the positioning of the sulfate group in the acyclic chain, in particular, the synthesis of the chain-modified analogues **4**–**7** (Chart 2).

2. Results and discussion

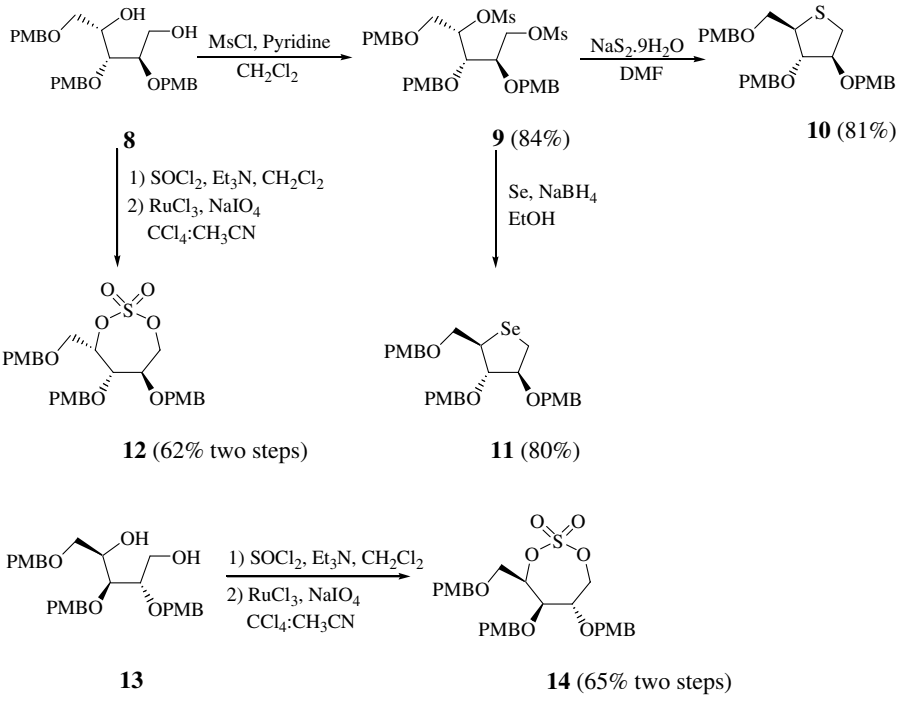
Retrosynthetic analysis revealed that the desired analogues could be synthesized by alkylation of a protected anhydro-D-heteroarabinitol moiety at the ring heteroatom by either an open chain electrophile or a cyclic sulfate derivative, whereby selective attack of the heteroatom at the least hindered primary centre would afford the desired products (Scheme 1).

The seven-membered cyclic sulfates (**12**, **14**), chosen as the alkylating agents, were synthesized from the corresponding diols. The diols were synthesized in turn from D- or L-xylose in six steps according to the procedure developed recently in our laboratory for the synthesis of the PMB-protected anhydro-D-selenoarabinitol **11** (Scheme 2).[16] Thus, diol **8** was used as a key intermediate to synthesize the thioether **10**,[17] the selenoether **11**, and the cyclic sulfate **12**. Treatment of the diol **8** with methanesulfonyl chloride in pyridine afforded the dimesylate **9**, which on treatment with $Na_2S{\cdot}9H_2O$ produced the thioether **10**; treatment of **9** with $Se/NaBH_4$ produced the selenoether **11** (Scheme 2). Treatment of the diol **8** with thionyl chloride and triethylamine gave



L= Leaving group, P= Protecting group

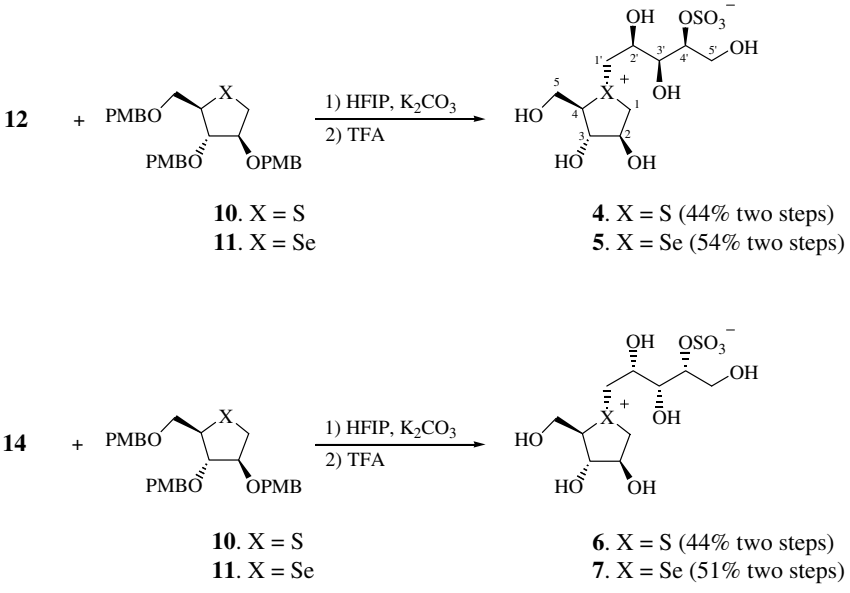
Scheme 1.



Scheme 2.

the cyclic sulfite, which was subsequently oxidized with sodium periodate and ruthenium(III) chloride as a catalyst to afford the cyclic sulfate **12**. The corresponding isomer **14** was synthesized in an analogous manner from the enantiomeric diol **13** (Scheme 2), which was obtained in turn from D-xylose.

The alkylation of **10** and **11** with the cyclic sulfates **12** and **14** was examined next (Scheme 3). Thus, the reaction of the thioarabinitol **10** with the cyclic sulfate **12** was found to proceed very slowly at 70 °C in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and was terminated before complete consumption of starting materials as we observed that longer reaction times led to decomposition. The coupled product was obtained as the sole product and immediate subsequent removal of the PMB groups by treatment with trifluoroacetic acid then afforded the target compound **4**. The stereochemistry at the stereogenic sulfonium center was assigned by means of a NOESY experiment which indicated the presence of the isomer with an *anti* relationship between C-5 and C-1′. The proton and carbon signals in the ^{1}H and ^{13}C NMR spectra of **4** were



Scheme 3.

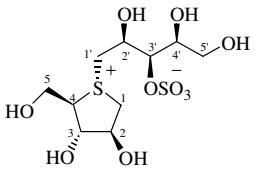
completely assigned with the help of ^{1}H–^{1}H COSY, HMQC, and HMBC experiments.

Analogously, the reaction of the selenoether **11** with the cyclic sulfate **12** in HFIP gave a coupled product, which was shown to be a 10:1 mixture of diastereomers at the stereogenic selenium center; the major diastereomer was isolated by flash chromatography. Removal of the PMB groups afforded the desired selenonium salt **5**. The stereochemistry at the stereogenic selenium center was also assigned as being *anti* with respect to C_5. In a similar manner, reaction of the enantiomeric cyclic sulfate **14** with the thio-**10** and seleno-**11** ethers produced the coupled products in 53% and 66% yield, respectively. Subsequent removal of the PMB groups using TFA yielded the desired products **6** and **7**.

It is of interest to comment on the inhibitory activities of the compounds synthesized in this study and previous studies against recombinant human maltase glucoamylase (MGA),[18] a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself. Compounds **4** and **5**, with the same configuration at the stereogenic centers in the acyclic chain, have K_i values of 20 ± 4 and 53 ± 5 μM, respectively. These compounds are less active than salacinol and blintol, with K_i values of 0.19 ± 0.02 and 0.49 ± 0.05 μM, respectively.[18] Interestingly, the analogue **15** (Chart 3), in which the sulfate moiety is located at the C-3′ and not the C-4′ position, is inactive.[13] A second 5-carbon chain-extended compound **16** (Chart 3), with the same configuration at C-3′ and C-4′ as **6**, but with the opposite configuration at C-2′ and in which the sulfate moiety is located at the C-3′ and not the C-4′ position, has a K_i value of 0.17 ± 0.03 μM. In contrast, the analogues **6** and **7** are not active. We note that Tanabe et al. have very recently reported the synthesis of de-O-sulfonated analogues of salacinol with monomethyl sulfate and chloride as external counter anions, and these analogues had almost equal inhibitory activities to salacinol against intestinal α-glucosidase in vitro.[19] Further rationalization of these data will have to await knowledge of the detailed contacts between the ligands and the active site from X-ray crystal structures of MGA complexes with candidate inhibitors.

In conclusion, two chain-modified analogues of both salacinol and blintol were synthesized using seven-membered cyclic sulfates as alkylating agents. The cyclic sulfates were prepared from D- and L-xylose. Compounds **4** and **5** showed inhibition of recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase, with K_i values of 20 ± 4 and 53 ± 5 μM.

The results, when compared with previous data on inhibitory activities of related compounds, add to our knowledge of the requirements for an effective inhibitor of MGA.



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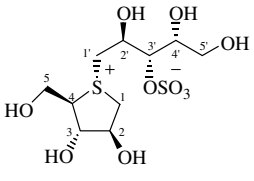

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Chart 3.

3. Experimental

3.1. General experimental

Optical rotations were measured at 23 °C. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional experiments (^{1}H–^{1}H COSY, HMQC, and HMBC). Column chromatography was performed with Merck Silica Gel 60 (230–400 mesh). MALDI-TOF mass spectra were recorded on a perSeptive Biosystems Voyager-DE spectrometer, using 2,5-dihydroxybenzoic acid as a matrix.

3.2. Enzyme activity assay

Analysis of MGA inhibition was performed using maltose as the substrate, and measuring the release of glucose. Reactions were carried out in 100 mM MES buffer pH 6.5 at 37 °C for 15 min. The reaction was stopped by boiling for 3 min. Aliquots (20 μL) were taken and added to 100 μL of glucose oxidase assay reagent (Sigma) in a 96-well plate. Reactions were allowed to proceed for 1 h and absorbance was measured at 450 nm to determine the amount of glucose produced by MGA activity in the reaction. One unit of activity is defined as the hydrolysis of one mole of maltose per minute. All reactions were performed in triplicate and absorbance measurements were averaged to give a final result.

3.3. Enzyme kinetics

Kinetic parameters of recombinant MGA were determined using the glucose oxidase assay to follow the production of glucose upon addition of enzyme (15 nM) at increasing maltose concentrations (from 1 to 3.5 mM) with a reaction time of 15 min. The program GRAFIT 4.0.14 was used to fit the data to the Michaelis–Menten equation and estimate the kinetic parameters, K_m and V_{max}, of the enzyme. K_i values for each inhibitor were determined by measuring the rate of maltose hydrolysis by MGA at varying inhibitor concentrations. Data were plotted in Lineweaver–Burk plots (1/rate vs 1/[substrate]) and K_i values were determined by the equation $K_i = K_m[I]/(V_{max})m - K_m$, where '$m$' is the slope of the

line. The K_i reported for each inhibitor was estimated by averaging the K_i values obtained from each of the different inhibitor concentrations.

3.4. 2,3,5-Tri-*O*-*p*-methoxybenzyl-L-xylitol-1,4-cyclic sulfate (12)

To a solution of 2,3,5-tri *p*-methoxybenzyl-L-xylitol (**8**) (11.2 g, 0.021 mol) and triethylamine (11.7 mL, 0.084 mol) in CH_2Cl_2 (150 mL) at 0 °C, was added thionyl chloride (2.4 mL, 0.031 mol) dropwise and the reaction mixture was stirred for 30 min. The mixture was poured into ice-cold water and extracted with additional CH_2Cl_2 (300 mL). The combined organic layers were washed with brine solution and dried over Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography to give an inseparable mixture of two diastereomeric cyclic sulfites as a pale brown oil (8.8 g, 72%). The mixture of the cyclic sulfites was redissolved in a mixture of CH_3CN/CCl_4 (1:1, 100 mL). Sodium periodate (5.0 g, 0.02 mol) and $RuCl_3$ (100 mg) were added followed by the addition of 50 mL of water. The mixture was stirred for 2 h and then filtered through a bed of silica and washed with CH_2Cl_2. The volatiles were removed and the residue was partitioned between EtOAc (200 mL) and H_2O (100 mL). The organic layer was washed with brine solution and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a pale yellow syrup that was purified by flash chromatography to give **12** as a colorless oil (7.8 g, 86%). $[\alpha]_D$ −10.0 (*c* 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 7.23–6.80 (12H, 3 × PMB), 4.99 (1H, dd, $J_{4,5a} = 7.1$, $J_{4,5b} = 6.4$ Hz, H-4), 4.53–4.32 (6H, 3 × CH_2–Ph), 4.75 (1H, d, $J_{1a,1b} = 13.0$ Hz, H-1a), 4.23 (1H, ddd, $J_{1b,2} = 3.2$ Hz, H-1b), 3.81 (6H, s, 2 × –OCH_3), 3.83 (3H, s, –OCH_3), 3.70 (1H, d, $J_{3,2} = 3.1$ Hz, H-3), 3.63 (1H, dd, $J_{5a,5b} = 9.8$ Hz, H-5a), 3.48 (1H, dd, H-5b), 3.46 (1H, dd, H-2); ^{13}C NMR ($CDCl_3$): δ 159.9–114.0 (18C, 3 × PMB), 78.6 (C-4), 73.6 (C-3), 73.1, 73.0, 71.0 (3 × –CH_2–Ph), 72.6 (C-2), 67.8 (C-1), 66.6 (C-5), 55.5 (3 × –OMe); MALDI-MS: *m*/*e* 597.0 $[M+Na]^+$. Anal. Calcd for $C_{29}H_{34}O_{10}S$: C, 60.61; H, 5.96. Found: C, 60.32; H, 5.76.

3.5. 1,4-Dideoxy-1,4[[2*S*,3*S*,4*S*]-2,3,5-trihydroxy-4-(sulfooxy)pentyl]-*epi*-sulfoniumylidene]-D-arabinitol inner salt (4)

The thioether **10** (257 mg, 0.50 mmol), the cyclic sulfate **12** (342 mg, 0.59 mmol), and K_2CO_3 (35 mg) were added to HFIP (3 mL) and the reaction mixture was stirred in a sealed tube for 72 h at 70 °C. The solvent was removed and the residue was purified by flash column chromatography (EtOAc/MeOH, 15:1) to afford the coupled product as a colorless foam (312 mg, 57%). The coupled product was redissolved in CH_2Cl_2 (2 mL), TFA (10 mL) was then added and the reaction mixture was stirred for 1 h at room temperature. The volatiles were removed under high vacuum and the residue was purified by column chromatography (EtOAc/MeOH/H_2O, 10:3:1) to give **4** as an amorphous solid (81 mg, 77%). $[\alpha]_D$ +40.0 (*c* 0.2, H_2O); ^{1}H NMR (D_2O): δ 4.57 (1H, td, $J_{2,1} = 4.0$ Hz, $J_{2,3} = 3.4$ Hz, H-2), 4.29 (1H, ddd, $J_{4',3'} = 3.3$, $J_{4',5a'} = 4.8$, $J_{4',5b'} = 7.0$ Hz, H-4′), 4.25 (1H, dd, $J_{3,4} = 3.2$ Hz, H-3), 4.17 (1H, ddd, $J_{2',3'} = 4.9$, $J_{2',1a'} = 3.6$, $J_{2',1b'} = 9.1$ Hz, H-2′), 3.98 (1H, dd, $J_{5a,4} = 4.4$, $J_{5a,5b} = 11.3$ Hz, H-5a), 3.95 (1H, ddd, $J_{4,5b} = 7.8$ Hz, H-4), 3.81–3.72 (6H, m, H-5b, H-1a, H-1b, H-1a′, H-3′, H-5a′), 3.70 (1H, dd, $J_{5b',5a'} = 12.3$ Hz, H-5b′), 3.67 (1H, dd, $J_{1b',1a'} = 13.2$ Hz, H-1b′). ^{13}C NMR (D_2O): δ 79.1 (C-4′), 77.4 (C-3), 76.7 (C-2), 71.2 (C-3′), 69.4 (C-4), 67.1 (C-2′), 59.8 (C-5′), 59.2 (C-5), 49.5 (C-1′), 47.7 (C-1); MALDI-MS: *m*/*e* 387.1 $[M+Na]^+$, 365.0 $[M+H]^+$, 285.2 $[M+H-SO_3]^+$. Anal. Calcd for $C_{10}H_{20}O_{10}S_2$: C, 32.96; H, 5.53. Found: C, 32.79; H, 5.56.

3.6. 1,4-Dideoxy-1,4[[2*S*,3*S*,4*S*]-2,3,5-trihydroxy-4-(sulfooxy)-pentyl]-*epi*-selenoniumylidene]-D-arabinitol inner salt (5)

The selenoether **11** (246 mg, 0.44 mmol), the cyclic sulfate **12** (305 mg, 0.53 mmol), and K_2CO_3 (35 mg) were added to HFIP (4 mL) and the mixture was stirred in a sealed tube for 48 h at 70 °C. The solvent was removed and the residue was purified by column chromatography. The coupled product was obtained as colorless foam (352 mg, 70%). The selenonium salts were deprotected using TFA following the same procedure that was used for compound **4**. Purification by flash column chromatography (EtOAc/MeOH/H_2O, 10:3:1) gave an amorphous solid **5** (98 mg, 76%). $[\alpha]_D$ +27.0 (*c* 1.0, H_2O); ^{1}H NMR (D_2O): δ 4.63 (1H, dd, $J_{2,3} = 4.0$, $J_{2,1} = 4.0$, H-2), 4.32 (1H, dd, $J_{3,4} = 4.7$ Hz, H-3), 4.29 (1H, m, H-4′), 4.19 (1H, ddd, $J_{2',1a'} = 4.3$, $J_{2',1b'} = 8.3$, $J_{2',3'} = 4.0$ Hz, H-2′), 4.02 (1H, ddd, H-4), 3.95 (1H, dd, $J_{5a,4} = 5.0$, $J_{5a,5b} = 12.5$ Hz, H-5a), 3.79 (1H, dd, $J_{5b,4} = 9.1$ Hz, H-5b), 3.76 (3H, m, H-1a′, H-5a′, H-3′), 3.69 (1H, dd, $J_{5b',5a'} = 12.3$, $J_{4',5b'} = 4.5$ Hz, H-5b′), 3.68 (1H, dd, $J_{1b',1a'} = 12.1$ Hz, H-1b′), 3.64 (2H, d, H_2-1); ^{13}C NMR (D_2O): δ 79.5 (C-4′), 78.1 (C-3), 77.4 (C-2), 71.7 (C-3′), 68.8 (C-4), 66.9 (C-2′), 59.9 (C-5′), 59.3 (C-5), 47.4 (C-1′), 45.0 (C-1); MALDI-MS: *m*/*e* 412.4 $[M+H]^+$, 332.2 $[M+H-SO_3]^+$. Anal. Calcd for $C_{10}H_{20}O_{10}SSe$: C, 29.20; H, 4.90. Found: C, 28.80; H, 4.56.

3.7. 2,3,5-Tri-*O*-*p*-methoxybenzyl-D-xylitol (13)

Compound **13** was synthesized from D-xylose in seven steps with 15% overall yield following the procedure reported for the synthesis of its L enantiomer.[16] $[\alpha]_D$

−5.0 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 7.26–6.83 (12H, 3 × PMB), 4.60–4.37 (6H, 3 × CH_2–Ph), 4.01 (1H, ddd, $J_{2,3} = 1.4$, $J_{2,1a} = 6.5$, $J_{2,1b} = 6.2$ Hz, H-2), 3.80 (9H, s, 2 × –OCH_3), 3.74 (1H, m, H-4), 3.68–3.63 (3H, m, *H*-3, *H*$_2$-5), 3.47 (1H, dd, $J_{1a,1b} = 9.4$ Hz, H-1a), 3.38 (1H, dd, H-1b); ^{13}C NMR ($CDCl_3$): δ 159.6–114.0 (18C, 3 × PMB), 78.3 (C-5), 76.9 (C-3), 73.9, 73.1, 72.5 (3 × –CH_2–Ph), 71.7 (C-1), 68.8 (C-2), 60.8 (C-4), 55.5 (3 × –OMe); MALDI-MS: *m*/*e* 535.7 $[M+Na]^+$. Anal. Calcd for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08. Found: C, 67.69; H, 6.88.

3.8. 2,3,5-Tri-*O*-*p*-methoxybenzyl-D-xylitol-1,4-cyclic sulfate (14)

To a solution of 2,3,5-tri-*O*-*p*-methoxybenzyl-D-xylitol (**13**) (9.8 g, 0.019 mol) and triethylamine (10.6 mL, 0.076 mol) in CH_2Cl_2 (150 mL) at 0 °C, was added thionyl chloride (2.2 mL, 0.028 mol) in CH_2Cl_2 (10 mL) dropwise. After stirring for 30 min, the mixture was poured into ice-cold water and extracted with additional CH_2Cl_2 (200 mL). The combined organic layers were washed with brine solution and dried over Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography to give an inseparable mixture of two diastereomeric cyclic sulfites as a pale brown oil (8.1 g, 76%). The cyclic sulfites were oxidized following the same procedure that was used for compound **12**. The residue was purified by flash column chromatography to give **14** as a colorless oil (7.2 g, 86%). $[\alpha]_D$ +11.4 (*c* 1.24, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 7.21–6.82 (12H, 3 × PMB), 4.99 (1H, dd, $J_{4,5a} = 7.1$, $J_{4,5b} = 6.4$ Hz, H-4), 4.53–4.32 (6H, 3 × CH_2–Ph), 4.75 (1H, d, $J_{1a,1b} = 13.0$ Hz, H-1a), 4.23 (1H, ddd, $J_{1b,2} = 3.2$ Hz, H-1b), 3.81 (6H, s, 2 × –OCH_3), 3.83 (3H, s, –OCH_3), 3.70 (1H, d, $J_{3,2} = 3.1$ Hz, H-3), 3.63 (1H, dd, $J_{5a,5b} = 9.8$ Hz, H-5a), 3.48 (1H, dd, H-5b), 3.46 (1H, dd, H-2); ^{13}C NMR ($CDCl_3$): δ 159.9–114.0 (18C, 3 × PMB), 78.6 (C-4), 73.6 (C-3), 73.1, 73.0, 71.0 (3 × –CH_2–Ph), 72.6 (C-2), 67.8 (C-1), 66.6 (C-5), 55.5 (3 × –OMe); MALDI-MS: *m*/*e* 597.2 $[M+Na]^+$. Anal. Calcd for $C_{29}H_{34}O_{10}S$: C, 60.61; H, 5.96. Found: C, 60.42; H, 5.86.

3.9. 1,4-Dideoxy-1,4[[2*R*,3*R*,4*R*]-2,3,5-trihydroxy-4-(sulfooxy)-pentyl]-*epi*-sulfoniumylidene]-D-arabinitol inner salt (6)

The thioether **10** (212 mg, 0.41 mmol) was coupled to the cyclic sulfate **14** (290 mg, 0.50 mmol) in HFIP (3 mL) following the same procedure that was used for the synthesis of **4**. The residue was purified by flash column chromatography (EtOAc/MeOH, 15:1) to give the sulfonium salt as an amorphous solid (240 mg, 53%). Deprotection of the sulfonium salt using TFA and purification by column chromatography (EtOAc/MeOH/H_2O, 10:3:1) gave **6** as an amorphous solid (67 mg, 83%). $[\alpha]_D$ −21.2 (*c* 0.8, H_2O); ^1H NMR (D_2O): δ 4.59 (1H, ddd, $J_{2,3} = 3.8$, $J_{2,1a} = 4.1$, $J_{2,1b} = 4.0$ Hz, H-2), 4.30 (1H, dd, $J_{3,4} = 3.2$ Hz, H-3), 4.28 (1H, m, H-4′), 4.17 (1H, m, H-2′), 3.95 (1H, ddd, $J_{4,5a} = 5.1$, $J_{4,5b} = 7.1$ Hz, H-4), 3.92 (1H, dd, $J_{5a,5b} = 11.0$ Hz, H-5a), 3.79 (1H, dd, H-5b), 3.78–3.70 (6H, m, H-1a, H-1a′, H-1b′, H-5a′, H-5b′, H-3′), 3.36 (1H, dd, $J_{1a,1b} = 11.8$ Hz H-1b); ^{13}C NMR (D_2O): δ 79.1 (C-4′), 77.7 (C-3), 76.8 (C-2), 71.2 (C-3′), 69.8 (C-4), 67.3 (C-2′), 59.9 (C-5′), 59.2 (C-5), 49.1 (C-1′), 49.3 (C-1); MALDI-MS: *m*/*e* 387.1 $[M+Na]^+$, 365.2 $[M+H]^+$, 285.4 $[M+H-SO_3]^+$. Anal. Calcd for $C_{10}H_{20}O_{10}S_2$: C, 32.96; H, 5.53. Found: C, 32.58; H, 5.82.

3.10. 1,4-Dideoxy-1,4[[2*R*,3*R*,4*R*]-2,3,5-trihydroxy-4-(sulfooxy)-pentyl]-*epi*-selenoniumylidene]-D-arabinitol inner salt (7)

The selenoether **11** (253 mg, 0.45 mmol) was coupled to the cyclic sulfate **14** (314 mg, 0.54) in HFIP (3 mL) following the same procedure that was used for the synthesis of **5**. Column chromatography (EtOAc/MeOH, 20:1) of the crude product gave the selenonium salt as an amorphous solid (341 mg, 66%). Removal of the protecting groups and purification by column chromatography (EtOAc/MeOH/H_2O, 10:3:1) gave **7** as an amorphous solid (97 mg, 78%). $[\alpha]_D$ −95.0 (*c* 0.2, H_2O); ^1H NMR (D_2O): δ 4.59 (1H, ddd, $J_{2,3} = 3.4$, $J_{2,1b} = 4.0$, $J_{2,1b} = 4.1$ Hz, H-2), 4.29 (1H, dd, $J_{3,4} = 3.8$ Hz, H-4), 4.24 (1H, ddd, $J_{4',5b'} = 4.8$, $J_{4',5a'} = 3.4$, $J_{4',3'} = 9.6$ Hz, H-4′), 4.15 (1H, m, H-2′), 4.07 (1H, ddd, $J_{4,5a} = 5.1$, $J_{4,5b} = 7.7$ Hz, H-4), 3.94 (1H, dd, $J_{5a,5b} = 12.5$ Hz H-5a), 3.84 (1H, dd, H-5b), 3.80–3.73 (4H, m, H-1a′, H-1b′, H-3′, H-5a′), 3.69 (1H, dd, $J_{5b',5a'} = 12.3$ Hz, H-5b′), 3.65 (1H, dd, $J_{1a,1b} = 12.3$ Hz, H-1a), 3.61 (1H, dd, H-1b); ^{13}C NMR (MeOH-d_4): δ 79.2 (C-4′), 78.8 (C-3), 78.2 (C-2), 71.8 (C-3′), 70.8 (C-4), 67.5 (C-2′), 60.0 (C-5′), 59.6 (C-5), 47.3 (C-1′), 45.0 (C-1); MALDI-MS: *m*/*e* 412.8 $[M+H]^+$, 332.6 $[M+H-SO_3]^+$. Anal. Calcd for $C_{10}H_{20}O_{10}SSe$: C, 29.20; H, 4.90. Found: C, 28.89; H, 4.82.

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