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Synthesis of analogues of salacinol containing a carboxylate inner salt and their inhibitory activities against human maltase glucoamylase

Wang Chen,[a] Lyann Sim,[b] David R. Rose[b,c] and B. Mario Pinto[a,*]

[a]*Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6*
[b]*Division of Cancer Genomics and Proteomics, Ontario Cancer Institute, Toronto, Canada M5G 1L7*
[c]*Department of Medical Biophysics, University of Toronto, Toronto, Canada M5G 1L7*

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Abstract—The syntheses of analogues of the naturally occurring glycosidase inhibitor, salacinol, containing a carboxylate inner salt are described. Salacinol is a sulfonium ion with an internal sulfate counterion. The synthetic strategy relies on the nucleophilic attack of 1,4-anhydro-2,3,5-tri-*O*-benzyl-4-thio-D- or L-arabinitol at the least hindered carbon of 4,5-anhydro-2,3-*O*-isopropylidene-D-ribonic acid benzyl ester to yield coupled adducts. Deprotection of the coupled products gives the target compounds. The compound derived from D-arabinitol inhibits recombinant human maltase glucoamylase, one of the key intestinal enzymes involved in the breakdown of glucose oligosaccharides in the small intestine, with a K_i value of 10 ± 1 μM.

Keywords: Glycosidase inhibitors; Salacinol analogues; Carboxylate counterion; Thioarabinitol; Epoxide opening; Human maltase glucoamylase

1. Introduction

Glycosidases are fundamentally involved in the control of several important biological phenomena such as the breakdown of oligosaccharides, cell–cell adhesion, cell growth, inflammatory processes, fertilization, and bacterial, viral and parasitic infections.[1] Because glycoside cleavage is a biologically widespread process, glycosidase inhibitors have many potential applications. The transition-state structure in the enzyme-mediated hydrolysis of glycosides is believed to be the oxacarbenium ion with a distorted conformation. Thus, mimicking this distorted, positively charged species is one factor that could lead to a strong inhibitor of glycosidase enzymes.[2]

The α-glucosidase inhibitors salacinol **1** and kotalanol **2** (Fig. 1) have been isolated from *Salacia reticulata* WIGHT,[3,4] and *Salacia oblonga* and *Salacia chinensis*,[5] traditionally used in the Ayurvedic system of India and Sri Lanka for the treatment of diabetes.[6] The sulfonium ion structure of these compounds has stimulated different groups to carry out the synthesis of salacinol,[7,8] and other carbohydrate-based cyclic sulfonium compounds,[9–15] such as **3**[11] and **4** (Fig. 2),[12] as a new class of glycosidase inhibitors. Our group has reported heteroanalogues of salacinol having nitrogen[16] or selenium[17] instead of sulfur, namely ghavamiol **5** and blintol **6** (Fig. 2), respectively. We reasoned that the interaction of a permanent positive charge with active site carboxylate residues would make a dominant contribution to the interaction energy.

The structure of salacinol is unique in that the ring sulfonium ion is stabilized by an internal sulfate counterion.[3a] Structural modification of salacinol represents a promising approach in the search for new glycosidase inhibitors. The fact that salacinol has greater inhibitory activity and specificity against α-glucosidases than the methyl sulfonium ion (**3**) indicates that the hydroxyl groups on the acyclic chain and/or the sulfate group

* Corresponding author. Tel.: +1 604 291 4152; fax: +1 604 291 4860; e-mail: bpinto@sfu.ca

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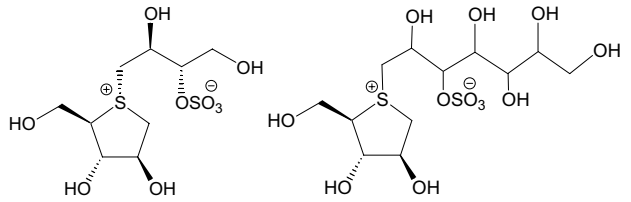
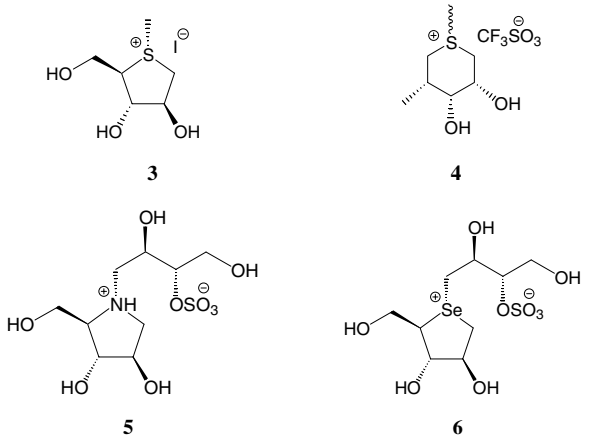


1 **2**

Figure 1. Structures of salacinol **1** and kotalanol **2**.



3 **4**

5 **6**

Figure 2. Structures of the cyclic sulfonium compounds **3** and **4**, ghavamiol **5**, and blintol **6**.

are advantageous.[18] Yuasa et al.[19] reported that docking of salacinol into the binding site of glucoamylase indicated close contacts between the sulfate ion with Arg305. Crystallographic analysis of the interactions of *Drosophila melanogaster* Golgi α-mannosidase II with salacinol and its analogues also shows that the sulfate group does interact with residues in the enzyme active site.[20] However, a recent study reported that compounds lacking the sulfate group are also active.[21]

An intriguing question is whether the corresponding carboxylate analogues of salacinol will act as inhibitors of glucosidases. We have recently described a novel class of amino acids patterned after salacinol **1** that consist of an iminoarabinitol alkylated with a polyhydroxylated chain containing a carboxylate residue **7** (Fig. 3).[22] This compound was found to be an inhibitor of recombinant human maltase glucoamylase, with a K_i value of 21 μM. In addition, this compound was also active against *D. melanogaster* Golgi mannosidase II (dGMII), with an IC_{50} of 0.3 mM.[22] We now report a synthetic route to the corresponding sulfonium ion-inner carboxylates **8** and **9**. These compounds also serve as the first representatives of a new class of hitherto undescribed molecules.

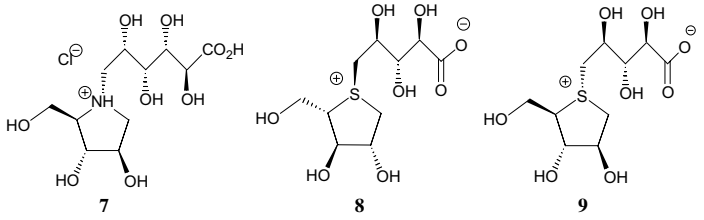
2. Results and discussion

Retrosynthetic analysis indicated that the carboxylate analogues **A** of salacinol could be obtained by alkylation of thioarabinitols **B** at the sulfur atom (Scheme 1). The alkylating agent could be epoxide **C**, whereby regioselective attack of the sulfur at the least hindered primary center should afford the desired sulfonium ions.[23] Epoxide **C** could be synthesized, in turn, from D-ribonolactone **D**.

Thioarabinitol **12** was synthesized from D-xylose following the same strategy that was used by Satoh et al. (Scheme 2).[24] Thus, treatment of diol **10** with methanesulfonyl chloride in pyridine afforded dimesylate **11** in 88% yield. Treatment of **11** with sodium sulfide in DMF produced compound **12** in 95% yield. Starting from L-xylose, enantiomer **15**[25] was synthesized in an analogous fashion.

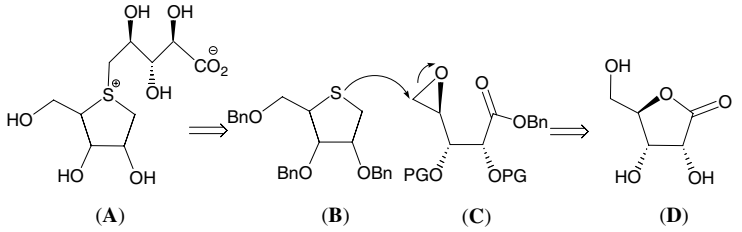
With **12** in hand, we turned our attention to the synthesis of epoxide **19**. D-Ribonolactone **16** was converted to 2,3-*O*-isopropylidene-D-ribonolactone **17**[26] that was then tosylated to give compound **18** in 88% yield (Scheme 3). Treatment of **18** with sodium benzylate afforded the desired epoxide **19**[27] in 86% yield.

The coupling reaction was examined next. Regioselective ring opening of epoxide **19** by the nucleophilic attack of the sulfur atom in thioether **12** occurred rapidly in a mixture of CF_3COOH and CH_2Cl_2 to give **20** in 58% yield. The unreacted starting materials were recovered, and no other polar spot was observed on TLC. Even after purification of compound **20** by flash chromatography, the ^1H and ^{13}C NMR spectra showed some extra peaks which could not be ascribed to the diastereomer. We concluded that these peaks resulted either from an inseparable impurity or by the presence of a similar compound with another external negative counterion. The compound was therefore processed as fol-

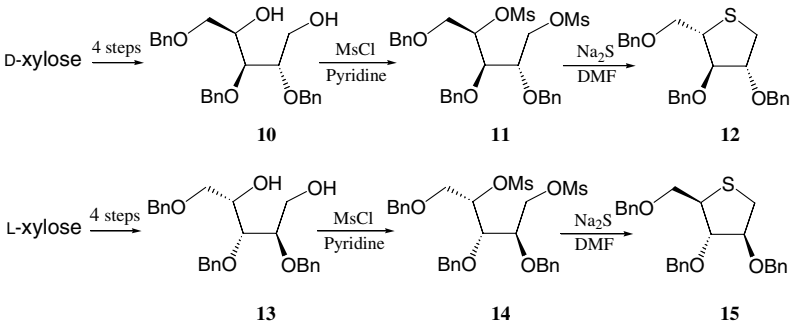


7 **8** **9**

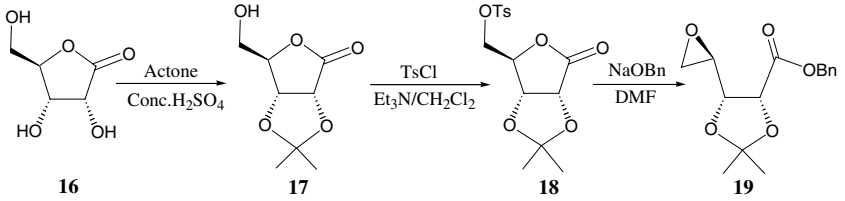
Figure 3. Structures of compounds **7**, **8**, and **9**.



Scheme 1.



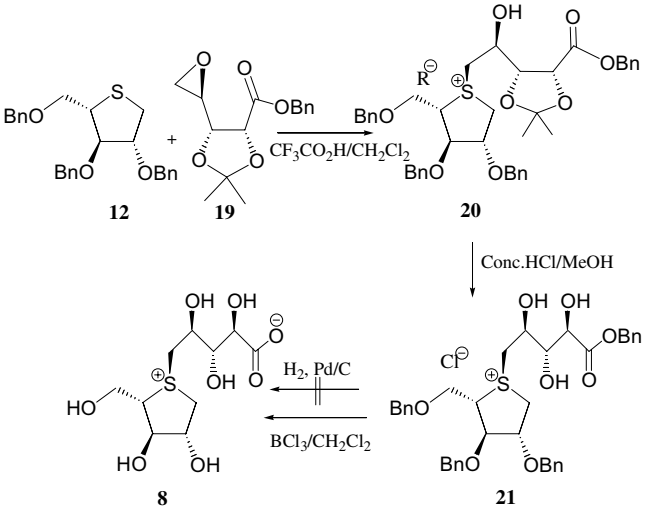
Scheme 2.



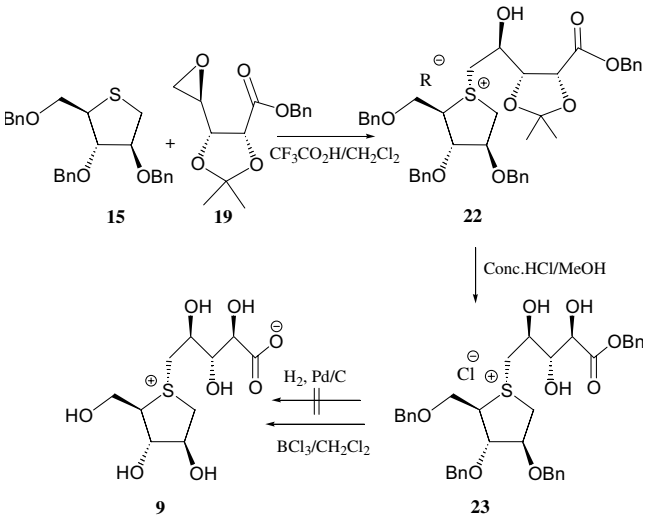
Scheme 3.

lows for the purpose of characterization. Counterion exchange and deprotection of the hydroxyl groups on the side chain were achieved in a mixture of concentrated hydrochloric acid and methanol, the resulting compound **21** being purified by flash chromatography. Hydrogenolysis of the coupled compound **21** over Pd–C catalyst did not go as planned to give compound **8** (Scheme 4) because of poisoning of the catalyst. Debenzylation of the protected compound **21** was therefore accomplished by treatment with boron trichloride[14] in CH_2Cl_2, affording **8** in 50% yield. No other product was obtained. The stereochemistry at the sulfur atom was determined by means of a 1D-NOE experiment.

Compound **9**, the diastereomer of **8**, was similarly obtained by reaction of thioether **15** with epoxide **19** to produce the protected compound **22** in 66% yield (Scheme 5). Unreacted starting materials were recovered, and no other polar spot was observed on TLC. As with compound **20**, the ^1H and ^{13}C NMR spectra showed that no diastereomer had been formed. Counterion exchange and deprotection of the hydroxyl groups on the side chain gave compound **23** in 75% yield. The stereochemistry at the sulfur atom was determined by means of a 1D-NOE experiment. Treatment of **23** with boron trichloride in CH_2Cl_2 afforded **9** in 52% yield. No other product was obtained.



Scheme 4.



Scheme 5.

Finally, we comment on the inhibitory activities of the compounds synthesized in this study against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself. Only compound **9**, with the D-arabinitol configuration in the heterocyclic ring displayed by salacinol, was active, with a K_i value of 10 ± 1 μM. Salacinol itself has a K_i value of 0.19 ± 0.02 μM.[28]

3. Experimental

3.1. General

Optical rotations were measured at 23 °C on an Autopol II automatic polarimeter. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with Merck Silica Gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light, and/or sprayed with a solution containing 1% $Ce(SO_4)_2$ and 1.5% molybdic acid in 10% aq H_2SO_4, and heated. Compounds were purified by flash chromatography on Kieselgel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on the following: Bruker AMX-400 NMR spectrometer at 400.13 MHz, Bruker AMX-600 NMR spectrometer at 600.13 MHz, and Varian INOVA 500 NMR spectrometer at 499.97 MHz. Chemical shifts are given in ppm downfield from TMS for those spectra measured in $CDCl_3$ and CD_3OD and from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for those spectra measured in D_2O. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. Assignments were fully supported by two-dimensional $^1H,^1H$ (COSY), and $^1H,^{13}C$ (HMQC) experiments using standard Bruker or Varian pulse programs. Processing of the spectra was performed with standard UXNMR and WINNMR software (Bruker) or MESTREC software (Varian). MALDI mass spectra were obtained on a PerSeptive Biosystems, Voyager DE time-of-flight spectrometer for samples dispersed in a 2,5-dihydroxybenzoic acid matrix. High resolution mass spectra were obtained by the electrospray ionization (ESI) technique, using a TOF mass spectrometer at 10,000 RP.

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 developed 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 1 mol 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 (1–3.5 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 was estimated by averaging the K_i values obtained from each of the different inhibitor concentrations.

3.4. 2,3-*O*-Isopropylidene-D-ribonolactone (17)[26]

To a suspension of D-ribonolactone **16** (10 g, 68 mmol) in acetone (200 mL) was added concentrated sulfuric acid (4 mL) dropwise while the solution was cooled in an ice bath. The starting material dissolved in 5 min. The mixture was stirred for 12 h at room temperature. Ammonia gas was passed through the ice-cooled solution. The resulting white solid was filtered and the

filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (1:3 hexanes–EtOAc) to afford **17** as a white solid (10.6 g, 80%): mp 134–137 °C; lit.[26] mp 135–138 °C.

3.5. 2,3-*O*-Isopropylidene-5-*O*-*p*-toluenesulfonyl-D-ribonolactone (18)[27]

To a solution of compound **17** (1.0 g, 5.3 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (0.59 g, 1.1 equiv). After 5 min, tosyl chloride (1.2 g, 1.2 equiv) was added in portions at 0 °C and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was poured into water (40 mL) and CH_2Cl_2 (30 mL). The organic phase was dried (Na_2SO_4) and concentrated on a rotary evaporator. The product was purified by flash chromatography (3:1 hexanes–EtOAc) to afford **18** as a white solid (1.6 g, 88%). ^{1}H NMR ($CDCl_3$): δ 7.77–7.37 (4 H, 2d, $J_{A,B} = 8.2$ Hz, Ar), 4.77 (1H, d, $J_{2,3} = 5.6$ Hz, H-2), 4.75 (1H, d, H-3), 4.68 (1H, dd, H-4), 4.34 (1H, dd, $J_{4,5b} = 1.9$ Hz, $J_{5a,5b} = 11.2$ Hz, H-5b), 4.18 (1H, dd, $J_{4,5a} = 2.5$ Hz, H-5a), 2.47 (3H, s, CH_3Ph), 1.46 and 1.39 (6H, 2s, C(CH_3)$_2$).

3.6. 4,5-Anhydro-2,3-*O*-isopropylidene-D-ribonic acid benzyl ester (19)[27]

A solution of sodium benzylate prepared from benzyl alcohol (0.71 g, 6.57 mmol) and NaH (60 mg, 1.5 mmol) in DMF (7.1 mL) was added to compound **18** (0.5 g, 1.46 mmol) in DMF (1.1 mL) at 0 °C. The reaction mixture was stirred for 1 h and the solvent was removed under high vacuum. The white solid was filtered and the filtrate was concentrated. The crude product was purified by column chromatography (5:1 hexanes–EtOAc) to afford **19** as a colorless oil (350 mg, 86%). ^{1}H NMR (CD_2Cl_2): δ 7.42–7.37 (5H, m, Ar), 5.22 and 5.17 (2H, 2d, $J_{A,B} = 12.1$ Hz, CH_2Ph), 4.80 (1H, d, $J_{2,3} = 6.9$ Hz, H-2), 4.11 (1H, dd, H-3), 2.93 (1H, ddd, $J_{3,4} = 6.19$ Hz, $J_{4,5a} = 3.9$ Hz, $J_{4,5b} = 2.6$ Hz, H-4), 2.64 (1H, dd, $J_{5a,5b} = 5.2$ Hz, H-5b), 2.61 (1H, dd, H-5a), 1.58 and 1.39 (6H, 2s, C(CH_3)$_2$).

3.7. Benzyl-5-(2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-epi-sulfoniumylidene-L-arabinitol)-5-deoxy-D-ribonate chloride (21)

A mixture of compound **19** (130 mg, 0.47 mmol) and compound **12** (196 mg, 1.0 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and CF_3CO_2H (53 mg, 1.0 equiv) was added. The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, and column chromatography (EtOAc–MeOH–H_2O, 40:1:1) of the crude product gave **20** as a colorless oil that was reacted as follows (190 mg, 58%). MALDI-TOF MS: m/z 699.42 (M^z). Without further purification, compound **20** (190 mg, 0.27 mmol) was dissolved in a mixture of concentrated HCl (1 mL) and methanol (40 mL). The mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and column chromatography (8:1 CH_2Cl_2–MeOH) of the crude product gave **21** as a colorless oil (128 mg, 71%). $[\alpha]_D$ +20 (c 1.0, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2): δ 7.43–7.35 (20H, m, Ar), 5.07 (2H, 2d, $J_{A,B} = 11.1$ Hz, CO_2CH_2Ph), 4.51–4.31 (6H, m, 3OCH_2Ph), 4.49 (1H, m, H-2′), 4.45 (1H, m, H-2), 4.42 (1H, m, H-4), 4.21 (1H, m, H-3′), 4.18 (1H, m, H-4′), 4.13 (1H, m, H-1′b), 4.07 (1H, m, H-3), 4.06 (1H, m, H-1b), 3.96 (1H, m, H-1′a), 3.32 (1H, br, H-1a), 3.28 (1H, m, H-5′b), 3.23 (1H, m, H-5′a); ^{13}C NMR (CD_2Cl_2): δ 173.54 (C-5), 139.13, 138.39, 138.35, 137.84 (4C$_{ipso}$), 130.57–129.52 (20C$_{Ar}$), 84.88 (C-3′), 84.82 (C-2′), 77.12 (C-3), 75.34, 74.11, 73.87 (3OCH_2Ph), 75.06 (C-4), 69.06 (C-5′), 68.89 (C-2), 68.58 (CO_2CH_2Ph), 67.04 (C-4′), 53.74 (C-1), 49.57 (C-1′). MALDI-TOF MS: m/z 659.20 (M^+). Anal. Calcd for $C_{38}H_{43}ClO_8S$: C, 65.65; H, 6.23. Found: C, 65.62; H, 6.40.

3.8. 5-(1,4-Dideoxy-1,4-episulfoniumylidene-L-arabinitol)-5-deoxy-D-ribonate inner salt (8)

Compound **21** (100 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (5 mL). BCl_3 was passed through the solution for 2 min at −78 °C. The solution was stirred at −78 °C for 1 h. Air was passed through the reaction flask until no white gas formed. H_2O was added slowly to quench the reaction. The resulting mixture was concentrated under reduced pressure. Column chromatography (7:3:1 EtOAc–MeOH–H_2O and then pure H_2O) of the crude product gave **8** as a colorless oil (21 mg, 50%). $[\alpha]_D$ +29 (c 0.2, H_2O). ^{1}H NMR (D_2O): δ 4.68 (1H, dt, $J_{1',2'} = 3.7$ Hz, H-2′), 4.40 (1H, t, $J_{2',3'} = J_{3',4'} = 3.3$ Hz, H-3′), 4.22 (1H, b, H-2), 4.14 (1H, d, $J_{3,4} = 2.7$ Hz, H-4), 4.08 (1H, ddd, H-4′), 4.03 (1H, dd, $J_{4',5'b} = 5.2$ Hz, $J_{5'a,5'b} = 12.3$ Hz, H-5′b), 3.95 (1H, b, H-3), 3.91 (1H, dd, $J_{4',5'a} = 8.1$ Hz, H-5′a), 3.82 (2H, m, H-1), 3.78 (2H, d, H-1′); ^{13}C NMR (D_2O): δ 179.81 (C-5), 79.87 (C-3′), 79.01 (C-2′), 76.89 (C-3), 75.55 (C-4), 71.99 (C-4′), 69.55 (C-2), 61.38 (C-5′), 51.80 (C-1), 49.17 (C-1′). MALDI-TOF MS: m/z 321.35 (M^++Na), 299.48 (M^++H). HRMS: (M+H) calcd for $C_{10}H_{19}O_8S$, 299.0801; found, 299.0801.

3.9. Benzyl-5-(2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-epi-sulfoniumylidene-D-arabinitol)-5-deoxy-D-ribonate triflate (23)

A mixture of compound **19** (277 mg, 1 mmol) and compound **15** (417 mg, 1.0 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and CF_3CO_2H (113 mg, 1.0 equiv) was

added. The mixture was stirred at room temperature for 3 h and the solvent was removed under reduced pressure. Column chromatography (EtOAc–MeOH–H_2O 40:1:1) of the crude product gave **22** as a colorless oil (460 mg, 66%; MALDI-TOF MS: m/z 699.46 M^+) that was reacted as follows. Without further purification, compound **22** (200 mg, 0.23 mmol) was dissolved in a mixture of concentrated HCl (1 mL) and methanol (40 mL). The mixture was stirred at rt for 6 h. The solvent was removed under reduced pressure. The resulting chloride salt was stirred with silver triflate (117 mg, 2.0 equiv) in CH_2Cl_2 (2 mL) for 1 h. The mixture was concentrated and column chromatography (8:1 CH_2Cl_2–MeOH) of the crude product gave **23** as a colorless oil (142 mg, 75%). $[\alpha]_D$ +15 (c 0.9, CH_2Cl_2). ^1H NMR (CD_3OD): δ 7.40–7.20 (20H, m, Ar), 5.17 (2H, s, CO_2CH_2Ph), 4.67–4.44 (6H, m, $3OCH_2Ph$), 4.63 (1H, d, H-2′), 4.43 (1H, s, H-3′), 4.35 (1H, d, $J_{3,4} = 3.5$ Hz, H-4), 4.30 (1H, dd, $J_{4',5'b} = 6.7$ Hz, $J_{4',5'a} = 9.6$ Hz, H-4′), 4.24 (1H, ddd, $J_{1a,2} = 7.2$ Hz, $J_{1b,2} = 3.4$ Hz, H-2), 4.02 (1H, d, $J_{1'a,1'b} = 13.1$ Hz, H-1′b), 3.96 (1H, dd, $J_{2,3} = 6.3$ Hz, H-3), 3.84 (1H, dd, $J_{1a,1b} = 13.0$ Hz, H-1b), 3.80 (1H, dd, H-5′b), 3.79 (1H, dd, $J_{1'a,2'} = 3.1$ Hz, H-1′a), 3.73 (1H, dd, H-1a), 3.70 (1H, dd, $J_{5'a,5'b} = 10.0$ Hz, H-5′a); ^{13}C NMR (CD_3OD): δ 173.40 (C-5), 138.56–138.02 ($4C_{ipso}$), 129.98–129.19 ($20C_{Ar}$), 84.45 (C-2′), 84.11 (C-3′), 76.30 (C-3), 74.46 (C-4), 73.68, 73.31, 73.15 ($3OCH_2Ph$), 68.55 (C-2), 68.02 (C-5′), 67.88 (CO_2CH_2Ph), 67.66 (C-4′), 51.84 (C-1), 49.81 (C-1′). MALDI-TOF MS: m/z 659.25 (M^+). Anal. Calcd for $C_{39}H_{43}F_3O_{11}S_2$: C, 57.91; H, 5.36. Found: C, 57.55; H, 5.49.

3.10. 5-(1,4-Dideoxy-1,4-episulfoniumylidene-D-arabinitol)-5-deoxy-D-ribonate inner salt (9)

Compound **23** (150 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (10 mL). BCl_3 was passed through the solution for 2 min at −78 °C. The solution was stirred at −78 °C for 1 h. Air was passed through the reaction flask until no white gas formed. H_2O was added slowly to quench the reaction. The resulting mixture was concentrated under reduced pressure. Column chromatography (7:3:1 EtOAc–MeOH–H_2O and then pure H_2O) of the crude product gave **9** as a colorless oil (33 mg, 52%). $[\alpha]_D$ −12 (c 0.6, H_2O). ^1H NMR (D_2O): δ 4.57 (1H, dt, $J_{1',2'} = 3.8$ Hz, H-2′), 4.26 (1H, dd, $J_{2',3'} = 3.5$ Hz, H-3′), 4.09 (1H, ddd, $J_{1a,2} = 8.8$ Hz, $J_{1b,2} = 3.1$ Hz, $J_{2,3} = 5.5$ Hz, H-2), 4.01 (1H, d, $J_{3,4} = 3.7$ Hz, H-4), 3.96 (1H, dd, $J_{4',5'b} = 4.7$ Hz, $J_{5'a,5'b} = 12.1$ Hz, H-5′b), 3.89 (1H, ddd, $J_{3',4'} = 3.2$ Hz, $J_{4',5'a} = 8.1$ Hz, H-4′), 3.86 (1H, dd, H-3), 3.77 (1H, m, H-5′a), 3.75 (1H, dd, $J_{1a,1b} = 13.4$ Hz, H-1b), 3.72 (2H, d, H-1′), 3.64 (1H, dd, H-1a); ^{13}C NMR (D_2O): δ 179.47 (C-5), 79.35 (C-3′), 78.65 (C-2′), 76.56 (C-3), 75.14 (C-4), 71.50 (C-4′), 69.14 (C-2), 61.02 (C-5′), 51.50 (C-1), 49.66 (C-1′). HRMS: (M+H) calcd for $C_{10}H_{19}O_8S$, 299.0801; found, 299.0795.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.06.003.

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