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Carbohydrate Research 343 (2008) 951–956
Carbohydrate RESEARCH

Note

# Synthesis of 2-deoxy-2-fluoro and 1,2-ene derivatives of the naturally occurring glycosidase inhibitor, salacinol, and their inhibitory activities against recombinant human maltase glucoamylase

Niloufar Choubdar,[a] Lyann Sim,[b] David R. Rose[b] and B. Mario Pinto[a,*]

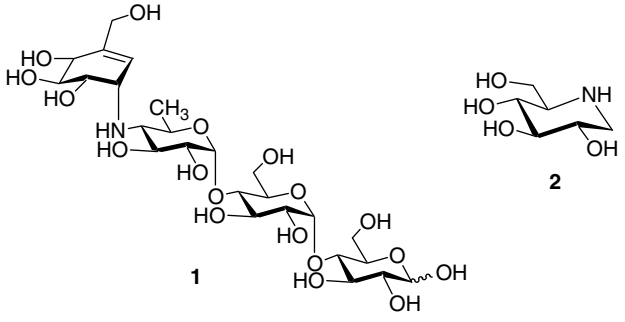
[a]*Department of Chemistry, Simon Fraser University, Burnaby, B.C., Canada V5A 1S6*
[b]*Department of Medical Biophysics, University of Toronto and Division of Cancer Genomics and Proteomics, Ontario Cancer Institute, Toronto, ON, Canada M5G 1L7*

Received 2 January 2008; received in revised form 17 January 2008; accepted 20 January 2008
Available online 29 January 2008

**Abstract**—2-Deoxy-2-fluorosalacinol and a 1,2-ene derivative of the naturally occurring glycosidase inhibitor salacinol were synthesized for structure activity studies with human maltase glucoamylase (MGA). 2-Deoxy-2-fluorosalacinol was synthesized through the coupling reaction of 2-deoxy-2-fluoro-3,5-di-*O*-*p*-methoxybenzyl-1,4-anhydro-4-thio-D-arabinitol with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate in hexafluoroisopropanol (HFIP) containing 0.3 equiv of $K_2CO_3$. Excess of $K_2CO_3$ resulted in the elimination of HF from the coupled product, and the formation of an alkene derivative of salacinol. Nucleophilic attack of the 1,4-anhydro-4-thio-D-arabinitol moiety on the cyclic sulfate did not proceed in the absence of $K_2CO_3$. No reaction was observed in acetonitrile containing $K_2CO_3$. The target compounds were obtained by deprotection with TFA. The 2-deoxy-1-ene derivative of salacinol and 2-deoxy-2-fluorosalacinol inhibited recombinant human maltase glucoamylase, one of the key intestinal enzymes involved in the breakdown of glucose, with an $IC_{50}$ value of 150 μM and a $K_i$ value of $6 \pm 1$ μM, respectively.


*Keywords:* Glycosidase inhibitors; Salacinol derivatives; 2-Deoxy-2-fluorosalacinol; 2-Deoxy-1-ene-salacinol; Cyclic sulfates; Human maltase glucoamylase (MGA) inhibition

Glycosidase enzymes are fundamental in the biochemical processing of carbohydrates.[1–5] For example, pancreatic α-amylase converts starch to maltooligosaccharides, and membrane-bound glucosidases convert these oligosaccharides to glucose in the small intestine. Inhibition of these enzymes in patients suffering from type II diabetes (noninsulin dependent diabetes) could be one strategy for controlling blood glucose levels by delaying the breakdown of carbohydrates.[6–8] One example of this class of inhibitors is acarbose **1**, a naturally occurring glycosidase inhibitor, which has been used for the oral treatment of type II diabetes.[7,9–11] Deoxynojirimycin **2** is another glucosidase inhibitor whose derivatives have been used in the treatment of diabetes, Gaucher's disease, and viral infections.[12–17]




Salacinol **3** and kotalanol **4** are two naturally occurring glycosidase inhibitors that have been isolated from roots and stems of a Sri Lankan plant, *Salacia reticulata*.[18,19] We and others have synthesized salacinol and compounds related to salacinol including heteroanalogues, stereoanalogues, chain-extended homologues, C-2 substituted analogues, and counterion variants.[20]

* Corresponding author. Tel.: +1 778 782 4152; fax: +1 778 782 4860; e-mail: bpinto@sfu.ca

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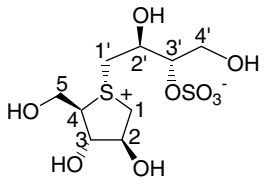
doi:10.1016/j.carres.2008.01.025

These inhibitors contain ammonium, selenonium, or sulfonium ion as putative mimics of the oxacarbenium-ion like transition states in glycosidase-mediated hydrolysis reactions.[21–25]



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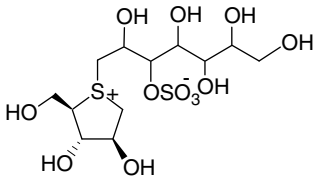

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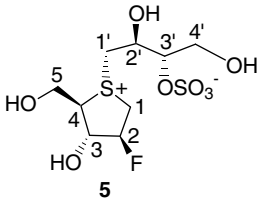
Theoretical and experimental studies on nucleotides containing 1,2,4-trideoxy-2-fluoro-1,4-anhydro-4-thio-D-arabinose sugar ring had indicated an unusual conformational preference due to steric and stereoelectronic effects.[26] In addition, the substitution of a fluorine atom for a hydroxyl group has proven advantageous in the design of carbohydrate-based enzyme inhibitors. Thus, a kinetic study with UDP-Gal*f* and its C3- fluorinated analogue, UDP-[3-F]Gal*f* showed that the catalytic efficiency ($k_{cat}/K_m$) of UDP-galactopyranose mutase for UDP-[3-F]Gal*f* decreased by approximately three orders of magnitude in comparison to that of UDP-Gal*f*.[27] This difference has been attributed, by STD-NMR and molecular dynamics, to the partial population of a binding mode of UDP-[3-F]Gal*f* that is non-productive with respect to reaction.[28] Therefore, it was of interest to synthesize a salacinol analogue with a fluorine atom at the C-2 position (**5**) to probe its glycosidase inhibitory activity.

We report herein the synthesis of **5** and its elimination product **6**, together with their inhibitory activities against human maltase glucoamylase (MGA), a key intestinal enzyme involved in the breakdown of malto-oligosaccharides into glucose.



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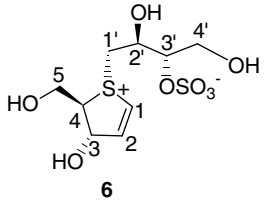

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Retrosynthetic analysis indicated that the target compound **5** could be synthesized by removal of the benzylidene and *p*-methoxybenzyl (PMB) protecting groups in compound **7**, which could be synthesized, in turn, by nucleophilic attack of compound **8** at the less hindered carbon of 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate **9**. Compound **8** could be synthesized from 1,4-anhydro-2-deoxy-2-fluoro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-4-thio-D-arabinitol **10** (Scheme 1).[26,29]

Compound **10** was synthesized from 1,4-anhydro-4-thio-D-arabinitol according to literature procedures.[26,29] The silyl protecting group in **10** was removed using tetrabutylammonium fluoride (TBAF), and the resulting diol was protected with the acid labile protecting group, *p*-methoxybenzyl (PMB), to afford compound **8** in 58% yield (Scheme 2).

The alkylation reaction of **8** with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate **9**[30,31] in hexafluoroisopropanol (HFIP) as the solvent containing an excess of $K_2CO_3$ in a sealed tube did not yield the desired compound **7**, but yielded the elimination product **11**. Presumably elimination follows alkylation owing to the increased acidity of the protons adjacent to the sulfonium-ion center. Compound **11** was deprotected using trifluoroacetic acid (TFA, 90%) to afford compound **6** for testing as a potential glycosidase inhibitor (Scheme 3).

The alkylation reaction of **8** with the cyclic sulfate **9** in HFIP did not proceed in the absence of $K_2CO_3$ at 50–70 °C, and at higher temperatures, the starting materials started to decompose. The alkylation reaction of **8** with the cyclic sulfate **9** in acetonitrile containing $K_2CO_3$ was attempted but the reaction did not proceed and starting compounds were recovered. This result suggested that HFIP might be the best choice of solvent for this type of reaction.

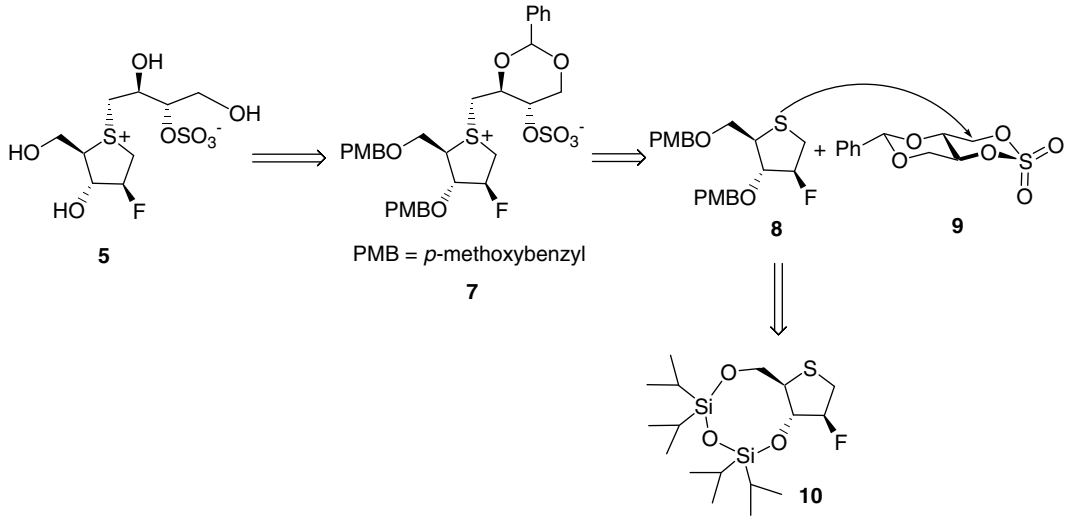
Interestingly, the alkylation reaction of **8** with the cyclic sulfate **9** in HFIP containing 0.3 M equiv of $K_2CO_3$ in a sealed tube at 68 °C proceeded smoothly to give the desired coupled product **7**. The benzylidene and *p*-methoxybenzyl protecting groups were then removed using trifluoroacetic acid (90%) to afford the desired product **5** (Scheme 3).

Finally, we comment on the inhibitory activities of compounds **5** and **6** against recombinant human maltase glucoamylase (MGA). Compound **6** inhibited MGA with an $IC_{50} = 150\ \mu M$, whereas compound **5** showed greater inhibition with $K_i = 6 \pm 1\ \mu M$. Because salacinol itself shows a $K_i = 0.2 \pm 0.02\ \mu M$,[32] it would appear that the OH group on C-2 of salacinol is critical as a hydrogen-bond donor with functional groups in the active site of MGA.

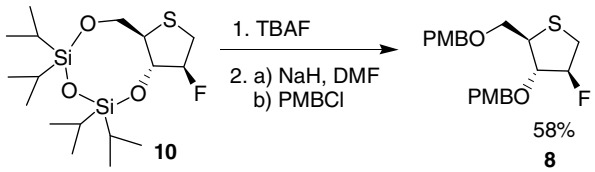
## 1. Experimental

### 1.1. General methods

Optical rotations were measured at 21 °C. $^1H$ and $^{13}C$ NMR were recorded with frequencies of 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional $^1H$, $^1H$ (gCOSY) and $^1H$, $^{13}C$ (gHMQC) experiments using standard Varian pulse programs. Processing of the data was performed with MestRec software. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with 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% $Ce(SO_4)_2$




**Scheme 1.**

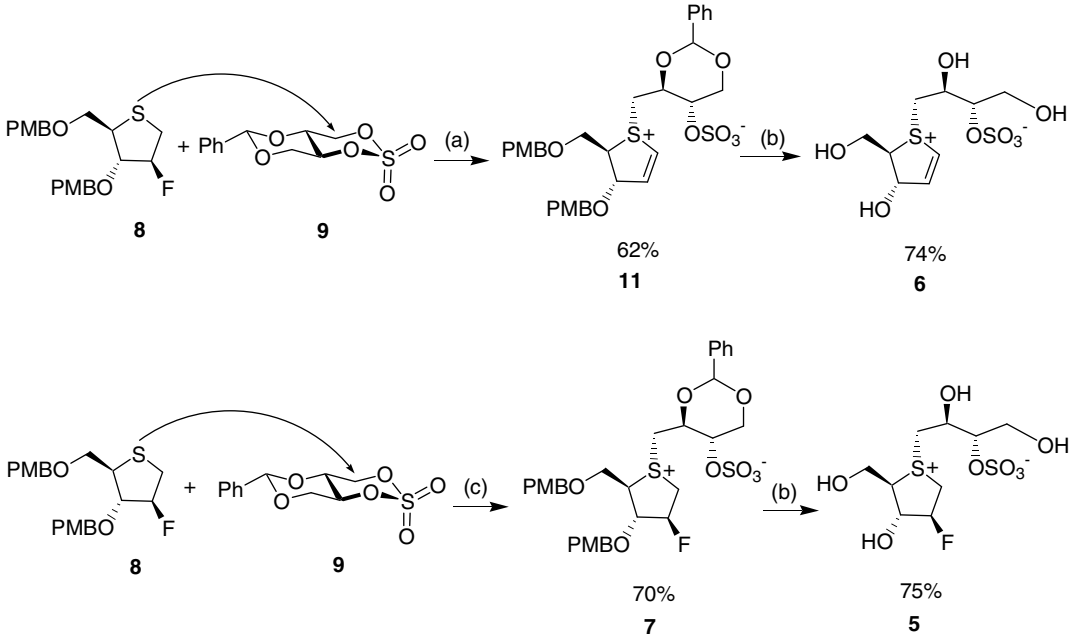



**Scheme 2.**

and 1.5% molybdic acid in 10% aqueous $H_2SO_4$, and heated. Column chromatography was performed with Silica Gel 60 (230–400 mesh). High resolution mass spectra were obtained by the electrospray ionization (ESI) technique, using a ZabSpec OA TOF mass spectrometer at 10,000 RP.

### 1.2. Enzyme assays

Enzyme assays of MGA with compounds **5** and **6** were determined using a *p*NP-glucoside assay to follow the production of *p*-nitrophenol upon the addition of enzyme (500 nM). Initially, $IC_{50}$ values were determined; in the case of **6**, a high value (150 μM) dictated that further detailed kinetic analysis was not justified, whereas in the case of **5**, further kinetic analysis was




**Scheme 3.** Reagents and conditions: (a) $K_2CO_3$ (excess), HFIP, 55–70 °C; (b) TFA (90%); (c) $K_2CO_3$ (0.3 M equiv), HFIP, 68 °C.

pursued. The latter assay was carried out in 96-well microtiter plates containing 100 mM MES buffer pH 6.5, inhibitor (at three different concentrations), and *p*-nitrophenyl-α-D-glucopyranoside (*p*NP-glucoside) as a substrate (2.5, 3.5, 5, 7.5, 15, and 30 mM) with a final volume of 50 μL. Reactions were incubated at 37 °C for 35 min and terminated by the addition of 50 μL of 0.5 M sodium carbonate. The absorbance of the reaction product was measured at 405 nm in a microtiter plate reader. All reactions were performed in triplicate, and absorbance measurements were averaged to give a final result. Reactions were linear within this time frame. The program GraFit 4.0.14 was used to fit the data to the Michaelis–Menten equation and estimate the kinetic parameters, $K_m$, $K_{mobs}$ ($K_m$ in the presence of inhibitor), and $V_{max}$ of the enzyme. $K_i$ value for the inhibitor was determined by the equation $K_i = [I]/((K_{mobs}/K_m) - 1)$. The $K_i$ reported for the inhibitor was determined by averaging the $K_i$ values obtained from three different inhibitor concentrations.

### 1.3. 1,4-Anhydro-2-deoxy-2-fluoro-3,5-di-*O*-(*p*-methoxybenzyl)-4-thio-D-arabinitol (8)

To a solution of compound **10** (1.9 g, 4.9 mmol) in distilled THF (25 mL) was added tetrabutylammonium fluoride (TBAF) in THF (9.8 mL, 1 M). The mixture was stirred at room temperature for 2 h and then quenched by the addition of ice. The organic phase was separated and the solvent was removed under reduced pressure. The crude product was dissolved in DMF (20 mL) and the solution was added dropwise to a suspension of sodium hydride (0.6 g, 26 mmol) in DMF (50 mL) at 0 °C. After addition was complete, the temperature was brought to room temperature and the mixture was stirred at room temperature for 1 h. PMBCl (2.3 g, 15 mmol) was added dropwise to the mixture, the mixture was stirred at room temperature overnight, and then the reaction was quenched by the addition of ice. The mixture was extracted with ether (150 mL), the organic phase was washed with brine, and dried over $Na_2SO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (5:1 hexane–EtOAc) to afford **8** as a syrup (1.1 g, 58%); $[\alpha]_D$ +21 (*c* 0.1, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$): δ 7.27–7.22, 6.90–6.85 (8H, m, Ar), 5.15 (1H, m, $J_{F,2} = 50.4$, $J_{3,2} = 3.2$, $J_{1a,2} = 7.4$ Hz, H-2), 4.59–4.50 (2H, d, $J_{AB} = 11.6$ Hz, $CH_2Ph$), 4.49–4.43 (2H, d, $CH_2Ph$), 4.21 (1H, m, $J_{F,3} = 11.4$ Hz, H-3), 3.82, 3.81 (6H, s, OMe), 3.61–3.56 (1H, m, H-4), 3.57 (1H, m, H-5a), 3.47 (1H, m, H-5b), 3.39–2.83 (2H, m, H-1a, H-1b); $^{13}$C NMR ($CDCl_3$): δ 159.6, 159.4, 130.3, 129.9, 129.7, 129.6, 114.1, 113.9 (8C, Ar), 97.7 (d, $J_{F,2} = 181.9$ Hz, C-2), 84.2 (d, $J_{F,3} = 24.2$ Hz, C-3), 73.0 ($CH_2Ph$), 71.8 (C-5), 71.7 ($CH_2$), 55.5 (2 × OMe), 49.5 (C-4), 34.5 (d, $J_{F,1} = 22.3$ Hz, C-1). HRMS Calcd for $C_{21}H_{25}O_4SFNa$ $[M+Na]^+$: 415.1349. Found: 415.1348.

### 1.4. 1,4-Dideoxy-1,2-ene-3,5-di-*O*-*p*-methoxybenzyl-1,4-[[(2*S*,3*S*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-episulfoniumylidene]-D-arabinitol inner salt (11)

Compound **8** (50 mg, 0.1 mmol), 2,4-benzylidene-L-erythritol-1,3-cyclic sulfate (**9**) (46 mg, 1.3 equiv), and $K_2CO_3$ (40 mg, 0.3 mmol) were dissolved in HFIP. The mixture was stirred in a sealed tube in an oil bath at 70 °C for 20 h. $K_2CO_3$ was removed by filtration and the solvent was removed under reduced pressure. Flash chromatography of the crude product (5:1 EtOAc–MeOH) afforded compound **11** as a syrup (51 mg, 62%); $[\alpha]_D$ +93 (*c* 0.3, MeOH); $^1$H NMR ($CD_3OD$): δ 7.40–7.32 (5H, m, Ar), 7.20, 7.13, 6.90, 6.84 (8H, dd, Ar), 7.00 (1H, dd, $J_{1,2} = 5.7$, $J_{3,2} = 2.7$ Hz, H-2), 6.57 (1H, d, H-1), 5.54 (1H, s, CHPh), 4.88 (1H, dd, H-3), 4.59 (1H, d, $J_{AB} = 11.6$ Hz, $CH_2Ph$), 4.50 (1H, d, $CH_2Ph$), 4.44 (1H, dd, $J_{4'b,4'a} = 10.6$, $J_{3',4'a} = 5.3$ Hz, H-4′a), 4.43 (1H, m, $J_{2',3'} = 4.1$ Hz, H-3′), 4.32 (1H, m, H-2′), 4.30, 4.28 (2H, d, $J_{AB} = 11.7$ Hz, $CH_2Ph$), 4.17 (1H, m, H-4), 4.11 (1H, d, $J_{1'b,1'a} = 13.9$, $J_{2',1'a} = 4.1$ Hz, H-1′a), 3.88 (1H, dd, $J_{2',1'b} = 3.4$ Hz, H-1′b), 3.80–3.73 (1H, m, H-4′b), 3.77, 3.76 (6H, s, 2 × OMe), 3.53 (1H, dd, $J_{5b,5a} = 10.7$, $J_{4,5a} = 3.9$ Hz, H-5a), 3.36 (1H, dd, $J_{4,5b} = 4.5$ Hz, H-5b); $^{13}$C NMR ($CD_3OD$): δ 160.1, 160.0 (2C, Ar), 146.5 (C-2), 137.8, 136.9 (2C, Ar), 130.2, 129.7, 128.2, 127.9 (4C, Ar), 129.3, 129.0, 128.9, 128.7, 126.2, 126.1 (6C, Ph), 119.4 (C-1), 114.0, 113.9 (4C, Ar), 101.1 (CHPh), 85.9 (C-3), 75.3 (C-2′), 72.8, 72.7 (2C, $CH_2Ph$), 68.6 (C-4′), 67.6 (C-3′), 66.2 (C-4), 65.3 (C-5), 54.6 (OMe), 49.4 (C-1′). HRMS Calcd for $C_{32}H_{37}O_{10}S_2$ $[M]^{+1}$: 645.1823. Found: 645.1828.

### 1.5. 1,4-Dideoxy-1,2-ene-1,4-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]episulfoniumylidene]-D-arabinitol inner salt (6)

Compound **11** (50 mg, 0.1 mmol) was dissolved in trifluoroacetic acid (2 mL, 90%) and the solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (3:1 EtOAc–MeOH) to afford compound **6** as a syrup (18.1 mg, 74%); $[\alpha]_D$ +50 (*c* 0.02, MeOH); $^1$H NMR ($CD_3OD$): δ 6.93 (1H, dd, $J_{1,2} = 5.7$, $J_{3,2} = 2.6$ Hz, H-2), 6.61 (1H, d, H-1), 5.18 (1H, m, $J_{4,3} = 1.0$ Hz, H-3), 4.39 (1H, m, $J_{3',2'} = 8.4$, $J_{1'b,2'} = 4.1$ Hz, H-2′), 4.32 (1H, m, $J_{4'b,3'} = 3.2$ Hz, H-3′), 4.16 (1H, m, H-4), 4.15 (1H, dd, $J_{5b,5a} = 12.7$, $J_{4,5a} = 3.6$ Hz, H-5a), 4.07 (1H, dd, $J_{1'b,1'a} = 13.4$, $J_{2',1'a} = 4.2$ Hz, H-1′a), 4.01 (1H, dd, $J_{4,5b} = 5.2$ Hz, H-5b), 3.95 (1H, dd, $J_{4'b,4'a} = 12.2$, $J_{3',4'a} = 3.4$ Hz, H-4′a), 3.86 (1H, dd, H-1′b), 3.84 (1H,

dd, H-4′b); $^{13}$C NMR ($CD_3OD$): $\delta$ 147.6 (C-2), 119.3 (C-1), 79.3 (C-3), 78.6 (C-3′), 70.9 (C-4), 65.7 (C-2′), 60.4 (C-4′), 58.7 (C-5), 53.6 (C-1′). HRMS Calcd for $C_9H_{17}O_8S_2$ $[M]^{+1}$: 317.0359. Found: 317.0362.

### 1.6. 1,2,4-Trideoxy-2-fluoro-3,5-di-*O*-*p*-methoxybenzyl-1,4-[[(2*S*,3*S*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-epi-sulfoniumylidene]-D-arabinitol inner salt (7)

Compound **8** (53 mg, 0.1 mmol), 2,4-benzylidene-L-erythritol-1,3-cyclic sulfate (**9**) (60 mg, 1.7 equiv), and $K_2CO_3$ (5 mg, 0.04 mmol) were dissolved in HFIP. The mixture was stirred in a sealed tube in an oil bath at 68 °C overnight. $K_2CO_3$ was removed by filtration and the solvent was removed under reduced pressure. Flash chromatography of the crude product (5:1 EtOAc–MeOH) afforded compound **7** as a syrup (63 mg, 70%); $[\alpha]_D$ +180 (*c* 0.008, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$): $\delta$ 7.46–7.43, 7.38–7.35 (5H, m, Ar), 7.21, 7.07 (4H, dd, Ar), 6.88–6.83 (4H, dd, Ar), 5.57 (1H, d, $J_{F,2} = 48.1$ Hz, H-2), 5.51 (1H, s, CHPh), 4.69 (1H, m, $J_{2',3'} = 9.8$, $J_{4'a,3'} = 5.4$ Hz, H-3′), 4.62 (1H, d, $J_{AB} = 11.9$ Hz, $CH_2Ph$), 4.60 (1H, dd, H-4′a), 4.53 (1H, d, $CH_2Ph$), 4.46 (1H, dd, $J_{5b,5a} = 13.9$, $J_{4,5a} = 3.0$ Hz, H-5a), 4.42 (1H, m, $J_{F,3} = 8.3$ Hz, H-3), 4.38 (1H, ddd, $J_{3,4} = 9.6$ Hz, H-4), 4.28 (1H, dd, $J_{4,5b} = 2.9$ Hz, H-5b), 4.26–4.19 (1H, m, H-1a), 4.23, 4.17 (2H, $J_{AB} = 11.5$ Hz, $CH_2Ph$), 4.12 (1H, m, H-2′), 4.10 (1H, m, $J_{1a,1b} = 9.9$ Hz, H-1b), 3.82 (1H, m, $J_{3',4'b} = 6.1$ Hz, H-4′b), 3.81, 3.78 (6H, s, OMe), 3.52 (1H, dd, $J_{1'b,1'a} = 10.1$ Hz, H-1′a), 3.48 (ddd, $J_{2',1'} = 7.1$, $J_{F,1'} = 2.2$ Hz, H-1′b); $^{13}$C NMR ($CDCl_3$): 160.1, 159.8, 136.8, 130.6, 130.2, 129.8 (6C, Ar), 129.6, 128.8, 128.6, 127.8, 126.4 (5C, Ph), 114.4, 114.2 (2C, Ar), 101.8 (CHPh), 95.6 (d, $J_{F,2} = 185.2$ Hz, C-2), 82.9 (d, $J_{F,3} = 25.5$ Hz, C-3), 76.5 (C-4), 73.4, 72.5 (2C, $CH_2Ph$), 69.3 (C-4′), 66.8 (C-3′), 65.8 (d, $J_{F,1'} = 6.8$ Hz, C-1′), 65.2 (C-2′), 55.5(2 × OMe), 49.7 (C-5), 47.9 (d, $J_{F,1} = 23.8$ Hz, C-1). HRMS Calcd for $C_{32}H_{37}O_{10}S_2FNa$ $[M+Na]^+$: 687.1704. Found: 687.1709.

### 1.7. 1,2,4-Trideoxy-2-fluoro-1,4-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]episulfoniumylidene]-D-arabinitol inner salt (5)

Compound **7** (50 mg, 0.1 mmol) was dissolved in trifluoroacetic acid (2 mL, 90%) and the solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (3:1 EtOAc–MeOH) to afford compound **5** as a syrup (19 mg, 75%); $[\alpha]_D$ +16 (*c* 0.24, MeOH); $^1$H NMR ($CD_3OD$): $\delta$ 5.51 (1H, d, $J_{F,2} = 48.4$ Hz, H-2), 4.77 (1H, d, $J_{F,3} = 4.8$ Hz, H-3), 4.38 (1H, ddd, $J_{2',3'} = 7.6$, $J_{4'a,3'} = 6.1$, $J_{4'b,3'} = 3.7$ Hz, H-3′), 4.32 (1H, ddd, H-2′), 4.19 (1H, dd, H-5a), 4.18 (1H, m, H-4), 4.12 (1H, dd, $J_{1b,1a} = 13.2$, $J_{2,1a} = 3.6$ Hz, H-1a), 4.09 (1H, dd, $J_{5a,5b} = 14.0$, $J_{4,5b} = 4.0$ Hz, H-5b), 4.01 (1H, dd, $J_{2,1b} = 6.0$ Hz, H-1b), 3.97 (1H, dd, $J_{4'b,4'a} = 11.9$, $J_{3',4'a} = 6.1$ Hz, H-4′a), 3.96 (1H, dd, $J_{1'b,1'a} = 12.2$, $J_{2',1'a} = 3.5$ Hz, H-1′a), 3.85 (1H, dd, $J_{2',1'b} = 1.9$ Hz, H-1′b), 3.83 (1H, dd, H-4′b); $^{13}$C NMR ($CD_3OD$): $\delta$ 97.7 (d, $J_{F,2} = 184$ Hz, C-2), 79.1 (C-2′), 76.5 (d, $J_{F,3} = 25$ Hz, C-3), 70.7 (C-4), 66.3 (C-3′), 60.5 (C-4′), 58.7 (d, $J_{F,1'} = 6.9$ Hz, C-1′), 51.9 (C-1), 47.2 (C-5). HRMS Calcd for $C_9H_{17}O_8S_2FNa$ $[M+Na]^+$: 359.0241. Found: 359.0247.


## Acknowledgment

We are grateful to the Canadian Institutes for Health Research for financial support.


## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.01.025.

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