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Facile synthesis of sulfonium ion derivatives of 1,5-anhydro-5-thio-L-fucitol as potential α-L-fucosidase inhibitors

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Abstract—Five sulfonium ion derivatives with 1,5-anhydro-5-thio-L-fucitol as a core structure were efficiently synthesized as potential α-L-fucosidase inhibitors. The key unit, the tri-*O*-benzyl derivative of L-fucitol, was readily synthesized from methyl α-D-mannopyranoside. Alkylation with methyl iodide or 5-methoxycarbonyl-1-pentyl iodide in acetonitrile containing $AgBF_4$ afforded the corresponding alkylated sulfonium tetrafluoroborates. Alternatively, ring opening of three 1,3-cyclic sulfates in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) containing K_2CO_3 afforded the corresponding zwitterionic sulfonium sulfates.

Keywords: 5-Thio-L-fucitol; Alkylation; Sulfonium tetrafluoroborates; Sulfonium sulfates; Potential α-L-fucosidase inhibitors

1. Introduction

Fucosylated oligosaccharides and glycoconjugates are implicated in several biological events such as antigenic determination, tumorigenesis/metastasis, and inflammatory responses.[1–3] The important roles played by the fucose residue have led to a focus on α-L-fucosidase,[4,5] an exoglycosidase that removes non-reducing terminal L-fucose residues linked via α-(1→2), α-(1→3), α-(1→4), or α-(1→6) linkages to oligosaccharides and their corresponding conjugates. This enzyme is associated with a variety of biological functions. For instance, an aberrant distribution of α-L-fucosidase has been linked to inflammation, cancer, and cystic fibrosis.[6–8] The accumulation of fucose-containing glycoconjugates in various tissues, because of low enzyme activity, results in the genetic neurovisceral storage disease fucosidosis.[9] It has also been reported that the degradation of the sub-endothelial extracellular matrix in invasive human ovarian carcinoma cells involves the action of fucosidase,[10] and the fucosidase level in blood serum can be used for the diagnosis of patients with early colorectal and hepatocellular cancers.[7,11]

Information related to the reaction mechanism of this enzyme has recently become available;[4] however, its detailed catalytic mechanism remains to be established. The development of fucosidase inhibitors could prove useful in this endeavor, as well as for the development of potential therapeutic drugs.

Several potent fucosidase inhibitors already exist.[12] These include 1-deoxyfuconojirimycin[13] (FNJ, **1**), the most powerful and specific inhibitor of α-L-fucosidase, and its *N*-methyl and 5-methoxycarbonyl-1-pentyl derivatives (**2**, **3**), which are also potent fucosidase inhibitors. The latter compounds also inhibit the cytopathic effect of human immunodeficiency virus (HIV-1) and the yield of infectious virus.[14,15]

Recently, sulfonium ions have been recognized as a new class of glycosidase inhibitors.[16–19] The inhibitory activities of sulfonium salts have been rationalized in terms of mimicking the transition state in a glycosidase-mediated reaction by virtue of the permanent positive charge that provides the necessary electrostatic interaction with the carboxylate residue in the enzyme active site.[16a] Naturally occurring examples of this class of compound are salacinol[17] and kotalanol,[18] which are

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effective α-glucosidase inhibitors. We report herein the synthesis of five sulfonium ion derivatives (**4**–**8**), having a 1,5-anhydro-5-thio-L-fucitol moiety as their core, as potential fucosidase inhibitors (Fig. 1).

2. Results and discussion

Retrosynthetic analysis indicated that the target molecules could be obtained by alkylation of the protected 1,5-anhydro-5-thio-L-fucitol with alkyl iodides or appropriately protected 1,3-cyclic sulfates (Scheme 1). The 1,5-anhydro-5-thio-L-fucitol unit can be readily prepared from a selectively protected mannopyranose derivative through the following steps: (i) nucleophilic addition of a methyl group via a Grignard reagent, (ii) selective oxidative cleavage with sodium periodate, followed by reduction with sodium borohydride, (iii) mesylation with methanesulfonyl chloride, followed by ring formation with sodium sulfide.

The nucleophilic addition of an organometallic reagent to an aldose or ketose has often been used to extend the carbon chain of carbohydrates. For example, it was reported that addition of a methyl organometallic reagent to 2,3-*O*-isopropylidene derivatives of furanose sugars afforded highly stereoselective *syn*/*anti*-products by using different organometallic reagents,[20] but for the pyranose sugars the products were usually *syn*/*anti*-mixtures.[21] We chose the selectively benzylated mannopyranose derivative **9** as the starting material, which was prepared, in turn, from commercially available methyl α-D-mannopyranoside according to the literature procedures.[22] Treatment of hemiacetal **9** with methylmagnesium bromide in THF at room temperature afforded compound **10** as an inseparable (3:2) mixture of diastereomers in a total yield of 80%; attempts to separate the diastereomers after acetylation of **10** were unsuccessful. Treatment of triol **10** with 1.0 equiv of sodium periodate in THF–H_2O (2:1 v/v), followed by reduction of the resulting aldehyde with sodium borohydride in methanol, gave an isomeric mixture **11** in 85% yield. Mesylation of the diol mixture **11** with mesyl chloride in pyridine, followed by ring-closure with sodium sulfide in DMF at 100 °C, generated the tri-*O*-benzyl derivatives of L-fucitol (**12**) and D-altritol (**13**) in a 2:1 ratio in 88% yield (Scheme 2).

Analysis of the vicinal coupling constants in the ^{1}H NMR spectra of **12** indicated values of $J_{1ax,2} = 9.5$,

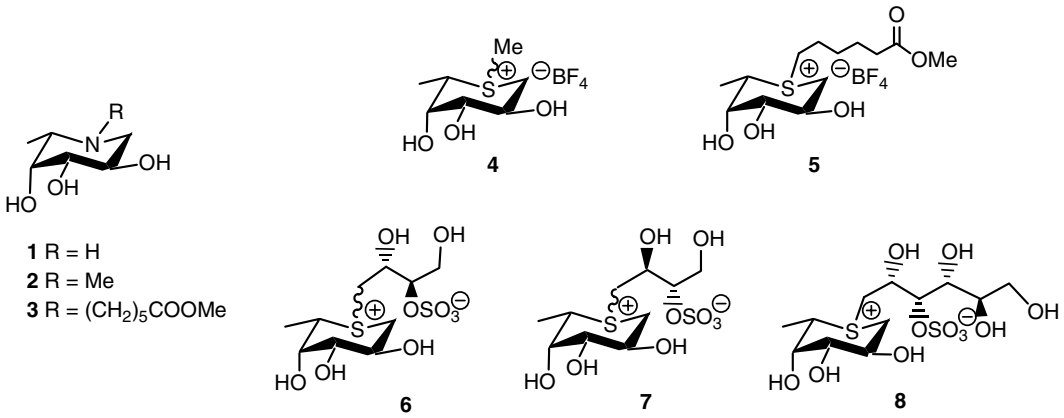
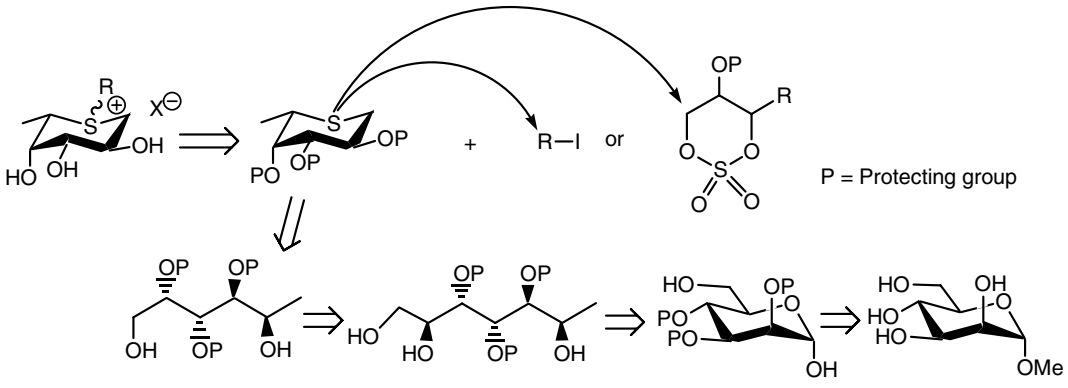
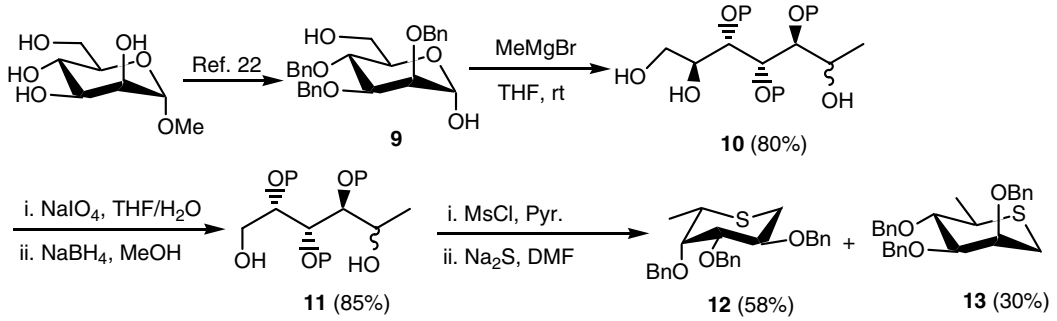


Figure 1. FNJ derivatives **1**–**3** and target molecules **4**–**8**.



Scheme 1. Retrosynthetic analysis of target molecules.



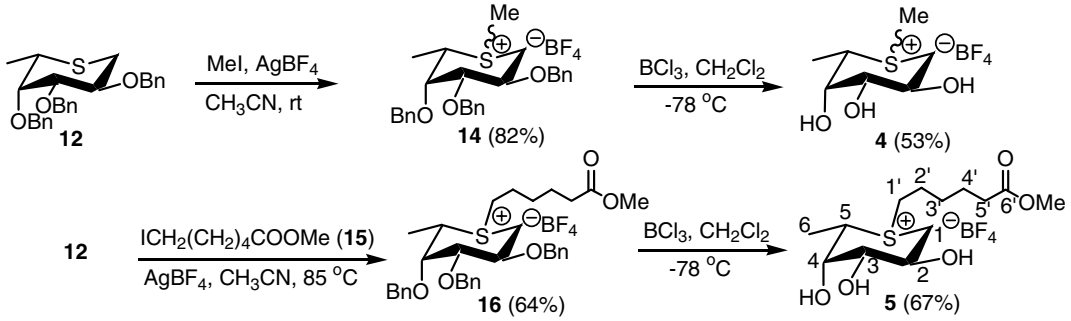
Scheme 2. Synthesis of 1,5-anhydro-5-thio-L-fucitol derivative **12**.

$J_{2,3} = 9.0$, and $J_{4,5} = 2.0$ Hz, which suggested the presence of a $^1C_4$ (L) conformation. The configuration at C-5 in **12** was established to be 5*S* since NOEs were observed for H-1ax, H-3, and H-4 upon irradiation of the H-5 resonance. Compound **13** was assigned to have a $^4C_1$ (D) conformation and a 5*R* configuration at C-5 by ^{1}H NMR spectroscopic analysis.

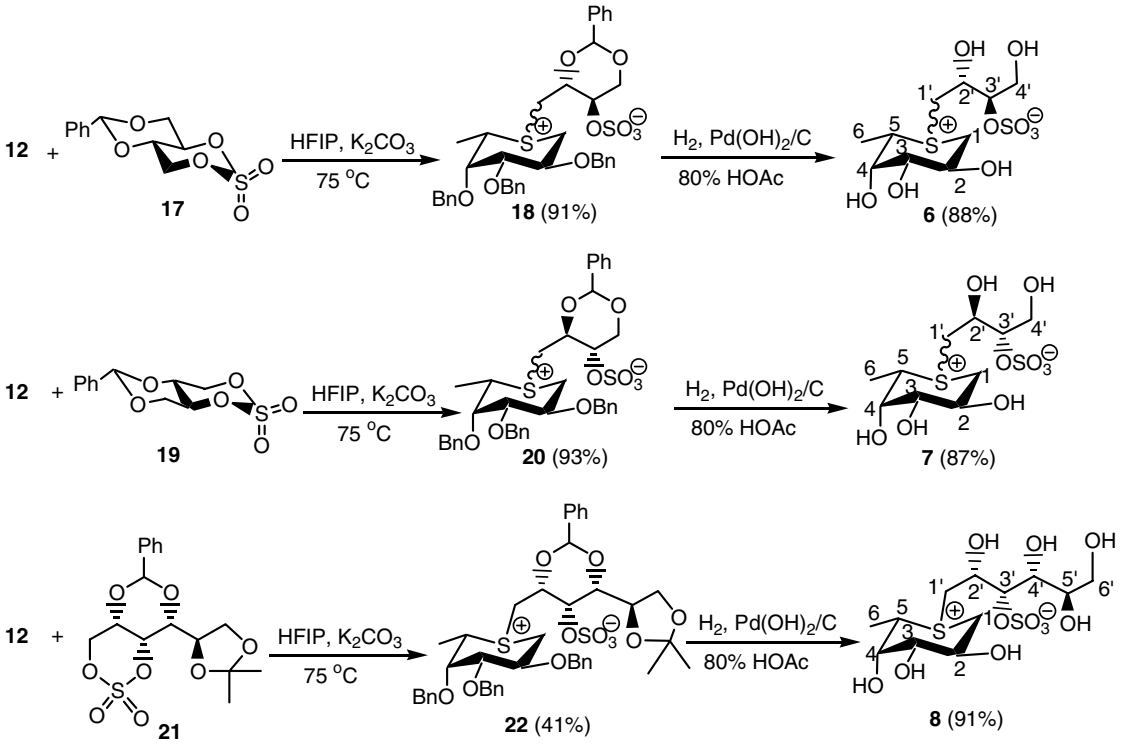
With thiofucitol **12** in hand, alkylation with methyl iodide was examined first. Thus, treatment of **12** with methyl iodide in the presence of silver tetrafluoroborate ($AgBF_4$) in acetonitrile at room temperature afforded methyl sulfonium tetrafluoroborate **14** (82%). The ratio of the diastereomers was 2:1, as judged by the ratio of the methyl group resonances in the ^{1}H NMR spectrum. Sulfonium ion formation was also confirmed by the downfield shifts of H-1 and H-5 in the ^{1}H NMR spectrum and of C-1 and C-5 in the ^{13}C NMR spectrum relative to precursor sulfide **12**. Similarly, sulfonium tetrafluoroborate **16** was obtained from the coupling of **12** and 5-methoxycarbonyl-1-pentyl iodide (**15**)[23] in 64% yield. In this case, only one isomer was formed. The configuration at the sulfonium center was assigned by means of a 1D NOESY experiment. The spectrum showed NOEs between H-5 and H-1′ax and H-1′eq, as well as the H-1ax, H-3, and H-4 resonances; however, no NOEs were observed between the H-1′ax and H-1′eq resonances and H-2, indicating that the 5-methoxycarbonyl-1-pentanol side chain was on the same face as H-5, and occupied the equatorial position on the sulfur atom. Debenzylation of sulfonium salts **14** and **16** with boron trichloride (BCl_3) in dichloromethane at −78 °C proceeded smoothly to yield the deprotected sulfonium salts **4** (2:1 *R*,*S*-mixtures) and **5** in 53% and 67% yields, respectively (Scheme 3).[24]

The coupling reactions of the benzylated 1,5-anhydro-5-thio-L-fucitol **12** with three different 1,3-cyclic sulfates were investigated next (Scheme 4). The condensation of **12** with 2,4-*O*-benzylidene-D and L-erythritol-1,3-cyclic sulfate **17**[19a] and **19**[25] in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) containing anhydrous potassium carbonate (K_2CO_3) at 75 °C afforded products **18** and **20** as mixtures of diastereomers (~2.2:1) in each case in yields of 91% and 93%, respectively. When 2,4-*O*-benzylidene-5,6-*O*-isopropylidene-D-sorbitol-1,3-cyclic sulfate **21**[26] was coupled with **12** in HFIP at 75 °C, the desired coupling product **22** was only obtained in 41% yield, accompanied by decomposition of the cyclic sulfate. Reactions at lower temperature (60 °C) or prolonged reaction time (7 days) at this temperature did not result in an improved yield, **22** being formed in 28% yield. The configuration of **22** was assigned, as before, by means of a 1D NOESY experiment. The sulfonium sulfates **18**, **20**, and **22** were then deprotected by hydrogenolysis in 80% HOAc with $Pd(OH)_2$/C as catalyst to give the target compounds **6**, **7**, and **8**, respectively, in high yields.

The configurations of the sulfonium salts **4**–**8** and **14**, **16**, **18**, **20**, **22** were also determined by a ^{13}C NMR-based method.[16e] In this method, the stereochemistry



Scheme 3. Synthesis of sulfonium tetrafluoroborates **4** and **5**.



Scheme 4. Synthesis of the sulfonium sulfates **6**, **7**, and **8**.

of S-substitution was assigned based on the chemical shifts of adjacent S-connected carbons (C-1 and C-5). In all cases, the chemical shifts of C-1 and C-5 in the major isomers appeared downfield (2–5 ppm for C-1 and 5–10 ppm for C-5) from those of the minor isomers (Table 1). In addition, the chemical shifts of C-2 in the minor isomers were shielded relative to those in the major isomers by virtue of the γ-gauche effect.[27] The major isomer in each case was thus assigned as having an equatorial *S*-alkyl orientation, with the minor isomer having an axial orientation of the S-substituent.

In summary, we have described a facile synthetic route for the preparation of sulfonium salts of 1,5-anhydro-5-thio-L-fucitol. The biological activity of these sulfonium salts as potential α-L-fucosidase inhibitors will be pursued in the near future.

3. Experimental

3.1. General

Optical rotations were measured with a Rudolph Research Autopol II automatic polarimeter at 23 °C. ^{1}H and ^{13}C NMR were recorded on the Bruker AMX-400 NMR spectrometer at 400.13 MHz and Varian INOVA 500 NMR spectrometer at 499.97 MHz for ^{1}H. Chemical shifts are given in parts per million (ppm) downfield from TMS for those spectra measured in $CDCl_3$ or CD_2Cl_2, and from 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for those measured in D_2O. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. All assignments were supported by two-dimensional ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMQC

Table 1. Selected ^{13}C NMR data for sulfonium ion compounds

Compound (major isomer)	Chemical shifts (ppm)				Compound (minor isomer)	Chemical shifts (ppm)			
	C-1	C-2	C-4	C-5		C-1	C-2	C-4	C-5
14-eq	37.9	73.2	76.7	53.4	**14**-ax	34.5	70.3	79.3	47.8
16-eq	36.4	73.6	77.5	53.0	**16**-ax	—	—	—	—
18-eq	36.2	74.3	74.6	51.5	**18**-ax	35.6	71.8	75.0	46.4
20-eq	36.5	74.3	75.3	51.1	**20**-ax	34.1	73.5	76.1	46.5
22-eq	37.0	75.2	76.0	51.7	**22**-ax	—	—	—	—
4-eq	41.7	64.8	72.8	55.6	**4**-ax	36.8	61.9	72.9	45.8
5-eq	39.1	64.8	72.8	54.3	**5**-ax	—	—	—	—
6-eq	41.9	64.7	72.7	54.8	**6**-ax	35.9	61.9	72.9	47.3
7-eq	40.6	64.8	72.7	54.6	**7**-ax	39.4	62.2	73.1	47.7
8-eq	41.8	64.9	72.9	54.9	**8**-ax	—	—	—	—

experiments using standard Bruker or Varian pulse program. The 1D NOESY spectra were obtained with a mixing time of 500 ms. NMR data for compounds **4**, **6**, **7**, **10**, **11**, **14**, **18**, and **20** are given for their major isomers. MALDI-TOF mass spectra were obtained on a PerSeptive Biochsysterms Voyager DE time-of-flight spectrometer with 2,5-dihydroxybenzonic acid (DHB) as the matrix. High-resolution mass spectra were performed by positive-mode electrospray ionization on a Hybird Sector-TOF mass spectrometer. 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% aqueous H_2SO_4, and heated. The compounds were purified on flash chromatography on Kieselgel 60 (230–400 mesh). The solvents were evaporated under reduced pressure below 50 °C.

3.2. (2*R*,3*R*,4*R*,5*R*,6*R*/*S*)-3,4,5-Tris-benzyloxy-heptane-1,2,6-triol (10)

To a solution of 2,3,4-tri-*O*-benzyl-α-D-mannopyranose **9**[22] (4.5 g, 10 mmol) in THF (50 mL) was slowly added methylmagnesium bromide (20 mL, 60 mmol, 3.0 M in Et_2O) at 0 °C under N_2. The reaction mixture was stirred at rt for 20 h, and then quenched with satd aqueous NH_4Cl. The resulting mixture was diluted with EtOAc (200 mL), and washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography with 2:1 EtOAc/hexane as the eluent to give the diastereomeric mixture of triol **10** (3.62 g, 80%) as a white solid. $[\alpha]_D$ +5 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, CD_2Cl_2): δ 7.31–7.39 (15H, m, Ar), 4.61–4.75 (6H, m, $3\times PhCH_2$), 4.08 (1H, m, H-6), 3.95 (1H, dd, $J = 5.5$, 4.0 Hz, H-4), 3.92 (1H, m, H-2), 3.77 (1H, dd, $J = 7.5$, 4.0 Hz, H-3), 3.74 (1H, m, H-1a), 3.68 (1H, dd, $J = 11.5$, 5.5 Hz, H-1b), 3.62 (1H, dd, $J = 5.5$, 3.0 Hz, H-5), 2.98 (1H, d, $J = 5.5$ Hz, O*H*), 2.71 (1H, d, $J = 6.5$ Hz, O*H*), 2.02 (1H, t, $J = 5.5$ Hz, O*H*), 1.24 (3H, d, $J = 6.5$ Hz, H-7); MALDI-TOF MS Calcd for $C_{28}H_{34}O_6$: 466.57 [M]; Found: 467.46 $[M+H]^+$, 489.50 $[M+Na]^+$, 505.43 $[M+K]^+$. Anal. Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35. Found: C, 71.96; H, 7.45.

3.3. (2*R*,3*S*,4*R*,5*R*/*S*)-2,3,4-Tris-benzyloxy-hexane-1,5-diol (11)

To a solution of compound **10** (3.36 g, 7.21 mmol) in THF–H_2O (80 mL, v/v 3:1) was added $NaIO_4$ (1.54 g, 7.21 mmol) at rt. The reaction mixture was stirred for 2 h, at which time TLC (2:1 EtOAc/hexane) indicated that the starting material has been consumed. The mixture was then filtered, and the filtrate was concentrated. The residue was diluted with CH_2Cl_2 (100 mL) and washed with brine (2×80 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude resulting aldehyde was then dissolved in MeOH (30 mL), and $NaBH_4$ (1.5 g, 39.7 mmol) was added in portions at rt. The resulting mixture was stirred for 1 h, and the solvent was then removed under reduced pressure. The residue was diluted with EtOAc (100 mL), and washed with aq HCl (2M), water, and brine. The organic layer was dried over Na_2SO_4 and concentrated. Column chromatography of the crude product with 2:1 hexane/EtOAc as the eluent afforded compound **11** (2.67 g, 85%) as a colorless oil. $[\alpha]_D$ −4 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, CD_2Cl_2): δ 7.30–7.38 (15H, m, Ar), 4.58–4.79 (6H, m, $3\times PhCH_2$), 4.00–4.05 (1H, m, H-5), 3.99 (1H, dd, $J = 5.5$, 3.5 Hz, H-3), 3.81–3.85 (1H, m, H-1a), 3.76–3.80 (2H, m, H-1b and H-2), 3.59 (1H, dd, $J = 7.5$, 3.5 Hz, H-4), 1.24 (3H, d, $J = 6.5$ Hz, H-6); MALDI-TOF MS Calcd for $C_{27}H_{32}O_5$: 436.54 [M]; Found: 437.34 $[M+H]^+$, 459.33 $[M+Na]^+$, 475.20 $[M+K]^+$. Anal. Calcd for $C_{27}H_{32}O_5$: C, 74.29; H, 7.39. Found: C, 74.01; H, 7.47.

3.4. 1,5-Anhydro-2,3,4-tri-*O*-benzyl-5-thio-L-fucitol (12) and 1,5-anhydro-6-deoxy-2,3,4-tri-*O*-benzyl-5-thio-D-altritol (13)

To a solution of compound **11** (2.36 g, 5.41 mmol) in pyridine (20 mL) was added MsCl (1.3 mL, 16.7 mmol) at 0 °C under N_2. The reaction mixture was stirred for 1 h, and then the excess MsCl was decomposed by addition of ice. The reaction mixture was partitioned between CH_2Cl_2 (80 mL) and H_2O (50 mL). The organic layer was washed with satd aq $NaHCO_3$ and brine, and then dried over anhydrous $MgSO_4$ and concentrated. The residue was co-evaporated with toluene (3×50 mL) and then dissolved in dry DMF (80 mL). To the above solution was added $Na_2S{\cdot}9H_2O$ (1.95 g, 8.12 mmol). The reaction mixture was heated at 100 °C for 1 h. After being cooled to room temperature, the mixture was diluted with Et_2O (100 mL) and washed with water, followed by brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. Purification of the residue by column chromatography with 10:1 hexane/EtOAc as the eluent gave the syrupy **12** (1.36 g, 58%) and **13** (703 mg, 30%). Data for **12**: $[\alpha]_D$ −25 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.26–7.38 (15H, m, Ar), 4.98, 4.74 (2H, 2d, $J = 11.5$ Hz, $PhCH_2$), 4.83, 4.73 (2H, 2d, $J = 12.0$ Hz, $PhCH_2$), 4.70, 4.67 (2H, 2d, $J = 11.5$ Hz, $PhCH_2$), 4.07 (1H, ddd, $J = 9.5$, 9.0, 4.0 Hz, H-2), 3.91 (1H, t, $J = 2.0$ Hz, H-4), 3.39 (1H, dd, $J = 9.0$, 2.0 Hz, H-3), 2.96 (1H, dq, $J = 7.0$, 2.0 Hz, H-5), 2.83 (1H, dd, $J = 13.5$, 4.0 Hz, H-1a), 2.59 (1H, dd, $J = 13.5$, 9.5 Hz, H-1b), 1.18 (3H, d, $J = 7.0$ Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.4–138.9 (18C, Ar), 84.4

(C-3), 79.7 (C-2), 76.7 (PhCH$_2$), 74.1 (C-4), 73.7, 72.6 (2C, PhCH$_2$), 40.6 (C-5), 30.1 (C-1), 17.0 (C-6). Anal. Calcd for $C_{27}H_{30}O_3S$: C, 74.62; H, 6.96. Found; C, 74.50; H, 6.97. Data for **13**: $[\alpha]_D$ −18 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20–7.38 (15H, m, Ar), 4.70, 4.53 (2H, 2d, $J = 12.0$ Hz, PhCH$_2$), 4.56, 4.41 (2H, 2d, $J = 12.0$ Hz, PhCH$_2$), 4.54, 4.52 (2H, 2d, $J = 11.5$ Hz, PhCH$_2$), 3.84 (1H, ddd, $J = 4.0$, 3.5, 1.0 Hz, H-2), 3.67–3.71 (2H, m, H-3 and H-4), 3.35 (1H, m, H-5), 3.14 (1H, dd, $J = 14.0$, 1.0 Hz, H-1a), 2.42 (1H, dd, $J = 14.0$, 3.5 Hz, H-1b), 1.28 (3H, d, $J = 7.0$ Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.6–138.6 (18C, Ar), 81.7 (C-3), 75.2 (C-2), 74.8 (C-4), 73.2, 72.4, 71.0 (3C, PhCH$_2$), 34.6 (C-5), 27.6 (C-1), 17.0 (C-6). Anal. Calcd for $C_{27}H_{30}O_3S$: C, 74.62; H, 6.96. Found: C, 74.35; H, 7.11.

3.5. General procedure for preparation of the protected sulfonium tetrafluoroborates (14) and (16)

A mixture of **12** (1 mmol), the alkyl iodide (1.5 equiv) and silver tetrafluoroborate (1.5 equiv) in dry acetonitrile (3 mL) was stirred for 16 h (for **14** at rt; for **16** at 85 °C). The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography.

3.5.1. 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[methyl-episulfoniumylidene]-L-fucitol tetrafluoroborate salt (14). Column chromatography [$CHCl_3$/MeOH, 10:1] of the crude product gave the syrupy **14** (440 mg, 82%). $[\alpha]_D$ −40 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.26 (15H, m, Ar), 4.93, 4.61 (2H, 2d, $J = 11.2$ Hz, PhCH$_2$), 4.83, 4.71 (2H, 2d, $J = 11.2$ Hz, PhCH$_2$), 4.66, 4.61 (2H, 2d, $J = 12.0$ Hz, PhCH$_2$), 4.16 (1H, ddd, $J = 10.8$, 8.8, 4.0 Hz, H-2), 4.06 (1H, br s, H-4), 3.95 (1H, q, $J = 6.4$ Hz, H-5), 3.88 (1H, dd, $J = 8.8$, 1.6 Hz, H-3), 3.78 (1H, dd, $J = 12.4$, 4.0 Hz, H-1a), 3.35 (1H, dd, $J = 12.4$, 10.8 Hz, H-1b), 2.91 (3H, s, Me), 1.40 (3H, d, $J = 6.4$ Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.7–138.9 (18C, Ar), 81.7 (C-3), 76.7 (C-4), 75.0, 74.4 (2C, PhCH$_2$), 73.2 (C-2), 73.0 (PhCH$_2$), 53.4 (C-5), 37.9 (C-1), 22.4 (Me), 13.6 (C-6). Anal. Calcd for $C_{28}H_{33}BF_4O_3S$: C, 62.69; H, 6.20. Found: C, 63.02; H, 6.29.

3.5.2. 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-[5-methoxycarbonyl-1-pentyl-episulfoniumylidene]-L-fucitol tetrafluoroborate salt (16). Column chromatography [$CHCl_3$/MeOH, 10:1] of the crude product gave the syrupy **16** (417 mg, 64%). $[\alpha]_D$ −10 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.22–7.28 (15H, m, Ar), 5.00, 4.48 (2H, 2d, $J = 11.5$ Hz, PhCH$_2$), 4.86, 4.68 (2H, 2d, $J = 11.5$ Hz, PhCH$_2$), 4.75 (2H, s, PhCH$_2$), 4.24 (1H, ddd, $J = 10.0$, 8.5, 4.0 Hz, H-2), 4.18 (1H, t, $J = 2.0$ Hz, H-4), 4.06 (1H, dq, $J = 7.0$, 2.0 Hz, H-5), 3.92 (1H, dd, $J = 8.5$, 2.0 Hz, H-3), 3.64 (3H, s, OCH$_3$), 3.54 (1H, dd, $J = 12.0$, 4.0 Hz, H-1a), 3.50 (1H, m, H-1a′), 3.37 (1H, dd, $J = 12.0$, 10.0 Hz, H-1b), 3.32 (1H, m, H-1b′), 2.23 (2H, t, $J = 7.0$ Hz, H-5′), 1.71–1.85 (2H, m, H-2′), 1.60–1.68 (2H, m, H-4′), 1.54 (3H, d, $J = 7.0$ Hz, H-6), 1.43–1.51 (2H, m, H-3′); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 173.8 (C-6′), 128.2–138.3 (18C, Ar), 81.8 (C-3), 77.5 (C-4), 75.8, 74.6, 73.8 (3C, PhCH$_2$), 73.6 (C-2), 53.0 (C-5), 51.8 (OCH$_3$), 40.6 (C-1′), 36.4 (C-1), 33.5 (C-5′), 27.9 (C-3′), 24.8 (C-4′), 24.2 (C-2′), 14.5 (C-6). Anal. Calcd for $C_{34}H_{43}BF_4O_5S$: C, 62.77; H, 6.66. Found: C, 62.42; H, 6.73.

3.6. General procedure for debenzylation of compounds (14) and (16) using BCl_3 in CH_2Cl_2

To a solution of the protected compound (0.2 mmol) in dried CH_2Cl_2 (5 mL) at −78 °C was bubbled BCl_3 for 2–3 min under N_2 atmosphere. The resulting mixture was stirred for 2 h and a stream of dry air was blown vigorously through the solution to remove excess BCl_3. The reaction was then quenched with MeOH (10 mL) at −78 °C and the solvent was removed under reduced pressure. The residue was co-evaporated with MeOH (3×10 mL), and the crude product was purified by column chromatography.

3.6.1. 1,5-Dideoxy-1,5-[methyl-episulfoniumylidene]-L-fucitol tetrafluoroborate salt (4). Column chromatography [MeOH/H_2O, 1:2] of the residue, followed by ion exchange with $AgBF_4$ in water, afforded **4** (27 mg, 53%) as a syrup. $[\alpha]_D$ −20 (*c* 0.1, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.22 (1H, br d, $J = 2.0$ Hz, H-4), 4.11 (1H, ddd, $J = 12.0$, 9.6, 8.0 Hz, H-2), 3.74 (1H, q, $J = 6.8$ Hz, H-5), 3.68 (1H, dd, $J = 12.0$, 8.0 Hz, H-1a), 3.61 (1H, dd, $J = 9.6$, 2.0 Hz, H-3), 3.16 (1H, t, $J = 12.0$ Hz, H-1b), 2.94 (3H, s, Me), 1.51 (3H, d, $J = 6.8$ Hz, H-6); ^{13}C NMR (100 MHz, D_2O): δ 74.3 (C-3), 72.8 (C-4), 64.8 (C-2), 55.6 (C-5), 41.7 (C-1), 22.6 (Me), 13.1 (C-6). HRMS Calcd for $C_7H_{15}BF_4O_3S$: 179.0736 $[M-BF_4]^+$; Found: 179.0737.

3.6.2. 1,5-Dideoxy-1,5-[5-methoxycarbonyl-1-pentyl-episulfoniumylidene]-L-fucitol tetrafluoroborate salt (5). Column chromatography [MeOH/H_2O, 1:2] of the residue, followed by ion exchange with $AgBF_4$ in water, afforded **5** (50 mg, 67%) as a white solid. $[\alpha]_D$ +10 (*c* 0.1, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.16 (1H, br d, $J = 3.0$ Hz, H-4), 4.06 (1H, ddd, $J = 11.5$, 9.8, 4.0 Hz, H-2), 3.73 (1H, q, $J = 7.0$ Hz, H-5), 3.61 (1H, dd, $J = 11.5$, 4.0 Hz, H-1a), 3.57 (3H, s, OCH$_3$), 3.55 (1H, dd, $J = 9.8$, 3.0 Hz, H-3), 3.40 (1H, m, H-1a′), 3.22 (1H, m, H-1b′), 3.04 (1H, t, $J = 11.5$ Hz, H-1b), 2.31 (2H, t, $J = 7.5$ Hz, H-5′), 1.67–1.77 (2H, m, H-2′), 1.52–1.60 (2H, m, H-4′), 1.46 (3H, d, $J = 7.0$ Hz, H-6), 1.33–1.41 (2H, m, H-3′); ^{13}C NMR (100 MHz, D_2O):

δ 174.3 (C-6′), 73.9 (C-3), 72.8 (C-4), 64.8 (C-2), 54.3 (C-5), 52.3 (O*C*H$_3$), 39.8 (C-1′), 39.1 (C-1), 33.3 (C-5′), 27.1 (C-3′), 23.6 (C-4′), 23.4 (C-2′), 13.4 (C-6); MALDI-TOF MS Calcd for $C_{13}H_{25}BF_4O_5S$: 380.21 [M]; Found: 381.34 $[M+H]^+$, 293.25 $[M-BF_4^-]^+$. HRMS Calcd for $C_{13}H_{25}BF_4O_5S$: 293.1417 $[M-BF_4]^+$; Found: 293.1416.

3.7. General procedure for preparation of the protected sulfonium sulfates (18), (20), and (22)

A mixture of **12** (1 mmol), the cyclic sulfate (1.2 equiv), and anhydrous K_2CO_3 (40 mg) in HFIP (1.5 mL) was stirred in a sealed tube in an oil-bath (75 °C) for 40 h. The solvent was removed under reduced pressure, and the product was purified by column chromatography.

3.7.1. 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-{[(2*R*,3*R*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene}-L-fucitol inner salt (18). Column chromatography [$CHCl_3$/MeOH, 10:1] of the crude product gave **18** (645 mg, 91%) as an amorphous solid. $[\alpha]_D$ −54 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.08–7.56 (20H, m, Ar), 5.55 (1H, s, PhC*H*), 4.75, 4.53 (2H, 2d, $J = 11.0$ Hz, PhCH_2), 4.74, 4.71, (2H, 2d, $J = 11.5$ Hz, PhCH_2), 4.67, 4.52 (2H, 2d, $J = 11.5$ Hz, PhCH_2), 4.54 (1H, dd, $J = 11.0$, 4.5 Hz, H-4a′), 4.53 (1H, ddd, $J = 7.5$, 4.5, 3.5 Hz, H-3′), 4.25 (1H, dt, $J = 8.0$, 3.5 Hz, H-2′), 4.17 (1H, ddd, $J = 8.0$, 7.0, 3.5 Hz, H-2), 4.16 (1H, dd, $J = 14.2$, 8.0 Hz, H-1a′), 4.09 (1H, t, $J = 2.5$ Hz, H-4), 3.97 (1H, dd, $J = 14.2$, 3.5 Hz, H-1b′), 3.96 (1H, dq, $J = 7.0$, 2.5 Hz, H-5), 3.90 (1H, dd, $J = 13.0$, 3.5 Hz, H-1a), 3.88 (1H, dd, $J = 7.0$, 2.5 Hz, H-3), 3.79 (1H, dd, $J = 11.0$, 7.5 Hz, H-4b′), 3.67 (1H, dd, $J = 13.0$, 8.0 Hz, H-1b), 1.47 (3H, d, $J = 7.0$ Hz, H-6); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 126.2–138.1 (24C, Ar), 101.8 (Ph*C*H), 79.4 (C-3), 76.3 (C-2′), 74.6 (C-4), 74.5 (Ph*C*H$_2$), 74.3 (2C, C-2 and Ph*C*H$_2$), 73.0 (Ph*C*H$_2$), 69.4 (C-4′), 66.9 (C-3′), 51.5 (C-5), 44.0 (C-1′), 36.2 (C-1), 14.3 (C-6). Anal. Calcd for $C_{38}H_{42}O_9S_2$: C, 64.57; H, 5.99. Found: C, 64.30; H, 5.91.

3.7.2. 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-{[(2*S*,3*S*)-2,4-*O*-benzylidene-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene}-L-fucitol inner salt (20). Column chromatography [$CHCl_3$/MeOH, 10:1] of the crude product gave **20** (655 mg, 93%) as an amorphous solid. $[\alpha]_D$ −22 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.12–7.68 (20H, m, Ar), 5.56 (1H, s, PhC*H*), 4.79, 4.68 (2H, 2d, $J = 11.0$ Hz, PhCH_2), 4.73 (2H, t, $J = 12.2$ Hz, PhCH_2), 4.54 (1H, dd, $J = 11.0$, 6.0 Hz, H-4a′), 4.52 (1H, ddd, $J = 11.0$, 9.0, 6.0 Hz, H-3′), 4.49, 4.43 (2H, 2d, $J = 11.5$ Hz, PhCH_2), 4.39 (1H, dd, $J = 14.0$, 4.0 Hz, H-1a′), 4.33 (1H, ddd, $J = 9.0$, 4.0, 3.0 Hz, H-2′), 4.17 (1H, dq, $J = 7.0$, 2.5 Hz, H-5), 4.14 (1H, t, $J = 2.0$ Hz, H-4), 4.12 (1H, dd, $J = 14.0$, 3.0 Hz, H-1b′), 4.08 (1H, ddd, $J = 7.5$, 7.0, 3.5 Hz, H-2), 3.85 (1H, dd, $J = 7.0$, 2.0 Hz, H-3), 3.78 (1H, t, $J = 11.0$ Hz, H-4b′), 3.62 (1H, dd, $J = 13.5$, 3.5 Hz, H-1a), 3.36 (1H, dd, $J = 13.5$, 7.5 Hz, H-1b), 1.63 (3H, d, H-6); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 126.3–138.2 (24C, Ar), 101.9 (Ph*C*H), 79.5 (C-3), 76.4 (C-2′), 75.3 (C-4), 74.7, 74.5 (2C, Ph*C*H$_2$), 74.3 (C-2), 72.9 (Ph*C*H$_2$), 69.6 (C-4′), 66.8 (C-3′), 51.1 (C-5), 43.3 (C-1′), 36.5 (C-1), 14.4 (C-6). Anal. Calcd for $C_{38}H_{42}O_9S_2$: C, 64.57; H, 5.99. Found: C, 64.76; H, 6.00.

3.7.3. 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-1,5-{[(2*R*,3*S*,4*R*,5*R*)-2,4-*O*-benzylidene-5,6-*O*-isopropylidene-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]-episulfoniumylidene}-L-fucitol inner salt (22). Column chromatography [EtOAc/MeOH, 15:1] of the crude product gave **22** (330 mg, 41%) as an amorphous solid. $[\alpha]_D$ −36 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.21–7.50 (20H, m, Ar), 5.71 (1H, s, PhC*H*), 4.80 (1H, d, $J = 11.0$ Hz, PhCH_2), 4.75, 4.71 (2H, 2d, $J = 11.5$ Hz, PhCH_2), 4.61, 4.46 (2H, 2d, $J = 11.5$ Hz, PhCH_2), 4.54–4.59 (2H, m, H-2′ and PhCH_2), 4.23–4.28 (4H, m, H-3′, H-4′, H-5′, and H-6a′), 4.20 (1H, dd, $J = 9.0$, 7.0 Hz, H-6b′), 4.17 (1H, dd, $J = 14.5$, 6.5 Hz, H-1a′), 4.09–4.14 (2H, m, H-2 and H-4), 3.95 (1H, dq, $J = 7.0$, 2.0 Hz, H-5), 3.88 (1H, dd, $J = 14.5$, 4.5 Hz, H-1b′), 3.84 (1H, dd, $J = 8.0$, 2.0 Hz, H-3), 3.78 (1H, dd, $J = 13.2$, 3.3 Hz, H-1a), 3.62 (1H, dd, $J = 13.2$, 7.8 Hz, H-1b), 1.49 (3H, d, $J = 7.0$ Hz, H-6), 1.36, 1.35 (6H, 2s, (CH_3)$_2$C); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 126.5–138.2 (24C, Ar), 108.5 ((CH$_3$)$_2$*C*), 101.3 (Ph*C*H), 80.0 (C-3), 79.5 (C-3′), 76.0 (C-4), 75.5 (C-4′), 75.2 (C-2), 74.9, 74.4 (2C, Ph*C*H$_2$), 73.7 (C-5′), 72.8 (Ph*C*H$_2$), 69.8 (C-2′), 65.0 (C-6′), 51.7 (C-5), 43.9 (C-1′), 37.0 (C-1), 26.5, 25.7 (2C, (*C*H$_3$)$_2$C), 14.4 (C-6). Anal. Calcd for $C_{43}H_{50}O_{11}S_2$: C, 64.00; H, 6.25. Found: C, 64.08; H, 6.08.

3.8. General procedure for the deprotection of compounds (18), (20), and (22) by hydrogenolysis with Pd(OH)$_2$/C

The protected compound (0.4 mmol) was dissolved in 80% HOAc (10 mL) (for **22**, the mixture was firstly stirred at 80 °C for 1 h to remove the isopropylidene group) and stirred with Pd(OH)$_2$/C (150 mg, 20 wt %) under H_2 (80 psi). After 50 h, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified on column chromatography.

3.8.1. 1,5-Dideoxy-1,5-{[(2*R*,3*R*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene}-L-fucitol inner salt (6). Column chromatography [EtOAc/MeOH/H_2O, 7:3:1] of the residue afforded **6** (123 mg, 88%) as an amorphous solid. $[\alpha]_D$ −24 (*c* 1.5, H_2O); ^{1}H NMR (500 MHz,

D_2O): δ 4.25 (1H, ddd, $J = 8.5$, 3.5, 3.0 Hz, H-2′), 4.16 (1H, q, $J = 3.5$ Hz, H-3′), 4.12 (1H, d, $J = 2.0$ Hz, H-4), 4.02 (1H, ddd, $J = 11.5$, 9.5, 4.5 Hz, H-2), 3.80 (1H, dd, $J = 12.2$, 3.5 Hz, H-4a′), 3.78 (1H, q, $J = 7.0$ Hz, H-5), 3.72 (1H, dd, $J = 14.0$, 3.0 Hz, H-1a′), 3.72 (1H, dd, $J = 11.5$, 4.5 Hz, H-1a), 3.68 (1H, dd, $J = 12.2$, 3.5 Hz, H-4b′), 3.48 (1H, dd, $J = 9.5$, 2.0 Hz, H-3), 3.42 (1H, dd, $J = 14.0$, 8.5 Hz, H-1b′), 3.15 (1H, t, $J = 11.5$ Hz, H-1b), 1.43 (3H, d, $J = 7.0$ Hz, H-6); ^{13}C NMR (100 MHz, D_2O): δ 80.5 (C-3′), 73.6 (C-3), 72.7 (C-4), 65.9 (C-2′), 64.7 (C-2), 59.4 (C-4′), 54.8 (C-5), 44.8 (C-1′), 41.9 (C-1), 13.6 (C-6). HRMS Calcd for $C_{10}H_{20}O_9S_2Na$: 371.0441; Found: 371.0444. Anal. Calcd for $C_{10}H_{20}O_9S_2$: C, 34.47; H, 5.79. Found: C, 33.98; H, 6.01.

3.8.2. 1,5-Dideoxy-1,5-{[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene}-L-fucitol inner salt (7). Column chromatography [EtOAc/MeOH/H_2O, 7:3:1] of the residue afforded **7** (121 mg, 87%) as an amorphous solid. $[\alpha]_D$ +12 (*c* 1.5, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.25 (1H, dt, $J = 8.0$, 3.5 Hz, H-2′), 4.22 (1H, ddd, $J = 8.0$, 3.5, 3.0 Hz, H-3′), 4.15 (1H, d, $J = 2.0$ Hz, H-4), 4.04 (1H, ddd, $J = 11.5$, 9.8, 4.0 Hz, H-2), 3.84 (1H, dd, $J = 13.0$, 3.5 Hz, H-4a′), 3.78 (1H, q, $J = 7.0$ Hz, H-5), 3.72 (1H, dd, $J = 13.0$, 3.0 Hz, H-4b′), 3.70 (1H, dd, $J = 11.5$, 4.0 Hz, H-1a), 3.64 (1H, dd, $J = 14.0$, 8.0 Hz, H-1a′), 3.58 (1H, dd, $J = 14.0$, 3.5 Hz, H-1b′), 3.51 (1H, dd, $J = 9.8$, 2.0 Hz, H-3), 3.16 (1H, t, $J = 11.5$ Hz, H-1b), 1.44 (3H, d, $J = 7.0$ Hz, H-6); ^{13}C NMR (100 MHz, D_2O): δ 80.3 (C-3′), 73.8 (C-3), 72.7 (C-4), 64.8 (C-2), 64.5 (C-2′), 59.6 (C-4′), 54.6 (C-5), 44.8 (C-1′), 40.6 (C-1), 13.6 (C-6). HRMS Calcd for $C_{10}H_{20}O_9S_2Na$: 371.0441; Found: 371.0438. Anal. Calcd for $C_{10}H_{20}O_9S_2$: C, 34.47; H, 5.79. Found: C, 34.12; H, 5.94.

3.8.3. 1,5-Dideoxy-1,5-{[(2*R*,3*S*,4*R*,5*R*)-2,4,5,6-tetrahydroxy-3-(sulfooxy)hexyl]-episulfoniumylidene}-L-fucitol inner salt (8). Column chromatography [EtOAc/MeOH/H_2O, 6:4:1] of the residue afforded **8** (150 mg, 91%) as an amorphous solid. $[\alpha]_D$ −13 (*c* 1.6, H_2O); ^{1}H NMR (500 MHz, D_2O): δ 4.54 (1H, dd, $J = 5.0$, 0.5 Hz, H-3′), 4.49 (1H, m, H-2′), 4.13 (1H, d, $J = 1.5$ Hz, H-4), 4.04 (1H, ddd, $J = 11.5$, 10.0, 4.0 Hz, H-2), 3.75–3.81 (2H, m, H-5 and H-5′), 3.73 (1H, dd, $J = 14.0$, 3.5 Hz, H-1a′), 3.62–3.72 (3H, m, H-1a, H-4′, and H-6a′), 3.48–3.56 (3H, m, H-3, H-1b′, and H-6b′), 3.16 (1H, t, $J = 11.5$ Hz, H-1b), 1.45 (3H, d, $J = 7.0$ Hz, H-6); ^{13}C NMR (100 MHz, D_2O): δ 77.5 (C-3′), 73.9 (C-3), 72.9 (C-4), 70.4 (C-4′), 68.8 (C-5′), 67.4 (C-2′), 64.9 (C-2), 62.8 (C-6′), 54.9 (C-5), 44.0 (C-1′), 41.8 (C-1), 13.7 (C-6). HRMS Calcd for $C_{12}H_{24}O_{11}S_2Na$: 431.0652; Found: 431.0651. Anal. Calcd for $C_{12}H_{24}O_{11}S_2$: C, 35.29; H, 5.92. Found; C, 35.46; H, 5.76.

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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.2006.08.002.

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