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Bioorganic & Medicinal Chemistry 14 (2006) 500–509
Bioorganic & Medicinal Chemistry

# Synthesis and biological evaluation of deoxy salacinols, the role of polar substituents in the side chain on the α-glucosidase inhibitory activity

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Received 14 July 2005; revised 13 August 2005; accepted 16 August 2005
Available online 29 September 2005

**Abstract**—Three analogs (**5**, **6**, and **7**) lacking polar substituents in the side chain of a naturally occurring α-glucosidase inhibitor, salacinol (**1a**), were synthesized by the coupling reaction of a thiosugar, 1,4-dideoxy-1,4-epithio-D-arabinitol (**3**), with cyclic sulfates (**8**, **9**, and **10**), and their α-glucosidase inhibitory activities were examined. All these simpler analogs (**5**, **6**, and **7**) showed less inhibitory activity compared to **1a**, and proved the importance of cooperative role of the polar substituents for the α-glucosidase inhibitory activity. A practical synthetic route to **3** starting from D-xylose is also described.
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## 1. Introduction

Salacinol (**1a**) is a potent glycosidase inhibitor isolated from aqueous extracts of roots and stems of *Salacia reticulata* WIGHT (known as 'Kotala himbutu' in Sinhalese), which is traditionally used for the treatment of diabetes in Sri Lanka and the southern region of India. The α-glucosidase inhibitory activities of **1a** are potent and have been revealed to be as strong as those of voglibose and acarbose, which are widely used clinically these days.[1] The structure of **1a** established by the X-ray crystallographic analysis is quite unique, the ring sulfonium ion being stabilized by the sulfate counteranion by forming a spirobicyclic-like configuration comprised of 1-deoxy-4-thioarabinofuranosyl cation and 1-deoxy-L-erythrosyl-3-sulfate anion, as shown in Scheme 1.[1] Due to both the strong glycosidase inhibitory activity and the intriguing structure, much attention has been focused on **1a** and related compounds.[2] Total synthesis of **1a** was accomplished by two groups by the use of nucleophilic ring opening reaction of a cyclic sulfate (**2**) with thiosugar (**3**) as the key reaction.[3] Intensive studies on the structure–activity relationship of **1a** and its heterocyclic analogs (**1b** and **1c**) have also been reported,[4] and the sulfonium ion structure has been recognized as one of the essential structural factors for the potent α-glucosidase inhibitory activity. Even the *S*-methylated thiosugar (**4**) had also been found to show slight α-glucosidase inhibitory activity, while the thiosugar **3** itself showed no inhibitory activity against the enzymes.[1b,4b,d]

Thus, as a continuous study on its structure–activity relationship, three deoxy-analogs of salacinol (**5**, **6**, and **7**) were synthesized by the coupling reaction of **3** with corresponding cyclic sulfates (**8**, **9**, and **10**), and their α-glucosidase inhibitory activities were examined. Full details of the practical synthetic method of **3** previously developed by the authors[5] are also described in the present study.

## 2. Results and discussion

### 2.1. Synthesis of thiosugar

According to the literature,[6a,b] D-xylose was converted into 1,2-monoacetonide, 1,2-*O*-isopropylidene-α-D-

*Keywords*: α-Glucosidase inhibitor; Salacinol; Deoxygenated salacinol; Thiosugar.
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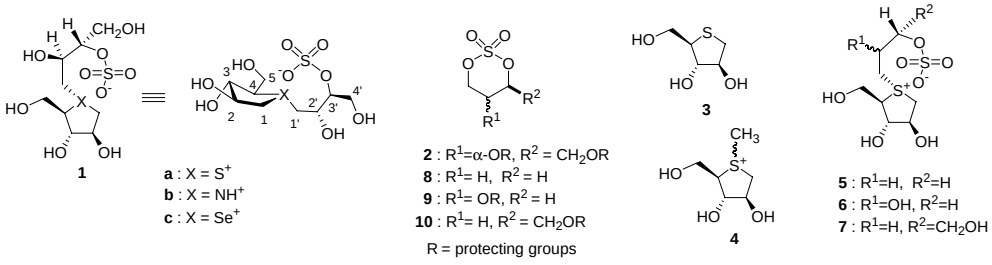
doi:10.1016/j.bmc.2005.08.040



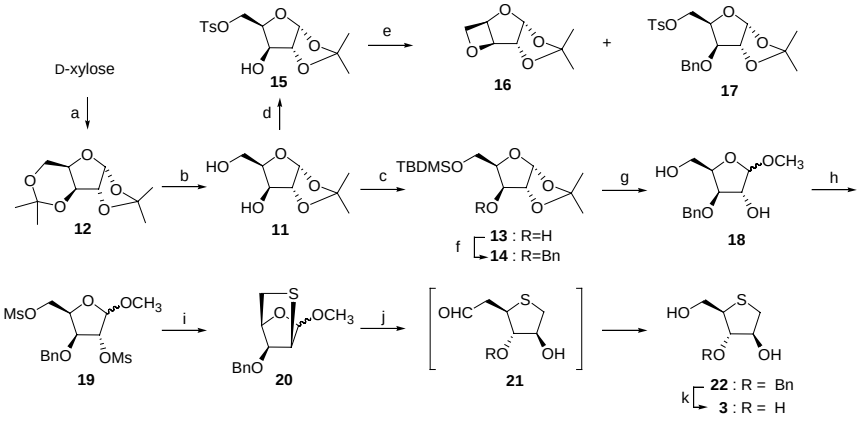

**Scheme 1.**

xylofuranose (**11**) via diacetonide, 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**12**), in 95% yield. The primary hydroxyl of **11** was selectively protected by the *tert*-butyldimethylsilyl (TBDMS) moiety, and the resulting silyl ether, 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose[7] (**13**), was treated with benzyl (Bn) bromide in the presence of sodium hydride, to afford the desired benzyl ether, 3-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose[7b] (**14**), in good yield. Simultaneous cyclization was found to occur when 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose[7c,8] (**15**), prepared by the treatment of **11** with tosyl chloride, was subjected to benzylation, giving ca. 1:1.1 mixture of 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose[9] (**16**) and the desired benzyl derivative, 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose[8,10] (**17**). Compound **14** was then treated with 5% methanolic hydrogen chloride, where the deacetalization was accompanied by methyl glycoside formation to afford ca. 1:1 anomeric mixture of methyl 3-*O*-benzyl-α- and β-D-xylofuranoside[11] (α- and β-**18**). Without separation of these anomers, the mixture was treated with methanesulfonyl chloride to afford the corresponding bismesylates, methyl 3-*O*-benzyl-2,5-di-*O*-mesyl-α- and β-D-xylofuranoside[11] (α- and β-**19**), which were then treated with sodium sulfide in DMF to give ca. 1.3:1 anomeric mixture of 2,5-dideoxy-2,5-epithio-3-*O*-benzyl-α- and β-D-lyxofuranoside[11] (α- and β-**20**). Hydrolysis of the mixture with 4 N hydrochloric acid in THF followed by the reduction of the resulting aldehyde (**21**) with sodium borohydride gave 3-*O*-benzyl-1,4-dideoxy-1,4-epithio-D-arabinitol[11] (**22**) in 58% overall yield from **14**. The conversion of **20** to **22** could be carried out in one-pot by neutralizing the reaction mixture with sodium hydrogen carbonate prior to the addition of sodium borohydride. Finally, the Birch reduction of **22** afforded the desired **3** in 97% yield (Scheme 2). The overall yield of this sequence via nine steps from D-xylose was around 53%, thus an efficient and practical alternative route[11] to **3** being developed.

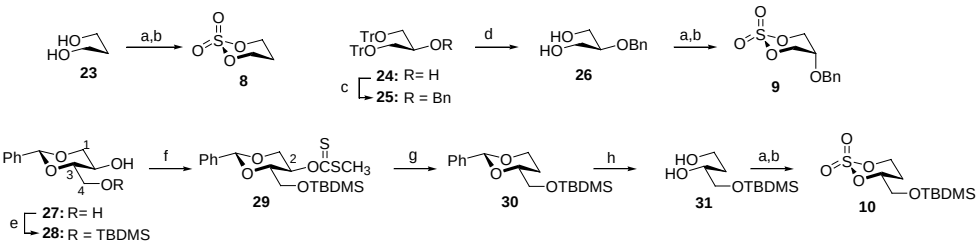
## 2.2. Synthesis of cyclic sulfates 8, 9, and 10

According to the reported method,[12] 1,3-propanediol 1,3-cyclic sulfate (**8**) was prepared in 80% yield by condensation of 1,3-propanediol (**23**) with thionyl chloride, followed by oxidation of the resulting cyclic sulfoxide with sodium periodate in the presence of ruthenium chloride. 2-*O*-Benzylglycerol 1,3-cyclic sulfate (**9**) as a fragment of the deoxymethylated salacinol **6** was synthesized starting from glycerol. Thus, its two primary hydroxyls were protected by the trityl moiety to afford bistrityl ether[13] (**24**). Benzylation of **24** followed by detritylation of the benzyloxyl derivative, 2-*O*-benzyl-1,3-di-*O*-tritylglycerol[13] (**25**), by acetic acid at 100 °C gave 2-*O*-benzylglycerol[13] (**26**) in 68% overall yield from glycerol. The diol **26** was converted into the desired 2-benzyloxy cyclic sulfate **9** in a manner similar to that for the synthesis of **8** (Scheme 3).

It is interesting to note that the benzyloxy group of compound **9** was proved to be axially oriented on the basis of the X-ray crystallographic analysis as shown in Figure 1. Small vicinal coupling constants of *J* 3.0 and




**Scheme 2.** Reagents and conditions: (a) acetone, $H_2SO_4$, $CuSO_4$, rt; (b) 0.1% aq HCl, rt; (c) TBDMSCl, imidazole, DMF, 0 °C; (d) TsCl, Py., $CHCl_3$, 0 °C–rt; (e) NaH, BnBr, THF, 0 °C; (f) NaH, BnBr, DMF, 0 °C; (g) HCl, MeOH, rt; (h) MsCl, Py., 0 °C–rt; (i) $Na_2S$, DMF, 100 °C; (j) 4 N aq HCl, THF, then $NaBH_4$, 0 °C–rt; (k) Na, liq. $NH_3$, −50 °C.




**Scheme 3.** Reagents and conditions: (a) $SOCl_2$, $Et_3N$, 0 °C; (b) $NaIO_4$, $NaHCO_3$, $RuCl_3.H_2O$, $CCl_4$, $CH_3CN$, $H_2O$, rt; (c) BnCl, KOH, toluene, reflux; (d) 80% aq AcOH, 100 °C; (e) TBDMSCl, imidazole, DMF, 0 °C; (f) $CS_2$, 5 N aq NaOH, DMSO, 0 °C, then $CH_3I$, 0 °C–rt; (g) $H_3PO_2$, $Et_3N$, EtOH, reflux; (h) $H_2$, Pd–C, EtOH, rt.

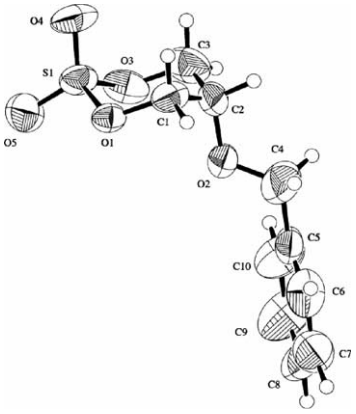


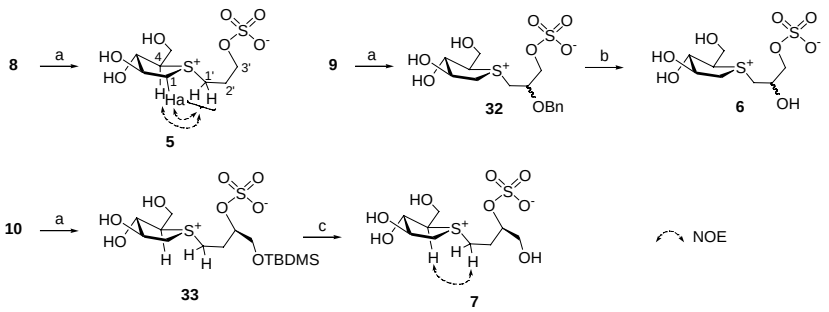

**Figure 1.** Perspective view of compound **9**.

2.5 Hz with respect to the signal at $\delta_H$ 3.65 due to the C-2 methine proton in its $^1H$ NMR spectrum showed that the group is in the same configuration also in solution state.[14]

For the synthesis of 4-*O*-*tert*-butyldimethylsilyl-2-deoxy-L-erythritol 1,3-cyclic sulfate (**10**), D-glucose was first converted into 1,3-*O*-benzylidene-L-erythritol[4a] (**27**). The remaining primary hydroxyl was protected with *tert*-butyldimethylsilyl chloride to afford 1,3-*O*-benzylidene-4-*O*-*tert*-butyldimethylsilyl-L-erythritol (**28**), which was then converted into the corresponding xantate, 1,3-*O*-benzylidene-2-*O*-[(*S*-methylthio)thiocarbonyl]-4-*O*-*tert*-butyldimethylsilyl-L-erythritol (**29**), in the usual manner. Subsequent deoxygenation by the use of hypophosphorous acid gave 1,3-*O*-benzylidene-4-*O*-*tert*-butyldimethylsilyl-2-deoxy-L-erythritol (**30**) in 80% overall yield from **27**. Hydrogenolysis followed by the cyclic sulfonation of the product, 4-*O*-*tert*-butyldimethylsilyl-2-deoxy-L-erythritol (**31**), gave the desired *O*-protected cyclic sulfate **10** in 75% yield. The protonated molecular-ion $[M+H]^+$ peak at *m*/*z* 283 in the FAB mass spectrum and other spectroscopic properties supported the structure of **10**.

### 2.3. Syntheses of deoxysalacinols (5, 6, and 7)

According to the literature, cyclic sulfates (**8**, **9**, and **10**) were treated with **3** in either DMF[3a] or 1,1,1,3,3,3-hexafluoroisopropanol[3b,c] (HFIP). Coupling reaction[3] of **8** with thiosugar **3** in HFIP afforded the corresponding sulfonium sulfate **5** in 61% yield. The peak at *m*/*z* 289 in the FAB mass spectrum run in the positive mode represented the protonated molecular-ion $[M+H]^+$ of the desired compound **5**. In its $^1H$ NMR spectrum, downfield shift owing to sulfonium ion formation was observed with respect to the signals due to C-1 methylene (at $\delta_H$ 3.78 and 3.90) and C-4 methine (at $\delta_H$ 3.94) protons. A pair of one-proton doublet of doublets, which appeared at $\delta_H$ 3.61 and 3.67, due to methylene protons α to the sulfur atom also supported the sulfonium ion structure. The relative stereochemistry of the side chain on the sulfur atom was determined to be in trans relationship to the hydroxymethyl group at C-4, as shown in Scheme 4, on the basis of nuclear Overhauser effect (NOE) experiments. NOE correlations were detected between the two ring protons α to the sulfur (H-4 and H-1a) and C-1′ methylene protons, suggesting the depicted configuration of the side chain.




**Scheme 4.** Reagents and conditions: (a) **3**, HFIP, $K_2CO_3$, 60 °C or **3**, DMF, $Na_2CO_3$, 45 °C; (b) $H_2$, Pd–C, AcOH–$H_2O$, rt; (c) 0.1% aq HCl, 40 °C.

When **9** was subjected to the coupling reaction with **3**, 1:1 diastereomeric mixture (**32**) with respect to the configuration of the benzyloxy moiety at C-2′ was obtained in 45% yield. Hydrogenolysis of the mixture **32** over palladium on carbon gave the desired deoxymethylated salacinol **6** in 60% yield. The mixture displayed similar $^{1}H$ NMR spectroscopic properties to those of **1a**, signals of five α-protons to the sulfur being deshielded due to the formation of the sulfonium ion. Two pairs of signals appeared at $\delta_C$ 50.8 and 51.3 (C-1′), and $\delta_C$ 70.2 and 70.3 (C-3′) in the $^{13}C$ NMR spectrum were ascribed to two carbons around the chiral center at C-2′, supporting the fact that the mixture was composed of two diastereomers of **6**.

Fortunately, single crystals of the mixture were obtained, and structural confirmation including the stereochemistry at the sulfonium center was established on the basis of the X-ray crystallographic analysis. Both diastereomers were packed to form $P2_12_12_1$ type orthorhombic crystals, and stereostructure of one of the diastereomers was extracted and its ORTEP drawing is presented in Figure 2. It is noteworthy that the two ionic centers in the molecule are far apart from each other (open-chain form), while **1a** had been proved to construct the inner salt structure between these two ionic centers (cyclic form).[1]

Inhibition mechanisms of salacinol (**1a**) have been proposed,[4d] where two ionic centers are shown to be the binding sites to the enzyme in the open-chain form. Decreased inhibitory activity of these synthesized compounds suggests the presence of another factor governed by the hydroxyls for the salacinol to bind the corresponding enzymes.

The reaction of the cyclic sulfates **10** with **3** was also performed to give the coupled product (**33**) in 20% yield. Subsequent hydrolysis of **33** with 0.1% aqueous HCl at 40 °C afforded the target compound **7** in 75% yield. Its MS and NMR spectra supported the desired coupled structure. The relative stereochemistry of the side chain on the sulfur was also established on the basis of NOESY experiments as shown in Scheme 4.

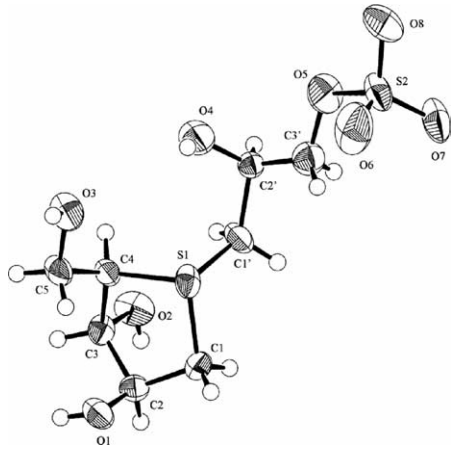



**Figure 2.** Perspective view of compound **6**.

**Table 1.** $IC_{50}$ values (μM) of compounds **1a**, **4**, **5**, **6**, and **7** against disaccharidase

| Compound | Maltase | Sucrase |
|---|---|---|
| **1a** | 9.6 | 2.5 |
| **4** | >1370 (38) | 445 |
| **5** | >1390 | >1390 (24) |
| **6** | >1320 (24) | 780 |
| **7** | >1260 | >1260 (29) |

Values in parentheses indicate inhibition (%) at 400 μg/ml.

### 2.4. α-Glucosidase inhibitory activity

The glycosidase inhibitory activity of synthesized compounds **5**, **6**, and **7** was tested for the intestinal α-glucosidase in vitro[15] and compared with that of **1a**, as shown in Table 1. Although maltase and sucrase were the enzymes effectively inhibited by **1a**, **5** showed no inhibition against both enzymes even at a high concentration of 1.39 mM. Thus, reduction of the two hydroxyls from **1a** caused the significant loss of activity. The inhibitory activities of **7**, deoxygenated at C-2′ of **1a**, also decreased considerably, indicating that the hydroxyl with *S*-configuration at C-2′ was essential for the activity. On the other hand, **6** slightly retained the inhibitory activity against sucrase, suggesting the superiority of the hydroxyl at C-2′ to the hydroxymethyl group at C-3′ in exhibiting the inhibitory activity against sucrase. These results suggest the importance of the cooperative role of the polar substituents in the side chain for the α-glucosidase inhibitory activity. Thus, all these substituents were found to be necessary to exhibit the inhibitory activity. Further studies on the structure–activity relationships of **1a** with the potential α-glucosidase inhibitory activity are under investigation.

## 3. Experimental

Mps were determined with a Yanagimoto MP-3S micromelting point apparatus, and mps and bps are uncorrected. IR spectra were measured on a Shimadzu IR-435 grating spectrophotometer. NMR spectra were recorded either on a JEOL JNM-GSX 270 (270 MHz $^{1}H$, 67.5 MHz $^{13}C$) or a JEOL JNM-GSX 500 (500 MHz $^{1}H$, 125 MHz $^{13}C$) spectrometer. Chemical shifts ($\delta$) and coupling constants ($J$) are given in parts per million and hertz, respectively. Low-resolution and high-resolution mass spectra (electron impact) were recorded either on a Shimadzu QP 1000EX spectrometer or a JEOL JMS-HX 100 spectrometer. Optical rotations were determined with a JASCODIP-370 digital polarimeter. Column chromatography was effected over Merck Kieselgel 60 (70–230 mesh). All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

### 3.1. 1,2-*O*-Isopropylidene-α-D-xylofuranose (11)

According to the literature,[6a] a mixture of D-xylose (30 g, 200 mmol), $CuSO_4$ (60 g, 376 mmol), sulfuric acid

(3 ml), and acetone (1 l) was stirred at room temperature for 12 h. After neutralization of the mixture with sodium carbonate, solid material was removed by filtration, and the filtrate was evaporated to give 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose (**12**, 46.5 g), which was used in the next step without purification.

The crude diacetonide **12** (46.5 g) was hydrolyzed with 0.2% hydrochloric acid (600 ml) by applying the procedure reported.[6b] The reaction was quenched with sodium hydrogen carbonate after the reaction mixture was stirred at room temperature for 1.5 h. The precipitates were removed by filtration, and the filtrate was concentrated in vacuo. The residue was triturated with ethyl acetate, and the ethyl acetate-insoluble solid material was filtered off. The filtrate was evaporated to give a pale yellow oil (39.4 g), which on distillation at reduced pressure (bp 158–160 °C/2 mmHg) gave monoacetonide **11** (36.1 g, 95% from D-xylose) as a pale yellow viscose oil. The oil solidified on keeping in a refrigerator, mp 40–41 °C, lit.[6b] 41–43 °C, lit.[6c] 42–44 °C, $[\alpha]_D^{20}$ −22.4 (*c* 1.10, $CHCl_3$), lit.[6c] −23 (*c* 0.7, MeOH). The spectral properties of **11** were in accord with those reported.[6c,6d]

### 3.2. 5-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose (13)

A mixture of the monoacetonide **11** (33.6 g, 176 mmol), imidazole (14.6 g, 215 mmol), *tert*-butyldimethylsilyl chloride (27 g, 179 mmol), and DMF (200 ml) was stirred at 0 °C for 1 h. The mixture was poured into ice water (800 ml) and extracted with diethyl ether. The extract was washed with brine and evaporated to give a colorless oil (54.4 g), which on distillation at reduced pressure gave silyl ether **13** (52.8 g, 98%) as a colorless oil, bp 127–129 °C/0.002 mmHg, $[\alpha]_D^{20}$ −5.40 (*c* 0.83, $CHCl_3$), lit.[7a] −9.3 (*c* 10.0, $CHCl_3$). The spectral properties of **13** were in accord with those reported.[7b,c]

### 3.3. 3-*O*-Benzyl-5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose (14)

A solution of **13** (52.8 g, 174 mmol) and benzyl bromide (21.2 ml, 178 mmol) in DMF (50 ml) was added dropwise to a suspension of sodium hydride (8.3 g, 208 mmol, 60% in liquid paraffin, washed with benzene) in DMF (150 ml) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was poured into ice water (700 ml) and extracted with diethyl ether. The extract was washed with brine and evaporated to give a colorless oil (70.8 g), which on distillation at reduced pressure gave the title compound **14** (66.8 g, 98%) as a colorless oil, bp 150–152 °C/0.002 mmHg, $[\alpha]_D^{20}$ −36.6 (*c* 0.80, $CHCl_3$). The spectral properties of **14** were in accord with those reported.[7b]

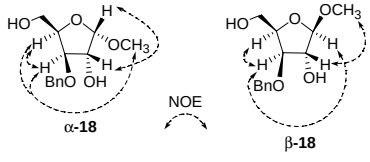
### 3.4. Benzylation of 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose (15)

A mixture of **15**[7c,8] (100 mg, 0.29 mmol), prepared by tosylation of monoacetonide **11**, and benzyl bromide (37μl, 0.31 mmol) in THF (2 ml) was added dropwise to a suspension of sodium hydride (17.4 mg, 0.44 mmol, 60% in liquid paraffin, washed with benzene) in THF (3 ml) at 0 °C. After being stirred at room temperature for 1.5 h, the mixture was poured into water (50 ml), and then the resulting mixture was extracted with $CHCl_3$. The extract was washed with brine and evaporated to give a colorless oil (67 mg). $^1$H NMR spectrum of the crude mixture indicated the formation of ca. 1.1:1 mixture of 3,5-anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose[9] (**16**) and 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose[8,10] (**17**). A signal due to the quaternary carbon in the acetonide moiety of **17**, which lacked in the literature,[10] was observed at $\delta_C$ 112.1 in the present study.

When **15** (100 mg, 0.29 mmol) was treated with sodium hydride (17.4 mg, 0.44 mmol, 60% in liquid paraffin, washed with benzene) in THF, the bicycle **16** (43 mg, 86%) was obtained as the sole product, bp 80–81 °C/2 mmHg, lit.[9b] 64 °C/0.1 mmHg, $[\alpha]_D^{22}$ +13.1 (*c* 2.5, $CHCl_3$), lit.[9a] +11.9 (*c* 0.75, $CHCl_3$), lit.[9c] +12.7 (*c* 2.1, $CHCl_3$). The spectral properties of **16** were in accord with those reported.[9a]

### 3.5. Methyl 3-*O*-benzyl-α- and β-D-xylofuranoside (18)

A mixture of **14** (58.8 g, 149 mmol) and 5% methanolic hydrogen chloride (400 ml) was stirred at room temperature for 3 h. After the reaction was quenched with sodium hydrogen carbonate, the precipitates were removed by filtration, and the filtrate was evaporated. The residue was dissolved in ethyl acetate, and ethyl acetate-insoluble solid material was filtered off. The filtrate was evaporated to give a colorless oil (46.2 g), which was washed with *n*-hexane to give **18** (37.9 g) as a ca. 1:1 anomeric mixture of α-**18** and β-**18**. Analytical samples of both anomers were obtained by means of column chromatography (hexane–ethyl acetate 3:1). Yoshimura et al.[11a] had identified the less polar anomer as the β-isomer (β-**18**). On the basis of differential NOE experiments in the present study, their assignment was found to be reversed with respect to these two anomers. Significant NOE was detected between the signals of $\delta$ 4.96 (H-1) and $\delta$ 4.29 (H-2) of the less polar isomer, which was thus identified as α-anomer (α-**18**). On the other hand, NOE was observed between the signals $\delta$ 4.80 (H-1) and $\delta$ 4.10 (H-3) in the case of β-**18** as shown below.




The two close signals at $\delta_C$ 77.5 and 77.9 in the $^{13}$C NMR spectrum of α-**18** were unambiguously assigned on the basis of two-dimensional NMR spectroscopic studies, and the reported assignments[11c] for signals due to two methine carbons (C-2 and C-4) were found interchanged with each other.

α-**18**: colorless oil. Bp 97–98 °C/0.025 mmHg, $[\alpha]_D^{20}$ +65.3 (*c* 0.78, $CHCl_3$). IR ($CHCl_3$): 3549, 1119, 1047 $cm^{-1}$. $^{13}C$ NMR ($CDCl_3$) δ: 55.5 ($OCH_3$), 62.1 (C-5), 72.0 ($OCH_2Ph$), 77.5 (C-4), 77.9 (C-2), 84.3 (C-3), 101.4 (C-1), 127.7/127.9/128.5 (d, arom.), 137.4 (s, arom.).

β-**18**: colorless oil. Bp 97–99 °C/0.025 mmHg, $[\alpha]_D^{20}$ −48.3 (*c* 0.60, $CHCl_3$). IR ($CHCl_3$): 3423, 1107, 1049 $cm^{-1}$. $^{13}C$ NMR ($CDCl_3$) δ: 55.8 ($OCH_3$), 62.2 (C-5), 72.6 ($OCH_2Ph$), 79.9 (C-2), 80.4 (C-4), 84.3 (C-3), 109.3 (C-1), 127.8/128.1/128.6 (d, arom.), 137.5 (s, arom.).

### 3.6. Methyl 3-*O*-benzyl-2,5-di-*O*-mesyl-α- and β-D-xylofuranoside (19)

Mesyl chloride (23.8 ml, 309 mmol) was added dropwise to a solution of the crude mixture of **18** (37.9 g) in pyridine (100 ml) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was poured into ice water (100 ml) and extracted with $CHCl_3$. The extract was washed with brine and evaporated to give an anomeric mixture of **19** as a pale yellow oil (64.0 g), which was used in the next step without purification. The ratio of α- and β-anomers in the mixture was determined to be ca. 1:1 on the basis of the $^1H$ NMR spectrum. As the mixture was found hardly separable, analytical samples of α-**19** and β-**19** were derived from pure α-**18** and β-**18**, respectively.

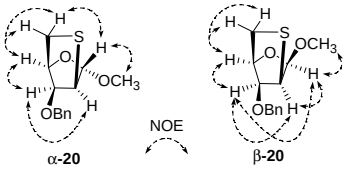
α-**19**: colorless oil. $[\alpha]_D^{20}$ +61.5 (*c* 1.30, $CHCl_3$), bp 180 °C/1.5 mmHg (decomp.). IR ($CHCl_3$): 1362, 1225, 1207, 1178, 1133, 1072 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ: 2.99 (3H, s, $OSO_2CH_3$), 3.06 (3H, s, $OSO_2CH_3$), 3.45 (3H, s, $OCH_3$), 4.32 (1H, dd, *J* = 10.5, 6.0 Hz, H-5a), 4.40 (1H, dd, *J* = 10.5, 2.5 Hz, H-5b), 4.42–4.46 (2H, m, H-3, H-4), 4.57 (1H, d, *J* = 11.5 Hz, OC*H*HPh), 4.73 (1H, d, *J* = 11.5 Hz, OCH*H*Ph), 4.97 (1H, dd, *J* = 5.0, 4.5 Hz, H-2), 5.13 (1H, d, *J* = 4.5 Hz, H-1), 7.30–7.40 (5H, m, arom.). $^{13}C$ NMR ($CDCl_3$) δ: 37.5/38.7 ($OSO_2CH_3$), 55.8 ($OCH_3$), 68.2 (C-5), 73.0 ($OCH_2Ph$), 74.2 (C-4), 79.5 (C-3), 81.7 (C-2), 100.2 (C-1), 128.0/128.3/128.6 (d, arom.), 136.6 (s, arom.). MS *m*/*z* (%): 410 ($M^+$, 2), 209 (46), 185 (17), 165 (60), 129 (17), 99 (50), 81 (100). HRMS *m*/*z*: 410.0717 ($C_{15}H_{22}O_9S_2$ requires 410.0705).

β-**19**: colorless oil. $[\alpha]_D^{20}$ −42.3 (*c* 1.20, $CHCl_3$), bp 180 °C/1.5 mmHg (decomp.). IR ($CHCl_3$): 1362, 1225, 1207, 1178, 1115, 1072 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ: 3.00 (3H, s, $OSO_2CH_3$), 3.04 (3H, s, $OSO_2CH_3$), 3.45 (3H, s, $OCH_3$), 4.31 (1H, dd, *J* = 6.0, 2.0 Hz, H-3), 4.41 (2H, d-like, *J* = 6.0 Hz, H-5a, H-5b), 4.56 (1H, dt, *J* = 6.0, 6.0 Hz, H-4), 4.57 (1H, d, *J* = 11.5 Hz, OC*H*HPh), 4.76 (1H, d, *J* = 11.5 Hz, OCH*H*Ph), 5.04 (1H, br s-like, H-2), 5.05 (1H, s, H-1), 7.31–7.40 (5H, m, arom.). $^{13}C$ NMR ($CDCl_3$) δ: 37.5/38.4 ($OSO_2CH_3$), 55.8 ($OCH_3$), 69.0 (C-5), 72.7 ($OCH_2Ph$), 78.7 (C-4), 80.7 (C-3), 84.3 (C-2), 107.0 (C-1), 128.3/128.55/128.63 (d, arom.), 136.5 (s, arom). MS *m*/*z* (%): 410 ($M^+$, 0.2), 209 (34), 187 (12), 165 (37), 99 (31), 81 (100). HRMS *m*/*z*: 410.0687 ($C_{15}H_{22}O_9S_2$ requires 410.0705).

### 3.7. 2,5-Dideoxy-2,5-epithio-3-*O*-benzyl-α- and β-D-lyxofuranoside (20)

A mixture of the crude dimesylate **19** (64.0 g), sodium sulfide nonahydrate (52.3 g, 218 mmol), and DMF (400 ml) was heated at 100 °C for 4 h. After being cooled, the mixture was poured into ice water (2 l) and extracted with diethyl ether. The extract was washed with brine and evaporated to give ca. 1.3:1 anomeric mixture of α- and β-**20** (36.2 g) as a pale brown oil, which was used in the next step without purification.

On the other hand, pure α-**19** and β-**19** obtained above were converted to the corresponding bicycles α-20 and β-**20**, respectively. The $^1H$ NMR spectroscopic properties of α-**20** were consistently in accordance with those of β-**20** in the literature.[11a] The structure of both isomers was unambiguously confirmed on the basis of differential NOE experiments in the present study.




α-**20**: colorless needles. Mp 51–52 °C (hexane–acetone), $[\alpha]_D^{22}$ +25.6 (*c* 1.20, $CHCl_3$). IR ($CHCl_3$): 1147, 1082, 1016 $cm^{-1}$. $^{13}C$ NMR ($CDCl_3$) δ: 34.9 (C-5), 48.6 (C-2), 55.0 ($OCH_3$), 72.1 ($OCH_2Ph$), 76.1 (C-4), 79.8 (C-3), 109.7 (C-1), 127.8/128.0/128.5 (d, arom.), 137.5 (s, arom.).

β-**20**: colorless oil. Bp 103–104 °C/2 mmHg, $[\alpha]_D^{20}$ −32.5 (*c* 0.40, $CHCl_3$). IR ($CHCl_3$): 1126, 1099, 1024 $cm^{-1}$. $^{13}C$ NMR ($CDCl_3$) δ: 35.1 (C-5), 50.5 (C-2), 56.5 ($OCH_3$), 71.7 ($OCH_2Ph$), 78.2 (C-4), 80.0 (C-3), 106.3 (C-1), 127.9/128.1/128.5 (d, arom.), 137.2 (s, arom.).

### 3.8. 3-*O*-Benzyl-1,4-dideoxy-1,4-epithio-D-arabinitol (22)

The crude mixture of **20** obtained above (36.2 g) was dissolved in THF (300 ml) and was treated with 4 N hydrochloric acid (450 ml) at room temperature for 1 h. The reaction was quenched with sodium hydrogen carbonate, and $NaBH_4$ (6.5 g, 172 mmol) was added in small portions with vigorous stirring at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The precipitates were filtered off, and the filtrate was extracted with $CHCl_3$. The extract was washed with brine and evaporated to give a pale brown oil (32.6 g), which on column chromatography (hexane–acetone, 3:1) gave **22** (20.7 g, 58% from **14**) as a pale yellow oil. The $^1H$ NMR spectroscopic properties of **22** were in accord with those reported.[11a]

**22**: colorless oil. Bp 127–128 °C (3 mmHg), $[\alpha]_D^{20}$ +20.0 (*c* 2.95, MeOH). IR ($CHCl_3$): 3370, 1070 $cm^{-1}$. $^{13}C$ NMR ($CDCl_3$) δ: 38.2 (C-1), 53.5 (C-4), 63.1 (C-5),

72.0 (O*C*H$_2$Ph), 76.5 (C-2), 89.0 (C-3), 127.7/127.9/128.5 (d, arom.), 137.7 (s, arom.).

### 3.9. 1,4-Dideoxy-1,4-epithio-D-arabinitol (3)

According to the literature,[11d] a solution of **22** (5.3 g, 22.1 mmol) in THF (50 ml) was treated with a solution of sodium (2.4 g, 104 mg-atom) in liquid ammonia (ca. 100 ml) at −50 °C for 1 h. After addition of methanol (30 ml) to the mixture, ammonia was gradually removed by increasing the temperature of the mixture, and the resulting mixture was acidified with conc. hydrochloric acid to pH 5. The resulting precipitates were filtered off and washed with methanol. The combined filtrate and washings were evaporated to give a pale yellow oil (3.6 g), which on column chromatography ($CHCl_3$–EtOH, 10:1) gave **3** (3.2 g, 97%) as a pale yellow oil, $[\alpha]_D^{20}$ +41.9 (*c* 0.82, MeOH), lit.[11d] +40.2 (*c* 1.28, MeOH). The spectral properties of **3** were in accord with those reported.[11d]

### 3.10. 1,3-*O*-Benzylidene-4-*O*-*tert*-butyldimethylsilyl-L-erythritol (28)

A mixture of 1,3-*O*-benzylidene-L-erythritol[4a] (**27**, 3.41 g, 16.2 mmol), *tert*-butyldimethylsilyl chloride (3.18 g, 21.0 mmol), imidazole (1.55 g, 22.8 mmol), and DMF (30 ml) was stirred at 0 °C for 1 h. The mixture was poured into ice water (100 ml) and extracted with diethyl ether. The extract was washed with brine and evaporated to give **28** (6.0 g) as a colorless oil, which was used in the next step without purification. Analytical sample of **28** was obtained as a colorless oil by means of column chromatography ($CHCl_3$–EtOH 20:1), $[\alpha]_D^{22}$ +5.7 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$): 3503, 1107, 1088 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 0.13 [6H, s, Si(CH$_3$)$_2$$^t$Bu], 0.92 [9H, s, SiMe$_2$C(C*H*$_3$)$_3$], 3.63 (1H, dd, *J* = 11.0, 10.0 Hz, H-1a), 3.73 (1H, ddd, *J* = 8.5, 8.5, 4.5 Hz, H-3), 3.85 (1H, dd, *J* = 10.0, 8.5 Hz, H-4a), 3.90 (1H, ddd, *J* = 10.0, 8.5, 5.0 Hz, H-2), 4.04 (1H, dd, *J* = 10.0, 4.5 Hz, H-4b), 4.32 (1H, dd, *J* = 11.0, 5.0 Hz, H-1b), 5.50 (1H, s, PhC*H*), 7.32–7.50 (5H, m, arom.). $^{13}$C NMR ($CDCl_3$) $\delta$: −5.62/−5.57 [Si(*C*H$_3$)$_2$$^t$Bu], 18.2 [SiMe$_2$*C*(CH$_3$)$_3$], 25.8 [SiMe$_2$C(*C*H$_3$)$_3$], 66.2 (C-4), 66.4 (C-2), 70.6 (C-1), 79.1 (C-3), 101.1 (Ph*C*H), 126.1/128.2/129.0 (d, arom.), 137.5 (s, arom.). MS *m*/*z* (%): 324 (M$^+$, 0.4), 161 (36), 143 (23), 131 (78), 117 (96), 91 (100), 75 (88), 59 (58). HRMS *m*/*z*: 324.1760 ($C_{17}H_{28}O_4Si$ requires 324.1757).

### 3.11. 1,3-*O*-Benzylidene-4-*O*-*tert*-butyldimethylsilyl-2-deoxy-L-erythritol (30)

A mixture of the crude silyl ether (**28**, 5.18 g), 5 N aqueous sodium hydroxide (3.5 ml), and dimethylsulfoxide (20 ml) was stirred at 0 °C for 15 min. To the mixture was added dropwise methyl iodide (2.0 ml, 32.1 mmol) at 0 °C, and the resulting mixture was stirred at that temperature for 10 min. The reaction mixture was diluted with ethyl acetate (40 ml), and the resulting mixture was washed with water. The organic phase was evaporated to give 1,3-*O*-benzylidene-2-*O*-[(*S*-methylthio)thiocarbonyl]-4-*O*-*tert*-butyldimethylsilyl-L-erythritol (**29**, 6.82 g) as a pale yellow oil, which was used in the next step without purification.

Under argon, a solution of the crude xantate (**29**, 6.62 g) in ethanol (40 ml) was added dropwise to a mixture of 50% aqueous hypophosphorous acid (5.3 ml, 48.2 mmol), triethylamine (14 ml, 101 mmol), azoisobutyronitrile (525 mg, 3.2 mmol), and ethanol (40 ml), and the resulting mixture was heated under reflux for 2 h. The mixture was poured into aqueous sodium hydrogen carbonate (400 ml) and extracted with ethyl acetate. The extract was washed with brine, and evaporated to give a pale brown oil (5.21 g), which on column chromatography (hexane–acetone, 25:1) gave title compound **30** (3.35 g, 80% from **27**) as a colorless oil, bp 180–181 °C (1 mmHg). IR ($CHCl_3$): 1215, 1107 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 0.07 [6H, s, Si(CH$_3$)$_2$$^t$Bu], 0.89 [9H, s, SiMe$_2$C(C*H*$_3$)$_3$], 1.64 (1H, dddd, *J* = 12.0, 3.0, 3.0, 1.5 Hz, H-2a), 1.81 (1H, dddd, *J* = 12.0, 12.0, 11.0, 5.0 Hz, H-2b), 3.62 (1H, dd, *J* = 10.5, 6.0 Hz, H-4a), 3.81 (1H, dd, *J* = 10.5, 5.5 Hz, H-4b), 3.95 (1H, dddd, *J* = 11.0, 6.0, 5.5, 3.0 Hz, H-3), 3.98 (1H, ddd, *J* = 12.0, 12.0, 3.0 Hz, H-1a), 4.30 (1H, ddd, *J* = 12.0, 5.0, 1.5 Hz, H-1b), 5.52 (1H, s, PhC*H*), 7.30–7.51 (5H, m, arom). $^{13}$C NMR ($CDCl_3$) $\delta$:−5.4/−5.3 [Si(*C*H$_3$)$_2$$^t$Bu], 18.3 [SiMe$_2$*C*(CH$_3$)$_3$], 25.9 [SiMe$_2$C(*C*H$_3$)$_3$], 28.3 (C-2), 66.2, 67.0 (C-1, C-4), 77.6 (C-3), 101.2 (Ph*C*H), 123.5/126.1/128.7 (d, arom.), 138.6 (s, arom.). MS *m*/*z* (%): 251 (M$^+$−$^t$Bu, 0.1), 143 (40), 117 (62), 91 (65), 73 (100), 59 (45). FABMS *m*/*z*: 309 [M+H]$^+$ (pos). FABHRMS *m*/*z*: 309.1893 ($C_{17}H_{29}O_3Si$ requires 309.1887).

### 3.12. 4-*O*-*tert*-Butyldimethylsilyl-2-deoxy-L-erythritol (31)

A suspension of 10% palladium-on-carbon (2.0 g) in ethanol (25 ml) was pre-equilibrated with hydrogen. To the suspension was added a solution of compound **30** (2.3 g, 7.47 mmol) in ethanol (25 ml), and the mixture was hydrogenated at 50 °C under atmospheric pressure until the uptake of hydrogen ceased. The catalyst was filtered off, and the filtrate was evaporated to give a colorless oil (1.64 g), which on column chromatography ($CHCl_3$–EtOH, 30:1) gave title compound **31** (1.33 g, 81%) as a colorless oil, bp 152 °C/7 mmHg (decomp.). $[\alpha]_D^{24}$ +17.9 (*c* 1.4, MeOH). IR (neat): 3356, 1253, 1072 cm$^{-1}$. $^1$H NMR ($CD_3OD$) $\delta$: 0.08 [6H, s, Si(CH$_3$)$_2$$^t$Bu], 0.91 [9H, s, SiMe$_2$C(C*H*$_3$)$_3$], 1.58 (1H, ddt, *J* = 14.0, 9.0, 6.0 Hz, H-2a), 1.78 (1H, dtd, *J* = 14.0, 7.0, 4.0 Hz, H-2b), 3.53 (1H, dd, *J* = 10.0, 5.0 Hz, H-4a), 3.58 (1H, dd, *J* = 10.0, 5.0 Hz, H-4b), 3.69 (2H, dd, *J* = 7.0, 6.0 Hz, H-1), 3.73 (1H, dddd, *J* = 9.0, 5.0, 5.0, 4.0 Hz, H-3). $^{13}$C NMR ($CDCl_3$) $\delta$:−5.3/−5.2 [Si(*C*H$_3$)$_2$$^t$Bu], 19.2 [SiMe$_2$*C*(CH$_3$)$_3$], 26.4 [SiMe$_2$C(*C*H$_3$)$_3$], 37.1 (C-2), 60.0 (C-1), 68.7 (C-4), 70.6 (C-3). MS *m*/*z* (%): 149 (17), 91 (35), 75 (80), 57 (100). FABMS *m*/*z*: 221 [M+H]$^+$ (pos). FABHRMS *m*/*z*: 221.1559 ($C_{10}H_{25}O_3Si$ requires 221.1573).

### 3.13. Preparation of cyclic sulfates (8, 9, and 10)

According to the literature,[12,3a] a mixture of 1,3-propandiol (**23**, 613 mg, 8.06 mmol), triethyl amine (2.79 ml, 20.2 mol), and dichloromethane (10 ml) was treated with

a solution of thionyl chloride (0.84 ml, 9.69 mmol) in dichloromethane (5 ml) at 0 °C for 10 min. Work-up gave a pale brown oil (983 mg), which was used in the next oxidation without purification.

In the presence of sodium hydrogen carbonate (1.49 g 17.7 mmol), the oil (983 mg) was treated with ruthenium (VIII) oxide[12,3a] generated in situ from sodium metaperiotate (3.62 g, 16.9 mmol) and ruthenium (III) chloride *n*-hydrate (90 mg), in a mixture of carbon tetrachloride (8 ml), acetonitrile (8 ml), and water (8 ml) at room temperature for 30 min. The reaction mixture was diluted with diethyl ether (100 ml) and washed successively with aqueous sodium thiosulfate–sodium hydrogen carbonate and brine, and evaporated to give a pale yellow oil (1.11 g), which on column chromatography (benzene–acetone, 10:1) gave 1,3-propanediol 1,3-cyclic sulfate (**8**, 890 mg, 80%) as colorless needles, mp 58.5–59.5 °C, lit.[12d] 60 °C. The spectral properties of **8** were in accord with those reported.[12e]

Following the method described above, diols **26**[13] (1.3 g, 7.14 mmol) and **31** (760 mg, 3.45 mmol) were converted to 2-*O*-benzylglycerol 1,3-cyclic sulfate (**9**, 1.52 g, 87%) and 4-*O*-*tert*-butyldimethylsilyl-2-deoxy-L-erythritol 1,3-cyclic sulfate (**10**, 730 mg, 75%), respectively.

**9**: colorless needles. Mp 75–77 °C (hexane–diethyl ether). IR (KBr): 1400, 1200 1011 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 3.65 (1H, tt, $J$ = 3.0, 2.5 Hz, H-2), 4.65 (2H, dd, $J$ = 12.0, 3.0 Hz, H-1a), 4.67 (2H, s, $OCH_2Ph$), 4.78 (2H, dd, $J$ = 12.0, 2.5 Hz, H-1b), 7.31-7.43 (5H, m, arom.). $^{13}C$ NMR ($CDCl_3$) $\delta$: 66.4 (C-2), 71.3 ($OCH_2Ph$), 74.4 (C-1), 127.8/128.5/128.8 (d, arom.), 136.3 (s, arom.). MS *m*/*z* (%): 244 ($M^+$, 5), 149 (42), 122 (14), 105 (100), 91 (98), 77 (42), 65 (38). HRMS *m*/*z*: 244.0400 ($C_{10}H_{12}O_5S$ requires 244.0406).

**10**: colorless needles. Mp 34–35 °C. $[\alpha]_D^{24}$ +8.7 (*c* 1.0, $CHCl_3$). IR (KBr): 1339, 1253, 1142, 1022 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 0.09 [6H, s, $Si(CH_3)_2{}^tBu$], 0.90 [9H, s, $SiMe_2C(CH_3)_3$], 1.86 (1H, dddd, $J$ = 15.0, 2.0, 2.0, 1.5 Hz, H-2a), 2.31 (1H, dddd, $J$ = 15.0, 13.0, 12.0, 5.5 Hz, H-2b), 3.79 (1H, dd, $J$ = 11.5, 4.5 Hz, H-4a), 3.82 (1H, dd, $J$ = 11.5, 4.5 Hz, H-4b), 4.61 (1H, ddd, $J$ = 11.0, 5.5, 1.5 Hz, H-1a), 4.81 (1H, ddd, $J$ = 13.0, 11.0, 2.0 Hz, H-1b), 4.91 (1H, dtd, $J$ = 12.0, 4.5, 2.0 Hz, H-3). $^{13}C$ NMR ($CDCl_3$) $\delta$: −5.5/−5.4 [$Si(CH_3)_2{}^tBu$], 18.2 [$SiMe_2C(CH_3)_3$], 25.6 (C-2), 25.7 [$SiMe_2C(CH_3)_3$], 64.0 (C-4), 71.9 (C-1), 85.0 (C-3). MS *m*/*z* (%): 225 ($M^+ - {}^tBu$, 5), 145 (17), 81 (44), 69 (100), 99 (31). FABMS *m*/*z*: 283 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 283.1028 ($C_{10}H_{23}O_5SiS$ requires 283.1035).

### 3.14. Coupling reaction between cyclic sulfates (8, 9, and 10) and thiosugar 3

According to the literature, cyclic sulfates (**8**, **9**, and **10**) were treated with **3** in either DMF[3a] or 1,1,1,3,3,3-hexafluoroisopropanol[3b,3c] (HFIP).

*Method A*. A mixture of **8** (138 mg, 1.0 mmol), **3** (100 mg, 0.67 mmol), sodium carbonate (212 mg, 2.0 mmol), and DMF (300 μl) was stirred at 45 °C for 60 h. The reaction mixture was diluted with methanol (10 ml), and the solid material was filtered off. The filtrate was concentrated in vacuo, and the residue was triturated with diethyl ether to give a pale brown oil (326 mg), which on column chromatography (AcOEt–MeOH–$H_2O$, 20:4:1) gave 1,4-dideoxy-1,4-(*S*)-[3-(sulfooxy)propyl]episulfoniumylidene-D-arabinitol inner salt (**5**, 38 mg, 20%) as a colorless oil.

*Method B*. A mixture of **8** (104 mg, 0.75 mmol), **3** (75 mg, 0.67 mmol), potassium carbonate (28 mg, 0.2 mmol), and HFIP (1.2 ml) was stirred at 60 °C for 60 h. After removal of the solvent, the residue was triturated with diethyl ether to give a pale yellow oil (212 mg), which on column chromatography (AcOEt–MeOH–$H_2O$, 20:4:1) gave **5** (88 mg, 61%) as a colorless oil.

**5**: colorless oil. $[\alpha]_D^{24}$ +0.4 (*c* 1.4, MeOH). IR (neat): 3514, 1651, 1285, 1177, 1098 $cm^{-1}$. $^1H$ NMR ($CD_3OD$) $\delta$: 2.24–2.34 (2H, m, H-2′), 3.61 (1H, ddd, $J$ = 12.9, 6.9, 6.3 Hz, H-1′a), 3.67 (1H, ddd, $J$ = 12.9, 7.5, 7.5 Hz, H-1′b), 3.78 (1H, dd, $J$ = 12.6, 3.4 Hz, H-1a), 3.88 (1H, t-like, $J$ = 10.9 Hz, H-5a), 3.90 (1H, d-like, $J$ = 12.6 Hz, H-1b), 3.94 (1H, dd, $J$ = 10.9, 4.0 Hz, H-4), 4.06 (1H, dd, $J$ = 10.9, 4.0 Hz, H-5b), 4.18 (2H, t, $J$ = 5.8 Hz, H-3′), 4.37 (1H, br s, H-3), 4.64 (1H, br s, H-2). $^{13}C$ NMR ($CD_3OD$) $\delta$: 27.1 (C-2′), 44.1 (C-1′), 49.3 (C-1), 60.9 (C-5), 66.4 (C-3′), 73.7 (C-4), 79.3 (C-2), 79.6 (C-3). FABMS *m*/*z*: 289 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 289.0429 ($C_8H_{17}O_7S_2$ requires 289.0416).

Following the method A, a mixture of **9** (342 mg, 1.4 mmol), **3** (142 mg, 0.93 mmol), sodium carbonate (297 mg, 2.8 mmol), and DMF (300 μl) was stirred at 45 °C for 60 h. Work-up gave a pale brown oil (745 mg), which on column chromatography (AcOEt–MeOH–$H_2O$, 20:4:1) gave 1,4-dideoxy-1,4-(*S*)-[2-benzyloxy-3-(sulfooxy)propyl]episulfoniumylidene-D-arabinitol inner salt (**32**, 92 mg, 25%) as a 1:1 diastereomeric mixture.

Following the method B, a mixture of **9** (366 mg, 1.5 mmol), **3** (150 mg, 1.0 mmol), potassium carbonate (69 mg, 0.5 mmol), and HFIP (1.5 ml) was stirred at 65 °C for 60 h. Work-up gave a pale yellow oil (685 mg), which on column chromatography (AcOEt–MeOH–$H_2O$, 20:4:1) gave **32** (179 mg, 45%) as a 1:1 diastereomeric mixture.

**32**: colorless prisms. Mp 161–164.5 °C (from MeOH–$Et_2O$). IR (KBr): 3435, 1269, 1196, 1011 $cm^{-1}$. $^1H$ NMR ($CD_3OD$) $\delta$: 3.55 (0.5H, br dd, $J$ = 12.6, 2.3 Hz, H-1a), 3.75 (0.5H, dd, $J$ = 12.6, 3.7 Hz, H-1b), 3.76–4.03 (4.5H, m, H-1a*, H-1b*, H-1′a, H-1′a*, H-1′b, H-1′b*, H-4, H-4*, H-5a, H-5a*, H-5b, H-5b*), 4.17–4.23 (2.5H, m, H-3′a, H-3′a*, H-3′b, H-3′b*, H-2′), 4.25–4.29 (0.5H, m, H-2′*), 4.34 (0.5H, br s, H-3), 4.37 (0.5H, br s, H-3*), 4.55–4.59 (1H, m, H-2, H-2*), 4.63 (0.5H, d, $J$ = 11.2 Hz, OC*H*HPh), 4.64 (0.5H, d, $J$ = 11.5 Hz, OC*H*HPh), 4.72 (0.5H, d, $J$ = 11.5 Hz, OCH*H*Ph), 4.79 (0.5H, d, $J$ = 11.2 Hz, OCH*H*Ph), 7.23–7.45 (10H, m, arom.). $^{13}C$ NMR ($CD_3OD$) $\delta$:

49.6/50.2 (C-1′), 50.7/52.1 (C-1), 60.8/60.9 (C-5), 67.1/67.3 (C-3′), 73.0/73.2 (O*C*$H_2$Ph), 73.8/73.9 (C-4), 73.9/74.5 (C-2′), 79.3/79.5 (C-2), 79.6/80.0 (C-3), 129.3/129.4/129.55/129.59/129.7/129.8 (d, arom.), 138.5/138.7 (s, arom.). FABMS *m*/*z*: 395 $[M+H]^+$ (pos). FABHRMS *m*/*z*: 395.0829 ($C_{15}H_{23}O_8S_2$ requires 395.0835).

Following the method A, a mixture of **10** (231 mg, 0.82 mmol), **3** (82 mg, 0.55 mmol), sodium carbonate (174 mg, 2.8 mmol), and DMF (200 μl) was stirred at 45 °C for 60 h. Work-up gave a pale brown oil (313 mg), which on column chromatography ($CHCl_3$–MeOH 7:1) gave 1,4-dideoxy-1,4-(*S*)-[(3*S*)-4-*tert*-butyldimethylsiloxy-3-(sulfooxy)butyl]episulfoniumylidene-D-arabinitol inner salt (**33**, 47 mg, 20%) as a colorless oil.

**33**: colorless oil. $[\alpha]_D^{25}$ +19.3 (*c* 0.81, MeOH). IR (neat): 3412, 1651, 1215, 1061 $cm^{-1}$. $^1H$ NMR ($CD_3OD$) *δ*: 0.10 [6H, s, $Si(CH_3)_2{}^tBu$], 0.91 [9H, s, $SiMe_2C(CH_3)_3$], 2.18–2.34 (2H, m, H-2′), 3.63 (1H, ddd, *J* = 12.1, 6.0, 5.6 Hz, H-1′a), 3.70–3.91 (7H, m, H-1a, H-1b, H-4, H-5a, H-1′b, H-4′a, H-4′b), 4.02–4.08 (1H, m, H-5b), 4.34 (1H, br s, H-3), 4.45–4.49 (1H, m, H-3′), 4.62 (1H, br s, H-2). $^{13}C$ NMR ($CD_3OD$) *δ*: −6.6/−6.5 [$Si(CH_3)_2{}^tBu$], 17.9 [$SiMe_2C(CH_3)_3$], 25.1 [$SiMe_2C(CH_3)_3$], 27.8 (C-2′), 42.2 (C-1′), 48.2 (C-1), 59.6 (C-5), 64.3 (C-4′), 72.8 (C-4), 75.6 (C-3′), 77.9 (C-2), 78.2 (C-3). FABMS *m*/*z*: 431 $[M-H]^-$ (neg.). FABHRMS *m*/*z*: 431.1222 ($C_{15}H_{31}O_8SiS_2$ requires 431.1230).

### 3.15. 1,4-Dideoxy-1,4-(*S*)-[2-hydroxy-3-(sulfooxy)propyl]episulfoniumylidene-D-arabinitol Inner Salt (6)

A solution of **32** (60 mg, 0.15 mmol) in a 20% aqueous acetic acid (2 ml) was hydrogenated in a manner similar to that used for hydrogenation of compound **30**. Work-up gave a colorless oil (98 mg), which on column chromatography (AcOEt–MeOH–$H_2O$, 20:4:1) gave **6** (28 mg, 60%) as a colorless solid, mp 148–151 °C (from MeOH–$Et_2O$). IR (KBr): 3464, 3360, 1258, 1204, 1061, 1030, 1011 $cm^{-1}$. $^1H$ NMR ($CD_3OD$) *δ*: 3.70 (0.5H, dd, *J* = 13.2, 8.3 Hz, H-1′a), 3.73 (0.5H, dd, *J* = 13.2, 7.8 Hz, H-1′a*), 3.79 (0.5H, dd, *J* = 13.2, 4.1 Hz, H-1′b), 3.83 (0.5H, dd, *J* = 13.2, 3.8 Hz, H-1′b*), 3.83–3.88 (2H, m, H-1a, H-1a*, H-1b, H-1b*), 3.92 (0.5H, dd, *J* = 13.5, 11.2 Hz, H-5a), 3.96 (0.5H, dd, *J* = 11.8, 8.6 Hz, H-5a*), 3.96–4.05 (3H, m, H-3′a, H-3′a*, H-5b, H-5b*, H-4, H-4*), 4.09 (0.5H, dd, *J* = 10.9, 2.6 Hz, H-3′b), 4.11 (0.5H, dd, *J* = 13.7, 2.6 Hz, H-3′b*), 4.31–4.35 (1H, m, H-2′, H-2′*), 4.37 (0.5H, dd, *J* = 2.6, 1.2 Hz, H-3), 4.41 (0.5H, dd, *J* = 2.0, 1.7 Hz, H-3*), 4.60–4.63 (1H, m, H-2, H-2*). $^{13}C$ NMR ($CD_3OD$) *δ*: 50.7/51.7 (C-1), 50.8/51.3 (C-1′), 60.9 (C-5), 67.3 (C-2′), 70.2/70.3 (C-3′), 73.3/73.7 (C-4), 79.4 (C-2), 79.5/79.8 (C-3). FABMS *m*/*z*: 305 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 305.0342 ($C_8H_{17}O_8S_2$ requires 305.0364).

### 3.16. 1,4-Dideoxy-1,4-(*S*)-[(3*S*)-4-hydroxy-3-(sulfooxy)-butyl]episulfoniumylidene-D-arabinitol Inner Salt (7)

A solution of **33** (29 mg, 0.07 mmol) and 0.1% hydrochloric acid (1 ml) was stirred at 40 °C for 4 h. Deposited solid was removed by filtration, and the filtrate was neutralized with ion exchange resin (IRA-67). After removal of the resin by filtration, the filtrate was concentrated in vacuo. The residue (20 mg) was purified on column chromatography (AcOEt–MeOH–$H_2O$ 20:4:1) to give **7** (16 mg, 75%) as a colorless oil, $[\alpha]_D^{24}$ +11.9 (*c* 1.2, MeOH). IR (neat): 3360, 1651, 1215, 1065, 1042, 1018 $cm^{-1}$. $^1H$ NMR ($CD_3OD$) *δ*: 2.23–2.27 (1H, m, H-2′), 3.63 (1H, dt, *J* = 12.9, 6.3 Hz, H-1′a), 3.71 (1H, dd, *J* = 12.9, 4.0 Hz, H-4′a), 3.72–3.77 (1H, m, H-1′b), 3.75 (1H, dd, *J* = 12.9, 4.9 Hz, H-4′b), 3.78 (1H, dd, *J* = 12.3, 3.2 Hz, H-1a), 3.85 (1H, d-like, *J* = 12.3, H-1b), 3.86 (1H, t-like, *J* = 9.8 Hz, H-5a), 3.90 (1H, br dd, *J* = 9.8, 3.2 Hz, H-4), 4.04 (1H, dd, *J* = 9.8, 3.2 Hz, H-5b), 4.34 (1H, br s, H-3), 4.47–4.53 (1H, m, H-3′), 4.63 (1H, br s, H-2). $^{13}C$ NMR ($CD_3OD$) *δ*: 28.8 (C-2′), 43.5 (C-1′), 49.3 (C-1), 60.9 (C-5), 64.5 (C-4′), 73.9 (C-4), 77.5 (C-3′), 79.2 (C-2), 79.5 (C-3). FABMS *m*/*z*: 319 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 319.0540 ($C_9H_{19}O_8S_2$ requires 319.0522).

### 3.17. X-ray crystallographic analysis

Data of both compounds **6** and **9** were taken on a Rigaku AFC5R diffractometer with graphite-monochromated Mo-Kα radiation (*λ* = 0.71069 Å). The structures of **6** and **9** were solved by direct methods with SAPI91[16] and SIR97,[17] respectively. Full-matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. All calculations were performed using the teXsan[18] crystallographic software package of Molecular Structure Corporation. ORTEP drawings of compounds **6** and **9** are shown in Figures 2 and 1, respectively. The data of **6** and **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 265901 and CCDC 265900, respectively.

**3.17.1. Crystal data for sulfonium sulfate 6.** Orthorhombic, space group $P2_12_12_1$, *a* = 9.719(5), *b* = 18.056(6), *c* = 6.872(4) Å, *V* = 1205.9(7) $Å^3$, *Z* = 4, μ(Mo-Kα) = 4.73 $cm^{-1}$, *F*(000) = 640, $D_c$ = 1.676 g/$cm^3$, crystal dimensions: 0.06 × 0.22 × 0.30 mm. A total of 1629 reflections (1609 unique) were collected using the *ω*–2*θ* scan technique to a maximum 2*θ* value of 55°, and 1400 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final *R* and $R_w$ values were 0.054 and 0.073, respectively. The maximum and minimum peaks in the difference map were 0.39 $e^- Å^{-3}$ and −0.30 $e^- Å^{-3}$, respectively.

**3.17.2. Crystal data for cyclic sulfate 9.** Monoclinic, space group $P2_1$, *a* = 9.306(3) Å, *b* = 12.839(2) Å, *c* = 9.956(2) Å, β = 101.58(2)°, *V* = 1165.4(5) $Å^3$, *Z* = 4, μ(Mo-Kα) = 2.8 $cm^{-1}$, *F*(000) = 512, $D_c$ = 1.392 g/$cm^3$, crystal dimensions: 0.12 × 0.14 × 0.30 mm. A total of 2740 reflections (2582 unique) were collected using the *ω*–2*θ* scan technique to a maximum 2*θ* value of 55°, and 1860 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final *R* and $R_w$ values were 0.057 and 0.091, respectively. The maximum and minimum peaks in the difference map were 0.56 $e^- Å^{-3}$ and −0.75 $e^- Å^{-3}$, respectively.

### 3.18. Enzyme inhibition assays

Rat small intestinal brush border membrane vesicles were prepared and their suspension in 0.1 M maleate buffer (pH 6.0) was used as small intestinal α-glucosidase of maltase and sucrase. Test compound was dissolved in dimethylsulfoxide DMSO, and the resulting solution was diluted with 0.1 M maleate buffer to prepare the test compound solution (concentration of DMSO: 10%). The substrate solution in the maleate buffer (maltose: 74 mM, sucrose: 74 mM, 100 μl), test compound solution (50 μl), and the enzyme solution (50 μl) were mixed and incubated at 37 °C for 30 min. After incubation, the solution was mixed with water (0.8 ml) and was immediately heated by boiling water for 2 min to stop the reaction. Glucose concentration was then determined by the glucose-oxidase method. Final concentration of DMSO in test solution was 2.5% and no influence of DMSO was detected on the inhibitory activity.

## Acknowledgments

This study was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science. The authors also thank Pharmaceutical Research and Technology Institute of Kinki University for financial support.

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