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Role of the side chain stereochemistry in the α-glucosidase inhibitory activity of kotalanol, a potent natural α-glucosidase inhibitor. Part 2

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ABSTRACT

To examine the role of the side chain of kotalanol (**2**), a potent natural α-glucosidase inhibitor isolated from *Salacia reticulata*, on inhibitory activity, four diastereomers (**11a**–**11d**) with reversed configuration (*S*) at the C-4′ position in the side chain were synthesized and evaluated. Two of the four (**11b** and **11d**) significantly lost their inhibitory activity against both maltase and sucrase, while the other two (**11a** and **11c**) sustained the inhibitory activity to a considerable extent, showing distinct activity in response to the change of stereochemistry of the hydroxyls at the 5′and 6′ positions. Different activities were rationalized with reference to in silico docking studies on these inhibitors with hNtMGAM. Against isomaltase, all four analogs showed potent inhibitory activity as well as **2**, and **11b** and **11d** exhibited enzyme selectivity.

1. Introduction

In the late 1990s the highly potent α-glucosidase inhibitor, salacinol (**1**), was isolated from *Salacia reticulata*, a traditional Ayurvedic medicine that has been used for the treatment of diabetes in Sri Lanka and the southern region of India.[1] The structure of **1**, established by X-ray crystallographic analysis, was quite unique. Specifically, the ring sulfonium ion was stabilized by the sulfate counter anion through spirobicyclic-like configuration comprised of 1-deoxy-4-thio-D-arabinofranosyl cation and 1-deoxy-L-erythro-syl-3-sulfate anion.[1] The α-glucosidase inhibitory activity of **1** was potent and was revealed to be as strong as that of voglibose and acarbose, which have been widely used clinically.[1] The related sulfonium sulfate, kotalanol (**2**), was subsequently isolated from *Salacia* extracts and was shown to possess even higher inhibitory power against α-glucosidases.[2] Human clinical trials, conducted with a *Salacia reticulata* extract on patients with type-2 diabetes have shown effective treatment with minimal side effects.[3] Thereafter, the side chain analogues, ponkolanol[4] (**3**) and salaprinol[4] (**4**), as well as the de-O-sulfonated analogues, neosalacinol[5] (**5**), neokotalanol[6] (**6**), neoponkoranol[7] (**7**), and neosaraprinol[7] (**8**), were also isolated from the same plant genus (Fig. 1). Other than **4** and **8**, these sulfonium salts (**3**, **5**, **6**, and **7**) were shown to have α-glucosidase inhibitory activities similar to **1** and **2**.[4–7]

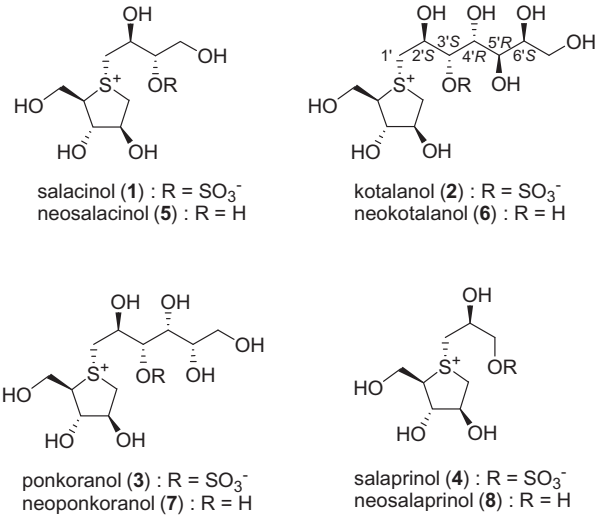

Figure 1. Thiosugar sulfonium salts as a new class of α-glucosidase inhibitors.

Because of sulfonium salts' intriguing structures and high α-glucosidase inhibitory activities, intensive structure–activity

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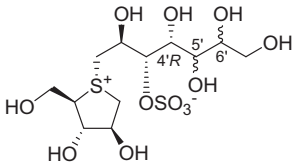

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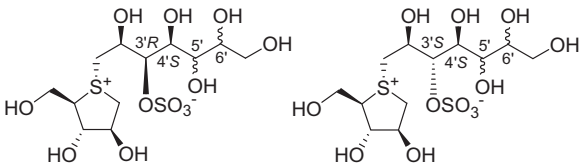
a : 5'α-OH, 6'α-OH
c : 5'α-OH, 6'β-OH **d** : 5'β-OH, 6'α-OH



10 **11**

a : 5'α-OH, 6'α-OH **b** : 5'β-OH, 6'β-OH
c : 5'α-OH, 6'β-OH **d** : 5'β-OH, 6'α-OH

Figure 2. Kotalanol (**2**) and its side chain diastereomers.

relationship (SAR) studies have been conducted.[8] Heterocyclic analogues, six-membered ring analogues, and those with different thiosugar stereochemistry, as well as their side chain stereoisomers, were extensively synthesized, by replacing the sulfonium center by a selenonium or an ammonium ion, and evaluated. Important structural determinants for the inhibitory activities have been revealed by this work.[8] The exact stereo-structure of the side chains of **1**, **3**, and **4** were elucidated soon after their isolation by total syntheses[9] and/or through the SAR studies[8l–n] described above; that of **2** was recently clarified by total synthesis performed by Pinto and co-workers.[10] In that process, side chain diastereomers (**9a**, **9c**, and **9d**) of **2** were synthesized and some important stereo-structural factors of the side chain activity were revealed.[8d,8f]

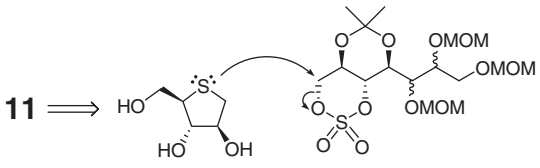
In the course of our independent efforts to elucidate the structure of **2**, a group of diastereomers (**10a**, **10b**, **10c**, and **10d**), which have reversed stereochemistry to **2** at both C-3′ and C-4′ positions, were also synthesized. SAR studies on the diastereomers had confirmed the known stereo-structural factors of the side chain activity.[11] In this continuing study, we synthesized and evaluated four sulfonium sulfates (**11a**, **11b**, **11c**, and **11d**) in which stereochemistry at C-4′ is diverted to *S* as a common feature (Fig. 2). Evaluation and comparison of the α-glucosidase inhibitory activities of these sulfonium sulfates with those of **2** and related diastereomers provided additional stereo-structural factors for the inhibitory activity. This suggested another binding mode and/or binding sites between the inhibitors and enzymes.

2. Results and discussion

2.1. Preparation of cyclic sulfates

The target compounds (**11a**–**11d**) were prepared by the regioselective ring-opening reaction of cyclic sulfates (**12a**–**12d**) with a thiosugar, 1,4-dideoxy-1,4-epithio-D-arabinitol (**13**), as the key reaction (Scheme 1).[9] A common synthon for the four cyclic sulfates (**12a**–**12d**), 3,5-di-*O*-benzyl-D-ribofuranose[12] (**14**) was selected and prepared by conversion of the C-3 stereochemistry starting from commercially available D-xylose (**15**).

Thus, 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose[8m] (**16**) was subjected to Swern oxidation. This was



13 **12**

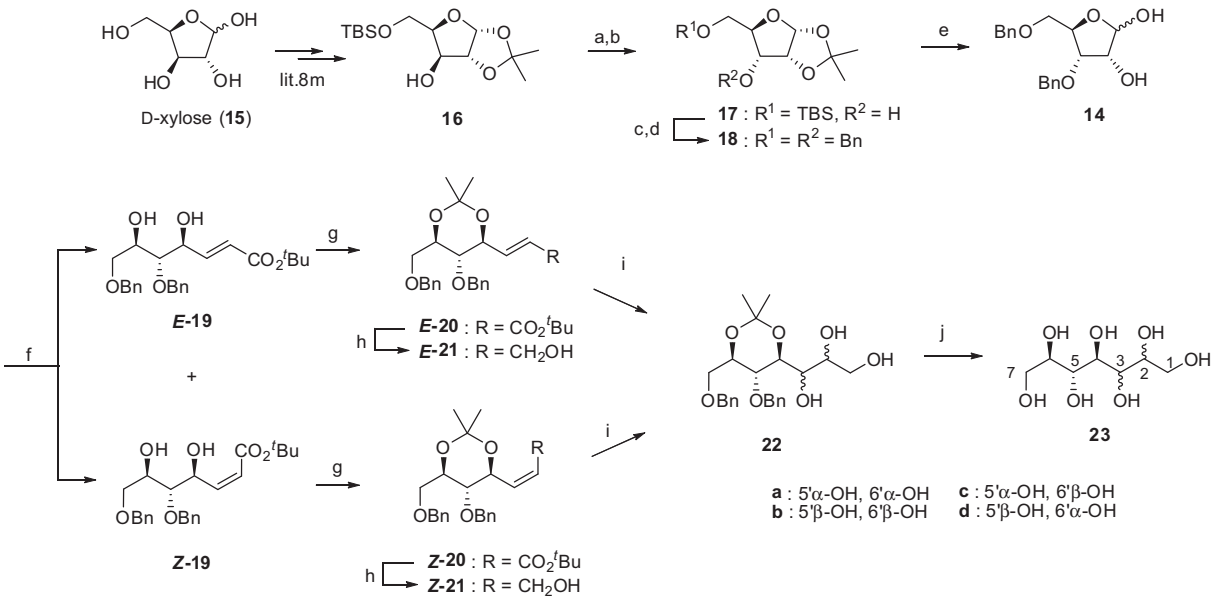
a : 5'α-OMOM, 6'α-OMOM **b** : 5'β-OMOM, 6'β-OMOM
c : 5'α-OMOM, 6'β-OMOM **d** : 5'β-OMOM, 6'α-OMOM

Scheme 1. The key step for the synthesis of **11a**–**11d**.

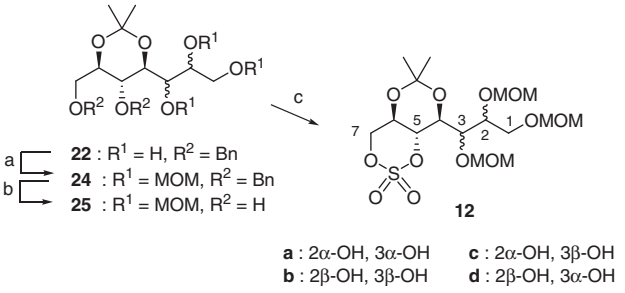
followed by the reduction of sodium borohydride of the resulting keto sugar to give a desired epimer of **16**, 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-ribofuranose[13] (**17**), in good yield. The TBS moiety of **17** was selectively hydrolyzed with diluted hydrochloric acid and subsequent dibenzylation of the resulting diol with benzyl (Bn) bromide gave 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribofuranose[12b,14] (**18**) in 81% yield from **16**. The acetal moiety of **18** was removed by the action of 0.5% aqueous sulfuric acid in 1,4-dioxane to give **14** as a *ca.* 1:1.5 anomeric mixture.

Next, the mixture of two anomers (α and β-**14**) was treated with *tert*-butoxycarbonylmethylenetriphenylphosphorane to give *tert*-butyl (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-D-*ribo*-hept-2-enoate (***E*-19**), and its *Z*-isomer (***Z*-19**) in 73% and 15% yields, respectively. The major 1,3-diol ***E*-19** was then converted to the corresponding acetal, *tert*-butyl (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*ribo*-hept-2-enoate (***E*-20**), by treatment with 2,2-dimetoxypropane. Subsequent reduction of the crude products with diisopropyl aluminum hydride (DIBAL) gave *E*-allyl alcohol, (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*ribo*-hept-2-enitol (***E*-21**), in 93% yield from enoate ***E*-19**. In a similar manner, the minor enoate ***Z*-19** was converted to the corresponding *Z*-allyl alcohol (***Z*-21**) in good yield. With compounds ***E*-** and ***Z*-21** in hand, osmium tetroxide catalyzed dihydroxylation was performed in the presence of *N*-methylmorphorine *N*-oxide (NMO). Upon reaction with *E*-allyl alcohol ***E*-21**, a *ca.* 3:1 mixture of two triols, 1,3-di-*O*-benzyl-2,4-*O*-isopropylidene-D-*glycero*-L-*allo*-heptitol (**22a**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-D-*gluco*-heptitol (**22b**), was obtained. Newly developed *threo* stereochemistry of triols **22a** and **22b** was confirmed after leading them to the known heptitols, D-*glycero*-L-*allo*-heptitol[15] (**23a**) and D-*glycero*-D-*gluco*-heptitol[15] (**23b**). Dihydroxylation of *Z*-isomer ***Z*-21** in a similar manner gave a *ca.* 1:1 mixture of 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-D-*allo*-heptitol (**22c**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-D-*manno*-heptitol (**22d**). The *erythro* stereochemistry at the 5 and 6 positions of **22c** and **22d** was also confirmed after derivatization to **23c**[15] and **23d**,[15] respectively. (Scheme 2)

A mixture of triols **22a** and **22b** was then treated with chloromethyl methyl ether (MOMCl) to give 1,3-di-*O*-benzyl-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-D-*glycero*-L-*allo*-heptitol (**24a**) and 5,7-di-*O*-benzyl-4,6-*O*-propylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*gluco*-heptitol (**24b**) in 68% and 23% yields from ***E*-21**,respectively. Similarly, a mixture of **22c** and **22d** was converted to 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*allo*-heptitol (**24c**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*manno*-heptitol (**24d**) in 42% and 45% yields from *Z*-**21**, respectively. The tri-MOM ethers (**24a**–**24d**) obtained were then subjected to hydrogenolysis in the presence of a small amount of sodium hydrogen carbonate, which was added to avoid undesirable deprotection of acid-labile protecting groups by a contaminated acid arising from the Pd–C catalysts,[16] to give corresponding diols: 2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxy-



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, –60 to –30 °C, then NEt_3; (b) $NaBH_4$, EtOH, H_2O, –30 to 10 °C; (c) 0.2% aq HCl, THF, rt; (d) BnBr, NaH, DMF, 0 °C; (e) 0.5% aq H_2SO_4, 1,4-dioxane, reflux; (f) $Ph_3P{=}CHCO_2{}^tBu$, CH_2Cl_2, reflux; (g) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, acetone, rt; (h) 1 M soln. of DIBAL in toluene, THF, –60 °C to rt; (i) OsO_4, NMO, acetone, H_2O, reflux, (j) H_2, Pd–C, 80% aq AcOH, 60 °C.



Scheme 3. Reagents and conditions: (a) MOMCl, $^iPr_2NEt$, DMF, 60 °C; (b) H_2, Pd-C, $NaHCO_3$, 1,4-dioxane, 60 °C; (c) $SOCl_2$, NEt_3, CH_2Cl_2, 0 °C, then $NaIO_4$, $RuCl_3{\bullet}n$-H_2O, $NaHCO_3$, CH_3CN, CCl_4, H_2O, 0 °C.

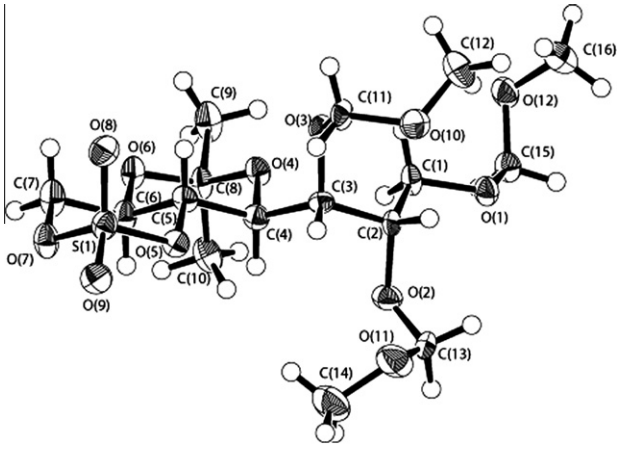


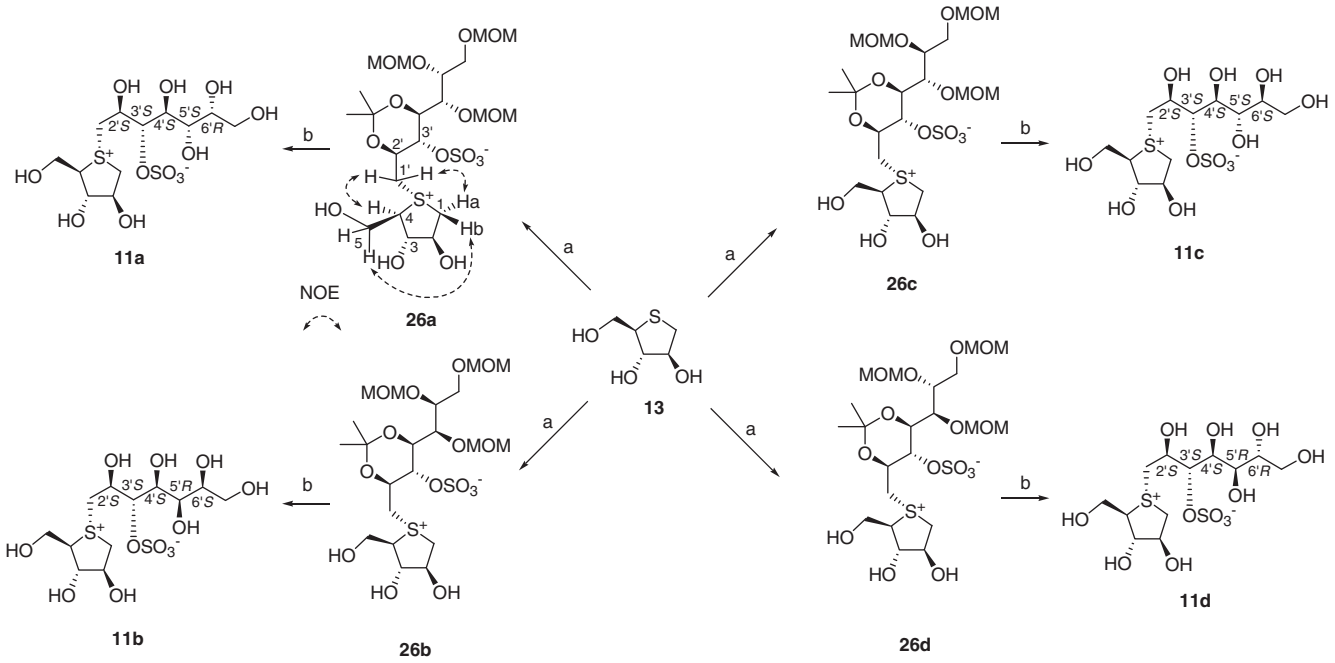
Figure 3. Perspective view of compound **12b**.

methyl-D-*glycero*-L-*allo*-heptitol (**25a**), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*gluco*-heptitol (**25b**), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*allo*-heptitol (**25c**), and 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*manno*-heptitol (**25d**) in approximately 95% yield. Finally, the diols (**25a**–**25d**) were converted to the desired cyclic sulfates (**12a**–**12d**) by cyclic sulfation in 43–75% yields (Scheme 3).

The spectroscopic properties of these cyclic sulfates were very similar. All the products (**12a**–**12d**) showed protonated molecular-ion $[M+H]^+$ peaks at *m*/*z* 447 in their fast atom bombardment (FAB) mass spectra. In their ^1H NMR spectra, highly deshielded signals due to C-1 methylene and C-3 methine protons were observed at around δ 4.5–4.9 [i.e., for **12a**: δ_H 4.46 (H-1_{eq}), 4.60 (H-1_{ax}), and δ_H 4.87 (H-3)], supporting the cyclic sulfate formation. Large vicinal coupling constants ($J_{2,3}$ = 9.8 and $J_{3,4}$ = 9.8 Hz) were observed for **12a**, which indicated that three protons at C-2, C-3, and C-4 were in axial orientation. With regard to compound **12b**, fine single crystals were obtained, and structural confirmation was also established based on X-ray crystallographic analysis (Fig. 3).

2.2. Preparation of kotalanol analogues (11a, 11b, 11c, and 11d)

The coupling reaction of thiosugar **13** and the cyclic sulfates (**12a**–**12d**) proceeded at 60 °C in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to give corresponding sulfoniums (**26a**–**26d**) in 91, 90, 86, and 92% yield, respectively (Scheme 4). The spectral properties of the products (**26a**–**26d**) were similar. In the FAB mass spectra run in a positive mode the peaks observed at *m*/*z* 597 corresponded to the protonated molecular-ion $[M+H]^+$. In the ^1H NMR spectrum, downfield signal shifts associated with sulfonium ion formation, were observed due to C-1 methylene (around δ_H 3.8) and C-4 methine (around δ_H 4.0) protons. A pair of one-proton doublet of doublets, which appeared at around δ_H 4.0 due to methylene protons α to the sulfur atom in the side chain, also supported the sulfonium ion formation. The relative stereochemistry between the side chain and the methanol moiety at C-4 of all the coupled products (**26a**–**26d**) was determined to be in *trans* on the basis of nuclear Overhauser effect (NOESY) experiments, as shown in Scheme 4. Deprotection of **26a**, **26b**, **26c**, and **26d**, by the action of 30% aqueous trifluoroacetic acid, gave the target sulfonium salts **11a**, **11b**, **11c**, and **11d** in 78, 82, 92, and 95% yields, respectively. All the compounds showed protonated molecular-ion peaks $[M+H]^+$ at *m*/*z* 425; their molecular formula $C_{12}H_{24}O_{12}S_2$ was confirmed by the HR–FAB mass spectra. The ^{13}C NMR spectroscopic properties of the products are shown in Table 1.



Scheme 4. Reagents and conditions: (a) cyclic sulfate **12a**, **12b**, **12c** or **12d**, HFIP, K_2CO_3, 60 °C; (b) 30% aq TFA, 50 °C.

Table 1
^{13}C NMR data for kotalanol (**2**), **11a**, **11b**, **11c** and **11d**

	2[b]	**11a**[a]	**11b**[a]	**11c**[b]	**11d**[a]
C-1	51.1	51.5	51.7	51.5	51.7
C-2	79.0	79.2	79.3	79.2	79.3
C-3	79.9	79.7	79.6	79.7	79.6
C-4	73.0	73.3	73.1	73.3	73.2
C-5	60.8	61.0	60.9	61.0	60.9
C-1′	53.3	52.7	51.7	52.5	51.6
C-2′	67.8	68.0	69.3	67.9	69.7
C-3′	79.0	81.9	80.2	81.0	79.9
C-4′	69.9	72.6	73.2	73.9	70.9
C-5′	70.5	72.2	70.8	73.8	71.2
C-6′	71.8	71.8	74.8	74.3	72.4
C-7′	65.1	64.7	64.0	64.4	65.1

[a] Measured at 125 MHz.
[b] Measured at 150 MHz, in CD_3OD.

Table 2
IC_{50} values (μM) of thiosugar sulfonium sulfate inner salts against disaccharidases

Entry	Compd	Maltase	Sucrase	Isomaltase
1	**1**[a]	5.2	1.6	1.3
2	**2**[a]	7.2	0.75	5.7
3	**10a**	>236 (25)[b]	>236 (8)[b]	16
4	**10b**	>236 (32)[b]	>236 (28)[b]	20
5	**10c**	>236 (45)[b]	>236 (34)[b]	21
6	**10d**	134	55	58
7	**11a**	49	67	1.6
8	**11b**	>236 (42)[b]	136	11
9	**11c**	58	32	6.5
10	**11d**	>236 (44)[b]	214	16

[a] Lit.4.
[b] Values in parentheses indicate inhibition (%) at 100 μg/ml [236 μM, (MW for **10a**–**10d** and **11a**–**11d**: 424)].

2.3. α-Glucosidase inhibitory activity

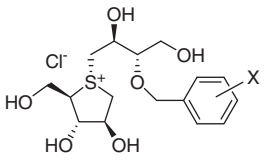
The glycosidase inhibitory activities of the synthesized compounds (**11a**–**11d**) against rat small intestinal α-glucosidases were tested in vitro and compared with those of **2** and related diastereomers (**10a**–**10d**), as shown in Table 2. In addition to the fundamental requirements for the thiosugar moiety, based on the intensive SAR studies, several important determinants with respect to the length and stereostructure of the side chain have been revealed: (a) 2′*S*-OH is essential for the activity; (b) a polyhydroxylated side chain longer than four carbons does not significantly enhance the inhibitory activity; (c) the cooperative role of 2′*S*-OH and 4′-OH is critical for onset of strong inhibition; and the *R* configuration of OH at C4′ is imperative to inhibitors bearing a side chain of more than four carbons.

As shown in Table 2, all four diastereomers (**11a**–**11d**) synthesized in this study showed less activity than kotalanol (**2**) against maltase and sucrase. In particular, two (**11b** and **11d**) lost considerable activity against these two enzymes, which is consistent with the previously known determinants [(a), (b), (c)]. However, it is noteworthy that among the eight diastereomers (**10a**–**10d**, **11a**–**11d**) with 4′*S*-OH configuration, two isomers (**11a** and **11c**), which have the reverse stereochemistry at the C5′ position (5′*S*-OH) to **2**, retained moderate activity against maltase and sucrase. The other six isomers lost considerable activity. The present results suggest that the OH groups at the C5′ and C6′ positions play a role in bindings with these enzymes and/or contribute to conformational stabilization of the polyhydroxylated chain by any intramolecular hydrogen bonding, although the previous SAR studies suggested that polyhydroxylated side chains longer than four carbons do not enhance inhibitory activity significantly (determinant b).

In humans, family GH31 glycoside hydrolases maltase-glucoamylase (MGAM) and sucrase-isomaltase (SI) are responsible for the digestion of terminal starch products left after the action of R-amylase. These membrane-bound enzymes are known to contain two catalytic subunits: an N-terminal subunit (ntMGAM and ntSI), which is proximal to the membrane-bound end and a C-terminal luminal subunit (ctMGAM and ctSI). Rat intestinal maltase is known to be homologous to hNtMGAM.[17] The substrate specificities of the catalytic subunits vary and overlap to include maltose, isomaltose, sucrose, and small linear and branched oligosaccharides.[18]

The binding features of these sulfonium type inhibitors to the subunit have been revealed by a recent X-ray crystallographic

study on the complex of **2** with human ntMGAM[19a] and an in silico docking study of **1** with the subunit.[19b] With the aid of an in silico docking study, we recently found that introduction of a monosubstituted benzyl group (**27**) at the C3′ position of neosalacinol (**5**) enhanced the inhibitory activity against maltase ca. 40-fold. This enhancement was caused by the different binding modes of the substituent to the surrounding amino acid residues.[20]



27

X = CH_3, Cl, CF_3, NO_2

The different activities of **11a** and **11d** were reasonably rationalized based on the results of an in silico docking simulation study. Calculations indicated that the binding modes of C2′-OH, C4′-OH, and C6′-OH in both **11a** and **11d** with ntMGAM were quite similar; four hydrogen bonds were detected with surrounding amino acid residues, as shown in Figure 4 (A and B, blue dotted line b, c, d, e). It is noteworthy that in **11d**, the 5′*R*-OH group is shown to make a rather flexible 8-membered ring by forming an intramolecular hydrogen bonding with one of the oxygen atom in SO_3^- at C3′ (Fig. 4B, blue dotted line *a*). In contrast, 5′*S*-OH in **11a** was found to form a stable 6 membered ring (C3′–C4′–C5′–C5′O–H–C3′O–C3′), which would contribute to the more efficient formation of the two hydrogen bondings (Fig. 4A, b and c) than the flexible 8-membered ring (Fig. 4B, b and c). Additionally, in **11a**, van der Waals interactions were detected between the oxygen atom at C5′ and the hydrophobic parts of Trp406 and Phe450 (Fig. 4A, green arrows *f* and *g*); however, these affinity factors were not observed in **11d**.

The compound (**11a**) is less potent than kotalanol (**2**) although the quantitative contributions of the intermolecular hydrogen bonds (i.e. four hydrogen bonds indicated by *b*, *c*, *d* and *e* in Figure 4) are the same between them. The less activity of **11a** would be caused by the intramolecular conformational strain induced by the two hydroxyls (2′*S*-OH and the 4′*S*-OH) in **11a**. Both the 4′*S*-OH and the 6′*S*-OH in **11a** and **2** are forming the hydrogen bonds with Asp203 as shown by *b* and *c*. In order to maximize the interactions to ntMGAM involving these interactions, the 2′*S*-OH and 4′*S*-OH in **11a** are compelled to be arranged in parallel as shown in Figure 4A, causing slight electrostatic repulsion between these two moieties, which is not observed in kotalanol (**2**). These unfavorable conformational deformations in **11a** would reduce the quality of hydrogen bonds with the protein, and caused the differences in the inhibitory activities.

As far as isomaltase is concerned, the four compounds (**11a**–**11d**) showed efficient activities. Two (**11b** and **11d**) selectively inhibited isomaltase. It is known that relatively small structural changes in a compound can result in significant changes in its ability to selectively inhibit one enzyme unit over others. For example, salacinol is a 4 to 5-fold better inhibitor of ctSI compared to the *N*-terminal enzymes and ctMGAM-N2. De-*O*-sulfonation of kotalanol resulted in a 10-fold change in activity against ntMGAM, with little effect on the other enzyme units.[21] Acarbose, an oral anti-diabetic medicine currently in use, shows a stronger level of inhibition against ctMGAM than ntMGAM.[22] The diastereomers of **2** with small stereostructural changes (**10a**–**10d**, **11a**–**11d**) and the previously synthesized isomers (**9a**, **9c**, **9d**) would be useful in further study to rationalize the different selectivity observed among them.

In summary, four diastereomers (**11a**–**11d**) of **2** with 4′C-*S* stereochemistry as the common structure were synthesized systematically by the coupling reaction of thiosugar (**13**) and cyclic sulfates (**12**) with appropriate stereochemistry. SAR studies based on the precise stereo-structural modification suggested an additional stereostructural factor with respect to the side chain properties of **2** in addition to the previously revealed requirements for this type of inhibitors to exert the activity. All the synthesized diastereomers were found to be potent inhibitors against isomaltase. These diastereomers of **2**, including those previously reported (**9a**, **9c**, **9d**, and **10a**–**10d**) would be useful in the study of the selectivity

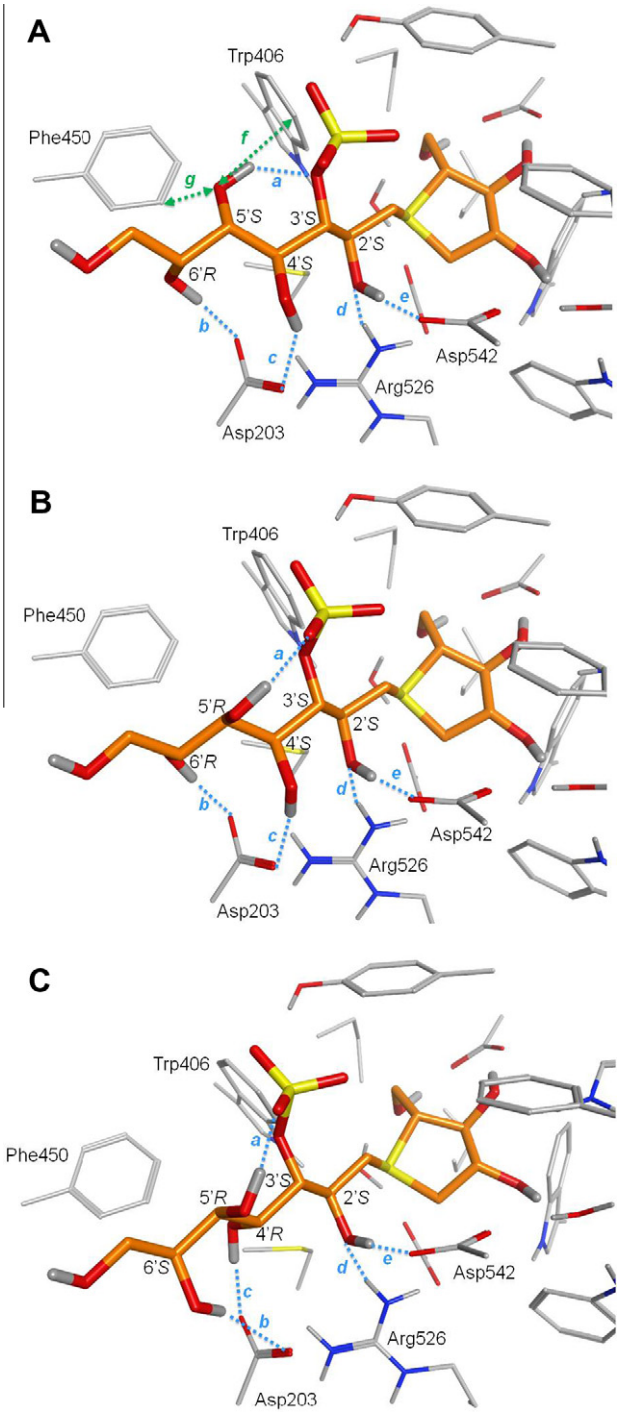


Figure 4. Superposition of **11a** [**A**], **11d** [**B**], and kotalanol (**2**) [**C**] in the hNtMGAM active site. The blue dotted lines show hydrogen bonding, and the double-headed green arrows show the van der Waals interactions of the oxygen atom with the amino acid residues (distances of *f*: 3.98 Å, *g*: 3.62 Å).

of these sulfonium type inhibitors against subunits of α-glucosidases. Further SAR studies, including in silico methods, to develop more potent inhibitors and to elucidate the factors that control the selectivity of these sulfoniums are in progress.

3. Experimental

Mps were determined on a Yanagimoto MP-3S micromelting point apparatus, and mps and bps are uncorrected. IR spectra were measured on either a Shimadzu IR-435 grating spectrophotometer or a Shimadzu FTIR-8600PC spectrophotometer. NMR spectra were recorded on a JEOL JNM-ECA 500 (500 MHz ^{1}H, 125 MHz ^{13}C) or a JEOL JNM-ECA 600 (600 MHz ^{1}H, 150 MHz ^{13}C) spectrometer. Low-resolution and high-resolution mass spectra were recorded on a JEOL JMS-HX 100 spectrometer. Optical rotations were determined with a JASCODIP-370 digital polarimeter. Column chromatography was effected over Fuji Silysia silica gel BW-200. All the organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

3.1. 5-*O*-(*tert*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (17)

A solution of 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose[8m] (**16**, 48 g, 158 mmol) in dichloromethane (65 ml) was added dropwise to a mixture of oxalyl chloride (20.5 ml, 240 mmol), dimethyl sulfoxide (34.1 ml, 480 mmol), and dichloromethane (200 ml) at −60 °C, and the reaction mixture was stirred for 1 h at −60 °C and another 30 min at −30 °C. After addition of a solution of triethylamine (78 ml, 561 mol) in dichloromethane (35 ml) at −30 °C, the reaction mixture was poured into water, and the resulting mixture was extracted with dichloromethane. The extract was washed with brine, and condensed to give the corresponding pentofuranos-3-ulose[13,23] (47.5 g) as an orange oil, which was used in the next step without purification. For analytical purpose a small portion was purified by means of column chromatography (*n*-hexane–AcOEt, 20/1) to give the ulose as colorless needles (from *n*-hexane). Mp. 38–39.5 °C, lit.[23] 40–43 °C. $[\alpha]_D^{24}$ +120.1 (c = 4.78, $CHCl_3$), lit.[13] $[\alpha]_D^{20}$ = +114 (c = 10.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.03/0.06 (each 3H, s, $Si(CH_3)_3{}^tBu$), 0.86 [9H, s, $SiMe_2C(CH_3)_3$], 1.45/1.46 [each 3H, s, $C(CH_3)_2$], 3.82 (1H, dd, J = 10.8, 2.2, H-5a), 3.88 (1H, dd, J = 10.8, 2.0, H-5b), 4.28 (1H, dd, J = 4.4, 1.1, H-2), 4.36 (1H, ddd, J = 2.2, 2.0, 1.1, H-4), 6.13 (1H, d, J = 4.4, H-1). ^{13}C NMR (150 MHz, $CDCl_3$) δ: −5.7/−5.5 [$SiC(CH_3)_3{}^tBu$], 18.1 [$SiMe_2C(CH_3)_3$], 25.7 [$SiMe_2C(CH_3)_3$], 27.2/27.7 [$C(CH_3)_2$], 63.9 (C-5), 77.1 (C-2), 81.7 (C-4), 103.8 (C-1), 114.1 [$C(CH_3)_2$], 211.0 (C-3).

To a solution of the crude ulose (47.3 g) in a mixture of ethanol (270 ml) and water (30 ml) was added sodium borohydride (11.8 g, 311 mmol) in small portions at −30 °C, and the reaction mixture was stirred at −10 °C for 2.5 h. After concentration of the mixture, the residue was diluted with water (500 ml) and extracted with dichloromethane. The extract was washed with brine, and condensed to give **17** as a colorless oil (47.8 g), which was used in the next step without purification. For analytical purpose a small portion was purified by means of column chromatography (*n*-hexane–AcOEt, 10/1) to give title compound **17**.[13]

3.1.1. Compound 17

Colorless oil. bp. 95–98 °C/0.004 mmHg. $[\alpha]_D^{24}$ = +31.8 (c = 1.46, $CHCl_3$), lit.[13] $[\alpha]_D$ = +25.7 (c = 4.1, $CHCl_3$). IR (neat): 3479, 1254, 1219, 1126, 1076, 1022 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.07/0.08 [each 3H, s, $Si(CH_3)_2{}^tBu$], 0.90 [9H, s, $SiMe_2C(CH_3)_2$], 1.37/1.57 [each 3H, s, $C(CH_3)_2$], 2.37 (1H, d, J = 9.7, OH), 3.79–3.84 (2H, m, H-4, H-5a), 3.89–3.93 (1H, m, H-5b), 4.00 (1H, ddd, J = 9.7, 5.0, 8.0, H-3), 4.57 (1H, dd, J = 5.0, 3.8, H-2), 5.81 (1H, d, J = 3.8, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.38/−5.34 [$Si(CH_3)_2{}^tBu$], 18.4 [$SiMe_2C(CH_3)_3$], 25.9 [$SiMe_2C(CH_3)_3$], 26.57/26.59 [$C(CH_3)_2$], 61.8 (C-5), 71.3 (C-3), 78.7 (C-2), 81.2 (C-4), 104.2 (C-1), 112.6 [$C(CH_3)_2$].

3.2. 3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-ribo-furanose (18)

A mixture of the crude alcohol **17** (23.6 g), tetrahydrofuran (650 ml), and 0.2% hydrochloric acid (500 ml) was stirred at room temperature for 2.5 h. After the reaction was quenched with sodium hydrogen carbonate, the resulting mixture was condensed in vacuo, and the resulting brown solid was washed with *n*-hexane. The *n*-hexane insoluble material was extracted with methanol (150 ml), and the brown methanol solution was treated with active charcoal. After filtration, the filtrate was condensed to give the corresponding diol, 1,2-*O*-isopropylidene-α-D-ribofuranose[14,24] as a pale yellow solid (15.6 g), which was used in the next step without purification. For analytical purpose a small portion was purified by means of column chromatography (*n*-hexane–AcOEt, 1/2) to give the diol as a colorless needles (from CH_2Cl_2). Mp. 85.0–87.0 °C, lit.[14b] 86–87.5 °C, lit.[24] 86–87 °C. $[\alpha]_D^{21}$ = +42.7 (c = 1.32, $CHCl_3$), lit.[24] $[\alpha]_D^{25}$ = +37 (c = 0.59, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38/1.58 [each 3H, s, $C(CH_3)_2$], 1.89 (1H, br dd-like, J = *ca.* 7.8, 4.0, OH), 2.41 (1H, d, J = 10.6, OH), 3.76 (1H, ddd, J = 12.1, 7.8, 3.8, H-5a), 3.85 (1H, ddd, J = 8.9, 3.8, 3.0, H-4), 3.96 (1H, ddd, J = 12.1, 4.0, 3.0, H-5b), 4.01 (1H, ddd, J = 10.6, 8.9, 5.1, H-3), 4.59 (1H, dd, J = 5.1, 4.0, H-2), 5.83 (1H, d, J = 4.0, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.49/26.54 [$C(CH_3)_2$], 60.9 (C-5), 70.9 (C-3), 78.7 (C-2), 80.7 (C-4), 104.0 (C-1), 112.8 [$C(CH_3)_2$].

A solution of the crude 1,2-*O*-isopropylidene-α-D-ribofuranose (15.5 g) in DMF (50 ml) was added dropwise to a mixture of sodium hydride (7.2 g, 180 mmol, 60% in liquid paraffin, washed with benzene), benzyl bromide (20.3 ml, 171 mmol), and DMF (50 ml) at 0 °C. After being stirred at 0 °C for 2 h, the mixture was poured into ice-water (400 ml) and extracted with a mixture of diethyl ether and *n*-hexane (1/2). The extract was washed with brine and condensed to give a colorless oil (29.3 g), which on distillation at reduced pressure gave title compound **18** (23.0 g, 81% from **16**).

3.2.1. Compound 18

Colorless oil. bp. 196–198 °C/1 mmHg, lit.[14b] bp. 178–182 °C/0.025 mmHg. $[\alpha]_D^{21}$ = +86.6 (c = 2.66, $CHCl_3$), lit.[14a] $[\alpha]_D^{25}$ = +84.5 (c = 0.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36/1.59 [each 3H, s, $C(CH_3)_2$], 3.56 (1H, dd, J = 11.2, 3.9, H-5a), 3.76 (1H, dd, J = 11.2, 2.0, H-5b), 3.86 (1H, dd, J = 9.0, 4.5, H-3), 4.18 (1H, ddd, J = 9.0, 3.9, 2.0, H-4), 4.55 (1H, dd, J = 4.5, 3.8, H-2), 4.49/4.56 (each 2H, d, J = 12.3, $PhCH_2$), 4.54/4.73 (each 2H, d, J = 12.0, $PhCH_2$), 5.75 (1H, d, J = 3.8, H-1), 7.25–7.35 (10H, m, arom.). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 26.5/26.8 [$C(CH_3)_2$], 67.9 (C-5), 72.2/73.4 ($PhCH_2$), 77.1 (C-3), 77.3 (C-2), 77.9 (C-4), 104.1 (C-1), 112.8 [$C(CH_3)_2$], 127.6/127.7/127.9/128.0/128.3/128.4 (d, arom.), 137.6/138.0 (s, arom.).

3.3. 3,5-Di-*O*-benzyl-α- and β-D-ribofuranose (α-14 and β-14)

A mixture of **18** (22.9 g, 61.9 mmol), 1,4-dioxane (170 ml) and 0.5% aqueous sulfuric acid (510 ml) was heated under reflux for 3 h. After the 1,4-dioxane was evaporated at the reduced pressure, the resulting aqueous residue was extracted with dichloromethane. The extract was washed with brine and condensed to give a *ca* 1.5:1 anomeric mixture of α- and β-**14**[12] (20.5 g) as a colorless oil, which was used in the next step without purification. For analytical purpose a small portion was recrystallized from *n*-hexane-diethyl ether to give a mixture of α- and β-**14**.

A mixture of α- and β-**14**: Colorless needles (from *n*-hexane-Et_2O). Mp. 78.0–79.0 °C, lit.[12a] mp 84–86 °C, lit.[12c] mp 78–79 °C. $[\alpha]_D^{21}$ + 50.3 (*c* = 1.13, $CHCl_3$), lit.[12a] $[\alpha]_D^{20}$ = +47.3 (*c* = 0.55, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.71 (0.4H, d, *J* = 3.2, OH_β), 2.91 (0.6H, d, *J* = 7.7, OH_α), 3.41 (0.4H, br d-like, *J* = *ca*. 7.2, OH_β), 3.46 (0.4H, dd, *J* = 10.4, 3.2, H-5a$_\beta$), 3.47 (0.6H, dd, *J* = 10.3, 4.0, H-5a$_\alpha$), 3.53 (0.6H, dd, *J* = 10.3, 4.0, H-5b$_\alpha$), 3.64 (0.4H, dd, *J* = 10.4, 3.2, H-5b$_\beta$), 3.67 (0.6H, d, *J* = 9.8, OH_α), 3.97 (0.6H, dd, *J* = 5.7, 4.0, H-3$_\alpha$), 4.03 (0.4H, br dd-like, *J* = 4.9, 3.2, H-2$_\beta$), 4.14 (0.6H, ddd, *J* = 7.7, 5.7, 4.3, H-2$_\alpha$), 4.19 (0.4H, ddd, *J* = 6.0, 3.2, 3.2, H-4$_\beta$), 4.25 (0.6H, ddd, *J* = 4.0, 4.0, 4.0, H-4$_\alpha$), 4.27 (0.4H, dd, *J* = 6.0, 4.9, H-3$_\beta$), 4.46–4.63 (4H, m, $PhCH_2$), 5.23 (0.4H, br d, *J* = 7.2, H-1$_\beta$), 5.27 (0.6H, dd, *J* = 9.8, 4.3, H-1$_\alpha$), 7.25–7.39 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$, α/β) δ: 69.6/69.7 (C-5), 70.6/74.5 (C-2), 72.98/73.04/73.5/73.6 (Ph*C*H_2), 77.9/78.2 (C-3), 80.2/81.0 (C-4), 97.1/102.5 (C-1), 127.6/127.8/127.9/128.1/128.3/128.36/128.42/128.56/128.64/128.7 (d, arom.), 136.9/137.0/137.1/ 137.8 (s, arom.).

3.4. *tert*-Butyl (*E*)- and (*Z*)-5,7-Di-*O*-benzyl-2,3-dideoxy-D-*ribo*-hept-2-enoate (*E*-19 and *Z*-19)

A solution of a crude mixture of α- and β-**14** (9.9 g), *tert*-butoxycarbonylethylenetriphenylphosphorane (14.8. g, 39.4 mmol) in dichloromethane (30 ml) was heated under reflux for 1 h. After removal of the solvent, the oily residue was triturated with a mixture of *n*-hexane and diethyl ether (5:1), and the deposited precipitates were filtered off and washed with a mixture of *n*-hexane and diethyl ether (5:1). The combined filtrate and washings were condensed to give a pale yellow oil (20.0 g), which on column chromatography (*n*-hexane–Et_2O, 2/1) gave title compounds ***E*-19** (9.3 g, 73% from **18**) and ***Z*-19** (1.9 g, 15% from **18**).

3.4.1. Compound *E*-19

Colorless needles (from *n*-hexane–Et_2O). mp. 58–59 °C. $[\alpha]_D^{24}$ – 5.74 (*c* = 1.30, $CHCl_3$). IR ($CHCl_3$): 3526, 1705, 1655, 1454, 1393, 1369, 1315, 1226, 1215, 1157, 1088 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.48 [9H, s, C(C*H*$_3$)$_3$], 2.69 (1H, br d, *J* = 5.5, OH), 3.15 (1H, br d, *J* = 4.0, OH), 3.53 (1H, dd, *J* = 7.2, 5.4, H-5), 3.60 (1H, dd, *J* = 9.8, 5.5, H-7a), 3.67 (1H, dd, *J* = 9.8, 3.7, H-7b), 3.91 (1H, dddd, *J* = 7.2, 5.5, 5.5, 3.7, H-6), 4.51/4.56 (each 1H, d, *J* = 11.8, $PhCH_2$), 4.51/4.62 (each 1H, d, *J* = 11.2, $PhCH_2$), 4.55 (1H, dddd, *J* = 5.4, 5.2, 4.0, 1.7, H-4), 6.06 (1H, dd, *J* = 15.8, 1.7, H-2), 6.99 (1H, dd, *J* = 15.8, 5.2, H-3), 7.23–7.38 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.1 [C(*C*H$_3$)$_3$], 70.6 (C-7), 71.7 (C-6), 72.3 (C-4), 73.5/74.1 (Ph*C*H_2) 80.4 [*C*(CH$_3$)$_3$], 81.4 (C-5), 123.6 (C-2), 127.9/127.99/128.04 /128.1/128.5 (d, arom.), 137.46/137.52 (s, arom.), 145.1 (C-3), 165.6 (C-1). FABMS *m*/*z*: 429 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 429.2293 ($C_{25}H_{33}O_6$ requires 429.2277).

3.4.2. Compound *Z*-19

Colorless needles (from *n*-hexane). mp. 61–62 °C. $[\alpha]_D^{24}$ + 2.73 (*c* = 1.20, $CHCl_3$). IR ($CHCl_3$): 3430, 1697, 1651, 1454, 1416, 1369, 1227, 1207, 1157, 1092 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.48 [9H, s, C(C*H*$_3$)$_3$], 3.23 (1H, d, *J* = 5.0, OH), 3.62 (1H, dd, *J* = 9.8, 5.5, H-7a), 3.69 (1H, dd, *J* = 9.8, 3.0, H-7b), 3.71 (1H, d, *J* = 5.1, OH), 3.77 (1H, dd, *J* = 7.7, 4.0, H-5), 3.85 (1H, dddd, *J* = 7.7, 5.5, 5.0, 3.0, H-6), 4.52/4.57 (each 1H, d, *J* = 11.8, Ph*C*H_2), 4.64/4.76 (each 1H, d, *J* = 11.3, Ph*C*H_2), 5.26 (1H, dddd, *J* = 7.2, 5.1, 4.0, 1.5, H-4), 5.83 (1H, dd, *J* = 11.9, 1.5, H-2), 6.34 (1H, dd, *J* = 11.9, 7.2, H-3), 7.25–7.36 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 28.1 [C(*C*H$_3$)$_3$], 69.0 (C-4), 70.7 (C-6), 70.9 (C-7), 73.4/73.7 (Ph*C*H_2), 81.5 [*C*(CH$_3$)$_3$], 81.7 (C-5), 122.9 (C-2), 147.4 (C-3), 127.7/127.76/127.84/128.1/128.4 (d, arom.), 138.0/138.2 (s, arom.), 166.7 (C-1). FABMS *m*/*z*: 429 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 429.2302 ($C_{25}H_{33}O_6$ requires 429.2277).

3.5. *tert*-Butyl (*E*)-5,7-Di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*ribo*-hept-2-enoate (*E*-20)

A mixture of ***E*-19** (12.0 g, 28 mmol), 2,2-dimethoxypropane (34.3 ml, 280 mmol), *p*-toluenesulfonic acid (24 mg), and acetone (120 ml) was stirred at room temperature for 1.5 h. After the reaction was quenched by the addition of aqueous sodium hydrogen carbonate (30 ml), the acetone was evaporated. The residual solution was diluted with water (30 ml) and extracted with dichloromethane. The extract was washed with brine and condensed to give a colorless solid (14.3 g), which was pure enough for further reaction. For analytical purpose a small portion was recrystallized from *n*-hexane to give title compound ***E*-20**.

3.5.1. Compound *E*-20

Colorless needles (from *n*-hexane). mp. 73–74 °C. $[\alpha]_D^{24}$ – 29.2 (*c* = 1.01, $CHCl_3$). IR ($CHCl_3$): 1709, 1654, 1454, 1369, 1312, 1211, 1153, 1096 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.48/1.494 [each 3H, s, C(C*H*$_3$)$_2$], 1.491 [9H, s, C(C*H*$_3$)$_3$], 3.30 (1H, dd, *J* = 9.7, 9.7, H-5), 3.63 (1H, dd, *J* = 10.9, 1.9, H-7a), 3.72 (1H, dd, *J* = 10.9, 4.3, H-7b), 3.91 (1H, ddd, *J* = 9.7, 4.3, 1.9, H-6), 4.34 (1H, ddd, *J* = 9.7, 5.1, 1.5, H-4), 4.39/4.49 (each 1H, d, *J* = 10.6, $PhCH_2$), 4.55/4.66 (each 1H, d, *J* = 12.2, $PhCH_2$), 6.09 (1H, dd, *J* = 15.6, 1.5, H-2), 6.97 (1H, dd, *J* = 15.6, 5.1, H-3), 7.15–7.37 (10 H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.2/29.3 [(C*H*$_3$)$_2$C], 28.1 [C(C*H*$_3$)$_3$], 69.2 (C-7), 72.3 (C-4), 73.2 (C-6), 73.5/74.8 (Ph*C*H_2), 74.5 (C-5), 80.4 [*C*(CH$_3$)$_3$], 98.9 [*C*(CH$_3$)$_2$], 124.2 (C-2), 127.7/127.9/128.1/128.2/128.4/ 128.5 (d arom.), 137.2/138.1 (s arom.), 143.1 (C-3), 165.5 (C-1). FABMS *m*/*z*: 469 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 469.2571 ($C_{28}H_{37}O_6$ requires 469.2590).

3.6. *tert*-Butyl (*Z*)-5,7-Di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*ribo*-hept-2-enoate (*Z*-20)

Following the method used for acetalization of diol ***E*-19**, ***Z*-19** (1.7 g, 4.0 mmol) was treated with dimethoxypropane (4.9 ml, 40 mmol) in acetone (30 ml). Work-up gave a colorless solid (1.87 g), which was pure enough for further reaction. For analytical purpose a small portion was recrystallized from *n*-hexane to give title compound ***Z*-20**.

3.6.1. Compound *Z*-20

Colorless needles (from *n*-hexane). mp. 58–59 °C. $[\alpha]_D^{24}$ + 96.6 (*c* = 4.60, $CHCl_3$). IR ($CHCl_3$): 1717, 1651, 1454, 1369, 1207, 1157, 1096 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.43 [9H, s, (C*H*$_3$)$_3$C], 1.46/1.57 [each 3H, s, (C*H*$_3$)$_2$C], 3.32 (1H, br dd, *J* = 9.8, 9.5, H-5), 3.62 (1H, dd, *J* = 10.9, 2.0, H-7a), 3.71 (1H, dd, *J* = 10.9, 4.3, H-7b), 3.96 (1H, ddd, *J* = 9.8, 4.3, 2.0, H-6), 4.35/4.47 (each 1H, d, *J* = 10.6, Ph*C*H_2), 4.55/4.65 (each 1H, d, *J* = 12.3, Ph*C*H_2), 5.61 (1H, dd, *J* = 9.5, 8.9, H-4), 5.86 (1H, d, *J* = 11.5, H-2), 5.98 (1H, dd, *J* = 11.5, 8.9, H-3), 7.11–7.38 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.6/29.4 [C(*C*H$_3$)$_2$], 28.1 [C(CH$_3$)$_3$], 68.2 (C-4), 69.4 (C-7), 72.8 (C-6), 73.5/74.2 (Ph*C*H_2), 73.9 (C-5), 80.8[*C*(CH$_3$)$_3$], 98.8 [*C*(CH$_3$)$_2$], 125.6 (C-2), 127.6/127.7/127.9/128.2/128.3 (d, arom.), 137.7/138.2 (s, arom.), 142.7 (C-3), 164.7 (C-1). FABMS *m*/*z*: 469 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 469.2617 ($C_{28}H_{37}O_6$ requires 469.2590).

3.7. (*E*)-5,7-di-*O*-Benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*ribo*-hept-2-enitol (*E*-21)

To a solution of a crude acetonide ***E*-20** (14.2 g) in tetrahydrofuran (190 ml) was added dropwise a 1 M solution of DIBAL in toluene (64 ml, 64 mmol) at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was allowed to reach room temperature, and stirred for 6 h. The reaction was quenched with water (150 ml). The deposited gel was filtered off through celite and

washed with tetrahydrofuran. The combined filtrate and washings were condensed to give a colorless solid (11.6 g), which on recrystallization from a mixture of *n*-hexane and ethyl acetate gave title compound ***E*-21** (9.2 g, 83% from ***E*-19**). Column chromatography ($CHCl_3$) of the mother liquid gave ***E*-21** (1.1 g, 10% from ***E*-19**).

3.7.1. Compound E-21

Colorless needles (from *n*-hexane–AcOEt). mp. 92–93 °C. $[\alpha]_D^{24}$ + 9.1 (*c* = 1.22, $CHCl_3$). IR (nujol): 3479, 1651, 1203, 1169, 1111, 1096, 1054, 1029 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.35 (1H, br t-like, *J* = *ca.* 4.3, OH), 1.47/1.51 [each 3H, s, $C(CH_3)_2$], 3.30 (1H, dd, *J* = 8.0, 8.0, H-5), 3.65 (1H, dd, *J* = 9.1, 1.7, H-7a), 3.72 (1H, dd, *J* = 9.1, 3.6, H-7b), 3.89 (1H, ddd, *J* = 8.0, 3.6, 1.7, H-6), 4.12 (2H, br t-like, *J* = *ca.* 4.3, H-1a and H-1b), 4.21, (1H, br dd, *J* = 8.0, 5.8, H-4), 4.40/4.48 (each 1H, d, *J* = 10.8, $PhCH_2$), 4.56/4.67 (each 1H, d, *J* = 12.3, $PhCH_2$), 5.72 (1H, ddt, *J* = 12.9, 5.8, 1.3, H-3), 6.00 (1H, dtd, *J* = 12.9, 4.3, 0.7, H-2), 7.14–7.39 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.4/29.4 [$C(CH_3)_2$], 62.9 (C-1), 69.3 (C-7), 73.0 (C-6), 73.5/74.4 ($PhCH_2$), 73.7 (C-4), 74.4 (C-5), 98.7 [$C(CH_3)_2$], 127.6/127.9/128.0/128.2/128.3/128.4 (d. arom.), 128.8 (C-3), 133.3 (C-2), 137.7/138.2 (s, arom.). FABMS *m*/*z*: 399 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 399.2180 ($C_{24}H_{31}O_5$ requires 399.2171).

3.8. (*Z*)-5,7-di-*O*-Benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*ribo*-hept-2-enitol (*Z*-21)

Following the method used for reduction of ***E*-20**, a crude acetonide ***Z*-20** (1.8 g) was treated with 1 M solution of DIBAL in toluene (9.5 ml, 9.5 mmol). Work-up gave quantitatively the title compound ***Z*-21** (1.53 g) as a pale yellow solid, which was used in the next step without purification. For analytical purpose a small portion was recrystallized from a mixture of *n*-hexane and ethyl acetate to give ***Z*-21**.

3.8.1. Compound *Z*-21

Colorless needles (from *n*-hexane–AcOEt). mp. 75–76 °C. $[\alpha]_D^{24}$ + 76.5 (*c* = 2.37, $CHCl_3$). IR ($CHCl_3$): 3472, 1650, 1219, 1165, 1096, 1030 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.47/1.53 [each 3H, s, $C(CH_3)_2$], 1.99 (1H, br t-like, *J* = *ca.* 6.4 Hz, OH), 3.34 (1H, dd, *J* = 9.7, 9.7, H-5), 3.64 (1H, dd, *J* = 11.0, 2.0, H-7a), 3.73 (1H, dd, *J* = 11.0, 4.3, H-7b), 3.91 (1H, ddd, *J* = 9.7, 4.3, 2.0, H-6), 4.15 (1H, dddd, *J* = 13.0, 6.4, 6.4, 1.4, H-1a), 4.18 (1H, dddd, *J* = 13.0, 6.4, 6.4, 1.4, H-1b), 4.44/4.50 (each 1H, d, *J* = 10.7, $PhCH_2$), 4.57/4.67 (each 1H, d, *J* = 12.2, $PhCH_2$), 4.63 (1H, ddd, *J* = 9.7, 8.3, 0.9, H-4), 5.57 (1H, ddt, *J* = 11.2, 8.3, 1.4, H-3), 5.89 (1H, dtd, *J* = 11.2, 6.4, 0.9, H-2), 7.13–7.38 (10H, m, arom). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.4/29.4 [$C(CH_3)_2$], 59.2 (C-1), 69.3 (C-7), 69.4 (C-4), 73.1 (C-6), 73.5/74.7 ($PhCH_2$), 74.3 (C-5), 98.8 [$C(CH_3)_2$], 127.7/127.9/128.1/128.2/128.4/128.5 (d arom.), 129.9 (C-3), 133.5 (C-2), 137.2/138.1 (s arom.). FABMS *m*/*z*: 399 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 399.2184 ($C_{24}H_{31}O_5$ requires 399.2171).

3.9. Dihydroxylation of olefinic alcohols *E*-21 and *Z*-21

A mixture of ***E*-21** (6.2 g, 15.6 mmol), 0.045 M aqueous osmium tetroxide (17.2 ml, 0.78 mmol), *N*-methylmorphorine *N*-oxide (3.65 g, 31.2 mmol), acetone (55 ml), and water (5 ml) was heated under reflux for 2.5 h. After the reaction was quenched by the addition of sodium sulfite (3.9 g, 31.2 mmol), the resulting mixture was diluted with water (200 ml), and extracted with diethyl ether. The extract was washed with brine and condensed to give a *ca.* 3:1 mixture of 1,3-di-*O*-benzyl-2,4-*O*-isopropylidene-D-*glycero*-L-*allo*-heptitol (**22a**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-D-*gluco*-heptitol (**22b**) as a pale yellow oil (6.9 g), which was used in the next step without purification. The ratio of products **22a** and **22b** in the mixture was determined on the basis of the ^1H NMR spectrum. Analytical samples of both diastereomers were obtained by means of column chromatography (*n*-hexane-acetone, 3/1).

3.9.1. Compound 22a

Colorless oil. $[\alpha]_D^{24}$ – 2.1 (*c* = 1.13, $CHCl_3$). IR (neat): 3418, 1454, 1384, 1265, 1203, 1169, 1107, 1030 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.45/1.49 [each, 3H, s, $C(CH_3)_2$], 2.25 (1H, dd, *J* = 7.4, 4.8, OH), 3.11 (1H, dd, *J* = 3.6, OH), 3.19 (1H, d, *J* = 6.5, OH), 3.53 (1H, ddd, *J* = 11.7, 7.4, 4.5, H-7a), 3.59 (1H, dd, *J* = 9.8, 9.2, H-3), 3.61 (1H, ddd, *J* = 11.7, 4.8, 4.5, H-7b), 3.66 (1H, dd, *J* = 11.2, 2.1, H-1a), 3.75 (1H, ddd, *J* = 6.5, 3.8, 1.6, H-5), 3.79 (1H, dd, *J* = 11.2, 3.6, H-1b), 3.86 (1H, ddd, *J* = 4.5, 4.5, 1.6, H-6), 3.88 (1H, ddd, *J* = 9.2, 3.6, 2.1, H-2), 3.99 (1H, dd, *J* = 9.8, 3.8, H-4), 4.45/4.52 (each 1H, d, *J* = 11.0, $PhCH_2$), 4.58/4.71 (each 1H, d, *J* = 12.0, $PhCH_2$), 7.16–7.39 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.0/29.3 [$C(CH_3)_2$], 64.7 (C-1), 69.1 (C-7), 69.9 (C-6), 71.3 (C-5), 71.7 (C-3), 73.3 (C-2), 73.7/73.9 ($PhCH_2$), 75.6 (C-4), 99.2 [$C(CH_3)_2$], 127.8/128.1/128.2/128.3/128.4/128.6 (d, arom.), 137.0/137.8 (s, arom). FABMS *m*/*z*: 433 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 433.2213 ($C_{24}H_{33}O_7$ requires 433.2226).

3.9.2. Compound 22b

Colorless plates (from *n*-hexane–AcOEt). mp. 121–122 °C. $[\alpha]_D^{24}$ + 11.7 (*c* = 1.09, $CHCl_3$). IR ($CHCl_3$): 3526, 1451, 1384, 1215, 1204, 1165, 1092, 1042 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.46/1.50 [each, 3H, s, $C(CH_3)_2$], 2.24 (1H, t, *J* = 6.0, OH), 2.67 (1H, dd, *J* = 9.5, OH), 3.13 (1H, d, *J* = 1.2, OH), 3.63 (1H, dd, *J* = 10.9, 2.0, H-7a). 3.68 (1H, dd, *J* = 10.9, 4.6, H-7b), 3.70 (2H, dd-like, *J* = *ca.* 6.0, 5.4, H-1a and H-1b), 3.76 (1H, dd, *J* = 9.7, 9.7, H-5), 3.80–3.88 [3H, m, H-2, H-3, including one-proton double multiplets due to H-4 at δ 3.83 (*J* = 9.7)], 3.90 (1H, ddd, *J* = 9.7, 4.6, 2.0, H-6), 4.49/4.62 (each 1H, d, *J* = 10.9, $PhCH_2$), 4.56/4.64 (each 1H, d, *J* = 12.1, $PhCH_2$), 7.17–7.39 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.4/29.3 [$C(CH_3)_2$], 64.0 (C-1), 68.6 (C-2), 69.3 (C-7), 69.6 (C-5), 73.1 (C-6), 73.4 (C-3), 73.5/74.6 ($PhCH_2$), 75.7 (C-4), 99.0 [($CCH_3)_2$], 127.7/127.97/128.03/128.4/128.5 (d, arom.), 137.6/138.0 (s, arom.). FABMS *m*/*z*: 433 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 433.2239 ($C_{24}H_{33}O_7$ requires 433.2226).

Following the method used for oxidation of ***E*-21**, a mixture of a crude olefinic alcohol ***Z*-21** (1.5 g), 0.045 M aqueous osmium tetroxide (4.2 ml, 0.19 mmol), *N*-methylmorphorine *N*-oxide (887 mg, 7.5 mmol), and acetone (10 ml) was heated under reflux for 30 min. Work-up gave a *ca.* 1:1 mixture of 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-D-*allo*-heptitol (**22c**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-D-*manno*-heptitol (**22d**) as a pale yellow oil (1.68 g), which was used in the next step without purification. Analytical samples of both diastereomers were obtained by means of column chromatography (*n*-hexane-acetone, 2/1).

3.9.3. Compound 22c

Colorless needles (from *n*-hexane–AcOEt). mp. 82–83 °C. $[\alpha]_D^{24}$ + 4.2 (*c* = 1.38, $CHCl_3$). IR ($CHCl_3$): 3533, 1520, 1454, 1223, 1204, 1092 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.45/1.50 [each 3H, s, $C(CH_3)_2$], 2.31 (1H, br s, OH), 2.79 (1H, br d, *J* = 2.2, OH), 2.94 (1H, br d, *J* = 3.7, OH), 3.68 (1H, dd, *J* = 11.2, 2.2, H-7a), 3.71 (1H, br dm, *J* = *ca.* 10.5, H-1a), 3.73–3.78 (1H, m, H-2), 3.78–3.84 [4H, m, H-1b, H-3, including two one-proton doublet of doublets due to H-7b and H-5 at δ 3.79 (*J* = 11.2, 3.7) and δ 3.81 (*J* = 9.6, 9.6), respectively], 3.89 (1H, ddd, *J* = 9.6, 3.7, 2.2, H-6), 3.93 (1H, dd, *J* = 9.6, 4.4, H-4), 4.56/4.59 (each 1H, d, *J* = 10.8, $PhCH_2$), 4.57/4.70 (each 1H, d, *J* = 12.2, $PhCH_2$), 7.16–7.39 (10H, m, arom). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.3/29.2 [$C(CH_3)_2$], 64.2 (C-1), 69.3 (C-7), 71.8 (C-2), 72.3 (C-5), 73.3 (C-3 and C-4), 73.7/74.2 ($PhCH_2$), 73.9 (C-6), 98.9 [$C(CH_3)_2$], 127.8/128.06/128.13/128.3/128.4/128.7

(d arom.), 136.8/ 137.8 (s arom.). FABMS *m*/*z*: 433 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 433.2200 ($C_{24}H_{33}O_7$ requires 433.2226).

3.9.4. Compound 22d

Colorless prisms (from *n*-hexane–AcOEt). mp. 91–92 °C. $[\alpha]_D^{24}$ + 8.5 (*c* = 2.46, $CHCl_3$). IR ($CHCl_3$): 3479, 1520, 1423, 1223, 1092, 1045 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.45/1.51 [each 3H, s, $C(CH_3)_2$], 2.04/2.37/2.48 (each 1H, br s, OH), 3.64 (1H, dd, *J* = 11.0, 2.2, H-7a), 3.70 (1H, dd, *J* = 11.0, 4.5, H-7b), 3.71 (1H, dd, *J* = 9.8, 9.8, H-5), 3.72–3.76 (3H, m, H-1a, H-2, H-3), 3.79 (1H, dm, *J* = *ca.* 10.5, H-1b), 3.92 (1H, ddd, *J* = 9.8, 4.5, 2.2, H-6), 4.01 (1H, d, *J* = 9.8, H-4), 4.49/4.59 (each 1H, d, *J* = 11.0, $PhCH_2$), 4.56/4.64 (each 1H, d, *J* = 12.2, $PhCH_2$), 7.17–7.38 (10H, m, arom). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.5/29.2 [$C(CH_3)_2$], 64.2 (C-1), 69.27 (C-2), 69.33 (C-7), 69.7 (C-5), 72.1 (C-4), 72.2 (C-3), 73.2 (C-6), 73.5/74.6 ($PhCH_2$), 98.9 [$C(CH_3)_2$], 127.7/127.96/128.00/128.4/128.5 (d arom.), 137.6/138.0 (s arom.). FABMS *m*/*z*: 433 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 433.2239 ($C_{24}H_{33}O_7$ requires 433.2226).

3.10. Identification of triols 23a, 23b, 23c and 23d

A suspension of 10% palladium-on-carbon (130 mg) in 80% aqueous acetic acid (2 ml) was pre-equilibrated with hydrogen. To the suspension was added a solution of **22a** (130 mg, 0.3 mmol) in 80% aqueous acetic acid (4 ml), and the mixture was hydrogenated at 60 °C under atmospheric pressure until the uptake of hydrogen ceased. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue (80 mg) was purified by means of column chromatography (AcOEt–MeOH–H_2O, 20/4/1) to give D-*glycero*-L-*allo*-heptitol **23a** (59 mg, 93%). ^{13}C NMR spectroscopic properties of **23a** were in good accordance with those reported.[15]

3.10.1. Compound 23a

Colorless oil. ^1H NMR (500 MHz, D_2O) δ: 3.51 (1H, dd, *J* = 10.0, 7.0 Hz, H-7a), 3.52 (1H, dd, *J* = 8.3, 3.4, H-1a), 3.54 (1H, dd, *J* = 10.0, 5.5, H-7b), 3.66 (1H, dd, *J* = 5.5, 1.8, H-5), 3.67 (1H, dd, *J* = 8.3, 3.4, H-1b), 3.73 (1H, dd, *J* = 7.0, 3.5, H-3), 3.74 (1H, dd, *J* = 5.5, 3.5, H-4), 3.79 (1H, ddd, *J* = 7.0, 3.4, 3.4, H-2), 3.82 (1H, ddd, *J* = 7.0, 5.5, 1.8, H-6). ^{13}C NMR (125 MHz, D_2O) δ: 64.0 (C-1), 64.4 (C-7), 72.0 (C-6), 72.1 (C-5), 72.9 (C-3), 73.3 (C-2), 74.2 (C-4).

Following the method used for the deprotection of **22a**, triol **22b** (130 mg, 0.3 mmol) was hydrogenated in 80% aqueous acetic acid (6 ml) at 60 °C. Work-up gave a colorless oil (78 mg), which on column chromatography (AcOEt–MeOH–H_2O, 20/4/1) gave D-*glycero*-D-*gluco*-heptitol **23b** (61 mg, 96%). ^{13}C NMR spectroscopic properties of **23b** were in good accordance with those reported.[15]

3.10.2. Compound 23b

Colorless amorphous. ^1H NMR (600 MHz, D_2O) δ: 3.45 (1H, dd, *J* = 11.8, 6.2 Hz, H-1a), 3.51 (1H, dd, *J* = 11.8, 7.4, H-7a), 3.57 (1H, dd, *J* = 11.8, 3.4, H-1b), 3.58 (1H, dd, *J* = 7.0, 1.9, H-4), 3.64 (1H, dd, *J* = 11.8, 3.1, H-7b), 3.65 (1H, dd, *J* = 7.0, 5.0, H-5), 3.68 (1H, ddd, *J* = 6.2, 6.2, 3.4, H-2), 3.70 (1H, dd, *J* = 6.2, 1.9, H-3), 3.76 (1H, ddd, *J* = 7.4, 5.0, 3.1, H-6). ^{13}C NMR (150 MHz, D_2O) δ: 63.5 (C-7), 63.8 (C-1), 71.3 (C-3), 72.8 (C-4), 73.0 (C-5), 73.9 (C-6), 74.3 (C-2).

Following the method used for the deprotection of **22a**, triol **22c** (130 mg, 0.3 mmol) was hydrogenated in 80% aqueous acetic acid (6 ml) at 50 °C. Work-up gave a colorless oil (78 mg), which on column chromatography (AcOEt–MeOH–H_2O, 20/4/1) gave D-*glycero*-D-*allo*-heptitol **23c** (58 mg, 91%). ^{13}C NMR spectroscopic properties of **23c** were in good accordance with those reported.[15]

3.10.3. Compound 23c

Colorless amorphous. ^1H NMR (500 MHz, D_2O) δ: 3.51 (2H, dd, *J* = 11.8, 6.6, H-1a), 3.66 (2H, dd, *J* = 11.8, 2.9, H-1b), 3.70–3.77 (5H, m, H-2, H-3, H-4). ^{13}C NMR (125 MHz, D_2O) δ: 63.9 (C-1 and C-7), 73.4 (C-2 and C-6), 73.7 (C-3 and C-5), 74.0 (C-4).

Following the method used for the deprotection of **22a**, triol **22d** (86 mg, 0.2 mmol) was hydrogenated in 80% aqueous acetic acid (4 ml) at 60 °C. Work-up gave a colorless oil (62 mg), which on column chromatography (AcOEt–MeOH–H_2O, 20/4/1) gave D-*glycero*-D-*manno*-heptitol **22d** (41 mg, 97%). ^{13}C NMR spectroscopic properties of **22d** were in good accordance with those reported.[15]

3.10.4. Compound 22d

Colorless amorphous. ^1H NMR (500 MHz, D_2O) δ: 3.51 (1H, dd, *J* = 11.8, 6.0, H-1a), 3.54 (1H, dd, *J* = 12.0, 7.7, H-7a), 3.60 (1H, ddd, *J* = 8.8, 6.0, 2.6, H-2), 3.65 (1H, dd, *J* = 8.8, 1.0, H-3), 3.66 (1H, dd, *J* = 8.3, 4.9, H-5), 3.67 (1H, dd, *J* = 12.0, 2.9, H-7b), 3.71 (1H, dd, *J* = 11.8, 2.6, H-1b), 3.75 (1H, dd, *J* = 8.3, 1.0, H-4), 3.79 (1H, ddd, *J* = 7.7, 4.9, 2.9, H-6). ^{13}C NMR (125 MHz, D_2O) δ: 63.4 (C-7), 64.6 (C-1), 70.9 (C-3), 71.0 (C-4), 72.1 (C-2), 72.8 (C-5), 74.2 (C-6).

3.11. Methoxymethylation of triols 22a, 22b, 22c and 22d

A mixture of a crude triols **22a** and **22b** (6.9 g), methoxymethylchloride (MOMCl, 14.6 ml, 192 mmol), diisopropylethylamine (55.6 ml, 319 mmol), and dimethylformamide (200 ml) was heated at 60 °C for 1 h. After being cooled, the reaction mixture was neutralized by addition of aqueous sodium hydrogen carbonate (140 ml), and the resulting mixture was extracted with diethyl ether. The extract was washed with brine and condensed to give a pale yellow oil (8.3 g), which on column chromatography (*n*-hexane–Et_2O, 2/1) gave 1,3-di-*O*-benzyl-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-D-*glycero*-L-*allo*-heptitol **24a** (6.0 g, 68% from ***E*-21**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*gluco*-heptitol **24b** (2.0 g, 23% from ***E*-21**).

3.11.1. Compound 24a

Colorless oil. Bp. 239–243 °C/0.004 mHg. $[\alpha]_D^{24}$ + 37.9 (*c* = 1.90, $CHCl_3$). IR (neat): 1454, 1381, 1258, 1207, 1150, 1026 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.45/1.48 [each 3H, s, $C(CH_3)_2$], 3.32/3.39/3.44 (each 3H, s, OCH_2OCH_3), 3.66 (1H, dd, *J* = 11.0, 2.2, H-1a), 3.720 (1H, dd, *J* = 9.5, 9.5, H-3), 3.722 (1H, dd, *J* = 10.8, 6.5, H-7a), 3.73 (1H, dd, *J* = 11.0, 4.5, H-1b), 3.77 (1H, dd, *J* = 10.8, 4.0, H-7b), 3.88 (1H, ddd, *J* = 9.5, 4.5, 2.2, H-2), 3.98 (1H, ddd, *J* = 7.2, 6.5, 4.0, H-6), 4.01 (1H, dd, *J* = 9.5, 1.0, H-4), 4.07 (1H, dd, *J* = 7.2, 1.0, H-5), 4.44/4.67 (each 1H, d, *J* = 10.8, $PhCH_2$), 4.57/4.66 (each 1H, d, *J* = 12.2, $PhCH_2$), 4.59/4.60 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.73/4.828 (each 1H, d, *J* = 6.7, OCH_2OCH_3), 4.812/4.826 (each 1H, d, *J* = 7.0 Hz, OCH_2OCH_3), 7.17–7.38 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.0/29.4 [$C(CH_3)_2$], 55.4/55.6/56.0 (OCH_2OCH_3), 67.9 (C-7), 69.6 (C-1), 70.7 (C-3), 73.47 (C-2), 73.52/73.8 ($PhCH_2$), 74.0 (C-4), 76.6 (C-6), 77.3 (C-5), 96.7/97.1/97.4 (OCH_2OCH_3), 98.7 [$C(CH_3)_2$], 127.6/127.7/127.88/127.93/128.3/128.4 (d, arom.), 137.7/138.2 (s, arom.). FABMS *m*/*z*: 565 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 565.2983 ($C_{30}H_{45}O_{10}$ requires 565.3012).

3.11.2. Compound 24b

Colorless oil. Bp. 245–248 °C/0.005 mHg. $[\alpha]_D^{24}$ – 3.0 (*c* = 1.53, $CHCl_3$). IR (neat): 1454, 1381, 1257, 1204, 1150, 1110, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.47/1.48 [each 3H, s, $C(CH_3)_2$], 3.33/3.34/3.41 (each 3H, s, OCH_2OCH_3), 3.64 (1H, dd, *J* = 11.2, 5.8, H-1a), 3.68 (1H, dd, *J* = 10.9, 2.0, H-7a), 3.74 (1H, dd, *J* = 9.7, 9.7, H-5), 3.77 (1H, dd, *J* = 10.9, 4.3, H-7b), 3.81 (1H, dd, *J* = 11.2, 2.1, H-1b), 3.90 (1H, ddd, *J* = 9.7, 4.3, 2.0, H-6), 3.96 (1H, dd, *J* = 9.7, 0.9, H-4), 4.02 (1H, ddd, *J* = 6.9, 5.8, 2.1, H-2), 4.08 (1H, dd, *J* = 6.9, 0.9, H-3), 4.49/4.71 (each 1H, d, *J* = 10.8, $PhCH_2$), 4.56/4.68 (each 1H, d, *J* = 12.2, $PhCH_2$), 4.62/4.64 (each 1H, d, *J* = 6.4 Hz, OCH_2OCH_3), 4.730/4.89 (each 1H, d, *J* = 6.6 Hz,

OCH_2OCH_3), 4.732/4.77 (each 1H, d, J = 6.6 Hz, OCH_2OCH_3), 7.17–7.38 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.0/29.5 [$C(CH_3)_2$], 55.4/55.7/56.0 (OCH_2OCH_3), 68.2 (C-1), 69.87 (C-5), 69.96 (C-7), 71.2 (C-4), 73.5/73.6 ($PhCH_2$), 73.7 (C-6), 76.6 (C-3), 78.3 (C-2), 96.7/97.4/98.4 (OCH_2OCH_3), 98.5 [$C(CH_3)_2$], 127.56/127.65/127.72/127.9/128.28/128.30 (d, arom.), 138.2/138.3 (s, arom.). FABMS m/z: 565 $[M+H]^+$ (pos.), FABHRMS m/z: 565.3013 ($C_{30}H_{45}O_{10}$ requires 565.3012).

Following the method described above, a mixture of triols **22c** and **22d** (925 mg) was treated with MOMCl (2 ml, 26 mmol) in DMF (30 ml) at 60 °C. Work-up gave a pale yellow oil (1.15 g), which on column chromatography (n-hexane–Et_2O, 2/1) gave 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*allo*-heptitol **24c** (489 mg, 42% from ***Z*-19**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*glycero*-D-*manno*-heptitol **24d** (527 mg, 45% from ***Z*-19**).

3.11.3. Compound 24c

Colorless oil$[\alpha]_D^{24}$ + 14.1 (c = 1.40, $CHCl_3$). IR (neat): 1454, 1381, 1258, 1207, 1150, 1107, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.46/1.50 [each 3H, s, $C(CH_3)_2$], 3.352/3.354/3.41 (each 3H, s, OCH_2OCH_3), 3.63 (1H, dd, J = 10.9, 2.0, H-7a), 3.70 (1H, dd, J = 10.9, 4.6, H-7b), 3.72 (1H, dd, J = 10.9, 4.9, H-1a), 3.75 (1H, dd, J = 9.8, 9.8, H-5), 3.87 (1H, ddd, J = 9.8, 4.6, 2.0, H-6), 3.94 (1H, dd, J = 10.9, 2.3, H-1b), 4.01 (1H, ddd, J = 7.2, 4.9, 2.3, H-2), 4.10 (1H, dd, J = 7.2, 1.2, H-3), 4.12 (1H, dd, J = 9.8, 1.2, H-4), 4.46/4.68 (each 1H, d, J = 10.9, $PhCH_2$), 4.55/4.64 (each 1H, d, J = 12.2, $PhCH_2$), 4.64/4.66 (each 1H, d, J = 6.3, OCH_2OCH_3), 4.72/4.755 (each 1H, d, J = 6.6, OCH_2OCH_3), 4.764/4.79 (each 1H, d, J = 6.3, OCH_2OCH_3), 7.20–7.38 (10H, m, arom). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.0/29.4 [$(CH_3)_2C$], 55.3/55.9/56.0 (OCH_2OCH_3), 68.2 (C-1), 69.6 (C-7), 71.2 (C-5), 73.4/74.1 ($PhCH_2$), 73.6 (C-6), 74.5 (C-4), 76.1 (C-3), 76.7 (C-2), 96.8/97.0/97.1 (OCH_2OCH_3), 98.8 [$(CH_3)_2C$], 127.6/127.7/127.8/ 128.30/ 128.34 (d arom.), 138.0/138.3 (s arom.). FABMS m/z: 565 $[M+H]^+$ (pos.), FABHRMS m/z: 565.3026 ($C_{30}H_{45}O_{10}$ requires 565.3013).

3.11.4. Compound 24d

Colorless oil. $[\alpha]_D^{24}$ + 4.45 (c = 1.37, $CHCl_3$). IR (neat): 1458, 1381, 1258, 1204, 1151, 1108, 1034 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.48 [6H, s, $C(CH_3)_2$], 3.36/3.39/3.40 (each 3H, s, OCH_2OCH_3), 3.68 (1H, dd, J = 11.0, 2.0, H-7a), 3.73 (1H, dd, J = 11.2, 4.5, H-1a), 3.76 (1H, dd, J = 11.0, 4.3, H-7b), 3.77 (1H, dd, J = 9.7, 9.7, H-5), 3.86 (1H, ddd, J = 6.9, 4.5, 2.5, H-2), 3.91 (1H, ddd, J = 9.7, 4.3, 2.0, H-6), 3.92 (1H, dd, J = 11.2, 2.4, H-1b), 3.97 (1H, dd, J = 9.7, 1.2, H-4), 4.11 (1H, dd, J = 6.9, 1.2, H-3), 4.50/4.76 (each 1H, d, J = 11.2 Hz, $PhCH_2$), 4.56/4.67 (each 1H, d, J = 12.2, $PhCH_2$), 4.65/4.66 (each 1H, d, J = 6.4, OCH_2OCH_3), 4.71/4.72 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.74/4.91 (each 1H, d, J = 6.7, OCH_2OCH_3), 7.21–7.38 (10H, m, arom). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.1/29.5 [$(CH_3)_2C$], 55.3/55.7/55.9 (OCH_2OCH_3), 67.8 (C-1), 69.96 (C-7), 70.02 (C-5), 71.9 (C-4), 73.55/73.6 ($PhCH_2$), 73.57 (C-6), 76.6 (C-3), 77.3 (C-2), 96.8/97.1/98.1 (OCH_2OCH_3), 98.5 [$(CH_3)_2C$], 127.56/127.62/127.9/128.27/128.30 (d arom.), 138.3/138.4 (s arom.). FABMS m/z: 565 $[M+H]^+$ (pos.), FABHRMS m/z: 565.3002 ($C_{30}H_{45}O_{10}$ requires 565.3013).

3.12. Hydrogenolysis of MOM ethers 24a, 24b, 24c and 24d

A suspension of 10% palladium-on-carbon (2.0 g) and sodium hydrogen carbonate (400 mg) in 1,4-dioxane (20 ml) was pre-equilibrated with hydrogen. To the suspension was added a solution of **24a** (2.85 g, 5.05 mmol) in 1,4-dioxane (25 ml), and the mixture was hydrogenated at 60 °C under atmospheric pressure until the uptake of hydrogen ceased. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue (1.98 g) was washed with n-hexane to give a practically pure 2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-D-*glycero*-L-*allo*-heptitol **25a** (1.87 g, 96%).

3.12.1. Compound 25a

Colorless oil. Bp. 176–179 °C/0.004 mmHg. $[\alpha]_D^{24}$ + 37.6 (c = 2.89, $CHCl_3$). IR (neat): 3418, 1454, 1384, 1265, 1207, 1151, 1108, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.39/1.50 [each 3H, s, $C(CH_3)_2$], 2.17 (1H, dd-like J = *ca.* 7.0, 6.0, OH), 3.38/3.41/3.44 (each 3H, s, OCH_2OCH_3), 3.66 (1H, ddd, J = 8.6, 8.6, 2.3, H-3), 3.68 (1H, dd, J = 10.3, 7.2, H-7a), 3.72–3.79 [3H, m, H-1a H-2, including one-proton doublet of doublets due to H-7b at δ 3.76 (J = 10.3, 5.7)], 3.82 (1H, d, J = 2.3, OH), 3.83–3.88 (1H, m, H-1b), 3.89 (1H, dd, J = 8.6, 6.0, H-4), 3.91 (1H, dd, J = 6.0, 2.6, H-5), 3.97 (1H, ddd, J = 7.2, 5.7, 2.6, H-6), 4.65 (2H, s-like, OCH_2OCH_3), 4.74/4.76 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.78/4.85 (each 1H, d, J = 6.0, OCH_2OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.4/29.3 [$(CH_3)_2C$], 55.6/56.0/56.4 (OCH_2OCH_3), 63.2 (C-1), 66.2 (C-3), 67.3 (C-7), 72.0 (C-4), 72.9 (C-2), 76.5 (C-6), 81.0 (C-5), 97.0/97.6/98.67 (OCH_2OCH_3), 98.70 [$C(CH_3)_2$]. FABMS m/z: 385 $[M+H]^+$ (pos.), FABHRMS m/z: 385.2072 ($C_{16}H_{33}O_{10}$ requires 385.2074).

Following the method described above, **24b** (864 mg, 1.53 mmol), **24c** (275 mg, 0.49 mmol), and **24d** (287 mg, 0.51 mmol) were converted to 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*gluco*-heptitol **25b** (567 mg, 96%), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*allo*-heptitol **25c** (170 mg, 91%) and 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*manno*-heptitol **25d** (179 mg, 92%), respectively.

3.12.2. Compound 25b

Colorless plates (from n-hexane–Et_2O). Mp. 64.5–65 °C. bp. 173–175 °C/0.005 mmHg. $[\alpha]_D^{24}$ – 59.2 (c = 1.27, $CHCl_3$). IR (neat): 3422, 1454, 1384, 1261, 1204, 1152, 1109, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.42/1.49 [each 3H, s, $C(CH_3)_2$], 2.14 (1H, dd-like *ca.* 7.8, 4.6, OH), 3.41/3.42/3.46 (each 3H, s, OCH_2OCH_3), 3.63 (1H, dd, J = 11.2, 3.2, H-1a), 3.72–3.82 [5H, m, H-5, H-6, H-7a, and OH, including one-proton doublet of doublets due to H-1b at δ 3.75 (J = 11.2, 2.3)], 3.82–3.86 (2H, m, H-4 and H-7b), 3.97 (1H, ddd, J = 8.3, 3.2, 2.3, H-2), 4.06 (1H, dd, J = 8.3, 2.9, H-3), 4.66/4.67 (each 1H, d, J = 6.6 Hz, OCH_2OCH_3), 4.76 (2H, br d, J = *ca.* 6.8, OCH_2OCH_3), 4.48 (1H, d, J = 6.9, OCH_2OCH_3), 4.87 (1H, d, J = 6.3, OCH_2OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.2/29.2 [$C(CH_3)_2$], 55.6/55.7/56.2 (OCH_2OCH_3), 63.1 (C-7), 63.3 (C-5), 67.1 (C-1), 73.0 (C-4), 73.1 (C-6), 77.3 (C-3), 77.5 (C-2), 96.9/97.0/99.5 (OCH_2OCH_3), 99.2 [$C(CH_3)_2$]. FABMS m/z: 385 $[M+H]^+$ (pos.), FABHRMS m/z: 385.2085 ($C_{16}H_{33}O_{10}$ requires 385.2074).

3.12.3. Compound 25c

Colorless oil. $[\alpha]_D^{24}$ + 22.4 (c = 3.30, $CHCl_3$). IR (neat): 3421, 1458, 1385, 1261, 1207, 1151, 1108, 1034 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.39/1.49 [each 3H, s, $C(CH_3)_2$], 2.19 (1H, br t-like, J = *ca* 5.3, OH), 3.37/3.42/3.43 (each 3H, s, OCH_2OCH_3), 3.648 (1H, ddd, J = 9.1, 9.1, 2.1, H-5), 3.650 (1H, dd, J = 10.5, 6.9, H-1a), 3.71–3.78 [3H, m, H-6, H-7a including one-proton doublet of doublets due to H-1b at δ 3.73 (J = 10.5, 4.7)], 3.85 (1H, ddd, J = 7.2, 5.3, 5.3, H-7b), 3.88 (1H, dd, J = 9.1, 4.4, H-4), 3.98 (1H, dd, J = 4.4, 3.1, H-3), 4.112 (1H, ddd, J = 6.9, 4.7, 3.1, H-2), 4.114 (1H, d, J = 2.1, OH), 4.63/4.64 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.77/4.80 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.78/4.83 (each 1H, d, J = 6.4, OCH_2OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.3/29.2 [$C(CH_3)_2$], 55.3/55.8/56.1 (OCH_2OCH_3), 63.4 (C-7), 64.6 (C-5), 67.5 (C-1), 72.2 (C-4), 73.0 (C-6), 76.3 (C-2), 79.3 (C-3), 96.6/96.87/96.93 (OCH_2OCH_3), 98.6 [$C(CH_3)_2$]. FABMS m/z: 385 $[M+H]^+$ (pos.), FABHRMS m/z: 385.2090 ($C_{16}H_{33}O_{10}$ requires 385.2074).

3.12.4. Compound 25d

Colorless oil. $[\alpha]_D^{24}$ – 9.1 (c = 3.16, $CHCl_3$). IR (neat): 3420, 1458, 1384, 1261, 1204, 1153, 1108, 1030 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.43/1.48 [each 3H, s, $C(CH_3)_2$], 2.16 (1H, br dd-like ca. 7.2, 4.0, OH), 3.39/3.42/3.49 (each 3H, s, OCH_2OCH_3), 3.55 (1H, d, J = 4.8, OH), 3.71 (1H, dd, J = 11.0, 3.1, H-1a), 3.72 (1H, ddd, J = 9.6, 9.6, 4.8, H-5), 3.76–3.87 [4H, m, H-6, H-7a, H-7b, including one-proton doublet of doublet of doublets due to H-2 at δ 3.85 (J = 8.4, 3.1, 2.4)], 3.90 (1H, dd, J = 11.0, 2.4, H-1b), 3.95 (1H, dd, J = 9.6, 2.4, H-4), 4.07 (1H, dd, J = 8.4, 2.4, H-3), 4.68/4.700 (1H, d, J = 6.5, OCH_2OCH_3), 4.69/4.74 (1H, d, J = 6.5, OCH_2OCH_3), 4.702/4.85 (1H, d, J = 6.5, OCH_2OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.4/29.4 [$C(CH_3)_2$], 55.6/55.7/56.8 (OCH_2OCH_3), 63.0 (C-7), 63.4 (C-5), 67.5 (C-1), 72.5 (C-4), 73.1 (C-6), 76.17 (C-3), 76.22 (C-2), 97.0/97.6/99.0 (OCH_2OCH_3), 99.1 [$C(CH_3)_2$]. FABMS m/z: 385 $[M+H]^+$ (pos.), FABHRMS m/z: 385.2097 ($C_{16}H_{33}O_{10}$ requires 385.2074).

3.13. Preparation of cyclic sulfates 12a, 12b, 12c and 12d

A solution of freshly distilled thionyl chloride (250 μl, 3.4 mmol) in dichloromethane (20 ml) was added dropwise to a stirred mixture of diol **25a** (1.0 g, 2.6 mmol), triethylamine (0.9 ml, 6.5 mmol) and dichloromethane (20 ml) at 0 °C. After being stirred at 0 °C for 30 min, the mixture was poured into ice-cooled and vigorously stirred aq. sodium hydrogen carbonate (40 ml), and extracted with dichloromethane. The extract was washed with brine, and condensed to give the corresponding sulfite (1.3 g) as a pale yellow oil, which was immediately used in the next step without purification.

To a well stirred mixture of the crude sulfite (1.3 g), sodium hydrogen carbonate (800 mg, 9.5 mmol), carbon tetrachloride (20 ml), acetonitrile (20 ml), and water (20 ml) was added dropwise a brown mixture of sodium metaperiodate (1.67 g, 7.8 mmol), ruthenium chloride n-hydrate (100 mg), and water (13 ml) at 0 °C. After being stirred at 0 °C for 30 min, the reaction was quenched by the addition of aqueous sodium thiosulfate–sodium hydrogen carbonate (20 ml). The resulting purple mixture was extracted with diethyl ether. The extract was washed with brine, and condensed to give a colorless oil (1.27 g), which on column chromatography (CH_2Cl_2–AcOEt, 5/1) gave 2,4-*O*-isopropylidene-5,6,7-methoxymethyl-D-*glycero*-L-*allo*-heptitol 1,3-cyclic sulfate **12a** (593 mg, 51%).

3.13.1. Compound 12a

Colorless oil. $[\alpha]_D^{22}$ + 5.02 (c = 2.57, $CHCl_3$). IR (neat): 1454, 1416, 1250, 1203, 1151, 1110, 1026 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.45/1.56 [each 3H, s, $C(CH_3)_2$], 3.38/3.41/3.43 (each 3H, s, OCH_2OCH_3), 3.74 (1H, dd, J = 11.0, 5.0, H-7a), 3.77 (1H, dd, J = 11.0, 3.4, H-7b), 3.92–3.77 (2H, m, H-5 and H-6), 4.22 (1H, ddd, J = 10.3, 9.8, 4.8, H-2), 4.25 (1H, dd, J = 9.8, 2.7, H-4), 4.46 (1H, dd, J = 10.3, 4.8, H-1 eq), 4.60 (1H, dd, J = 10.3, 10.3, H-1ax), 4.64/4.66 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.74/4.77 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.75/4.78 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.87 (1H, dd, J = 9.8, 9.8 Hz, H-3). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.1/28.7 [$C(CH_3)_2$], 55.5/55.8/56.2 (OCH_2OCH_3), 64.3 (C-2), 68.0 (C-7), 71.0 (C-4), 73.0 (C-1), 76.5/76.6 (C-5 and C-6), 78.1 (C-3), 96.8/97.1/97.9 (OCH_2OCH_3), 101.2 [$C(CH_3)_2$]. FABMS m/z: 447 $[M+H]^+$ (pos.), FABHRMS m/z: 447.1561 ($C_{16}H_{31}O_{12}S_1$ requires 447.1537).

Following the method described above, **25b** (539 mg, 1.4 mmol), **25c** (148 mg, 0.38 mmol), and **25d** (154 mg, 0.4 mmol) were converted to 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-D-*gluco*-heptitol 5,7-cyclic sulfate **12b** (356 mg, 57%), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxy-methyl-D-*glycero*-D-*allo*-heptitol 5,7-cyclic sulfate **12c** (74 mg, 43%), and 4,6-*O*-isopropylidene-1,2,3-methoxymethyl-D-*glycero*-D-*manno*-heptitol 5,7-cyclic sulfate **12d** (134 mg, 75%), respectively.

3.13.2. Compound 12b

Colorless prisms (from n-hexane–AcOEt). mp. 79–80 °C. $[\alpha]_D^{24}$ – 29.4 (c = 2.50, $CHCl_3$). IR ($CHCl_3$): 1416, 1231, 1200, 1150, 1107, 1018 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.46/1.56 [each 3H s, $C(CH_3)_2$], 3.38/3.40/3.46 (each 3H, s, OCH_2OCH_3), 3.60 (1H, dd, J = 11.5, 6.0, H-1a), 3.81 (1H, dd, J = 11.5, 2.6, H-1b), 3.94 (1H, dd, J = 6.6, 1.7, H-3), 4.01 (1H, dd, J = 6.6, 6.0, 2.6, H-2), 4.25 (1H, ddd, J = 10.6, 9.5, 4.9, H-6), 4.26 (1H, dd, J = 9.5, 1.7, H-4), 4.47 (1H, dd, J = 10.6, 4.9, H-7 eq), 4.61 (1H, dd, J = 10.6, 10.6, H-7ax), 4.63/4.65 (each 1H, d, J = 6.6, OCH_2OCH_3), 4.71 (1H, dd, J = 9.5, 9.5, H-5), 4.74 (2H, d, J = 6.6, OCH_2OCH_3), 4.78 (1H, d, J = 6.6, OCH_2OCH_3), 4.81 (1H, d, J = 6.6, OCH_2OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.1/28.8 [$C(CH_3)_2$], 55.4/55.8/56.5 (OCH_2OCH_3), 64.6 (C-6), 68.0 (C-1), 69.6 (C-4), 73.1 (C-7), 73.5 (C-3), 76.5 (C-5), 77.2 (C-2), 96.8/97.3/98.2 (OCH_2OCH_3), 101.3 [$C(CH_3)_2$]. FABMS m/z: 447 $[M+H]^+$ (pos.), FABHRMS m/z: 447.1545 ($C_{16}H_{31}O_{12}S$ requires 447.1537).

3.13.3. compound 12c

Colorless oil. $[\alpha]_D^{24}$ – 12.5 (c = 5.68, $CHCl_3$). IR (neat): 1458, 1420, 1252, 1204, 1152, 1114, 1026 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.43/1.56 [each 3H, s, $C(CH_3)_2$], 3.38 (3H, s, OCH_2OCH_3), 3.43 (6H, s, OCH_2OCH_3), 3.69 (1H, dd, J = 10.5, 4.0, H-1a), 3.85 (1H, ddd, J = 7.7, 4.0, 2.8, H-2), 3.87 (1H, ddd, J = 10.5, 2.8, H-1b), 3.97 (1H, dd, J = 7.7, 2.0, H-3), 4.24 (1H, ddd, J = 10.5, 9.8, 4.8, H-6), 4.43 (1H, dd, J = 9.8, 2.0, H-4), 4.47 (1H, dd, J = 10.5, 4.8, H-7 eq), 4.60 (1H, dd, J = 10.5, 10.5, H-7ax), 4.66 (2H, s, OCH_2OCH_3), 4.74/4.78 (each 1H, d, J = 6.5, OCH_2OCH_3), 4.77 (2H, s, OCH_2OCH_3), 4.83 (1H, dd, J = 9.8, 9.8, H-5). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.1/28.7 [$(CH_3)_2C$], 55.4/56.0/56.4 (OCH_2OCH_3), 64.3 (C-6), 66.9 (C-1), 71.1 (C-4), 73.0 (C-7), 75.8 (C-2), 76.1 (C-3), 77.9 (C-5), 96.7/96.9/97.9 (OCH_2OCH_3), 101.2 [$(CH_3)_2C$]. FABMS m/z: 447 $[M+H]^+$ (pos.), FABHRMS m/z: 447.1549 ($C_{16}H_{31}O_{12}S$ requires 447.1537).

3.13.4. Compound 12d

Colorless oil. $[\alpha]_D^{24}$ – 9.9 (c = 6.00, $CHCl_3$). IR (neat): 1458, 1420, 1253, 1204, 1153, 1112, 1034 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.47/1.55 [each 3H, s, $C(CH_3)_2$], 3.39/3.42/3.46 (each 3H, s, OCH_2OCH_3), 3.72 (1H, dd, J = 11.2, 3.6, H-1a), 3.80 (1H, ddd, J = 7.8, 3.6, 2.4, H-2), 3.91 (1H, dd, J = 11.2, 2.4, H-1b), 3.97 (1H, dd, J = 7.8, 1.6, H-3), 4.26 (1H, ddd, J = 10.3, 9.8, 4.8, H-6), 4.29 (1H, dd, J = 9.8, 1.6, H-4), 4.49 (1H, dd, J = 10.3, 4.8, H-7 eq), 4.62 (1H, dd, J = 10.3, 10.3, H-7ax), 4.68 (2H, s, OCH_2OCH_3), 4.71/4.73 (each 1H, d, J = 6.7, OCH_2OCH_3), 4.71 (1H, dd, J = 9.8, 9.8, H-3), 4.72/4.80 (1H, d, J = 6.2, OCH_2OCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.2/28.8 [$C(CH_3)_2$], 55.5/55.8/56.5 (OCH_2OCH_3), 64.5 (C-6), 67.0 (C-1), 70.0 (C-4), 73.1 (C-7), 73.6 (C-3), 75.9 (C-2), 76.8 (C-5), 96.9/97.2/98.6 (OCH_2OCH_3), 101.4 [$C(CH_3)_2$]. FABMS m/z: 447 $[M+H]^+$ (pos.), FABHRMS m/z: 447.1559 ($C_{16}H_{31}O_{12}S$ requires 447.1537).

3.14. Coupling reaction between cyclic sulfates (12a, 12b, 12c, and 12d) and Thiosugar 13

According to the literature,[9c] a mixture of cyclic sulfate **12a** (200 mg, 0.45 mmol), thiosugar[8m] **13** (51.7 mg, 0.35 mmol), potassium carbonate (15 mg, 0.11 mmol), and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, 0.5 ml) in a sealed tube was stirred at 60 °C for 42 h. After removal of the solvent, the residue was triturated with diethyl ether to give a yellow amorphous (272 mg), which on column chromatography ($CHCl_3$ → $CHCl_3$–MeOH, 10/1→5/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*S*,6*R*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt **26a** (187 mg, 91%).

3.14.1. Compound 26a

Colorless prisms (from MeOH–Et_2O). mp. 160–161 °C. $[\alpha]_D^{22}$ + 17.7 (*c* = 0.84, CH_3OH). IR (nujol): 3344, 1265, 1211, 1150, 1103, 1030 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 1.47/1.54 [each 3H, s, $C(CH_3)_2$], 3.36/3.39/3.41 (each 3H s, OCH_2OCH_3), 3.78 (1H, dd, *J* = 12.8, 3.8, H-1a), 3.81 (2H, d-like, *J* = *ca.* 4.5, H-7′a and H-7′b), 3.85 (1H, dd, *J* = 12.8, 1.8, H-1b), 3.94 (1H, dd, *J* = 10.6, 1.7, H-5a), 3.98 (1H, dd, *J* = 10.6, 4.6, H-5b), 3.98–4.02 (1H, m, H-4), 4.06 (1H, dd, *J* = 13.8, 4.9, H-1′a), 4.08 (1H, dd, *J* = 6.9, 1.5, H-5′), 4.14 (1H, dd, *J* = 13.8, 3.2, H-1′b), 4.18 (1H, dd, *J* = 9.5, 1.5, H-4′), 4.24 (1H, dt-like, *J* = 6.9, 4.5, H-6′), 4.40 (1H, ddd, *J* = 9.5, 4.9, 3.2, H-2′), 4.43 (1H, br d, *J* = 2.0, H-3), 4.50 (1H, dd, *J* = 9.5, 9.5, H-3′), 4.60–4.63 (1H, br m, H-2), 4.63/4.65 (each 1H, d, *J* = 6.3, OCH_2OCH_3), 4.70/4.76/4.89 (each 1H, d, *J* = 6.6, OCH_2OCH_3, a signal due to one of the methylene protons in MOM groups overlapped with that of CD_3OH). ^{13}C NMR (125 MHz, CD_3OD) δ: 19.3/29.2 [$(CH_3)_2C$], 50.5 (C-1′), 51.4 (C-1), 55.7/56.1/56.4 (OCH_2OCH_3), 60.9 (C-5), 69.9 (C-7′), 70.8 (C-3′), 71.3 (C-2′), 73.4 (C-4), 74.5 (C-4′), 78.7 (C-6′), 78.8 (C-5′), 79.2 (C-2). 80.1 (C-3), 97.8/98.7/98.8 (OCH_2OCH_3), 101.1 [$(CH_3)_2C$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 597.1863 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

Following the method described above, cyclic sulfate **12b** (300 mg, 0.67 mmol) was treated with thiosugar **13** (78 mg, 0.52 mmol) at 60 °C for 54 h. Work-up gave a colorless oil (394 mg), which on column chromatography ($CHCl_3$ → $CHCl_3$–MeOH, 10/1→5/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*R*,6*S*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfooxy)heptyl]-episulfoniumylidene}-D-arabinitol inner salt **26b** (278 mg, 90%).

3.14.2. Compound 26b

Colorless prisms (from MeOH–Et_2O). Mp. 153–154 °C. $[\alpha]_D^{24}$ + 40.8 (*c* = 1.15, CH_3OH). IR (nujol): 3420, 3329, 1261, 1207, 1149, 1103, 1038 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 1.45/1.55 [each 3H, s, $C(CH_3)_2$], 3.35/3.400/3.402 (each 3H, s, OCH_2OCH_3), 3.55 (1H, dd, *J* = 11.5, 7.8, H-7′a), 3.78 (1H, dd, *J* = 12.9, 3.8, H-1a), 3.83 (1H, dd, *J* = 12.9, 2.3, H-1b), 3.88 (1H, dd, *J* = 11.5, 1.5, H-7′b), 3.94 (1H, br dd, *J* = 7.2, 6.6, H-4 and 1H, dd, *J* = 8.0, 6.6, H-5a), 3.99 (1H, dd, *J* = 8.0, 7.2, H-5b), 4.02 (1H, dd, *J* = 13.8, 4.6, H-1′a), 4.12 (1H, dd, *J* = 13.8, 3.2, H-1′b), 4.15–4.20 [3H, m, H-4′, H-5′ and H-6′], 4.35 (1H, dd, *J* = 9.5, 9.5, H-3′), 4.40 (1H, ddd, *J* = 9.5, 4.6, 3.2, H-2′), 4.44 (1H, br d, *J* = 1.8, H-3), 4.59–4.61 (1H, m, H-2), 4.60/4.63 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.68/4.77 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.74/5.01 (each 1H, d, *J* = 6.9, OCH_2OCH_3). ^{13}C NMR (125 MHz, CD_3OD) δ: 19.3/29.1 [$(CH_3)_2C$], 50.5 (C-1′), 51.3 (C-1), 55.6/56.2/56.5 (OCH_2OCH_3), 60.9 (C-5), 69.7 (C-3′), 69.9 (C-7′), 70.9 (C-4′), 71.4 (C-2′), 73.5 (C-4), 77.5 (C-6′), 79.1 (C-2), 79.6 (C-5′), 80.1 (C-3), 97.6/98.3/100.7 (OCH_2CH_3), 101.0 [$(CH_3)_2C$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 597.1861 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

Following the method described above, cyclic sulfate **12c** (73 mg, 0.16 mmol) was treated with thiosugar **13** (21 mg, 0.14 mmol) at 60 °C for 54 h. Work-up gave a pale orange oil (96.4 mg), which on column chromatography ($CHCl_3$→$CHCl_3$–MeOH, 20/1→10/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*S*,6*S*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt **26c** (72 mg, 86%).

3.14.3. Compound 26c

Colorless amorphous. $[\alpha]_D^{26}$ – 10.5 (*c* = 3.38, CH_3OH). IR (nujol): 3383, 1262, 1211, 1150, 1103, 1022 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ: 1.47/1.55 [each 3H, s, $C(CH_3)_2$], 3.35/3.40/3.42 (each 3H, s, OCH_2OCH_3), 3.65 (1H, dd, *J* = 11.0, 6.0, H-7′a), 3.77 (1H, dd, *J* = 12.7, 3.6, H-1a), 3.84 (1H, dd, *J* = 12.7, 1.6, H-1b), 3.94 (1H, dd, *J* = 8.1, 4.9, H-5a), 3.97 (1H, dd, *J* = 11.0, 1.9, H-7′b), 3.97–3.99 (1H, m, H-4), 3.99 (1H, dd, *J* = 8.1, 3.6, H-5b), 4.06 (1H, dd, *J* = 13.8, 4.6, H-1′a), 4.08 (1H, ddd, *J* = 6.4, 6.0, 1.9, H-6′), 4.13 (1H, dd, *J* = 13.8, 3.2, H-1′b), 4.18 (1H, dd, *J* = 6.4, 1.2, H-5′), 4.24 (1H, dd, *J* = 9.6, 1.2, H-4′), 4.38 (1H, ddd, *J* = 9.6, 4.6, 3.2, H-2′), 4.43 (1H, d-like, *J* = 2.2, H-3), 4.48 (1H, dd, *J* = 9.6, 9.6, H-3′), 4.60–4.63 (1H, m, H-2), 4.62/4.67 (each 1H, d, *J* = 6.5, OCH_2OCH_3), 4.70/4.92 (each 1H, d, *J* = 6.3, OCH_2OCH_3), 4.74/4.75 (each 1H, d, *J* = 6.7, OCH_2OCH_3). ^{13}C NMR (150 MHz, CD_3OD) δ: 19.2/29.2 [$(CH_3)_2C$], 50.5 (C-1′), 51.4 (C-1), 55.6/56.3/56.5 (OCH_2OCH_3), 60.9 (C-5), 69.7 (C-7′), 70.9 (C-3′), 71.4 (C-2′), 73.5 (C-4), 74.8 (C-4′), 77.8 (C-6′), 78.0 (C-5′), 79.2 (C-2), 80.1 (C-3), 97.8/97.9/98.7 (OCH_2CH_3), 101.1 [$(CH_3)_2C$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 597.1890 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

Following the method described above, cyclic sulfate **12d** (130 mg, 0.29 mmol) was treated with thiosugar **13** (37 mg, 0.25 mmol) at 60 °C for 72 h. Work-up gave a pale orange amorphous (215 mg), which on column chromatography ($CHCl_3$→ $CHCl_3$–MeOH, 10/1→5/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*R*, 6*R*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfoxy) heptyl]episulfoniumylidene}-D-arabinitol inner salt **26d** (135 mg, 92%).

3.14.4. Compound 26d

Colorless amorphous. $[\alpha]_D^{25}$ + 29.7 (*c* = 4.20, CH_3OH). IR (nujol): 3391, 1255, 1207, 1157, 1103, 1022 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 1.46/1.55 [each 3H, s, $C(CH_3)_2$], 3.36/3.39/3.44 (each 3H, s, OCH_2OCH_3), 3.72 (1H, dd, *J* = 10.9, 5.4, H-7a′), 3.77–3.82 [2H, m, H-6′, including one-proton doublet of doublets due to H-1a at δ 3.79 (*J* = 12.6, 3.7)], 3.84 (1H, dd, *J* = 12.6, 1.6, H-1b), 3.90 (1H, dd, *J* = 10.9, 2.3, H-7b′), 3.93–3.99 (2H, m, H-4 and H-5a), 4.00 (1H, dd, *J* = 10.4, 4.0, H-5b), 4.04 (1H, dd, *J* = 13.5, 5.2, H-1a′), 4.11 (1H, dd, *J* = 9.5, 0.9, H-4′), 4.15 (1H, dd, *J* = 13.5, 2.9, H-1b′), 4.18 (1H, dd, *J* = 6.6, 0.9, H-5′), 4.41 (1H, dm, *J* = *ca.* 9.5, H-2′), 4.43 (1H, br d, *J* = 2.3, H-3), 4.48 (1H, dd, *J* = 9.5, 9.5, H-3′), 4.60–4.62 (1H, m, H-2), 4.62/4.64 (each 1H, d, *J* = 6.6 Hz, OCH_2OCH_3), 4.70/4.72 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.88/4.90 (each 1H, d, *J* = 6.3, OCH_2OCH_3). ^{13}C NMR (125 MHz, CD_3OD) δ: 19.5/29.1 [$C(CH_3)_2$], 50.6 (C-1′), 51.3 (C-1), 55.7/56.2/56.6 (OCH_2OCH_3), 60.9 (C-5), 68.9 (C-7′), 70.3 (C-3′), 71.2 (C-2′), 72.3 (C-4′), 73.5 (C-4), 77.0 (C-5′), 78.6 (C-6′), 79.2 (C-2), 80.0 (C-3), 97.8/ 98.0/100.3 (OCH_2CH_3), 101.1 [$C(CH_3)_2$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 597.1912 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

3.15. Preparation of kotalanol analogs 11a, 11b, 11c and 11d

A solution of coupled product **26a** (158 mg, 0.27 mol) in 30% aqueous trifluoroacetic acid (15 ml) was stirred at 50 °C for 2 h. Removal of the solvent in vacuo left a colorless oil (156 mg), which on column chromatography ($CHCl_3$–MeOH–H_2O, 10/5/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*S*,6*R*)-2,4,5,6,7-pentahydroxy-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt **11a** (88 mg, 78%).

3.15.1. Compound 11a

Colorless viscous oil. $[\alpha]_D^{24}$ + 12.4 (*c* = 0.97, H_2O). IR (neat): 3380, 1297, 1271, 1238, 1215, 1135, 1108, 1065, 1025 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 3.62 (1H, dd, *J* = 10.5, 6.5, H-7′a), 3.64 (1H, dd, *J* = 10.5, 5.8, H-7′b), 3.76 (1H, dd, *J* = 8.3, 2.0, H-5′), 3.84 (2H, d-like, *J* = *ca.* 2.6, H-1a and H-1b), 3.88–3.93 [2H, m, H-1′a, including one-proton broad doublet of doublets due to H-6′ at δ 3.91 (*J* = 6.5, 5.8)], 3.93 (1H, dd, *J* = 8.6, 5.7, H-5a), 3.95–4.00 [2H, m, H-4, including one-proton doublet of doublets due to H-1′b at δ 3.99 (*J* = 13.5, 4.0)], 4.03 (1H, dd, *J* = 8.6, 3.5, H-5b), 4.16 (1H, dd, *J* = 8.3, 2.6, H-4′), 4.38 (1H, d-like, *J* = *ca.* 2.6, H-3), 4.54 (1H, ddd, *J* = 6.3, 6.3, 4.0, H-2′), 4.59 (1H, dt-like, *J* = *ca.* 2.6, 2.6, H-2), 4.73 (1H, dd, *J* = 6.3, 2.6, H-3′). ^{13}C NMR spectrum of **11a** was

summarized in Table 1. FABMS *m*/*z*: 425 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 425.0795 ($C_{12}H_{25}O_{12}S_2$ requires 425.0788).

Following the method described above, **26b** (112 mg, 0.19 mmol) was hydrolyzed with 30% aqueous TFA (11 ml) at 50 °C for 2 h. Work-up gave a colorless oil (114 mg), which on column chromatography ($CHCl_3$–MeOH–H_2O, 10/5/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*R*,6*S*)-2,4,5,6,7-pentahydroxy-3-(sulfooxy) heptyl]episulfoniumylidene}-D-arabinitol inner salt **11b** (65.3 mg, 82%).

3.15.2. Compound 11b

Colorless amorphous. $[\alpha]_D^{24}$ – 8.1 (*c* = 1.13, H_2O). IR (nujol): 3390, 1260, 1235, 1205, 1162, 1107, 1060, 1016 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 3.61 (1H, dd, *J* = 11.2, 6.2, H-7′a), 3.68 (1H, dd, *J* = 11.2, 4.5, H-7′b), 3.79 (1H, ddd, *J* = 6.2, 4.6, 4.5, H-6′), 3.84 (2H, d-like, *J* = *ca.* 2.6, H-1a and H-1b), 3.89 (1H, dd, *J* = 4.6, 1.7, H-5′), 3.90–3.99 [3H, m, H-4, including one-proton doublet of doublets due to H-1′a at δ 3.92 (*J* = 13.5, 3.7) and one-proton doublet of doublets due to H-5a at δ 3.94 (*J* = 10.0, 8.0)], 3.98 (1H, dd, *J* = 13.5, 8.1, H-1′b), 3.99 (1H, dd, *J* = 6.9, 1.7, H-4′), 4.03 (1H, dd, *J* = 10.0, 4.9, H-5b), 4.38 (1H, dd, *J* = 2.6, 1.5, H-3), 4.47 (1H, dd, *J* = 6.9, 4.6, H-3′), 4.53 (1H, ddd, *J* = 8.1, 4.6, 3.7, H-2′), 4.60 (1H, dt-like, *J* = *ca.* 2.6, 2.6, H-2). ^{13}C NMR spectrum of **11b** was summarized in Table 1. FABMS *m*/*z*: 425 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 425.0809 ($C_{12}H_{25}O_{12}S_2$ requires 425.0788).

Following the method described above, **26c** (41 mg, 0.069 mmol) was hydrolyzed with 30% aqueous TFA (4 ml) at 50 °C for 1 h. Work-up gave a colorless oil (43 mg), which on column chromatography ($CHCl_3$–MeOH–H_2O, 10/5/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*S*,6*S*)-2,4,5,6,7-pentahydroxy-3-(sulfooxy)-heptyl]episulfoniumylidene}-D-arabinitol inner salt (**11c**, 27 mg, 92%).

3.15.3. Compound 11c

Colorless solid. $[\alpha]_D^{24}$ + 4.4 (*c* = 2.31, H_2O). IR (nujol): 3391, 1262, 1215, 1108, 1061 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 3.65 (1H, dd, *J* = 11.2, 5.2, H-7′a), 3.77 (1H, dd, *J* = 11.2, 3.2, H-7b′), 3.77–3.82 (2H, m, H-5′ and H-6′), 3.84 (2H, d-like, *J* = *ca.* 2.6, H-1a and H-1b), 3.92 (1H, dd, *J* = 13.5, 6.9, H-1a′), 3.95 (1H, dd, *J* = 9.7, 7.5, H-5a), 3.97–4.03 [2H, m, H-4, including one-proton doublet of doublets due to H-1′b at δ *ca.* 4.00 (*J* = *ca.* 13.5, 3.8)], 4.03 (1H, dd, *J* = 9.7, 4.9, H-5b), 4.23 (1H, dd, *J* = 6.0, 2.9, H-4′), 4.39 (1H, dd, *J* = 2.6, 1.2, H-3), 4.54 (1H, ddd, *J* = 6.9, 6.0, 3.8, H-2′), 4.60 (1H, dt-like, *J* = *ca.* 2.6, 2.6, H-2), 4.72 (1H, dd, *J* = 6.0, 2.9, H-3′). ^{13}C NMR spectrum of **11c** was summarized in Table 1. FABMS *m*/*z*: 425 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 425.0760 ($C_{12}H_{25}O_{12}S_2$ requires 425.0788).

Following the method described above, **26d** (78 mg, 0.13 mmol) was hydrolyzed with 30% aqueous TFA (7 ml) at 50 °C for 2 h. Work-up gave a pale yellow oil (71 mg), which on column chromatography ($CHCl_3$–MeOH–H_2O, 10/5/1) gave 1,4-dideoxy-1,4-{(*S*)-[(2*S*,3*S*,4*S*,5*R*,6*R*)-2,4,5,6,7-pentahydroxy-3-(sulfoxy)-heptyl]episulfoniumylidene}-D-arabinitol inner salt **11d** (53 mg, 95%).

3.15.4. Compound 11d

Colorless solid. $[\alpha]_D^{24}$ – 9.6 (*c* = 2.64, H_2O). IR (nujol): 3368, 1260, 1227, 1163, 1150, 1105, 1072 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ: 3.63 (1H, dd, *J* = 11.0, 6.0, H-7′a), 3.67 (1H, ddd, *J* = 8.6, 6.0, 3.0, H-6′), 3.78 (1H, dd, *J* = 8.6, 0.9, H-5′), 3.80 (1H, dd, *J* = 11.0, 3.0, H-7b′), 3.84 (2H, d-like, *J* = *ca.* 2.6, H-1a and H-1b), 3.89 (1H, dd, *J* = 13.3, 3.5, H-1a′), 3.92 (1H, dd, *J* = 10.7, 8.5, H-5a), 3.96 (1H, dd, *J* = 13.3, 7.7, H-1′b), 3.97–4.01 (1H, m, H-4), 4.03 (1H, dd, *J* = 10.7, 5.2, H-5b), 4.11 (1H, dd, *J* = 7.8, 0.9, H-4′), 4.38 (1H, dd-like, *J* = *ca.* 2.6, 1.4, H-3), 4.45 (1H, dd, *J* = 7.8, 4.2, H-3′), 4.54 (1H, ddd, *J* = 7.7, 4.2, 3.5, H-2′), 4.60 (1H, dt-like, *J* = *ca.* 2.6, 2.6, H-2). ^{13}C NMR spectrum of **11d** were summarized in Table 1. FABMS *m*/*z*: 425 $[M+H]^+$ (pos.), FABHRMS *m*/*z*: 425.0760 ($C_{12}H_{25}O_{12}S_2$ requires 425.0788).

3.16. X-Ray crystallographic analysis

Data of compound **12b** were taken on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation. The structure of **12b** was solved by direct methods with SIR97 and SHELXL97. Full-matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. All calculations were performed using the Crystal Structure (Ver. 3.6, Rigaku/MSC) crystallographic software package. ORTEP drawing of compound **12b** is shown in Figure 3. The data of **12b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 884491.

3.17. Crystal data for cyclic sulfate 12b

Monoclinic, space group *C*2, *a* = 30.63(3), *b* = 8.98(1), *c* = 19.50(2) Å, β = 125.50(3)°, *V* = 4350(7) $Å^3$, *Z* = 8, μ(Mo-Kα) = 2.07 cm^{-1}, *F*(000) = 1904, D_c = 1.363 g/cm^3, crystal dimensions: 0.24 × 0.30 × 0.32 mm. A total of 19,955 reflections (9450 unique) were collected using the ω-2θ scan technique to a maximum 2θ value of 55°, and 1400 reflections with $I > 2\sigma(I)$ were used in the structure determination. Final *R* and R_w values were 0.048 and 0.140, respectively. The maximum and minimum peaks in the difference map were 0.51 $e^-Å^{-3}$ and –0.40 e^- $Å^{-3}$, respectively.

3.17.1. Enzyme inhibition assays

Rat small intestinal brush border membrane vesicles were prepared and its suspension in 0.1 M maleate buffer (pH 6.0) was used as small intestinal α-glucosidases of maltase and sucrase. A test compound was dissolved in dimethyl sulfoxide (DMSO), and the resulting solution was diluted with 0.1 M maleate buffer to prepare the test compound solution (concentration of DMSO: 10%). A substrate solution in the maleate buffer (maltose: 74 mM, sucrose: 74 mM, 100 µl), a test compound solution (50 µl), and an 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 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.

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