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

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ABSTRACT

Synthesis and evaluation of four diastereomers (**9a**, **9b**, **9c** and **9d**) of kotalanol, a potent α-glucosidase inhibitor isolated from an Ayurvedic medicinal plant *Salacia* species, are described. Stereo-inversion at C-3′ and C-4′ of kotalanol (**2**) caused significant decrease of the inhibitory activities against maltase and sucrase, whereas inhibitory activity against isomaltase sustained, thus resulted in exerting selectivity against isomaltase.

1. Introduction

Glucosidases are enzymes that catalyze the cleavage of glycosidic bonds in oligosaccharides or glycoconjugates. The activity of glucosidases is fundamental to several important biochemical processes, and glucosidase enzyme-catalyzed hydrolysis of complex carbohydrates is a biologically widespread phenomenon in living systems.[1] Multi-function of glucosidase in organisms makes itself an attractive target, and inhibition of the glucosidase has been used as a potential therapeutic principle to treat diseases such as diabetes, obesity, glycosphingolipid lysosomal storage disease, HIV infections, cancers and Gaucher's disease.[2] Thus, during the past few decades, considerable attention has been paid on designing potent glucosidase inhibitors in the chemical and medicinal research. One special category of potent glucosidase inhibitor is naturally occurring and synthesized azasugars such as deoxynojirimycin, acarbose, voglibose and miglitol.[3] The effective inhibition of azasugars against glucosidase enzymes is attributed to bearing the positive charge under physiological pH, which is postulated to bind in the active sites of glucosidase enzymes. This evidence indicates that a potent glucosidase inhibitor might include an atom that carries a permanent positive charge at a suitable position that mimic the oxacarbenium ion-like transition state of the enzyme-catalyzed reaction, and thus establish electrostatic interactions between inhibitors and the active sites of the carboxylate residue.[4]

In late 1990's, salacinol (**1**) was isolated by the authors as one of the physiologically active components of an Ayurvedic medicinal plant *Salacia reticulata*, which have traditionally been used for the treatment of diabetes in Sri Lanka and the south region of India.[5] Its α-glucosidase inhibitory activities were revealed to be as potent as those of voglibose and acarbose which are widely used clinically these days. Besides, the structure of **1** was found quite unique, bearing thiosugar sulfonium sulfate inner salt comprised of 1-deoxy-4-thio-D-arabinofranosyl cation and 3′-sulfate anion as shown in Figure 1.[5] Since the discovery of **1**, related sulfonium sulfates, kotalanol[6] (**2**), salaprinol[7] (**3**) and ponkoranol[7] (**4**) as well as their de-*O*-sulfonated analogues, neosalacinol[8] (**5**), neokotalanol[9] (**6**), neosalaprinol[10] (**7**), and neoponkoranol[10] (**8**) have subsequently been isolated from the same *Salacia* genus plants. All these sulfonium salts (**2**–**8**) showed potent α-glucosidase inhibitory activities as **1**, composing a new class of naturally occurring α-glycosidase inhibitors. Because of both their intriguing structures and high α-glucosidase inhibitory activities, intensive structure–activity relationship (SAR) studies have been reported,[11] and structural determinants of these sulfoniums for the α-glucosidase inhibitory activities have been revealed to a considerable extent.

On the other hand, although the exact stereostructure of the sulfonium sulfates **1**, **3** and **4** had been determined soon after their

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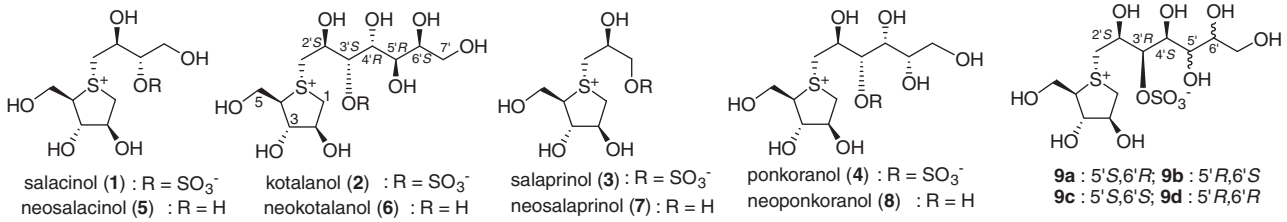


Figure 1.

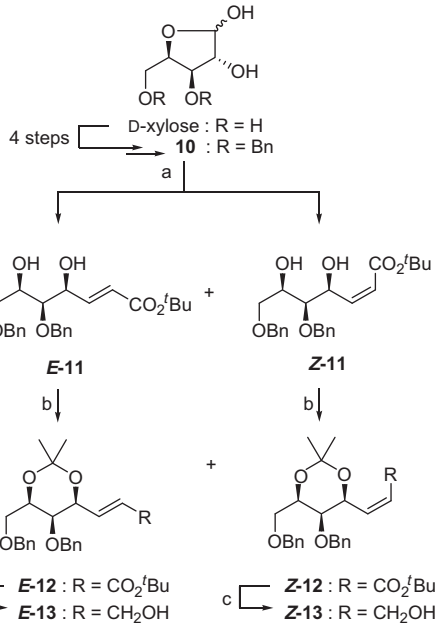
isolation, that of **2** had long been not clarified until recently when it was elucidated through the total synthesis by Pinto and co workers,[12a] and our degradation study of a natural kotalanol (**2**).[12b] In their previous synthetic studies directed toward the stereochemical structure determination of **2**, they synthesized few side chain stereoisomers, and discussed on the role of the side chain stereochemistry to the inhibitory activity against recombinant human maltase glucoamylase (MGA).[11d] In the course of our synthetic studies on **2**, we also had synthesized several diastereomers of **2**, and evaluated their α-glucosidase inhibitory activities against rat small intestinal α-glucosidases, maltase, sucrase and isomaltase, as a part of SAR studies on this new class of inhibitors. In this paper are described full details on the synthesis, evaluation and SAR studies on four kotalanol diastereomers (**9a**, **9b**, **9c** and **9d**), which have reversed stereochemistries at both C-3′ and C-4′ positions to kotalanol (**2**). Out of the four compounds examined, three (**9a**, **9b**, and **9d**) considerably lost their activities against both maltase and sucrase, while sustained the activity against isomaltase to a large extent, thus resulted in exerting selectivity against isomaltase.

2. Results and discussion

2.1. Preparation of cyclic sulfates

As a common synthon for the four target compounds with 3′*R*,4′*S* stereochemistries (**9a**, **9b**, **9c** and **9d**), 3,5-di-*O*-benzyl-D-xylofuranose (**10**),[13] which was easily obtained via 4 steps from a commercially available D-xylose, was selected. Thus, the Wittig reaction of **10** with *tert*-butoxycarbonylmethylenetriphenylphosphorane gave *tert*-butyl (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-D-*xylo*-hept-2-enoate (***E*-11**) and its *Z*-isomer (***Z*-11**) with a ratio of 6.5:1. The major enoate ***E*-11** was then converted to the corresponding acetal, *tert*-butyl (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*xylo*-hept-2-enoate (***E*-12**) by treatment with 2,2-dimethoxypropane, and subsequent reduction of the product with diisobutyl aluminum hydride (DIBAH) gave the corresponding *E*-enitol, (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*xylo*-hept-2-enitol (***E*-13**) in 89% yield from enoate ***E*-11**. In a similar manner, the minor enoate ***Z*-11** was also converted to the corresponding *Z*-enitol (***Z*-13**) in good yield (Scheme 1).

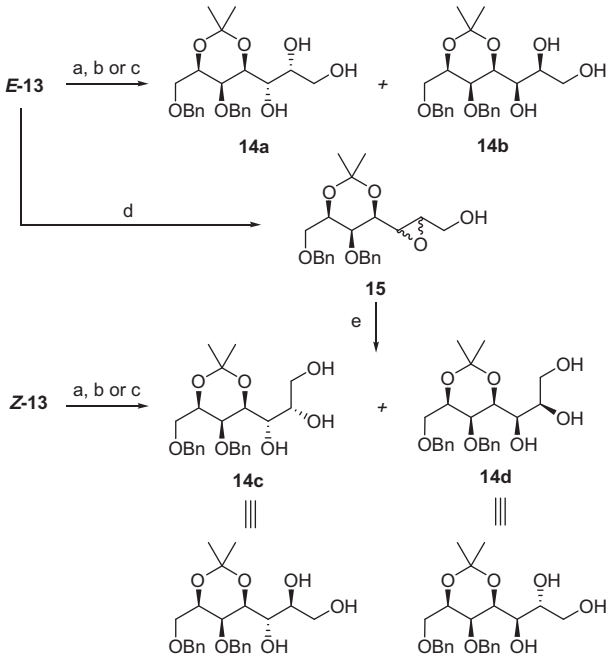
With compounds ***E***- and ***Z*-13** in hand, osmium tetroxide (OsO_4) catalyzed dihydroxylation was performed in the presence of *N*-methylmorphorine *N*-oxide (NMO) as a reoxidant. Upon reaction with *E*-enitol (***E*-13**), α-facial *syn*-dihydroxylation predominantly proceeded to give a corresponding triol, 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (**14a**), accompanied by β-attack leading to its diastereomer, 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*ido*-heptitol (**14b**) in a ratio of ca. 6:1 (Scheme 2 and Table 1, run 1).[14] Dihydroxylation of *Z*-isomer (***Z*-13**) showed the same face-selectivity, giving a mixture of hardly separable diastereomers 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*talo*-heptitol (**14c**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*gulo*-heptitol (**14d**) in a ratio of ca. 7:1



Scheme 1. Reagents and conditions: (a) $Ph_3P{=}CHCO_2{}^tBu$, CH_2Cl_2, reflux; (b) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, acetone, (c) 1 M soln of DIBAH in toluene, THF, −50 °C to rt.

(Scheme 2 and Table 1, run 5). Thus, it was found that by the OsO_4 dihydroxylation of ***E***- and ***Z*-13**, no sufficient amounts of triols **14b** and **14d** for further steps could be obtained. Therefore, the Sharpless asymmetric dihydroxylation[15] was applied to the enitols ***E***- and ***Z*-13**. It is interesting to note that AD-mix-α [ligand: $(DHQ)_2PHAL$] and AD-mix-β [ligand: $(DHQD)_2PHAL$] showed quite similar selectivity in the dihydroxylation, giving α-facial *syn*-dihydroxylated products **14a** or **14c** predominantly in all the attempts (Scheme 2 and Table 1, run 2, 3, 6, 7). After trial-and-error testing on reagents of the asymmetric dihydroxylation, $(DHQD)_2PYR$ was found most effective to increase the formation of **14b** or **14d**, although the diastereoselectivity was still insufficient (Scheme 2 and Table 1, run 4 and 8). Finally, base catalyzed hydrolysis of an epoxide (**15**) was employed as another approach for dihydroxylated product (**14d**). Thus ***E*-13** was first converted to epoxide (**15**) in good yield. Alkaline hydrolysis of **15** gave a mixture of **14c** and **14d** in a ratio of ca. 1.2:1, resulting in much more preferable formation of **14d** (Scheme 2).

The newly constructed stereochemistries of triols **14a** and **14b** were confirmed to be in *threo* relationship after leading them to known heptitols, D-*glycero*-L-*galacto*-heptitol (**16a**)[16] and D-*glycero*-L-*ido*-heptitol (**16b**),[16] respectively, via acidic hydrogenolysis. Owing to their too close polarity to be separated on TLC, stereochemistry of **14c** and **14d** were determined at the next stage. Four triols **14a**, **14b**, **14c** and **14d**, thus obtained were then converted to corresponding tri-*O*-MOM ethers, 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*galacto*-heptitol (**17a**), 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxy-



Scheme 2. Reagents and conditions: (a) OsO_4, NMO, acetone, H_2O, reflux; (b) AD-mix-α or AD-mix-β, ^tBuOH, H_2O, rt; (c) $(DHQD)_2PYR$, $K_2OsO_2(OH)_4$, $MeSO_2NH_2$, $KFe(CN)_6$, K_2CO_3, ^tBuOH, H_2O, 4 °C; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (e) 0.5 N aq NaOH, 1,4-dioxane, reflux, 4 h.

Table 1
Dihydroxylation of ***E***- and ***Z***-**13**

Run	Compd	Conditions	Product	Ratio[a]	Yield (%)
1	***E*-13**	(a) OsO_4, NMO	**14a**/**14b**	ca. 6/1	82
2	***E*-13**	(b) AD-mix-β	**14a**/**14b**	ca. 10/1	75
3	***E*-13**	(c) AD-mix-α	**14a**/**14b**	ca. 10/1	79
4	***E*-13**	(d) $(DHQD)_2PYR$	**14a**/**14b**	ca. 1/1.2	83
5	***Z*-13**	(a) OsO_4, NMO	**14c**/**14d**	ca. 7/1	76
6	***Z*-13**	(b) AD-mix-β	**14c**/**14d**	ca. 10/1	78
7	***Z*-13**	(c) AD-mix-α	**14c**/**14d**	ca. 10/1	70
8	***Z*-13**	(d) $(DHQD)_2PYR$	**14c**/**14d**	ca. 3.5/1	85

[a] Determined by 500 MHz NMR spectrum.

methyl-D-*glycero*-L-*ido*-heptitol (**17b**), 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*talo*-heptitol (**17c**), and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*gulo*-heptitol (**17d**), respectively, by treatment with chloromethyl methyl ether (MOMCl) in the presence of Hünig base ($^iPr_2NEt$). The tri-MOM ethers **17a**, **17b**, **17c** and **17d** were then subjected to hydrogenolysis in the presence of a small amount of sodium hydrogen carbonate,[17] to give corresponding diols, 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*galacto*-heptitol (**18a**), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*ido*-heptitol (**18b**), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*talo*-heptitol (**18c**) and 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*gulo*-heptitol (**18d**) in good yields. The stereochemistries of **18c** and **18d** were confirmed after leading them to known heptitols, D-*glycero*-L-*talo*-heptitol (**16c**)[16] and D-*glycero*-L-*gulo*-heptitol (**16d**)[16] by trifluoroacetic acid (TFA) catalyzed hydrolysis. Diols **18a**, **18b**, **18c** and **18d** were then subjected to the modified cyclic sulfation[11b] to give desired cyclic sulfates, 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*galacto*-heptitol 5,7-cyclic sulfate (**19a**), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*ido*-heptitol 5,7-cyclic sulfate (**19b**), 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*talo*-heptitol 5,7-cyclic sulfate (**19c**) and 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*gulo*-heptitol 5,7-cyclic sulfate (**19d**) in 65–70% yield. Their FAB mass spectra showed peaks at *m*/*z* 447 corresponding to the protonated molecular-ion $[M+H]^+$. In the ^1H NMR spectrum of **19a**, characteristic downfield shift signals due to methylene protons on C-7 and methine proton on C-5 were observed at δ_H 4.90 (H-7 equiv), 4.55 (H-7 ax) and δ_H 4.98 (H-5), respectively, supporting the cyclic sulfate formation. The signal due to H-5 appeared as doublet of doublets ($J_{5,6}$ = 1.5 and $J_{5,4}$ = 1.5 Hz) indicated the *cis*-decaline type bicyclic ring formation.(Scheme 3). The spectroscopic properties of these four cyclic sulfates were very similar with each other.

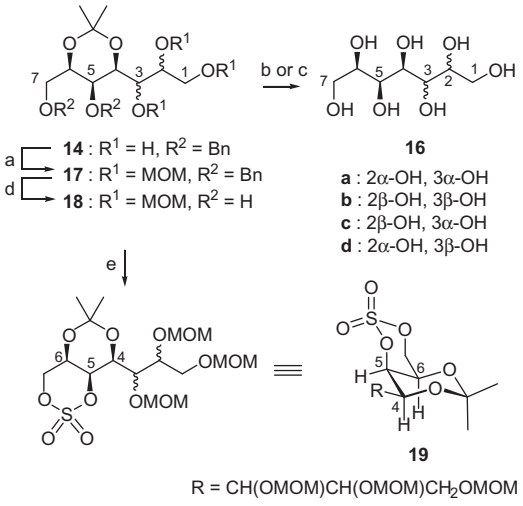
2.2. Preparation of sulfonium salts

The target sulfonium sulfates were prepared through ring opening of cyclic sulfates (**19a**, **19b**, **19c** and **19d**) by nucleophilic attack of thiosugar (**20**).[18] The reaction of cyclic sulfates (**19a**, **19b**, **19c** and **19d**) with thiosugar (**20**) proceeded slowly in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 65 °C, giving corresponding coupled products (**21a**, **21b**, **21c** and **21d**) in around 70% yield. The relative stereochemistry between the side chain and the methanol moiety at C-4 of the coupled products (**21a**, **21b**, **21c** and **21d**) were determined to be in *trans* relationship on the basis of nuclear Overhauser effect (NOE) experiments as shown in Scheme 4.

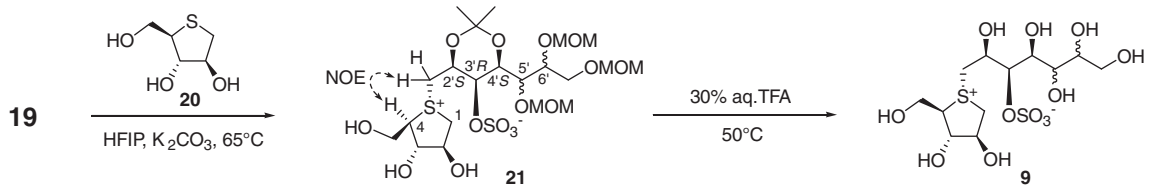
Finally, removal of both the MOM and isopropylidene groups was carried out by using 30% aqueous TFA at 50 °C to give the desired compounds (**9a**, **9b**, **9c** and **9d**) in 76–85% yields. FAB mass spectra of these four products showed peaks at *m*/*z* 425 due to the protonated molecular-ion $[M+H]^+$, corresponded to the deprotected structures.

2.3. α-Glucosidase inhibitory activity

Glucosidase inhibitory activities of four compounds (**9a**, **9b**, **9c** and **9d**) were tested for rat intestinal α-glucosidases, that is, maltase, sucrase and isomaltase in vitro, and the results are listed in Table 2. Based on intensive SAR studies on salacinol (**1**) and related sulfoniums,[11] several important structural determinants for the inhibitory activity against the maltase and sucrase, as well as those for human intestinal N-terminal maltase-glucoamylase have already been disclosed. For example: (a) 2*S*, 3*S*, 4*R* configurations



Scheme 3. Reagents and conditions: (a) MOMCl, $^iPr_2NEt$, DMF, 60 °C; (b) H_2, Pd-C, 80% aq AcOH, 60 °C; (c) 30% aq TFA 50 °C; (d) H_2, Pd-C, $NaHCO_3$, 1,4-dioxane, 60 °C; (e) $SOCl_2$, NEt_3, CH_2Cl_2, 0 °C, then $NaIO_4$, $RuCl_3{\cdot}nH_2O$, $NaHCO_3$, CH_3CN, CCl_4, H_2O, 0 °C to rt.



a : 5′*S*-OH (⋯OH), 6′*R*-OH (⋯OH); **b** : 5′*R*-OH (━OH), 6′*S*-OH (━OH) ; **c** : 5′*S*-OH (⋯OH), 6′*S*-OH (━OH); **d** : 5′*R*-OH (━OH), 6′*R*-OH (⋯OH)

Scheme 4.

Table 2
IC_{50} Values (μM) of thiosugar sulfonium sulfate inner salts and two diabetics against disaccharidases

Entry	Compd	Sucrase	Maltase	Isomaltase
1	**1**[a]	1.6	5.2	1.3
2	**2**[a]	0.75	7.2	5.7
3	**3**[a]	0.29	3.2	2.6
4	**4**[a]	>100	>100	—
5	**9a**	>236 (8)	>236 (25)	16
6	**9b**	>236 (28)	>236 (32)	8.5
7	**9c**	23	57	25
8	**9d**	>236 (34)	>236 (45)	9
9	Voglibose[a]	1.2	0.2	2.1
10	Acarbose[a]	2.0	1.7	155

[a] Ref. 7. Values in parentheses indicate inhibition (%) at 100 μg/mL (236 μM).

of the thiosugar moiety are important as a common feature. (b) The α-orientation of the side chain is essential for the inhibitory activity. (c) Polyhydroxylated side chain longer than four carbons does not enhance the inhibitory activity significantly. (d) Cooperative role of 2′*S*-OH and 4′-OH is critical for onset of strong inhibitions. Furthermore, it is of prime importance that *R* configuration of OH at C4′ is imperative to inhibitors bearing the side chain more than four carbons. (e) For the compounds bearing six or seven carbon side chain, 5′*S*-OH is preferred for the activity.

All the four compounds prepared in the present study satisfied the determinants (a) and (b), however had disadvantageous stereochemical features with respect to the determinants (c) and (d). Thus, out of these four sulfates, three compounds **9a**, **9b** and **9d** lost considerably their inhibitory activity against both maltase and sucrase owing probably to their 4′*S* configuration [against determinant (d)]. It is interesting to note that compound **9c** sustained the inhibitory activities against maltase and sucrase to a large extent, which could be attributed to its 5′*S* configuration on the side chain. However, compound **9a**, the 6′ epimer of **9c**, was found inactive against these enzymes, suggesting that the cooperative role of 5′*S* and 6′*S* could trigger the revival of inhibition against maltase and sucrase.

Against isomaltase, the four sulfoniums sustained their activities to a large extent. Especially compounds **9b** and **9d** showed nearly equal activity to kotalanol **2**, and among these four compounds, **9b** was found to be the most selective isomaltase inhibitor, while compound **9c** lost completely the selectivity against these three enzymes, and was found to be a moderate inhibitor against all enzymes.

Selectivity in inhibition against enzymes with similar function is often so important as was exemplified by three clinically used antidiabetics (voglibose, acarbose and miglitiol). Acarbose has been proved to be inactive against isomaltase, but it has a much greater inhibitory activity on pancreatic α-amylase, which catalyzes the first step in the breakdown of polysaccharides, such as starch, whereas voglibose has almost no effect on this enzyme.[19] Miglitol also shows no inhibition against α-amylase, but it can selectively inhibit lactase and trehalase.[20]

Present findings will contribute the elucidation of the mode of bindings of substrates to these three enzymes. Further SAR studies on the series of thiosugar sulfoniums for the stronger α-glucosidase inhibitors and also for the elucidation of factors for selectivity to the glucosidases 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 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) or a JEOL JNM-ECA 700 (170 MHz ^{1}H, 175 MHz ^{13}C) spectrometer. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. 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. *tert*-Butyl (*E*)- and (*Z*)- 5,7-di-*O*-benzyl-2,3-dideoxy-D-*xylo*-hept-2-enoate (*E*-11 and *Z*-11)

A mixture of **10**[13] (36.1 g, 0.11 mol) and *tert*-butoxycarbonylmethylenetriphenylphosphorane (60 g, 0.16 mol) and CH_2Cl_2 (180 mL) was heated under reflux for 3 h. After removal of the solvent, the oily residue was triturated with a 2:3 mixture of *n*-hexane and diethyl ether (Et_2O), and the deposited precipitates were filtered off and washed with a 2:3 mixture of *n*-hexane and Et_2O. The combined filtrate and washings were concentrated to give a pale yellow oil (62 g), which on column chromatography (*n*-hexane/AcOEt, 5:1) gave a ca. 6.5:1 mixture of title compounds ***E***- and ***Z*-11** (45.8 g, 98% from **10**) as a colorless solid, which on recrystallization from a mixture of *n*-hexane and AcOEt (8/1) gave ***E*-11** (21.4 g, 46%) as colorless needles. Condensation of the mother liquid gave a ca. 3:1 mixture of ***E***- and ***Z*-11** (24.4 g, 52%), which was used in the next step without purification. An analytical sample of ***Z*-11** was obtained as a colorless oil by means of column chromatography (*n*-hexane/Et_2O = 5:1 → 2:1 → 1:1) of a small amount of the crude mixture of ***E***- and ***Z*-11**.

Compound ***E*-11**: Mp 86–87 °C. $[\alpha]_D^{24}$ −54.2 (*c* 1.07, $CHCl_3$). IR (nujol): 3364, 1709, 1655, 1281, 1153, 1138, 1130, 1103 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.49 [9H, s, (CH_3)$_3$C], 2.65 (1H, br d, J = ca. 5.7, OH), 2.99 (1H, br d, J = ca. 6.0, OH), 3.53 (1H, dd, J = 9.8, 5.7, H-7a), 3.594 (1H, dd, J = 9.8, 5.7, H-7b), 3.597 (1H, dd, J = 5.7, 4.3, H-5), 3.95 (1H, dddd, J = 5.7, 5.7, 5.7, 4.3, H-6), 4.47 (1H, dddd, J = 6.0, 4.6, 4.3, 1.9, H-4), 4.50/4.52 (each 1H, d, J = 11.9, PhCH_2), 4.58/4.64 (each 1H, d, J = 11.2, PhCH_2), 6.06 (1H, dd, J = 15.7, 1.9, H-2), 6.90 (1H, dd, J = 15.7, 4.6, H-3), 7.25–7.37 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 28.1 [(CH_3)$_3$C], 70.81 (C-7), 70.83 (C-6), 71.2 (C-4), 73.5/74.8 (PhCH_2), 80.4 [(CH_3)$_3$*C*], 80.9 (C-5), 123.6 (C-2), 127.9/128.1/128.2/128.48/

128.50 (d, arom.), 137.4/137.5 (s, arom.), 145.7 (C-3), 165.5 (C-1). FABMS *m*/*z*: 429 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 429.2278 ($C_{25}H_{33}O_6$ requires 429.2277).

Compound ***Z*-11**: $[\alpha]_D^{24}$ −78.4 (*c* 1.78, $CHCl_3$). IR (neat): 3418, 1747, 1651, 1601, 1496, 1454, 1357, 1269, 1161, 1092, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.47 [9H, s, (CH_3)$_3$C], 3.22 (1H, br s, OH), 3.58 (1H, dd, *J* = 9.7, 6.1, H-7a), 3.61 (1H, dd, *J* = 9.7, 6.1, H-7b), 3.67 (1H, dd, *J* = 4.9, 3.2, H-5), 3.84 (1H, br s, OH), 4.03 (1H, ddd, *J* = 6.1, 6.1, 3.2, H-6), 4.50/4.55 (each 1H, d, *J* = 11.8, PhCH_2), 4.64/4.67 (each 1H, d, *J* = 11.3, PhCH_2), 5.18 (1H, ddd, *J* = 7.2, 4.9, 1.5, H-4), 5.79 (1H, dd, *J* = 12.0, 1.5, H-2), 6.26 (1H, dd, *J* = 12.0, 7.2, H-3), 7.26–7.36 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.0 [(CH_3)$_3$C], 69.2 (C-4), 70.7 (C-6), 71.0 (C-7), 73.4/74.8 (PhCH_2), 80.7 (C-5), 81.5 [(CH_3)$_3$C], 122.9 (C-2), 127.7/127.87/127.92/128.2/128.38/ 128.42 (d, arom.), 137.89/ 137.92 (s, arom.), 148.0 (C-3), 166.4 (C-1). FABMS *m*/*z*: 429 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 429.2256 ($C_{25}H_{33}O_6$ requires 429.2277).

3.2. Acetalization of enoates *E*-11 and *Z*-11

A mixture of ***E*-11** (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 rt for 1.5 h. After the reaction was quenched by addition of aqueous sodium hydrogen carbonate (30 mL), acetone was evaporated. The residual solution was diluted with water (30 mL), and extracted with dichloromethane. The extract was washed with brine, and concentrated to give *tert*-butyl (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*xylo*-hept-2-enoate (***E*-12**, 13.2 g) as a colorless waxy solid, which was used for the next reaction without purification.

Following the method used for acetalization of ***E*-11**, a ca. 3:1 mixture of ***E***- and ***Z*-11** (24 g, 56 mmol) was converted to a mixture of the corresponding acetonides ***E***- and ***Z*-12** (23.5 g, 90%), which on column chromatography (*n*-hexane/AcOEt, 50:1) gave ***E*-12** (14.8 g, 57%), ***Z*-12** (4.6 g, 17.6%), and a ca. 2.3:1 mixture of ***E*-12** and ***Z*-12** (3.6 g, 14%).

Compound ***E*-12**: Mp 69–70 °C. $[\alpha]_D^{24}$ −31.6 (*c* 4.40, $CHCl_3$). IR (KBr): 1703, 1653, 1456, 1377, 1369, 1307, 1202, 1155, 1094, 1067, 1047, 1028 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.45/1.48 [each 3H, s, (CH_3)$_2$C], 1.47 [9H, s, (CH_3)$_3$C], 3.44 (1H, dd, *J* = 1.7, 1.7, H-5), 3.53 (1H, dd, *J* = 9.1, 5.3, H-7a), 3.63 (1H, dd, *J* = 9.1, 7.5, H-7b), 4.15 (1H, ddd, *J* = 7.5, 5.3, 1.7, H-6), 4.45/4.51 (each 1H, d, *J* = 11.7, PhCH_2), 4.50/4.56 (each 1H, d, *J* = 11.3, PhCH_2), 4.52 (1H, ddd, *J* = 4.6, 1.7, 1.7, H-4), 6.06 (1H, dd, *J* = 15.6, 1.7, H-2), 6.81 (1H, dd, *J* = 15.6, 4.6, H-3), 7.23–7.36 (10H, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.0/29.5 [(CH_3)$_2$C], 28.1 [(CH_3)$_3$C], 69.2 (C-7), 71.4 (C-6), 71.7 (C-5), 72.1 (C-4), 73.6/74.3 (PhCH_2), 80.3 [(CH_3)$_3$C], 99.1 [(CH_3)$_2$C], 123.9 (C-2), 127.7/127.8/127.9/128.2/ 128.4 (d, arom.), 137.78/137.82 (s, arom.), 143.1 (C-3), 165.5 (C-1). FABMS *m*/*z*: 469 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 469.2618 ($C_{28}H_{37}O_6$ requires 469.2590).

Compound ***Z*-12**: Mp 57–58 °C. $[\alpha]_D^{24}$ +61.1 (*c* 1.04, $CHCl_3$). IR (KBr): 1707, 1647, 1456, 1373, 1368, 1235, 1199, 1159, 1134, 1093, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.47/1.50 [each 3H, s, (CH_3)$_2$C], 1.48 [9H, s, (CH_3)$_3$C], 3.52 (1H, dd, *J* = 9.5, 6.0, H-7a), 3.55 (1H, dd, *J* = 9.5, 6.6, H-7b), 3.68 (1H, dd, *J* = 1.5, 1.5, H-5), 4.21 (1H, ddd, *J* = 6.6, 6.0, 1.5 Hz, H-6), 4.44/4.530 (each 1H, d, *J* = 11.8, PhCH_2), 4.50/4.531 (each 1H, d, *J* = 12.0, PhCH_2), 5.45 (1H, ddd, *J* = 6.9, 1.5, 1.5, H-4), 5.63 (1H, dd, *J* = 11.8, 1.5, H-2), 6.21 (1H, dd, *J* = 11.8, 6.9, H-3), 7.22–7.36 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.3/29.7 [(CH_3)$_2$C], 28.1 [(CH_3)$_3$C], 69.5 (C-7), 69.9 (C-4), 71.2 (C-6), 71.8 (C-5), 73.4/74.5 (PhCH_2), 80.7 [(CH_3)$_3$C], 98.9 [(CH_3)$_2$C], 122.0 (C-2), 127.6/127.7/127.8/ 128.2/128.3/128.4 (d, arom.), 138.0/138.1 (s, arom.), 146.2 (C-3), 165.0 (C-1). FABMS *m*/*z*: 469 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 469.2608 ($C_{28}H_{37}O_6$ requires 469.2590).

3.3. DIBAH reduction of acetonides *E*-12 and *Z*-12

General procedure: To a solution of ***E*-12** (5.0 g, 10.7 mmol) in THF (120 mL) was added dropwise a 1 M solution of diisobutyl aluminium hydride (DIBAH) in toluene (32 mL, 32 mmol) at −50 °C. The reaction mixture was allowed to reach rt, and was stirred for 4 h. After the reaction was quenched by addition of water (300 mL), the deposited gel was filtered off through a celite, and washed with THF. The combined filtrate and washings were concentrated, and the residual aqueous solution was extracted with CH_2Cl_2. The extract was washed with brine and concentrated to give a pale yellow oil (4.5 g), which on column chromatography (*n*-hexane/AcOEt, 3:1) gave (*E*)-5,7-di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*xylo*-hept-2-enitol (***E*-13**, 3.8 g, 89%) as a colorless oil.

Compound ***E*-13**: $[\alpha]_D^{24}$ −38.8 (*c* 1.24, $CHCl_3$). IR (neat): 3418, 1497, 1381, 1265, 1204, 1169, 1103, 1069, 1026 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.23 (1H, br s, OH), 1.47 [6H, s, (CH_3)$_2$C], 3.36 (1H, dd, *J* = 1.7, 1.7, H-5), 3.54 (1H, dd, *J* = 9.1, 5.3, H-7a), 3.66 (1H, dd, *J* = 9.1, 7.7, H-7b), 3.99 (1H, br dd, *J* = ca. 11.5, 5.3, H-1a), 4.04 (1H, br dd, *J* = ca. 11.5, 5.3, H-1b), 4.14 (1H, ddd, *J* = 7.7, 5.3, 1.7, H-6), 4.35 (1H, ddd, *J* = 6.5, 1.7, 1.0, H-4), 4.47/ 4.53 (each 1H, d, *J* = 11.9, PhCH_2), 4.54/4.63 (each 1H, d, *J* = 11.9, PhCH_2), 5.68 (1H, dddd, *J* = 15.6, 6.5, 1.6, 1.6, H-3), 5.85 (1H, dddd, *J* = 15.6, 5.3, 5.3, 1.0, H-2), 7.26–7.36 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.1/29.6 [(CH_3)$_2$C], 63.0 (C-1), 69.1 (C-7), 71.3 (C-6), 72.4 (C-5), 73.1 (C-4), 73.5/74.4 (PhCH_2), 98.9 [(CH_3)$_2$C], 127.7/127.8/127.9/128.2/128.4/128.6 (d, arom.), 128.7 (C-3), 131.7 (C-2), 137.8/138.3 (s arom.). FABMS *m*/*z*: 399 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 399.2163 ($C_{24}H_{31}O_5$ requires 399.2171).

Following the method used for DIBAH reduction of acetonide ***E*-12**, ***Z*-12** (5.0 g, 10.7 mmol) was reduced with 1 M solution of DIBAH in toluene (32 mL, 32 mmol). Work-up and column chromatography (*n*-hexane/AcOEt, 3:1) gave (*Z*)-5,7-di-*O*-benzyl-2,3-dideoxy-4,6-*O*-isopropylidene-D-*xylo*-hept-2-enitol (***Z*-13**, 3.62 g, 85%) as a colorless oil.

Compound ***Z*-13**: $[\alpha]_D^{24}$ −39.8 (*c* 1.03, $CHCl_3$). IR (neat): 3445, 1454, 1381, 1265, 1203, 1169, 1146, 1096, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ:1.46/1.49 (each 3H, s, (CH_3)$_2$C), 1.76 (1H, br s, OH), 3.34 (1H, dd, *J* = 1.7, 1.7, H-5), 3.52 (1H, dd, *J* = 9.2, 5.5, H-7a), 3.62 (1H, dd, *J* = 9.2, 7.8, H-7b), 4.10 (br d, *J* = ca. 12.9, H-1a), 4.14 (1H, ddd, *J* = 7.8, 5.5, 1.7, H-6), 4.24 (1H, dd, *J* = ca. 12.9, 6.9, H-1b), 4.45/4.50 (each 1H, d, *J* = 11.7, PhCH_2), 4.59/4.63 (each 1H, d, *J* = 10.6, PhCH_2), 4.68 (1H, ddd, *J* = 6.6, 1.7, 1.2, H-4), 5.67 (1H, dddd, *J* = 11.5, 6.6, 1.2, 1.2, H-3), 5.75 (1H, dddd, *J* = 11.5, 6.9, 5.7, 1.2, H-2), 7.25–7.36 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.1/29.6 [(CH_3)$_2$C], 59.0 (C-1), 69.2 (C-7), 69.7 (C-4), 71.3 (C-6), 72.1 (C-5), 73.6/74.6 (PhCH_2), 99.0 [(CH_3)$_2$C], 127.7/127.8/ 128.0/128.2/128.36/128.43 (d, arom.), 129.4 (C-3), 132.0 (C-2), 137.8/138.0 (s, arom.). FABMS *m*/*z*: 399 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 399.2189 ($C_{24}H_{31}O_5$ requires 399.2171).

3.4. Dihydroxylation of D-*xylo*-hept-2-enitols *E*-13 and *Z*-13

3.4.1. Method A

A mixture of ***E*-13** (270 mg, 0.68 mmol), 0.039 M aqueous osmium tetroxide (0.84 mL, 0.033 mmol), 4-methylmorpholine *N*-oxide (170 mg, 1.45 mmol), acetone (2 mL) and water (0.5 mL) was heated under reflux for 1 h. After the reaction was quenched by addition of sodium sulfite (150 mg), the reaction mixture was poured into water (10 mL) and extracted with Et_2O. The extract was washed with brine and concentrated to give a pale brown oil (300 mg), which on column chromatography (*n*-hexane/AcOEt,

1:1) gave a ca. 6:1 mixture of 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*galacto*-heptitol (**14a**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*ido*-heptitol (**14b**) as a colorless oil (241 mg, 82%).

Following the method A, ***Z*-13** (1.8 g, 4.5 mmol) was dihydroxylated to give a ca. 7:1 hardly separable mixture of 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*talo*-heptitol (**14c**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-D-*glycero*-L-*gulo*-heptitol (**14d**) as a colorless oil (1.5 g, 77%).

3.4.2. Method B

A mixture of ***E*-13** (50 mg, 0.125 mmol), AD-mix-α (180 mg), methanesulfonamide (12 mg, 0.125 mmol), *tert*-butanol (1 mL), and water (1 mL) was stirred at rt for 2 days. After the reaction was quenched by addition of sodium sulfite (190 mg), the resulting mixture was diluted with water (2 mL) and extracted with AcOEt. The organic layer was subsequently washed with 2 M aqueous potassium hydroxide (1 mL) and brine, and concentrated to give a pale yellow oil (56 mg), which on column chromatography (*n*-hexane/AcOEt, 3:1) gave a ca. 10:1 mixture of **14a** and **14b** as a colorless oil (43 mg, 79%).

Following the method B, ***E*-13** (50 mg, 0.125 mmol) was dihydroxylated with AD-mix-β (180 mg). Work-up gave a ca. 10:1 mixture of **14a** and **14b** (41 mg, 76%).

Following the method B, ***Z*-13** (50 mg, 0.125 mmol) was dihydroxylated with AD-mix-α (180 mg). Work-up gave a ca. 10:1 mixture of **14c** and **14d** (38 mg, 70%).

Following the method B, ***Z*-13** (50 mg, 0.125 mmol) was dihydroxylated with AD-mix-β (180 mg). Work-up gave a ca. 10:1 mixture of **14c** and **14d** (42 mg, 77%).

3.4.3. Method C

A mixture of ***E*-13** (4.9 g, 12.3 mmol), $(DHQD)_2PYR$ (550 mg, 0.6 mmol), potassium osmate(VI) dihydrate (463 mg, 1.2 mmol), methanesulfonamide (1.2 g, 12.6 mmol), potassium hexacyanoferrate(III) (12.3 g, 37.0 mmol), potassium carbonate (5.2 g, 37.0 mmol), *tert*-butanol (75 mL) and water (75 mL) was stirred at 4 °C for 6.5 h. After the reaction was quenched by addition of sodium sulfite (2.7 g), the resulting mixture was diluted with water (100 mL) and extracted with AcOEt. The organic layer was subsequently washed with 2 M aqueous potassium hydroxide (100 mL) and brine, and concentrated to give a pale yellow oil (6.4 g), which on column chromatography (*n*-hexane/AcOEt, 3:1) gave **14a** (2.0 g, 38%) and **14b** (2.46 g, 46%) both as a colorless oil.

Compound **14a**: $[\alpha]_D^{24}$ −47.8 (*c* 1.14, $CHCl_3$). IR (neat): 3410, 1454, 1380, 1265, 1203, 1169, 1103 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.42/1.45 [each 3H, s, $(CH_3)_2C$], 2.31 (1H, d, *J* = 6.0, OH), 2.35/2.70 (each 1H, br s, OH), 3.53 (1H, dd, *J* = 9.2, 5.7, H-7a), 3.63 (1H, dd, *J* = 9.2, 7.8, H-7b), 3.64 (1H, dd, *J* = ca. 1.5, 1.5, H-5), 3.71 (2H, br d, *J* = ca. 4.6, H-1a and H-1b), 3.76 (1H, ddd, *J* = 8.9, 6.0, 2.0, H-3), 3.85 (1H, br m, H-2), 3.87 (1H, dd, *J* = 8.9, 1.5, H-4), 4.10 (1H, ddd, *J* = 7.8, 5.7, 1.5, H-6), 4.46/4.53 (each 1H, d, *J* = 11.7, $PhCH_2$), 4.69/4.71 (each 1H, d, *J* = 12.0, $PhCH_2$), 7.26–7.37 (10 H, m, arom.) ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.2/29.5 [$(CH_3)_2C$], 65.6 (C-1), 69.0 (C-5), 69.2 (C-7), 69.6 (C-2), 70.3 (C-3), 71.7 (C-6), 72.0 (C-4), 73.5/74.0 ($PhCH_2$), 127.8/127.88/127.93/128.3/128.41/128.43 (d, arom.), 137.8/138.5 (s, arom.). FABMS *m*/*z*: 433 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 433.2217 ($C_{24}H_{33}O_7$ requires 433.2226).

Compound **14b**: $[\alpha]_D^{24}$ −35.6 (*c* 1.22, $CHCl_3$). IR (neat): 3429, 1454, 1380, 1265, 1204, 1096, 1030 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.46 [6H, s, $(CH_3)_2C$], 2.39/2.71/3.02 (each 1H, br s, OH), 3.14 (1H, br, H-2), 3.41 (1H, dd, *J* = 11.5, 4.1, H-1a), 3.56 (1H, dd, *J* = 8.9, 5.3, H-7a), 3.57 (1H, dd, *J* = 11.5, 3.8, H-1b), 3.59 (1H, dd, *J* = ca. 1.5, 1.2, H-5), 3.72 (1H, dd, *J* = 8.9, 8.9, H-7b), 3.80 (1H, dd, *J* = 6.9, 2.4, H-3), 3.99 (1H, dd, *J* = 6.9, 1.5, H-4), 4.13 (1H, ddd, *J* = 8.9, 5.3, 1.2, H-6), 4.50/4.58 (each 1H, d, *J* = 11.7, $PhCH_2$), 4.52/4.74 (each 1H, d, *J* = 11.7, $PhCH_2$), 7.27–7.38 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.2/29.5 [$(CH_3)_2C$], 64.8 (C-1), 68.4 (C-7), 69.2 (C-2), 69.9 (C-5), 71.4 (C-6), 71.7 (C-4), 72.3 (C-3), 73.5/73.8 ($PhCH_2$), 99.4 [$(CH_3)_2C$], 127.9/128.00/128.03/128.49/128.54 (d, arom.), 137.5/137.7 (s, arom.). FABMS *m*/*z*: 433 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 433.2247 ($C_{24}H_{33}O_7$ requires 433.2226).

Following the method C, ***Z*-13** (400 mg, 0.1 mmol) was dihydroxylated. Work-up gave a ca. 3.5:1 hardly separable mixture of **14c** and **14d** (367 mg, 85%) as a colorless oil.

Data for **14c** extracted from the ^1H and ^{13}C NMR spectra of a mixture of **14c** and **14d**: ^1H NMR (700 MHz, pyridine-d_5) δ: 1.44/1.51 [each 3 H, s, $(CH_3)_2C$], 3.79 (1H, dd, *J* = 9.2, 5.6, H-7a), 3.99 (1H, dd, *J* = 9.2, 7.4, H-7b), 4.19 (1H, br s, H-5), 4.40 (1H, dd, *J* = 11.2, 3.7, H-1a), 4.43 (1H, br dd, *J* = ca. 7.4, 5.6, H-6), 4.44 (1H, dd, *J* = 11.2, 7.0, H-1b), 4.51 (1H, br d, *J* = ca. 9.2, H-4), 4.54/4.57 (each 1H, d, *J* = 11.7, $PhCH_2$), 4.64 (1H, ddd, *J* = 7.0, 3.7, 2.6, H-2), 4.83 (1H, dd, *J* = 9.2, 2.6, H-3), 4.88/5.17 (each 1H, d, *J* = 11.0, $PhCH_2$), 7.2–7.5 (10 H, m, arom.). ^{13}C NMR (175 MHz, pyridine-d_5) δ: 19.3/29.9 [$(CH_3)_2C$], 63.5 (C-1), 70.3 (C-7), 71.0 (C-5), 71.9 (C-3), 72.3 (C-6), 73.2 (C-2), 73.5/75.0 ($PhCH_2$), 73.8 (C-4), 98.9 [$(CH_3)_2C$], 127.6/127.9/128.2/128.4/128.5/128.8 (d, arom.), 139.0/139.8 (s, arom.).

Data for **14d** extracted from the ^1H and ^{13}C NMR spectra of a mixture of **14c** and **14d**: ^1H NMR (700 MHz, pyridine-d_5) δ: 1.47/1.54 [each 3H, s, $(CH_3)_2C$], 3.78 (1H, dd, *J* = 8.8, 5.6, H-7a), 3.98 (1H, dd, *J* = 8.8, 7.6, H-7b), 4.05 (1H, br dd, *J* = ca. 1.4, 1.4, H-5), 4.35 (1H, dd, *J* = 10.9, 5.8, H-1a), 4.42–4.47 (2H, m, H-2 and H-6), 4.52 (1H, dd, *J* = 10.9, 5.8, H-1b), 4.53–4.56 (1H, m, H-3), 4.56/4.59 (each 1H, d, *J* = ca. 11.5, $PhCH_2$), 4.73 (1H, dd, *J* = 4.3, 1.4, H-4), 4.80/5.04 (each 1H, d, *J* = ca. 11.5, $PhCH_2$), 7.20–7.51 (10 H, m, arom.). ^{13}C NMR (175 MHz, pyridine-d_5) δ: 19.5/29.8 [$(CH_3)_2C$], 64.7 (C-1), 69.9 (C-7), 72.1 (C-4), 72.2 (C-6), 72.8 (C-2), 73.5/74.6 ($PhCH_2$), 73.7 (C-3), 74.3 (C-5), 99.3 [$(CH_3)_2C$], 127.9/128.0/128.3/128.6/128.7 (d, arom.), 138.9/139.2 (s, arom.).

3.5. Epoxidation of enitol *E*-13 and preparation of heptitols 14c and 14d via hydrolysis of epoxides 15

Under Ar atmosphere, a solution of ***E*-13** (7.2 g, 18 mmol) in CH_2Cl_2 (230 mL) was added dropwise to a suspension of *m*-chloroperbenzoic acid (4.6 g, 33.3 mmol) and sodium hydrogen carbonate (2.6 g, 31 mmol) in CH_2Cl_2 (360 mL), and the mixture was stirred in dark for 12 h. After the reaction was quenched by addition of an aqueous mixture of sodium thiosulfate and sodium hydrogen carbonate (300 mL), the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, and concentrated to give a pale yellow oil (7.6 g), which on column chromatography (*n*-hexane/AcOEt, 2:1) gave **15** (7.3 g, 97%) as a colorless oil. The oil (6.0 g, 14.5 mmol) was then heated under reflux in a mixture of 0.5 M aqueous sodium hydroxide (30 mL) and 1,4-dioxane (90 mL) for 4.5 h. After being cooled, the reaction mixture was extracted with AcOEt. The extract was washed with brine, and concentrated to give a pale yellow oil (6.2 g), which on column chromatography (*n*-hexane/AcOEt, 1:1) gave a ca. 1.2:1 hardly separable mixture of **14c** and **14d** (5.3 g, 68%) as a colorless oil. The NMR spectroscopic properties of the mixture were in good accord with those of a mixture of **14c** and **14d** obtained by dihydroxylation of ***Z*-13** (in Section 3.4.3).

3.6. Methoxymethylation of heptitols 14a, 14b, 14c and 14d

General procedure: A mixture of **14a** (1.8 g, 4.2 mmol), chloromethyl methyl ether (5 mL, 67.0 mmol), *N*-ethyldiisopropylamine (23 mL, 113 mmol), and DMF (45 mL) was heated at 60 °C for 4.5 h. After the reaction was quenched by addition of aqueous

sodium hydrogen carbonate (16 mL), the resulting mixture was diluted with water (16 mL), and extracted with a 2:1 mixture of *n*-hexane/Et_2O. The extract was washed with brine and concentrated to give a pale yellow oil (2.6 g), which on column chromatography (*n*-hexane/AcOEt, 5:1) gave 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*galacto*-heptitol (**17a**, 2.1 g, 88%) as a colorless oil.

Compound **17a**: $[\alpha]_D^{24}$ -14.0 (*c* 1.34, $CHCl_3$). IR (neat): 1454, 1381, 1265, 1204, 1153, 1103, 1034 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ:1.44/1.45 [each 3H, s, $(CH_3)_2C$], 3.32/3.38/3.40 (each 3H, s, OCH_2OCH_3), 3.58 (1H, dd, *J* = 9.5, 5.8, H-7a), 3.68 (1H, dd, *J* = 9.6, 7.7, H-1a), 3.69 (1H, dd, *J* = 9.5, 7.2, H-7b), 3.71 (1H, dd, *J* = 1.4, 1.4, H-5), 3.75 (1H, dd, *J* = 9.6, 6.0, H-1b), 4.00 (1H, ddd, *J* = 7.7, 6.0, 1.5, H-2), 4.02 (1H, dd, *J* = 8.8, 1.4, H-4), 4.08 (1H, dd, *J* = 8.8, 1.5, H-3), 4.15 (1H, ddd, *J* = 7.2, 5.8, 1.4, H-6), 4.48/4.55 (each 1H, d, *J* = 11.8, $PhCH_2$), 4.60/4.62 (each 1H, d, *J* = 6.5, OCH_2OCH_3), 4.69/4.746 (each 1H, d, *J* = 6.5, OCH_2OCH_3), 4.71/4.750 (each 1H, d, *J* = 6.5, OCH_2OCH_3), 4.742/4.82 (each 1H, d, *J* = 12.0, $PhCH_2$), 7.22–7.35 (10H, m, arom.). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 19.0/29.6 [$(CH_3)_2C$], 55.5/55.7/56.1 (OCH_2OCH_3), 67.5 (C-1), 69.5 (C-7), 69.6 (C-5), 71.6 (C-4), 72.4 (C-6), 73.1/73.4 ($PhCH_2$), 76.2 (C-2), 77.2 (C-3), 96.9/98.3/98.6 (OCH_2OCH_3), 99.0 [$(CH_3)_2C$], 127.2/127.7/127.8/128.2/128.4 (d, arom.), 138.0/139.1 (s, arom.). FABMS *m*/*z*: 565 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 565.3043 ($C_{30}H_{45}O_{10}$ requires 565.3013).

In a similar manner, 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*ido*-heptitol (**17b**, 2.6 g, 85%) was obtained from triol **14b** (2.3 g, 5.3 mmol) as a colorless oil.

Compound **17b**: $[\alpha]_D^{24}$ +7.55 (*c* 1.13, $CHCl_3$). IR (neat): 1454, 1381, 1265, 1204, 1153, 1103, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.45/1.46 [each 3H, s, $(CH_3)_2C$], 3.30/3.35/3.40 (each 3H, s, OCH_2OCH_3), 3.57 (1H, dd, *J* = 9.2, 5.8, H-7a), 3.58 (1H, dd, *J* = 10.1, 5.8, H-1a), 3.71 (1H, dd, *J* = 9.2, 7.5, H-7b), 3.73 (1H, dd, *J* = 1.5, 1.5, H-5), 3.74 (1H, dd, *J* = 10.1, 6.3, H-1b), 3.82 (1H, ddd, *J* = 6.3, 5.8, 1.4, H-2), 3.99 (1H, dd, *J* = 8.6, 1.4, H-3), 4.12 (1H, ddd, *J* = 7.5, 5.8, 1.5, H-6), 4.22 (1H, dd, *J* = 8.6, 1.5, H-4), 4.51/4.56 (each 1H, d, *J* = 11.7, $PhCH_2$), 4.54/4.56 (each 1H, d, *J* = 6.9, OCH_2OCH_3), 4.60/4.87 (each 1H, d, *J* = 7.0, OCH_2OCH_3), 4.66/4.76 (each 1H, d, *J* = 11.8, $PhCH_2$), 4.67/4.90 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 7.23–7.36 (10H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.1/29.6 [$(CH_3)_2C$], 55.3/56.1/56.3 (OCH_2OCH_3), 68.2 (C-1), 69.1 (C-7), 69.6 (C-5), 72.0 (C-6), 73.5/73.7 ($PhCH_2$), 74.0 (C-4), 74.6 (C-2), 76.5 (C-3), 96.67/96.72/98.7 (OCH_2OCH_3), 99.0 [$(CH_3)_2C$], 127.5/127.7/127.75/127.82/128.2/128.4 (d, arom.), 137.9/138.6 (s, arom.). FABMS *m*/*z*: 565 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 565.2983 ($C_{30}H_{45}O_{10}$ requires 565.3013).

In a similar manner, 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*talo*-heptitol (**17c**) and 5,7-di-*O*-benzyl-4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*gulo*-heptitol (**17d**) were obtained as a ca. 1.1:1 hardly separable mixture (5.3 g, 81%) from a ca. 1.1:1 mixture of **14c** and **14d** (5.0 g, 11.5 mmol). A ca. 7:1 mixture of **13c** and **13d** (1.5 g, 3.5 mmol) was also converted to the corresponding tri-*O*-MOM ethers **17c** and **17d** (1.7 g, 86%).

Data for **17c** extracted from the ^1H and ^{13}C NMR spectra of a ca. 7:1 mixture of **17c** and **17d**: ^1H NMR (700 MHz, $CDCl_3$) δ:1.43/1.45 [each 3H, s, $(CH_3)_2C$], 3.35/3.36/3.39 (each 3H, s, OCH_2OCH_3), 3.55 (1H, dd, *J* = 9.4, 5.8, H-7a), 3.64 (1H, dd, *J* = 1.6, 1.6, H-5), 3.66 (1H, dd, *J* = 9.4, 7.4, H-7b), 3.67 (1H, dd, *J* = 10.8, 7.6, H-1a), 3.75 (1H, dd, *J* = 10.8, 4.0, H-1b), 3.93 (1H, dd, *J* = 9.0, 1.6, H-4), 4.06 (1H, dd, *J* = 9.0, 1.6, H-3), 4.12 (1H, ddd, *J* = 7.4, 5.8, 1.6, H-6), 4.16 (1H, ddd, *J* = 7.6, 4.0, 1.6, H-2), 4.47/4.54 (each 1H, d, *J* = 12.0, $PhCH_2$), 4.61/4.63 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.70/4.74 (each 1H, d, *J* = 6.2, OCH_2OCH_3), 4.71/4.76 (each 1H, d, *J* = 11.6, $PhCH_2$), 4.72/4.73 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 7.25–7.35 (10H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 18.8/29.5 [$(CH_3)_2C$], 55.1/55.5/56.3 (OCH_2OCH_3), 67.5 (C-1), 69.5 (C-7), 69.7 (C-5), 72.0 (C-4), 72.2 (C-6), 73.4/73.5 ($PhCH_2$), 76.8 (C-2), 76.9 (C-3), 96.4/96.5/97.8 (OCH_2OCH_3), 99.0 [$(CH_3)_2C$], 127.3/127.7/127.8/128.2/128.4 (d, arom.), 138.0/139.0 (s, arom.).

Data for **17d** extracted from the ^1H and ^{13}C NMR spectra of a ca. 1.1:1 mixture of **17c** and **17d**: ^1H NMR (700 MHz, $CDCl_3$) δ:1.45/1.46 [each 3H, s, $(CH_3)_2C$], 3.28/3.34/3.40 (each 3H, s, OCH_2OCH_3), 3.54 (1H, dd, *J* = 9.4, 5.6, H-7a), 3.55 (1H, br dd, *J* = ca. 1.6, 1.4, H-5), 3.67 (1H, dd, *J* = 9.4, 7.6, H-7b), 3.72 (1H, dd, *J* = 10.4, 6.6, H-1a), 3.79 (1H, dd, *J* = 10.4, 5.0, H-1b), 4.00 (1H, dd, *J* = 8.6, 1.6, H-4), 4.01 (1H, ddd, *J* = 6.6, 5.0, 2.5, H-2), 4.09 (1H, ddd, *J* = 7.6, 5.6, 1.4, H-6), 4.16 (1H, dd, *J* = 8.6, 2.5, H-3), 4.46/4.51 (each 1H, d, *J* = 11.8, $PhCH_2$), 4.61/4.64 (each 1H, d, *J* = 6.8, OCH_2OCH_3), 4.62 (2H, br s, OCH_2OCH_3), 4.73/4.84 (each 1H, d, *J* = 11.6, $PhCH_2$), 4.73/4.80 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 7.25–7.37 (10H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 19.1/29.6 [$(CH_3)_2C$], 55.4/55.5/55.6 (OCH_2OCH_3), 67.1 (C-1), 69.2 (C-7), 70.2 (C-5), 71.9 (C-6), 73.1/73.5 ($PhCH_2$), 73.9 (C-4), 74.7 (C-2), 76.5 (C-3), 95.2/96.8/97.7 (OCH_2OCH_3), 98.9 [$(CH_3)_2C$], 127.2/127.8/127.9/128.2 (d, arom.), 137.8/138.8 (s, arom.).

3.7. Hydrogenolysis of MOM ethers 17a, 17b, 17c and 17d

General procedure: A suspension of 10% palladium on carbon (2.0 g) and sodium hydrogen carbonate (300 mg) in 1,4-dioxane (35 mL) was pre-equilibrated with hydrogen. To the suspension was added a solution of MOM ether **17a** (2.0 g, 3.5 mmol) in 1,4-dioxane (20 mL), and the mixture was hydrogenated at 60 °C under atmospheric pressure for 3 h. The catalysts were filtered off, washed with ethyl acetate. The combined filtrate and washings were concentrated in vacuo to give practically pure 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*galacto*-heptitol (**18a**, 1.3 g, 97%) as a colorless oil, which was used in the next step without further purification.

Compound **18a**: $[\alpha]_D^{24}$ −10.2 (*c* 1.16, $CHCl_3$). IR (neat): 3460, 1458, 1384, 1265, 1203, 1158, 1108, 1061, 1029 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.456/1.463 [each 3H, s, $(CH_3)_2C$], 2.34 (1H, dd, *J* = 8.0, 3.6, OH), 3.24 (1H, d, *J* = 8.6, OH), 3.38/3.39/3.45 (each 3H, s, OCH_2OCH_3), 3.68 (1H, dd, *J* = 9.7, 8.3, H-1a), 3.71 (1H, ddd, *J* = 8.6, 1.4, 1.2, H-5), 3.76 (1H, dd, *J* = 9.7, 5.7, H-1b), 3.78 (1H, ddd, *J* = 11.5, 8.0, 4.2, H-7a), 3.90, (1H, ddd, *J* = 11.5, 6.3, 3.6, H-7b), 3.93 (1H, dd, *J* = 9.2, 1.8, H-3), 3.95 (1H, ddd, *J* = 8.3, 5.7, 1.8, H-2), 3.98 (1H, ddd, *J* = 6.3, 4.2, 1.4, H-6), 4.01 (1H, dd, *J* = 9.2, 1.2, H-4), 4.64/4.66 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.71/4.72 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.79/4.82 (each 1H, d, *J* = 6.3, OCH_2OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.1/29.6 [$(CH_3)_2C$], 55.6/55.8/56.5 (OCH_2OCH_3), 63.2 (C-5), 63.6 (C-7), 67.1 (C-1), 70.7 (C-4), 72.7 (C-6), 75.6 (C-2), 76.5 (C-3), 97.0/98.0/99.0 (OCH_2OCH_3), 99.4 [$(CH_3)_2C$]. FABMS *m*/*z*: 385 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 385.2063 ($C_{16}H_{33}O_{10}$ requires 385.2074).

In a similar manner, 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*ido*-heptitol (**18b**, 1.6 g, 95%) was obtained as a colorless oil from **17b** (2.5 g, 4.4 mmol).

Compound **18b**: $[\alpha]_D^{24}$ +59.3 (*c* 3.2, $CHCl_3$). IR (neat): 3445, 1458, 1385, 1265, 1204, 1153, 1107, 1018 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 1.47/1.48 [each 3H, s, $(CH_3)_2C$], 2.11 (1H, br s, OH), 2.72 (1H, d, *J* = 10.2, OH), 3.37/3.39/3.42 (each 3H, s, OCH_2OCH_3), 3.73–3.77 (1H, br m, H-7a), 3.75 (1H, dd, *J* = 10.2, 5.5, H-1a), 3.77 (1H, dd, *J* = 10.2, 6.2, H-1b), 3.79 (1H, br d, *J* = ca. 10.2, H-5), 3.82 (1H, br dd, *J* = ca. 11.0, 6.6, H-7b), 3.92 (1H, ddd, *J* = 6.6, 4.8, 1.4, H-6), 3.94 (1H, dd, *J* = 8.0, 2.2, H-3), 4.05 (1H, ddd, *J* = 6.2, 5.5, 2.2, H-2), 4.16 (1H, dd, *J* = 8.0, 1.2, H-4), 4.63/4.65 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.68/4.89 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.68/4.86 (each 1H, d, *J* = 6.4, OCH_2OCH_3). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 19.1/29.7 [$(CH_3)_2C$], 55.4/56.0/56.2 (OCH_2OCH_3), 63.2 (C-7), 64.0

(C-5), 67.9 (C-1), 72.9 (C-6), 74.2 (C-4), 75.3 (C-2), 76.5 (C-3), 96.8/96.9/98.2 (OCH_2OCH_3), 99.6 [$(CH_3)_2C$]. FABMS *m*/*z*: 385 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 385.2054 ($C_{16}H_{33}O_{10}$ requires 385.2074).

In a similar manner, from a ca. 1.1:1 mixture of **17c** and **17d** (5.2 g, 9.2 mmol) was obtained a mixture (3.3 g, 93%) of 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*talo*-heptitol (**18c**) and 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*gulo*-heptitol (**18d**), which (500 mg) on column chromatography (*n*-hexane/AcOEt, 100:1) gave an analytical sample of **18c** (80 mg) and a ca. 1:1.5 mixture of **18c** and **18d** (405 mg) both as a colorless oil.

Compound **18c**: $[\alpha]_D^{24}$ +5.5 (*c* 1.03, $CHCl_3$) IR (neat): 3468, 2943, 2893, 2824, 1466, 1443, 1385, 1265, 1153, 1103, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.45/1.46 [each 3H, s, $(CH_3)_2C$], 2.33 (1H, br s, OH), 3.08 (1H, d, *J* = 8.6, OH), 3.37/3.40/3.42 (each 3H, s, OCH_2OCH_3), 3.65 (1H, dd, *J* = 10.7, 7.2, H-1a), 3.71 (1H, br d, *J* = ca. 8.6, H-5), 3.73 (1H, dd, *J* = 10.7, 4.6, H-1b), 3.76 (1H, dd, *J* = 11.6, 4.6, H-7a), 3.86 (1H, dd, *J* = 11.6, 6.3, H-7b), 3.94 (1H, ddd, *J* = 6.3, 4.6, 1.5, H-6), 3.96 (1H, dd, *J* = ca. 9.0, 1.5, H-3), 3.98 (1H, br d, *J* = ca. 9.0, H-4), 4.08 (1H, ddd, *J* = 7.2, 4.6, 1.5, H-2), 4.63/4.75 (each 2H, s, OCH_2OCH_3), 4.75/4.80 (each 1H, d, *J* = 6.0, OCH_2OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.9/29.5 [$(CH_3)_2C$], 55.2/55.6/56.1 (OCH_2OCH_3), 63.39 (C-5), 63.45 (C-7), 67.2 (C-1), 71.3 (C-4), 72.9 (C-6), 75.99 (C-3), 76.04 (C-2), 96.2/96.5/97.6 (OCH_2OCH_3), 99.4 [$(CH_3)_2C$]. FABMS *m*/*z*: 385 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 385.2065 ($C_{16}H_{33}O_{10}$ requires 385.2074).

Data for **18d** extracted from the ^1H and ^{13}C NMR spectra of a mixture of **18c** and **18d**: ^1H NMR (500 MHz, $CDCl_3$) δ: 1.45 [6H, s, $(CH_3)_2C$], 2.17 (1H, br s, OH), 2.85 (1H, d, *J* = 10.0, OH), 3.37 (3H, s, OCH_2OCH_3), 3.40 (6H, s, OCH_2OCH_3), 3.61 (1H, br d, *J* = ca. 10.0, H-5), 3.70 (1H, dd, *J* = 10.3, 6.3, H-1a), 3.73 (1H, br dm, *J* = ca. 11.2, H-7a), 3.78 (1H, dd, *J* = 10.3, 6.0, H-1b), 3.81 (1H, dd, *J* = 11.2, 6.2, H-7b), 3.91 (1H, ddd, *J* = 6.2, 4.9, 1.5, H-6), 3.98 (1H, dd, *J* = 7.5, 1.0, H-4), 4.01 (1H, dd, *J* = 7.5, 2.0, H-3), 4.04 (1H, ddd, *J* = 6.3, 6.0, 2.0, H-2), 4.61/4.64 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.70/4.76 (each 1H, d, *J* = 6.9, OCH_2OCH_3), 4.74/4.78 (each 1H, d, *J* = 6.6, OCH_2OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.1/29.7 [$(CH_3)_2C$] 55.4/55.7 (2C) (OCH_2OCH_3), 63.2 (C-7), 64.6 (C-5), 67.0 (C-1), 72.7 (C-6), 73.9 (C-4), 75.0 (C-2), 77.2 (C-3), 95.9/96.7/97.4 (OCH_2OCH_3), 99.6 [$(CH_3)_2C$].

3.8. Elucidation of stereochemistries of heptitols

General procedure: A suspension of 10% palladium on carbon (200 mg) in 80% acetic acid (3 mL) was pre-equilibrated with hydrogen. To the suspension was added a solution of MOM ether **14a** (112 mg, 0.26 mmol) in 80% acetic acid (2 mL), and the mixture was hydrogenated at 60 °C under atmospheric pressure for 2 h. The catalysts were filtered off and washed with ethyl acetate. The combined filtrate and washings were concentrated in vacuo to give a colorless oil (93 mg), which on column chromatography (AcOEt/MeOH/H_2O, 20:4:1) gave D-*glycero*-L-*galacto*-heptitol (**16a**, 54 mg, 98%) as a colorless oil. ^{13}C NMR spectroscopic properties of **16a** were in accord with those reported.[16]

In a similar manner, diol **14b** (112 mg, 0.26 mmol) was converted to D-*glycero*-L-*ido*-heptitol (**16b**, 41 mg, 74%). ^{13}C NMR spectroscopic properties of **16b** were in accord with those reported.[16]

A mixture of diol **18c** (50 mg, 0.13 mmol) and 30% aqueous TFA (5 mL) was heated at 50 °C for 2 h. After the reaction mixture was concentrated at reduced pressure, the residue was subjected to column chromatography (AcOEt/MeOH/H_2O, 20:4:1) to give D-*glycero*-L-*talo*-heptitol (**16c**, 24 mg, 87%). ^{13}C NMR spectroscopic properties of **16c** were in accord with those reported.[16]

In a similar manner, a ca. 1.2:1 mixture of diols **18c** and **18d** (50 mg, 0.13 mmol) was converted to a mixture (22 mg, 80%) of **16c** and D-*glycero*-L-*gulo*-heptitol (**16d**). ^{13}C NMR spectroscopic properties of **16d** extracted from the spectrum were in accord with those reported.[16]

3.9. Preparation of cyclic sulfates 19a, 19b, 19c and 19d

General procedure: To a solution of diol **18a** (1.0 g, 2.6 mmol) and triethylamine (0.9 mL, 6.5 mmol) in CH_2Cl_2 (30 mL) was added a solution of freshly distilled thionyl chloride (0.23 mL, 3.2 mmol) in CH_2Cl_2 (30 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min, and then poured into ice-cooled and vigorously stirred aqueous sodium hydrogen carbonate (2 mL), and extracted with CH_2Cl_2. The extract was washed with brine and concentrated to give the corresponding sulfite (1.0 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 (1.0 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 (1.5 g, 7.0 mmol), ruthenium chloride *n*-hydrate (90 mg) in water (20 mL) at 0 °C. After being stirred at 0 °C for 3 h, the reaction was quenched by addition of an aqueous mixture of sodium thiosulfate and sodium hydrogen carbonate (85 mL). The resulting purple mixture was extracted with Et_2O. The extract was washed with brine and concentrated to give a pale yellow oil (0.9 g), which on column chromatography (*n*-hexane/AcOEt, 2:1) gave 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*galacto*-heptitol 5,7-cyclic sulfate (**19a**, 0.8 g, 69%) as a colorless solid. An analytical sample of cyclic sulfate **19a** was obtained by recrystallization from a mixture of *n*-hexane and AcOEt (10/1) as colorless prisms.

Compound **19a**: Mp: 102–103 °C. $[\alpha]_D^{24}$ +9.06 (*c* 1.76, $CHCl_3$). IR (nujol): 1462, 1385, 1196, 1157, 1132, 1107, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ:1.47/1.50 [each 3H, s, $(CH_3)_2C$], 3.38/3.39/3.44 (each 3H, s, OCH_2OCH_3), 3.69 (1H, dd, *J* = 9.8, 8.6, H-1a), 3.78 (1H, dd, *J* = 9.8, 5.8, H-1b), 3.93 (1H, ddd, *J* = 8.6, 5.8, 1.5, H-2), 3.95 (1H, ddd, *J* = 1.7, 1.5, 1.5, H-6), 4.00 (1H, dd, *J* = 9.2, 1.5, H-3), 4.21 (1H, dd, *J* = 9.2, 1.5, H-4), 4.55 (1H, dd, *J* = 12.3, 1.5, H-7a), 4.64/4.66/4.70/4.71 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.75/4.77 (each 1H, d, *J* = 6.3, OCH_2OCH_3), 4.90 (1H, dd, *J* = 12.3, 1.7, H-7b), 4.98 (1H, dd, *J* = 1.5, 1.5, H-5). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.8/29.1 [$(CH_3)_2C$], 55.6/55.9/56.6 (OCH_2OCH_3), 61.9 (C-6), 66.9 (C-1), 68.5 (C-4), 74.8 (C-3), 75.2 (C-7), 75.5 (C-2), 76.4 (C-5), 97.0/98.1/99.0 (OCH_2OCH_3), 99.72 [$(CH_3)_2C$]. FABMS *m*/*z*: 445 $[M-H]^-$ (neg.). FABHRMS *m*/*z*: 445.1387 ($C_{16}H_{29}O_{12}S$ requires 445.1380).

In a similar manner, 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*ido*-heptitol 5,7-cyclic sulfate (**19b**, 0.75 g, 65%) was obtained from **18b** (1.0 g, 2.6 mmol) as a colorless oil.

Compound **19b**: $[\alpha]_D^{24}$ −9.66 (*c* 1.08, $CHCl_3$). IR (neat): 1454, 1396, 1253, 1196, 1153, 1107, 1026 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.48/1.52 [each 3H, s, $(CH_3)_2C$], 3.39/3.40/3.41 (each 3H, s, OCH_2OCH_3), 3.75 (1H, dd, *J* = 10.5, 4.8, H-1a), 3.82 (1H, dd, *J* = 10.5, 5.8, H-1b), 3.90 (1H, ddd, *J* = 1.9, 1.5, 1.4, H-6), 3.94 (1H, ddd, *J* = 5.8, 4.8, 2.8, H-2), 4.01 (1H, dd, *J* = 8.4, 2.8, H-3), 4.36 (1H, dd, *J* = 8.4, 1.4, H-4), 4.53 (1H, dd, *J* = 12.4., 1.5, H-7a), 4.64 (2H, s, OCH_2OCH_3), 4.67/4.82 (each 1H, d, *J* = 6.7, OCH_2OCH_3), 4.73/4.83 (each 1H, d, *J* = 6.5, OCH_2OCH_3), 4.87 (1H, dd, *J* = 12.4, 1.9, H-7b), 5.18 (1H, dd, *J* = 1.4, 1.4, H-5). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 18.9/29.1 [$(CH_3)_2C$], 55.5/56.0/56.2 (OCH_2OCH_3), 61.5 (C-6), 67.5 (C-1), 71.4 (C-4), 74.4 (C-3), 74.9 (C-2), 75.3 (C-7), 76.9 (C-5), 96.6/96.9/98.3 (OCH_2OCH_3), 99.7 [$(CH_3)_2C$]. FABMS *m*/*z*: 445 $[M-H]^-$ (neg.). FABHRMS *m*/*z*: 445.1368 ($C_{16}H_{29}O_{12}S$ requires 445.1380).

In a similar manner, 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*talo*-heptitol 5,7-cyclic sulfate (**19c**, 1.29 g, 37%) and 4,6-*O*-isopropylidene-1,2,3-tri-*O*-methoxymethyl-D-*glycero*-L-*gulo*-heptitol 5,7-cyclic sulfate (**19d**, 1.08 g, 31%) were obtained from a ca. 1.2:1 mixture of **18c** and **18d** (3.0 g, 7.8 mmol) both as a colorless oil. ^1H and ^{13}C NMR spectroscopic properties of **19c**

were in accord with those of a specimen prepared from the analytical sample of **18c** obtained in the Section 3.7.

Compound **19c**: $[\alpha]_D^{24}$ −17.7 (*c* 1.21, $CHCl_3$). IR (neat): 1446, 1402, 1261, 1198, 1152, 1110, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.47/1.50 [each 3H, s, $(CH_3)_2C$], 3.36/3.39/3.44 (each 3H, s, OCH_2OCH_3), 3.63 (1H, dd, *J* = 10.5, 7.2, H-1a), 3.70 (1H, dd, *J* = 10.5, 5.5, H-1b), 3.93 (1H, br ddd, *J* = ca. 2.0, 1.5, 1.5, H-6), 3.99 (1H, dd, *J* = 9.5, 1.2, H-3), 4.13 (1H, ddd, *J* = 7.2, 5.5, 1.2, H-2), 4.27 (1H, dd, *J* = 9.5, 1.5, H-4), 4.53 (1H, dd, *J* = 12.3, 1.5, H-7a), 4.61/4.75 (each 2H, s, OCH_2OCH_3), 4.72/4.73 (each 1H, d, *J* = 6.3, OCH_2OCH_3), 4.88 (1H, dd, *J* = 12.3, 2.0, H-7b), 4.95 (1H, br dd, *J* = ca. 1.5, 1.5, H-5). ^{13}C NMR (125 MH, $CDCl_3$) δ: 18.6/29.0 [$(CH_3)_2C$], 55.3/55.6/56.6 (OCH_2OCH_3), 61.9 (C-6), 67.4 (C-1), 68.8 (C-4), 73.7 (C-3), 75.3 (C-7), 75.6 (C-2), 76.4 (C-5), 96.3/96.5/97.1 (OCH_2OCH_3), 99.6 [$(CH_3)_2C$]. FABMS *m*/*z*: 469 $[M+Na]^+$ (pos.). FABHRMS *m*/*z*: 469.1359 ($C_{16}H_{30}O_{12}SNa$ requires 469.1356).

Compound **19d**: $[\alpha]_D^{22}$ −20.6 (*c* 0.3, $CHCl_3$). IR (neat): 1442, 1404, 1257, 1196, 1153, 1107, 1026 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 1.48/1.52 [each 3H, $(CH_3)_2C$], 3.38/3.40/3.41 (each 3H, s, CH_2OCH_3), 3.66 (1H, dd, *J* = 9.9, 5.3, H-1a), 3.80 (1H, dd, *J* = 9.9, 7.6, H-1b), 3.90 (1H, br ddd, *J* = ca. 1.6, 1.3, 1.3, H-6), 3.97 (1H, ddd, *J* = 7.6, 5.3, 1.6, H-2), 4.10 (1H, dd, *J* = 8.2, 1.6, H-3), 4.23 (1H, dd, *J* = 8.2, 1.6, H-4), 4.53 (1H, dd, *J* = 12.4, 1.3, H-7a), 4.62/4.64 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.70/4.71 (each 1H, d, *J* = 6.8, OCH_2OCH_3), 4.75/4.77 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.87 (1H, dd, *J* = 12.4, 1.6, H-7b), 4.90 (1H, br dd, *J* = ca. 1.6, 1.3, H-5). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 18.8/29.2 [$(CH_3)_2C$], 55.6/55.7/55.8 (OCH_2OCH_3), 61.3 (C-6), 66.3 (C-1), 70.9 (C-4), 74.1 (C-2), 75.3 (C-7), 75.9 (C-3), 77.2 (C-5), 95.9/96.9/97.6 (OCH_2OCH_3), 99.6 [$(CH_3)_2C$]. FABMS *m*/*z*: 469 $[M+Na]^+$ (pos.). FABHRMS *m*/*z*: 469.1352 ($C_{16}H_{30}O_{12}SNa$ requires 469.1356).

3.10. Preparation of sulfonium sulfate inner salts 21a, 21b, 21c and 21d

General procedure: A solution of compound **19a** (500 mg, 1.12 mmol), thiosugar (**20**, 112 mg, 0.75 mmol) and potassium carbonate (25 mg) in 1,1,1,3,3,3-hexafluoroisopropanol (2.5 mL) was stirred in a sealed flask at 65 °C for one week. The mixture was concentrated to give a yellow oil (450 mg), which on column chromatography ($CHCl_3$/MeOH, 20:1) gave 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5S*,*6R*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (**21a**, 320 mg, 72%) as a colorless amorphous.

Compound **21a**: $[\alpha]_D^{24}$ −25.0 (*c* 1.17, CH_3OH). IR (nujol): 3364, 1262, 1207, 1153, 1107, 1026 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ: 1.45/1.52 [each 3H, s, $(CH_3)_2C$], 3.35/3.37/3.39 (each 3H, s, OCH_2OCH_3), 3.76 (1H, dd, *J* = 9.8, 6.7, H-7′a), 3.79 (1H, br dd, *J* = ca. 12.8, 3.5, H-1a), 3.81 (1H, dd, *J* = 9.8, 7.2, H-7′b), 3.82 (1H, br dd, *J* = ca. 12.8, 2.0, H-1b), 3.88 (1H, dd, *J* = 13.4, 3.6, H-1′a), 3.91 (1H, dd, *J* = *J* = 11.0, 8.6, H-5a), 3.94 (1H, br dd, *J* = ca. 6.7, 6.7, H-6′), 3.97–4.01 (1H, m, H-4), 4.01 (1H, dd, *J* = 13.4, 7.9, H-1′b), 4.03 (1H, dd, *J* = 11.0, 5.5, H-5b), 4.07 (2H, br s, H-4′ and H-5′), 4.39 (1H, br dd, *J* = ca. 1.5, 1.5, H-3), 4.56 (1H, br s, H-3′), 4.57 (1H, br dd, *J* = ca. 7.9, 3.6, H-2′), 4.59–4.61 (1H, m, H-2), 4.61/4.63 (each 1H, d, *J* = 6.5, OCH_2OCH_3), 4.67/4.71 (each 1H, d, *J* = 6.5, OCH_2OCH_3), 4.79/4.92 (each 1H, d, *J* = 6.7, OCH_2OCH_3). ^{13}C NMR (150 MHz, CD_3OD) δ: 19.5/29.5 [$(CH_3)_2C$], 50.2 (C-1′), 51.2 (C-1), 55.8/56.1/56.2 (OCH_2OCH_3), 60.9 (C-5), 68.8 (C-7′), 70.1 (C-2′), 72.2 (C-3′), 72.6 (C-4′), 73.4 (C-4), 77.4 (C-6′), 78.0 (C-5′), 79.2 (C-2), 79.8 (C-3), 97.9/99.1/100.4 (OCH_2OCH_3), 101.2 [$(CH_3)_2C$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 597.1865 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

In a similar manner, coupling reaction of **19b** (500 mg, 1.12 mmol) with **20** (112 mg, 0.75 mmol) gave 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5R*,*6S*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (**21b**, 350 mg, 79%) as a colorless oil.

Compound **21b**: $[\alpha]_D^{24}$ +6.38 (*c* 1.05, CH_3OH). IR (neat): 3428, 1636, 1446, 1387, 1265, 1207, 1150, 1022 cm^{-1}. ^1H NMR (700 MHz, CD_3OD) δ: 1.47/1.52 [each 3H, s, $(CH_3)_2C$] 3.34/3.38/3.42 (each 3H, s, OCH_2OCH_3), 3.71 (1H, dd, *J* = 10.6, 3.2, H-7′a), 3.765 (1H, dd, *J* = 12.6, 3.4, H-1a), 3.772 (1H, dd, *J* = 10.6, 8.4, H-7′b), 3.82 (1H, dd, *J* = 12.6, 1.8, H-1b), 3.91 (1H, dd, *J* = 13.2, 4.0, H-1′a), 3.90–3.92 (1H, m, H-4), 3.930 (1H, dd, *J* = 10.8, 1.6, H-5a), 3.932 (1H, dd, *J* = 13.2, 6.6, H-1′b), 3.96 (1H, dd, *J* = 8.6, 1.6, H-5′), 4.03 (1H, dd, *J* = 10.8, 5.5, H-5b), 4.35 (1H, dd, *J* = 8.6, 1.2, H-4′), 4.36 (1H, ddd, *J* = 8.4, 3.2, 1.6, H-6′), 4.40 (1H, m, H-3), 4.47 (1H, dd, *J* = 1.4, 1.2, H-3′), 4.52 (1H, ddd, *J* = 6.6, 4.0, 1.4, H-2′), 4.58–4.60 (1H, m, H-2), 4.60/4.61 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.63/4.80 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.70/4.87 (each 1H, d, *J* = 6.6, OCH_2OCH_3). ^{13}C NMR (175 MHz, CD_3OD) δ: 19.5/29.6 [$(CH_3)_2C$], 50.3 (C-1′), 51.4 (C-1), 55.5/56.4/56.8 (OCH_2OCH_3), 60.9 (C-5), 69.7 (C-2′), 70.8 (C-7′), 71.5 (C-3′), 73.3 (C-4′), 73.5 (C-4), 77.3 (C-5′), 77.6 (C-6′), 79.2 (C-2), 79.9 (C-3), 97.6/99.4/99.9 (OCH_2OCH_3), 101.6 [$(CH_3)_2C$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 597.1867 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

In a similar manner, coupling reaction of **19c** (1.0 g, 2.24 mmol) with **20** (224 mg, 1.5 mmol) gave 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5S*,*6S*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (**21c**, 550 mg, 62%) as a colorless oil.

Compound **21c**: $[\alpha]_D^{25}$ −22.3 (*c* 0.98, MeOH). IR (neat): 3422, 1645, 1447, 1387, 1258, 1206, 1149, 1103, 1028 cm^{-1}. ^1H NMR (700 MHz, CD_3OD) δ: 1.44/1.51 [each 3H, s, $(CH_3)_2C$], 3.34/3.39/3.41 (each 3H, s, OCH_2OCH_3), 3.66 (1H, dd, *J* = 10.7, 7.6, H-7′a), 3.72 (1H, dd, *J* = 10.7, 4.2, H-7′b), 3.77 (1H, dd, *J* = 12.7, 3.5, H-1a), 3.81 (1H, dd, *J* = 12.7, 2.0, H-1b), 3.88 (1H, dd, *J* = 13.3, 4.0, H-1′a), 3.90–3.94 (1H, m, H-5a), 3.92–3.95, (1H, m, H-4), 3.97 (1H, dd, *J* = 13.3, 7.4, H-1′b), 4.02 (1H, dd, *J* = 9.0, 3.4, H-5b), 4.08–4.10 (2H, m, H-4′ and H-5′), 4.18 (1H, ddd, *J* = 7.6, 4.2, 0.6, H-6′), 4.38 (1H, br d, *J* = ca. 1.6, H-3), 4.50 (1H, br dd, *J* = ca. 1.2, 1.2, H-3′), 4.56 (1H, ddd, *J* = 7.4, 4.0, 1.2, H-2′), 4.58–4.60 (1H, m, H-2), 4.59/4.62 (each 1H, d, *J* = 6.4, OCH_2OCH_3), 4.71/4.77 (each 1H, d, *J* = 6.6, OCH_2OCH_3), 4.75/4.96 (each 1H, d, *J* = 6.0, OCH_2OCH_3). ^{13}C NMR (175 MHz, CD_3OD) δ: 19.3/29.4 [$(CH_3)_2C$], 50.3 (C-1′), 51.3 (C-1), 55.5/55.9/56.7 (OCH_2OCH_3), 60.9 (C-5), 69.0 (C-7′), 70.0 (C-2′), 72.0 (C-3′), 72.9 (C-4′), 73.3 (C-4), 78.1 (C-6′), 78.2 (C-5′), 79.2 (C-2), 79.8 (C-3), 97.4/97.5/100.0 (OCH_2OCH_3), 101.5 [$(CH_3)_2C$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 597.1899 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

In a similar manner, coupling reaction of **19d** (1.0 g, 2.24 mmol) with **20** (224 mg, 1.5 mmol) gave 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5R*,*6R*)-2,4-*O*-isopropylidene-5,6,7-tri-*O*-methoxymethyl-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (**21d**, 670 mg, 75%) as a colorless oil.

Compound **21d**: $[\alpha]_D^{24}$ +33.6 (*c* 0.45, MeOH) IR (neat): 3447, 1636, 1456, 1385, 1258, 1215, 1155, 1107, 1020 cm^{-1}. ^1H NMR (700 MHz, CD_3OD) δ: 1.47/1.50 [each 3H, s, $(CH_3)_2C$], 3.36/3.38/3.40 (each 3H, s, OCH_2OCH_3), 3.66 (1H, dd, *J* = 10.2, 5.6, H-7′a), 3.75 (1H, dd, *J* = 12.8, 3.6, H-1a), 3.81 (1H, dd, *J* = 12.8, 1.8, H-1b), 3.84 (1H, dd, *J* = 10.2, 6.9, H-7′b), 3.90 (1H, dd, *J* = 13.5, 4.0, H-1′a), 3.90–3.93 (1H, m, H-4), 3.93, (1H, dd, *J* = 10.2, 8.3, H-5a), 3.98 (1H, dd, *J* = 13.5, 6.8, H-1′b), 4.02 (1H, dd, *J* = 10.2, 5.0, H-5b), 4.14 (1H, dd, *J* = 8.8, 2.0, H-5′), 4.24 (1H, dd, *J* = 8.8, 1.3, H-4′), 4.32 (1H, ddd, *J* = 6.9, 5.6, 2.0, H-6′), 4.38 (1H, dd, *J* = 1.4, 1.3, H-3′), 4.40 (1H, br d, *J* = ca. 1.8, H-3), 4.51 (1H, ddd, *J* = 6.8, 4.0, 1.4, H-2′), 4.58–4.60 (1H, m, H-2), 4.59/4.61 (each 1H, d, *J* = 6.3, OCH_2OCH_3), 4.70/4.75 (each 1H, d, *J* = 6.3, OCH_2OCH_3), 4.79/4.96 (each 1H, d, *J* = 6.3, OCH_2OCH_3). ^{13}C NMR (175 MHz, CD_3OD) δ: 19.5/29.6 [$(CH_3)_2C$], 50.5 (C-1′), 51.4 (C-1), 55.8/56.0/56.2 (OCH_2OCH_3), 60.9 (C-5), 67.8 (C-7′), 69.6 (C-2′), 72.4 (C-3′), 73.2

(C-4), 73.3 (C-4′), 76.8 (C-6′), 78.3 (C-5′), 79.2 (C-2), 79.9 (C-3), 97.7/97.9/99.2 (OCH_2OCH_3), 101.6 [$(CH_3)_2C$]. FABMS *m*/*z*: 597 $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 597.1857 ($C_{21}H_{41}O_{15}S_2$ requires 597.1887).

3.11. Acidic hydrolysis of sulfonium sulfate inner salts 21a, 21b, 21c and 21d

General procedure: A mixture of 2**1a** (250 mg 0.42 mmol) and 30% aqueous TFA (25 mL) was stirred at 50 °C for 3 h. The mixture was then concentrated to give a residue (200 mg) which on column chromatography ($CHCl_3$/MeOH/H_2O, 10:5:1) gave 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5S*,*6R*)-2,4,5,6,7-pentahydroxy-3-(sulfooxy)heptyl]-episulfoniumylidene}-D-arabinitol inner salt (**9a**, 150 mg, 84%) as a colorless amorphous.

Compound **9a**: $[\alpha]_D^{24}$ −27.3 (*c* 1.06, H_2O). IR (nujol): 3348, 1647, 1258, 1219, 1072 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ: 3.64 (1H, dd, *J* = 10.3, 7.2, H-7′a), 3.66 (1H, dd, *J* = 10.3, 4.6, H-7′b), 3.73 (1H, dd, *J* = 9.5, 1.4, H-5′), 3.83 (1H, dd, *J* = 13.0, 3.2, H-1a), 3.85 (1H, dd, *J* = 13.0, 2.2, H-1b), 3.89–3.93 (2H, m, H-5a and H-6′), 3.94 (1H, br dd, *J* = ca. 13.8, 1.2, H-1′a), 3.97 (1H, br dd, *J* = ca. 13.8, 5.3, H-1′b), 4.00 (1H, br dd, *J* = ca. 8.9, 5.2, H-4), 4.04 (1H, dd, *J* = 10.8, 5.2, H-5b), 4.09 (1H, dd, *J* = 9.5, 1.2, H-4′), 4.37 (1H, br dd, *J* = ca. 2.2, 1.2, H-3), 4.57–4.61 (1H, m H-2′), 4.62 (1H, br ddd, *J* = ca. 3.2, 2.2, 2.2, H-2), 4.70 (1H, dd, *J* = 5.1, 1.2, H-3′). ^{13}C NMR (150 MHz, CD_3OD) δ: 51.1 (C-1′), 51.4 (C-1), 60.9 (C-5), 65.0 (C-7′), 69.1 (C-2′), 70.1 (C-4′), 70.7 (C-5′), 71.4 (C-6′), 73.4 (C-4), 78.7 (C-3′), 79.4 (C-2), 79.6 (C-3). FABMS *m*/*z*: 423, $[M-H]^-$ (neg.). FABHRMS *m*/*z*: 423.0617 ($C_{12}H_{23}O_{12}S_2$ requires 423.0634).

In a similar manner, 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5R*,*6S*)-2,4,5,6,7-pentahydroxy-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (**9b**, 135 mg, 76%) was obtained from **21b** (250 mg 0.42 mmol) as a colorless viscous oil.

Compound **9b**: $[\alpha]_D^{24}$ 75.3 (*c* 1.05, H_2O). IR (neat): 3421, 1684, 1647, 1411, 1253, 1220, 1126, 1096, 1071, 1018 cm^{-1}. ^1H NMR (700 MHz, D_2O) δ: 3.64 (1H, dd, *J* = 12.0, 7.2, H-7′a), 3.70 (1H, dd, *J* = 12.0, 4.0, H-7′b), 3.79 (1H, dd, *J* = 5.1, 4.0, H-5′), 3.900 (1H, dd, *J* = 12.8, 4.0, H-1a), 3.906 (1H, ddd, *J* = 7.2, 4.0, 4.0, H-6′), 3.912 (1H, dd, *J* = 12.8, 3.0, H-1b), 3.940 (1H, dd, *J* = 13.6, 4.0, H-1′a), 3.944 (1H, dd, *J* = 12.4, 11.2, H-5a), 3.97 (1H, dd, *J* = 13.6, 9.2, H-1′b), 4.10 (1H, ddd, *J* = 11.2, 4.8, 3.0, H-4), 4.13 (1H, dd, *J* = 5.1, 4.0, H-4′), 4.14 (1H, dd, *J* = 12.4, 4.8, H-5b), 4.45 (1H, br dd, *J* = ca. 3.0, 3.0, H-3), 4.53 (1H, dd, *J* = 4.0, 4.0, H-3′), 4.58 (1H, ddd, *J* = 9.2, 4.0, 4.0, H-2′), 4.76 (1H, ddd, *J* = ca. 4.0, 3.0, 3.0, H-2). ^{13}C NMR (175 MHz, D_2O) δ: 50.3 (C-1), 51.9 (C-1′), 61.7 (C-5), 65.5 (C-7′), 68.9 (C-2′), 72.0 (C-4′), 72.4 (C-4), 72.9 (C-5′), 74.2 (C-6′), 79.5 (C-2), 80.1 (C-3′), 81.9 (C-3). FABMS *m*/*z*: 425, $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 425.0768, ($C_{12}H_{25}O_{12}S_2$ requires 425.0787).

In a similar manner, 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5S*,*6S*)-2,4,5,6,7-pentahydroxy-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (**9c**, 149 mg, 84%) was obtained from **21c** (250 mg, 0.42 mmol) as a colorless viscous oil.

Compound **9c**: $[\alpha]_D^{23}$ +15.6 (*c* 1.04, H_2O). IR (neat): 3418, 1684, 1418, 1258, 1206, 1136, 1067, 1024, 1001 cm^{-1}. ^1H NMR (700 MHz, D_2O) δ: 3.68 (1H, dd, *J* = 11.8, 7.6, H-7′a), 3.78 (1H, dd, *J* = 11.8, 3.2, H-7′b), 3.85 (1H, dd, *J* = 9.0, 4.0, H-5′), 3.88 (1H, dd, *J* = 13.2, 4.0, H-1a), 3.91 (1H, dd, *J* = 13.2, 3.2, H-1b), 3.91–3.94 (2H, m, H-1′a and H-1′b), 3.92 (1H, dd, *J* = 12.5, 9.7, H-5a), 3.96 (1H, ddd, *J* = 7.6, 4.0, 3.2, H-6′), 4.01 (1H, dd, *J* = 9.0, 1.6, H-4′), 4.07 (1H, ddd, *J* = 9.7, 4.8, 3.0, H-4), 4.13 (1H, dd, *J* = 12.5, 4.8, H-5b), 4.44 (1H, dd, *J* = 3.2, 3.0, H-3), 4.61 (1H, ddd, *J* = 7.6, 5.0, 5.0, H-2′), 4.69 (1H, dd, *J* = *J* = 5.0, 1.6, H-3′), 4.75 (1H, ddd, *J* = 4.0, 3.2, 3.2, H-2). ^{13}C NMR (175 MHz, D_2O) δ: 50.3 (C-1), 51.4 (C-1′), 61.8 (C-5), 64.5 (C-7′), 69.5 (C-2′), 72.0 (C-4′), 72.5 (C-4), 73.6 (C-5′), 75.1 (C-6′), 79.6 (C-2), 80.2 (C-3), 80.4 (C-3′). FABMS *m*/*z*: 425, $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 425.0798 ($C_{12}H_{25}O_{12}S_2$ requires 425.0787).

In a similar manner, 1,4-dideoxy-1,4-{(*S*)-[(*2S*,*3R*,*4S*,*5R*,*6R*)-2,4,5,6,7-pentahydroxy-3-(sulfooxy)heptyl]episulfoniumylidene}-D-arabinitol inner salt (**9d**, 140 mg, 79%) was obtained from **21d** (250 mg 0.42 mmol) as a colorless viscous oil.

Compound **9d**: $[\alpha]_D^{24}$ −15.2 (*c* 0.13, H_2O). IR (neat): 3381, 1682, 1414, 1260, 1207, 1134, 1067, 1024 cm^{-1}. ^1H NMR (600 MHz, D_2O) δ: 3.65 (1H, dd, *J* = 11.6, 5.8, H-7′a), 3.72 (1H, dd, *J* = 8.2, 2.0, H-5′), 3.78 (1H, ddd, *J* = 8.2, 5.8, 3.0, H-6′), 3.81 (1H, dd, *J* = 11.6, 3.0, H-7′b), 3.87 (1H, dd, *J* = 13.2, 4.0, H-1a), 3.90 (1H, dd, *J* = 13.2, 3.6, H-1b), 3.90–3.93 (2H, m, H-1′a and H-1′b), 3.92 (1H, dd, *J* = 12.3, 9.0, H-5a), 4.08 (1H, ddd, *J* = 9.0, 4.8, 2.8, H-4), 4.12 (1H, dd, *J* = 12.3, 4.8, H-5b), 4.23 (1H, dd, *J* = 5.6, 2.0, H-4′), 4.42 (1H, dd, *J* = 3.6, 2.8, H-3), 4.49 (1H, dd, *J* = 5.6, 3.0, H-3′), 4.50–4.53 (1H, m, H-2′), 4.74 (1H, ddd, *J* = 4.0, 3.6, 3.6, H-2). ^{13}C NMR (175 MHz, D_2O) δ: 50.3 (C-1), 52.2 (C-1′), 61.7 (C-5), 65.3 (C-7′), 68.5 (C-2′), 70.7 (C-4′), 72.3 (C-4), 72.6 (C-5′), 73.4 (C-6′), 79.4 (C-2), 80.1 (C-3), 83.4 (C-3′). FABMS *m*/*z*: 425, $[M+H]^+$ (pos.). FABHRMS *m*/*z*: 425.0758 ($C_{12}H_{25}O_{12}S_2$ requires 425.0787).

3.12. α-Glucosidase inhibitory activity

Testing method already described[5] was modified and used. Briefly, rat small intestinal brush border membrane vesicles were prepared[21] and its suspension in 0.1 M maleate buffer (pH 6.0) was used as small intestinal α-glucosidases of maltase, sucrase, and isomaltase. A 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 maleate buffer (maltose, 74 mM, sucrose, 74 mM, isomaltose, 7.4 mM, 50 μL), a test compound solution (25 μL), and the enzyme solution (25 μL) were mixed and incubated at 37 °C for 30 min. After incubation, the solution was immediately heated by boiling water for 2 min to stop the reaction, and the solution was mixed with water (150 μL). Glucose concentration was determined by the glucose-oxidase method. Final concentration of DMSO in the test solution was 2.5% and no influence of DMSO was detected on the inhibitory activity. The IC_{50} value was determined graphically by a plot of percent inhibition versus log of the test compound.

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