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Hydrophobic substituents increase the potency of salacinol, a potent α-glucosidase inhibitor from Ayurvedic traditional medicine '*Salacia*'

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ABSTRACT

Using an in silico method, seven analogs bearing hydrophobic substituents (**8a**: Me, **8b**: Et, **8c**: *n*-Pent, **8d**: *n*-Hept, **8e**: *n*-Tridec, **8f**: isoBu and **8g**: neoPent) at the 3′-O-position in salacinol (**1**), a highly potent natural α-glucosidase inhibitor from Ayurvedic traditional medicine '*Salacia*', were designed and synthesized. In order to verify the computational SAR assessments, their α-glucosidase inhibitory activities were evaluated in vitro. All analogs (**8a**–**8g**) exhibited an equal or considerably higher level of inhibitory activity against rat small intestinal α-glucosidases compared with the original sulfonate (**1**), and were as potent as or higher in potency than the clinically used anti-diabetics, voglibose, acarbose or miglitol. Their activities against human maltase exhibited good relationships to the results obtained with enzymes of rat origin. Among the designed compounds, the one with a 3′-*O*-neopentyl moiety (**8g**) was most potent, with an approximately ten fold increase in activity against human maltase compared to **1**.

1. Introduction

The roots and stems of plants belonging to the genus *Salacia*, including, *Salacia reticulata*, *S. oblonga*, *S. chinensis* have traditionally been used in the Ayurvedic system for treating diabetes. In 1997, a novel thiosugar sulfonate, salacinol (**1**), was isolated from a methanol extract of *S. reticulata* as a constituent responsible for the antidiabetic property of the extract. The structure of **1** is quite unique that comprises of 1,4-anhydro-4-thio-D-arabinitol cation and deoxyalditol side chain. The crystal structure revealed by X-ray crystallographic analysis showed that the sulfonate anion and the sulfonium cation established an internal bond, forming a spirobicyclic structure as shown in Figure 1. The mechanism of action of **1** was revealed to be α-glucosidase inhibition, with its inhibitory activity as effective as those of voglibose and acarbose, which are widely used clinically.[1,2] Two years later, a side chain-extended analog kotalanol (**2**) was isolated from the same genus of plants as a constituent with an even greater inhibitory activity.[3] Thereafter, a related sulfonium sulfonate such as ponkoranol[4] (**3**) as well as its desulfonated analogs, neosalacinol[5] (**4**) neokotalanol[6] (**5**) and neoponkoranol[7] (**6**), was subsequently isolated (Fig. 1), and was revealed to exhibit the same level of inhibitory activity. On this basis, human clinical trials on patients with type-2 diabetes were conducted with extracts of *Salacia reticulata*, which demonstrated effective treatment of type-2 diabetes with minimal side effects.[8]

Because of their intriguing structure and the potent glucosidase inhibitory activity, much attention has been focused on these natural inhibitors **1**–**6**, and intensive structure–activity relationship (SAR) studies including the total syntheses of these inhibitors have been reported.[9] Following detailed X-ray crystallographic studies on salacinol (**1**) in a complex with human N-terminal catalytic domain of maltase-glucoamylase (hNtMGAM), Pinto and co-workers concluded that the 3′-*O*-sulfonate anion of **1** was constrained by the surrounding hydrophobic residues (Phe575, Tyr299 and Trp406) of the enzyme, which possibly caused the negative binding interactions of 1 with the residues (Fig. 2-A).[9g] Based on these findings, several 3′-*O*-benzylated analogs (**7**), in which the sulfonate anion of **1** was substituted by a hydrophobic benzyl moiety, were designed. These analogs exhibited activities (IC_{50} = 0.13–0.98 μM) superior to the original compound **1** (IC_{50} = 5.2 μM).[9e,9f]

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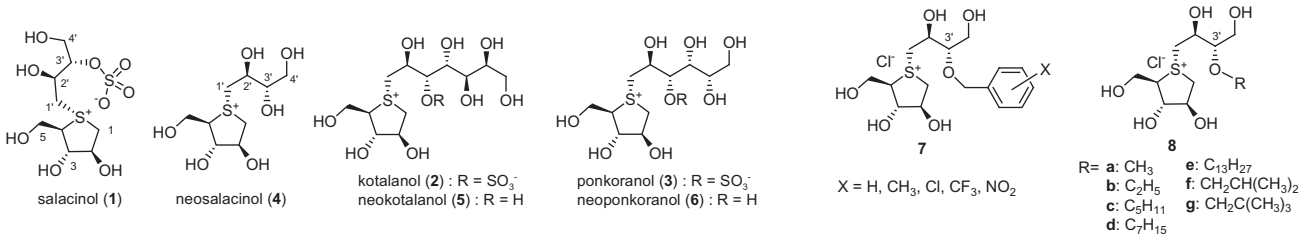


Figure 1. Cyclic sulfonium salts as a new class of α-glucosidase inhibitors.

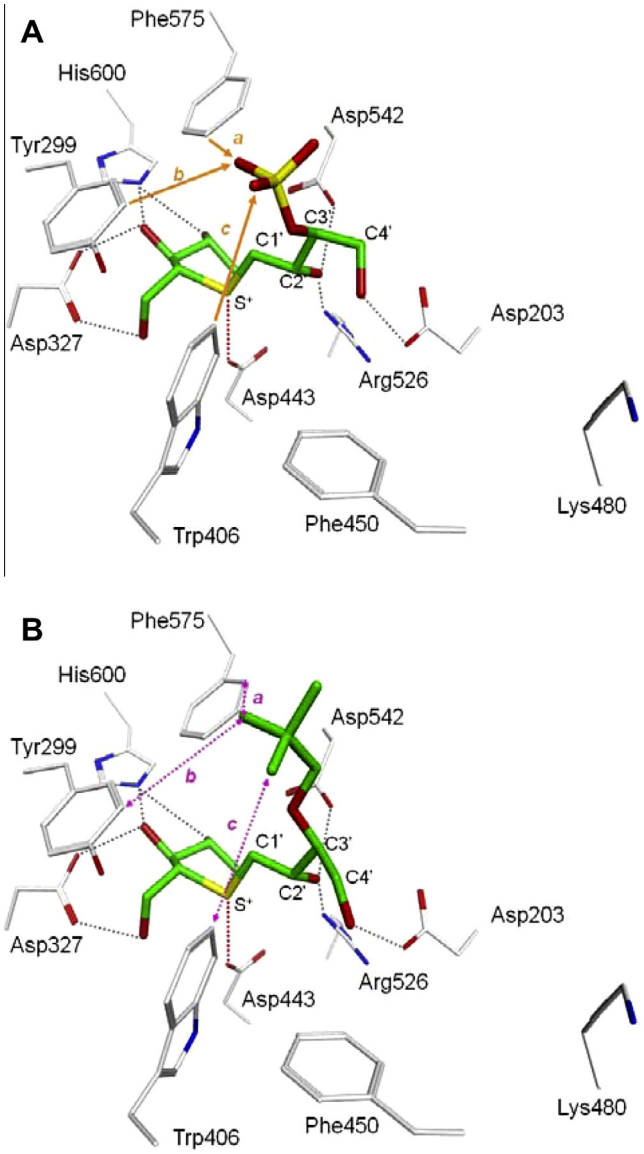


Figure 2. Superpositions of salacinol (**1**) (A) and **8g** (B) in the hNtMGAM active site. Dotted lines show hydrogen bonding (gray) and salt bridge (red). Orange arrows (a), (b), (c) in salacinol (**1**) (A) and double-headed pink dotted arrows (a), (b), (c) in **8g** (B) show the distances between the alkyl group and amino acid residues. (A: salacinol (**1**), (*a*): 3.6 Å, (*b*): 3.7 Å, (*c*): 4.0 Å, B: **8g**, (*a*): 3.9 Å, (*b*): 4.5 Å, (*c*): 4.7 Å).

In this paper, as another attempt to reduce the hydrophilicity at the 3′-O-position in **1**, several derivatives bearing simple alkyl . groups (**8a**: Me, **8b**: Et, **8c**: *n*-Pent, **8d**: *n*-Hept, **8e**: *n*-Tridec, **8f**: isoBu and **8g**: neoPent) at the position were designed using an in silico method. The binding affinities of these compounds calculated by the MM/GBVI method[10] are provided in Table 1. Among the 7 candidates (**8a**–**8g**), all compounds except **8a** were supposed to be superior inhibitors according to the calculation. Thus, these 3′-*O*-alkylated analogs (**8a**, **8b**, **8c**, **8d**, **8e**, **8f** and **8g**) were synthesized and their inhibitory activities were examined to evaluate the computational assessment. Their inhibitory activities were measured against not only rat intestinal maltase but also human intestinal maltase.

2. Results and discussion

2.1. Chemistry

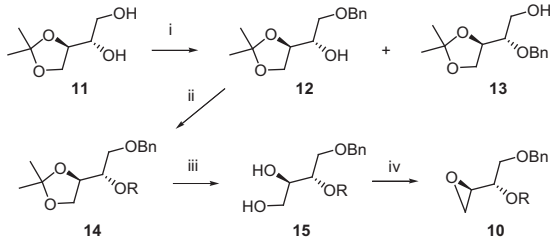
Syntheses of **8a**–**8g** were carried out by applying a regioselective ring-opening reaction between appropriate epoxides (**10a**–**10g**) and thiosugar, 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-epithio-D-arabinitol (**9**), which was prepared by the method described in our earlier work.[9m] First, epoxides **10a**–**10g** were prepared in the following manner. 3,4-*O*-Isopropylidene-D-erythritol[11] (**11**), readily obtained via 4 steps starting from D-isoascorbic acid, was subjected to selective benzylation of the primary hydroxyl to give 1-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritol[12] (**12**) and 2-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritol[13] (**13**) in 91% and 7% yields, respectively. Alkylation of the major alcohol **12** with seven kinds of alkyl halides, MeI, EtI, *n*-PentBr, *n*-HeptBr, *n*-TridecBr, isoBuBr or neoPentBr in DMF in the presence of NaH, and subsequent deacetonization of the resulting 2-*O*-alkylated 1-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritols (**14a**–**14g**) by action of hydrochloric acid gave 2-*O*-alkyl-1-*O*-benzyl-D-erythritols (**15a**–**15g**), respectively, in good yields. Glycols **15a**, **15b**, **15c**, **15d**, **15e**, **15f** and **15g** were then subjected to the Mitsunobu reaction by treatment with DEAD and Ph_3P in refluxing toluene to give 2-*O*-alkylated 3,4-anhydro-1-*O*-benzyl-2-*O*-(pent-1-yl)-D-erythritols (**10a**, **10b**, **10c**, **10d**, **10e**, **10f** and **10g**), in 77%, 76%, 82%, 85%, 81%, 82% and 89% yields, respectively (Scheme 1).

With epoxides **10a**–**10g** in hand, the coupling reaction of these epoxides with thiosugar **9** was carried out in the presence of either tetrafluoroboric acid dimethyl ether complex or diethyl ether complex ($HBF_4{\cdot}Me_2O$ or $HBF_4{\cdot}Et_2O$) at −60 °C in CH_2Cl_2. In every case, the reaction proceeded regiospecifically and stereoselectively, giving predominantly corresponding α-sulfonates (α-**16a**–α-**16g**, X = BF_4) along with a small amount of its β-isomer (β-**16a**–β-**16g**, α/β = ca. ~9/1) in good yields. After the BF_4^- anion of the coupled products was exchanged with a Cl^- anion,[9d,9f] by treatment with ion exchange resins IRA-400 J (Cl^- form), the mixture of chlorides (**16a**–**16g**, X = Cl) were subjected to silica gel column chromatography to give pure α-isomers (α-**16a**–α-**16g**, X = Cl) in approximately 70% isolated yield. In the FAB mass spectra run in a positive mode, the products α-**16a**, α-**16b**, α-**16c**, α-**16d**, α-**16e**, α-**16f** and α-**16g** showed peaks due to the sulfonium ions at *m*/*z* 629, 643, 685, 713, 797, 671 and 685, respectively, which represented the corresponding cation structure. The ^{13}C NMR spectral properties of the products (α-**16a**–α-**16g**) were similar with each other except for signals due to C-3′-*O*-alkyl moieties, and chemical shifts due to the core nine carbons (C1–C5 and

Table 1
E_{bind} (kcal/mol) of **8a**–**8g**, **7** (*o*-NO_2), **1**, and **4** to hNtMGAM, and their IC_{50} (μM) values against rat and human intestinal disaccharidases

Entry	Compound	E_{bind}[a]	Rat			Human	Entry	Compound	E_{bind}[a]	Rat			Human
			Maltase	Sucrase	Isomaltase	Maltase				Maltase	Sucrase	Isomaltase	Maltase
1	**8a** (CH_3)	−35.4	5.3[c]	0.46[c]	0.39[c]	2.0	8	**7** (*o*-NO_2)	−38.9[b]	0.13[b]	0.042[b]	0.21[b]	0.15
2	**8b** (C_2H_5)	−38.2	1.7[c]	0.12[c]	0.27[c]	0.96	9	**1**	−37.0[b]	5.2[d]	1.6[d]	1.3[d]	4.9[f]
3	**8c** (C_5H_{11})	−38.0	1.5	0.50	0.47	1.5	10	**4**	−36.4[b]	8.0[d]	1.3[d]	0.3[d]	9.0[f]
4	**8d** (C_7H_{15})	−41.3	0.80	0.24	0.25	0.64	11	Voglibose		1.2[c]	0.2[c]	2.1[c]	1.3[f]
5	**8e** ($C_{13}H_{27}$)	−41.9	1.04[c]	1.3[c]	0.95[c]	1.1	12	Acarbose		1.7[e]	1.5[e]	646[e]	15.2[f]
6	**8f** [$CH_2CH(CH_3)_2$]	−36.6	0.79	0.09	0.34	0.69	13	Miglitol		8.2	0.43	4.6	3.7[f]
7	**8g** [$CH_2C(CH_3)_3$]	−38.6	0.30	0.09	0.28	0.47							

[a] Calculation has been performed using the reported scheme.[9h]
[b] Lit.[9e]
[c] Lit.[9f]
[d] Lit.[4]
[e] Lit.[18]
[f] Lit.[19]



a : R = CH_3, **b** : R = C_2H_5, **c** : R = C_5H_{11}, **d** : R = C_7H_{15}
e : R = $C_{13}H_{27}$, , **f** : R = $CH_2CH(CH_3)_2$, **g** : R = $CH_2C(CH_3)_3$

Scheme 1. Synthesis of epoxides **10a**–**10g**. Reagents and conditions: (i) Bu_2SnO, toluene, reflux, then BnBr, CsF, DMF, 60 °C; (ii) alkyl halides, NaH, DMF, 0 °C–rt; (iii) 0.5% aq HCl, EtOH, reflux; (iv) Ph_3P, DEAD, toluene, reflux.

C1′–C4′) were in good accord with each other as shown in Table 2. The relative stereochemistry of the side chain of the major isomers was confirmed to be in anti-relationship to the benzyloxymethyl moiety at C-4 on the basis of observed nuclear Overhauser effect (NOE) as shown in Scheme 2. In the ^{13}C NMR spectra of minor isomers (β-**16a**–β-**16g**), characteristic upfield shift, induced by the *cis*-oriented β-substituent effect,[14] was observed with respect to the signals due to carbons C-1 (δ_C: 45) and C-4 (δ_C: 61) when compared with those of α-isomer [α-**16a**–α-**16g**: C-1 (δ_C: 48) and C-4 (δ_C: 66)], supporting the β-orientation of the side chain.

Attempted hydrogenolysis of α-isomers α-**16a**–α-**16g** with palladium on carbon in 80% aqueous acetic acid at 50–60 °C gave the corresponding debenzylated products with a concomitant formation of partially acetylated products. Then, the crude products were subjected to acidic methanolysis to give the target compounds **8a**–**8g** in around 70% yields. MS spectra of **8a**, **8b**, **8c**, **8d**, **8e**, **8f** and **8g** run in a positive mode showed peaks at *m*/*z* 269, 283, 325, 353, 311 and 325, respectively, due to corresponding sulfonium cations. Downfield shifted signals due to C-3′ carbons (around δ_C 84) of the products compared with that of neosalacinol (**4**: $\delta_{C\text{-}3'}$ 75.3) supported the 3′-*O*-alkylated neosalacinol-type structure (Table 3). Finally, the anti-relationship between the side chain and the hydroxymethyl moiety on C-4 of **8a**–**8g** was confirmed by means of NOE experiments as shown in Scheme 2.

Table 2
^{13}C NMR data for nine carbons (C1–C5 and C1′–C4′) of sulfonium salts **16a**–**16g**

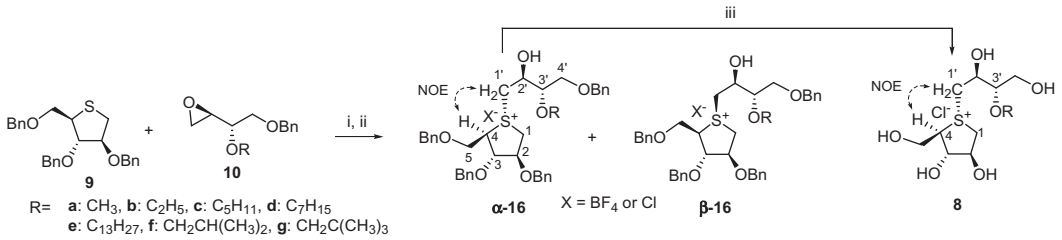
	α-**16a**[a]	α-**16b**[a]	α-**16c**[b]	α-**16d**[b]	α-**16e**[a]	α-**16f**[a]	α-**16g**[a]
C1	48.4	48.3	48.2	48.2	48.2	48.2	48.0
C2	82.4	82.5	82.4	82.51	82.5	82.4	82.3
C3	82.3	82.4	82.5	82.45	82.4	82.4	82.5
C4	66.1	65.8	65.9	65.9	65.8	66.0	66.2
C5	66.9	67.0	67.0	67.0	67.0	67.0	67.1
C1′	51.9	51.8	51.9	51.9	51.9	51.9	51.8
C2′	68.1	68.0	68.1	68.1	68.1	68.1	68.1
C3′	82.0	80.4	80.7	80.7	80.7	80.9	81.3
C4′	67.4	68.5	68.4	68.5	68.4	68.3	68.5
	β-**16a**[a,d]	β-**16b**[a,d]	β-**16c**[a,d]	β-**16d**[c,d]	β-**16e**[b]	β-**16f**[a,d]	β-**16g**[b,d]
C1	45.1	45.3	45.1	45.2	45.3	45.2	44.9
C2	82.5	82.5	82.5	82.5	82.5	82.5	82.5
C3	84.6	84.6	84.6	84.6	84.6	84.6	84.5
C4	60.7	60.8	60.6	60.7	60.8	60.8	60.7
C5	65.3	65.3	65.2	65.3	65.3	65.3	65.1
C1′	42.8	42.9	42.9	42.9	42.9	42.9	42.9
C2′	66.1	66.1	66.2	66.3	66.3	66.3	66.1
C3′	81.9	80.2	80.6	80.6	80.6	80.9	81.5
C4′	68.8	69.6	69.6	69.6	69.6	69.5	69.6

[a] All spectra were measured in $CDCl_3$ 125 MHz.
[b] All spectra were measured in $CDCl_3$ 175 MHz.
[c] All spectra were measured in $CDCl_3$ 200 MHz.
[d] Chemical shift values extracted from the spectrum of a mixture of α- and β-isomer. Other signals due to the alkyl moieties at 3′-O-position are provided in Section 4.

2.2 α-Glucosidase inhibitory activity

α-Glucosidase catalytic domains in maltose digestion in rats are known to be homologous to those in humans. For instance, the N-terminal catalytic domain of maltase-glucoamylase (rNtMGAM) and that of human (hNtMGAM) were reported to share 60% amino acid sequence similarity.[15] In this study inhibitory activities of the synthesized compounds **8a**, **8b**, **8c**, **8d**, **8f**, **8e**, **8g** were evaluated using both enzymes from rat and human origin, and the activities compared (Table 1).

First, inhibitory activities against rat α-glucosidases were evaluated. The inhibitory activities against maltase significantly varied according to the alkyl species. The potency of **8a** was almost equal to that of **1**, indicating that replacement of the sulfonate moiety with a methyl group caused no significant effect on the inhibitory activity. Analogs **8b**, **8c**, **8d**, and **8e** bearing linear alkyl chains and an isobutyl group exhibited slightly higher activities than **1**, although **8d** and **8e** were predicted to have superior inhibitory action according to the analysis. Among the seven derivatives evaluated in this study, **8g** was found to be the most potent, approximately 20–25-times more active than **1**. It is interesting to note that the analog bearing the most bulky side chain (**8g**) exhibited the strongest activity. Against sucrase, compounds bearing the bulky substituents [**8f**: $CH_2CH(CH_3)_2$ and **8g**: $CH_2C(CH_3)_3$] also showed a high inhibitory activity of approximately 20 times greater than that of **1**. Isomaltase inhibitory activities of all the analogs were either the same or very similar to that of **1** regardless of the alkyl species. The results indicated that simple alkylation at



Scheme 2. Synthesis of sulfonium salts **8a**–**8g**. Reagents and conditions: (i) $HBF_4{\cdot}(CH_3)_2O$ or $HBF_4{\cdot}(C_2H_5)_2O$, CH_2Cl_2, −60 °C; (ii) IRA-400J (Cl^- form), MeOH–H_2O, rt; (iii) H_2, Pd–C, 80% AcOH, 50–60 °C, then 10% aq HCl–CH_3OH, rt.

Table 3
^{13}C NMR data of neosalacinol[4b] (**4**) and compounds **8a**-**8g**

	4	8a[a]	8b[b]	8c[a]	8d[a]	8e[b]	8f[a]	8g[a]
C1	52.1	52.1	52.1	52.2	52.2	52.2	52.2	52.3
C2	79.4	79.4	79.4	79.46	79.48	79.5	79.47	79.5
C3	79.5	79.5	79.5	79.52	79.52	79.6	79.52	79.5
C4	73.7	73.7	73.7	73.8	73.8	73.8	73.8	73.8
C5	61.0	61.0	61.1	61.0	61.1	61.1	61.0	61.0
C1′	51.8	51.8	51.8	51.8	51.8	51.8	51.9	51.9
C2′	69.6	68.6	68.7	68.7	68.7	68.8	68.8	68.9
C3′	75.3	85.1	83.5	83.7	83.7	83.7	83.9	84.2
C4′	64.0	60.0	60.8	60.7	60.7	60.8	60.7	60.8

Signals due to the alkyl moieties at the 3′-O-position were described in Section 4.
[a] All spectra were measured in CD_3OD 125 MHz.
[b] All spectra were measured in CD_3OD 175 MHz.

the 3′-O-position of the side chain caused a beneficial effect, enhancing the inhibitory activity against α-glucosidases of rat origin.

Next, inhibitory activities against human intestinal maltase were examined and compared with those against rat intestinal maltase. All analogs showed satisfactory potent inhibitory activities with IC_{50} values ranging from 2.0 to 0.47 μM. The relative inhibitory potencies were equivalent to those against rat intestinal maltase. It is of interest that against human maltase, compound bearing a CH_3 group (**8a**, entry 1, 2.0 μM) exhibited more potency than the parent sulfonium salts **1** and **4** (4.9 and 9.0 μM, respectively), which was not forecasted by in silico docking studies. As a result, all analogs were shown to be more potent inhibitors than either **1** or **4** as well as the three anti-diabetics. Among them, **8g** (entry 7, IC_{50} value of 0.47 μM) was the most potent compound also against human intestinal maltase.

The superposition of the most potent analogue **8g** in the hNtMGAM is provided in Figure 2-B. As the binding pocket of hNtMGAM was rigid, their inhibitory activities were affected by physicochemical properties of the substituents. Instead of the negative binding effects between aromatic residues and the sulfonate oxygens of salacinol (weak CH—O interaction: orange arrows a, b, and c in Fig. 2-A, but penalized by desolvation of polar groups), intermolecular van der Waals interactions were detected between the neopentyl moiety and the surrounding hydrophobic parts, Phe575, Tyr299, and Trp406 (double-headed pink dotted arrows a, b, c in Fig. 2-B). The distances between the terminal methyl groups of the neopentyl moiety and the residues, Phe575, Tyr299, and Trp406, were calculated to be approximately 3.9, 4.5, and 4.7 Å, respectively. These distances induced effective van der Waals interactions. This interaction and less desolvation penalty of the nonpolar group might contribute to the enhanced inhibitory activity.

As shown in Table 1, compounds bearing long alkyl chains (**8d** and **8e**) were calculated to bind to hNtMGAM more effectively than **8g** whereas, the observed inhibitory potency of **8d** and **8e** against enzymes was less when compared with **8g**. This discrepancy could be attributable to the entropic disadvantage caused by the loss of rotational flexibility of the long straight alkyl chain through protein binding. Furthermore, the contribution of other catalytic domains including a C-terminal maltase-glucoamylase (CtMGAM) and/or sucrase-isomaltase (CtSI) has been shown to affect the hydrolysis of maltose, which could be another reason for the discrepancy mentioned above.[16]

3. Conclusions

Thus, using an in silico method, α-glucosidase inhibitors (**8c**–**8g**) with higher activities than the seed compound salacinol (**1**) were effectively designed and developed. The activity of **8g**, the most active compound, is approximately 10 times as potent as **1**, but less potent than the previously developed *ortho*-nitrobenzyl derivative (**7**: X = *o*-nitro).[9e] As a nitro group is reported to occasionally cause toxicity during the metabolism of some drug candidates,[17] an alkylated analog **8g** would overcome this disadvantage, and will be a promising candidate as a new type of α-glucosidase inhibitor. Further SAR studies using in silico methods are currently in progress.

4. Experimental section

4.1. General method

Mps were determined on an AS ONE ATM-02 melting point apparatus and are uncorrected. IR spectra were measured on a Shimadzu IRAffinity-1 spectrophotometer. NMR spectra were recorded on a JEOL JNM-ECA 500 (500 MHz ^1H, 125 MHz ^{13}C), JEOL JNM-ECA 700 (700 MHz ^1H, 175 MHz ^{13}C), or a JEOL JNM-ECA 800 (800 MHz ^1H, 200 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-700T spectrometer. Optical rotations were determined with a JASCO P-2200 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.

4.2. Chemistry

4.2.1. 1-*O*-Benzyl-3,4-*O*-isopropylidene-D-erythritol (12) and 2-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritol (13)

In a egg-plant flask equipped with Dean Stark condenser, a mixture of diol[11] (**11**, 6 g, 37.0 mmol), dibutyltinoxide(IV) (Bu_2SnO, 11.1 g, 44.6 mmol) and toluene (60 mL) was heated under reflux for 1 h, and the reaction mixture was condensed at reduced pressure. To the residue were subsequently added DMF (60 mL), cesium fluoride (8.5 g, 55.9 mmol), and benzyl bromide (6.6 mL, 55.2 mmol), and the resulting suspension was heated at 60 °C for 1 h. After being cooled, the reaction mixture was diluted with

diethyl ether (200 mL), and diethyl ether-insoluble materials were filtered off and washed with diethyl ether. The combined filtrate and washings were made alkaline (pH >11) by addition of 10% aqueous sodium hydroxide. The deposited gel was filtered off through celite and washed with diethyl ether. The organic layer was washed with brine and condensed to give a pale yellow oil (11.3 g), which on column chromatography (*n*-hexane–AcOEt, 10:1→5:1→1:1) gave title compounds **12**[12] (8.5 g, 91%) and **13**[13] (651 mg, 7%).

4.2.2. Alkylation of 1-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritol (12)

4.2.2.1. With methyl iodide. A solution of compound (**12**, 1.9 g, 7.54 mmol) in DMF (10 mL) was added dropwise to a mixture of sodium hydride (452 mg, 11.3 mmol, 60% in liquid paraffin), methyl iodide (1 mL, 16 mmol), and DMF (10 mL) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was poured into ice-water (100 mL) and extracted with a mixture of *n*-hexane and diethyl ether (v/v, 1:1). The extract was washed with brine and condensed to give a pale yellow oil (2.31 g), which on column chromatography (*n*-hexane–AcOEt, 100:1→10:1) gave 1-*O*-benzyl-2-*O*-methyl-3,4-*O*-isopropylidene-D-erythritol (**14a**, 1.96 g, 98%) as colorless oil, $[\alpha]_D^{20}$ +13.5 (*c* 1.10, $CHCl_3$). IR (neat): 1454, 1370, 1253, 1211, 1153, 1100, 1053 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.35/1.41 [each 3H, s, $C(CH_3)_2$], 3.38 (1H, ddd, *J* = 6.6, 4.9, 2.9, H-2), 3.48 (3H, s, OCH_3), 3.55 (1H, dd, *J* = 10.6, 4.9, H-1a), 3.71 (1H, dd, *J* = 10.6, 2.9, H-1b), 3.93 (1H, dd, *J* = 8.3, 6.1, H-4a), 4.05 (1H, dd, *J* = 8.3, 6.3, H-4b), 4.14 (1H, ddd, *J* = 6.6, 6.3, 6.1, H-3), 4.56/4.58 (each 1H, d, *J* = 12.1, OCH_2Ph), 7.26–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.3/26.6 [$C(CH_3)_2$], 58.7 (OCH_3), 66.5 (C-4), 69.3 (C-1), 73.5 (OCH_2Ph), 75.3 (C-3), 81.0 (C-2), 109.1 [$C(CH_3)_2$], 127.6/128.3 (d, arom.), 138.2 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 289 $[M+Na]^+$. HRMS (FAB, pos.): calcd for $C_{15}H_{22}O_4Na$, 289.1416, found 289.1444.

4.2.2.2. With ethyl iodide. In a similar manner, 1-*O*-benzyl-2-*O*-ethyl-3,4-*O*-isopropylidene-D-erythritol (**14b**, 2.13 g, 96%) was obtained from **12** (2.0 g, 7.94 mmol) as colorless oil, $[\alpha]_D^{24}$ +10.4 (*c* 0.85, $CHCl_3$). IR (neat): 1456, 1371, 1260, 1213, 1099, 1074 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.19 (3H, t, *J* = 7.2, OCH_2CH_3), 1.35/1.40 [each 3H, s, $C(CH_3)_2$], 3.48 (1H, ddd, *J* = 6.6, 5.2, 3.2, H-2), 3.54 (1H, dd, *J* = 10.3, 5.2, H-1a), 3.57/3.75 (each 1H, dq, *J* = 9.5, 7.2, OCH_2CH_3), 3.68 (1H, dd, *J* = 10.3, 3.2, H-1b), 3.93 (1H, dd, *J* = 8.3, 6.1, H-4a), 4.05 (1H, dd, *J* = 8.3, 6.3, H-4b), 4.14 (1H, ddd, *J* = 6.6, 6.3, 6.1, H-3), 4.55/4.57 (each 1H, d, *J* = 12.3 Hz, OCH_2Ph), 7.26–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.6 (OCH_2CH_3), 25.4/26.6 [$C(CH_3)_2$], 66.5 (OCH_2CH_3), 66.6 (C-4), 70.1 (C-1), 73.4 (OCH_2Ph), 75.5 (C-3), 79.3 (C-2), 109.1 [$C(CH_3)_2$], 127.5/1278.3 (d, arom.), 138.3 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 303 $[M+Na]^+$. HRMS (FAB, pos.): calcd for $C_{16}H_{24}O_4Na$ 303.1572, found 303.1593.

4.2.2.3. With pentyl bromide. In a similar manner, 1-*O*-benzyl-2-*O*-(pent-1-yl)-3,4-*O*-isopropylidene-D-erythritol (**14c**, 1.1 g, 96%) was obtained from **12** (900 mg, 3.57 mmol) as colorless oil, $[\alpha]_D^{23}$ +16.0 (*c* 0.91, $CHCl_3$). IR (neat): 1454, 1370, 1258, 1211, 1099, 1072 cm^{-1}. ^1H NMR (500 Hz, $CDCl_3$) δ: 0.89 [3H, t, *J* = 7.1, $O(CH_2)_4CH_3$], 1.28–1.34 [4H, m, $OCH_2CH_2(CH_2)_2CH_3$], 1.35/1.40 [each 3H, s, $C(CH_3)_2$], 1.52–1.59 [2H, m, $OCH_2CH_2(CH_2)_2CH_3$], 3.46 (1H, ddd, *J* = 6.6, 5.2, 3.1, H-2), 3.48/3.68 [each 1H, dt, *J* = 9.0, 6.9, $OCH_2(CH_2)_3CH_3$], 3.54 (1H, dd, *J* = 10.3, 5.2, H-1a), 3.69 (1H, dd, *J* = 10.3, 3.1, H-1b), 3.93 (1H, dd, *J* = 8.3, 6.0, H-4a), 4.05 (1H, dd, *J* = 8.3, 6.6, H-4b), 4.15 (1H, ddd, *J* = 6.6, 6.6, 6.0, H-3), 4.55/4.57 (each 1H, d, *J* = 12.3, OCH_2Ph), 7.26–7.36 (5H, m, arom). ^{13}C NMR (125 Hz, $CDCl_3$) δ: 14.0 [$O(CH_2)_4CH_3$], 22.5 [$O(CH_2)_3CH_2CH_3$], 25.4/26.6 [$C(CH_3)_2$], 28.3 [$O(CH_2)_2CH_2CH_2CH_3$], 29.8 [$OCH_2CH_2(CH_2)_2CH_3$], 66.7 (C-4), 70.0 (C-1), 71.2 [$OCH_2(CH_2)_3CH_3$], 73.4 (OCH_2Ph), 75.4 (C-3), 79.5 (C-2), 109.0 [$C(CH_3)_2$], 127.5/128.3 (d, arom.), 138.3 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 345 $[M+Na]^+$. HRMS (FAB, pos.): calcd for $C_{19}H_{30}O_4Na$ 345.2042, found 345.2035.

4.2.2.4. With heptyl bromide. In a similar manner, 1-*O*-benzyl-2-*O*-(hept-1-yl)-3,4-*O*-isopropylidene-D-erythritol (**14d**, 673 mg, 97%) was obtained from **12** (500 mg, 1.98 mmol) as colorless oil, $[\alpha]_D^{23}$ +13.3 (*c* 0.97, $CHCl_3$). IR (neat): 1454, 1369, 1346, 1273, 1253, 1215, 1099, 1076 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 [3H, t, *J* = 7.0, $O(CH_2)_6CH_3$], 1.22–1.34 [8H, m $O(CH_2)_2(CH_2)_4CH_3$], 1.35/1.40 [each 3H, s, $C(CH_3)_2$], 1.52–1.59 [2H, m $OCH_2CH_2(CH_2)_4CH_3$], 3.46 (1H, ddd, *J* = 6.6, 5.2, 3.1, H-2), 3.47/3.68 [each 1H, dt, *J* = 9.2, 7.0, $OCH_2(CH_2)_5CH_3$], 3.54 (1H, dd, *J* = 10.3, 5.2, H-1a), 3.69 (1H, dd *J* = 10.6, 3.1, H-1b), 3.93 (1H, dd, *J* = 8.3, 6.0, H-4a), 4.05 (1H, dd, *J* = 8.3, 6.3, H-4b), 4.14 (1H, ddd, *J* = 6.6, 6.3, 6.0, H-3), 4.58/4.54 (each 1H, d, *J* = 12.0, OCH_2Ph), 7.25–7.35 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_6CH_3$], 22.6 [$O(CH_2)_5CH_2CH_3$], 25.4/26.6 [$C(CH_3)_2$], 26.1 [$O(CH_2)_2CH_2(CH_2)_3CH_3$], 29.1 [$O(CH_2)_3CH_2CH_2CH_3$], 30.1 [$OCH_2CH_2(CH_2)_4CH_3$], 31.8 [$O(CH_2)_4CH_2CH_2CH_3$], 66.7 (C-4), 70.0 (C-1), 71.3 [$OCH_2(CH_2)_5CH_3$], 73.4 (OCH_2Ph), 75.4 (C-3), 79.5 (C-2), 109.0 [$C(CH_3)_2$], 127.5/128.3 (d, arom.), 138.3 (s, arom). LRMS (FAB, pos.) *m*/*z*: 373 $[M+Na]^+$. HRMS (FAB, pos.): calcd for $C_{21}H_{34}O_4Na$ 373.2355, found 373.2365.

4.2.2.5. With tridecyl bromide. In a similar manner, 1-*O*-benzyl-2-*O*-(tridec-1-yl)-3,4-*O*-isopropylidene-D-erythritol (**14e**, 1.2 g, 87%) was obtained from **12** (800 mg, 3.17 mmol) as colorless oil, $[\alpha]_D^{24}$ +10.7 (*c* 1.03, $CHCl_3$). IR (neat): 1456, 1377, 1369, 1256, 1213, 1099, 1076 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 [3H, t, *J* = 6.9, $O(CH_2)_{12}CH_3$], 1.22–1.33 [20H, $O(CH_2)_2(CH_2)_{10}CH_3$], 1.35/1.40 [each 3H, s, $C(CH_3)_2$], 1.51–1.59 [2H, m, $OCH_2CH_2(CH_2)_{10}CH_3$], 3.45 (1H, ddd, *J* = 6.6, 5.2, 3.2, H-2), 3.48/3.68 [each 1H, dd, *J* = 9.2, 6.9, $OCH_2(CH_2)_{11}CH_3$], 3.54 (1H, dd, *J* = 10.3, 5.2, H-1a), 3.69 (1H, dd, *J* = 10.3, 3.2, H-1b), 3.93 (1H, dd, *J* = 8.3, 6.3, H-4a), 4.05 (1H, dd, *J* = 8.3, 6.6, H-4b), 4.15 (1H, ddd, *J* = 6.6, 6.6, 6.3, H-3), 4.55/4.58 (each 1H, d, *J* = 12.1, OCH_2Ph), 7.25–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_{12}CH_3$], 22.7 [$O(CH_2)_{11}CH_2CH_3$], 25.4/26.6 [$C(CH_3)_2$], 26.1 [$O(CH_2)_{10}CH_2CH_2CH_3$], 29.3/29.5/29.61/29.64/29.7 [$O(CH_2)_3(CH_2)_7(CH_2)_2CH_3$], 30.1 [$OCH_2CH_2(CH_2)_{10}CH_3$], 31.9 [$O(CH_2)_2CH_2(CH_2)_9CH_3$], 66.7 (C-4), 70.0 (C-1), 71.3 [$OCH_2(CH_2)_{11}CH_3$], 73.4 (OCH_2Ph), 75.4 (C-3), 79.5 (C-2), 109.0 [$C(CH_3)_2$], 127.5/128.3 (d, arom.), 138.3 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 457 $[M+Na]^+$. HRMS (FAB, pos.): calcd for $C_{27}H_{46}O_4Na$ 457.3294, found 457.3279.

4.2.2.6. With isobutyl bromide. In a similar manner, 1-*O*-benzyl-2-*O*-isobutyl-3,4-*O*-isopropylidene-D-erythritol (**14f**, 503 mg, 82%) was obtained from **12** (500 mg, 1.98 mmol). In this reaction, a excess amount of isobutyl bromide (5 equiv) and sodium hydride (2 equiv) were added thrice to the reaction mixture, because the E2 elimination of isobutyl bromide competed with the O-alkylation of **12**. Colorless oil, $[\alpha]_D^{23}$ +14.4 (*c* 1.02, $CHCl_3$). IR (neat): 1454, 1369, 1254, 1215, 1084, 1080, 1057 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.89/0.90 [each 3H, d, *J* = 6.6, $OCH_2CH(CH_3)_2$], 1.35/1.40 [each 3H, s, $C(CH_3)_2$], 1.83 [1H, triple hept., *J* = 6.6, 6.6, $OCH_2CH(CH_3)_2$], 3.23/3.47 [each 1H, dd, *J* = 8.9, 6.6, $OCH_2CH(CH_3)_3$], 3.45 (1H, ddd, *J* = 6.3, 5.2, 3.2, H-2), 3.55 (1H, dd, *J* = 10.3, 5.2, H-1a), 3.69 (1H, dd, *J* = 10.3, 3.2, H-1b), 3.94 (1H, dd, *J* = 8.3, 6.3, H-4a), 4.06 (1H, dd, *J* = 8.3, 6.3, H-4b), 4.16 (1H, ddd, *J* = 6.3, 6.3, 6.3, H-3), 4.55/4.58 (each 1H, d, *J* = 12.3, OCH_2Ph), 7.26–7.35 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.3/19.4 [$OCH_2CH(CH_3)_2$], 25.4/26.6 [$C(CH_3)_2$], 28.8 [$OCH_2CH(CH_3)_2$], 66.7 (C-4), 69.9 (C-1), 73.4 (OCH_2Ph), 75.5 (C-3), 78.0 [$OCH_2CH(CH_3)_2$], 79.7 (C-2), 109.0 [$C(CH_3)_2$], 127.51/127.54/128.3 (d, arom.), 138.4 (s, arom.). LRMS (FAB, pos.)

m/*z*: 331 [M+Na]$^+$. HRMS (FAB, pos.): calcd for $C_{18}H_{28}O_4Na$ 331.1885, found 331.1900.

4.2.2.7. With neopentyl bromide. In the presence of tetrabutylammonium iodide (738 mg, 2.0 mmol), **12** (800 mg, 3.71 mmol) was alkylated with neopentyl bromide (2.4 mL, 19 mmol) at 50 °C in DMF to give 1-*O*-benzyl-2-*O*-neopentyl-3,4-*O*-isopropylidene-D-erythritol (**14g**, 409 mg, 40%) as colorless oil, $[\alpha]_D^{23}$ +15.0 (*c* 1.05, $CHCl_3$). IR (neat): 1477, 1454, 1369, 1253, 1215, 1084, 1061, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.90 [9H, s, $OCH_2C(CH_3)_3$], 1.35/1.41 [each 3H, s, $C(CH_3)_2$], 3.13/3.35 [each 1H, d, *J* = 8.3, $OCH_2C(CH_3)_3$], 3.46 (1H, ddd, *J* = 6.3, 4.9, 3.2, H-2), 3.55 (1H, dd, *J* = 10.6, 4.9, H-1a), 3.68 (1H, dd, *J* = 10.6, 3.2, H-1b), 3.95 (1H, dd, *J* = 8.3, 6.3, H-4a), 4.05 (1H, dd, *J* = 8.3, 6.3, H-4b), 4.16 (1H, ddd, *J* = 6.3, 6.3, 6.3, H-3), 4.56 (2H, s, OCH_2Ph), 7.25–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.4/26.7 [$C(CH_3)_2$], 26.7 [$OCH_2C(CH_3)_3$], 32.2 [$OCH_2C(CH_3)_3$], 66.7 (C-4), 70.0 (C-1), 73.4 (OCH_2Ph), 75.6 (C-3), 79.9 (C-2), 81.5 [$OCH_2C(CH_3)_3$], 108.9 [$C(CH_3)_2$], 127.5/128.3 (d, arom.), 138.4 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 345 [M+Na]$^+$. HRMS (FAB, pos.): calcd for $C_{19}H_{30}O_4Na$ 345.2042, found 345.2052.

4.2.3. Hydrolysis of 2-*O*-alkylated 1-*O*-benzyl-3,4-*O*-isopropylidene-D-erythritols (14a–14g)

4.2.3.1. 1-*O*-Benzyl-2-*O*-methyl-D-erythritol (15a). A mixture of **14a** (2.0 g, 7.5 mmol), 1% hydrochloric acid (4 mL), and ethanol (6 mL) was heated under reflux for 30 min. After removal of the solvent, the residue was dissolved in ethanol (20 mL), and the resulting mixture was neutralized with ion exchange resin (IRA67). The resin was filtered off, and the filtrate was condensed to give an oil (2.0 g), which was triturated with *n*-hexane to give a practically pure title compound (**15a**, 1.63 g, 96%) as colorless oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.27 (2H, br s, OH), 3.446 (3H, s, OCH_3), 3.448 (1H, ddd, *J* = 5.2, 5.2, 4.6, H-2), 3.66 (1H, dd, *J* = 10.3, 4.6, H-1a), 3.69 (1H, dd, *J* = 10.3, 5.2, H-1b), 3.71 (2H, d-like, *J* = ca. 4.6, H-4a and H-4b), 3.83 (1H, dt, *J* = 5.2, 4.6, H-3), 4.55/4.58 (each 1H, d, *J* = 12.0, OCH_2Ph), 7.28–7.38 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 58.4 (OCH_3), 63.5 (C-4), 69.0 (C-1), 71.9 (C-3), 73.7 (OCH_2Ph), 80.6 (C-2), 127.8/127.9/128.6 (d, arom.), 137.5 (s, arom.).

4.2.3.2. 1-*O*-Benzyl-2-*O*-ethyl-D-erythritol (15b). In a similar manner, **14b** (2.1 g, 7.5 mmol) was hydrolyzed in a mixture of 1% hydrochloric acid (3 mL) and ethanol (6 mL). A similar work-up used for the preparation of **15a** gave a practically pure title compound (**15b**, 1.72 g, 96%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.19 (3H, t, *J* = 7.2, OCH_2CH_3), 2.37/2.90 (each 1H, br s, OH), 3.55/3.70 (each 1H, dq, *J* = 9.5, 7.2, OCH_2CH_3), 3.56 (1H, ddd-like, *J* = ca. 5.2, 5.2, 5.2, H-2), 3.64 (1H, dd, *J* = 10.0, 5.2, H-1a), 3.67 (1H, dd, *J* = 10.0, 5.2, H-1b), 3.72 (2H, d-like, *J* = ca. 4.3, H-4a and H-4b), 3.83 (1H, dt-like, *J* = ca. 5.2, 4.3, H-3), 4.55/4.58 (each 1H, d, *J* = 12.0, OCH_2Ph), 7.28–7.38 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.5 (OCH_2CH_3), 63.5 (C-4), 66.3 (OCH_2CH_3), 69.7 (C-1), 72.1 (C-3), 73.7 (OCH_2Ph), 78.9 (C-2), 127.7/127.9/128.5 (d, arom.), 137.6 (s, arom.).

4.2.3.3. 1-*O*-Benzyl-2-*O*-(pent-1-yl)-D-erythritol (15c). In a similar manner, **14c** (798 mg, 2.5 mmol) was hydrolyzed in a mixture of 1% hydrochloric acid (2 mL) and ethanol (3 mL). After being cooled, the reaction mixture was poured into water (25 mL), and the resulting mixture was neutralized by addition of sodium hydrogen carbonate and extracted with diethyl ether. The extract was washed with brine and condensed to give a practically pure title compound (**15c**, 610 mg, 87%) as colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J* = 6.9 Hz, $O(CH_2)_4CH_3$], 1.27–1.35 [4H, m, $OCH_2CH_2(CH_2)_2CH_3$], 1.52–1.59 [2H, m, $OCH_2CH_2(CH_2)_2CH_3$], 2.42 (1H, t, *J* = 6.0, OH), 2.93 (1H, d, *J* = 5.2, OH), 3.47/3.62 (each 1H, dt, *J* = 9.2, 6.9, $OCH_2(CH_2)_5CH_3$], 3.54 (1H, ddd, *J* = 5.5, 5.2, 5.2, H-2), 3.64 (1H, dd, *J* = 10.0, 5.5, H-1a), 3.66 (1H, dd, *J* = 10.0, 5.2, H-1b), 3.72 (2H, dd-like, *J* = ca. 6.0, 4.5, H-4a and H-4b), 3.81 (1H, ddt, *J* = 5.2, 5.2, 4.5, H-3), 4.55/4.57 (each 1H, d, *J* = 11.8, OCH_2Ph), 7.28–7.38 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0 [$O(CH_2)_4CH_3$], 22.5 [$O(CH_2)_3CH_2CH_3$], 28.2 [$O(CH_2)_2CH_2CH_2CH_3$], 29.7 [$OCH_2CH_2(CH_2)_2CH_3$], 63.5 (C-4), 69.6 (C-1), 71.1 [$OCH_2(CH_2)_5CH_3$], 72.1 (C-3), 73.6 (OCH_2Ph), 79.1 (C-2), 127.7/127.9/128.5 (d, arom.), 137.6 (s, arom.).

4.2.3.4. 1-*O*-Benzyl-2-*O*-(hept-1-yl)-D-erythritol (15d). In a similar manner, **14d** (637 mg, 1.82 mmol) was hydrolyzed in a mixture of 1% hydrochloric acid (2 mL) and ethanol (3 mL). A similar work-up used for the preparation of **15c** gave a practically pure title compound (**15d**, 553 mg, 98%) as colorless oil, ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0, $O(CH_2)_6CH_3$], 1.22–1.34 [8H m $O(CH_2)_2(CH_2)_4CH_3$], 1.51–1.58 [2H, m $OCH_2CH_2(CH_2)_4CH_3$], 2.38 (1H, t, *J* = 6.2, OH), 2.90 (1H, d, *J* = 5.4, OH), 3.46/3.62 (each 1H, dt, *J* = 9.2, 7.0, $OCH_2(CH_2)_5CH_3$], 3.54 (1H, ddd, *J* = 5.4, 5.3, 4.8, H-2), 3.64 (1H, dd, *J* = 10.0, 5.4, H-1a), 3.66 (1H, dd, *J* = 10.0, 4.8, H-1b), 3.72 (2H, dd-like, *J* = ca. 6.2, 4.5, H-4a and H-4b), 3.81 (1H, ddt, *J* = 5.4, 5.4, 4.5, H-3), 4.55/4.57 (each 1H, d, *J* = 12.0, OCH_2Ph), 7.28–7.37 (5H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_6CH_3$], 22.6 [$O(CH_2)_5CH_2CH_3$], 26.0 [$O(CH_2)_2CH_2(CH_2)_3CH_3$], 29.1 [$O(CH_2)_3CH_2(CH_2)_2CH_3$], 30.0 [$OCH_2CH_2(CH_2)_4CH_3$], 31.8 [$O(CH_2)_4CH_2CH_2CH_3$], 63.5 (C-4), 69.7 (C-1), 71.1 [$OCH_2(CH_2)_5CH_3$], 72.2 (C-3), 73.7 (OCH_2Ph), 79.2 (C-2), 127.7/127.9/128.5 (d, arom.), 137.6 (s, arom.).

4.2.3.5. 1-*O*-Benzyl-2-*O*-(tridec-1-yl)-D-erythritol (15e). In a similar manner, **14e** (950 mg, 2.19 mmol) was hydrolyzed in a mixture of 1% hydrochloric acid (3 mL) and ethanol (9 mL). A similar work-up used for the preparation of **15c** gave a practically pure title compound (**15e**, 818 mg, 95%) as colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0, $O(CH_2)_{12}CH_3$], 1.22–1.34 [20H m $O(CH_2)_2(CH_2)_{10}CH_3$], 1.50–1.59 [2H, m $OCH_2CH_2(CH_2)_{10}CH_3$], 2.37 (1H, br t, *J* = ca. 5.2, OH), 2.89 (1H, d, *J* = 5.2, OH), 3.46/3.62 (each 1H, dt, *J* = 9.2, 7.0, $OCH_2(CH_2)_{11}CH_3$], 3.54 (1H, ddd, *J* = 5.5, 5.2, 5.2, H-2), 3.64 (1H, dd, *J* = 10.0, 5.5, H-1a), 3.66 (1H, dd, *J* = 10.0, 5.2, H-1b), 3.72 (2H, dd-like, *J* = ca. 5.2, 5.2, H-4a and H-4b), 3.81 (1H, ddt, *J* = 5.2, 5.2, 5.2, H-3), 4.54/4.57 (each 1H, d, *J* = 12.0, OCH_2Ph), 7.28–7.37 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_{12}CH_3$], 22.6 [$O(CH_2)_{11}CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_9CH_3$], 29.3/29.4/29.57/29.59/29.64/29.67 [$O(CH_2)_3(CH_2)_7(CH_2)_2CH_3$], 30.0 [$OCH_2CH_2(CH_2)_{10}CH_3$], 31.9 [$O(CH_2)_{10}CH_2CH_2CH_3$], 63.5 (C-4), 69.7 (C-1), 71.1 [$OCH_2(CH_2)_{11}CH_3$], 72.1 (C-3), 73.7 (OCH_2Ph), 79.1 (C-2), 127.7/127.9/128.5 (d, arom.), 137.6 (s, arom.).

4.2.3.6. 1-*O*-Benzyl-2-*O*-isobutyl-D-erythritol (15f). In a similar manner, **14f** (352 mg, 1.14 mmol) was hydrolyzed in a mixture of 1% hydrochloric acid (1.3 mL) and ethanol (2 mL). A similar work-up used for the preparation of **15c** gave a practically pure title compound (**15f**, 294 mg, 96%) as colorless oil, ^{1}H NMR (800 MHz, $CDCl_3$) δ: 0.89/0.90 [each 3H, d, *J* = 6.4, $OCH_2CH(CH_3)_2$], 1.83 [1H, triple hept, *J* = 6.4, 6.4, $OCH_2CH(CH_3)_2$], 2.41 (1H, t, *J* = 5.6, OH), 2.93 (1H, d, *J* = 5.6, OH), 3.24/3.40 [each 1H, dd, *J* = 8.8, 6.4, $OCH_2CH(CH_3)_2$], 3.53 (1H, ddd, *J* = 6.4, 5.6, 4.8, H-2), 3.65 (1H, dd, *J* = 10.4, 5.6 H-1a), 3.67 (1H, dd, *J* = 10.4, 4.8, H-1b), 3.73 (2H, dd-like, *J* = 5.6, 4.8, H-4a and H-4b), 3.82 (1H, ddt, *J* = 6.4, 5.6, 4.8, H-3), 4.55/4.57 (each 1H, d, *J* = 12.0, OCH_2Ph), 7.30–7.37 (5H, m, arom.). ^{13}C NMR (200 MHz, $CDCl_3$) δ: 19.27/19.29 [$OCH_2CH(CH_3)_2$], 28.8 [$OCH_2CH(CH_3)_2$], 63.5 (C-4),

69.6 (C-1), 72.2 (C-3), 73.6 (OCH_2Ph), 77.8 [$OCH_2CH(CH_3)_2$], 79.3 (C-2), 127.7/127.9/128.5 (d, arom.), 137.6 (s, arom).

4.2.3.7. 1-*O*-Benzyl-2-*O*-neopentyl-D-erythritol (15g). In a similar manner, **14g** (161 mg, 0.5 mmol) was hydrolyzed in a mixture of 1% hydrochloric acid (0.5 mL) and ethanol (1 mL). A similar work-up used for the preparation of **15c** gave a practically pure title compound (**15g**, 121 mg, 86%) as colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.90 [9H, s, $OCH_2C(CH_3)_3$], 3.13/3.30 [each 1H, d, J = 8.6, $OCH_2C(CH_3)_3$], 3.54 (1H, ddd, J = 5.8, 5.8, 4.6, H-2), 3.64 (1H, dd, J = 10.1, 5.8 H-1a), 3.67 (1H, dd, J = 10.1, 4.6, H-1b), 3.74 (2H, d-like, J = ca. 4.6, H-4a and H-4b), 3.83 (1H, dt, J = 5.8, 4.6, H-3), 4.56 (2H, s-like, OCH_2Ph), 7.28–7.38 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.6 [$OCH_2C(CH_3)_3$], 32.1 [$OCH_2C(CH_3)_3$], 63.5 (C-4), 69.6 (C-1), 72.3 (C-3), 73.7 (OCH_2Ph), 79.6 (C-2), 81.4 [$OCH_2C(CH_3)_3$], 127.7/127.9/128.5 (d, arom.), 137.6 (s, arom).

4.2.4. Epoxydation of diols (15a–15g)

4.2.4.1. 3,4-Anhydro-1-*O*-benzyl-2-*O*-methyl-D-erythritol (10a). To a mixture of **15a** (1.51 g, 6.7 mmol), triphenylphosphine (2.1 g, 8.0 mmol), and toluene (10 mL) was added dropwise 40% solution of diethyl azodicarboxylate (DEAD) in toluene (3.9 mL, 8.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min and heated under reflux for further 4 h. After removal of the solvent, the residue was triturated with a 1:1 mixture of diethyl ether and *n*-hexane. The deposited solid was filtered off, and the filtrate was condensed to give an orange oil (2.61 g), which on column chromatography (petroleum ether–AcOEt, 20:1→10:1) gave the title compound (**10a**, 1.07 g, 77%), as colorless oil, $[\alpha]_D^{24}$ +11.2 (c 1.08, $CHCl_3$). IR (neat): 1454, 1366, 1335, 1249, 1200, 1099 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.77 (1H, dd, J = 5.2, 2.9, H-4a), 2.83 (1H, dd, J = 5.2, 4.0, H-4b), 3.05 (1H, ddd, J = 5.5, 4.0, 2.9, H-3), 3.26 (1H, ddd, J = 5.5, 5.5, 4.0, H-2), 3.45 (3H, s, OCH_3), 3.61 (1H, dd, J = 10.4, 5.5, H-1a), 3.66 (1H, dd, J = 10.4, 4.0, H-1b), 4.59 (2H, s-like, OCH_2Ph), 7.26–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 45.5 (C-4), 50.9 (C-3), 58.4 (OCH_3), 70.2 (C-1), 73.5 (OCH_2Ph), 79.7 (C-2), 127.6/128.4 (d, arom.), 138.0 (s, arom.). LRMS (FAB, pos.) m/z: 231 [M+Na]$^+$. HRMS (FAB, pos.): calcd for $C_{12}H_{16}O_3Na$ 231.0997, found 231.0969.

4.2.4.2. 3,4-Anhydro-1-*O*-benzyl-2-*O*-ethyl-D-erythritol (10b). In a similar manner, **15b** (1.36 g, 5.7 mmol) was subjected to the epoxidation. Work-up and column chromatography (petroleum ether–AcOEt, 20:1→10:1) gave the title compound (**10b**, 956 mg, 76%) as colorless oil, $[\alpha]_D^{24}$ +6.0 (c 1.20, $CHCl_3$). IR (neat): 1456, 1364, 1325, 1252, 1101 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.20 (3H, t, J = 7.0, OCH_2CH_3), 2.77 (1H, dd, J = 5.5, 2.8, H-4a), 2.81 (1H, dd, J = 5.5, 4.0, H-4b), 3.06 (1H, ddd, J = 5.4, 4.0, 2.8, H-3), 3.37 (1H, ddd, J = 5.4, 5.4, 4.2, H-2), 3.59/3.65 (each 1H, dt, J = 9.2, 7.0, OCH_2CH_3), 3.61 (1H, dd, J = 10.2, 5.4, H-1a), 3.64 (1H, dd, J = 10.2, 4.2, H-1b), 4.59 (2H, s-like, OCH_2Ph), 7.27–7.35 (5H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 15.5 (OCH_2CH_3), 45.5 (C-4), 51.3 (C-3), 66.2 (OCH_2CH_3), 70.6 (C-1), 73.5 (OCH_2Ph), 78.0 (C-2), 127.6/128.3 (d, arom.), 138.2 (s, arom.). LRMS (FAB, pos.) m/z: 245 [M+Na]$^+$. HRMS (FAB, pos.): calcd for $C_{13}H_{18}O_3Na$ 245.1154, found 245.1173.

4.2.4.3. 3,4-Anhydro-1-*O*-benzyl-2-*O*-(pent-1-yl)-D-erythritol (10c). In a similar manner, **15c** (600 mg, 2.12 mmol) was subjected to the epoxidation. Work-up and column chromatography (*n*-hexane–AcOEt, 50:1→25:1) gave the title compound (**10c** 460 mg, 82%) as colorless oil, $[\alpha]_D^{22}$ +6.4 (c 1.02, $CHCl_3$). IR (neat): 1454, 1366, 1342, 1254, 1207, 1099, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 [3H, t, J = 6.9, $O(CH_2)_4CH_3$), 1.27–1.36 [4H, m, $O(CH_2)_2(CH_2)_2CH_3$], 1.52–1.61 [2H, m, $OCH_2CH_2(CH_2)_2CH_3$], 2.77 (1H, dd, J = 5.4, 2.6, H-4a), 2.80 (1H dd, J = 5.4, 3.7, H-4b), 3.05 (1H,ddd, J = 5.2, 3.7, 2.6, H-3), 3.36 (1H, ddd, J = 5.5, 5.2, 4.3, H-2), 3.51/3.58 [each 1H, dt, J = 9.2, 6.9, $OCH_2(CH_2)_3CH_3$], 3.61 (1H dd J = 10.3, 5.5, H-1a), 3.64 (1H, dd, J = 10.3, 4.3, H-1b), 4.59 (2H, s, OCH_2Ph), 7.25–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0 [$O(CH_2)_4CH_3$], 22.5 [$O(CH_2)_3CH_2CH_3$], 28.2 [$O(CH_2)_2CH_2CH_2CH_3$], 29.7 [$OCH_2CH_2(CH_2)_2CH_3$], 45.4 (C-4), 51.3 (C-3), 70.6 (C-1), 71.0 [$OCH_2(CH_2)_3CH_3$], 73.4 (OCH_2Ph), 78.1 (C-2), 127.6/128.3 (d, arom.), 138.2 (s, arom). LRMS (FAB, pos.) m/z: 287 [M+Na]$^+$. HRMS (FAB, pos.): calcd for $C_{16}H_{24}O_3Na$ 287.1623, found 287.1628.

4.2.4.4. 3,4-Anhydro-1-*O*-benzyl-2-*O*-(hept-1-yl)-D-erythritol (10d). In a similar manner, **15d** (544 mg, 1.75 mmol) was subjected to the epoxidation. Work-up and column chromatography (*n*-hexane–AcOEt, 50:1→25:1) gave the title compound (**10d**, 435 mg, 85%) as a colorless oil, $[\alpha]_D^{25}$ +4.7 (c 0.93, $CHCl_3$). IR (neat): 1454, 1366, 1254, 1099, 1030 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 6.9, $O(CH_2)_6CH_3$], 1.22–1.35 [8H, m $O(CH_2)_2(CH_2)_4CH_3$], 1.53–1.59 [2H, m $OCH_2CH_2(CH_2)_4CH_3$], 2.77 (1H, dd J = 5.4, 2.6 H-4a), 2.81 (1H, dd, J = 5.4, 4.0, H-4b), 3.05 (1H, ddd, J = 5.2, 4.0, 2.6, H-3), 3.36 (1H, ddd, J = 5.4, 5.2, 4.2, H-2), 3.51/3.57 [each 1H, dt, J = 9.2, 6.9, $OCH_2(CH_2)_5CH_3$], 3.61 (1H, dd J = 10.2, 5.4, H-1a), 3.64 (1H, dd, J = 10.2, 4.2, H-1b), 4.58 (2H, s-like, OCH_2Ph), 7.26–7.36 (5H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_6CH_3$], 22.6 [$O(CH_2)_5CH_2CH_3$], 26.0 [$O(CH_2)_2CH_2(CH_2)_3CH_3$], 29.1 [$O(CH_2)_3CH_2CH_2CH_3$], 30.0 [$OCH_2CH_2(CH_2)_4CH_3$], 31.8 [$O(CH_2)_4CH_2CH_2CH_3$], 45.4 (C-4), 51.4 (C-3), 70.6 (C-1), 71.0 [$OCH_2(CH_2)_5CH_3$], 73.5 (OCH_2Ph), 78.1 (C-2), 127.6/128.4 (d, arom.), 138.2 (s, arom.). LRMS (FAB, pos.) m/z: 315 [M+Na]$^+$. HRMS (FAB, pos.): calcd for $C_{18}H_{28}O_3Na$ 315.1936, found 315.1924.

4.2.4.5. 3,4-Anhydro-1-*O*-benzyl-2-*O*-(tridec-1-yl)-D-erythritol (10e). In a similar manner, **15e** (1.0 g, 2.5 mmol) was subjected to epoxidation. Work-up and column chromatography (*n*-hexane–AcOEt, 50:1→30:1) gave the title compound (**10e** 772 mg, 81%) as colorless oil, $[\alpha]_D^{24}$ +11.4 (c 0.94 $CHCl_3$). IR (neat): 1466, 1456, 1364, 1250, 1101, 1028 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 7.0, $O(CH_2)_{12}CH_3$], 1.22–1.34 [20H m $O(CH_2)_2(CH_2)_{10}CH_3$], 1.53–1.59 [2H, m $OCH_2CH_2(CH_2)_{10}CH_3$], 2.76 (1H, dd, J = 5.4, 2.8, H-4a), 2.80 (1H, dd, J = 5.4, 4.0, H-4b), 3.05 (1H, ddd, J = 5.2, 4.0, 2.8, H-3), 3.36 (1H, ddd, J = 5.4, 5.2, 4.2, H-2), 3.50/3.57 [each 1H, dt, J = 9.2, 7.0, $OCH_2(CH_2)_{11}CH_3$], 3.61 (1H, dd, J = 10.2, 5.4, H-1a), 3.64 (1H, dd, J = 10.2, 4.2, H-1b), 4.59 (2H, s-like, OCH_2Ph), 7.26–7.36 (5H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_{12}CH_3$], 22.7 [$O(CH_2)_{11}CH_2CH_3$], 26.0 [$O(CH_2)_2CH_2(CH_2)_9CH_3$], 29.3/29.5/29.61/29.63/29.65/29.67 [$O(CH_2)_3(CH_2)_7(CH_2)_2CH_3$], 30.0 [$OCH_2CH_2(CH_2)_{10}CH_3$], 31.9 [$O(CH_2)_{10}CH_2CH_2CH_3$], 45.4 (C-4), 51.4 (C-3), 70.6 (C-1), 71.0 [$OCH_2(CH_2)_{11}CH_3$], 73.5 (OCH_2Ph), 78.1 (C-2), 127.6/128.4 (d, arom.), 138.2 (s, arom.). LRMS (FAB, pos.) m/z: 399 [M+Na]$^+$. HRMS (FAB, pos.): calcd for $C_{24}H_{40}O_3Na$ 399.2875, found 399.2896.

4.2.4.6. 3,4-Anhydro-1-*O*-benzyl-2-*O*-isobutyl-D-erythritol (10f). In a similar manner, **15f** (150 mg, 0.56 mmol) was subjected to the epoxidation. Work-up and column chromatography (*n*-hexane–AcOEt, 100:1→25:1) gave the title compound (**10f**, 115 mg, 82%) as colorless oil, $[\alpha]_D^{23}$ +9.0 (c 0.66, $CHCl_3$). IR (neat): 1470, 1454, 1366, 1096, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89/0.90 [each 3H, d, J = 6.6, $OCH_2CH(CH_3)_2$], 1.84 [1H, triple hept., J = 6.6, 6.6, $OCH_2CH(CH_3)_2$], 2.77 (1H, dd, J = 5.4, 2.6, H-4a), 2.80 (1H, dd, J = 5.4, 4.0, H-4b), 3.06 (1H, ddd, J = 5.2, 4.0, 2.6, H-3), 3.28/3.34 [each 1H, d, J = 8.9, 6.6, $OCH_2CH(CH_3)_2$], 3.37 (1H, ddd, J = 5.2, 5.2, 4.3, H-2), 3.61 (1H, dd, J = 10.3, 5.2, H-1a), 3.64 (1H, dd, J = 10.3, 4.3, H-1b), 4.59 [2H, s-like, OCH_2Ph], 7.26–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.3 [$OCH_2CH(CH_3)_2$], 28.8 [$OCH_2CH(CH_3)_2$], 45.3 (C-4), 51.4 (C-3), 70.6 (C-1), 73.5

(OCH_2Ph), 77.8 [$OCH_2CH(CH_3)_2$] 78.2 (C-2), 127.6/128.4 (d, arom.), 138.2 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 273 $[M+Na]^+$. HRMS (FAB, pos.): calcd for $C_{15}H_{22}O_3Na$ 273.1467, found 273.1445.

4.2.4.7. 3,4-Anhydro-1-*O*-benzyl-2-*O*-neopentyl-D-erythritol (10g). In a similar manner, **15g** (110 mg, 0.39 mmol) was subjected to the epoxidation. Work-up and column chromatography (*n*-hexane–AcOEt, 100:1→20:1) gave the title compound (**10g**, 92 mg, 89%) as colorless oil, $[\alpha]_D^{23}$ +11.2 (*c* 0.99, $CHCl_3$). IR (neat): 2955, 2866, 1454, 1362, 1258, 1099, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 [9H, s, $OCH_2C(CH_3)_3$], 2.79 (2H, d-like, *J* = 3.4, H-4a and H-4b), 3.06 (1H, dt, *J* = 4.9, 3.4 H-3), 3.16 [each 1H, d, *J* = 8.6, $OCH_2C(CH_3)_3$], 3.40 (1H, ddd, *J* = 4.9, 4.9, 4.9, H-2), 3.61 (1H, dd, *J* = 10.8, 4.9, H-1a), 3.64 (1H, dd, *J* = 10.8, 4.9, H-1b), 4.59 [2H, s-like, OCH_2Ph], 7.25–7.36 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.7 [$OCH_2C(CH_3)_3$], 32.2 [$OCH_2C(CH_3)_3$], 45.0 (C-4), 51.7 (C-3), 70.7 (C-1), 73.4 (OCH_2Ph), 78.4 (C-2), 81.5 [$OCH_2C(CH_3)_3$], 127.5/127.6/128.4 (d, arom.), 138.3 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 287 $[M+Na]^+$. HRMS (FAB, pos.): calcd for $C_{16}H_{24}O_3Na$ 287.1623, found 287.1635.

4.2.5. *S*-Alkylation of reaction of thiosugar (9) with epoxides (10a–10g)

4.2.5.1. 2,3,5-Tri-*O*-benzyl-1,4-{(*R*)-[1-*O*-benzyl-4-deoxy-3-*O*-methyl-D-erythritol-4-yl]episulfoniumylidene}-1,4-dideoxy-D-arabinitol chloride (α-16a). To a mixture of epoxide **10a** (100 mg, 0.48 mmol), thiosugar **9** (168 mg, 0.4 mmol), and CH_2Cl_2 (2 mL) was added tetrafluoroboric acid dimethyl ether complex ($HBF_4{\cdot}(CH_3)_2O$, 63 μL, 0.52 mmol) at −60 °C. The reaction mixture was stirred for 3 h and concentrated in vacuo. The residue was treated with ion exchange resin IRA-400J (Cl^- form) in methanol (3 mL) at room temperature. The resin was filtered off, and the filtrate was concentrated to give a colorless oil (290 mg), which on column chromatography ($CHCl_3$ → $CHCl_3$–MeOH, 100:1→50:1) gave the title compound (**α-16a**, 191 mg, 72%) and a mixture of α and β-isomers (77 mg). Re-purification of the mixture by column chromatography gave **α-16a** (43 mg, 16%). Colorless oil. $[\alpha]_D^{24}$ −7.3 (*c* 0.65, $CHCl_3$). IR (neat): 3174, 1454, 1404, 1365, 1261, 1095, 1072, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.41 (3H, s, OCH_3), 3.67 (1H, dd-like, *J* = ca. 11.5, 2.5, H-4′a), 3.68 (1H, ddd-like, *J* = ca. 6.0, 3.8, 2.5, H-3′), 3.76 (2H, d-like, *J* = ca. 8.0, H-5a and H-5b), 3.80 (1H, dd, *J* = 11.5, 3.8, H-4′b), 4.10 (1H, dd, *J* = 12.6, 3.7, H-1′a), 4.11–4.15 (2H, m, H-1a and H-4), 4.15 (1H, dd-like, *J* = ca. 12.6, 7.4, H-1′b), 4.17 (1H, m, H-3), 4.31 (1H, dd, *J* = 13.2, 3.8, H-1b), 4.34–4.39 (1H, m, H-2′), 4.39–4.41 (1H, m, H-2), 4.39 (1H, d, *J* = 11.7, OCH_2Ph), 4.47–4.61 (7H, m, OCH_2Ph), 6.65 (1H, br s, OH), 7.13–7.37 (20H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 48.4 (C-1), 51.9 (C-1′), 57.9 (OCH_3), 66.1 (C-4), 66.9 (C-5), 67.4 (C-4′), 68.1 (C-2′), 71.9/72.3/73.6(2xC) (OCH_2Ph), 82.0 (C-3′), 82.3 (C-3), 82.4 (C-2), 127.7/127.8/127.96/127.99/128.2/128.3/128.4/128.5/128.56/128.6/128.7/128.8 (d, arom), 135.8/136.0/136.7/ 137.9 (arom). LRMS (FAB, pos.) *m*/*z*: 629 $[M-Cl]^+$ (pos.).

4.2.5.2. 2,3,5-Tri-*O*-benzyl-1,4-{(*R*)-[1-*O*-benzyl-4-deoxy-3-*O*-ethyl-D-erythritol-4-yl]episulfoniumylidene}-1,4-dideoxy-D-arabinitol chloride (α-16b). In a similar manner, title compound (**α-16b**, 186 mg, 73%) was obtained by the *S*-alkylation of thiosugar **9** (158 mg, 0.38 mmol) with epoxide **10b** (100 mg, 0.45 mmol) as colorless oil, $[\alpha]_D^{24}$ −8.8 (*c* 1.02, $CHCl_3$). IR (neat): 3186, 1497, 1454, 1400, 1366, 1327, 1257, 1207, 1099, 1072, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.15 (3H, t, *J* = 7.0, OCH_2CH_3), 3.56/3.70 (each 1H, dq-like, *J* = 9.2, 7.0, OCH_2CH_3), 3.67 (1H, dd-like, *J* = ca. 10.6, 2.0, H-4′a), 3.74 (1H, dd-like, *J* = ca. 10.6, 2.6, H-4′b), 3.72–3.76 (1H, m, H-3′), 3.78 (2H, d-like, *J* = 7.5, H-5a and H-5b), 4.07 (1H, br d-like, *J* = ca. 13.2, H-1a), 4.13 (1H, br dd-like, *J* = ca. 13.0, 3.5, H-1′a), 4.13–4.17 (1H, m, H-4), 4.17 (1H, dd-like, *J* = ca. 13.0, 7.8, H-1′b), 4.19 (1H, br s-like, H-3), 4.31 (1H, dd-like, *J* = ca. 13.2, 3.2, H-1b), 4.33–4.37 (1H, m, H-2′), 4.39 (1H, d, *J* = 11.8, OCH_2Ph), 4.37–4.41 (1H, m, H-2), 4.43–4.62 (7H, m, OCH_2Ph), 6.57 (1H, br s, OH), 7.12–7.36 (20H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.5 (OCH_2CH_3), 48.3 (C-1), 51.8 (C-1′), 65.8 (C-4), 66.0 (OCH_2CH_3), 67.0 (C-5), 68.0 (C-2′), 68.5 (C-4′), 71.9/72.2/73.5/73.6 (OCH_2Ph), 80.4 (C-3′), 82.4 (C-3), 82.5 (C-2), 127.6/127.8/127.9/128.1/128.2/128.3/128.4/128.47/128.54/128.68/128.72/128.83 (d, arom.), 135.9/136.0/136.7/137.9 (s, arom.). LRMS (FAB, pos.) (pos.) *m*/*z*: 643 $[M-Cl]^+$.

4.2.5.3. 2,3,5-Tri-*O*-benzyl-1,4-{(*R*)-[1-*O*-benzyl-4-deoxy-3-*O*-(pent-1-yl)-D-erythritol-4-yl]episulfoniumylidene}-1,4-dideoxy-D-arabinitol chloride (α-16c). In a similar manner, title compound (**α-16c**, 242 mg, 71%) was obtained by the *S*-alkylation of thiosugar **9** (200 mg, 0.48 mmol) with epoxide **10c** (150 mg, 0.57 mmol) as colorless oil, $[\alpha]_D^{23}$ −6.4 (*c* 0.96, $CHCl_3$). IR (neat): 3167, 1497, 1454, 1400, 1362, 1207, 1096, 1030 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$) δ: 0.87 [3H, t, *J* = 7.0, $O(CH_2)_4CH_3$], 1.23–1.32 [4H m $O(CH_2)_2(CH_2)_2CH_3$], 1.48–1.56 [2H, m, $OCH_2CH_2(CH_2)_2CH_3$], 3.48/3.61 [each 1H, dt, *J* = 9.2, 7.0, $OCH_2(CH_2)_3CH_3$], 3.67 (1H dd, *J* = 11.4, 3.9, H-4′a), 3.74 (1H, br dd-like, *J* = ca. 6.0, 3.9, H-3′), 3.75 (1H, br d-like, *J* = ca. 11.4, H-4′b), 3.77 (2H, d-like, *J* = 7.4, H-5a and H-5b), 4.07 (1H, br d, *J* = 13.2, H-1a), 4.13 (1H, dd,, *J* = 13.0, 4.0, H-1′a), 4.14–4.18 (1H, m, H-4), 4.17 (1H, dd-like, *J* = *ca*, 13.0, 7.8, H-1′b), 4.19 (1H, br s-like, H-3), 4.31 (1H, dd, *J* = 13.2, 3.4, H-1b), 4.34–4.38 (1H, m, H-2′), 4.38–4.40 (1H, br m, H-2), 4.38–4.61 (8H, m, OCH_2Ph), 6.60 (1H, br s, OH), 7.23–7.36 (20H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.0 [$O(CH_2)_4CH_3$], 22.4 [$O(CH_2)_3CH_2CH_3$], 28.1 [$O(CH_2)_2CH_2CH_2CH_3$], 29.6 [$OCH_2CH_2(CH_2)_2CH_3$], 48.2 (C-1), 51.9 (C-1′), 65.9 (C-4), 67.0 (C-5), 68.1 (C-2′), 68.4 (C-4′), 70.8 [$OCH_2(CH_2)_3CH_3$], 71.9/72.3/73.6/73.6 (OCH_2Ph), 80.7 (C-3′), 82.4 (C-3), 82.5 (C-2), 127.7/127.8/127.9/128.0/128.2/128.3/128.4/128.49/128.54/128.6/128.7/128.8 (d, arom.), 135.9/136.0/136.7/138.0 (s, arom). LRMS (FAB, pos.) *m*/*z*: 685 $[M-Cl]^+$.

4.2.5.4. 2,3,5-Tri-*O*-benzyl-1,4-{(*R*)-[1-*O*-benzyl-4-deoxy-3-*O*-(hept-1-yl)-D-erythritol-4-yl]episulfoniumylidene}-1,4-dideoxy-D-arabinitol chloride (α-16d). In a similar manner, title compound (**α-16d**, 192 mg, 69%) was obtained by the *S*-alkylation of thiosugar **9** (156 mg, 0.37 mmol) with epoxide **10d** (130 mg, 0.45 mmol) as colorless oil, $[\alpha]_D^{23}$ −15.0 (*c* 1.32, $CHCl_3$). IR (neat): 3167, 1454, 1404, 1362, 1207, 1096, 1030 cm^{-1}. H NMR (700 MHz, $CDCl_3$) δ: 0.87 (3H, t, *J* = 7.0, $O(CH_2)_6CH_3$], 1.21–1.31 [8H, m $O(CH_2)_2(CH_2)_4CH_3$], 1.47–1.55 [2H, m $OCH_2CH_2(CH_2)_4CH_3$], 3.49/3.60 [each 1H, dt, *J* = 9.2, 7.0, $OCH_2(CH_2)_5CH_3$], 3.67 (1H, dd-like, *J* = ca. 11.0, 3.8, H-4′a), 3.72–3.76 (1H, m, H-3′), 3.75 (1H dd-like, *J* = ca. 11.0, 3.5, H-4′b), 3.77 (2H, d-like, *J* = 7.4, H-5a and H-5b), 4.07 (1H, br d, *J* = ca. 13.2, H-1a), 4.13 (1H, dd-like, *J* = ca. 13.5, 3.8, H-1′a), 4.15–4.18 (1H, m, H-4), 4.16 (1H, dd, *J* = 13.5, 7.5, H-1′b), 4.19 (1H, br s-like, H-3), 4.30 (1H, dd, *J* = 13.2, 3.2, H-1b), 4.34–4.37 (1H, m, H-2′), 4.38 (1H, m. H-2), 4.38/4.47 (each 1H, d, *J* = 11.6, OCH_2Ph), 4.48–4.61 (6H, m, OCH_2Ph), 6.58 (1H, d, *J* = 7.2, OH), 7.13–7.36 (20H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_6CH_3$], 22.6 [$O(CH_2)_5CH_2CH_3$], 26.0 [$O(CH_2)_2CH_2(CH_2)_3CH_3$], 29.1 [$O(CH_2)_3CH_2CH_2CH_3$], 30.0 [$OCH_2CH_2(CH_2)_4CH_3$], 31.8 [$O(CH_2)_4CH_2CH_2CH_3$], 48.2 (C-1), 52.0 (C-1′), 65.9 (C-4), 67.0 (C-5), 68.1 (C-2′), 68.5 (C-4′), 70.9 [$OCH_2(CH_2)_5CH_3$], 71.9/72.3/73.58/73.63 (OCH_2Ph), 80.7 (C-3′), 82.45 (C-3), 82.51 (C-2), 127.7/127.8/127.9/128.0/128.2/128.3/128.4/128.50/128.54/128.6/128.7/128.8 (d, arom.), 135.9/136.0/136.7/138.0 (s, arom). LRMS (FAB, pos.) *m*/*z*:713 $[M-Cl]^+$.

4.2.5.5. 2,3,5-Tri-*O*-benzyl-1,4-{(*R*)-[1-*O*-benzyl-4-deoxy-3-*O*-(tridec-1-yl)-D-erythritol-4-yl]episulfoniumylidene}-1,4-dideoxy-D-arabinitol chloride (16e). In a similar manner, title compound (**α-16e**, 135 mg, 73%) was obtained by the *S*-alky-

lation of thiosugar **9** (93 mg, 0.22 mmol) with epoxide **10e** (100 mg, 0.27 mmol) as colorless oil. Small amount of a sample of minor β-isomer β-**16e** suitable for NMR analysis was obtained with a purity of >ca. 90% from the later chromatographic fractions.

The major isomer α-**16e**: $[\alpha]_D^{24}$ −3.9 (*c* 0.96 $CHCl_3$). IR (neat): 3333, 1456, 1361, 1096, 1074, 1028 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 [3H, t, *J* = 7.0, $O(CH_2)_{12}CH_3$], 1.21–1.31 [20H, m, $O(CH_2)_2(CH_2)_{10}CH_3$], 1.46–1.58 [2H, m, $OCH_2CH_2(CH_2)_{10}CH_3$], 3.48/3.60 [each 1H, dt, *J* = 9.2, 7.0, $OCH_2CH_2(CH_2)_{10}CH_3$], 3.67 (1H, dd-like, *J* = 11.4, 4.0, H-4′a), 3.72–3.76 (1H, m, H-3′), 3.74 (1H, dd, *J* = 11.4, 3.6, H-4′b), 3.77 (2H, d-like, *J* = 7.4, H-5a and H-5b), 4.07 (1H, dd, *J* = 13.4, 2.0, H-1a), 4.13 (1H, dd-like, *J* = ca. 13.0, 4.0, H-1′a), 4.13–4.18 (1H, m, H-4), 4.17 (1H, dd-like, *J* = ca. 13.0, 7.0, H-1′b), 4.19 (1H, br m, H-3), 4.31 (1H, dd, *J* = 13.4, 3.8, H-1b), 4.33–4.37 (1H, m, H-2′), 4.37–4.41 (1H, m, H-2), 4.39 (1H, d, *J* = 11.8, OCH_2Ph), 4.44–4.60 (8H, m, OCH_2Ph), 6.60 (1H, d, *J* = 7.2, OH), 7.14–7.35 (20H, m, arom). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_{12}CH_3$], 22.7 [$O(CH_2)_{11}CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_9CH_3$], 29.3/29.5/29.6/29.7 [$O(CH_2)_3(CH_2)_7(CH_2)_2CH_3$], 30.0 [$OCH_2CH_2(CH_2)_{10}CH_3$], 31.9 [$O(CH_2)_{10}CH_2CH_2CH_3$], 48.2 (C-1), 51.9 (C-1′), 65.9 (C-4), 67.0 (C-5), 68.1 (C-2′), 68.4 (C-4′), 70.9 [$OCH_2(CH_2)_{11}CH_3$], 71.9/72.3/73.56/73.60 (OCH_2Ph), 80.7 (C-3′), 82.4 (C-3), 82.5 (C-2), 127.6/127.8/127.9/128.0/128.2/1283/128.4/128.50/128.54/128.6/128.7/128.8 (d, arom), 135.8/136.0/136.7/138.0 (4C, s, arom). LRMS (FAB, pos.) *m*/*z*: 797 $[M-Cl]^+$.

The minor isomer β-**16e**: ^1H NMR (700 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0, $O(CH_2)_{12}CH_3$], 1.22–1.34 [20H m $O(CH_2)_2(CH_2)_{10}CH_3$], 1.45–1.50 [2H, m $OCH_2CH_2(CH_2)_{10}CH_3$], 3.47/3.61 [each 1H, dt, *J* = 9.4, 7.0, $OCH_2CH(CH_3)_2$], 3.57 (1H, dd, *J* = 10.6, 4.2, H-4′a), 3.66 (1H, ddd-like, *J* = ca. 5.6, 4.2, 3.2, H-3′), 3.71 (1H, dd, *J* = 10.6, 3.2, H-4′b), 3.72–3.76 (1H, m, H-1a), 3.75 (1H, dd, *J* = 10.4, 5.8, H-5a), 3.85 (1H, dd, *J* = 10.4, 8.6, H-5b), 3.88 (1H, dd, *J* = 12.4, 5.8, H-1′a), 4.06 (1H, dd, *J* = 12.4, 3.8, H-1′b), 4.13 (1H ddd-like, *J* = ca. 8.6, 5.8, 2.0, H-4), 4.22 (1H, br s-like, H-3), 4.34/4.43 (each 1H, d, *J* = 11.8, OCH_2Ph), 4.38 (1H, br s-like, H-2), 4.44/4.48 (each 1H, d, *J* = 12.0, OCH_2Ph), 4.43–4.46 (1H, m, H-2′), 4.44 (2H, s, OCH_2Ph), 4.52/4.80 (each 1H, d, *J* = 12.0, OCH_2Ph), 4.75 (1H, d, *J* = 14.6, H-1b), 7.13–7.36 (20H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 14.1 [$O(CH_2)_{12}CH_3$], 22.7 [$O(CH_2)_{11}CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_9CH_3$], 29.3/29.5/29.6/29.7, [$O(CH_2)_3(CH_2)_7(CH_2)_2CH_3$], 30.1 [$OCH_2CH_2(CH_2)_{10}CH_3$], 31.9 [$O(CH_2)_{10}CH_2CH_2CH_3$], 42.9 (C-1′), 45.3 (C-1), 60.8 (C-4), 65.3 (C-5), 66.3 (C-2′), 69.6 (C-4′), 71.0 [$OCH_2(CH_2)_{11}CH_3$], 72.2/72.3/73.4/73.5 (OCH_2Ph), 80.6 (C-3′), 82.5 (C-2), 84.6 (C-3), 127.6/127.7/127.97/128.01/128.3/12 8.39/12 8.42/128.6/128.65/128.71128.8 (d, arom.), 135.9/136.1/136.3/138.1 (s, arom.). LRMS (FAB, pos.) *m*/*z*: 797 $[M-Cl]^+$.

4.2.5.6. 2,3,5-Tri-*O*-benzyl-1,4-{(*R*)-[1-*O*-benzyl-4-deoxy-3-*O*-isobutyl-D-erythritol-4-yl]episulfoniumylidene}-1,4-dideoxy-D-arabinitol chloride (α-16f).

In a similar manner, title compound (α-**16f**, 135 mg, 73%) was obtained by the *S*-alkylation of thiosugar **9** (110 mg, 0.26 mmol) with epoxide **10f** (78 mg, 0.31 mmol) as a colorless oil, $[\alpha]_D^{20}$ −9.3 (*c* 0.98, $CHCl_3$). IR (neat): 3152, 1497, 1454, 1400, 1366, 1327, 1254, 1207, 1177, 1092, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.84/0.85 [each 3H, d, *J* = 6.6, $OCH_2CH(CH_3)_2$], 1.78 [1H, triple hept., *J* = 6.6, 6.6, $OCH_2CH(CH_3)_2$], 3.23/3.39 [each 1H, dd, *J* = 9.2, 6.6, $OCH_2C(CH_3)_3$], 3.67 (1H, dd-like, *J* = ca. 10.5, 2.0, H-4′a), 3.70–3.75 (1H, m, H-3′), 3.73–3.77 (1H, m, H-4′b), 3.77 (2H, d-like, *J* = ca. 7.2, H-5a and H-5b), 4.10 (1H, br d-like, *J* = ca. 13.0, H-1a), 4.09–4.17 (3H, m, H-1′a, H-1′b and H-4), 4.18 (1H, br s-like, H-3), 4.31 (1H, br d-like, *J* = ca. 13.0, H-1b), 4.34–4.40 (1H, m, H-2′), 4.40/4.49 (each 1H, d, *J* = 12.1, OCH_2Ph), 4.41 (1H, m, H-2), 4.52–4.60 (6H, m, OCH_2Ph), 7.14–7.36 (20H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.3/19.4 [$OCH_2CH(CH_3)_2$], 28.6 [$OCH_2CH(CH_3)_2$], 48.2 (C-1), 51.9 (C-1′), 66.0 (C-4), 67.0 (C-5), 68.1 (C-2′), 68.3 (C-4′), 71.9/72.4/73.5/73.6 (OCH_2Ph), 77.4 [$OCH_2C(CH_3)_3$], 80.9 (C-3′), 82.4 (C-2 and C-3), 127.6/127.8/128.0/128.2/128.26/128.34/128.49/128.53/128.6/128.7/128.8 (d, arom.), 135.8/136.0/136.7/138.0 (s, arom). LRMS (FAB, pos.) *m*/*z*: 671 $[M-Cl]^+$ (pos.).

4.2.5.7. 2,3,5-Tri-*O*-benzyl-1,4-{(*R*)-[1-*O*-benzyl-4-deoxy-3-*O*-neopentyl-D-erythritol-4-yl]episulfoniumylidene}-1,4-dideoxy-D-arabinitol chloride (α-16g).

In a similar manner, title compound (α-**16g**, 79 mg, 67%) was obtained by the *S*-alkylation of thiosugar **9** (69 mg, 0.16 mmol) with epoxide **10g** (60 mg, 0.23 mmol) as colorless oil, $[\alpha]_D^{20}$ −11.8 (*c* 1.05, $CHCl_3$). IR (neat): 3167, 1454, 1404, 1361, 1327, 1254, 1211, 1095, 1061, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.85 [9H, s, $OCH_2C(CH_3)_3$], 3.13/3.31 [each 1H, d, *J* = 8.9, $OCH_2C(CH_3)_3$], 3.68 (1H, dd, *J* = 10.4, 3.5, H-4′a), 3.69–3.73 (1H, m, H-3′), 3.73 (1H dd *J* = 10.8, 8.9, H-5a), 3.77 (1H, dd, *J* = 10.8, 7.2, H-5b), 3.78 (1H, dd, *J* = 10.4, 2.3, H-4′b), 4.08 (1H, dd, *J* = 12.3, 3.4, H-1′a), 4.148 (1H, dd-like, *J* = ca. 12.3, 8.0, H-1′b), 4.152 (1H, br s-like, H-3), 4.16 (1H, dd-like, *J* = 13.2, 2.3, H-1a), 4.14–4.18 (1H, m, H-4), 4.30 (1H, dd, *J* = 13.2, 3.7, H-1b), 4.34–4.40 (1H, m, H-2′), 4.40 (1H, m, H-2), 4.44 (1H, d, *J* = 11.8, OCH_2Ph), 4.47–4.61 (7H, m, OCH_2Ph), 7.14–7.36 (20H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.7 [$OCH_2C(CH_3)_3$], 32.1 [$OCH_2C(CH_3)_3$], 48.0 (C-1), 51.8 (C-1′), 66.2 (C-4), 67.1 (C-5), 68.1 (C-2′), 68.5 (C-4′), 71.9/72.4/73.5/73.7 (OCH_2Ph), 81.0 [$OCH_2C(CH_3)_3$], 81.3 (C-3′), 82.3 (C-2), 82.5 (C-3), 127.6/127.7/127.97/127.99/128.2/128.3/128.4/128.5/128.6/128.76/128.81(d, arom.), 135.8/136.0/136.2/138.2 (s, arom). LRMS (FAB, pos.) *m*/*z*: 685 $[M-Cl]^+$.

4.2.6. Hydrogenolysis of sulfonium salts (α-16a–α-16g)

4.2.6.1. 1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-3-*O*-methyl-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (8a).

A suspension of 10% Pd–C (100 mg) in 80% aqueous acetic acid (2 mL) was pre-equilibrated with hydrogen. To the suspension was added a solution of α-**16a** (160 mg, 0.24 mmol) in 80% aqueous acetic acid (3 mL), and the mixture was hydrogenated at 50 °C for 12 h. The catalysts were filtered off, and the filtrate was condensed to give colorless oil (78 mg), in which a partially acetylated product was contaminated. The oil was then treated with a mixture of 10% hydrochloric acid (0.1 mL) and methanol (1 mL) at room temperature for 3 h. Removal of the solvent at reduced pressure left a colorless oil (74 mg), which on column chromatography ($CHCl_3$–MeOH, 10:1 → $CHCl_3$–MeOH–H_2O, 6:4:1) gave title compound (**8a**, 53 mg, 72%) as colorless oil, $[\alpha]_D^{26}$ +2.1 (*c* 1.97, CH_3OH). IR (neat): 3333, 1651, 1408, 1261, 1084, 1053, 1026 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) δ: 3.29 (1H, ddd-like, *J* = ca. 6.0, 4.0, 4.0, H-3′), 3.47 (3H, s, OCH_3), 3.66 (1H, dd, *J* = 12.3, 4.0, H-4′a), 3.73 (1H, dd, *J* = 12.9, 9.2, H-1′a), 3.80 (1H, dd, *J* = 12.3, 4.0, H-4′b), 3.82 (1H, dd, *J* = 12.9, 3.4, H-1′b), 3.85 (2H, d-like, *J* = ca. 2.3, H-1a and H-1b), 3.92 (1H, dd, *J* = 10.9, 9.5, H-5a), 3.99 (1H, br dd-like, *J* = ca. 9.5, 4.9, H-4), 4.05 (1H, dd, *J* = 10.9, 4.9, H-5b), 4.20 (1H, ddd, *J* = 9.2, 6.0, 3.4, H-2′), 4.36 (1H, dd, *J* = 2.3, 1.1, H-3), 4.62 (1H, dt, *J* = 2.3, 2.3, H-2). ^{13}C NMR (125 MHz, CD_3OD) δ: 51.8 (C-1′), 52.1 (C-1), 58.5 (OCH_3), 60.0 (C-4′), 61.0 (C-5), 68.6 (C-2′), 73.7 (C-4), 79.4 (C-2), 79.5 (C-3), 85.1 (C-3′). LRMS (FAB, pos.) *m*/*z*: 269 $[M-Cl]^+$. HRMS (FAB, pos.): calcd for $C_{10}H_{21}O_6S$ 269.1059, found 269.1059.

4.2.6.2. 1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-3-*O*-ethyl-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (8b).

In a similar manner, sulfonium salt α-**16b** (110 mg, 0.16 mmol) was subjected to the hydrogenolysis. Work-up and column chromatography gave title compound (**8b**, 39 mg, 75%) as a colorless oil, $[\alpha]_D^{24}$ +3.3 (*c* 0.68, CH_3OH). IR (neat): 3333, 1647, 1408, 1261, 1173, 1084, 1030 cm^{-1}. ^1H NMR (700 MHz, CD_3OD) δ: 1.21 (3H, t, *J* = 7.0, OCH_2CH_3), 3.39 (1H, dd, *J* = 5.8, 4.2, 4.0, H-3′), 3.59/3.75

(each 1H, dq, J = 9.4, 7.0, OCH_2CH$_3$), 3.65 (1H, dd, J = 12.1, 4.0, H-4′a), 3.74 (1H, dd, J = 13.2, 9.0, H-1′a), 3.76 (1H, dd, J = 12.1, 4.2, H-4′b), 3.83 (1H, dd, J = 13.2, 3.4, H-1′b), 3.86 (2H, d-like, J = ca. 2.6, H-1a and H-1b), 3.92 (1H, dd, J = 11.4, 9.6, H-5a), 3.99 (1H, br dd-like, J = ca. 9.6, 5.2, H-4), 4.05 (1H, dd, J = 11.4, 5.2, H-5b), 4.19 (1H, ddd, J = 9.0, 5.8, 3.4, H-2′), 4.37 (1H, dd, J = 2.4, 1.2, H-3), 4.62 (1H, td, J = 2.6, 2.4, H-2). ^{13}C NMR (175 MHz, CD$_3$OD) δ: 15.8 (OCH$_2$*C*H$_3$), 51.8 (C-1′), 52.1 (C-1), 60.8 (C-4′), 61.1 (C-5), 67.2 (O*C*H$_2$CH$_3$), 68.7 (C-2′), 73.7 (C-4), 79.4 (C-2), 79.5 (C-3), 83.5 (C-3′). LRMS (FAB, pos.) m/z: 283 [M–Cl]$^+$. HRMS (FAB, pos.): calcd for $C_{11}H_{23}O_6S$ 283.1215, found 283.1212.

4.2.6.3. 1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-3-*O*-(pent-1-yl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (8c).

In a similar manner, sulfonium salt **α-16c** (80 mg, 0.11 mmol) was subjected to hydrogenolysis. Work-up and column chromatography gave title compound (**8c**, 31 mg, 73%) as a colorless oil, $[\alpha]_D^{23}$ +10.2 (c 1.27, CH$_3$OH). IR (neat): 3032, 1454, 1404, 1373, 1254, 1215, 1157, 1072 cm^{-1}. ^{1}H NMR (500 MHz, CD$_3$OD) δ: 0.92 [3H, t, J = 6.9, O(CH$_2$)$_4$C*H*$_3$], 1.31–1.38 [4H m O(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$], 1.54–1.64 [2H, m, OCH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$], 3.38 (1H, ddd, J = 5.7, 4.3, 4.1, H-3′), 3.52/3.69 [each 1H, dt, J = 9.2, 6.9, OC*H*$_2$(CH$_2$)$_3$CH$_3$], 3.66 (1H, dd, J = 12.0, 4.1, H-4′a), 3.74 (1H, dd, J = 13.2, 9.2, H-1′a), 3.76 (1H, dd, J = 12.0, 4.3, H-4′b), 3.83 (1H, dd, J = 13.2, 3.5, H-1′b), 3.85 (1H, d-like, J = 2.6, H-1a and H-1b), 3.92 (1H, dd, J = 10.6, 9.8, H-5a), 3.98 (1H, br dd-like, J = ca. 9.8, 4.3, H-4), 4.05 (1H, dd, J = 10.6, 4.3, H-5b), 4.20 (1H, ddd, J = 9.2, 5.7, 3.5, H-2′), 4.37 (1H, dd, J = 2.6, 1.1, H-3), 4.62 (1H, dt, J = 2.6, 2.6, H-2). ^{13}C NMR (125 MHz, CD$_3$OD) δ: 14.3 [O(CH$_2$)$_4$CH$_3$], 23.6 [O(CH$_2$)$_3$*C*H$_2$CH$_3$], 29.4 [O(CH$_2$)$_2$CH$_2$CH$_2$CH$_3$], 30.8 [OCH$_2$CH$_2$(CH$_2$)$_2$*C*H$_3$], 51.8 (C-1′), 52.2 (C-1), 60.7 (C-4′), 61.0 (C-5), 68.7 (C-2′), 71.9 [O*C*H$_2$(CH$_2$)$_3$C*H*$_3$], 73.8 (C-4), 79.46 (C-2), 79.52 (C-3), 83.7 (C-3′). LRMS (FAB, pos.) m/z: 325 [M–Cl]$^+$. HRMS (FAB, pos.): calcd for $C_{14}H_{29}O_6S$ 325.1685, found 325.1639.

4.2.6.4. 1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-3-*O*-(hept-1-yl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (8d).

In a similar manner, sulfonium salt **α-16d** (50 mg, 0.07 mmol) was subjected to hydrogenolysis. Work-up and column chromatography gave title compound (**8d**, 18.5 mg, 71%) as a colorless oil, $[\alpha]_D^{23}$ +10.0 (c 0.96, CH$_3$OH). IR (neat): 3287, 1454, 1404, 1315, 1261, 1215, 1173, 1088, 1022 cm^{-1}. ^{1}H NMR (500 MHz, CD$_3$OD) δ: 0.90 (3H, t, J = 6.9, O(CH$_2$)$_6$C*H*$_3$], 1.26–1.40 [8H, m O(CH$_2$)$_2$(C*H*$_2$)$_4$CH$_3$], 1.55–1.63 [2H, m OCH$_2$C*H*$_2$(CH$_2$)$_4$CH$_3$], 3.38 (1H, ddd, J = 5.7, 4.6, 4.0, H-3′), 3.53/3.69 [each 1H, dt, J = 9.2, 6.9, OC*H*$_2$(CH$_2$)$_5$CH$_3$], 3.66 (1H, dd, J = 12.0, 4.0, H-4′a), 3.74 (1H, dd, J = 13.2, 8.9, H-1′a), 3.76 (1H, dd, J = 12.0, 4.6, H-4′b), 3.83 (1H, dd, J = 13.2, 3.4, H-1′b), 3.85 (2H, d-like, J = 2.6, H-1a and H-1b), 3.93 (1H, dd, J = 10.3, 9.5, H-5a), 3.97 (1H, br dd-like, J = ca. 9.5, 4.3, H-4), 4.05 (1H, dd, J = 10.3, 4.3, H-5b), 4.20 (1H, ddd, J = 8.9, 5.7, 3.4, H-2′), 4.37 (1H, dd, J = 2.3, 1.2, H-3), 4.62 (1H, td, J = 2.6, 2.3, H-2). ^{13}C NMR (125 MHz, CD$_3$OD) δ: 14.4 [O(CH$_2$)$_6$CH$_3$], 23.7 [O(CH$_2$)$_5$CH$_2$CH$_3$], 27.2 [O(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$CH$_3$], 30.3 [O(CH$_2$)$_3$CH$_2$-CH$_2$CH$_3$], 31.1 [OCH$_2$*C*H$_2$(CH$_2$)$_4$CH$_3$], 33.0 [O(CH$_2$)$_4$CH$_2$CH$_2$CH$_3$], 51.8 (C-1′), 52.2 (C-1), 60.7 (C-4′), 61.1 (C-5), 68.7 (C-2′), 72.0 [O*C*H$_2$(CH$_2$)$_5$CH$_3$], 73.8 (C-4), 79.48 (C-2), 79.52 (C-3), 83.7 (C-3′). LRMS (FAB, pos.) m/z: 353 [M−Cl]$^+$. HRMS (FAB, pos.): calcd for $C_{16}H_{33}O_6S$ 353.1998, found 353.2024.

4.2.6.5. 1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-3-*O*-(tridec-1-yl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (8e).

In a similar manner, sulfonium salt **α-16e** (83 mg, 0.10 mmol) was subjected to hydrogenolysis. Work-up and column chromatography gave title compound (**8e**, 37 mg, 78%) as a colorless oil, $[\alpha]_D^{26}$ +11.0 (c 0.51, CH$_3$OH). IR (neat): 3433, 1645, 1506, 1408, 1262, 1086, 1053, 1026 cm^{-1}. ^{1}H NMR (700 MHz, CDCl$_3$) δ: 0.89 [3H, t, J = 7.0, O(CH$_2$)$_{12}$C*H*$_3$], 1.25–1.34 [20H, m, O(CH$_2$)$_2$(C*H*$_2$)$_{10}$CH$_3$], 1.54–1.63 [2H, m, OCH$_2$C*H*$_2$(CH$_2$)$_{10}$-CH$_3$], 3.37 (1H, ddd, J = 5.6, 4.4, 4.0, H-3′), 3.52/3.68 [each 1H, dt, J = 9.2, 7.0, OC*H*$_2$(CH$_2$)$_{11}$CH$_3$], 3.66 (1H, dd, J = 12.0, 4.0, H-4′a), 3.74 (1H, dd, J = 13.2, 9.0, H-1′a), 3.76 (1H, dd, J = 12.0, 4.4, H-4′b), 3.82 (1H, dd, J = 13.2, 3.4, H-1′b), 3.85 (2H, d-like, J = ca. 2.8, H-1a and H-1b), 3.92 (1H, dd, J = 11.0, 9.8, H-5a), 3.97 (1H, dd-like, J = ca. 9.8, 4.8, H-4), 4.04 (1H, dd, J = 11.0, 4.8, H-5b), 4.20 (1H, ddd, J = 9.0, 5.6, 3.4, H-2′), 4.37 (1H, dd, J = 2.2, 1.2, H-3), 4.62 (1H, td-like, J = 2.8, 2.2, H-2). ^{13}C NMR (175 MHz, CDCl$_3$) δ: 14.4 [O(CH$_2$)$_{12}$CH$_3$], 23.7 [O(CH$_2$)$_{11}$CH$_2$CH$_3$], 27.2 [O(CH$_2$)$_2$CH$_2$(CH$_2$)$_9$CH$_3$], 30.4/30.6/3 0.7 [O(CH$_2$)$_3$(CH$_2$)$_7$(CH$_2$)$_2$CH$_3$], 31.1 [OCH$_2$-CH$_2$(CH$_2$)$_{10}$CH$_3$], 33.0 [O(CH$_2$)$_{10}$CH$_2$CH$_2$CH$_3$], 51.8 (C-1′), 52.2 (C-1), 60.8 (C-4′), 61.1 (C-5), 68.8 (C-2′), 72.0 [O*C*H$_2$(CH$_2$)$_{12}$CH$_3$], 73.8 (C-4), 79.5 (C-2), 79.6 (C-3), 83.7 (C-3′). LRMS (FAB, pos.) m/z: 437 [M–Cl]$^+$. HRMS (FAB, pos.): calcd for $C_{22}H_{45}O_6S$ requires 437.2937, found 437.2949.

4.2.6.6. 1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-3-*O*-isobutyl-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (8f).

In a similar manner, sulfonium salt **α-16f** (79 mg, 0.11 mmol) was subjected to hydrogenolysis. Work-up and column chromatography gave title compound (**8f**, 29 mg, 75%) as a colorless oil, $[\alpha]_D^{23}$ +9.3 (c 0.66, CH$_3$OH). IR (neat): 3306, 1470, 1404, 1369, 1327, 1250, 1172, 1084, 1022 cm^{-1}. ^{1}H NMR (500Mz, CD$_3$OD) δ: 0.91/0.93 [each 3H, d, J = 6.6, OCH$_2$CH(C*H*$_3$)$_2$], 1.85 [1H, triple hept., J = 6.6, 6.6, OCH$_2$C*H*(CH$_3$)$_2$], 3.29/3.46 [each 1H, dd, J = 8.9, 6.6, OC*H*$_2$C(CH$_3$)$_3$], 3.36 (1H, ddd, J = 5.8, 4.0, 4.0, H-3′), 3.67 (1H, dd, J = 12.1, 4.0, H-4′a), 3.75 (1H, dd, J = 12.9, 9.2, H-1′a), 3.76 (1H, dd, J = 12.1, 4.0, H-4′b), 3.84 (1H, dd, J = 12.9, 3.2, H-1′b), 3.85 (1H, dd-like, J = 12.5, 3.5, H-1a), 3.87 (1H, dd-like, J = 12.5, 1.8, H-1b), 3.92 (1H, dd, J = 10.9, 9.8, H-5a), 3.98 (1H, br dd-like, J = ca. 9.8, 4.6, H-4), 4.05 (1H, dd, J = 10.9, 4.6, H-5b), 4.22 (1H, ddd, J = 9.2, 5.8, 3.2, H-2′), 4.38 (1H, dd, J = 2.0, 1.2, H-3), 4.62 (1H, ddd, J = 3.5, 2.0, 1.8, H-2). ^{13}C NMR (125 MHz, CD$_3$OD) δ: 19.7/19.8 [CH(*C*H$_3$)$_2$], 30.0 [*C*H(CH$_3$)$_2$], 51.9 (C-1′), 52.2 (C-1), 60.7 (C-4′), 61.0 (C-5), 68.8 (C-2′), 73.8 (C-4), 78.7 [OCH$_2$CH(CH$_3$)$_2$], 79.47 (C-2), 79.52 (C-3), 83.9 (C-3′). LRMS (FAB, pos.) m/z: 311 [M]$^+$. HRMS (FAB, pos): calcd for $C_{13}H_{27}O_6S$ 311.1529, found 311.1550.

4.2.6.7. 1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-3-*O*-neopentyl-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (8g).

In a similar manner, sulfonium salt **α-16g** (60 mg, 0.08 mmol) was subjected to hydrogenolysis. Work-up and column chromatography gave title compound (**8g**, 21 mg, 70%) as a colorless oil, $[\alpha]_D^{24}$ +12.7 (c 0.66, CH$_3$OH). IR (neat): 3267, 1632, 1408, 1361, 1323, 1265, 1219, 1172, 1087, 1023 cm^{-1}. ^{1}H NMR (500 MHz, CD$_3$OD) δ: 0.92 [9H, s, C(C*H*$_3$)$_3$], 3.20/3.37 [each 1H, d, J = 8.6, OC*H*$_2$C(CH$_3$)$_3$], 3.35 (1H, ddd, J = 6.0, 4.3, 4.0, H-3′), 3.68 (1H, dd, J = 12.0, 4.0, H-4′a), 3.75 (1H, dd, J = 13.0, 9.5, H-1′a), 3.76 (1H, dd, J = 12.0, 4.3, H-4′b), 3.83 (1H, dd, J = 12.6, 3.5, H-1a), 3.86 (1H, dd, J = 13.0, 3.5, H-1′b), 3.87 (1H, dd, J = 12.6, 1.7, H-1b), 3.93 (1H, dd, J = 10.6, 9.8, H-5a), 3.97 (1H, br dd-like, J = ca. 9.8, 4.3, H-4), 4.05 (1H, dd, J = 10.6, 4.3, H-5b), 4.23 (1H, ddd, J = 9.5, 6.0, 3.5, H-2′), 4.38 (1H, br d-like, J = ca. 1.5, H-3), 4.62 (1H, ddd, J = 3.5, 1.7, 1.5, H-2). ^{13}C NMR (125 MHz, CD$_3$OD) δ: 27.1 [C(*C*H$_3$)$_3$], 33.1 [*C*(CH$_3$)$_3$], 51.9 (C-1′), 52.3 (C-1), 60.8 (C-4′), 61.0 (C-5), 68.9 (C-2′), 73.8 (C-4), 79.5 (C-2 and C-3), 82.2 [OCH$_2$C(CH$_3$)$_3$], 84.2 (C-3′). LRMS (FAB, pos.) m/z: 325 [M−Cl]$^+$. HRMS (FAB, pos.) calcd for $C_{14}H_{29}O_6S$ 325.1685, found 325.1678.

4.3. Bioassay

4.3.1. Inhibitory effects on rat intestinal α-glucosidases

The experiments were performed according to the method reported.[19,20] Thus, rat small intestinal brush border membrane vesicles were prepared and their suspensions in 0.1 M maleate buffer (pH 6.0) were used as small intestinal α-glucosidases of maltase, sucrose, and isomaltase.[21] A test sample was dissolved in dimethyl sulfoxide (DMSO), and the resulting solution was diluted with 0.1 M maleate buffer to prepare the test sample solution (concentration of DMSO 10 %). A substrate solution in the maleate buffer (maltose 74 mM, sucrose 74 mM, isomaltase 7.4 mM, 50 μL), the test sample solution (25 μL), and the enzyme solution (25 μL) were mixed at 37 °C for 30 min, and then immediately heated by boiling water for 2 min to stop the reaction. The glucose concentrations were determined by a glucose-oxidase method. The final concentration of DMSO in the test solution was 2.5% and no influence of DMSO on the inhibitory activity was detected.

4.3.2. Inhibitory effects on human intestinal maltase

A human small intestinal microsome (batch MIC318017, purchased from BIOPREDIC International, Rennes, France) in 0.1 M maleate buffer (pH 6.0) was used to determine the small intestinal a-glucosidase activity of maltase. Through a similar procedure, the effect of maltase inhibitory activity was measured as described above.

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Supplementary data

Supplementary data (^{1}H and ^{1}3C NMR spectra of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2016.06.013.

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