DOI: 10.1002/chem.201102109

Probing the Intestinal α-Glucosidase Enzyme Specificities of Starch-Digesting Maltase-Glucoamylase and Sucrase-Isomaltase: Synthesis and Inhibitory Properties of 3′- and 5′-Maltose-Extended De-*O*-sulfonated Ponkoranol

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Abstract: The synthesis and glucosidase inhibitory activities of two C-3′- and C-5′-β-maltose-extended analogues of the naturally occurring sulfonium-ion inhibitor, de-*O*-sulfonated ponkoranol, are described. The compounds are designed to test the specificity towards four intestinal glycoside hydrolase family 31 (GH31) enzyme activities, responsible for the hydrolysis of terminal starch products and sugars into glucose, in humans. The target sulfonium-ion compounds were synthesized by means of nucleophilic attack of benzyl protected 1,4-anhydro-4-thio-D-arabinitol at the C-6 position of 6-*O*-trifluoromethanesulfonyl trisaccharides as alkylating agents. The alkylating agents were synthesized from D-glucose by glycosylation at C-4 or C-2 with maltosyl trichloroacetimidate. Deprotection of the coupled products by using a two-step sequence, followed by reduction afforded the final compounds. Evaluation of the target compounds for inhibition of the four glucosidase activities indicated that selective inhibition of one enzyme over the others is possible.

Keywords: enzyme catalysis · inhibitors · intestinal glucosidases · maltose-extended-de-*O*-sulfonated ponkoranol · sulfonium ions

Introduction

Type II (noninsulin-dependent) diabetes, is a metabolic disorder characterized by elevated blood glucose levels with defects in insulin secretion, insulin action or both. In the treatment of type II diabetes, controlling blood glucose levels is critical. One strategy is to slow down the breakdown of ingested carbohydrates and starches and thus delay glucose absorption by inhibiting the enzymes that are involved in the breakdown of dietary starches and sugars into glucose. In humans, six enzyme activities are involved in the complete digestion of dietary starches and sugars into glucose. Two endohydrolases, salivary and pancreatic α-amylases are responsible for digestion of starch into shorter linear and branched dextrin chains and four exohydrolase α-glucosidase activities, maltase-glucoamylase (MGAM) and sucrase-isomaltase (SI), are responsible for the hydrolysis of terminal starch products and sugars into glucose.[1,2] MGAM and SI are anchored to the brush-border epithelial cells of the small intestine, each containing two catalytic subunits classified under glycosyl hydrolase family 31 (GH31): an N-terminal subunit (ntMGAM and ntSI) near the membrane bound end of the enzyme and a C-terminal luminal subunit (ctMGAM and ctSI) (Figure 1).[3] SI exhibits hydrolytic activity on branched α-1,6 linkages, complemented by the hydrolytic activity of both SI and MGAM on α-1,4 linkages.[4] These complementary activities of the human enzymes permit digestion of starches of plant origin comprising two-thirds of most diets; however, the main substrate of SI is that with α-1,4 linkages.[5]

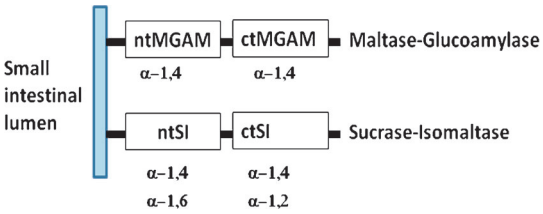

Figure 1. Diagram of MGAM and SI indicating hydrolytic activity.

SI is more abundant than MGAM; however, to counteract this deficit in abundance, MGAM displays higher hydrolytic activities.[6–8] With respect to similarity in sequence, SI and MGAM show 59% amino acid sequence similarity. The catalytic subunits of MGAM and SI are 40–60% identical in

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102109.

amino acid sequence.[3] N-terminal catalytic subunits and the C-terminal catalytic subunits of MGAM and SI are more closely related in sequence to one another than the N- and C-terminal subunits within the same protein.[9] There are also multiple spliceforms of C-terminal MGAM in mammals, two of which are studied here (ctMGAM-N2 and ctMGAM-N20).[9,10] In recent years, the aqueous extracts of the plant *Salacia reticulata* found in Sri Lanka and Southern India, have been used by patients as a remedy for the treatment of type II diabetes.[11] The active compounds of *S. reticulata* were found to be a novel class of sulfonium-ion glucosidase inhibitors, including salaprinol (**1**),[12b] salacinol (**2**),[13] ponkoranol (**3**),[12a,b] kotalanol (**4**),[14] de-*O*-sulfonated kotalanol (**5**),[14b,15] de-*O*-sulfonated salacinol (**6**),[16] de-*O*-sulfonated ponkoranol (**7**)[17a,b] and de-*O*-sulfonated salaprinol (**8**),[17b] the structures of which comprise a 1,4-anhydro-4-thio-D-arabinitol core and polyhydroxylated acyclic chain (Figure 2).

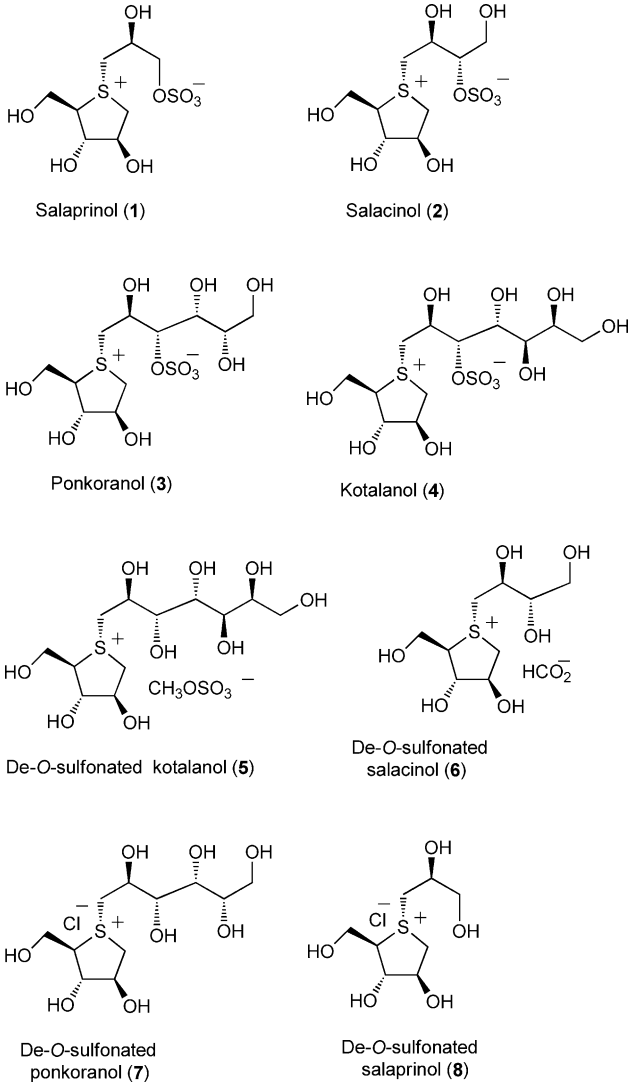

Figure 2. Components **1–8** isolated from *Salacia* species.

They have been shown to be stronger inhibitors of ntMGAM, with K_i values in the low micromolar range (i.e., 0.03–0.19 μM) compared to acarbose ($K_i = 62(\pm 13)$ μM), the naturally occurring α-glucosidase inhibitor currently in use for the treatment of type II diabetes.[18–23] Interestingly, **7** was one of our synthetic compounds,[17a] isolated recently from the same plant.[17b] Acarbose (**9**; Figure 3) has been

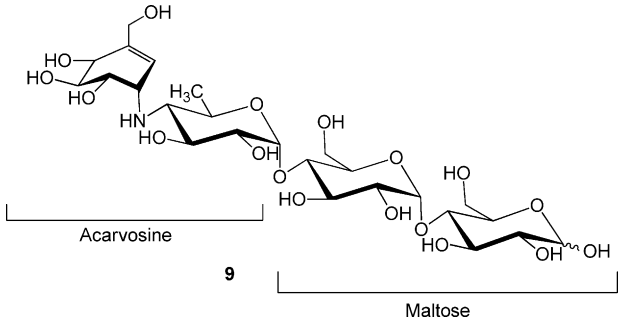

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Figure 3. Structure of acarbose **9**, an α-glucosidase inhibitor currently used in the treatment of type II diabetes.

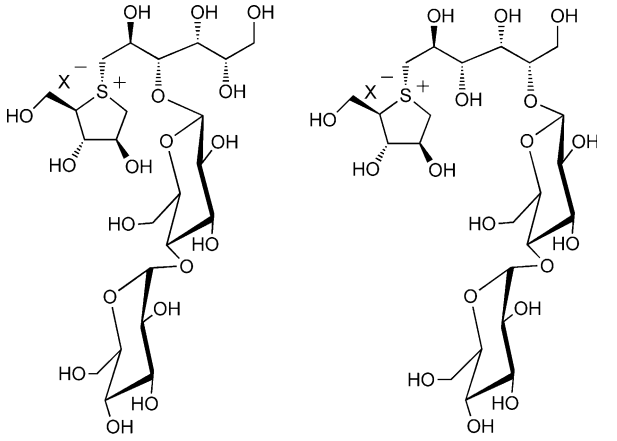
shown to be an efficient inhibitor of α-amylase with a reported K_i of 15 nM[24] and of the C-terminal domain of MGAM-N2 ($K_i = 0.009(\pm 0.002)$ μM),[4,9] but a weaker inhibitor of the N-terminal domain ($K_i = 62(\pm 13)$ μM; Table 1).[4,19]

The study of ntMGAM in complex with acarbose has indicated that acarbose is bound to the ntMGAM active site primarily through side chain interactions with its acarvosine unit and almost no interactions were made with its other sugar rings. Since it is suggested that additional subsite interactions with the acarbose sugar rings would significantly increase its inhibitory properties for ctMGAM[4,25] it is of interest to examine whether glucose residues appended to the polyhydroxylated carbon chain of salacinol-based compounds would lead to differential inhibition of the four enzyme activities. We have shown recently that extension of the acyclic carbon chain beyond six carbons in salacinol-based compounds is not essential for activity; and furthermore, that the de-*O*-sulfonated analogues were more potent inhibitors than the parent compounds.[17a] Therefore, de-*O*-sulfonated ponkoranol has been chosen for modification at C-3′-OH and C-5′-OH of its side chain in our preliminary studies. We report here the synthesis of C-3′-β-maltose-extended de-*O*-sulfonated ponkoranol analogue **10** and C-5′-β-maltose extended-de-*O*-sulfonated ponkoranol **11** (Figure 4) to investigate the individual roles of the four catalytic subunits comprising human intestinal MGAM and SI. These candidates were chosen to test whether occupying the subsite with glucosyl units would suffice, irrespective of their orientation (reducing or non-reducing positional substitution) or α- or β-stereochemistry at the anomeric centre. The β-isomers were chosen as initial candidates because their syntheses were more tractable.

Table 1. Comparison of inhibition profiles against MGAM and SI subunits, K_i (μM).

	ctMGAM-N2	ctMGAM-N20	ntMGAM	ctSI	ntSI
7[32]	no inhibition[a]	0.096 ± 0.015	0.043 ± 0.001	0.103 ± 0.037	0.302 ± 0.123
9	0.009 ± 0.002	0.028 ± 0.005	62 ± 13	0.246 ± 0.005	14 ± 1
10	no inhibition[a]	0.655 ± 0.063	0.039 ± 0.025	0.062 ± 0.005	0.046 ± 0.018
11	0.077 ± 0.015	0.067 ± 0.012	0.008 ± 0.002	0.045 ± 0.001	0.019 ± 0.008
26[33]	0.060 ± 0.015	0.055 ± 0.014	0.50 ± 0.04[29]	0.007 ± 0.002	0.035 ± 0.013

[a] at 200 nM.

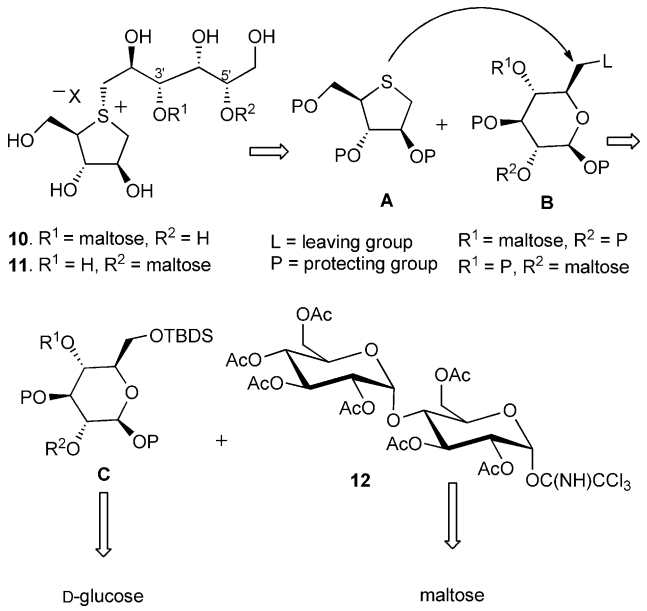


10 **11**

Figure 4. 3′-*O*-β-Maltosyl-de-*O*-sulfonated ponkoranol **10** and 5′-β-maltosyl-de-*O*-sulfonated ponkoranol **11**.

Results

Synthesis: Retrosynthetic analysis revealed that the target molecules could be synthesized by alkylation at the sulfur atom of suitably protected alkylating agents (Scheme 1).



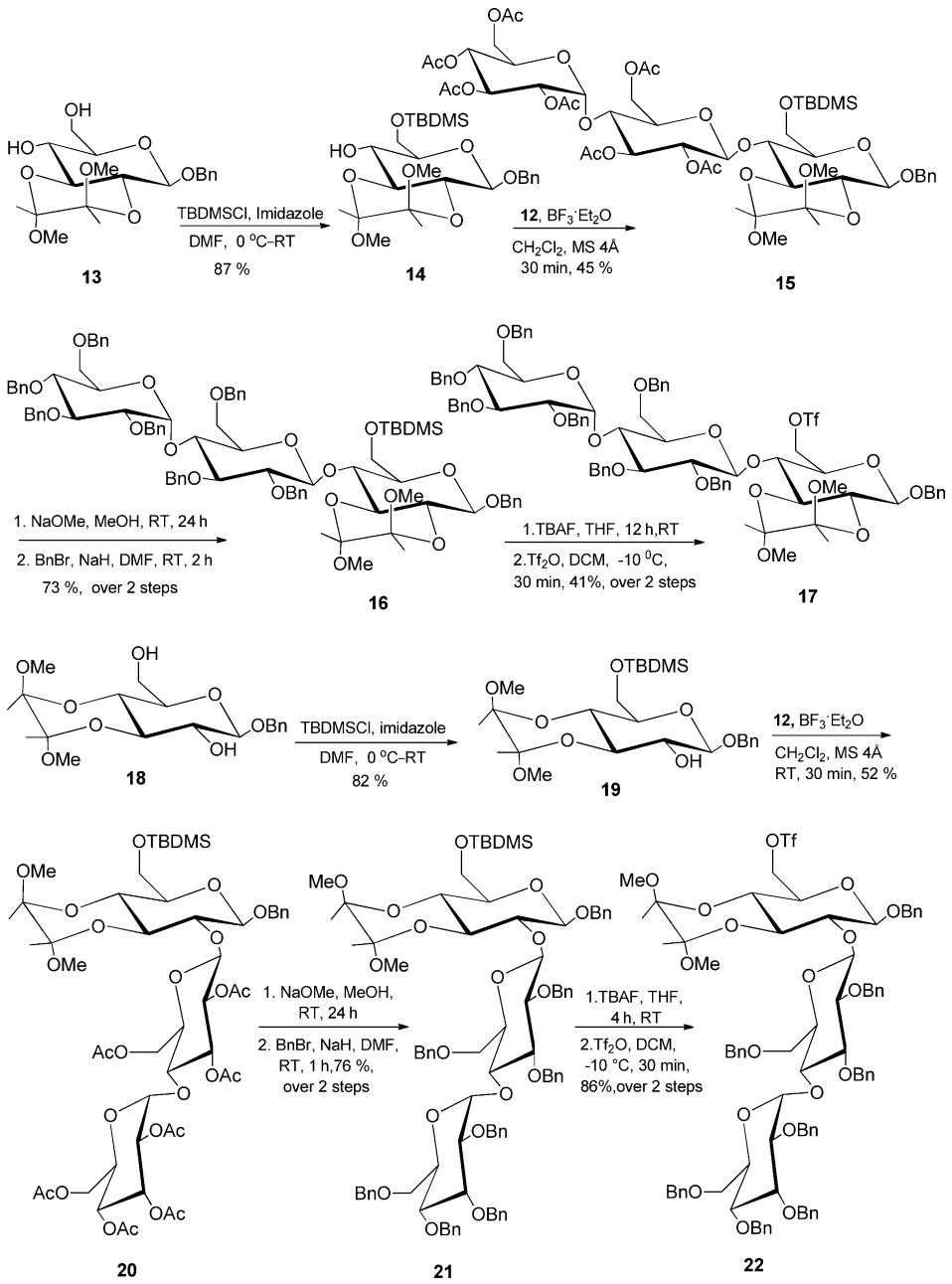
Scheme 1. Retrosynthetic analysis.

The alkylating agents (**B**) could be obtained by glycosylation of protected D-glucose (**C**) at C-4 or C-2 with maltosyl trichloroacetimidate (**12**). The required maltosyl trichloroacetimidate donor (**12**) could be prepared from maltose, according to the literature procedure.[26]

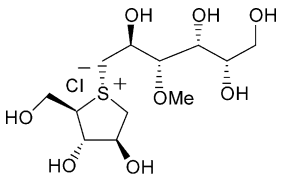
To synthesize the desired β-(1→4) and β-(1→2)-maltosyl-linked glucopyranosides, we chose to use benzyl 2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (**14**) and benzyl 3,4-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (**19**) as glycosyl acceptors. The acceptors **14** and **19** were synthesized by selective protection of their primary hydroxyl groups as *tert*-butyldimethylsilyl (TBDMS) ethers from butane-2,3-diacetal (BDA) protected glucopyranosides **13** and **18**, which were readily obtained from benzyl β-D-glucopyranoside by a known procedure.[27] The syntheses of the desired trisaccharides **15** and **20** were achieved by treatment of maltosyl trichloroacetimidate **12** with the acceptors **14** and **19** in dichloromethane, by using a catalytic amount of boron trifluoride etherate as promoter at room temperature to give the compounds maltosyl-(1→4)-β-linked 6-*O*-*tert*-butyldimethylsilyl-D-glucopyranoside **15** and maltosyl-(1→2)-β-linked 6-*O*-*tert*-butyldimethylsilyl-D-glucopyranoside **20** in 45 and 52% yield, respectively. The *O*-deacetylation of **15** and **20** was carried out by using NaOMe, followed by protection of the hydroxyl groups as benzyl ethers to afford benzyl-protected maltosyl-(1→4)-β-linked 6-*O*-*tert*-butyldimethylsilyl-D-glucopyranoside **16** and benzyl protected maltosyl-(1→2)-β-linked 6-*O*-*tert*-butyldimethylsilyl-D-glucopyranoside **21**. 6-*O*-Desilylation of trisaccharides **16** and **21** with TBAF in THF and subsequent triflation of the free hydroxyl group afforded maltosyl-(1→4)-β-linked 6-*O*-trifluoromethanesulfonyl-D-glucopyranoside **17** and maltosyl-(1→2)-β-linked 6-*O*-trifluoromethanesulfonyl-D-glucopyranoside **22** in 41 and 86% yield, respectively (Scheme 2).

The coupling reaction of the benzyl-protected anhydrothioarabinitol **23**[28] with 6-*O*-trifluoromethanesulfonyl trisaccharides **17** and **22** as alkylating agents was carried out in dichloromethane at room temperature to give the corresponding sulfonium ions **24** and **25**, respectively, as a 5:1 and 2.8:1 mixture of diastereomers at the stereogenic sulfur center (Scheme 3).

The diastereoisomers of **24** and **25** were found to be inseparable, even by HPLC, although repeated attempts to separate the mixture of diastereomers of **25** were partially successful. Prior to choosing 6-*O*-trifluoromethanesulfonyl trisaccharides **17** and **22** as alkylating agents, the coupling reaction of 6-*O*-*p*-toluenesulfonyl trisaccharides was carried out in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), based on the procedure that has been reported for synthesis of 3′-*O*-methyl ponkoranol (**26**);[29] but the reaction failed and no product formation was observed. Temperature variation to



Scheme 2. Synthesis of benzyl 6-*O*-trifluoromethanesulfonyl-D-glucopyranoside derivatives **17** and **22**, with benzylated maltose units at C-2 or C-4.



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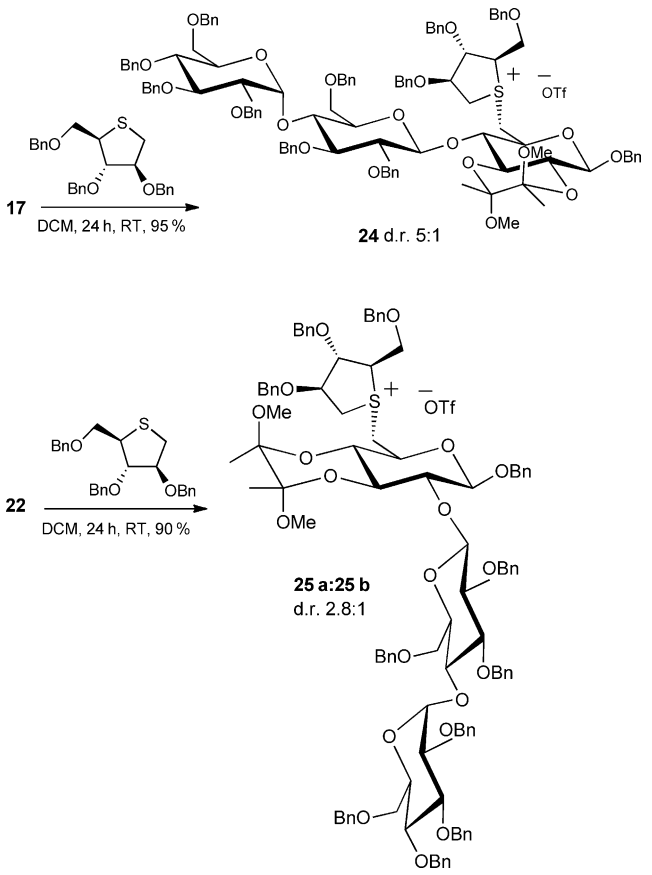
−78 and −25 °C failed to give a single isomer. The reaction was also carried out at 0 °C and reflux conditions in dichloromethane, but the same ratio was observed.

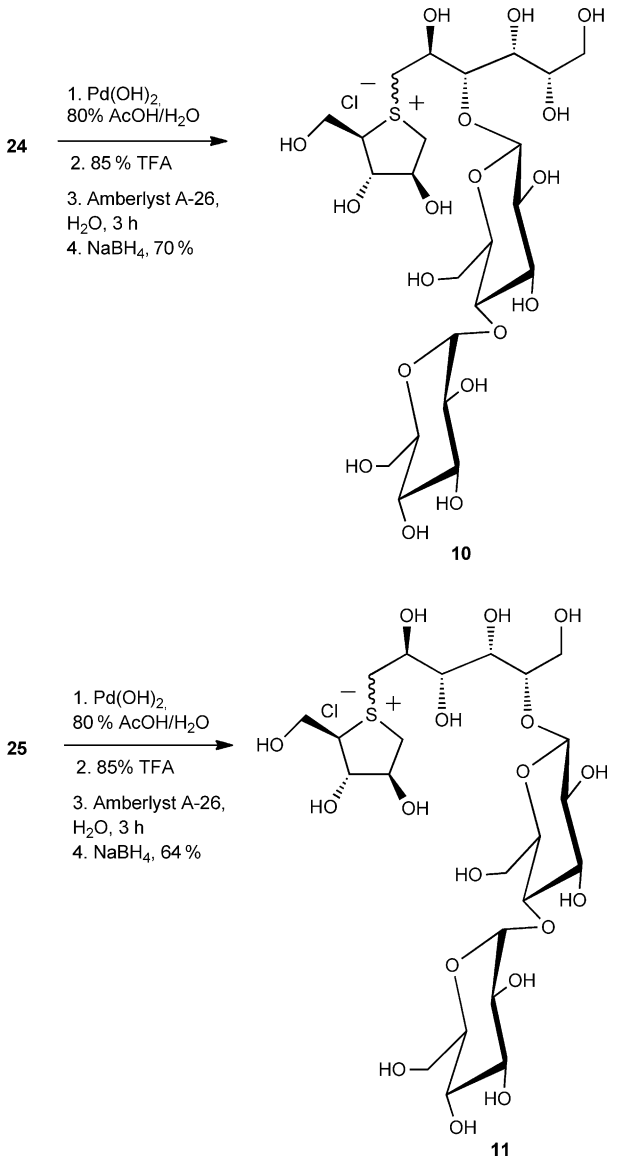
Deprotection of the coupled products **24** and **25** was carried out by a two-step procedure, first hydrogenolysis of the benzylethers followed by butane-2,3-diacetal (BDA) deprotection. The corresponding crude materials were then treated with Amberlyst A-26 resin (chloride form) to completely exchange their triflate counterions to chloride ions.[29] Finally, the corresponding hemiacetals were reduced with $NaBH_4$ in water to provide the desired C-3′-β-maltose-extended de-*O*-sulfonated ponkoranol **10** (d.r. 5:1) and C-5′-β-maltose-extended de-*O*-sulfonated ponkoranol **11** (d.r. 2.8:1) in 70 and 64 % yield, respectively, over four steps (Scheme 4).

The absolute stereochemistry at the stereogenic sulfur center for the major isomer of **24** was established by means of a 2D-NOESY experiment (Figure 5). A NOESY correlation was observed between the H-4 proton and H-6′a; this implies that these two hydrogen atoms are *syn* facial with respect to the sulfonium ring. In the case of **25**, the absolute configuration at the sulfonium centre for the major isomer was assigned to be the same as in **24**, since a NOESY experiment was not possible, owing to overlapping signals for H-4 and H-6′.

Enzyme kinetics: Kinetic parameters were determined by measuring the amount of glucose produced upon the addition of enzyme at increasing maltose concentrations (from 0.5 to 30 mM) in the presence of increasing inhibitor concentration (0–200 nM) by a two-step glucose oxidase assay in a 96-well plate. The enzyme was allowed to act on the maltose substrate in the presence of inhibitor for 45 min at 37 °C. The reactions were then quenched with Tris-HCl to a final concentration of 1 M. Glucose oxidase reagent (Sigma–Aldrich) was then added to each well (125 μL) and the reactions were allowed to develop for 30 min at 37 °C. Reactions were performed in quadruplicate and absorbance was measured at 405 nm with a SpectraMax 190 plate reader (Molecular Devices). Absorbance readings were averaged to give the final value, which was compared to a glucose standard curve to determine the amount of glucose released by the enzyme from the substrate. The program KaleidaGraph 4.1 was used to fit the data to the Michaelis–Menton equation and the



Scheme 3. Coupling reactions to give sulfonium ions.



Scheme 4. Synthesis of compounds **10** and **11**.

K_M, K_M^{obs} (K_M in the presence of the inhibitor) and V_{max} of the catalytic subunits were estimated. The K_i values for each inhibitor were determined by using the equation: $K_i=[I]/(K_M^{obs}/K_M)-1)$. The K_i values reported for each inhibitor were determined by averaging the K_i values from three different inhibitor concentrations. The weights of compounds **10** and **11** were adjusted for the presence of major isomer. The data were also plotted on Lineweaver–Burk plots to verify that the inhibitors were acting as competitive inhibitors (see the Supporting Information). The methods used for kinetic assays were reported previously.[30,31]

Kinetic analysis: The inhibition constants (K_i) of acarbose,[19,25,30] C-3′-β-maltose-extended de-*O*-sulfonated ponkoranol **10** and C-5′-β-maltose-extended de-*O*-sulfonated ponkoranol **11** against MGAM and SI were determined by using the glucose oxidase assay and maltose as a substrate. There are also multiple, alternatively spliced isoforms of ctMGAM; the two studied in this context, referred to as ctMGAM-N2 and ct-MGAM-N20, occur in humans.[9] The experimentally determined inhibition constants for acarbose[19,25,30] **10** and **11** are listed in Table 1. The current antidiabetic compound, acarbose, was found to be a micromolar inhibitor of both ntMGAM ($K_i=62(\pm13)$ μM)[19] and ntSI ($K_i=14(\pm1)$ μM).[30] In contrast, acarbose is a 1000-fold better inhibitor of ctMGAM-N2 ($K_i=0.009(\pm0.002)$ μM), ctMGAM-N20 ($K_i=0.028(\pm0.005)$ μM) and 100-fold better inhibitor of ctSI ($K_i=0.246(\pm0.005)$ μM). C-3′-β-Maltose-extended de-*O*-sulfonated ponkoranol **10**, generally showed some selectivity for inhibiting N-terminal MGAM, as com-

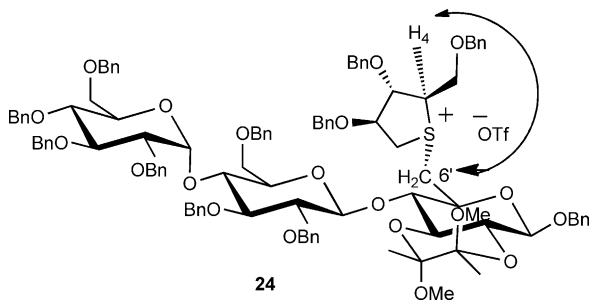


Figure 5. NOESY correlations in compound **24**.

pared to C-terminal enzymes: ntMGAM ($K_i = 0.039(\pm 0.025)$ μM) over ctMGAM-N2 (K_i = no inhibition) and ctMGAM-N20 ($K_i = 0.655(\pm 0.063)$ μM), ctSI ($K_i = 0.062(\pm 0.005)$ μM) and ntSI ($K_i = 0.046(\pm 0.018)$ μM). Surprisingly, C-5′-β-maltose-extended de-*O*-sulfonated ponkoranol **11**, shows improved inhibition of ntMGAM ($K_i = 0.008(\pm 0.002)$ μM) with little distinction between the other N-terminal and C-terminal catalytic enzyme subunits: ctMGAM-N20 ($K_i = 0.067(\pm 0.012)$ μM), ctSI ($K_i = 0.045(\pm 0.001)$ μM), ctMGAM-N2 ($K_i = 0.077(\pm 0.015)$ μM), and ntSI ($K_i = 0.019(\pm 0.008)$ μM).

Discussion

In this study, we report the design, synthesis, and glucosidase inhibitory activities of two ponkoranol-based compounds **10** and **11** against recombinant human maltase-glucoamylase (ntMGAM and ctMGAM) and sucrase-isomaltase (ntSI and ctSI). These compounds were intended to probe whether one could differentiate between the different enzymes, that is, to toggle between the different enzymes even though they are not strictly analogous to acarbose. Kinetic analysis confirmed the enzyme activity of the recombinant proteins, and inhibition analysis confirmed classic competitive inhibition by the α-glucosidase inhibitors. The results indicate that despite the overall similarity between the subunits in terms of amino acid sequence (Table 1), they exhibit different biochemical and structural properties. Compound **11** demonstrates the ability to inhibit all of the catalytic subunits very well, especially ntMGAM. In fact, compound **11** is the most potent inhibitor of ntMGAM to date.

Compound **10** is also a good inhibitor of ctSI, ntSI, and ntMGAM, with K_i values in the nanomolar range. Although elongation of the scaffold does not result in a significant gain in binding energy, nonetheless, it does result in some interesting selectivities in inhibitory activities. A significant finding is that **10** differentiates between the two C-terminal catalytic subunits. Compound **10** is a very poor inhibitor of ctMGAM-N20 and shows no inhibition against ctMGAM-N2. By confirming the higher potency of **10** against other subunits as compared with ctMGAM, our results suggest that this inhibitor shows specificity towards these different α-glucosidases. Since ctMGAM is expressed in more than one spliceform,[9] it provides further complexity to the system. It is hypothesized that these units act in a complementary manner depending on the organism's nutritional sources and requirements, as well as its physical and environmental conditions. Therefore, with compound **10**, we are able to keep the ctMGAM activity on and dampen the others, and we are in a position to test this hypothesis.

According to previous studies, acarbose is a very powerful inhibitor of ctMGAM over ntMGAM and SI subunits.[9] Therefore, we are now also in a position to turn off the ctMGAM unit and study the effect of other subunits in starch digestion. The results also demonstrate that the ability to selectively inhibit one enzyme unit over the others can result from relatively small changes in the structure of the compound and we are closer to being able to independently toggle each subunit on and off. This observation is important clinically because the design of α-glucosidase inhibitors for the treatment of type II diabetes might require specificity for enzymes later in the starch digestion pathway in order to reduce unwanted side-effects. The initial results of the inhibition assays are promising; at this point, analysis of structure–activity relationships can only be somewhat speculative. However, the very interesting and unprecedented enzyme selectivity observed in this study set the stage for improvement of the specificity and affinity of these compounds for their potential development as antidiabetic agents, irrespective of whether or not the binding of these compounds occurs through a mechanism analogous to that of acarbose. It is noteworthy that de-*O*-sulfonated ponkoranol **7** (Figure 2)[32] and 3′-*O*-methyl ponkoranol (**26**)[33] also show interesting selectivity profiles for the different subunits (Table 1). Further confirmation of the importance of inhibitor structure and how it affects binding in the ctMGAM active site will be possible with an analysis of the atomic structure of the ctMGAM binding site in the presence of bound inhibitors. Determination of this structural information will be a valuable tool in future design and synthesis of α-glucosidase inhibitors effective against and specific to MGAM and SI subunits. These inhibitors should be promising lead candidates as oral agents for the treatment and prevention of type II diabetes.

Experimental Section

Benzyl 6-*O*-*tert*-butyldimethylsilyl-2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (14): Imidazole (270 mg, 3.9 mmol) was added to a solution of **13** (500 mg, 1.3 mmol) in DMF (15 mL). The reaction was cooled in an ice bath, TBDMSCl (226 mg, 1.4 mmol) was added portion-wise, and the mixture was stirred at 0 °C for 15 min and at room temperature for 1 h. The reaction was quenched by the addition of ice-water, and the mixture was extracted with Et_2O (3×30 mL). The combined organic solvents were washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated to give the crude. The crude was purified by column chromatography (hexanes/EtOAc 2:1) to afford **14** as foam (564 mg, 87%). $[\alpha]_D^{23} = -124.5$ ($c = 2.3$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 7.28$–7.15 (m, 5H; Ar), 4.79, 4.55 (2d, $J_{A,B} = 12.3$ Hz, 2H; CH_2Ph), 4.51 (d, $J_{1,2} = 8.0$ Hz, 1H; H-1), 3.83 (dd, $J_{6a,6b} = 5.5$, $J_{5,6a} = 10.3$ Hz, 1H; H-6a), 3.75 (dd, $J_{6a,6b} = 5.8$, $J_{5,6b} = 10.7$ Hz, 1H; H-6b), 3.63 (m, 2H; H-3, H-4), 3.49 (t, $J_{1,2} = J_{2,3} = 8.5$ Hz, 1H; H-2), 3.30 (ddd, $J_{5,6a} = 5.7$, $J_{5,6b} = 8.6$, $J_{4,5} = 10.7$ Hz, 1H; H-5), 3.21, 3.19 (2s, 6H; 2OMe), 3.06 (br, 1H; OH), 1.25, 1.23 (2s, 6H; 2Me), 0.81 (s, 9H; 3Me), 0.00 ppm (s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): $\delta = 137.7$–127.5 (m, Ar), 99.9 (C-1), 99.5, 99.4 (2MeO*C*Me), 74.9 (C-5), 72.5 (C-3), 70.8 (*C*H$_2$Ph), 70.3 (C-4), 69.2 (C-2), 64.8 (C-6), 48.0, 47.9 (2OMe), 25.9 (3Me), 18.32 (*C*Me$_3$), 17.7 (2Me), −5.4, −5.5 ppm (2Me); HRMS calcd for $C_{25}H_{42}NaO_8Si$ [M+Na]: 521.2541, found: 521.2537.

Benzyl 6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl)]-β-D-glucopyranoside (19): The compound was obtained as white solid (654.4 mg, 82%) from **18** (614 mg, 1.6 mmol) by using the procedure that was used to obtain **14**. M.p. 145–147 °C; $[\alpha]_D^{23} = +81.8$ ($c = 1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 7.38$–7.27 (m, 5H; Ar), 4.90 (d, $J_{AB} = 11.4$ Hz, 1H; CH_2Ph), 4.60 (d, $J_{AB} = 11.4$ Hz, 1H; CH_2Ph), 4.39 (d, $J_{1,2} = 7.4$ Hz, 1H; H-1), 3.90 (dd, $J_{6a,6b} = 11.6$, $J_{6a,5} = 2.2$ Hz, 1H; H-6a), 3.85 (dd, $J_{6b,6a} = 11.6$, $J_{6b,5} = 3.8$ Hz, 1H; H-6b), 3.77–3.68 (m, 2H; H-3, H-4), 3.59

(t, $J_{1,2}=J_{2,3}=9.6$ Hz, 1H; H-2), 3.44 (ddd, $J_{5,6a}=2.2$, $J_{5,6b}=3.7$, $J_{5,4}=9.4$ Hz, 1H; H-5), 3.29, 3.27 (2s, 6H; 2OMe), 2.53 (br, 1H; OH), 1.33, 1.29 (2s, 6H; 2Me), 0.90 (s, 9H; 3Me), 0.10, 0.08 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): $\delta=137.0$–127.9 (m, Ar), 101.9 (C-1), 99.5, 99.0 (2MeO*C*Me), 74.7 (C-5), 71.9 (C-3), 71.2 (C-2), 70.7 (*C*H_2Ph), 65.1 (C-4), 61.3 (C-6), 48.0, 47.9 (2OMe), 25.8 (3Me), 18.3 (*C*Me_3), 17.6 (2Me), −5.0, −5.4 ppm (2Me); HRMS calcd for $C_{25}H_{42}NaO_8Si$ [*M*+Na]: 521.2541, found: 521.2546.

Benzyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl-(1→4)-6-*O*-*tert*-butyldimethylsilyl-2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (15): $BF_3{\cdot}Et_2O$ (0.02 mL, 0.2 equiv) was added to a solution of the acceptor glycoside **14** (0.7 g, 1.4 mmol) and maltosyl trichloroacetimidate **12** (1.3 g, 1.68 mmol) in dry CH_2Cl_2 (10 mL) under N_2, at room temperature. After being stirred for 30 min, the mixture was quenched with NEt_3 (0.2 equiv) with vigorous stirring. The mixture was concentrated and purified by column chromatography (hexanes/EtOAc 1:1) to give the coupled product **15** as white foam (0.7 g, 45%). $[\alpha]_D^{23}=-9$ ($c=0.7$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=7.39$–7.28 (m, 5H; Ar), 5.42 (d, $J_{1'',2''}=4.1$ Hz, 1H; H-1″), 5.38 (t, $J_{2'',1''}=J_{2'',3''}=10.4$ Hz, 1H; H-2″), 5.19 (t, $J_{3',4'}=J_{2',3'}=7.7$ Hz, 1H; H-3′), 5.08 (t, $J_{3'',4''}=J_{4'',5''}=9.9$ Hz, 1H; H-4″), 4.90, 4.66 (2d, $J_{A,B}=12.0$ Hz, 2H; CH_2Ph), 4.87 (t, $J_{3'',4''}=J_{2'',3''}=4.1$ Hz, 1H; H-3″), 4.83 (m, 2H; H-1′, H-2′), 4.55 (d, $J_{1,2}=7.8$ Hz, 1H; H-1), 4.42 (dd, $J_{6'a,6'b}=3.1$, $J_{5',6'a}=12.5$ Hz, 1H; H-6′a), 4.29 (dd, $J_{6'a,6'b}=3.6$, $J_{5',6'b}=12.2$ Hz, 1H; H-6′b), 4.24 (dd, $J_{6''a,6''b}=3.6$, $J_{5'',6''a}=12.5$ Hz, 1H; H-6″a), 4.06 (m, 2H; H-6″b, H-4′), 3.94 (ddd, $J_{5'',6a''}=3.1$, $J_{5'',6b''}=2.6$, $J_{4'',5''}=10.0$ Hz, 1H; H-5″), 3.88 (dd, $J_{6a,6b}=1.5$, $J_{5,6a}=11.5$ Hz, 1H; H-6a), 3.82 (t, $J_{3,4}=J_{2,3}=9.6$ Hz, 1H; H-3), 3.71 (m, 2H; H-4, H-6b), 3.67 (ddd, $J_{5',6a'}=3.2$, $J_{5',6b'}=3.0$, $J_{4',5'}=9.5$ Hz, 1H; H-5′), 3.59 (dd, $J_{1,2}=7.8$, $J_{2,3}=10.0$ Hz, 1H; H-2), 3.34 (ddd, $J_{5,6a}=1.5$, $J_{5,6b}=5.1$, $J_{4,5}=6.8$ Hz, 1H; H-5), 3.32, 3.30 (2s, 6H; 2OMe), 2.14, 2.12, 2.06, 2.05, 2.04, 2.02, 2.01 (7s, 21H; 7OAc), 1.34, 1.32 (2s, 6H; 2Me), 0.94 (s, 9H; 3Me), 0.11, 0.10 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): $\delta=170.4$–169.3 (m, *C*O), 137.4–127.4 (m, Ar), 100.0 (C-1′), 99.4, 99.3 (2MeO*C*Me), 99.2 (C-1), 95.4 (C-1″), 76.1 (C-5), 75.5 (C-3′), 75.4 (C-4), 72.8 (C-2′), 72.3 (C-4′), 71.9 (C-5′), 71.4 (C-3), 70.3 (*C*H_2Ph), 69.8 (C-3″), 69.4 (C-2), 69.2 (C-2“), 68.3 (C-5”), 67.8 (C-4“), 62.9 (C-6′), 61.9 (C-6), 61.2 (C-6”), 47.8, 47.7 (2OMe), 25.8 (3Me), 20.7–20.4 (m, OAc), 18.22 (*C*Me_3), 17.5, 17.4 (2Me), −5.1, −5.3 ppm (2Me); HRMS calcd for $C_{51}H_{76}NaO_{25}Si$ [*M*+Na]: 1139.4337; found: 1139.4330.

Benzyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (20): The compound was obtained as white solid (1.7 g, 52%) from **19** (1.5 g, 2.95 mmol) by using the same procedure that was used to obtain **15**. M.p. 95–98 °C; $[\alpha]_D^{23}=+64.4$ ($c=0.1$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=7.40$–7.29 (m, 5H; Ar), 5.37 (d, $J_{1'',2''}=4.0$ Hz, 1H; H-1″), 5.32 (t, $J_{3'',2''}=J_{3'',4''}=9.5$ Hz, 1H; H-3″), 5.16 (t, $J_{3',2'}=J_{3',4'}=9.1$ Hz, 1H; H-3′), 5.03 (t, $J_{4'',3''}=J_{4'',5''}=10.1$ Hz, 1H; H-4″), 4.94–4.91 (m, 2H, H-1′, CH_2Ph), 4.85 (dd, $J_{2'',1''}=7.5$, $J_{2'',3''}=4.0$ Hz, 1H; H-2″), 4.81 (dd, $J_{2',1'}=7.5$, $J_{2',3'}=2.1$ Hz, 1H; H-2′), 4.62 (d, $J_{AB}=11.7$ Hz, 1H; CH_2Ph), 4.50 (d, $J_{1,2}=6.9$ Hz, 1H; H-1), 4.28 (dd, $J_{6'b,6'a}=12.2$, $J_{6'b,5'}=2.6$ Hz, 1H; H-6′b), 4.23 (dd, $J_{6''a,6''b}=12.6$, $J_{6''a,5''}=3.8$ Hz, 1H; H-6″a), 4.08–3.96 (m, 3H; H-6′a, H-6″b, H-4′), 3.89 (ddd, $J_{5'',4''}=10.1$, $J_{6''a,5''}=3.3$, $J_{6''b,5''}=2.3$ Hz, 1H; H-5″), 3.86–3.84 (m, 2H; H-6a, H-6b), 3.75–3.64 (m, 3H; H-2, H-4, H-5), 3.49 (ddd, $J_{5',4'}=9.7$, $J_{5',6'a}=3.7$, $J_{5',6'b}=2.4$, 1H; H-5′), 3.37 (dd, $J_{3,2}=3.4$, $J_{3,4}=1.8$, 1H; H-3), 3.24, 3.20 (2s, 6H; 2OMe), 2.07–2.00 (7s, 21H; 7OAc), 1.26, 1.25 (2s, 6H; 2Me), 0.88 (s, 9H; 3Me), 0.07, 0.05 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=170.5$–169.4 (m, *C*O), 137.6–127.4 (m, Ar), 101.8 (C-1), 99.9 (C-1′), 99.6, 99.4 (2MeO*C*Me), 95.6 (C-1″), 77.9 (C-2), 75.8 (C-3′), 74.4 (C-3), 73.3 (C-2′), 72.6 (C-4′), 72.2 (C-5′), 71.2 (C-5), 70.7 (*C*H_2Ph), 69.9 (C-2″), 69.4 (C-3″), 68.4 (C-5″), 68.0 (C-4″), 65.2 (C-4), 63.0 (C-6′), 61.4 (C-6″), 61.3 (C-6), 48.0, 47.9 (2OMe), 25.8 (3Me), 21.0–20.6 (m, OAc), 18.4 (*C*Me_3), 17.6, 17.5 (2Me), −5.0, −5.4 ppm (2Me); HRMS calcd for $C_{51}H_{76}NaO_{25}Si$ [*M*+Na]: 1139.4337, found: 1139.4325.

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-6-*O*-*tert*-butyldimethylsilyl-2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (16): A catalytic amount of NaOMe (1M) was added to a solution of compound **15** (500 mg, 4.5 mmol) in MeOH (15 mL) and the reaction was stirred at room temperature, overnight. The solvent was removed under vacuum to give the crude product, which was used directly in the next step without further purification. The crude product was dissolved in DMF (20 mL), and NaH (130 mg, 5.4 mmol) and BnBr (0.5 mL, 4 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then quenched with ice, and extracted with ether (3×50 mL). The organic solution was washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated and the residue was purified by flash chromatography (EtOAc/hexanes 1:5) to yield **16** as white foam (475 mg, 73%). $[\alpha]_D^{23}=-15$ ($c=0.8$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=7.40$–7.11 (m, 40H; Ar), 5.73 (d, $J_{1'',2''}=3.7$ Hz, 1H; H-1″), 4.96–4.52 (m, 14H; 7CH_2Ph), 4.63 (m, 1H; H-1′), 4.60 (m, 1H; H-1), 4.45, 4.26 (2d, $J_{A,B}=12.1$ Hz, 2H; CH_2Ph), 4.18 (t, $J_{3'',4''}=J_{4'',5''}=8.9$ Hz, 1H; H-4″), 4.01 (t, $J_{3',4'}=J_{4',5'}=9.5$ Hz, 1H; H-4′), 3.95–3.77 (m, 8H; H-6a, H-3″, H-4′, H-6″a, H-3, H-6b, H-6b″, H-3′), 3.66 (m, 2H; H-5′, H-2), 3.54–3.49 (m, 3H; H-5″, H-6′a, H-2″), 3.46 (dd, $J_{2',1'}=8.0$, $J_{2',3'}=9.0$ Hz, 1H; H-2′), 3.38 (dd, $J_{6'a,6'b}=1.8$, $J_{5',6'b}=10.9$ Hz, 1H; H-6′b), 3.33 (ddd, $J_{5,6a}=1.8$, $J_{5,6b}=3.5$, $J_{4,5}=5.3$ Hz, 1H; H-5), 3.31, 3.28 (2s, 6H; 2OMe), 1.34, 1.32 (2s, 6H; 2Me), 1.32, 1.21 (2s, 6H; 2Me), 0.91 (s, 9H; 3Me), 0.07, 0.06 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): $\delta=138.3$–126.1 (m, Ar), 101.3 (C-1′), 99.2 (C-1), 99.1, 99.0 (2MeO*C*Me), 96.2 (C-1″), 84.6 (C-3′), 82.3 (C-2′), 81.6 (C-4′), 78.8 (C-5″), 77.3 (C-5′), 76.3 (C-5), 75.0, 74.5, 74.2, 73.6, 73.2, 73.0, 72.8, 69.8 (8*C*H_2Ph), 74.4 (C-2“), 72.5 (C-4), 71.6 (C-3″), 70.4 (C-3), 70.3 (C-4”), 69.4 (C-2), 68.1 (C-6″), 67.7 (C-6′), 61.2 (C-6), 47.5, 47.4 (2OMe), 25.5 (3Me), 17.93 (*C*Me_3), 17.2, 17.1 (2Me), −5.4, −5.6 ppm (2Me); HRMS calcd for $C_{86}H_{104}NaO_{18}Si$ [*M*+Na]: 1477.6941, found: 1477.6941.

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (21): The compound was obtained as white solid (585 mg, 76%) from **20** (592 mg, 0.53 mmol) by using the same procedure that was used to obtain **16**. M.p. 90–92 °C; $[\alpha]_D^{23}=+76.8$ ($c=1.0$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=7.43$–7.17 (m, 40H; Ar), 5.77 (d, $J_{1'',2''}=3.6$ Hz, 1H; H-1″), 5.05–4.84 (m, H-1′, 8H; 7CH_2Ph), 4.71–4.51 (m, H-1, 9H; 8CH_2Ph), 4.40 (d, $J_{A,B}=12.1$ Hz, 1H; CH_2Ph), 4.24 (t, $J_{4',3'}=J_{4',5'}=9.2$ Hz, 1H; H-4′), 4.18 (t, $J_{4'',3''}=J_{4'',5''}=8.9$ Hz, 1H; H-4″), 4.13–3.80 (m, 8H; H-6a, H-6b, H-3, H-3′, H-3″, H-4, H-6′a, H-6″a), 3.76–3.66 (m, 4H; H-6″b, H-6′b, H-2, H-5″), 3.58–3.48 (m, 4H; H-2″, H-2′, H-5′, H-5), 3.35, 3.17 (2s, 6H; 2OMe), 1.33, 1.30 (2s, 6H; 2Me), 0.98 (s, 9H; 3Me), 0.18, 0.16 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): $\delta=138.8$–126.5 (m, Ar), 101.9 (C-1′), 101.2 (C-1), 99.5, 99.4 (2MeO*C*Me), 96.7 (C-1″), 84.8 (C-5″), 83.0 (C-2′), 81.9 (C-3″), 79.2 (C-2″), 77.7 (C-4″), 75.4, 74.9, 74.6 (3CH_2Ph), 74.4 (C-5, C-5′), 73.8, 73.4 (*C*H_2Ph), 73.3 (C-3), 73.1 (*C*H_2Ph), 72.3 (C-4′), 70.8 (C-3′), 70.9 (C-2), 69.7 (*C*H_2Ph), 68.2 (C-6″), 68.1 (C-6′), 65.1 (C-4), 61.4 (C-6), 48.0 (2OMe), 25.8, 25.5 (3Me), 18.3 (*C*Me_3), 17.8, 17.6 (2Me), −5.0, −5.4 ppm (2Me); HRMS calcd for $C_{86}H_{104}NaO_{18}Si$ [*M*+Na]: 1477.6941, found: 1476.6938.

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-6-*O*-trifluoromethanesulfonyl-2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (17): TBAF (1.0M solution in THF, 0.28 mL, 0.28 mmol) was added to a solution of **16** (205 mg, 0.14 mmol) in THF (15 mL) and the reaction mixture was stirred at room temperature. After 12 h it was concentrated and further dried under high vacuum for 1 h. The crude product was dissolved in CH_2Cl_2 (10 mL) and pyridine (0.013 mL, 1.2 equiv) was added. The mixture was cooled to −10 °C, and Tf_2O (0.036 mL, 1.5 equiv) was added under N_2. After 30 min the reaction was quenched by the addition of cold saturated $NaHCO_3$ (1.5 mL). The organic layers were washed with 1N HCl (5 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated, in vacuo. Chromatographic purification of the crude product (EtOAc/hexanes 1:10) gave **17** as a foam (85 mg, 41%). $[\alpha]_D^{23}=-5.5$ ($c=0.2$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=7.38$–7.11 (m, 40H; Ar), 5.62 (d, $J_{1'',2''}=3.7$ Hz, 1H; H-1″), 4.91–4.32 (m, 16H; 8CH_2Ph), 4.85 (m, 1H; H-6a), 4.60 (m, 1H; H-6b), 4.59 (m, 1H; H-1′), 4.53 (m, 1H; H-1), 4.05 (m, 2H; H-5″, H5′), 3.91 (t, $J_{3,4}=J_{4,5}=9.7$ Hz, 1H; H-4), 3.85 (t, $J_{3',4'}=J_{4',5'}=9.6$ Hz, 1H; H-4′), 3.76 (m, 4H; H-4″, H-6′a,b, H-3′), 3.66 (m, 2H; H-2, H-3), 3.56–3.48 (m, 4H; H-6″a, H-5, H-2′, H-2″), 3.42 (dd, $J_{6''a,6''b}=1.8$, $J_{5'',6''b}=10.5$ Hz, 1H; H-6″b), 3.30, 3.29 (2s, 6H; 2OMe), 1.32, 1.23 ppm

(2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): δ=138.6–126.5 (m, Ar), 118.4 (m, *C*F_3), 100.6 (C-1′), 99.7, 99.5 (2MeO*C*Me), 99.4 (C-1), 96.9 (C-1″), 84.9 (C-4″), 82.2 (C-2′), 81.9 (C-4), 79.1 (C-5), 77.6 (C-3), 75.5, 75.0, 74.7, 74.3, 73.9, 73.4, 73.3, 73.2 (8*C*H_2Ph), 74.6 (C-2″), 74.5 (C-4′), 72.8 (C-3′), 72.6 (C-5″), 71.0 (C-3‴), 70.7 (C-6), 69.6 (C-2), 69.1 (C-6′), 68.4 (C-5′), 68.1 (C-6″), 48.6, 47.9 (2OMe), 17.5 ppm (2Me); HRMS calcd for $C_{81}H_{89}F_3NaO_{20}S$ [*M*+Na]: 1493.5512, found: 1493.5543.

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-6-*O*-triflouromethanesulfonyl-3,4-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (22): Compound was obtained as white solid (227 mg, 86%) from **21** (262 mg, 0.18 mmol) by using the same procedure that was used to obtain **17**. M.p. 80–82 °C; $[\alpha]_D^{23}$ = +51.4 (c=0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ=7.34–7.10 (m, 40H; Ar), 5.67 (d, $J_{1'',2''}$=3.7 Hz, 1H; H-1″), 4.95–4.73 (m, 9H; H-1′, H-6b, 7CH_2Ph), 4.63–4.45 (m, 10H; H-1, H-6a, 8CH_2Ph), 4.33 (d, $J_{A,B}$= 12.1 Hz, 1H; CH_2Ph), 4.14 (t, $J_{4',3'}$=$J_{4',5'}$=9.2 Hz, 1H; H-4′), 4.05 (t, $J_{5,4}$= $J_{5,6a}$=9.3 Hz, 1H; H-5), 3.91–3.84 (m, 2H; H-3″, H-4), 3.78–3.73 (m, 4H; H-5″, H-6″a, H-3′, H-2), 3.70–3.64 (m, 3H; H-3, H-4″, H-6″b), 3.60 (dd, $J_{6'b,6'a}$=10.7, $J_{6'b,5'}$=2.7 Hz, 1H; H-6′b), 3.50–3.42 (m, 4H; H-2″, H-2′, H-5′, H-6′a), 3.24, 3.07 (2s, 6H; 2OMe), 1.26, 1.21 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): δ=138.6–126.5 (m, Ar), 121.8, 119.6, 117.5, 115.4 (m, *C*F_3), 102.0 (C-1′), 101.3(C-1), 99.8, 99.7 (2MeO*C*Me), 96.8 (C-1″), 84.8 (C-5″), 82.9 (C-2′), 82.0 (C-3″), 79.2 (C-2″), 77.7 (C-4″), 75.5, 75.0 (*C*H_2Ph), 74.7 (C-6, C-5), 74.5 (C-5′), 73.9, 73.8, 73.5, 73.3, 73.2 (6*C*H_2Ph), 72.6 (C-4), 72.4 (C-4′), 71.0 (C-3′), 70.9 (C-2), 68.3 (C-6″), 68.2 (C-6′), 65.3 (C-3), 48.1 (2OMe), 17.7, 17.5 ppm (2Me); HRMS calcd for $C_{81}H_{89}F_3NaO_{20}S$ [*M*+Na]: 1493.5512, found: 1493.5487.

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-6-deoxy-6-[2,3,5-tri-*O*-benzyl-1,4-dideoxy-episulfoniumylidene-D-arabinitol]-2,3-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside trifluoromethanesulfonate (24): The mixture of the thioether **23** (64 mg, 0.15 mmol) and **17** (75 mg, 0.051 mmol) in CH_2Cl_2 (1 mL) were stirred, overnight, at room temperature for 24 h. The mixture was concentrated and purified by column chromatography ($CHCl_3$/MeOH 20:1) to give the sulfonium salt **24** as syrup (90 mg, 95%). Analysis by NMR spectroscopy showed that the product was a mixture of two isomers (~5:1) at the stereogenic sulfur center. The major component of the mixture was assigned to be the diastereomer with a *cis* relationship between H-4 and H-6' on the basis of analysis of the NOESY spectrum.

Data for the major diastereomer (*trans*-**24**) were: ^{1}H NMR ($CDCl_3$): δ= 7.36–7.11 (m, 55H; Ar), 5.56 (d, $J_{1''',2'''}$=3.6 Hz, 1H; H-1‴), 4.90–4.36 (m, 22H; CH_2Ph), 4.67 (m, 1H; H-1″), 4.56 (m, 1H; H-1′), 4.46 (m, 1H; H-2), 4.27 (m, 1H; H-3), 4.11–4.01 (m, 4H; H-5′, H-4, H-4′, H-5‴), 3.92 (t, $J_{3''',2'''}$=$J_{3''',4'''}$=9.5 Hz, 1H; H-3‴), 3.83–3.70 (m, 8H; H-1a, H-5″, H-3″, H-5a, H-5b, H-6′a, H-3, H-6‴a), 3.68–3.56 (m, 6H; H-4‴, H-6′b, H-4″, H-6″a, H-6‴b, H-2′), 3.52–3.47 (m, 3H; H-2‴, H-2″, H-6″b), 3.43 (dd, $J_{1a,1b}$=4.0, $J_{1b,2}$=13.4 Hz, 1H; H-1b), 3.31, 3.29 (2s, 6H; 2OMe), 1.34, 1.23 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): δ=138.6–126.6 (m, Ar), 120.8 (m, *C*F_3), 100.7 (C-1′), 100.3 (H-1″), 99.7, 99.6 (2MeO*C*Me), 99.0 (C-1‴), 84.6 (C-5″), 82.4 (C-3), 82.3 (C-2), 81.8 (C-3‴), 81.5 (C-2″), 79.2 (C-2‴), 77.6 (C-4‴), 76.5 (H-3″), 75.5, 75.0, 74.0, 73.6, 73.5, 73.2, 73.0, 72.4, 72.1, 71.8 (m, *C*H_2Ph), 74.5 (H-2′), 73.3 (H-4′), 71.5 (C-5′), 71.1 (C-3′), 69.5 (C-4″), 69.3 (C-5), 68.1 (C-6″), 67.7 (C-5‴), 67.1 (C-4), 66.4 (C-6‴), 48,8 47.9 (2OMe), 47.2 (C-1), 46.9 (C-6′), 17.5, 17.4 ppm (2Me); HRMS calcd for $C_{106}H_{118}O_{20}S$ [*M*+H]: 1742.7932, found: 1742.7932.

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-6-deoxy-6-(2,3,5-tri-*O*-benzyl-1,4-dideoxy-episulfoniumylidene-D-arabinitol)-3,4-*O*-[(2*R*,3*R*)-2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside trifluoromethanesulfonate (25): The mixture of the thioether **23** (64 mg, 0.15 mmol) and **22** (80 mg, 0.054 mmol) in CH_2Cl_2 (1 mL) was stirred, overnight, at room temperature for 24 h. The mixture was concentrated and purified by column chromatography ($CHCl_3$/MeOH 20:1) to give the sulfonium salts **25a** and **25b** as syrups (91.8 mg, 90%). Analysis by crude NMR spectroscopy showed that the product was a mixture of two isomers (~2.8:1) at the stereogenic sulfur center.

Data for the major diastereomer (**25a**) are: $[\alpha]_D^{23}$ = +62.5 (c=0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ=7.34–7.08 (m, 55H; Ar), 5.64 (d, $J_{1''',2'''}$= 3.6 Hz, 1H; H-1‴), 4.93–4.72 (m, 8H; H-1″, 7CH_2Ph), 4.64 (d, $J_{A,B}$= 12.6 Hz, 1H; *CH*$_2$*Ph*), 4.60–4.40 (m, 15H; H-2, H-1′, 13CH_2Ph), 4.39 (br d, J=7.5 Hz, 1H; H-4), 4.31–4.27 (m, H-3, 2H; CH_2Ph), 4.09 (t, $J_{4''',3'''}$=$J_{4''',5'''}$=9.2 Hz, 1H; H- 4″), 3.99–3.92 (m, 3H; H-2′, H-6′b, H-1b), 3.90–3.85 (m, 1H; H-5′, H-3‴), 3.83–3.73 (m, 2H; H-3′, H-1a), 3.77–3.71 (6H, H-5‴, H-6‴a, H-6‴b, H-3″, H-6″a, H-6′a), 3.65–3.62 (m, 2H; H-6″b, H-4‴), 3.57–3.54 (m, 2H; H-4′, H-5a), 3.49–3.40 (m, 4H; H-2‴, H-2″, H-5″, H-5b), 3.19, 3.06 (2s, 6H; 2OMe), 1.25, 1.20 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): δ=138.7–126.5 (m, Ar), 121.9, 119.7 (*C*F_3), 102.5 (C-1′), 102.1 (C-1″), 100.1, 99.8 (2MeO*C*Me), 96.8 (C-1‴), 84.8 (C-5‴, C-2″), 82.7 (C-2, C-3), 82.0 (C-3‴), 79.2 (C-2‴), 77.7 (C-4‴), 75.5, 75.0, 74.7 (3*C*H_2Ph), 74.5 (C-5″), 74.4 (C-2′), 73.9, 73.7, 73.5, 73.4, 73.3 (5*C*H_2Ph), 72.6 (C-4″), 72.5, 72.2 (*C*H_2Ph), 72.0 (C-3′), 71.3 (*C*H_2Ph), 71.0 (C-3″), 70.0 (C-5′), 68.8 (C-6″), 68.2 (C-5, C-4′), 66.5 (C-4, C-6‴), 48.6 (OMe), 48.2 (C-1), 48.1 (OMe), 46.6 (C-6′), 17.7, 17.3 ppm (2Me); HRMS calcd for $C_{106}H_{118}O_{20}S$ [*M*+H]: 1742.7932, found: 1742.7882.

Data for the minor diastereomer (**25b**) are: $[\alpha]_D^{23}$ = −25.0 (c=0.04, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ=7.38–7.12 (m, 55H; Ar), 5.68 (d, $J_{1''',2'''}$= 3.6 Hz, 1H; H-1‴), 4.97–4.88 (m, 4H; H-1″, 3*CH*$_2$*Ph*), 4.83–4.78 (m, 5H; 5CH_2Ph), 4.66 (d, $J_{1',2'}$=7.5 Hz, 1H; H-1′), 4.63–4.46 (m, 12H; H-3, 11CH_2Ph), 4.48–4.46 (m, 2H; 2CH_2Ph), 4.44 (m, 1H; H-2), 4.37–4.33 (m, 2H; H-4, CH_2Ph), 4.13 (t, $J_{4'',3''}$=$J_{4'',5''}$=9.2 Hz, 1H; H-4″), 4.08 (dd, $J_{6''a,5''}$=4.1, $J_{6''a,6''b}$=11.7 Hz, 1H; H-6″a), 3.98 (dd, $J_{2',1'}$=9.7, $J_{2',3'}$=2.2 Hz, 1H; H-2′), 3.95–3.89 (m, 4H; H-3‴, H-5′, H-6″b, H-6′a), 3.84 (t, $J_{3',4'}$= $J_{3',2'}$=9.6 Hz, 1H; H-3′), 3.82–3.76 (m, 4H; H-5‴, H-6‴a, H-3″, H-6′b), 3.75–3.70 (m, 2H; H-6‴b, H-1a), 3.67 (t, $J_{3''',4'''}$=$J_{5''',4'''}$=9.5 Hz, 1H; H-4‴), 3.63–3.59 (m, 2H; H-1b, H-5a), 3.55 (t, $J_{4',3'}$=$J_{5',4'}$=9.7 Hz, 1H; H-4′), 3.52–3.45 (4H, H-2‴, H-2″, H-5″, H-5b), 3.07, 2.97 (2s, 6H; 2OMe), 1.19, 1.06 ppm (2s, 6H; 2Me); ^{13}C NMR ($CDCl_3$): δ=138.7–126.5 (m, Ar), 121.9, 119.8 (*C*F_3), 102.8 (C-1′), 102.1 (C-1″), 100.0, 99.7 (2MeO*C*Me), 96.8 (C-1‴), 84.8 (C-5‴), 83.2 (C-2), 83.5 (C-3), 82.7 (C-2″), 82.0 (C-3‴), 79.2 (C-2‴), 77.7 (C-4‴), 75.5, 75.0 (*C*H_2Ph), 74.7 (C-2′), 74.6 (C-5″), 73.8–72.9 (9*C*H_2Ph), 72.6 (C-4″), 71.9 (C-3′), 71.0 (C-3″), 69.1(C-5′), 68.8 (C-6‴), 68.2 (C-5), 67.1 (C-4′), 65.0 (C-6″), 63.3 (C-4), 48.0, 48.1 (2OMe), 46.5 (C-1), 38.6 (C-6′), 17.7, 17.3 ppm (2Me); HRMS calcd for $C_{106}H_{118}O_{20}S$ [*M*+H]: 1742.7932, found: 1742.7882.

1,4-Dideoxy-1,4-[[2*S*,3*S*,4*R*,5*S*]-2,4,5,6-tetrahydroxy-3-(4-*O*-α-D-glucopyranosyl-D-glucosyl) hexyl]-(*R*/*S*)-epi-sulfoniumylidine]-D-arabinitol chloride (10): $Pd(OH)_2$, 20% weight on carbon (200 mg) was added to a solution of sulfonium salt **24** (85 mg, 0.045 mmol, 5:1 mixture of isomers) in 85% AcOH/H_2O (40 mL) and the mixture was stirred under 100 Psi H_2 for 24 h. The catalyst was removed by filtration through a bed of Celite, and then washed with water. The solvents were removed under reduced pressure and the residue was dissolved in 80% TFA (5 mL) and stirred at room temperature for 2 h. The solvents were removed under reduced pressure; the residue was dissolved in water (5 mL) and washed with CH_2Cl_2 (2×5 mL). The water layer was evaporated to give the crude product. The residue was dissolved in H_2O (10 mL), Amberlyst A-26 resin (100 mg) was added, and the reaction mixture was stirred at room temperature for 2 h. Filtration through cotton, followed by solvent removal gave the crude hemiacetal. The crude product was dissolved in water (5 mL), and the solution was stirred at room temperature while $NaBH_4$ (7 mg, 0.18 mmol) was added. Stirring was continued for another 3 h and the mixture was acidified to pH<4 by dropwise addition of HCl (2M). The mixture was evaporated to dryness and the residue was co-evaporated with anhydrous MeOH (3×10 mL). The residue was purified by crystallization with EtOAc/MeOH/H_2O (10:3:1) followed by reverse phase chromatography (H_2O) to give **10** (d.r. 5:1) as a colorless solid (21 mg, 70%).

Data for the major diastereomer (**10**) are: ^{1}H NMR (D_2O): δ=5.34 (d, $J_{1''',2'''}$=3.7 Hz, 1H; H-1‴), 4.68 (m, 1H; H-2), 4.61 (d, $J_{1'',2''}$=7.6 Hz, 1H; H-1″), 4.36 (m, 2H; H-3, H-2′), 4.08 (dd, $J_{4,5a}$=5.0, $J_{5a,5b}$=12.2 Hz, 1H; H-5a), 4.02 (m, 2H; H-1a, H-3‴), 3.92 (m, 1H; H-3′), 3.89–3.57 (m, 16H; H-4″, H-5b, H-1′a, H-1′b, H1b, H-6‴a, H-4, H-6‴b, H-6″a, H-6″b, H-4′, H-3″, H-6′a, H-5″, H-5′, H-6′b), 3.51 (m, 2H; H-4‴, H-2‴), 3.33 ppm (m, 2H; H-5‴, H-2″); ^{13}C NMR (D_2O): δ=102.9 (H-1″), 99.5 (C-1‴), 81.5

(C-3′), 77.3 (C-3), 76.9 (H-2), 66.2 (C-5″), 76.0 (C-3″), 74.4 (C-4‴), 73.1 (C-2″), 72.7 (C-5′), 72.6 (C-4′), 71.9 (C-4), 71.5 (H-2‴), 69.8 (H-3‴), 69.3 (H-5‴), 69.2 (H-2″), 67.9 (C-2′), 62.3 (C-6′), 60.4 (C-6‴), 60.3 (H-6″), 59.2 (C-5), 49.2 (C-1), 48.2 ppm (C-1′); HRMS calcd for $C_{23}H_{43}O_{18}S$ [$M+$]: 639.2165, found: 639.2152.

1,4-Dideoxy-1,4-[[2*S*,3*S*,4*R*,5*S*]-2,3,4,6-tetrahydroxy-5-(4-*O*-α-D-glucopyranosyl-D-glucosyl)hexyl]-(*R*/*S*)-epi-sulfoniumylidine]-D-arabinitol chloride (11): Compound was obtained as white solid (18 mg, 64%, 2.8:1 mixture of isomers) from a mixture of **25a** and **25b** (79 mg, 0.042 mmol, 2.8:1 mixture of isomers) by using the same procedure that was used to obtain **10**.

Data for the major isomer (**11**) are: ^{1}H NMR (D_2O): $\delta = 5.33$ (d, $J_{1''',2'''} = 2.6$ Hz, 1H; H-1‴), 4.70 (m, 1H; H-2), 4.57 (d, $J_{1'',2''} = 7.9$ Hz, 1H; H-1″), 4.39 (brs, 1H; H-3), 4.19 (brs, 1H; H-2′), 4.08–4.04 (m, 2H; H-4, H-6′a), 3.98–3.50 (m, 20H; H-6″b, H-1a, H-1b, H-5a, H-5b, H-1′a, H-3′,H-4′, H-6′b, H-6‴a, H-6‴b, H-3″, H-6″a, H-1′b, H-5′, H-3‴, H-5‴, H-4″, H-2‴, H-5″), 3.36–3.26 ppm (m, 2H; H-4‴, H-2″); ^{13}C NMR (D_2O): $\delta = 103.0$ (C-1″), 99.5 (C-1‴), 83.1 (C-5′), 77.0 (C-3, C-2), 76.5 (C-3′, C-4″), 74.5 (C-5″), 73.2 (C-2″), 72.8 (C-5‴), 72.6 (C-3‴), 72.5 (C-3″), 71.6 (C-2‴), 70.0 (C-4), 69.3 (C-4‴), 68.5 (C-4′), 67.5 (C-2′), 61.1 (C-5), 60.6 (C-6″), 60.4 (C-6‴), 59.2 (C-6′), 50.1 (C-1′), 48.2 ppm (C-1); HRMS calcd for $C_{23}H_{43}O_{18}S$ [$M+$]: 639.2165, found: 639.2160.

Acknowledgements

We thank Buford L. Nichols, Roberto Quezada-Calvillo and Hassan Naim for reagents for recombinant expression, and Lyann Sim for MGAM and SI enzyme purification. K.J. was supported by a scholarship from the Canadian Institutes of Health Research (CIHR) and the Canadian Digestive Health Foundation. We also thank the CIHR (111237) and the Heart and Stroke Foundation of Ontario (NA-6305) for financial support.

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Received: July 9, 2011
Published online: November 30, 2011

