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Synthesis of the mannosyl erythritol lipid MEL A; confirmation of the configuration of the *meso*-erythritol moiety

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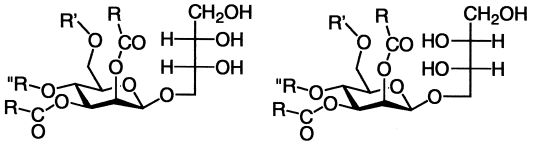
Abstract—The total synthesis of the two possible diastereomers of mannosylerythritol lipid A, a novel biosurfactant from *Candida antartica* T-34 with promising anti-proliferative properties in several cell lines, is described. By comparison with an authentic sample, the natural material is confirmed as a single diastereomer with the 4-*O*-(β-D-mannopyranosyl) D-erythritol configuration.

1. Introduction

The mannosylerythritol lipids, MEL A–C, are a promising class of biosurfactants[1] produced in high yield by the yeast *Candida antartica* T-34 when grown on soy bean oil.[2] They have drawn increasing interest in recent years following the discoveries that they induce apoptosis and differentiation in malignant mouse melanoma cells,[3] and inhibit the growth of the human promyelocytic leukemia cell line HL 60.[4] Additionally, they have been shown to form giant vesicles and to bind tightly to the mannose-binding protein concanavalin A.[5] Structurally, the MEL's have been shown by a combination of degradation and spectroscopic studies to consist of a β-mannosyl glycoside of *meso*-erythritol with the linkage occurring through a primary hydroxyl group of *meso*-erythritol.[2,5] The remaining three hydroxyl groups of the erythritol moiety are free whereas all three MEL's are acylated with a mixture of C_8–C_{14} hydrocarbon acids on positions 2- and 3- of the mannose sugar. MEL's A, B, and C are differentiated by the degree of acetylation on positions 4- and 6- of the mannose ring with MEL A being the diacetate and B, and C each being one of the two possible mono-acetates. Glycosylation of *meso*-erythritol on one or the other of the two enantiotopic primary hydroxyl groups provides two diastereomers **1** and **2**. In the original paper[2] the MEL's were drawn with configuration **1** [4-*O*-(β-D-mannopyranosyl D-erythritol] whereas a more recent paper[5] appears to show the diastereomer **2**.



1 **2**

MEL A: R = C_nH_{n+1} (n = 7-13), R' = R" = Ac
MEL B: R = C_nH_{n+1} (n = 7-13), R' = Ac, R" = H
MEL C: R = C_nH_{n+1} (n = 7-13), R' = H, R" = Ac

The configuration of the erythritol was originally assigned on the grounds that deacylation of a mixture of MEL's A, B, and C led to a single, free β-D-mannosyl erythritol whose melting point (159–161°C) and specific rotation (−36.5°, *c* 1, H_2O) matched those of a free β-D-mannosyl erythritol obtained by saponification of MEL B7, a less highly acylated mannosyl erythritol lipid previously isolated by the same group.[6] The configuration of the latter material was assigned[6] by comparison of the melting point and specific rotation of the deacylated material with those of the authentic substance.[7,8] Two further partially acylated mannosyl erythritols, the schizonellin's A and B, were subsequently isolated and assigned as the 4-*O*-(β-D-mannopyranosyl D-erythritol configuration,[9] again by comparison of the melting point and specific rotation of the deacylated material with the literature values.[7,8] 4-*O*-(β-D-Mannopyranosyl D-erythritol (**3**) itself (mp 160–162°C, $[\alpha]_D$=−38°, *c* 1, H_2O) was originally isolated from cultures of the fungus *Ustilago* sp. by Boothroyd and coworkers.[7] Its configuration was assigned first by isotopic tracer experiments,[10] then by classical rules based on specific rotations,[11] and finally by preparation of an authentic sample by degradation of 6-*O*-(β-D-mannopyranosyl) D-glucose.[8] A free mannosyl erythritol was subsequently isolated from

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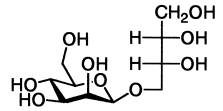
Candida sp. KSM-1529 and it was assumed to be the same as the one from *Ustilago*, even though no melting point or specific rotation data were given for comparison purposes.[12] The configuration of all of the MEL's rests therefore on the comparison of a single melting point and specific rotation with the literature values for the authentic 4-*O*-(β-D-mannopyranosyl) D-erythritol. The close concordance between the melting points and specific rotations of the mannosyl erythritol obtained by saponification of the MEL's and those of authentic 4-*O*-(β-D-mannopyranosyl D-erythritol (**3**) make it highly likely that the MEL's were originally correctly assigned as diastereomer **1**. Nevertheless, the absence of the corresponding data for the diastereomeric deacylated compound for comparison, and the current pharmaceutical potential of these molecules, both indicated to us that a further check was in order. We reasoned that this might best be realized through total synthesis using one or other of the direct β-mannosylation protocols developed in this laboratory.[13,14] Here we report the successful accomplishment of this task and the unambiguous assignment of the MEL's as diastereomer **1**.

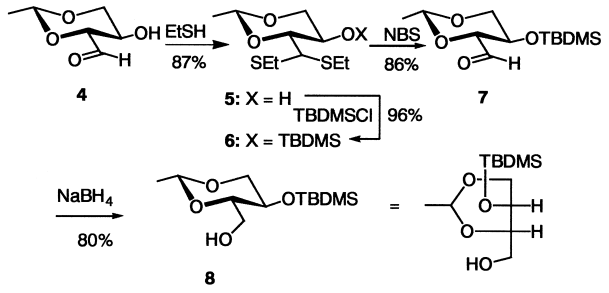


4-*O*-(β-D-mannopyranosyl)
D-erythritol

3: Mannosyl Erythritol

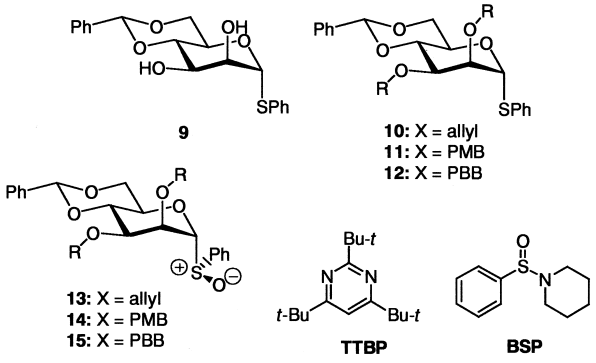
2. Results and discussion

Our study began with the standard preparation of 2,4-*O*-ethylidene-D-erythrose (**4**) from D-glucose.[15,16] It was converted to the diethyl dithioacetal **5** and from there to the silyl ether **6** by the usual methods. Release of the dithioacetal gave the aldehyde **7**, which was reduced with sodium borohydride to give the glycosyl acceptor **8** (Scheme 1). Direct protection of the hydroxyl group in **4**, leading straight to **7**, is not possible owing to the dimeric nature[17] of this substance.



Scheme 1.

Turning to the donor, differential protection of the four hydroxyl groups in such a way that *O*-2 and *O*-3 could be released before *O*-4 and *O*-6 was required. As the mannosylation protocol requires the 4,6-*O*-benzylidene group in order for high β-selectivity to be obtained[13,14,18] this meant that the protecting groups on *O*-2 and *O*-3 must be released other than by hydrogenation or acidolysis. Simple benzyl groups were therefore excluded. Silyl groups were ruled out because of the need for orthogonality with the silyl moiety in the acceptor (**8**) and because of their known[19] detrimental effect (at *O*-2 and *O*-3) on diastereoselectivity in the mannosylation. In the event the 2,3-di-*O*-allyl (**10**) and 2,3-di-*O*-*p*-methoxybenzyl (**11**) ethers, both readily prepared from the known diol **9**,[13] were selected for investigation. The 2,3-di-*O*-*p*-bromobenzyl ether **12** was also prepared but was only employed in the subsequent synthesis of the second diastereomer. The three thioglycosides **10**–**12** were oxidized to the corresponding glycosyl sulfoxides **13**–**15**, respectively, with mcpba or MMPP, and, in line with the precedent,[20] all gave a single diastereomer assigned as R_S by analogy with the structures previously assigned crystallographically.[20]



Turning to the glycosylation, the diallyl donor (**13**) was activated with triflic anhydride at −75°C in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[†,21] followed by addition of acceptor **8**. The β-mannoside **16** was obtained in 80% isolated yield as a single anomer from this coupling (Table 1). Similarly, acceptor **8** was coupled with the bis-*p*-methoxybenyl protected sulfoxide (**14**) in excellent yield and diastereoselectivity (Table 1). The stereochemistry in these and all other mannosides described here is very readily assigned from the somewhat upfield chemical shift of the mannose H-5 resonance, which is characteristic of 4,6-*O*-benzylidene protected β-mannopyranosides.[13] In addition to the well-established sulfoxide coupling[13,22] we also investigated our new 1-benzenesulfinyl piperidine (BSP)/triflic anhydride method for the activation of thioglycosides.[14] In this very convenient method the thioglycoside **10** and BSP were stirred in the presence of TTBP in dichloromethane at −60°C and treated with triflic anhydride, followed shortly by the acceptor. The selectivity of this coupling was excellent (Table 1), unfortunately the yield was not as high as that obtained from the sulfoxide.

The diallyl ether **16** was converted to the diol **18** in 88% yield by sequential treatment with Felkin's Ir(I) catalyst[23] then mercuric oxide and water (Scheme 2). The bis-PMB ether **17** was converted to **18** on treatment with DDQ but only in 37% yield (Scheme 2). Of the two protection strategies employed, the allyl ether route was therefore the

[†] TTBP is a convenient, crystalline, non-hygroscopic replacement for the more familiar 2,6-di-*tert*-butylpyridines. It is readily prepared in a one pot protocol[21] and is also commercially available from Aldrich Chemical Company.

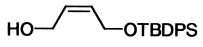
Table 1. Formation of the mannosyl erythritol bond

Donor	Acceptor	Method[a]	Temperature (0°C)	Product (% yield)	Anomeric ratio
13	**8**	A	−75	**16** (80)	β only
14	**8**	A	−75	**17** (82)	β only
10	**8**	B	−60	**16** (66)	β only
15	**23**	A	−75	**24** (73)	β only
12	**23**	B	−60	**24** β (84) +**24** α (6)	14/1 β/α

[a] (A) glycosyl sulfoxide/Tf_2O; (B) thioglycoside/BSP/Tf_2O.

preferred one. Diol **18** was next converted to the bis-dodecyl ester **19** with lauryl chloride in pyridine. The MELs themselves are composites, being variously esterified at the mannose *O*-2 and *O*-3 positions with mixtures C_8 to C_{14} acids; the C_{12} acid was chosen here in a purely arbitrary fashion. Hydrogenolysis of the 4,6-*O*-benzylidene group gave the new diol **20** and this was converted to the diacetate **21**, thereby fulfilling the esterification requirements of the MEL series, with acetic anhydride and pyridine in the usual manner. Finally, the TBDMS and ethylidene groups were both removed from **21** on treatment with BF_3.etherate and thiophenol[24] to give the target molecule **22** as a single diastereomer (Scheme 2).

In order to obtain the second diastereomeric possibility, the known monosilylated diol **23**[25] was coupled to the sulfoxide and thioglycoside donors **12** and **15** using the triflic anhydride and BSP/Tf_2O methods, respectively (Table 1). Of the two methods the BSP one gave the higher yield but less perfect selectivity than the sulfoxide one.



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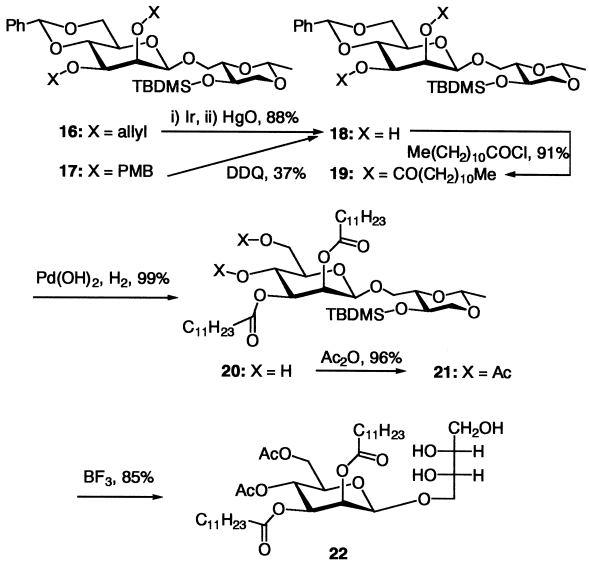
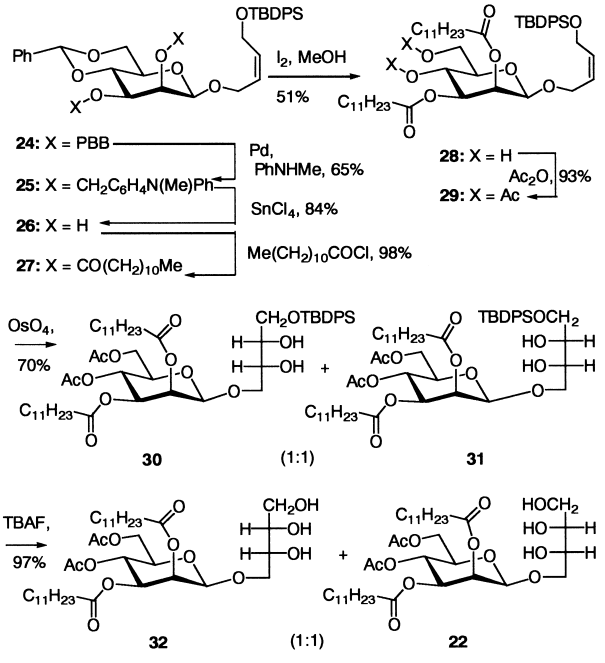
The bis *p*-bromobenzyl ether **24** was then converted to the corresponding bis *p*-(*N*-methyl-*N*-phenylamino)benzyl ether **25** in 65% yield according to the method of Buchwald and Seeberger by treatment with catalytic $Pd(dba)_2$ in the presence of potassium *tert*-butoxide and a bulky phosphine ligand.[26] Exposure of this compound to tin tetrachloride[26] then gave the diol **26** in 84% yield. Reaction with dodecanoyl chloride gave the bis-lauroate ester **27** from which the 4,6-*O*-benzylidene group was removed, giving **28**, in 51% yield, by heating to reflux with iodine in methanol.[27] The acetate esters were then introduced in the standard manner to afford the fully esterified system **29**. Dihydroxylation of **29** using the Van Rheenan protocol[28] afforded an inseparable mixture of **30** and **31** with little or no selectivity. A similar lack of diastereoselectivity was recently reported in the OsO_4 dihydroxylation of the β-glucoside of *cis*-2-butene-1,4-diol.[29] Treatment with TBAF then gave the final compounds **32** and **22**, unfortunately also as an inseparable mixture (Scheme 3). At this stage the total synthesis of both diastereomers was complete, one (**22**) as a pure compound and the other (**32**) in admixture with the first. Doubtless it would be possible to optimize the stereoselectivity in the dihydroxylation sequence in favor of **32**, with use of one or other of several catalytic asymmetric dihydroxylation systems available.[30] However, as the object of the exercise was the identification of configuration of the *meso*-erythritol portion, this avenue was not pursued.

The ^1H NMR spectrum (Fig. 1A) of an authentic sample of MEL A, with a fatty acid composition of 27% C_8, 65% C_{10}, and 8% C_{10}, supplied by Professor Kitamoto, did not match that of the pure diastereomer **22** (Fig. 1C). Obvious inconsistencies between the two spectra are the minor differences in chemical shift of the singlet at ~δ 4.75 (mannose H-1), the double doublet at ~δ 5.1 (mannose H-3), the



Scheme 2.



Scheme 3.

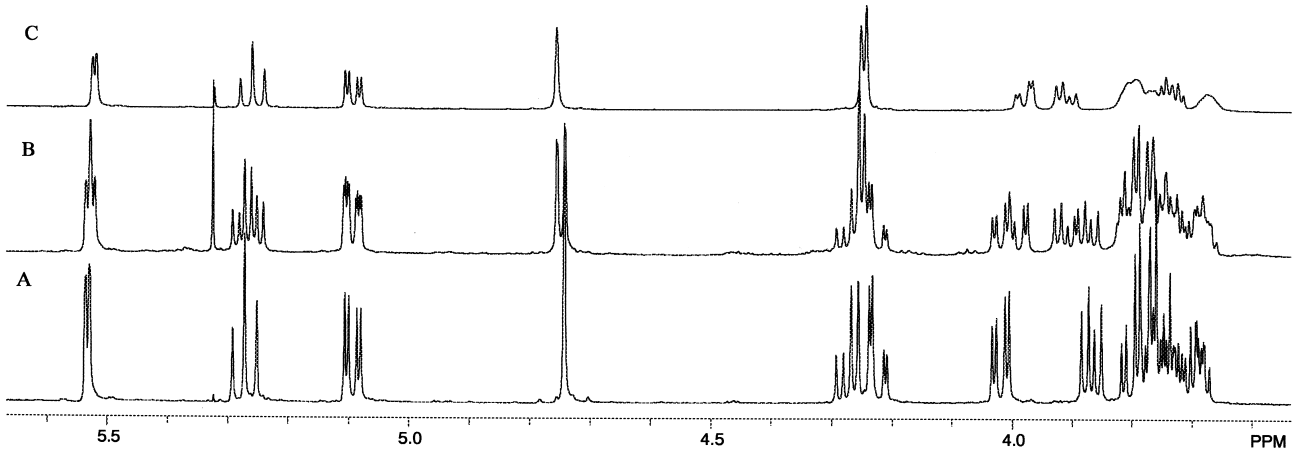


Figure 1. Partial 500 MHz ^{1}H NMR spectra of: (A) authentic MEL A; (B) the mixture of **32** and **22**, and (C) pure **22**.

triplet at ~δ 5.3 (mannose H-4), and the doublet at ~δ 5.5 (mannose H-2). Even more striking is the coupling pattern of the two mannose H-6's (~δ 4.25), which in **22** (Fig. 1C) exhibit minimal coupling between themselves and H-5 appearing as two broad singlets, whereas in authentic MEL A (Fig. 1A) they are both double doublets. Fig. 1B is clearly the spectrum of a mixture of MEL A and its diastereomer. On this basis it can be stated that MEL A, and on the grounds that they are all hydrolyzed to a single free mannosyl erythritol,[2,6] MEL's B, C, and B7 are diastereomerically pure substances having the relative configuration generalized in formula **1** and not **2**. Moreover, it can be stated that the mannosyl erythritol obtained from the MEL's on saponification is the 4-(*O*-β-D-mannopyranosyl) D-erythritol (**3**) previously isolated[7] from fungal sources. It is also likely that the free mannosyl erythritol isolated from *Candida* sp. KSM-1529, and suggested to be the biosynthetic precursor to the MEL's, is substance **3**.[12] Inspection of the ^{13}C NMR spectra of authentic MEL A and those of **22** and of the **22/32** mixture fully concur with the assignment based on the ^{1}H NMR spectra. By adroit manipulation of the 4,6-*O*-benzylidene group in **27**, standard techniques in carbohydrate chemistry, the chemistry described herein should be adaptable to the synthesis of either MEL B or C should the need arise.

3. Experimental

3.1. General

Unless otherwise stated all ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz, respectively. All specific rotations are for $CHCl_3$ solutions. All extracts were dried over $MgSO_4$.

3.2. Preparation of the acceptor 8

3.2.1. 2,4-*O*-Ethylidene-D-erythrose diethyl thioacetal (5). A cold solution of $ZnC1_2$ (8 g, 58.7 mmol) in ethanethiol (12.6 mL, 170.2 mmol) and dry THF (25 mL) was added to a solution of 2,4-*O*-ethylidene-D-erythrose (**4**)[15,16] (8.3 g, 56.8 mmol) at 0°C under argon. The reaction mixture was stirred for 2 h at 0°C, diluted with ether (200 mL), washed with 2 M HCI, water and brine, dried, filtered and evaporated under reduced pressure. The resulting oil was purified by column chromatography (eluent: ether/pentane 2:3) to give the title compound as a colorless oil (12.42 g, 87%). $[\alpha]^{22}_D=-25.4°$ (*c* 0.9); ^{1}H NMR 4.60 (q, *J*=5.1 Hz, 1H), 4.03 (m, 2H), 3.92 (m, 1H), 3.64 (dd, *J*=3.5, 9.0 Hz, 1H), 3.32 (t, *J*=10.4 Hz, 1H), 2.91 (d, 1H), 2.67 (m, 4H), 1.25 (d, 3H), 1.20 (t, *J*=7.4 Hz, 3H), 1.19 (t, *J*=7.4 Hz, 3H); ^{13}C NMR δ 99.3, 84.8, 70.3, 63.7. 52.0, 25.5, 25.4, 20.5, 14.5 (2 C's); HRMS Calcd for $C_{10}H_{20}O_3S_2$ [M^+]: 252.0854. Found: 252.0855.

3.2.2. 2,4-*O*-Ethylidene-3-*O*-*tert*-butyldimethylsilyl-D-erythose diethyl thioacetal (6). To a solution of **5** (10.10 g, 40.1 mmol) in dry DMF (20 mL) imidazole (7.4 g, 108.7 mmol) and *tert*-butyldimethylsilyl chloride (8.16 g, 54.1 mmol) were added. The solution was kept at 46°C for 3 h and subsequently stirred at room temperature for 12 h. It was then diluted with ether, washed with water, 2 M HC1, sat. $NaHCO_3$, water and brine, dried, filtered and evaporated under reduced pressure. Purification was achieved by column chromatography (eluent: ether/pentane 1:24) and the title compound isolated as an oil (12.39 g, 96%). $[\alpha]^{22}_D=-12.4°$ (*c* 0.9); ^{1}H NMR δ 4.62 (q, *J*=5.0 Hz, 1H), 4.04 (d, *J*=1.6 Hz, 1H), 3.96 (m, 2H), 3.70 (b d, *J*=8.5 Hz, 1H), 3.30 (m, 1H), 2.67 (m, 4H), 1.28 (d, 3H), 1.22 (t, *J*=7.3 Hz, 3H), 1.20 (t, *J*=7.5 Hz, 3H), 0.81 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13} C NMR δ 99.3, 86.6, 71.0, 63.8, 51.2, 25.7, 25.5, 24.9, 20.6, 17.9, 14.7, 14.4, −4.9. Anal. Calcd for $C_{16}H_{34}O_3S_2Si$: C, 52.41; H, 9.35. Found: C, 52.73; H, 9.43.

3.2.3. 2,4-*O*-Ethylidene-3-*O*-*tert*-butyldimethylsilyl-D-erythrose (7). A solution of **6** (3.77 g, 10.3 mmol) in acetonitrile (5 mL) was added dropwise to a solution of NBS (11 g, 61.8 mmol) in 80% aqueous acetonitrile at −20°C. The reaction mixture was stirred for 30 min at that temperature, diluted with chloroform, washed twice each with sat. Na_2SO_3, 2 M HCI, $NaHCO_3$, and water, dried, filtered and evaporated under reduced pressure. The oily product was dried at 60°C in high vacuum for 3 h (2.29 g, 86%) and used without further purification in the next step. $[\alpha]^{22}_D=-35.9°$ (*c* 0.6, $CHCI_3$); IR: 1743 cm^{-1} ($CHCl_3$); ^{1}H NMR δ 9.68 (d, *J*=1.1 Hz, 1H), 4.69 (q, *J*=5.1 Hz, 1H), 4.05 (dd, *J*=5.0, 10.8 Hz, 1H), 3.90 (dd, *J*=1.1, 9.5 Hz, 1H), 3.77 (m, 1H), 3.41 (dd, *J*=9.7, 10.7 Hz, 1H), 1.35 (d, *J*=5.1 Hz, 3H), 0.83

(s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 197.3, 98.8, 84.5, 71.3, 62.7, 25.8, 20.4, 17.9, −4.3, −4.9.

3.2.4. 2,4-*O*-Ethylidene-3-*O*-*tert*-butyldimethylsilyl-D-erythritol (8). To a stirred solution of **7** (1.10 g, 4.2 mmol), in CH_2Cl_2 (20 mL) was added sodium borohydride (0.16 g, 12.6 mmol) in ethanol (5 mL). The reaction mixture was stirred for 2 h at room temperature, then quenched with H_2O (2 mL), diluted with CH_2Cl_2 (30 mL), washed with saturated $NaHCO_3$ solution (1×20 mL), H_2O (1×20 mL), and brine (1×20 mL). The organic layer was dried, filtered, concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=1:1) to give **8** (0.90 g, 80%): $[\alpha]^{23}_D$=−39.0° (*c* 1.9); ^{1}H NMR δ 4.69 (q, *J*=5.1 Hz, 1H), 3.99 (dd, *J*=5.1, 10.8 Hz, 1H), 3.81 (b d, *J*=11.7 Hz, 1H), 3.69–3.61 (m, 2H), 3.45–3.38 (m, 1H), 3.34 (t, *J*=10.5 Hz, 1H), 2.04 (b t, 1H), 1.31 (d, *J*=5.4 Hz, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 98.9, 81.8, 71.1, 62.5, 62.0, 25.7, 20.6, 18.0, −4.3, −4.9. Anal. Calcd for $C_{12}H_{26}O_4Si$: C, 54.92; H, 9.99. Found: C, 55.51; H, 9.78.

3.3. Preparation of diastereomer 22

3.3.1. *S*-Phenyl 2,3-di-*O*-allyl-4,6-*O*-benzylidene-1-thia-α-D-mannopyranoside (10). A flask containing diol **9**[13] (1.0 g, 2.76 mmol) was purged with nitrogen and charged with DMF (20 mL) and NaH (0.24 g, 10.08 mmol, 60% dispersion in oil), previously washed with hexane (3×10 mL), was added. After stirring for 20 min, the reaction mixture was cooled to 0°C followed by addition of allyl bromide (1.85 mL, 6.07 mmol). The reaction was stirred for 3 h at room temperature then quenched by dropwise addition of methanol (1.0 mL) and saturated $NaHCO_3$ solution (10 mL), diluted with EtOAc washed with H_2O (1×20 mL), and brine (1×20 mL). The organic layer was dried, filtered, concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=1:9) to give **10** (1.2 g, 98%): $[\alpha]^{23}_D$=+139.7° (*c* 2.4); ^{1}H NMR δ 7.54–7.28 (m, 10H), 6.00–5.88 (m, 2H), 5.63 (s, 1H), 5.57 (s, 1H), 5.37 (b d, *J*=17 Hz, 1H), 5.34 (b d, *J*=17.2 Hz, 1H), 5.22 (d, *J*=10.5 Hz, 2H), 4.39–4.05 (m, 9H), 3.92 (d, *J*=3 Hz, 1H), 3.88 (m, 2H); ^{13}C NMR δ 137.7, 134.9, 131.5, 129.3, 129.0, 128.3, 127.7, 126.2, 118.1, 117.1, 101.7, 87.4, 79.3, 78.3, 75.9, 72.6, 72.2, 68.6, 65.4, 21.2, 11.8, 10.0; ESI HRMS Calcd for $C_{25}H_{28}O_5S$ [M+Na$^+$]: 463.1555. Found: 463.1565.

3.3.2. *S*-Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-methoxybenzyl-1-thia-α-D-mannopyranoside (11). A mixture of diol **9**[13] (3.0 g, 8.3 mmol), sodium hydride (0.660 g, 27.5 mmol, 60% dispersion in oil) previously washed with hexanes (3×10 mL), and tetrabutylammonium iodide (0.610 g, 1.7 mmol) were dried under vacuum for 30 min, then blanketed with nitrogen and dissolved in DMF (30 mL). The reaction mixture was stirred for 20 min, then cooled to 0°C followed by addition of *p*-methoxybenzyl chloride (1.84 mL, 18.1 mmol). After stirring for 3 h at room temperature the reaction was quenched by dropwise addition of methanol (1.0 mL) and saturated $NaHCO_3$ solution (15 mL), diluted with EtOAc (50 mL), washed with H_2O (1×30 mL), and brine (1×30 mL). The organic layer was dried, filtered, concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) to give **11** (4.71 g, 95%): $[\alpha]^{23}_D$=+96.7° (*c* 1.8); ^{1}H NMR δ 7.58–7.25 (m, 14H), 6.80–6.90 (m, 4H), 5.68 (s, 1H), 5.50 (d, *J*=1.2 Hz, 1H), 4.77 (d, *J*=11.7 Hz, 1H), 4.68 (s, 2H), 4.62 (d, *J*=11.7 Hz, 1H), 4.33–4.14 (m, 3H), 4.04–3.91 (m, 3H), 3.83 (s, 3H), 3.82 (s, 3H); ^{13}C NMR δ 159.5, 159.4, 137.8, 134.0, 131.8, 130.6, 130.0, 129.9, 129.5, 129.3, 129.0, 128.3, 127.7, 126.3, 114.0, 113.9, 101.6, 87.4, 79.2, 77.7, 75.9, 72.8, 68.7, 65.7, 55.4; ESI HRMS Calcd for $C_{35}H_{36}O_7S$ [M+Na$^+$]: 623.2079. Found: 623.2079.

3.3.3. *S*-Phenyl 2,3-di-*O*-*p*-bromobenzyl-4,6-*O*-benzylidene-1-thia-α-D-mannopyranoside (12). The title compound was prepared in quantitative yield, as a white crystalline solid from diol **9**[13] and *p*-bromobenzyl bromide according to the protocol described for the allyl analog **10**: $[\alpha]^{23}_D$=+66.7° (*c* 2.3); mp=113–115°C, ^{1}H NMR δ 7.51–7.18 (m, 18H), 5.64 (s, 1H), 5.50 (d, *J*=1.5 Hz, 1H), 4.77 (d, *J*=12.3 Hz, 1H), 4.7–4.57 (m, 3H), 4.3–4.21 (m, 3H), 4.01 (m, 1H), 3.97–3.86 (m, 2H); ^{13}C NMR δ 137.6, 137.4, 136.8, 131.8, 131.7, 131.6, 129.8, 129.4, 129.3, 129.1, 128.4, 127.9, 126.2, 122.0, 121.7, 101.7, 87.1, 79.2, 78.5, 76.4, 72.6, 72.4, 68.6, 65.5; Calcd for $C_{33}H_{30}Br_2O_5S$: C, 56.75; H, 4.33. Found: 56.37; H, 4.26; ESI HRMS Calcd for $C_{33}H_{30}Br_2O_5S$ [M+Na$^+$]: 719.0078. Found: 719.0066.

3.3.4. *S*-Phenyl 2,3-di-*O*-allyl-4,6-*O*-benzylidene-1-thia-α-D-mannopyranoside *S*-oxide (13). To a solution of the thioglycoside **10** (0.450 g, 1.02 mmol), in a mixture of THF (10 mL), and H_2O (1.0 mL) was added portionwise MMPP (0.25 g, 0.51 mmol) at 0°C until the substrate was consumed completely. The reaction mixture was concentrated, taken up with EtOAc (20 mL), washed with water (20 mL), saturated $NaHCO_3$ solution (10 mL), and brine (20 mL). The organic layer was dried, filtered, concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=3:7) to give **13** (0.420 g, 90%): $[\alpha]^{23}_D$=−29.7° (*c* 2.3); ^{1}H NMR δ 7.66–7.35 (m, 10H), 5.99–5.75 (m, 2H), 5.59 (s, 1H), 5.34 (dt, *J*=1.5, 17.4 Hz, 1H), 5.25–5.15 (m, 3H), 4.50 (d, *J*=1.2 Hz, 1H), 4.40–4.33 (m, 2H), 4.26–4.02 (m, 9H), 3.73 (t, *J*=9.6 Hz, 1H); ^{13}C NMR δ 141.8, 137.3, 134.7, 134.1, 131.8, 129.1, 128.3, 126.2, 124.5, 118.3, 117.2, 101.7, 98.1, 78.2, 76.0, 73.0, 72.9, 72.4, 70.2, 68.3, 11.82; ESI HRMS Calcd for $C_{25}H_{28}O_6S$ [M+Na$^+$]: 479.1504. Found: 479.1507.

3.3.5. *S*-Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-methoxybenzyl-1-thia-α-D-mannopyranoside *S*-oxide (14). To a solution of the azeotropically dried sulfide **11** (0.200 g, 0.33 mmol) in CH_2Cl_2 (10 mL) was added MCPBA (0.068 g, 0.39 mmol) at −78°C. The reaction mixture was stirred for 3 h at this temperature, then quenched with saturated $NaHCO_3$ solution (2.0 mL), diluted with CH_2Cl_2 (10 mL), washed with saturated $NaHCO_3$ solution (1×10 mL), H_2O (1×10 mL), and brine (1×10 mL). The organic layer was dried, filtered, concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=4:6) to give **14** (0.190 g, 93%): $[\alpha]^{23}_D$=−52.2° (*c* 2.5); ^{1}H NMR δ 7.52 (m, 7H), 7.40 (m, 3H), 7.27 (d, *J*=7.0 Hz, 2H), 7.13 (d, *J*=7.0 Hz, 2H), 6.89 (d, *J*=7.0 Hz, 2H), 6.79 (d, *J*=7.0 Hz, 2H), 5.62 (s, 1H), 4.73 (d, *J*=12.0 Hz, 1H), 4.59 (d, *J*=11.7 Hz, 1H), 4.48

(m, 3H), 4.34 (b s, 1H), 4.29–4.19 (m, 4H), 4.15–4.08 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.80 (t, J=9.9 Hz, 1H); ^{13}C NMR δ 159.5, 159.4, 141.7, 137.4, 131.7, 130.5, 130.1, 129.6, 129.5, 129.1, 128.3, 126.2, 124.5, 113.9, 101.7, 98.7, 78.1, 76.1, 73.2, 73.0, 72.3, 70.2, 60.3, 55.4; ESI HRMS Calcd for $C_{35}H_{36}O_8S$ [M+Na$^+$]: 639.2029. Found: 639.2028.

3.3.6. *S*-Phenyl 2,3-di-*O*-*p*-bromobenzyl-4,6-*O*-benzylidene-1-thia-α-D-mannopyranoside *S*-oxide (15). The title compound was prepared in 84% yield, as a white solid, from **12** analogously to the protocol described for the formation of **14** from **11**: $[\alpha]^{23}_D$=−57.4° (c 1.4); mp=154–156°C; ^{1}H NMR δ 7.60–7.25 (m, 14H), 7.20 (d, J=7.0 Hz, 2H), 7.05 (d, J=7.0 Hz, 2H), 5.62 (s, 1H), 4.76 (d, J=12.3 Hz, 1H), 4.58 (d, J=12.0 Hz, 1H), 4.53–4.45 (m, 3H), 4.27–4.21 (m, 4H), 4.15–4.10 (m, 1H), 3.75 (t, J=9.9 Hz, 1H); ^{13}C NMR δ 141.4, 137.3, 136.2, 131.8, 131.6, 130.0, 129.9, 129.6, 129.2, 128.4, 126.1, 124.4, 124.3, 122.1, 101.8, 97.7, 78.1, 76.6, 72.9, 72.8, 70.1 68.3; ESI HRMS Calcd for $C_{33}H_{30}Br_2O_6S$ [M+H$^+$]: 713.0208. Found: 713.0213.

3.3.7. Preparation of 1-*O*-(2,3-di-*O*-allyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-3-*O*-*tert*-butyldimethylsilyl-2,4-*O*-ethylidene-D-erythitol (16) from sulfoxide 13. To a stirred solution of the azeotropically dried sulfoxide **13** (0.500 g, 1.10 mmol), TTBP (0.510 g, 2.18 mmol), and 3 Å powdered molecular sieves in dry CH_2Cl_2 (8.0 mL) was added triflic anhydride (0.147 mL, 0.88 mmol) at −75°C and under Ar. The reaction mixture was stirred for 15 min at this temperature followed by addition of the acceptor **8** (0.430 g, 1.64 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was stirred for 1 h at −70°C, quenched with saturated $NaHCO_3$ solution (5 mL), washed with H_2O (1×50 mL), and brine (1×50 mL). The organic layer was dried and concentrated under vacuum. Flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) gave **16** (0.520 g, 80%) as a foam: $[\alpha]^{23}_D$=−60.1° (c 4.0); ^{1}H NMR δ 7.48–7.25 (m, 5H), 6.05–5.84 (m, 1H), 5.57 (s, 1H), 5.30 (m, 2H), 5.17 (d, J=10.8 Hz, 2H), 4.67–4.63 (m, 2H), 4.40 (dd, J=6, 12.9 Hz, 1H), 4.34–4.25 (m, 3H), 4.18–3.99 (m, 4H), 3.95–3.72 (m, 5H), 3.53 (dd, J=3.0, 9.8 Hz, 1H), 3.46–3.43 (m, 1 H), 3.38–3.26 (m, 2H), 1.32 (d, J=5.4 Hz, 3H), 0.85 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 137.7, 135.7, 135.0, 128.9, 128.3, 126.2, 117.3, 116.9, 101.9, 101.5, 99.0, 81.5, 78.8, 77.9, 77.6, 74.5, 71.7, 71.4, 68.7, 67.6, 66.8, 61.8, 25.8, 20.8, 17.9, −4.2, −4.8; ESI HRMS Calcd for $C_{31}H_{48}O_9Si$ [M+Na$^+$]: 615.2965. Found: 615.2964.

3.3.8. 1-*O*-(4,6-*O*-Benzylidene-2,3-di-*O*-*p*-methoxybenzyl-β-D-mannopyranosyl)-3-*O*-*tert*-butyldimethylsilyl-2,4-*O*-ethylidene-D-erythritol (17). The title compound was prepared from **14** and **8** in 82% yield analogously to the preparation of **16** from **13** and **8**. $[\alpha]^{23}_D$=−63.9° (c 1.7); ^{1}H NMR δ 7.87–6.80 (m, 13H), 5.60 (s, 1H), 4.90 (d, J=11.7 Hz, 1H), 4.82 (d, J=12.0 Hz, 1H), 4.69 (q, J=5.0 Hz, 1H), 4.60 (s, 1H), 4.56 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.0 Hz, 1H), 4.28 (dd, J=4.8, 10.5 Hz, 1H), 4.11–4.03 (m, 2H), 3.95 (d, J=3.0 Hz, 1H), 3.93 (t, J=10.2 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.55–3.46 (m, 3H), 3.33 (t, J=10.0 Hz, 1H), 3.30 (m, 1H), 1.33 (d, J=4.8 Hz, 3H), 0.86 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 159.2, 137.8, 130.8, 130.5, 130.3, 129.2, 128.9, 128.3, 126.2, 113.7, 113.6, 102.4, 101.4, 99.0, 81.3, 78.7, 77.4, 75.4, 74.4, 71.9, 71.4, 68.8, 67.7, 67.3, 61.9, 55.3, 52.3, 25.8, 25.7, 20.8, 18.0, 11.8, 0.11, −4.2, −4.8; ESI HRMS Calcd for $C_{41}H_{56}O_{11}Si$ [M+Na$^+$]: 775.3491. Found: 775.3491.

3.3.9. Preparation of 1-*O*-(2,3-di-*O*-allyl-4,6-*O*-benzylidene-β-D-mannopyranosyl)-3-*O*-*tert*-butyldimethyl-silyl-2,4-*O*-ethylidene-D-erythitol (16) from sulfide 10. To a mixture of the azeotropically dried thioglycoside **10** (0.080 g, 0.19 mmol), BSP (0.040 g, 0.19 mmol), TTBP (0.095 g, 0.38 mmol), and 3 Å powdered molecular sieves in dry CH_2Cl_2 (3.0 mL) was added under Ar triflic anhydride (0.035 mL, 0.21 mmol) at −60°C. The reaction mixture was stirred for 5 min, before the acceptor **8** was added (0.080 g, 0.21 mmol) in CH_2Cl_2 (2.0 mL). The dry-ice bath was removed and the reaction mixture was slowly warmed up to room temperature, then quenched with saturated $NaHCO_3$ solution (3.0 mL), washed with H_2O (1×20 mL), and brine (1×20 mL). The organic layer was dried and concentrated under vacuum. Flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) afforded **16** (0.075 g, 66%) identical in all respects to the sample isolated earlier.

3.3.10. Preparation of 1-*O*-(4,6-*O*-benzylidene-β-D-mannopyranosyl)-3-*O*-*tert*-butyldimethylsilyl-2,4-*O*-ethylidene-D-erythritol (18) from the diallyl ether 16. A red solution of bis(methyldiphenylphosphine)(1,5-cyclooctadiene)-iridium(I) hexafluorophosphate (0.042 g, 0.05 mmol), 3 Å powdered molecular sieves and dry THF (3.0 mL) was purged with argon for 8 min, then with H_2 for 5 min until the solution became colorless. The H_2 atmosphere was swept out with Ar before a solution of **16** (0.300 g, 0.51 mmol), 3 Å molecular sieves in dry THF (3.0 mL) was added via cannula. The reaction mixture was stirred at room temperature for 24 h then diluted with EtOAc (25 mL), filtered through a thin layer of Celite, washed with saturated $NaHCO_3$ solution (1×20 mL), water (1×20 mL), and brine (1×20 mL). The organic layer was dried and concentrated under vacuum. Flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) afforded the bis enol ether (0.290 g, 96%) as an yellow oil. To a solution of this bis enol ether (0.250 g, 0.42 mmol) in a mixture of acetone/water (9:1 v/v), was added HgO (0.200 g, 0.93 mmol) and $HgCl_2$ (0.250 g, 0.93 mmol). After stirring at room temperature for 2 h H_20 (10 mL) and EtOAc (15 mL) were added. The layers were separated and the aqueous was further extracted with EtOAc (2×110 mL). The combined organic phases were dried, concentrated in vacuo and purified by chromatography on silica gel (eluent: EtOAc/hexanes=2:8) to afford **18** (0.200 g, 92%) as a colorless oil: $[\alpha]^{23}_D$=−73.5° (c 1.3); ^{1}H NMR δ 7.50–7.25 (m, 5H), 5.54 (s, 1H), 4.68–4.64 (m, 2H), 4.29 (dd, J=5.4, 10.2 Hz, 1H), 4.15 (d, J=3.3 Hz, 1H), 4.05–3.99 (m, 2H), 3.92–3.77 (m, 4H), 3.72–3.64 (m, 1H), 3.53–3.48 (m, 1H), 3.38–3.29 (m, 2H), 2.84 (b s, 2H), 1.33 (d, J=5.1 Hz, 3H), 0.86 (s, 9H), 0.085 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 137.3, 129.3, 128.4, 126.4, 102.2, 99.9, 99.1, 81.0, 78.8, 71.3, 70.9, 68.6, 62.1, 25.8, 20.7, 11.8, −4.0, −4.8; ESI HRMS Calcd for $C_{25}H_{40}O_9Si$ [M+Na$^+$]: 535.2338. Found: 535.2339.

3.3.11. Preparation of 1-*O*-(4,6-*O*-benzylidene-β-D-mannopyranosyl)-3-*O*-*tert*-butyldimethylsilyl-2,4-*O*-ethylidene-D-erythritol (18) from the bis *p*-methoxybenzyl ether 17. To a stirred solution of **17** (1.30 g, 1.73 mmol) dissolved in a mixture of CH_2Cl_2 (17 mL) and H_2O (1.0 mL) was added DDQ (1.76 g, 7.77 mmol) at 0°C. The reaction mixture was stirred at this temperature for 30 min, then slowly warmed up to room temperature and stirred for 1.5 h until the starting material was consumed. The reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (25 mL), washed with water (20 mL), and brine (20 mL), dried, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=1:1), to give **18** (0.32 g, 37%) as a colorless oil identical with the sample described earlier.

3.3.12. 1-*O*-(4,6-*O*-Benzylidene-2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-3-*O*-*tert*-butyldimethylsilyl-2,4-*O*-ethylidene-D-erythritol (19). To a solution of the diol **18** (0.100 g, 0.20 mmol), DMAP (0.050 g, 0.43 mmol), and pyridine (0.034 mL, 0.38 mmol) in dry CH_2Cl_2 (5.0 mL) was added lauroyl chloride (0.100 mL, 0.43 mmol) at room temperature under Ar. After stirring for 5 h, the reaction mixture was quenched with water (1.0 mL), diluted with CH_2Cl_2 (5.0 mL), washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried, filtered, concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) to give **19** (0.156 g, 91%): $[\alpha]^{23}_D$=−60.9° (*c* 3.0); ^{1}H NMR δ 7.45–7.25 (m, 5H), 5.64 (d, *J*=3.3 Hz, 1H), 5.54 (s, 1H), 5.17 (dd, *J*=3.3, 10.2 Hz, 1H), 4.95 (s, 1H), 4.62 (q, *J*=5.0 Hz, 1H), 4.34 (dd, *J*=4.5, 10.3 Hz, 1H), 4.04–3.87 (m, 5H), 3.72–3.64 (m, 1H), 3.53–3.40 (m, 1H), 3.31 (t, *J*=10.2 Hz, 1H), 2.43 (t, *J*=7.5 Hz, 2H), 2.24 (t, *J*=6.6 Hz, 2H), 1.68–1.53 (m, 4H), 1.33 (d, *J*=4.8 Hz, 3H), 1.25 (b s, 35H), 0.91–0.84 (m, 15H), 0.03 (s, 6H); ^{13}C NMR δ 172.8, 172.7, 137.2, 129.1, 128.3, 126.2, 101.8, 99.4, 99.0, 81.7, 76.1, 71.2, 70.2, 69.3, 68.6, 67.4, 67.1, 61.5, 60.4, 52.3, 34.2, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 25.7, 25.1, 24.8, 22.8, 20.1, 17.9, 14.3, 14.2, −4.3, −5.0; ESI HRMS Calcd for $C_{49}H_{84}O_{11}Si$ [M+Na$^+$]: 899.5681. Found: 899.5677.

3.3.13. 3-*O*-*tert*-Butyldimethylsilyl-1-*O*-(2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-2,4-*O*-ethylidene-D-erythritol (20). To a solution of the ester **19** (0.100 g, 0.11 mmol) in ethanol (5.0 mL) was added palladium hydroxide (0.025 g, 25% in weight). The reaction mixture was stirred for 3 h at room temperature under 1 atm of hydrogen then diluted with CH_2Cl_2 (3.0 mL) filtered through a thin layer of Celite, washed thoroughly with ethanol and concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) to give diol **20** (0.89 g, 99%) as a colorless oil: $[\alpha]^{23}_D$=−59.9° (*c* 0.6); ^{1}H NMR δ 5.54 (d, *J*=3.3 Hz, 1H), 4.91–4.86 (m, 2H), 4.62 (q, *J*=5.0 Hz, 1H), 4.03–3.82 (m, 6H), 3.71–3.63 (m, 1H), 3.43–3.37 (m, 2H), 3.31 (t, *J*=10.2 Hz, 1H), 2.37 (t, *J*=7.5 Hz, 2H), 2.28 (t, *J*=7.5 Hz, 2H), 1.62 (m, 4H), 1.32–1.14 (m, 35H), 0.90–0.79 (m, 15H), 0.03 (s, 6H); ^{13}C NMR δ 173.6, 172.7, 98.9, 98.7, 81.5, 75.7, 74.0, 71.1, 68.7, 67.1, 66.4, 62.4, 61.5, 34.1, 31.9, 29.6, 29.4, 29.3, 29.1, 25.6, 25.0, 24.6, 22.6, 20.6, 17.7, 14.1; Calcd for $C_{42}H_{80}O_{11}Si$: C, 63.92; H, 10.22. Found: C, 64.13; H, 10.10.

3.3.14. 1-*O*-(4,6-Di-*O*-acetyl-2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-3-*O*-*tert*-butyldimethylsilyl-2,4-*O*-ethylidene-D-erythritol (21). To a solution of diol **20** (0.090 g, 0.11 mmol) in pyridine (0.092 mL, 1.14 mmol) was added acetic anhydride (0.11 mL, 1.14 mmol) at room temperature. The reaction mixture was stirred for 6 h, diluted with ether (10 mL), washed twice each with 1 M HCl (5 mL), 1 M NaOH (5 mL) and water (10 mL), once with brine (10 mL), dried and concentrated under vacuum. Purification of the residue by chromatography on silica gel (eluent: EtOAc/hexanes=1:9) afforded **21** (0.095 g, 96%): $[\alpha]^{23}_D$=−36.5° (*c* 0.5); ^{1}H NMR δ 5.54 (d, *J*=3 Hz, 1H), 5.23 (t, *J*=10.0 Hz, 1H), 5.04 (dd, *J*=3.0, 10.5 Hz, 1H), 4.87 (s, 1H), 4.61 (q, *J*=5.0 Hz, 1H), 4.27 (dd, *J*=4.8, 12.0 Hz, 1H), 4.12 (dd, *J*=2.1, 11.7 Hz, 1H), 4.02–3.94 (m, 2H), 3.82 (d, *J*=12.0 Hz, 1H), 3.73–3.60 (m, 2H), 3.39 (d, *J*=8.7 Hz, 1H), 3.29 (t, *J*=10.0 Hz, 1H), 2.43–2.37 (m, 2H), 2.19 (t, *J*=9.3 Hz, 2H), 2.07 (s, 3H), 1.99 (s, 3H), 1.66–1.50 (m, 4H), 1.31–1.17 (m, 35H), 0.88–0.82 (m, 15H), 0.03 (s, 6H); ^{13}C NMR δ 172.9, 170.8, 169.5, 99.0, 98.9, 81.7, 72.4, 71.2, 71.1, 68.6, 67.0, 66.3, 62.7, 61.4, 52.3, 34.2, 34.1, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.7, 25.1, 24.8, 22.8, 20.9, 20.8, 20.7, 17.9, 14.2, 11.8, −4.41, −5.0; ESI HRMS Calcd for $C_{46}H_{84}O_{13}$ Si [M+Na$^+$]: 895.5579. Found: 895.5582.

3.3.15. Preparation of 1-*O*-(4,6-di-*O*-acetyl-2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-D-erythritol (22) from 21. To a solution of **21** (0.070 g, 0.08 mmol), and thiophenol (0.032 mL, 0.32 mmol) in CH_2Cl_2(5.0 mL) was added $BF_3.OEt_2$ (0.025 mL, 0.20 mmol) at 0°C under Ar. The reaction mixture was stirred for 6 h at room temperature, then diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ solution (2×20 mL), H_2O (1×20 mL), and brine (1×20 mL). The organic layer was dried and concentrated under vacuum. Flash column chromatography of the residue on silica gel (eluent: EtOAc/hexanes=6:4) gave **22** (0.050 g, 85%) as a colorless oil: $[\alpha]^{23}_D$=−25.9° (*c* 1.5); ^{1}H NMR (500 MHz) δ 5.52 (d, *J*=3.1 Hz, 1H), 5.26 (t, *J*=9.9 Hz, 1H), 5.09 (dd, *J*=3.2, 10.0 Hz, 1H), 4.75 (s, 1H), 4.24 (b s, 1H), 4.23 (b s, 1H), 3.98 (dd, *J*=3.1, 11.0 Hz, 1H), 3.90 (dd, *J*=5.5, 11.0 Hz, 1H), 3.80–3.67 (m, 8H), 2.45 (td, *J*=2.0, 7.0 Hz, 2H), 2.24 (td, *J*=1.5, 7.0 Hz, 2H), 2.12 (s, 3H), 2.06 (s, 3H), 1.69 (m, 2H), 1.55 (m, 2H), 1.27 (b s, 32H), 0.89 (t, *J*=6.7 Hz, 6H); ^{13}C NMR (125 MHz) δ 173.7, 173.1, 171.2, 169.9, 99.6, 72.9, 72.8, 72.1, 71.9, 70.1, 68.9, 66.3, 64.2, 62.8, 34.5, 34.4, 32.3, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 25.4, 25.1, 23.1, 21.1, 14.5. Anal. Calcd for $C_{36}H_{68}O_{13}$: C, 62.27; H, 9.35. Found: C, 62.39, H, 9.29.

3.4. Preparation of the mixture of 22 and 23

3.4.1. 4-*tert*-Butyldiphenylsiloxy-2*Z*-buten-1-ol (23). NaH (60% oil dispersion, 0.54 g, 22.5 mmol) was washed with hexane (3×20 mL) dried under vacuum for 1 h and suspended in dry ether (50 mL). *Z*-2-Butene-1,4-diol (0.93 mL, 11.3 mmol) was added dropwise to this suspension followed by stirring for 1 h at room temperature. The

mixture was then cooled to 0°C and *tert*-butyldiphenylsilyl chloride (2.9 mL, 11.3 mmol) was added slowly. The reaction mixture was stirred for 3 h at room temperature, then diluted with ether (100 mL), washed with saturated $NaHCO_3$ solution (3×20 mL), H_2O (1×50 mL), and brine (1×50 mL). The organic layer was dried and concentrated under vacuum. Flash column chromatography on silica gel (eluent: EtOAc/hexanes=3:7) then afforded **23** (3.0 g, 81%) as colorless oil with spectral parameters identical to the literature.[25]

3.4.2. Preparation of 4-*tert*-Butyldiphenylsiloxy-2*Z*-buten-1-yl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-bromobenzyl-β-D-mannopyranoside (24) from sulfoxide 15. To a stirred solution of the azeotropically dried sulfoxide **15** (0.600 g, 0.84 mmol), TTBP (0.395 g, 1.69 mmol), and 3 Å powdered molecular sieves in dry CH_2Cl_2 (8.0 mL) was added triflic anhydride (0.113 mL, 0.68 mmol) at −75°C under Ar. The reaction mixture was stirred for 15 min at this temperature before the acceptor **23** (0.550 g, 1.69 mmol) in dry CH_2Cl_2 (5.0 mL) was added. The reaction mixture was stirred for 1 h at −70°C, then quenched with saturated $NaHCO_3$ solution (2 mL), washed with H_2O (1×20 mL), and brine (1×20 mL). The organic layer was dried and concentrated under vacuum after which flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) gave **24** (0.56 g, 73%) as a colorless foam: $[\alpha]^{23}_D$=−28.6° (*c* 2.2); ^{1}H NMR δ 7.7–7.6 (m, 4H), 7.5–7.25 (m, 15H), 7.10 (d, *J*=7.0 Hz, 4H), 5.82–5.75 (m, 1H), 5.61 (s, 1H), 5.53–5.44 (m, 1H), 4.85 (d, *J*=12.6 Hz), 4.70 (d, *J*=12.6 Hz), 4.61 (d, *J*=12.6 Hz), 4.49 (d, *J*=12.6 Hz), 4.35 (s, 1H), 4.35–4.00 (m, 6H), 3.85 (t, *J*=10.2 Hz, 1H), 3.77 (d, *J*=2.7 Hz, 1H), 3.49 (dd, *J*=3.0, 9.9 Hz, 1H), 3.20 (m, 1H), 1.06 (s, 9H); ^{13}C NMR δ 137.6, 137.4, 135.7, 133.6, 132.9, 131.6, 131.3, 130.2, 129.9, 129.0, 128.3, 127.9, 126.1, 126.0, 101.6, 100.9, 78.7, 78.1, 76.6, 74.3, 71.9, 68.6, 67.5, 65.3, 60.6, 26.9, 19.2, 11.8; ESI HRMS Calcd for $C_{47}H_{50}Br_2O_7Si$ [M+Na$^+$]: 935.1590. Found: 935.1556.

3.4.3. Preparation of 4-*tert*-butyldiphenylsiloxy-2*Z*-buten-1-yl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-bromobenzyl-β-D-mannopyranoside (24) from thioglycoside 12. To a mixture of the azeotropically dried sulfide **12** (0.500 g, 0.72 mmol), BSP (0.150 g, 0.72 mmol), TTBP (0.350 g, 1.41 mmol), and powdered molecular sieves in dry CH_2Cl_2 (3.0 mL) was added triflic anhydride (0.130 mL, 0.790 mmol) at −60°C under Ar. The reaction mixture was stirred for 5 min before the acceptor **23** (0.470 g, 1.44 mmol) was added in CH_2Cl_2 (2.0 mL). The dry-ice bath was removed and the reaction mixture was warmed up to room temperature, quenched with saturated $NaHCO_3$ solution (5.0 mL), washed with H_2O (1×20 mL), and brine (1×20 mL). The organic layer was dried and concentrated under vacuum. Flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) then afforded **24**α (0.040 g, 6%) and **24**β (0.550 g, 84%). The β-anomer was identical to the above-prepared sample. The α-anomer had $[\alpha]^{23}_D$=+13.1° (*c* 6.7); ^{1}H NMR δ 7.75 (m, 4H), 7.55–7.45 (m, 15H), 7.22 (d, *J*=7.0 Hz, 2H), 7.20 (d, *J*=7.0 Hz, 2H), 5.82–5.75 (m, 1H), 5.61 (s, 1H), 5.53–5.44 (m, 1H), 4.70–4.52 (m 5H), 4.25–4.12 (m, 4H), 4.03 (dd, *J*=5.7, 13.2 Hz, 1H), 3.95–3.68 (m, 5H), 1.06 (s, 9H); ^{13}C NMR δ 137.8, 137.2, 135.7, 133.1, 131.9, 131.7, 131.6, 131.5, 129.9, 129.8, 129.4, 129.2, 129.0, 128.4, 128.0, 127.9, 126.2, 125.8, 121.8, 121.5, 101.6, 98.5, 79.3, 77.6, 77.2, 77.0, 76.8, 76.6, 73.0, 72.6, 68.8, 64.3, 63.2, 60.4, 26.9, 19.28.

3.4.4. 4-*tert*-Butyldiphenylsiloxy-2*Z*-buten-1-yl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-(*N*-methyl-*N*-phenylamino)-benzyl-β-D-mannopyranoside (25). The bis bromobenzyl ether **24** (0.250 g, 0.27 mmol) was loaded into a round-bottom flask and azeotropically dried with toluene (3×4 mL) followed by additional drying overnight under vacuum. The flask was purged with Ar and *N*-methylaniline (0.070 mL, 0.66 mmol) was added and the residue dissolved in toluene (4.0 mL). An ovendried two neck flask was evacuated and backfilled with Ar, then charged with $Pd_2(dba)_3$ (2.5 mg, 0.003 mmol), (*o*-biphenyl)P(*t*Bu)$_2$ (3.2 mg, 0.011 mmol) KO*t*Bu (0.085 g, 0.76 mmol), re-evacuated and backfilled with Ar. The aryl bromide/amine solution was then added via cannula and the reaction mixture was heated to 70°C with vigorous stirring for 5 h. After cooling to room temperature the reaction mixture was diluted with diethyl ether, filtered through a pad of Celite and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=1:9), to give **25** (0.89 g, 65%) as a yellow oil: $[\alpha]^{23}_D$=−14.9° (*c* 0.5); ^{1}H NMR δ 7.69–6.91 (m, 33H), 5.83–5.77 (m, 1H), 5.63–5.55 (m, 2H), 4.87 (d, *J*=12.0 Hz, 1H), 4.79 (d, *J*=12.0 Hz, 1H), 4.64 (d, *J*=12.0 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 4.35 (s, 1H), 4.35–4.12 (m, 6H), 4.03 (dd, *J*=7.5, 12.6 Hz, 1H), 3.87 (m, 2H), 3.54 (dd, *J*=3.6, 9.8 Hz, 1H), 3.28 (s, 6H), 3.26–3.17 (m, 1H), 1.05 (s, 9H); ^{13}C NMR δ 148.6, 137.7, 135.7, 133.6, 132.5, 131.3, 130.9, 130.1, 129.8, 129.3, 129.30, 129.0, 128.9, 128.3, 128.2, 127.9, 126.4, 126.2, 121.6, 121.2, 120.9, 120.4, 120.3, 119.9, 106.2, 101.5, 101.2, 78.7, 77.6, 77.5, 77.1, 76.7, 75.3, 74.5, 72.1, 68.7, 67.6, 65.3, 60.6, 40.4, 26.9, 14.3, 11.8; ESI HRMS Calcd for $C_{61}H_{66}N_2O_7Si$ [M+Na$^+$]: 966.4639. Found: 966.4636.

3.4.5. 4-*tert*-Butyldiphenylsiloxy-2*Z*-buten-1-yl 4,6-*O*-benzylidene-β-D-mannopyranoside (26). A solution of **25** (0.400 g, 0.41 mmol) in dry CH_2Cl_2 (15 mL) was treated with $SnCl_4$ (0.096 mL, 0.82 mmol) and stirred for 30 min at room temperature, then diluted with CH_2Cl_2 (25 mL), washed with H_2O (1×20 mL), saturated $NaHCO_3$ solution (1×20 mL), and brine (1×20 mL). The organic layer was dried and concentrated under vacuum then subjected to flash column chromatography on silica gel (eluent: EtOAc/hexanes=1:1) which gave **26** (0.21 g, 84%) as a colorless oil: $[\alpha]^{23}_D$=−8.8° (*c* 2.0); ^{1}H NMR δ 7.7–7.6 (m, 4H), 7.55–7.35 (m, 11H), 5.83–5.78 (m, 1H), 5.61–5.55 (m, 1H), 5.52 (s, 1H), 4.44 (d, *J*=0.6 Hz, 1H), 4.30–4.09 (m, 5H), 4.0 (d, *J*=3.0 Hz, 1H), 3.87–3.73 (m, 3H), 3.75–3.17 (m, 1H), 3.72 (d, *J*=6.6 Hz, 1H), 2.59 (s, 1H), 1.05 (s, 9H); ^{13}C NMR δ 128.3, 135.7, 133.6, 133.5, 133.4, 129.9, 129.3, 128.4, 127.9, 126.4, 125.6, 102.2, 98.9, 78.8, 77.1, 70.9, 68.5, 66.6, 65.0, 60.5, 26.9, 19.2; ESI HRMS Calcd for $C_{33}H_{40}O_7Si$ [M+Na$^+$]: 599.2441. Found: 599.2441.

3.4.6. 4-*tert*-Butyldiphenylsiloxy-2*Z*-buten-1-yl 4,6-*O*-benzylidene-2,3-di-*O*-dodecyl-β-D-mannopyranoside (27). To a solution of diol **26** (0.100 g, 0.17 mmol), DMAP

(46 mg, 0.38 mmol), and pyridine (0.03 mL, 0.38 mmol) in dry CH_2Cl_2 (5.0 mL) was added lauroyl chloride (0.088 mL, 0.38 mmol) at room temperature under Ar. After stirring for 5 h the reaction mixture was quenched with water (1.0 mL), diluted with CH_2Cl_2 (5.0 mL), washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried, filtered, concentrated in vacuo and purified by flash column chromatography on silica gel (eluent: EtOAc/hexanes=2:8) to give **27** (0.160 g, 98%): $[\alpha]^{23}_D=-34.3°$ (*c* 1.6; ^{1}H NMR δ 7.7 (m, 4H), 7.5–7.25 (m, 11H), 5.83–5.76 (m, 1H), 5.62 (s, 1H), 5.54 (d, *J*=3.0 Hz, 1H), 5.11 (m, 2H), 4.56 (s, 1H), 4.23–4.08 (m, 5H), 3.94 (t, *J*=10.0 Hz, 1H), 3.82 (t, *J*=10.2 Hz, 1H), 3.37–3.29 (m, 1H), 2.42 (t, *J*=7.2 Hz, 2H), 2.24 (t, *J*=7.2 Hz, 2H), 1.69–1.53 (m, 4H), 1.23 (b s, 32H), 1.04 (s, 9H), 0.87 (t, *J*=7 Hz, 6H); ^{13}C NMR δ 173.0, 172.8, 137.2, 135.7, 133.5, 133.3, 130.0, 129.9, 129.2, 128.3, 127.9, 126.2, 125.6, 101.8, 97.8, 75.9, 70.1, 69.3, 68.5, 67.2, 65.2, 60.5, 53.2, 34.2, 34.1, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 26.9, 25.2, 24.8, 22.8, 19.2, 14.27; ESI HRMS Calcd for $C_{57}H_{84}O_9Si$ [M+Na$^+$]: 963.5782. Found: 953.5782.

3.4.7. 4-*tert*-Butyldiphenylsiloxy-2*Z*-buten-1-yl 2,3-di-*O*-dodecyl-β-D-mannopyranoside (28). Compound **27** (0.100 g, 0.11 mmol) was dried under vacuum for 1 h then treated with a 1% solution of iodine in methanol (3 mL) and heated to 70°C for 3 h. After cooling to room temperature the reaction was quenched with sodium thiosulfate solution (1.0 mL), and concentrated under vacuum. The residue was extracted with chloroform (2×5 mL) and the extracts dried and concentrated to dryness. Flash column chromatography on silica gel (eluent: EtOAc/hexanes=1:1) then gave **28** (0.047 g, 51%) as a yellow oil: $[\alpha]^{23}_D=-11.7°$ (*c* 5.0); ^{1}H NMR δ 7.7–7.6 (m, 4H), 7.5–7.3 (m, 6H), 5.80–5.74 (m, 1H), 5.54–5.45 (m, 1H), 5.40 (d, *J*=3.0 Hz, 1H), 4.83 (dd, *J*=3.3, 9.9 Hz, 1H), 4.52 (d, *J*=1.2 Hz, 1H), 4.22–3.77 (m, 7H), 3.25–3.19 (m, 1H), 2.36 (t, *J*=7.5 Hz, 3H), 2.27 (t, *J*=7.2 Hz, 3H), 1.63–1.47 (m, 4H), 1.24 (b s, 32H), 1.03 (s, 9 H), 0.87 (t, *J*=6.6 Hz, 6H); ^{13}C NMR δ 173.6, 173.0, 135.7, 135.6, 133.5, 133.2, 129.9, 128.4, 127.9, 125.7, 97.4, 75.7, 73.9, 68.9, 66.2, 65.1, 62.4, 60.4, 34.2, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 26.8, 25.2, 24.7, 22.8, 19.2, 14.2; ESI HRMS Calcd for $C_{50}H_{80}O_9Si$ [M+Na$^+$]: 875.5469. Found: 875.5474.

3.4.8. 4-*tert*-Butyldiphenylsiloxy-2*Z*-buten-1-yl 4,6-di-*O*-acetyl-2,3-di-*O*-dodecyl-β-D-mannopyranoside (29). To a solution of diol **28** (0.080 g, 0.094 mmol) in pyridine (0.151 mL) was added acetic anhydride (0.175 mL, 1.88 mmol) at room temperature. The reaction mixture was then stirred for 4 h, before it was diluted with ether (10 mL), washed twice each with 1 M HCl (10 mL), 1 M NaOH (10 mL) and water (10 mL), once with brine (10 mL), dried, and concentrated under vacuum. Purification of the residue by chromatography on silica gel (eluent: EtOAc/hexanes=1:9) afforded **29** (0.082 g, 93%): $[\alpha]^{23}_D=-14.8°$ (*c* 1.0); ^{1}H NMR δ 7.6–7.7 (m, 4H), 7.5–7.3 (m, 6H), 5.80–5.74 (m, 1H), 5.60–5.45 (m, 1H), 5.40 (d, *J*=3.3 Hz, 1H), 5.21 (t, *J*=10.0 Hz, 1H), 4.99 (dd, *J*=2.7, 12.3 Hz, 2H), 4.30–3.90 (m, 6H), 3.45 (m, 1H), 2.40 (t, *J*=7.8 Hz, 2H), 2.20 (t, *J*=7.5 Hz, 2H), 2.00 (s, 6H), 1.64–1.50 (m, 4H), 1.24 (b s, 32H), 1.03 (s, 9H), 0.87 (t, *J*=6.3 Hz, 6H); ^{13}C NMR δ 173.2, 170.8, 169.5, 135.7, 135.6, 133.5, 133.4, 129.9, 128.3, 127.9, 125.6, 106.9, 100.1, 97.2, 72.3, 71.0, 68.7, 66.0, 65.0, 62.4, 60.4, 34.2, 34.1, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 26.8, 25.8, 25.1, 24.8, 22.8, 20.8, 14.2, 11.8; ESI HRMS Calcd for $C_{54}H_{84}O_{11}Si$ [M+Na$^+$]: 959.5681. Found: 959.5682.

3.4.9. 4-*O*-(4,6-Di-*O*-acetyl-2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-1-*O*-*tert*-butyldiphenylsilyl-D-erythritol (30) and 1-*O*-(4,6-di-*O*-acetyl-2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-4-*O*-*tert*-butyldiphenylsilyl-D-erythritol (31). To a stirred solution of OsO_4 (0.015 mL, 0.0064 mmol), and NMO (0.012 g, 0.089 mmol) in acetone–water (2:1 v/v) was added the alkene **29** (0.056 g, 0.060 mmol) in acetone (3.0 mL) at room temperature. The resulting reaction mixture was stirred for 24 h before $Na_2S_2O_3$ (0.037 g, 0.24 mmol) was added. The mixture was then stirred for a further 1.5 h before the acetone was removed under vacuum and EtOAc (15 mL) and H_2O (15 mL) were added to the residue. The water phase was saturated with NaCl and then extracted with EtOAc. The combined organic phases were washed with water (10 mL), brine (10 mL), dried and concentrated to dryness. Flash column chromatography on silica gel (eluent: EtOAc/hexanes=3:7) gave **30** and **31** (0.041 g, 70%) as an inseparable 1:1 mixture in the form of an oil: ^{1}H NMR δ 7.6–7.7 (m, 4H), 7.3–7.5 (m, 6H), 5.48 (m, 1H), 5.22 (m, 1H), 5.05 (m, 1H), 4.66 (s, 1H), 4.24–4.11 (m, 2H), 4.01 (m, 1H), 3.87–3.64 (m, 6H), 2.6 (m, 1H), 2.40 (t, *J*=7.5 Hz, 2H), 2.21 (t, *J*=7.8 Hz, 2H), 2.04 (2s, 3H), 2.02 (s, 6H), 1.64–1.50 (m, 4H), 1.24 (bs, 32H), 1.55 (s, 9H), 0.87 (t, *J*=9.9 Hz, 6H); ^{13}C NMR δ 172.8, 135.6, 133.0, 130.0, 127.9, 99.6, 73.7, 73.0, 72.5, 71.8, 71.7, 71.2, 70.7, 70.6, 68.8, 68.7, 66.1, 66.0, 65.0, 62.6, 34.2, 34.1, 32.0, 29.8, 29.6, 29.5, 29.4, 29.2, 27.0, 25.1, 24.8, 22.8, 20.8, 19.4, 14.2; ESI HRMS Calcd for $C_{54}H_{86}O_{13}Si$ [M+Na$^+$]: 993.5735. Found: 993.5738.

3.4.10. 4-*O*-(4,6-Di-*O*-acetyl-2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-D-erythritol (32) and 1-*O*-(4,6-di-*O*-acetyl-2,3-di-*O*-dodecyl-β-D-mannopyranosyl)-D-erythritol (22). To a solution of the diols **30** and **31** (0.015 g, 0.015 mmol) in THF (3.0 mL) at 0°C, under Ar, was added TBAF 1 M in THF (0.008 mL, 0.031 mmol). The reaction mixture was stirred at room temperature for 4 h, then quenched with water (1.0 mL), and the organic layer washed with saturated $NaHCO_3$ solution (2×10 mL), H_2O (1×10 mL), and brine (1×50 mL), dried and concentrated to dryness. Flash column chromatography on silica gel (EtOAc/hexanes=6:4) gave an inseparable 1:1 mixture of **32** and **22** (0.011 g, 97%) as a microanalytically pure yellow oil. Anal. Calcd for $C_{36}H_{68}O_{13}$: C, 62.27; H, 9.35. Found: C, 62.39; H, 9.29. The spectral data of **22** were as presented above. The data of **32** were extracted from the mixture: ^{1}H NMR (500 MHz) δ 5.54 (dd, *J*=3.2, 0.7 Hz, 1H), 5.28 (t, *J*=10.1 Hz, 1H), 5.10 (dd, *J*=3.3, 9.8 Hz, 1H), 4.74 (d, *J*=0.7 Hz, 1H), 4.27 (dd, *J*=5.7, 12.4 Hz, 1H), 4.22 (dd, *J*=2.4, 12.4 Hz, 1H), 4.02 (dd, *J*=3.1, 10.6 Hz, 1H), 3.87 (dd, *J*=5.7, 10.6 Hz 1H), 3.80 (dd, *J*=3.9, 11.4 Hz, 1H), 3.77–3.66 (m, 4H), 2.45 (dt, *J*=2.9, 7.5 Hz, 2H), 2.30 (b s, 2H), 2.25 (t, *J*=7.5 Hz, 2H), 2.12 (s, 3H), 2.06 (s, 3H), 1.67 (m, 2H), 1.58 (m, 2H), 1.20–1.40 (b s, 32H), 0.90 (m, 6H); ^{13}C NMR δ 173.8, 173.1, 171.1, 169.8, 99.7, 72.9, 72.8, 72.0, 71.6, 71.0, 68.8, 66.2, 64.0, 63.0, 34.5, 34.4,

32.3, 30.1 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 25.4, 25.1, 23.1, 21.2, 21.1, 14.5.

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