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SYNTHETIC STUDIES ON GLYCOSPHINGOLIPIDS FROM PROTOSTOMIA PHYLA: SYNTHESIS OF GLYCOSPHINGOLIPID FROM THE MARINE SPONGE *SPHECIOSPONGIA VESPARIA* AND ITS ANALOGUE

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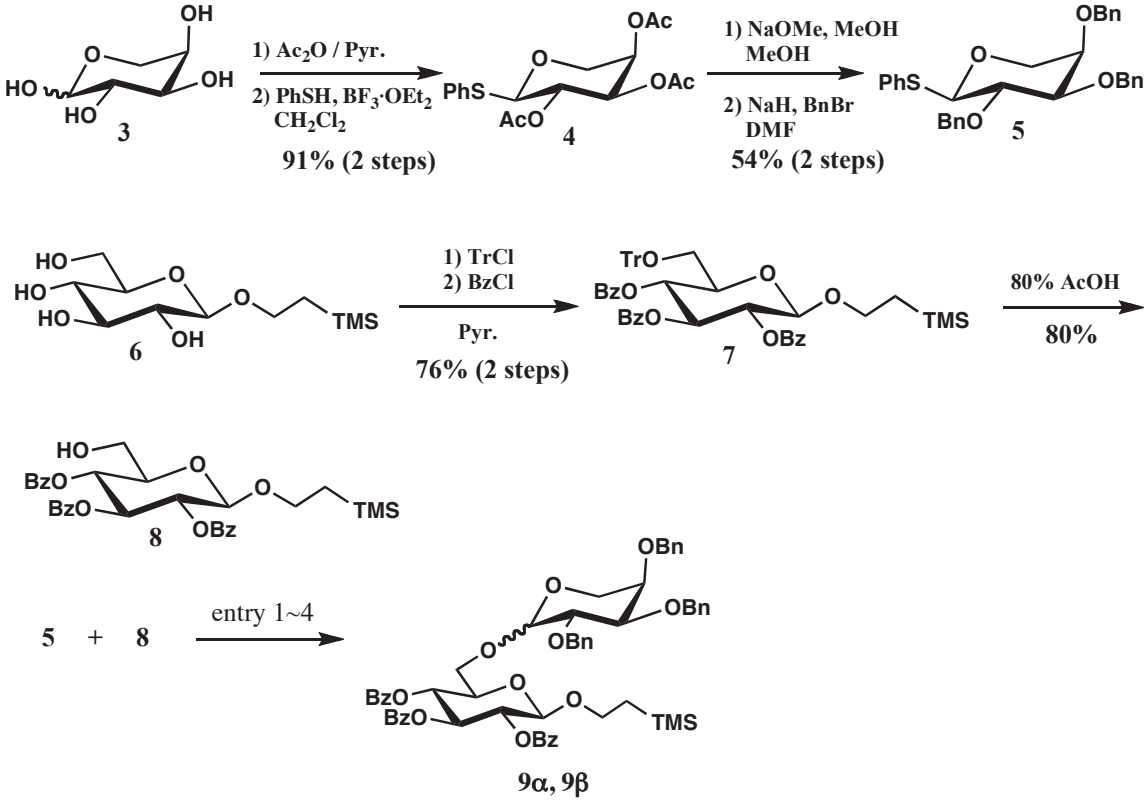
‡This paper is dedicated to Professor Victor Snieckus on celebration of his 77th birthday.

Abstract – Stereocontrolled syntheses of a neutral glycosphingolipid found from a marine sponge *Spheciospongia vesparia* and its analogue have been accomplished. Disaccharide glycosphingolipids, β-D-Ara*p*-(1→6)-β-D-Glc*p*-(1↔1)-Cer (**1**) and α-D-Ara*p*-(1→6)-β-D-Glc*p*-(1↔1)-Cer (**2**), were synthesized from suitable monosaccharide donors and an acceptor by stepwise synthesis.

In our continuing systematic studies on the role and biological functions of glycosphingolipids, we have synthesized glycolipids found in various lower animal species.[1] Glycolipids found from various marine sponges are especially interesting molecules from the viewpoint of drug discovery. For example, it is well established that sponges of the genus *Agelas* produce α-galactosyl ceramides (α-GalCer),[2] which are potent ligands of the MHC class I-like CD1d protein and found to activate iNKT cells strongly.[3] On the other hand, marine sponges are a rich source of novel glycosphingolipids which are often characterized by unprecedented structural features.[4] Therefore, we are interested in the structure and function of glycosphingolipids found from various marine sponges. In our previous papers, we synthesized a glycosphingolipid, β-D-GalNAc*p*(1→4)[α-D-Fuc*p*(1→3)]-β-D-GlcNAc*p*(1↔1)Cer (**A**), isolated from a marine sponge *Aplysinella rhax* and five analogues and examined their structure-activity relationships on LPS-induced NO production.[1e,1g] Recently, Mangoni et al. isolated and characterized a novel neutral glycosphingolipid, β-D-Ara*p*-(1→6)-β-D-Glc*p*-(1↔1)-Cer (**1**, Scheme 3) from a marine sponge *Spheciospongia vesparia*.[4d] The carbohydrate part of **1** consists of a D-arabinose attached to the

reducing-end D-glucose through an β1→6 linkage and this was the first example of a natural diglycosylceramide whose carbohydrate chain contains a pentose unit. In this study, we report the synthesis of glycosphingolipid **1** and its structural analogue **2**.

Phenyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-arabinopyranoside (**5**) was selected as a glycosyl donor at first, and 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (**8**) as a glycosyl acceptor (Scheme 1). The glycosyl donor (**5**) was prepared from D-arabinose by a sequence of acetylation, thioglycosylation, deacetylation and subsequent benzylation using standard conditions. On the other hand, the acceptor **8** was prepared from 2-(trimethylsilyl)ethyl β-D-glucopyranoside (**6**)[5] by the following three-step procedure. Regioselective tritylation of the starting material **6** with triphenylmethyl chloride, followed by benzoylation (**7**) and acid hydrolysis of the trityl group, gave compound **8**. We first carried out glycosylation of **8** with **5** under argon atmosphere with several combinations of solvents and promoters. The results are summarized in Table 1.



Scheme 1. Synthesis of monosaccharide donor **5** and acceptor **8**

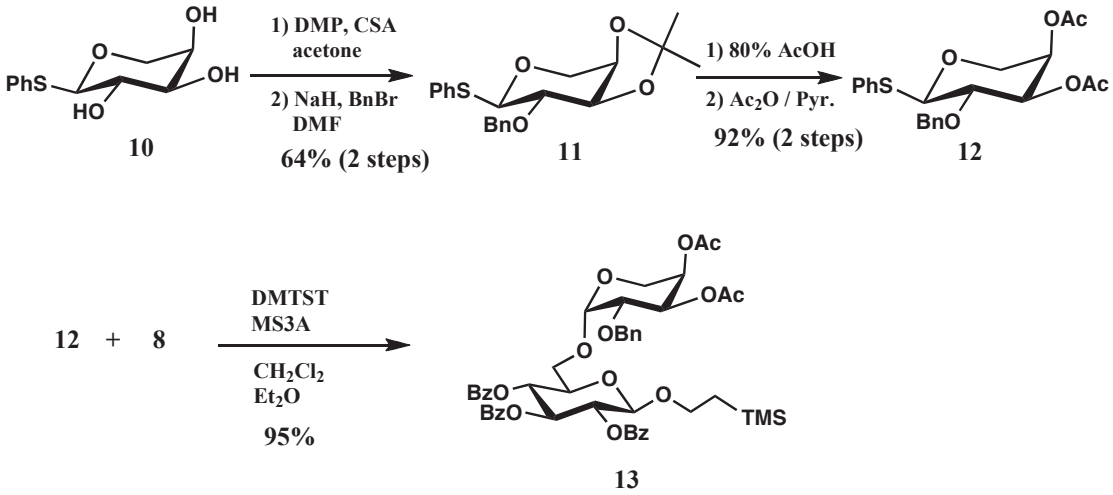
When a combination of NIS and TfOH was used as a promoter[6] in 1:1 ether-CH_2Cl_2, the ratio of **9α** : **9β** was 1.2 : 1.0 (entry 1), and the ratio of **9β** was higher with MeOTf,[7] although the yield was not so good (entry 3). When a combination of NIS/AgOTf in cyclopentyl methyl ether (CPME) was used,[8] the ratio of α : β was 1.0 : 1.1 (entry 2), but the yield was excellent (100%). The ratio of the β-arabinoside was

improved with dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST, entry 4) as a promoter and the yield was also excellent.[9] However, sufficient stereoselectivity of desired β-arabinoside was not obtained (α : β = 1.2 : 1.0～1.0 : 2.5). Thus, the activation of thioglycoside **5** under these conditions led to non stereoselective glycosylation.

Table 1. Glycosylation of **8** with **5** under various conditions

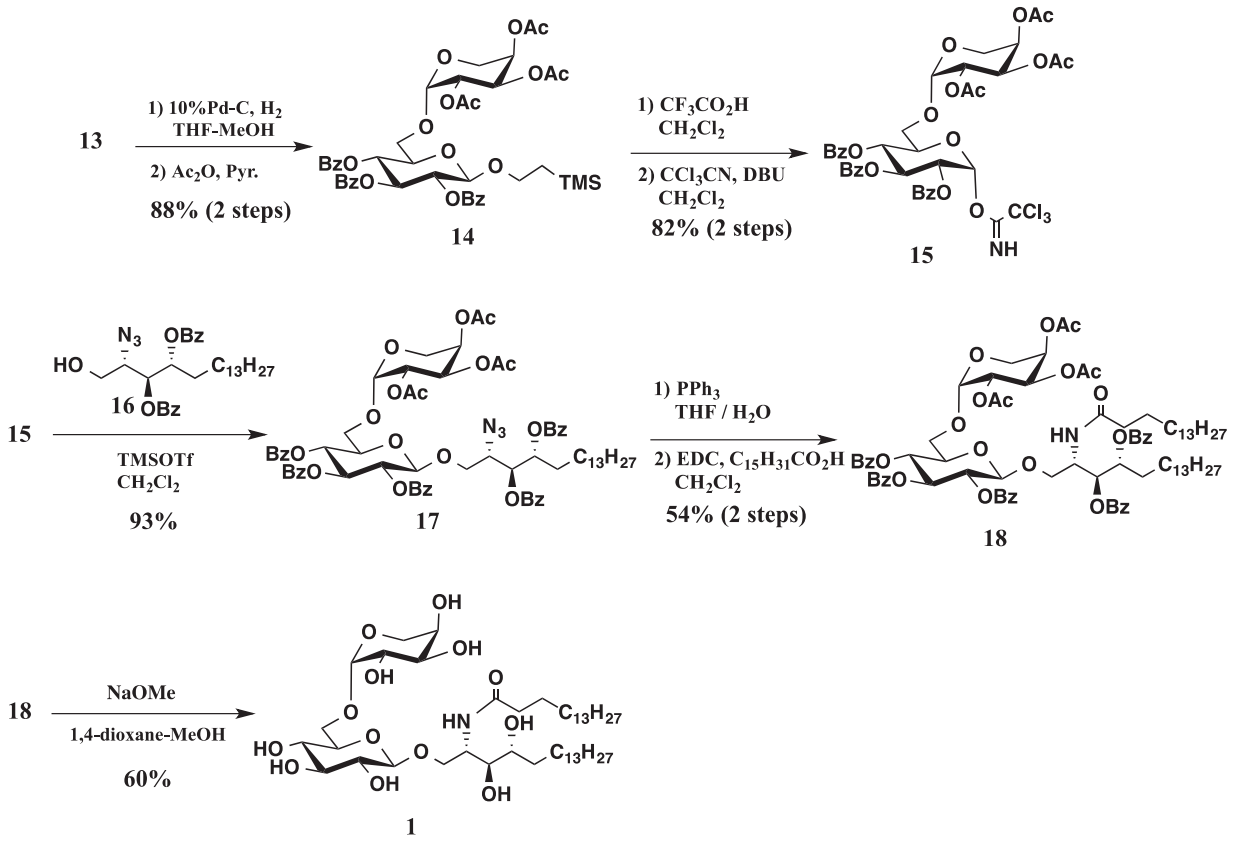
entry	**5** (eq.)	solvent	promoter	temp. (°C)	time	α:β	yield (%)
1	1.2	Et_2O:CH_2Cl_2 (1:1)	NIS (2.0 eq.), TfOH (0.3 eq.)	−60→−40	4 h	1.2:1.0	60
2	1.2	CPME	NIS (1.5 eq.), AgOTf (1.2 eq.)	0	1 h	1.0:1.1	100
3	1.2	Et_2O:CH_2Cl_2 (1:1)	MeOTf (4 eq.)	25	15 h	1.0:2.0	40
4	1.2	CH_2Cl_2:CPME (1:1)	DMTST (4 eq.)	0	1 h	1.0:2.5	96

Li *et al*. reported a rational design of a highly α-selective galactopyranosyl donor based on the influence of remote protecting groups.[10] They demonstrated that a galactosyl donor with acetyl groups at 3- and 4-positions and a benzyl group at 2-position showed excellent stereoselectivity, probably though blockage of β-side attack to the cationic intermediate by intramolecular acetal formation with the acetyl groups, to give only α-product. Therefore, we applied this method to the β-selective D-arabinosylation which corresponds to α-selective D-galactosylation. Compound **12** was chosen as a new glycosyl donor and was prepared from phenyl thio-α-D-arabinopyranoside **10** by a four-step procedure. Protection of hydroxyl groups at 3- and 4-positions of **10**, which was obtained from deacetylation of **4**, with an isopropylidene group, followed by benzylation gave compound **11**. Removal of the isopropylidene group of **11** under acidic condition followed by acetylation afforded desired glycosyl donor **12**. Glycosylation of the acceptor **8** with **12** in the presence of DMTST and MS 3Å in CH_2Cl_2-Et_2O afforded desired disaccharide **13** in 95% yield (Scheme 2). The ^{1}H NMR spectra of **13** showed a doublet at δ 5.04 for anomeric proton with $J_{1,2}$ = 3.0 Hz, which confirmed the β-stereochemistry.



Scheme 2. Stereoselective synthesis of disaccharide derivative

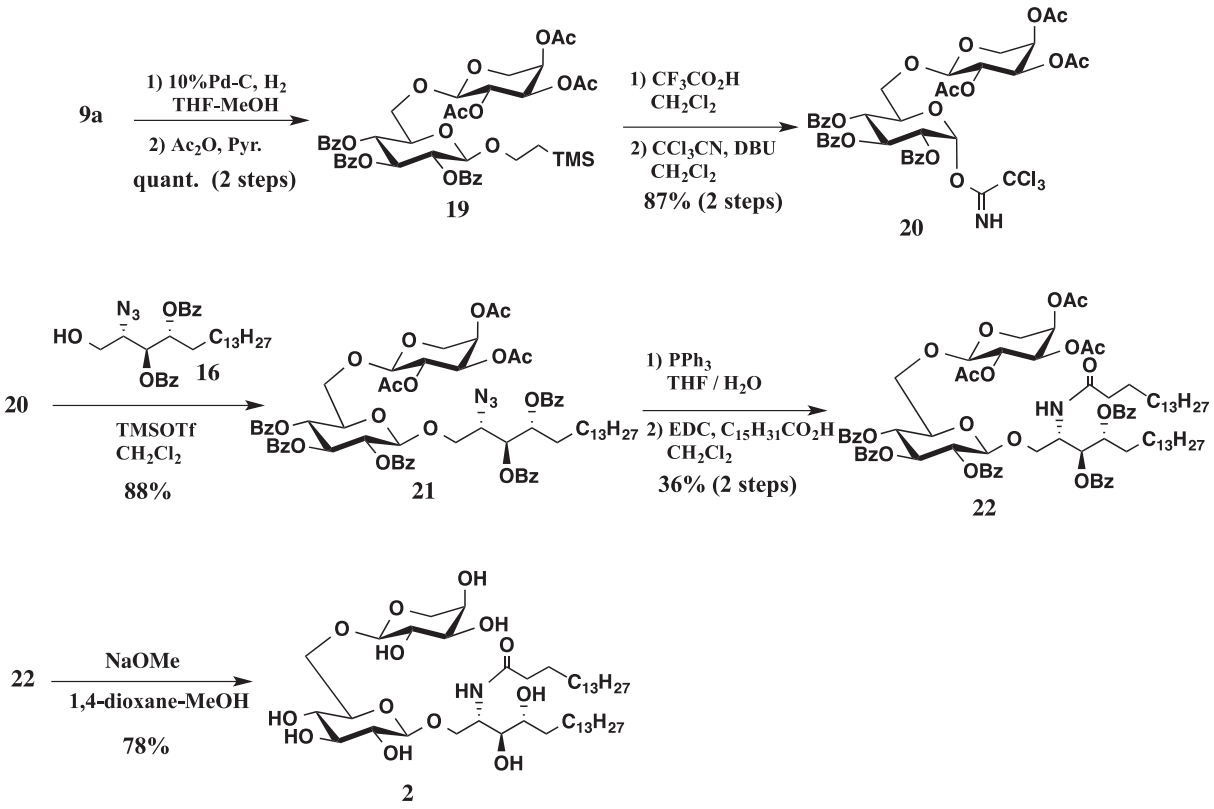
Removal of the benzyl protecting group of **13** by catalytic hydrogenation over 10% Pd-C in THF-MeOH and acetylation gave protected disaccharide **14**. Selective removal of the 2-(trimethylsilyl)ethyl (TMS-ethyl) group in **14** with TFA, followed by exposure of resulted hemiacetal to CCl_3CN and 1,8-diazabicyclo[5,4,0]-7-undecene (DBU)[11] afforded corresponding α-trichloroacetimidate **15**. Glycosylation of (2*S*,3*S*,4*R*)-2-azido-3-*O*-benzoyl-4-octadecane-1,3,4-triol (**16**)[12] with the glycosyl donor **15** was carried out in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[13] and MS 4Å for 8 h at 0 °C, to afford desired β-glycoside **17** in 93% yield. Selective reduction[14] of the azido group in **17** with triphenylphosphine in THF-water gave corresponding amine, which on condensation with stearic acid using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in CH_2Cl_2, gave fully protected derivative **18** (54%, 2-steps). Finally, standard deacetylation of **18** and purification by column chromatography on Sephadex LH-20 furnished glycolipid **1** (Scheme 3). The structure and purity of **1** were demonstrated by its ^{1}H NMR and HR-FABMS data.



Scheme 3. Synthesis of glycosphingolipid **1**

As we had a good amount of **9α** as a glycosyl donor in hand, the synthesis of α-D-Ara*p*-(1→6)-β-D-Glc*p*-(1↔1)-Cer (**2**) was also carried out in order to compare biological activities of natural and non natural products. Deprotection of benzyl groups of **9α** by catalytic hydrogenation over 10% Pd-C in THF-MeOH and acetylation provided **19**. Compound **19** was exposed to TFA and resulted hemiacetal was converted to glycosyl imidate **20** using standard conditions. Glycosylation of the azidosphingosin **16** with

20 produced glycosyl azidosphingosin **21** which was further converted into glycosyl ceramide **2** by a series of reactions as described for **1** (Scheme 4). The structure and purity of **2** were demonstrated by its ^{1}H NMR and HR-FABMS data.



Scheme 4. Synthesis of glycosphingolipid **2**

In conclusion, a stereoselective synthesis of the glycosphingolipid **1** found from *Spheciospongia vesparia* together with a synthesis of its analogue **2** have been accomplished. We have succeeded in the first total synthesis of D-arabinose-containing glycosphingolipid found from invertebrate species in good yield.

EXPERIMENTAL

General

Optical rotations were measured with a Jasco P-1020 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 or 500 FT NMR spectrometer. Me_4Si was used as an internal standard. MALDI-TOFMS was recorded on an AB SCIEX Voyager RP mass spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-700 under FAB conditions. TLC was performed on Silica Gel 60 F254 (E. Merck) with detection by quenching of UV fluorescence and by charring with 10% H_2SO_4. Column chromatography was carried out on Silica Gel 60 (E. Merck). 2-(Trimethylsilyl)ethyl β-D-glucopyranoside (**7**)[5] was prepared as reported. (2*S*,3*S*,4*R*)-2-Azido-3-*O*-benzoyl-4-octadecane-1,3,4-triol (**16**) was prepared from phytosphingosine, which was purchased from Degussa (The Netherlands), according to the synthesis of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol.[12]

Phenyl 2,3,4-tri-*O*-acetyl-1-thio-α-D-arabinopyranoside (4)

A solution of D-arabinopyranose **3** (5.0 g, 33.3 mmol) and acetic anhydride (12 mL) in pyridine (18 mL) was stirred for 20 h at room temperature. After the reaction was quenched with MeOH, toluene was added and co-evaporated several times. To a solution of the residue in CH_2Cl_2 (30 mL) cooled at 0 °C were added PhSH (5.13 mL, 50.0 mmol) and $BF_3 \cdot OEt_2$ (6.27 mL, 50.0 mmol). The reaction mixture was stirred for 2 h at room temperature. The mixture was poured into ice-water and extracted with $CHCl_3$. The extract was successively washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (10:1 hexane-EtOAc) to give **4** (11.1 g, 2 steps 91%). $[\alpha]_D^{25}$ +18.1 (*c* 2.9, $CHCl_3$). HR-FABMS: calcd for $C_{17}H_{21}O_7S$: *m/z* 369.1008, found: *m/z* 369.0990 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50—7.26 (m, 5H, Ph), 5.26 (dd, 1H, $J_{3,4}$ = 3.0 Hz, H-4), 5.24 (t, 1H, $J_{1,2} = J_{2,3}$ = 8.3 Hz, H-2), 5.10 (dd, 1H, H-3), 4.81 (d, 1H, H-1), 4.15 (dd, 1H, $J_{4,5a}$ = 4.2 Hz, $J_{5a,5b}$ = 12.7 Hz, H-5a), 3.67 (dd, 1H, $J_{4,5b}$ = 2.0 Hz, H-5b). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 169.8, 169.3, 132.2, 132.0, 129.0, 128.9, 127.9, 86.7, (C-1), 70.4 (C-3), 68.4 (C-2), 67.4 (C-4), 75.2 (C-5), 20.79, 20.76, 20.6.

Phenyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-arabinopyranoside (5)

To a solution of **4** (11.1 g, 30.0 mmol) in MeOH (40 mL) was added NaOMe (300 mg) and the mixture was stirred for 1.5 h at room temperature. After completion of the reaction, the reaction mixture was neutralized with Amberlite IR 120 [H^+]. After filtration, the solution was concentrated, and the residue was dissolved in dry *N*,*N*-dimethylformamide (DMF, 30 mL). To the stirred solution was added sodium hydride (NaH, 7.2 g, 180 mmol: 60% oil dispersion), and the mixture was stirred for 30 min at 0 °C and then benzyl bromide (16.5 mL, 122.0 mmol) was added. The stirring was continued for 4 h at 0 °C and then MeOH was added to destroy excess NaH. The mixture was poured into iced-water and extracted with EtOAc. The extract was successively washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (10:1 hexane-EtOAc) to give **5** (8.29 g, 2 steps 54%). $[\alpha]_D^{25}$ +24.3 (*c* 1.6, $CHCl_3$). HR-FABMS: calcd for $C_{32}H_{32}O_4S$: *m/z* 512.2021, found: *m/z* 512.2059 $[M]^+$. MALDI-TOFMS: *m/z* 535.9 $[M+Na]^+$ ($C_{32}H_{32}O_4SNa$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.53—7.19 (m, 20H, 4×Ph), 4.91 (d, 1H, $J_{1,2}$ = 6.0 Hz, H-1), 4.70—4.58 (m, 6H, 3×CH_2), 4.26 (dd, 1H, $J_{4,5a}$ = 5.8 Hz, $J_{5a,5b}$ = 11.9 Hz, H-5a), 3.93 (t, 1H, $J_{2,3}$ = 6.5 Hz, H-2), 3.82 (dd, 1H, $J_{3,4}$ = 2.5 Hz, H-4), 3.68 (dd, 1H, H-3), 3.44 (br.d, 1H, H-5b). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.14, 138.09, 137.97, 135.5, 131.1, 128.8, 128.4, 128.31, 128.30, 128.0, 127.8, 127.73, 127.71, 127.6, 126.9, 87.1 (C-1), 78.4 (C-3), 77.2 (C-2), 74.1, 72.3 (C-4), 72.2, 71.0, 63.1 (C-5).

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzoyl-6-*O*-trityl-β-D-glucopyranoside (7)

A solution of **6** (1.0 g, 3.57 mmol) and NaOMe (200 mg) in MeOH (50 mL) was stirred for 30 min, and then neutralized with Amberlite IR 120 [H^+]. The mixture was filtered and concentrated. A mixture of the resulted deacetyl compound (2.89 g) and triphenylmethyl chloride (TrCl, 1.39 g, 4.99 mmol) in pyridine (10 mL) was stirred for 4 h at 80 °C. After completion of the reaction, the reaction mixture was added benzoyl chloride (1.49 mL, 12.8 mmol), and the mixture was stirred for 20 h at 80 °C. Toluene was added and the mixture was concentrated to dryness, then the residue was dissolved in $CHCl_3$, washed successively with 5% HCl, aq $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (8:1 hexane-EtOAc) to give **7** (2.26 g, 2 steps 76%).
$[\alpha]_D^{25}$ +0.4 (*c* 1.9, $CHCl_3$). HR-FABMS: calcd for $C_{51}H_{50}O_9SiNa$: *m/z* 857.3122, found: *m/z* 857.3104 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.97—7.09 (m, 30H, 6×Ph), 5.78 (t, 1H, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3), 5.60 (t, 1H, $J_{4,5} = 9.7$ Hz, H-4), 5.48 (dd, 1H, $J_{1,2} = 8.1$ Hz, H-2), 4.83 (d, 1H, H-1), 4.15—4.10 (m, 1H, $OC\underline{H}_2CH_2$), 3.86 (dt, 1H, $J_{5,6a} = 2.6$ Hz, $J_{5,6b} = 5.1$ Hz, H-5), 3.75—3.70 (m, 1H, $OC\underline{H}_2CH_2$), 3.33 (dd, 2H, $J_{6a,6b} = 10.6$ Hz, H-6a, 6b), 1.04—0.96 (m, 2H, $OCH_2C\underline{H}_2$), –0.02 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 165.1, 164.8, 143.6, 133.03, 132.99, 129.77, 129.75, 129.63, 129.57, 129.2, 129.0, 128.6, 128.23, 128.19, 128.1, 127.9, 127.7, 126.9, 100.5 (C-1), 86.7, 73.9 (C-5), 73.4 (C-3), 72.2 (C-2), 69.6 (C-4), 67.3 ($O\underline{C}H_2CH_2$), 62.5 (C-6), 18.0 ($OCH_2\underline{C}H_2$), –1.4 ($Si(\underline{C}H_3)_3$).

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (8)

A solution of **7** (2.26 g, 2.71 mmol) in 80% AcOH (9 mL) was stirred at 90 °C for 1 h, then diluted with toluene and concentrated. The product was purified by silica gel column chromatography (4:1 hexane-EtOAc) to give **8** (1.29 g, 80%). $[\alpha]_D^{25}$ –4.8 (*c* 0.8, $CHCl_3$). HR-FABMS: calcd for $C_{32}H_{36}O_9SiNa$: *m/z* 615.2026, found: *m/z* 615.2023 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.96—7.26 (m, 15H, 3×Ph), 5.93 (t, 1H, $J_{2,3} = J_{3,4} = 9.8$ Hz, H-3), 5.52—5.48 (m, 2H, H-2, 4), 4.85 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1), 4.08—4.03 (m, 1H, $OC\underline{H}_2CH_2$), 3.89—3.74 (m, 3H, H-5, 6a, 6b), 3.66—3.60 (m, 1H, $OC\underline{H}_2CH_2$), 0.96—0.87 (m, 2H, $OCH_2C\underline{H}_2$), –0.06 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.0, 165.8, 165.0, 133.6, 133.2, 133.1, 129.9, 129.73, 129.69, 129.4, 128.8, 128.6, 128.5, 128.3, 100.6 (C-1), 74.5 (C-5), 72.9 (C-3), 71.9 (C-2), 69.6 (C-4), 67.7 ($O\underline{C}H_2CH_2$), 61.4 (C-6), 18.0 ($OCH_2\underline{C}H_2$), –1.5 ($Si(\underline{C}H_3)_3$).

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-benzyl-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (9)

entry 1

A mixture of **8** (200 mg, 0.34 mmol), **5** (223 mg, 0.44 mmol) and powdered MS AW300 (300 mg) in dry CH_2Cl_2-Et_2O (1:1, 3 mL) was stirred under Ar atmosphere for 2 h at room temperature, then cooled to –40 °C. NIS (195 mg, 0.87 mmol) and TfOH (10.9 μL, 0.09 mmol) were added to the mixture, which was stirred for 3 h at –40 °C, then neutralized with Et_3N. The precipitates were filtered off and washed with

$CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$ and water, dried ($MgSO_4$), and concentrated. The residue was separated by silica gel column chromatography (20:1 toluene-EtOAc) to give **9α** (110 mg, 33%) and **9β** (90 mg, 27%).

9α $[\alpha]_D^{25}$ –17.6 (*c* 0.65, $CHCl_3$). HR-FABMS: calcd for $C_{58}H_{62}O_{13}SiNa$: *m/z* 1017.3857, found: *m/z* 1017.3890 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.96—7.14 (m, 30H, 6×Ph), 5.85 (t, 1H, $J_{2,3}$=$J_{3,4}$= 9.6 Hz, H-3), 5.51 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.47 (t, 1H, $J_{1,2}$ = 8.0 Hz, H-2), 4.76 (d, 1H, H-1), 4.71—4.55 (m, 6H, 3×benzyl methylene), 4.39 (d, 1H, $J_{1',2'}$ = 6.2 Hz, H-1'), 4.07—3.94 (m, 3H, H-6a, 5'a, C$\underline{H}_2$CH_2Si$(CH_3)_3$), 3.83 (br. d, 1H, H-6b), 3.72 (dd, 1H, H-2'), 3.66 (br.s, 1H, H-4'), 3.66-3.53 (m, 1H, C$\underline{H}_2$CH_2Si$(CH_3)_3$), 3.49 (dd, 1H, H-3'), 3.20(d, 1H, H-5'a), 0.93—0.80 (m, 2H, $CH_2C\underline{H}_2Si(CH_3)_3$), –0.10 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 165.1, 165.0, 138.7, 138.4, 133.2, 133.03, 132.97, 129.8, 129.72, 129.71, 129.5, 129.1, 129.0, 128.9, 128.31, 128.27, 128.22, 128.20, 128.16, 127.84, 127.82, 127.60, 127.55, 127.50, 127.47, 103.3 (C-1'), 100.5 (C-1), 78.8 (C-3'), 78.4 (C-2'), 74.6, 73.8, 73.3 (C-3), 72.2, 72.0 (C-2), 71.1 (C-5), 70.2 (C-4), 68.3(C-6), 67.3, 62.1 (C-5'), 17.8, –1.5 ($Si(CH_3)_3$).

9β $[\alpha]_D^{25}$ –40.7 (*c* 2.3, $CHCl_3$). HR-FABMS: calcd for $C_{58}H_{62}O_{13}SiNa$: *m/z* 1017.3857, found: *m/z* 1017.3859 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.95—7.22 (m, 30H, 6×Ph), 5.84 (t, 1H, $J_{2,3}$= $J_{3,4}$= 9.7 Hz, H-3), 5.50—5.46 (m, 2H, H-2, 4), 4.89 (d, 1H, $J_{1',2'}$ = 3.0 Hz, H-1'), 4.79 (d, 1H, $J_{1,2}$= 7.6 Hz, H-1), 4.78—4.49 (m, 6H, 3×benzyl methylene), 4.07 (br.t, 1H, H-5), 4.02—3.98 (m, 1H, C$\underline{H}_2$CH_2Si$(CH_3)_3$), 3.96 (dd, 1H, $J_{2',3'}$= 9.0 Hz, H-2'), 3.86—3.76 (m, 3H, H-6a, 6b, 3'), 3.70 (br.s, 1H, H-4'), 3.67-3.53 (m, 3H, H-5'a, 5'b, C$\underline{H}_2$CH_2Si$(CH_3)_3$), 0.89—0.81 (m, 2H, $CH_2C\underline{H}_2Si(CH_3)_3$), –0.11 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 165.2, 165.0, 138.9, 138.7, 138.3, 133.1, 133.0, 129.8, 129.72, 129.68, 129.5, 129.0, 128.9, 128.4, 128.3, 128.22, 128.18, 127.8, 127.6, 127.54, 127.52, 127.43, 127.39, 100.4 (C-1), 99.1 (C-1'), 76.8 (C-3'), 76.3 (C-2'), 73.9 (C-4'), 73.7 (C-5), 73.22 (C-3), 73.18, 72.6, 71.9, 71.7 (C-2), 70.2 (C-4), 67.7 (C-6), 67.3, 60.6 (C-5'), 17.8, –1.5 ($Si(CH_3)_3$).

MALDI-TOFMS: *m/z* 1018.4 $[M+Na]^+$ ($C_{58}H_{62}O_{13}SiNa$).

entry 2 (Table 1)

A mixture of **8** (150 mg, 0.25 mmol), **5** (155 mg, 0.30 mmol) and powdered MS AW300 (300 mg) in dry cyclopentyl methyl ether (CPME, 3 mL) was stirred under Ar atmosphere for 2 h at room temperature, then cooled to 0 °C. NIS (102 mg, 0.45 mmol) and AgOTf (93 mg, 0.36 mmol) were added to the mixture, which was stirred for 1 h at 0 °C, then neutralized with Et_3N. The precipitates were filtered off and washed with $CHCl_3$. The combined filtrate and washings were successively washed with saturated aqueous $Na_2S_2O_3$ and water, dried ($MgSO_4$), and concentrated. The residue was separated by silica gel column chromatography (20:1 toluene-EtOAc) to give **9α** (120 mg, 48%) and **9β** (130 mg, 52%).

entry 3 (Table 1)

A mixture of **8** (50 mg, 0.08 mmol), **5** (52 mg, 0.09 mmol) and MS 3Å (150 mg) in dry CH_2Cl_2-Et_2O (1:1, 1.0 mL) was stirred for 1.5 h at room temperature. MeOTf (50 μL, 0.38 mmol) was added, and the mixture was stirred for 2 h at room temperature, then neutralized with Et_3N. The precipitates were filtrated off and washed with $CHCl_3$. The combined filtrate and washings were washed with water, dried ($MgSO_4$), and concentrated. The residue was separated by silica gel column chromatography (20:1 toluene-EtOAc) to give **9α** (10 mg, 13%) and **9β** (22 mg, 27%).

entry 4 (Table 1)

A mixture of **8** (135 mg, 0.23 mmol), **5** (140 mg, 0.28 mmol) and MS 3Å (300 mg) in dry Et_2O-CPME (1:1, 2.0 mL) was stirred for 2 h at room temperature, then cooled to 0 °C. Dimethyl(methylthio)-sulfonium triflate (DMTST, 570 mg, 1.1 mmol) was added, and the mixture was stirred for 2 h at room temperature, then neutralized with Et_3N. The precipitates were filtrated off and washed with $CHCl_3$. The combined filtrate and washings were washed with water, dried ($MgSO_4$), and concentrated. The residue was separated by silica gel column chromatography (20:1 toluene-EtOAc) to give **9α** (62 mg, 27%) and **9β** (155 mg, 69%).

Phenyl 3,4-*O*-isopropylidene-2-*O*-benzyl-1-thio-α-D-arabinopyranoside (11)

A mixture of **10** (4.46 g, 18.4 mmol) in acetone (30 mL), camphorsulfonic acid (CSA, 2.14 g, 9.20 mmol) and 2,2-dimethoxypropane (DMP, 4.5 mL, 36.8 mmol) was stirred for 1.5 h at 40 °C, then neutralized with Et_3N. The precipitates were filtrated off and the filtrated was concentrated. The product was purified by silica gel column chromatography (1:1 hexane-EtOAc) to give an isopropylidene derivative. To a solution of this compound (3.97 g, 14.1 mmol) in DMF (60 mL) was added NaH (1.12 g, 28.1 mmol: 60% of oil dispersion), and the mixture was stirred for 30 min at 0 °C and then BnBr (6.9 mL, 28.1 mmol) was added. The stirring was continued for 3 h at 0 °C and then MeOH was added to destroy excess NaH. The mixture was poured into iced-water and extracted with EtOAc. The extract was successively washed with aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (10:1 hexane-EtOAc) to give **11** (4.41 g, 2 steps 64%). $[\alpha]_D^{25}$ +18.9 (*c* 2.3, $CHCl_3$). HR-FABMS: calcd for $C_{21}H_{24}O_4S$: *m/z* 372.1395, found: *m/z* 372.1420 $[M]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52—7.24 (m, 10H, 2×Ph), 4.82(d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 4.79 and 4.68 (each d, J_{gem} = 11.5 Hz, benzyl methylene), 4.28 (dt, 1H, $J_{3,4}$ = 7.7 Hz, $J_{4,5a}$ = $J_{4,5b}$ =3.9, H-4), 4.24 (t, 1H, $J_{2,3}$ = 5.5 Hz, H-3), 4.18 (dd, 1H, Hz, $J_{5a,5b}$ = 12.9 Hz, H-5a), 3.75 (dd, 1H, H-5b), 3.62 (dd, 1H, H-2), 1.47, 1.37 (each s, 6H, 2×CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.7, 134.1, 131.8, 128.8, 128.3, 128.1, 127.7, 127.3, 109.9, 86.3 (C-1), 78.1 (C-2), 78.0 (C-3), 73.3, 72.4 (C-4), 64.5 (C-5), 27.7, 26.1.

Phenyl 3,4-di-*O*-acetyl-2-*O*-benzyl-1-thio-α-D-arabinopyranoside (12)

A solution of **11** (4.41 g, 11.8 mmol) in 80% AcOH (40 mL) was stirred at 50 °C for 18 h, then diluted with toluene and concentrated. The residue was acetylated with acetic anhydride (15 mL) in pyridine (20 mL). The reaction was quenched with MeOH, then toluene was added and co-evaporated several times. The product was purified by silica gel column chromatography (4:1 hexane-EtOAc) to give **12** (4.53 g, 2 steps 92%). $[\alpha]_D^{25}$ –1.5 (*c* 1.2, $CHCl_3$). HR-FABMS: calcd for $C_{22}H_{24}O_6S$: *m/z* 416.1294, found: *m/z* 416.1328 $[M]^+$. MALDI-TOFMS: *m/z* 440.1 $[M+Na]^+$ ($C_{22}H_{24}O_6SNa$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.55—7.25 (m, 10H, 2×Ph), 5.29 (br.d, 1H, H-4), 5.11 (dd, 1H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 8.1 Hz, H-3), 4.85 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.81 and 4.61 (each d, J_{gem} = 11.1 Hz, benzyl methylene), 4.12 (dd, 1H, $J_{4,5a}$ = 4.0 Hz, Hz, $J_{5a,5b}$ = 12.6 Hz, H-5a), 3.81 (t, 1H, H-2), 3.65 (dd, 1H, $J_{4,5b}$ = 1.9 Hz, H-5b), 2.11, 2.01 (each s, 6H, 2×$COCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 169.9, 137.6, 134.0, 131.8, 129.0, 128.4, 127.84, 127.79, 127.6, 87.8 (C-1), 75.9 (C-2), 72.2 (C-3), 67.9 (C-4), 65.0 (C-5), 20.9, 20.8.

2-(Trimethylsilyl)ethyl 3,4-di-*O*-acetyl-2-*O*-benzyl-β-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (13)

A mixture of **8** (150 mg, 0.25 mmol), **12** (126 mg, 0.30 mmol) and MS 3Å (300 mg) in dry CH_2Cl_2-Et_2O (1:1, 3.0 mL) was stirred for 1 h at room temperature, then cooled to 0 °C. DMTST (623 mg, 1.21 mmol) was added, and the mixture was stirred for 3 h at 0 °C, then neutralized with Et_3N. The precipitates were filtrated off and washed with $CHCl_3$. The combined filtrate and washings were washed with water, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (2:1 hexane-EtOAc) to give **13** (214 mg, 95%). $[\alpha]_D^{25}$ –58.3 (*c* 2.1, $CHCl_3$). HR-FABMS: calcd for $C_{48}H_{54}O_{15}SiNa$: *m/z* 921.3130, found: *m/z* 921.3171 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 8.03—7.32 (m, 20H, 4×Ph), 5.93 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 5.56 (t, 1H, $J_{1,2}$ = 8.1 Hz, H-2), 5.51 (t, 1H, $J_{4,5}$ = 9.9 Hz, H-4), 5.38 (dd, 1H, $J_{2',3'}$ = 10.1 Hz, $J_{3',4'}$ = 3.3 Hz, H-3'), 5.35 (br.s, 1H, H-4'), 5.04 (d, 1H, $J_{1',2'}$ = 3.0 Hz H-1'), 4.87 (d, 1H, H-1), 4.76 and 4.72 (each d, 2H, J_{gem} = 12.3 Hz, benzyl methylene), 4.14 (br.t, 1H, H-5), 4.11—4.07 (m, 1H, C$\underline{H}_2$$CH_2Si(CH_3)_3$), 3.96—3.82 (m, 4H, H-6a, 6b, 2', 5'a), 3.67-3.60 (m, 2H, H-5'b, C$\underline{H}_2$$CH_2Si(CH_3)_3$), 2.17, 2.07 (each s, 6H, 2x$COCH_3$), 0.95—0.88 (m, 2H, CH_2C$\underline{H}_2$$Si(CH_3)_3$), –0.03 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 169.9, 165.7, 165.3, 165.0, 138.2, 133.4, 133.1, 133.0, 129.8, 129.74, 129.70, 129.5, 128.9, 128.8, 128.44, 128.35, 128.3, 128.21, 128.20, 127.70, 127.66, 127.4, 100.4 (C-1), 98.5 (C-1'), 74.0 (C-5), 73.9 (C-2'), 73.2 (C-3), 72.6 (benzyl methylene), 71.9 (C-2), 70.0 (C-4), 69.3 (C-4'), 69.0 (C-3'), 67.7 (C-6), 67.5 (O$\underline{C}$$H_2CH_2$-), 60.5 (C-5'), 20.9, 20.8, 17.8, –1.5 ($Si(CH_3)_3$).

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (14)

Compound **13** (202 mg, 0.22 mmol) in MeOH–THF (1:1, 4.0 mL) was hydrogenolyzed (0.4 MPa) under hydrogen in the presence of 10% Pd/C (200 mg) for 3 h at room temperature, then the mixture was filtered and concentrated. The residue was acetylated with acetic anhydride (2.0 mL) in pyridine (3.0 mL). The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was successively washed with 5% HCl, aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (10:1 toluene-EtOAc) to give **14** (165 mg, 2 steps 88%). $[\alpha]_D^{25}$ –73.5 (*c* 2.0, $CHCl_3$). HR-FABMS: calcd for $C_{43}H_{50}O_{16}SiNa$: *m/z* 873.2766, found: *m/z* 873.2771 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94—7.18 (m, 15H, 3×Ph), 5.85 (t, 1H, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3), 5.55 (t, 1H, $J_{4,5} = 9.7$ Hz, H-4), 5.49 (t, 1H, $J_{1,2} = 8.0$ Hz, H-2), 5.37 (dd, 1H, $J_{2',3'} = 9.0$ Hz, $J_{3',4'} = 3.3$ Hz, H-3'), 5.35 (br.s, 1H, H-4'), 5.19 (dd, 1H, $J_{1',2'} = 3.5$ Hz, H-2'), 5.10 (d, 1H, H-1'), 4.81 (d, 1H, H-1), 4.07—4.02 (m, 1H, C<u>H</u>$_2$CH$_2$Si(CH$_3$)$_3$), 3.99—3.95 (m, 2H, H-6a, 5), 3.89 (d, 1H, H-5'), 3.68—3.60 (m, 2H, H-6b, C<u>H</u>$_2$CH$_2$Si(CH$_3$)$_3$), 3.67-3.60 (m, 2H, H-5'b, C<u>H</u>$_2$CH$_2$Si(CH$_3$)$_3$), 2.01, 1.99 (each s, 6H, 2xCOCH$_3$), 0.94—0.88 (m, 2H, CH$_2$C<u>H</u>$_2$Si(CH$_3$)$_3$), –0.05 (s, 9H, Si(CH$_3$)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.3, 169.8, 165.8, 165.0, 164.9, 133.4, 133.09, 133.10, 129.7, 129.5, 129.0, 128.9, 128.4, 128.21, 128.19, 100.5 (C-1), 96.9 (C-1'), 73.6 (C-5), 73.3 (C-3), 71.8 (C-2), 69.3 (C-4), 69.4 (C-4), 69.0 (C-3'), 68.0 (C-2'), 67.4 (C-4'), 67.2 (O<u>C</u>H$_2$CH$_2$-), 66.5 (C-6), 60.3 (C-5'), 30.8, 20.9, 20.74, 20.66, 17.8, –1.5 (Si(CH$_3$)$_3$).

2,3,4-Tri-*O*-acetyl-β-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (15)

A solution of **14** (165 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL) cooled to 0 °C was added CF_3CO_2H (1.0 mL), and the mixture was stirred for 2 h at room temperature and then concentrated. EtOAc and toluene (1:2) were added and evaporated to give corresponding reducing sugar. To a solution of the residue in CH_2Cl_2 (1.0 mL) cooled at 0 °C were added DBU (15.0 mL, 0.10 mmol) and CCl_3CN (0.30 mL, 3.00 mmol). The reaction mixture was stirred for 1 h at 0 °C. After completion of the reaction, the mixture was concentrated. The product was purified by silica gel column chromatography (3:1 hexane-EtOAc) as eluent to give **15** (139 mg, 2 steps 82%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.65 (s, 1H, NH), 7.96—7.26 (m, 15H, 3×Ph), 6.82 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1), 6.24 (t, 1H, $J_{2,3} = J_{3,4} = 10.0$ Hz, H-3), 5.77 (t, 1H, $J_{4,5} = 10.0$ Hz, H-4), 5.60 (dd, 1H, H-2), 5.40—5.36 (m, 2H, H-3', 4'), 5.21 (dd, 1H, $J_{1',2'} = 3.5$ Hz, $J_{2',3'} = 10.5$ Hz, H-2'), 5.04 (d, 1H, H-1'), 4.42 (dt, 1H, H-5), 3.95 (d, 1H, H-5'a), 3.94 (dd, 1H, $J_{5,6a} = 2.2$ Hz, $J_{5,6b} = 11.8$ Hz, H-6a), 3.65 (dd, 1H, H-5'b), 3.59 (dd, 1H, $J_{5,6a} = 4.1$ Hz, H-6a). 2.14, 2.13, 2.03 (each, s, 9H, 3×OAc).

2,3,4-Tri-*O*-acetyl-β-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→1)-(2*S*,3*S*,4*R*)-2-azido-3,4-di-*O*-benzoyl-octadecane-1,3,4-triol (17)

A mixture of **15** (139 mg, 0.16 mmol), **16** (167 mg, 0.30 mol) and MS 4Å (300 mg) in dry CH_2Cl_2 (1.3 mL) was stirred for 16 h at room temperature, then cooled to 0 °C. TMSOTf (25 mL, 0.14 mmol) was added, and the mixture was stirred for 1.5 h at 0 °C, then neutralized with Et_3N. The precipitates were filtrated off and washed with $CHCl_3$. The combined filtrate and washings were washed with water, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (10:1 toluene-EtOAc) to give **17** (185 mg, 93%). $[\alpha]_D^{25}$ –23.9 (*c* 0.54, $CHCl_3$). HR-FABMS: calcd for $C_{70}H_{81}O_{20}N_3Na$: *m/z* 1306.5311, found: *m/z* 1306.5334 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 4.95 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1'), 4.78 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1).

2,3,4-Tri-*O*-acetyl-β-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→1)-(2*S*,3*S*,4*R*)-3,4-di-*O*-benzoyl-2-hexadecanamido-octadecane-1, 3, 4-triol (18)

To an emulsion of **17** (185 mg, 0.14 mmol) in THF-H_2O (5:1, 4.8 mL) was added triphenylphosphine (113 mg, 0.43 mmol), and the mixture was stirred for 20 h at 50 °C. The mixture was concentrated, and the residue was stirred with palmitic acid (108 mg, 0.42 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC: 80 mg, 0.42 mmol) in dry CH_2Cl_2 (2.0 mL) for 24 h at rt. The mixture was diluted with $CHCl_3$, washed with water, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (15:1 toluene-acetone) to give **18** (117 mg, 2 steps 54%). $[\alpha]_D^{25}$ –31.4 (*c* 1.7, $CHCl_3$). MALDI-TOFMS: *m/z* 1534.5 $[M+K]^+$ ($C_{86}H_{113}NO_{21}K$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.13—7.16 (m, 25H, 5×Ph), 6.30 (d, 1H, *J* = 9.4 Hz, NH), 5.78 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.7 Hz, H-3), 5.64 (dd, 1H, H-3 of sphingosin), 5.43—5.35 (m, 2H, H-2, 4), 5.27—5.24 (m, 2H, H-3', 4'), 5.09 (dd, 1H, $J_{1',2'}$ = 3.4 Hz, $J_{2',3'}$ = 10.1 Hz, H-2'), 4.90 (d, 1H, H-1'), 4.71 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.64 (br.t, 1H, C<u>H</u>(NHR)). ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.9, 178.6, 173.1, 170.6, 170.2, 169.8, 166.1, 165.6, 165.1, 165.02, 164.96, 133.4, 133.3, 133.2, 133.0, 130.1, 129.84, 129.76, 129.71, 129.6, 128.99, 128.93, 128.8, 128.7, 128.5, 128.43, 128.37, 128.3, 128.21, 128.17, 125.3, 100.4 (C-1), 97.0 (C-1'), 73.8, 73.6, 72.8, 71.8, 69.2, 69.0, 68.1, 67.1, 66.9, 66.4, 60.4, 47.8, 36.3, 35.3, 33.9, 31.9, 29.7, 29.64, 29.61, 29.55, 29.5, 29.40, 29.37, 29.3, 29.21, 29.15, 29.0, 28.9, 28.8, 25.5, 24.7, 24.2, 22.6, 20.9, 20.73, 20.65, 14.1.

β-D-Arabinopyranosyl-(1→6)-β-D-glucopyranosyl-(1→1)-(2*S*,3*S*,4*R*)-2-hexadecanamido-octadecane-1,3,4-triol (1)

A solution of **18** (68 mg, 0.05 mol) and NaOMe (40 mg) in 1,4-dioxane-MeOH (1:1, 4 mL) was stirred at 50 °C for 48 h, and then neutralized with Amberlite IR 120 $[H^+]$. The mixture was filtered and concentrated. The product was purified by Sephadex LH-20 column chromatography with 1:

$CHCl_3$-MeOH to give **1** (23 mg, 60%). $[\alpha]_D^{25}$ –28.0 (*c* 0.46, $CHCl_3$-MeOH). HR-FABMS: calcd for $C_{45}H_{87}NONa$: *m/z* 872.6075 found: *m/z* 872.6031 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$-CD_3OD): δ 4.89 (br.d, 1H, H-1'), 4.31 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1). ^{13}C NMR (125 MHz, $CDCl_3$-CD_3OD): δ 175.2, 104.2 (C-1), 100.3 (C-1'), 76.8, 75.9, 74.8, 72.5, 70.7, 70.16, 70.10, 69.9, 69.8, 63.8, 63.5, 61.3, 50.8, 36.9, 32.6, 32.4, 30.3, 30.2, 30.14, 30.06, 30.0, 29.9, 29.8, 26.5, 26.4, 23.1, 14.3.

2-(Trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (19)

Compound **19** was prepared from **9α** (181 mg, 0.18 mmol) as described for preparation of **14**. The product was purified by silica gel column chromatography (8:1 toluene-EtOAc) to give **19** (161 mg, 2 steps, quant.). $[\alpha]_D^{25}$ +9.2 (*c* 0.17, $CHCl_3$). HR-FABMS: calcd for $C_{43}H_{50}O_{16}SiNa$: *m/z* 873.2766, found: *m/z* 873.2784 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94—7.27 (m, 15H, 3×Ph), 5.84 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 5.54 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.45 (dd, 1H, $J_{1,2}$ = 7.9 Hz, H-2), 5.22 (br.s, 1H, H-4'), 5.17 (dd, 1H, $J_{1',2'}$ = 6.2 Hz, $J_{2',3'}$ = 8.6 Hz, H-2'), 5.06 (dd, 1H, $J_{3',4'}$ = 3.6 Hz, H-3'), 4.80 (d, 1H, H-1), 4.61 (d, 1H, H-1'), 4.08—4.03 (m, 1H, $C\underline{H}_2CH_2Si(CH_3)_3$), 4.01—3.96 (m, 4H, H-5, 6a, 6b, 5'a), 3.86 (br.d, 1H, H-6b), 3.66—3.61 (m, 1H, $C\underline{H}_2CH_2Si(CH_3)_3$), 3.55 (dd, 1H, H-5'), 2.12, 2.09, 2.06 (each s, 9H, 3×$COCH_3$), 0.93—0.87 (m, 2H, $CH_2C\underline{H}_2Si(CH_3)_3$), –0.05 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 170.1, 169.3, 165.8, 165.00, 164.9, 133.3, 133.1, 133.0, 129.73, 129.71, 129.65, 129.4, 129.0, 128.9, 128.3, 128.22, 128.20, 100.6 (C-1), 100.4 (C-1'), 73.8 (C-5), 73.3 (C-3), 71.9 (C-2), 69.7 (C-3'), 69.4 (C-4), 69.0 (C-2'), 67.5, 67.2 (C-4), 67.0 (C-6), 62.1 (C-5'), 20.82, 20.76, 20.7, 17.9, –1.5 ($Si(CH_3)_3$).

2,3,4-Tri-*O*-acetyl-α-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (20)

Compound **20** was prepared from **19** (159 mg, 0.19 mmol) as described for preparation of **15**. The product was purified by silica gel column chromatography (2:1 hexane-EtOAc) to give **20** (146 mg, 2 steps 87%). $[\alpha]_D^{25}$ +52.3 (*c* 0.52, $CHCl_3$). HR-FABMS: calcd for $C_{40}H_{38}O_{16}NCl_3Na$: *m/z* 916.1154, found: *m/z* 916.1160 $[M+Na]^+$.^1H NMR (500 MHz, $CDCl_3$): δ 8.62 (s, 1H, NH), 7.96—7.26 (m, 15H, 3×Ph), 6.82 (d, 1H, $J_{1,2}$ = 2.1 Hz, H-1), 6.21 (t, 1H, $J_{2,3} = J_{3,4}$ = 10.0 Hz, H-3), 5.76 (t, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 5.53 (dd, 1H, H-2), 5.21—5.19 (m, 2H, H-4', 2'), 5.05 (dd, 1H, $J_{2',3'}$ = 3.0 Hz, $J_{3',4'}$ = 7.5 Hz, H-3'), 4.61 (d, 1H, $J_{1',2'}$ = 6.0 Hz, H-1'), 4.46 (dt, 1H, H-5), 4.00 (d, 1H, $J_{5,6a}$ = 4.5 Hz, H-6a), 3.92 (dd, 1H, $J_{5,6b}$ = 4.0 Hz, H-6b), 3.86 (dd, 1H, H-5'a), 3.56 (dd, 1H, $J_{4',5'}$ = 2.5 Hz, H-5'b). 2.14, 2.11, 2.07 (each, S, 9H, 3×OAc). ^{13}C NMR (125 MHz, $CDCl_3$): 170.3, 170.2, 169.3, 165.7, 165.4, 164.8, 160.5, 133.5, 133.4, 133.2, 129.9, 129.8, 129.7, 128.9, 128.5, 128.40, 128.37, 128.3, 100.2 (C-1'), 93.2 (C-1), 90.7, 72.1, 70.7,

70.4, 69.7, 68.9, 68.1, 67.3, 65.8, 62.2, 20.9, 20.8, 20.7.

2,3,4-Tri-*O*-acetyl-α-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→1)-(2*S*,3*S*,4*R*)-2-azido-3,4-di-*O*-benzoyl-octadecane-1,3,4-triol (21)

Compound **21** was prepared from **20** (233 mg, 0.26 mmol) and **16** (169 mg, 0.29 mmol) as described for preparation of **17**. The product was purified by silica gel column chromatography (10:1 toluene-EtOAc) to give **21** (294 mg, 88%). $[\alpha]_D^{25}$ +3.8 (*c* 0.50, $CHCl_3$). HR-FABMS: calcd for $C_{70}H_{81}O_{20}N_3Na$: *m/z* 1306.5311, found: *m/z* 1306.5277 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ 7.99—7.26 (m, 25H, 5×Ph), 5.80 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 5.56 (t, 1H, $J_{4,5} = 9.5$ Hz, H-4), 5.50—5.45 (m, 2H, H-2, C<u>H</u>(OBzR)), 5.21 (br.d, 1H, H-4'), 5.16 (dd, 1H, $J_{1',2'} = J_{2',3'} = 6.5$ Hz, H-2'), 5.04 (dd, 1H, $J_{3',4'} = 3.4$ Hz, H-3'), 4.82 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1), 4.61 (d, 1H, H-1'), 3.95-3.90 (m, 2H, H-5, 6a), 3.54 (d, 1H, $J_{5,6} = 11.3$ Hz, H-6b). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.1, 169.5, 165.8, 165.7, 165.1, 164.9, 164.8, 133.5, 133.3, 133.22, 133.18, 133.11, 129.9, 129.78, 129.75, 129.7, 129.3, 129.2, 129.1, 128.8, 128.6, 128.5, 128.34, 128.26, 100.6 (C-1,C-1'), 74.1 (C-5), 73.1 (C-3), 72.9 (C-2), 72.6, 71.6, 70.0 (C-3'), 69.2 (C-2'), 68.9 (C-4), 67.5 (C-4'), 66.5, 62.6 (C-6), 61.0 (C-5'), 31.9, 29.8, 29.7, 29.62, 29.58, 29.5, 29.41, 29.36, 29.34, 29.26, 22.7, 20.9, 20.8, 20.7, 14.1.

2,3,4-Tri-*O*-acetyl-α-D-arabinopyranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl-(1→1)-(2*S*,3*S*,4*R*)-3,4-di-*O*-benzoyl-2-hexadecanamido-octadecane-1,3,4- triol (22)

Compound **22** was prepared from **21** (168 mg, 0.13 mmol) as described for preparation of **18**. The product was purified by silica gel column chromatography (9:1 toluene-EtOAc) to give **22** (71 mg, 2 steps 36%). $[\alpha]_D^{25}$ +16.1 (*c* 1.4, $CHCl_3$). MALDI-TOFMS: *m/z* 1517.6 $[M+Na]^+$ ($C_{86}H_{113}NO_{21}Na$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.05—7.18 (m, 25H, 5×Ph), 6.23 (d, 1H, $J = 9.4$ Hz, NH), 5.76 (t, 1H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 5.53 (t, 1H, $J_{4,5} = 9.7$ Hz, H-4), 5.37—5.31 (m, 2H, H-2, C<u>H</u>(OBzR)), 4.63 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 170.3, 170.0, 169.5, 166.1, 165.7, 165.1, 165.0, 164.7, 133.4, 133.3, 133.21, 133.17, 132.97, 133.04, 129.84, 129.80, 129.76, 129.74, 129.66, 129.1, 129.00, 128.96, 128.8, 128.6, 128.44, 128.35, 128.3, 128.24, 128.19, 101.1, 100.5, 74.0, 73.7, 72.8, 72.5, 72.1, 70.0, 69.5, 68.7, 68.1, 67.6, 66.6, 62.4, 47.9, 36.4, 31.9, 29.70, 29.67, 29.65, 29.62, 29.60, 29.56, 29.4, 29.34, 29.28, 28.4, 25.52, 25.50, 22.7, 20.9, 20.7, 14.1.

α-D-Arabinopyranosyl-(1→6)-β-D-glucopyranosyl-(1→1)-(2*S*,3*S*,4*R*)-2-hexadecanamido-octadecane-1,3,4-triol (2)

Compound **2** was prepared from **22** (133 mg, 0.09 mmol) as described for preparation of **1**. The product was purified by Sephadex LH-20 column chromatography in 1:1 $CHCl_3$-MeOH to give **2** (58 mg, 78%).

$[\alpha]_D^{25}$ +4.4 (*c* 0.86, $CHCl_3$-MeOH). HR-FABMS: calcd for $C_{45}H_{87}NONa$: *m/z* 872.6075 found: *m/z* 872.6118 $[M+Na]^+$. ^1H NMR (500 MHz, $CDCl_3$-CD_3OD): δ 4.32 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1'), 4.27 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1). ^{13}C-NMR (500 MHz, $CDCl_3$-CD_3OD): δ 175.1, 104.2 (C-1), 103.6 (C-1'), 76.6, 75.4, 74.7, 74.2, 73.1, 72.3, 71.6, 70.1, 69.9, 68.3, 67.7, 66.0, 50.8, 36.9, 32.40, 32.25, 30.25, 30.16, 30.13, 30.0, 29.94, 29.83, 26.4, 23.1, 14.3.

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REFERENCES AND NOTES

1. (a) I. Ohtsuka, N. Hada, T. Atsumi, and N. Kakiuchi, *Tetrahedron*, 2013, **69**, 1470; (b) T. Kanaya, F. Schweizer, T. Takeda, F. Kiuchi, and N. Hada, *Carbohydr. Res*., 2012, **361**, 55; (c) A. Koizumi, K. Yamano, T. Tsuchiya, F. Schweizer, F. Kiuchi, and N. Hada, *Molecules*, 2012, **17**, 9023; (d) A. Koizumi, K. Yamano, F. Schweizer, T. Takeda, F. Kiuchi, and N. Hada, *Eur. J. Med. Chem*., 2011, **46**, 1768; (e) Y. Fujita, N. Ohshima, A. Hasegawa, F. Schweizer, T. Takeda, F. Kiuchi, and N. Hada, *Molecules*, 2011, **16**, 637; (f) N. Hada, Y. Shida, H. Shimamura, Y. Sonoda, T. Kasahara, and T. Takeda, *Carbohydr. Res*., 2008, **343**, 2221; (g) N. Hada, T. Nakashima, S. P. Shrestha, R. Masui, Y. Narukawa, K. Tani, and T. Takeda, *Bioorg. Med. Chem. Lett*., 2007, **17**, 5912; (h) T. Yamamura, N. Hada, A. Kaburaki, K. Yamano, and T. Takeda, *Carbohydr. Res*., 2004, **339**, 2749; (i) I. Ohtsuka, N. Hada, M. Sugita, and T. Takeda, *Carbohydr. Res*., 2002, **337**, 2037.
2. (a) T. Natori, M. Morita, K. Akimoto, and H. Koezuka, *Tetrahedron*, 1994, **50**, 2771; (b) T. Natori, Y. Koezuka, and T. Higa, *Tetrahedron Lett*., 1993, **34**, 5591.
3. T. Kawano, J. Cui, Y. Koezuka, I. Toura, Y. Kaneko, K. Motoki, H. Ueno, R. Nakagawa, H. Sato, E. Kondo, H. Koseki, and M. Taniguchi, *Science*, 1997, **278**, 1626.
4. (a) V. Costantino, E. Fattorusso, A. Mangoni, R. Teta, E. Panza, and A. Ianaro, *Bioorg. Med. Chem. Lett*., 2010, **18**, 5310; (b) V. Costantino, E. Fattorusso, C. Imperatore, A. Mangoni, and R. Teta, *Eur. J. Org. Chem*., 2009, 2112; (c) V. Costantino, E. Fattorusso, C. Imperatore, A. Mangoni, S. Freigang, and L. Teyton, *Bioorg. Med. Chem. Lett*., 2008, **16**, 2077; (d) V. Costantino, E. Fattorusso, C. Imperatore, and A. Mangoni, *Eur. J. Org. Chem*., 2005, 368; (e) V. Costantino, E. Fattorusso, A. Mangoni, M. D. Rosa, and A. Ianaro, *Tetrahedron*, 2000, **56**, 1393; (f) V. Costantino, E. Fattorusso, A. Mangoni, M. D. Rosa, A. Ianaro, and P. Maffia, *Tetrahedron*, 1996, **52**, 1573.

5. U. Ellervik and G. Magnusson, *J. Org. Chem.*, 1998, **63**, 9314.
6. (a) G. H. Veeneman, S. H. van Leeuwen, and J. H. van Boom, *Tetrahedron Lett.,* 1990, **31**, 1331; (b) P. Konradsson, U. E. Udodong, and B. Fraser-Reid, *Tetrahedron Lett*., 1990, **31**, 4313.
7. (a) P. Fugedi, W. Birberg, P. J. Garegg, and A. Pilotti, *Carbohydr. Res*., 1987, **164**, 297; (b) H. Lonn, *Carbohydr. Res*., 1985, **139**, 105.
8. H. Tokimoto, Y. Fujimoto, K. Fukase, and S. Kusumoto, *Tetrahedron: Asymmetry*, 2005, **16**, 441.
9. (a) P. Fugedi and P. J. Garegg, *Carbohydr. Res*., 1986, **149**, c9; (b) M. Ravenscroft, R. M. G. Roberts, and J. G. Tillett, *J. Chem. Soc*., *Perkin Trans. 2*, 1982, 1569.
10. Z. Li, L. Zhu, and J. Kalikanda, *Tetrahedron Lett*., 2011, **52**, 5629.
11. R. R. Schmidt and G. Grundler, *Synthesis*, 1981, 885.
12. M. Kiso, A. Nakamura, Y. Tomita, and A. Hasegawa, *Carbohydr. Res*., 1986, **158**, 101.
13. R. R. Schmidt, *Angew. Chem*., *Int. Ed. Engl*., 1986, **25**, 212.
14. N. Ohtsubo, H. Ishida, M. Kiso, and A. Hasegawa, *Carbohydr. Res*., 1998, **306**, 517.