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Stereoselective β-mannosylation via anomeric O-Alkylation: Concise synthesis of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe, a trisaccharide oligomer of the hyriopsis schlegelii glycosphingolipid

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Stereoselective β-mannosylation via anomeric O-Alkylation: Concise synthesis of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe, a trisaccharide oligomer of the *hyriopsis schlegelii* glycosphingolipid

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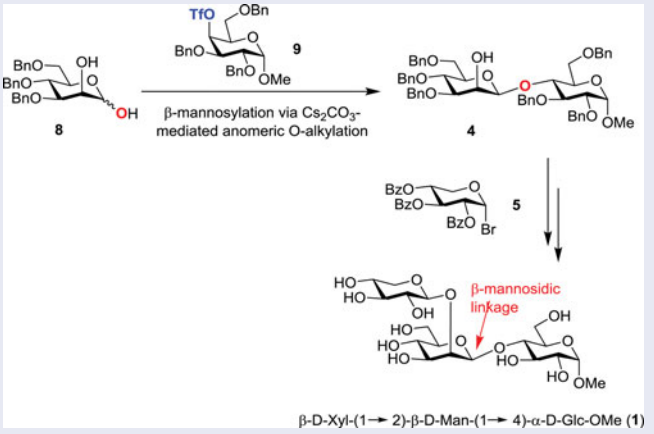
ABSTRACT

Synthesis of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**), a trisaccharide oligomer of the *Hyriopsis schlegelii* glycosphingolipid is described. The synthesis involves a key β-mannosylation via cesium carbonate-mediated anomeric *O*-alkylation for direct synthesis of partially protected disaccharide β-D-Man-(1→4)-α-D-Glc-OMe (**4**) bearing a free C_2–OH in the mannose moiety. In addition, a silver triflate-promoted glycosylation of **4** with 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl bromide (**5**) followed by deprotection affords the desired trisaccharide component (**1**) of the *Hyriopsis schlegelii* glycosphingolipid.

GRAPHICAL ABSTRACT



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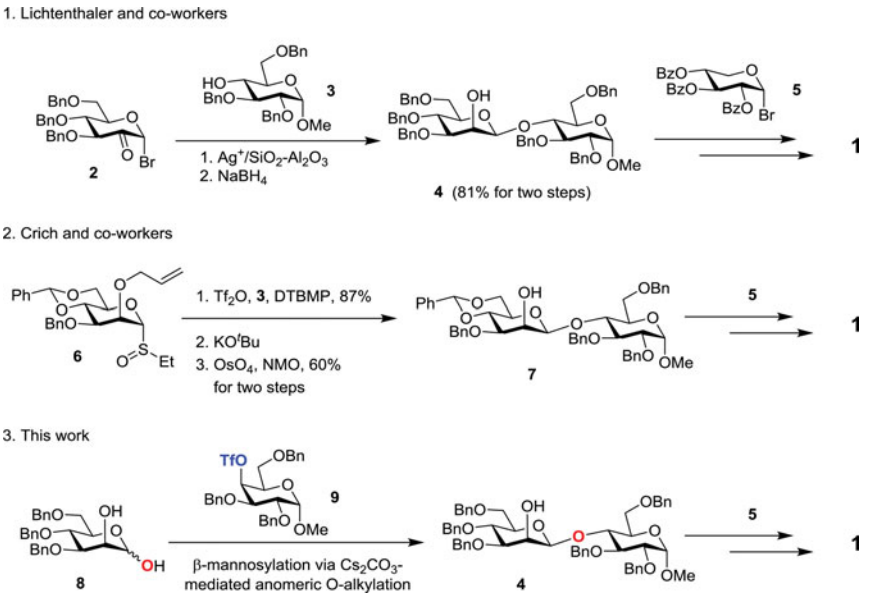
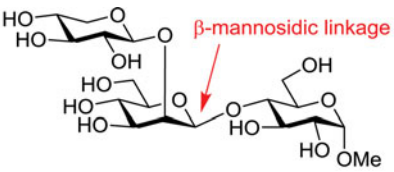
Introduction

Stereoselective construction of biologically significant β-mannopyranosides has been a long-standing synthetic challenge in carbohydrate chemistry, due to steric effect of the axial C_2-substituents as well as the absence of anomeric effect and anchimeric assistance (also known as neighbouring group participation (NGP)).[1] Consequently, tremendous efforts have been devoted to solving this difficulty for the synthesis complex carbohydrates bearing β-mannosidic linkage. Thus far, typical efforts include: 1) direct β-mannosylation using non-participating protecting group[2] for O_2 and insoluble silver salts for activation of mannosyl halides;[2a-d] 2) inversion of the C_2 stereochemistry of β-glucosides[3] or stereoselective reductionof β-2-ulosyl glycosides;[4] 3) *de novo* synthesis of β-mannopyranosides via α-selective quenching of C1-alkoxy radicals by suitable hydrogen atom donors;[5] 4) synthesis of β-mannopyranosides involving intramolecular aglycone delivery;[6,7,8] 5) use of 4,6-*O*-benzylidene,[9] 4,6-*O*-arylboronate,[10] or 4,6-*O*-silylene[11] protected α-mannopyranosyl triflates; 6) use of hydrogen-bond-mediated aglycone delivery mediated by a remote 3- and/or 6-*O*-picoloyl group;[12] 7) use of glycosyl-acceptor-derived borinic ester[13] or boronic ester[14] as catalysts for activation of 1,2-anhydromannose donors; 8) use of mannosyl donors bearing 2,6-[15] or 3,6-lactone moieties;[16] 9) β-selective anomeric *O*-alkylation of mannose-derived lactols[17] or 1,2-*O*-dibutylstannylenes.[18]

Early in 2016, we reported an efficient β-mannosylation method involving cesium carbonate-mediated anomeric *O*-alkylation of D-mannose-derived 1,2-diols with primary or secondary electrophiles.[17c] This β-mannosylation was developed based on our previous experiences in the stereoselective synthesis of 2-deoxy-β-glycosides[19] or 2-deoxy-α-glycosides[20] via anomeric *O*-alkylation. In particular, this easily operable β-mannosylation directly affords the desired β-mannosides



Scheme 1. Previous synthesis of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**) and our strategy.

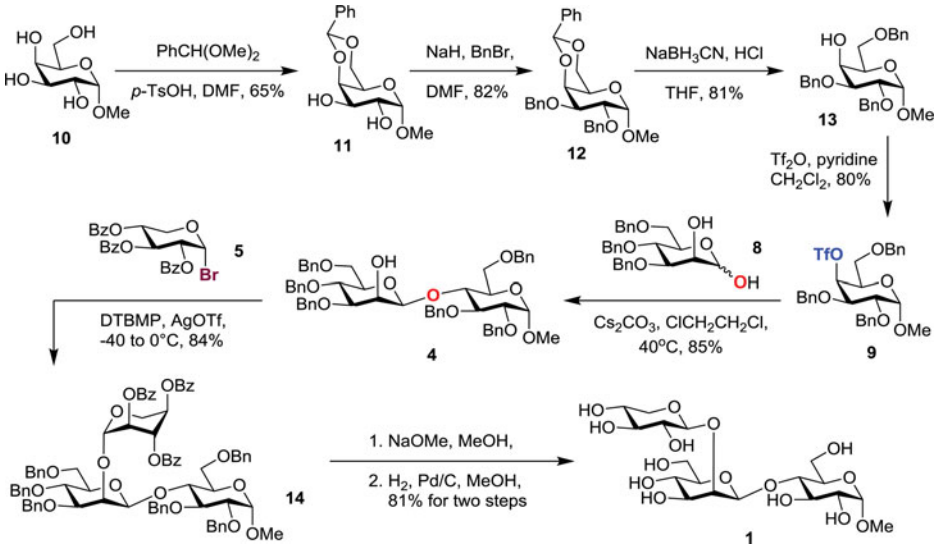


β-D-Xyl-(1→ 2)-β-D-Man-(1→ 4)-α-D-Glc-OMe (**1**)

Figure 1. The structure of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**), a trisaccharide oligomer of the *Hyriopsis schlegelii* Glycosphingolipid.

with a free C_2−OH at the mannose residue (*cf.* **4**, Scheme 1). The free C_2-alcohol can be directly subjected to the next chemical transformation, such as acylation and glycosylation, without the necessity of additional deprotection steps. Recently, this β-mannosylation was successfully employed in a highly efficient formal synthesis of potent calcium signal modulator acremomannolipin A,[17d] in which the free C_2−OH of corresponding mannose residue was directly subjected to acylation. In this Communication, we would like to demonstrate its application to the synthesis of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**, Figure 1), a trisaccharide oligomer of the *Hyriopsis schlegelii* glycosphingolipid. In this synthesis the free C_2−OH at the mannose residue of the disaccharide **4** is directly subjected to another glycosylation with protected xylosyl bromide donor **5** to furnish the corresponding trisaccharide (*cf.* **14**).

The trisaccharide oligomer of the *Hyriopsis schlegelii* glycosphingolipid, β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**),[21] has been previously synthesized independently by two groups (Scheme 1). The first synthesis of **1** was reported by Lichtenthaler and co-workers in 1994.[22] In their synthesis, ulosyl bromide **2** reacted with acceptor **3** in the presence of excess silver aluminosilicate promoter to afford the corresponsing β-uloside (87% yield) which was subsequently reduced by sodium borohydride to furnish β-mannoside **4** (81% yield overall for two steps). This β-mannoside **4** was then subjected to glycosylation with xylosyl bromide donor **5**[23] followed by removal of the protecting group afforded desired trisaccharide oligomer **1**. A few years later, Crich and Dai disclosed the second synthesis of trisaccharide **1** employing so-called "Crich β-mannosylation".[24] As shown in Scheme 1, 4,6-*O*-benzylidene-protected D-mannosyl sulfoxide donor **6** reacted with acceptor **3** in the presence of triflic anhydride/DTBMP to afford corresponding desired β-mannoside (β/α = 12/1, 87% yield) which was subjected to a two-step de-allylation to give rise to the β-mannoside **7** (60% yield for two steps). Similarly, glycosylation of β-mannoside **7** with xylosyl bromide donor **5** followed by removal of the protecting group afforded desired trisaccharide oligomer **1**. In addition, Takeda and co-workers synthesized the protected form of **1**[25] and incorporated it into a more complex octasaccharide in the same glycosphingolipid.[26] Obviously, the Lichtenthaler approach required additional steps, i.e. oxidation of the C_2-alcohol of the glycosyl donor to the ketone (2-oxo) and reduction of the 2-oxo to the C_2-axial alcohol after glycosylation. It is worth noting that the sodium borohydride reduction may result in lower diastereoselectivites.[27] The Crich synthesis required an additional two-step deprotection of the O-2 allyl protecting group in the



Scheme 2. Concise Synthesis of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**) involving β-mannosylation via Cs_2CO_3-mediated anomeric O-alkylation.

mannose moiety to free the C_2-alcohol (*cf.* **7**) for subsequent glycosylation with xylosyl bromide donor **5**. In this report, we will describe the synthesis of trisaccharide oligomer of the *Hyriopsis schlegelii* glycosphingolipid, β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**) in which the key intermediate β-mannoside **4** bearing a free C_2−OH at the mannose moiety is directly prepared from known D-mannose-derived lactol **8**[28] and methyl α-D-galactoside-derived axial C_4-triflate **9** via cesium carbonate-mediated anomeric *O*-alkylation (Scheme 1).

Results and Discussion

Our preparation of the known methyl α-D-galactoside-derived C_4-axial triflate **9**[29] commenced with the 4,6-*O*-benzylidenation of commercially available methyl α-D-galactoside **10**. As depicted in Scheme 2, standard acid-catalyzed 4,6-*O*-benzylidenation of methyl α-D-galactoside **10** using benzaldehyde dimethyl acetal in DMF afforded methyl 4,6-*O*-benzylidene-α-D-galactoside **11** (65% yield) and subsequently the 2,3-diol of **11** underwent double benzylation to furnish methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactoside **12** (82% yield). Regioselective reductive opening of the 4,6-*O*-benzylidene of **12** using sodium cyanoborohydride in the presence of acid provided methyl 2,3,6-tri-*O*-benzyl-α-D-galactoside **13** (81% yield) bearing an axial free C_4-alcohol. Next, this C_4-alcohol in **13** underwent standard triflation to give rise to axial C_4-triflate **9** in 80% yield. Under our previously reported optimal condition, cesium carbonate-mediated stereoselective anomeric *O*-alkylation of known D-mannose-derived lactol **8** with C_4-triflate **9** afforded desired key intermediate β-mannoside **4** in 85% yield (β only) which contains a free C_2-alcohol ready for next glycosylation with xylosyl bromide donor **5**.

Previously, Lichtenthaler and co-workers described that treatment of β-mannoside **4** (1 eq.) with xylosyl bromide donor **5** (1.5 eq.) in the presence of silver triflate (*ca.* 2.0 eq.) in the absence of base at −40 °C for 30 minutes gave desired trisaccharide **14** in 71% yield (experimental section).[22] However, in our hands applying the exactly same reaction condition reported by Lichtenthaler *et al*[22] to β-mannoside **4** and xylosyl bromide donor **5** only afforded desired trisaccharide **14** in low conversion. We then turned our attention to the experimental procedure reported by Crich *et al* for glycosylation of a similar substrate β-mannoside **7** with xylosyl bromide donor **5** in which a general bulky base 2,6-di-tert-butyl-4-methylpyridine (DTBMP) was used.[24b] Indeed, under the exactly same condition reported by Crich *et al* (**4** (1 eq.), **5** (1.15 eq.), AgOTf (2.1 eq.), DTBMP (3.25 eq.), 4Å molecular sieves), desired trisaccharide **14** was obtained in 43% yield (84% based on recovered disaccharide **4**). After extensive studies, finally we found out that treatment of β-mannoside **4** (1 eq.) with xylosyl bromide donor **5** (3.5 eq.) in the presence of silver triflate (4.0 eq.), DTBMP (5.0 eq.), and 4Å molecular sieves from –40 to 0°C gave desired trisaccharide **14** in 84% yield. Next, standard global de-benzoylation of **14** followed by Pd/C-catalyzed global hydrogenolysis of remaining benzyl groups produced the β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**) in 81% yield over two steps.[22]

In conclusion, we have described a concise synthesis of β-D-Xyl-(l→2)-β-D-Man-(1→4)-α-D-Glc-OMe (**1**), a trisaccharide oligomer of the *Hyriopsis schlegelii* glycosphingolipid. The synthesis involves a key stereoselective β-mannosylation via cesium carbonate-mediated anomeric *O*-alkylation for the preparation of partially protected disaccharide β-D-Man-(1→4)-α-D-Glc-OMe (**4**). Application of this Cs_2CO_3-mediated β-mannosylation to the synthesis of other biologically significant oligosaccharides and glycoconjugates is in progress.

Experimental

Materials and methods

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on either Bruker 600 (^{1}H NMR-600 MHz; ^{13}C NMR 150) or INOVA 600 (^{1}H NMR-600 MHz; ^{13}C NMR-150 MHz) at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to residual protic solvent internal standard CDCl3: ^{1}H NMR at δ 7.26, ^{13}C NMR at δ 77.36. Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hertz. All ^{13}C NMR spectra were recorded with complete proton decoupling. Low resolution mass spectra (LRMS) were acquired on a Waters Acuity Premiere XE TOF LC-MS by electrospray ionization. Optical rotations were measured with Autopol-IV digital polarimeter; concentrations are expressed as g/100 mL.

All reagents and chemicals were purchased from Acros Organics, Sigma Aldrich, Fisher Scientific, Alfa Aesar, and Strem Chemicals and used without further purification. THF, methylene chloride, toluene, and diethyl ether were purified by passing through two packed columns of neutral alumina (Innovative Technology). Anhydrous DMF and benzene were purchased from Acros Organics and Sigma-Aldrich and used without further drying. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash column chromatography was performed using 200–400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated.

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→4)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (4)

To a mixture of 3,4,6-tri-*O*-benzyl-D-mannopyranose **8** (45 mg, 0.1 mmol), D-galactose-derived C_4-triflate **9** (119 mg, 0.2 mmol), and cesium carbonate (81.5 mg, 0.25 mmol), was added 1,2-dichloroethane (1.0 mL). The reaction mixture was stirred at 40°C for 12 hours. The crude reaction mixture was diluted with dichloromethane and purified by preparative thin layer chromatography (hexanes: EtOAc: methanol = 2:1:1%) to furnish 77 mg (85% yield) of β-mannose **4**. The β-configuration of the mannosidic linkage in **4** was assigned by measuring the $J_{(C,H)}$ of anomeric carbon of the mannose moiety (159 Hz). $[\alpha]_D^{21} = +14.3^\circ$ ($c = 1.0$, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 2.62 (br, s, 1 H), 3.27 – 3.31 (m, 2 H), 3.34 – 3.37 (m, 1 H), 3.40 – 3.42 (m, 5 H), 3.55 (dd, $J = 9.4$, 3.6 Hz, 2 H), 3.61 (d, $J = 4.6$ Hz, 1 H), 3.63 (d, $J = 4.6$ Hz, 1 H), 3.65 – 3.66 (m, 1 H), 3.67 – 3.69 (m, 1 H), 3.69 – 3.71 (m, 1 H), 3.79 (d, $J = 3.3$ Hz, 1 H), 3.80 – 3.84 (m, 2 H), 3.88 (t, $J = 9.5$ Hz, 2 H), 3.96 – 4.00 (m, 3 H), 4.04 (t, $J = 9.3$ Hz, 2 H), 4.48 (s, 1 H) 4.49 – 4.51 (m, 5 H), 4.53 (d, $J = 6.1$ Hz, 2 H), 4.55 (s, 1 H), 4.59 (d, $J = 11.9$ Hz, 2 H), 4.62 – 4.65 (m, 4 H), 4.65 – 4.68 (m, 2 H), 4.81 (d, $J = 12.1$ Hz, 2 H), 4.88 (d, $J = 10.8$ Hz, 1 H), 4.94 (d, $J = 11.0$ Hz, 2 H), 5.02 (d, $J = 11.0$ Hz, 2 H), 7.21 – 7.24 (m, 3 H), 7.25 – 7.31 (m, 14 H), 7.31 – 7.37 (m, 30 H), 7.41 (d, $J = 7.3$ Hz, 3 H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ 55.27, 67.87, 68.73, 69.00, 69.57, 71.09, 73.44, 73.55, 73.95, 75.18, 75.59, 75.65, 75.77, 76.91, 77.12, 77.33, 79.55, 80.74, 81.57, 98.19, 99.98, 127.47, 127.67, 127.73, 127.77, 127.79, 127.82, 127.89, 127.96, 128.09, 128.14, 128.21, 128.30, 128.38, 128.46, 128.49, 128.52, 128.57, 137.86, 137.96, 138.12, 138.34, 138.42, 139.00. **FT-IR (thin flim):** 3468, 3035, 2880, 1728, 1501, 1456, 1053, 751, 695 cm^{-1}. **ESILRMS $[M+Na]^+$** calculated $C_{55}H_{60}O_{11}Na$ 919.40, found 919.50.

Methyl 2,3,4-tri-O-benzoyl-β-D-xylopyranosyl-(1→2)-3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→4)-2,3,6-tri-O-benzyl-α-D-glucopyranoside (14)

To β-mannoside acceptor **4** (90 mg, 0.1 mmol) in dry CH_2Cl_2 (5 mL) were added powdered molecular sieves (100 mg) and DTBMP (102 mg, 0.5 mmol). The reaction mixture was cooled to -40°C and stirred for 0.5 h under argon. A solution of

xylosyl bromide donor **5** (183 mg, 0.35 mmol) in CH_2Cl_2 (2.3 mL) was added followed by dropwise addition of AgOTf (103 mg, 0.4 mmol) in toluene (1.6 mL). The reaction mixture was stirred at -40°C for 0.5 h and then warmed up to 0°C and stirred for another 1 h before being filtered through a pad of celite. The combined organic solutions were washed with 10% aq. Na_2SO_3 and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (Toluene: EtOAc = 15:1) to afford 113 mg (84%) of trisaccharide **14**. $[\alpha]_D^{21} = -41.6^\circ$ ($c = 1.0$, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 3.25 – 3.31 (m, 3 H), 3.32 (d, $J = 2.9$ Hz, 1 H), 3.42 – 3.47 (m, 1 H), 3.54 – 3.58 (m, 1 H), 3.59 – 3.68 (m, 4 H), 3.70 – 3.76 (m, 2 H), 3.87 (t, $J = 9.5$ Hz, 1 H), 4.00 (t, $J = 9.3$ Hz, 1 H), 4.11 (d, $J = 2.9$ Hz, 1 H), 4.15 (d, $J = 12.1$ Hz, 1 H), 4.36 – 4.42 (m, 3 H), 4.42 – 4.46 (m, 2 H), 4.54 – 4.60 (m, 3 H), 4.63 (d, $J = 12.1$ Hz, 1 H), 4.70 – 4.74 (m, 2 H), 4.75 (d, $J = 2.8$ Hz, 1 H), 4.81 (dd, $J = 13.0$, 2.6 Hz, 1 H), 4.84 (s, 1 H), 5.14 (d, $J = 11.4$ Hz, 1 H), 5.19 (q, $J = 3.1$ Hz, 1 H), 5.43 (d, $J = 2.2$ Hz, 1 H), 5.49 – 5.51 (m, 1 H), 5.56 (t, $J = 4.0$ Hz, 1 H), 7.12 – 7.16 (m, 3 H), 7.18 (dd, $J = 7.3$, 1.8 Hz, 2 H), 7.19 – 7.22 (m, 2 H), 7.23 – 7.27 (m, 10 H), 7.29 – 7.30 (m, 4 H), 7.31 – 7.35 (m, 10 H), 7.37 – 7.41 (m, 5 H), 7.48 – 7.52 (m, 2 H), 7.57 – 7.61 (m, 1 H), 7.98 – 8.01 (m, 2 H), 8.05 – 8.10 (m, 4 H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 55.28, 71.69, 73.34, 73.66, 74.98, 75.13, 75.27, 76.83, 77.05, 77.26, 80.01, 98.56, 126.81, 127.22, 127.56, 127.58, 127.62, 127.68, 127.71, 127.82, 127.92, 128.14, 128.19, 128.22, 128.33, 128.37, 128.39, 128.49, 128.57, 130.02, 130.08, 133.29, 133.31, 138.04, 138.74. **FT-IR (thin flim):** 3056, 2915, 1721, 1452, 1252, 1093, 700 cm^{-1}. **ESILRMS [M+Na]$^+$** calculated $C_{81}H_{80}O_{18}Na$, 1363.52 observed 1363.80.

Methyl β-D-xylopyranosyl-(1→2)-β-D-mannopyranosyl-(1→4)-α-D-glucopyranoside (1)

To trisaccharide **14** (17 mg, 0.012 mmol) in methanol (0.26 mL) was added a small drop of sodium methoxide solution (*ca.* 3 μL, 5.4 M in methanol). The resulting mixture was stirred at room temperature overnight and then neutralized by acidic ion exchange resin (Dowex H^+ resin). The mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography with CH_2Cl_2: MeOH (20:1) to afford a syrup (11.1 mg) which was directly subjected to hydrogenolysis over Pd/C (1 mg) in methanol (1 mL) for 24 h. Filtration and removal of the solvent furnished **1** as a white solid (5 mg, 81% for two steps). $[\alpha]_D^{21} = +19.3^\circ$ ($c = 0.15$, H_2O). **^{1}H NMR (600 MHz, D_2O)** δ ppm 3.14 (s, 1 H), 3.23 – 3.29 (m, 2 H), 3.30 (s, 3 H), 3.32 (d, $J = 9.2$ Hz, 2 H), 3.46 (s, 1 H), 3.47 – 3.50 (m, 2H), 3.50 – 3.55 (m, 3 H), 3.66 (s, 3 H), 3.71 (s, 1 H), 3.74 (s, 1 H), 3.82 (s, 1 H), 4.13 (d, $J = 3.3$ Hz, 1 H), 4.38 (d, $J = 7.7$ Hz, 1 H), 4.69 (br, s, 1 H). **^{13}C NMR (151 MHz, D_2O)** δ ppm 54.96, 55.09, 60.09, 60.42, 64.98, 66.80, 69.19, 70.05, 70.84, 71.56, 71.74, 73.17, 75.30, 76.36, 77.75, 78.73, 98.93, 100.11, 104.01, 128.49, 129.25, 189.71, 195.62, 204.99, 208.78, 210.50, 211.63. **FT-IR (thin flim):** 3227, 29256, 1728, 1382, 1156, 1038, 525 cm^{-1}. **ESILRMS [M + Na]$^+$** $C_{55}H_{60}O_{11}Na$, Calculated 511.16, found 511.10.

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Reference

[1] (a) Nigudkar, S. S.; Demchenko, A. V. Stereocontrolled 1,2-cis Glycosylation As the Driving Force of Progress in Synthetic Carbohydrate Chemistry. *Chem. Sci.* **2015**, *6*, 2687–2704. (b) Ishiwata, A.; Lee, Y. J.; Ito, Y. Recent Advances in Stereoselective Glycosylation Through Intramolecular Aglycon Delivery. *Org. Biomol. Chem.* **2010**, *8*, 3596–3608. (c) Barresi, F.; Hindsgaul, O. *Modern Methods in Carbohydrate Synthesis*; Khan, S. H.; O'Neill, R. A., Eds.; Harwood Academic Publishers: Amsterdam, **1996**; pp. 251–276. Toshima, K.; Tatsuta, K. Recent Progress in *O*-Glycosylation Methods and Its Application to Natural Products Synthesis. *Chem. Rev.* **1993**, *93*, 1503–1531. (e) Paulsen, H. Advances In Selective Chemical Syntheses of Complex Oligosaccharides. *Angew. Chem., Int. Ed.* **1982**, *21*, 155–173.

[2] (a) Gorin, P. A. J.; Perlin, A. S. Configuration of Glycosidic Linkages in Oligosaccharides: IX. Synthesis of α- and β-D-Mannopyranosyl Disaccharides. *Can. J. Chem.* **1961**, *39*, 2474–2485. (b) Garegg, P. J.; Iversen, T.; Johansson, R. Synthesis of Disaccharides Containing β-D-Mannopyranosyl Groups. *Acta Chem. Scand.* **1980**, *B34*, 505–508. (c) Wulff, G.; Wichelhaus, J. Untersuchungen zur Glycosidsynthese, IX. Zur Synthese von β-D-Mannopyranosiden. *Chem. Ber.* **1979**, *112*, 2847–2853. (d) Paulsen, H.; Lockhoff, O. Building Units for Oligosaccharides. XXX. New effective β-glycoside synthesis of mannose glycosides. Synthesis of mannose containing oligosaccharides. *Chem. Ber.* **1981**, *114*, 3102–3114. (e) Srivastava, V. K.; Schuerch, C. A Synthesis of β-D-Mannopyranosides by Glycosidation at C-1. *Carbohydr. Res.* **1980**, *79*, C13–C16. (f) Srivastava, V. K.; Schuerch, C. Synthesis of β-D-Mannopyranosides and β-L-Rhamnopyranosides by Glycosidation at C-1. *J. Org. Chem.* **1981**, *46*, 1121–1126.

[3] (a) Theander, O. Oxidation of Glycosides. X. Reduction of Methyl D-Oxoglucopyranosides. *Acta Chem. Scand.* **1958**, *12*, 1883–1885. (b) Ekborg, G.; Lindberg, B.; Lonngren, J. Synthesis of β-D-Mannopyranosides. *Acta Chem. Scand. B.* **1972**, *26*, 3287–3292. (c) Liu, K. K.-C.; Danishefsky, S. J. Route from Glycals to Mannose β-Glycosides. *J. Org. Chem.* **1994**, *59*, 1892–1894. (d) Miljkovic, M.; Gligorijevie, M.; Glisin, D. Steric and Electrostatic Interactions in Reactions of Carbohydrates. III. Direct displacement of the C-2 sulfonate of methyl 4,6-O-benzylidene-3-O-methyl-2-O-methylsulfonyl-β-D-gluco- and -mannopyranosides. *J. Org. Chem.* **1974**, *39*, 3223–3226. (e) Alais, J.; David, S. Preparation of Disaccharides Having a β-D-Mannopyranosyl Group from N-Phthaloyllactosamine Derivatives By Double Or Triple SN2 Substitution. *Carbohydr. Res.* **1990**, *201*, 69–77. (f) Kunz, H.; Gunther, W. β-Mannosides from β-Glucosides by Intramolecular Nucleophilic Substitution With Inversion of Configuration. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1086–1087.

[4] Lichteathalet, F. W.; Schneider-Adams, T. 3, 4, 6-Tri-O-Benzyl-α-D-Arabino-Hexopyranos-2-Ulosyl bromide: A Versatile Glycosyl Donor for the Efficient Generation of β-D-Mannopyranosidic Linkages. *J. Org. Chem.* **1994**, *59*, 6728–6734.

[5] (a) Kahne, D.; Yung, D.; Lira, J. J.; Miller, R.; Paguaga, E. The Use of Alkoxy-Substituted Anomeric Radicals for the Construction of β-Glycosides. *J. Am. Chem. Soc.* **1988**, *110*, 8716–8717. (b) Brtaw.kova, J.; Crich, D.; Yao, Q. Intramolecular Hydrogen Atom Abstraction in Carbohydrates and Nucleosides: Inversion of an α-to β-Mannopyranoside and Generation of Thymidine C-4′ radicals. *Tetrahedron Lett.* **1994**, *35*, 6619–6622. (c) Crich, D.; Sun, S.; Brunckova, J. Chemistry of 1-alkoxy-1-Glycosyl Radicals: The Manno-and

Rhamnopyranosyl Series. Inversion of α-to β-Pyranosides and the Fragmentation of Anomeric Radicals. *J. Org. Chem.* **1996**, *61*, 605–615. (d) Yamazaki, N.; Eichenberget, E.; Curran, D. P. Synthesis of β-Mannopyranosides from α-Epimers By Radical Inversion: 1, 6-Hydrogen Transfer Reactions of 2-O-(2-bromoaryl) Dimethylsilyl-α-methyl-D-Mannopyranosides. *Tetrahedron Lett*. **1994**, *35*, 6623–6626.

[6] (a) Barresi, F.; Hindsgaul, O. The Synthesis of β-Mannopyranosides by Intramolecular Aglycon Delivery: Scope and Limitations of the Existing Methodology. *Can. J. Chem.* **1994**, *72*, 1447–1465. (b) Barresi, F.; Hindsgaul, O. Improved Synthesis of β-Mannopyranosides by Intramolecular Aglycon Delivery. *Synlett.* **1992**, 759–761. (c) Barresi, F.; Hindsgaul, O. Synthesis of. Beta.-Mannopyranosides by Intramolecular Aglycon Delivery. *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377.

[7] (a) Stork, G.; La Clair, J. J. Stereoselective Synthesis of β-Mannopyranosides via the Temporary Silicon Connection Method. *J. Am. Chem. Soc.* **1996**, *118*, 247–248. (b) Stork, G.; Kim, G. Stereocontrolled Synthesis of Disaccharides Via the Temporary Silicon Connection. *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088. (c) Packard, G. K.; Rychnovsky, S. D. β-Selective Glycosylations with Masked D-Mycosamine Precursors. *Org. Lett.* **2001**, *3*, 3393–3396.

[8] (a) Ito, Y.; Ogawa, T. A Novel Approach to the Stereoselective Synthesis of β-Mannosides. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1765–1767. (b) Ito, Y.; Ogawa, T. Intramolecular Aglycon Delivery On Polymer Support: Gatekeeper Monitored Glycosylation. *J. Am. Chem. Soc.* **1997**, *119*, 5562–5566.

[9] (a) Crich, D.; Sun, S. Formation of β-Mannopyranosides of Primary Alcohols Using the Sulfoxide Method. *J. Org. Chem.* **1996**, *61*, 4506–4507. (b) Crich, D.; Sun, S. Direct Chemical Synthesis of β-Mannopyranosides and Other Glycosides Via Glycosyl Triflates. *Tetrahedron.* **1998**, *54*, 8321–8348. (c) Crich, D.; Sun, S. Are Glycosyl Triflates Intermediates in the Sulfoxide Glycosylation Method? A Chemical and 1H, 13C, and 19F NMR Spectroscopic Investigation. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223.

[10] Crich, D.; Smith, M. Solid-Phase Synthesis of β-Mannosides. *J. Am. Chem. Soc.* **2002**, *124*, 8867–8869.

[11] Heuckendorff, M.; Bendix, J.; Pedersen, C. M.; Bols, M. β-Selective Mannosylation with a 4, 6-Silylene-Tethered Thiomannosyl Donor. *Org Lett*. **2014**, *16*, 1116–1119.

[12] Pistorio, S. G.; Yasomanee, J. P.; Demchenko, A. V. Hydrogen-Bond-Mediated Aglycone Delivery: Focus on β-Mannosylation. *Org. Lett.* **2014**, *16*, 716–719.

[13] Tanaka, M.; Nashida, J.; Takahashi, D.; Toshima, K. Glycosyl-Acceptor-Derived Borinic Ester-Promoted Direct and β-Stereoselective Mannosylation with a 1, 2-Anhydromannose Donor. *Org Lett*. **2016**, *18*, 2288–2291.

[14] Nishi, N.; Nashida, J.; Kaji, E.; Takahashi, D.; Toshima, K. Regio- and Stereoselective β-Mannosylation Using a Boronic Acid Catalyst And its Application In the Synthesis Of A Tetrasaccharide Repeating Unit of Lipopolysaccharide Derived From *E. coli* O75. *Chem. Commun.* **2017**, *53*, 3018–3021.

[15] Hashimoto, Y.; Tanikawa, S.; Saito, R.; Sasaki, K. β-Stereoselective Mannosylation Using 2,6-Lactones. *J. Am. Chem. Soc.* **2016**, *138*, 14840–14843.

[16] Elferink, H.; Mensink, R. A.; White, P. B.; Boltje, T. J. Stereoselective β-Mannosylation by Neighboring-Group Participation. *Angew. Chem., Int. Ed.* **2016**, *55*, 11217–11220.

[17] (a) Tamura, J.; Schmidt, R. R. Effect of Protecting Groups And Solvents in anomeric *O*-Alkylation of Mannopyranose. *J. Carbohydr. Chem.* **1995**, *14*, 895–911. (b) Schmidt, R. R.; Moering, U.; Reichrath, M. *O*-Alkylation at the anomeric center, 4. 1-*O*-Alkylation of D-mannofuranose und D-mannopyranose. *Chem. Ber.* **1982**, *115*, 39–49. (c) Nguyen, H.; Zhu, D.; Li, X.; Zhu, J. Stereoselective Construction of β-Mannopyranosides By Anomeric O-Alkylation: Synthesis of the Trisaccharide Core of N-Linked Glycans. *Angew. Chem., Int. Ed.* **2016**, *55*, 4767–4771. (d) Li, X.; Berry, N.; Saybolt, K.; Ahmed, U.; Yuan, Y. Stereoselective β-Mannosylation via Anomeric O-alkylation: Formal Synthesis

of Potent Calcium Signal Modulator Acremomannolipin A. *Tetrahedron Lett.* **2017**, *58*, 2069–2072.

[18] (a) Srivastava, V. K.; Schuerch, C. Synthesis of β-D-Mannopyranosides and Regioselective *O*-Alkylation of Dibutylstannylene Complexes. *Tetrahedron Lett*. **1979**, *20*, 3269–3272. (b) Hodosi, G.; Kováč, P. A Fundamentally New, Simple, Stereospecific Synthesis of Oligosaccharides Containing the β-mannopyranosyl and β-Rhamnopyranosyl Linkage. *J. Am. Chem. Soc.* **1997**, *119*, 2335–2336. (c) Nicolaou, K. C.; van Delft, F. L.; Conley, S. R.; Mitchell, H. J.; Jin, Z.; Rodríguez, R. M. New Synthetic Technology For the Stereocontrolled Construction of 1,1′-Disaccharides and 1,1′:1″,2-trisaccharides. Synthesis of the FG Ring System of Everninomicin 13,384–1. *J. Am. Chem. Soc.* **1997**, *119*, 9057–9058.

[19] Zhu, D.; Baryal, K. N.; Adhikari, S.; Zhu, J. Direct Synthesis of 2-Deoxy-β-Glycosides Via Anomeric *O*-alkylation with Secondary Electrophiles. *J. Am. Chem. Soc.* **2014**, *136*, 3172–3175.

[20] Zhu, D.; Adhikari, S.; Baryal, K. N.; Abdullah, B. N.; Zhu, J. Synthesis of α-Digitoxosides and α-Boivinosides via Chelation-Controlled Anomeric *O*-Alkylation. *J. Carbohydr. Chem.* **2014**, *33*, 438–451.

[21] Hori, T.; Sugita, M.; Ando, S.; Kuwahara, M.; Kumauchi, K.; Sugie, E.; Itasaka, O. Characterization of a Novel Glycosphingolipid, Ceramide Nonasaccharide, Isolated From Spermatozoa of The Fresh Water Bivalve, *Hyriopsis schlegelii. J. Biol. Chem.* **1981**, *256*, 10979–10985.

[22] Lichtenthaler, F.; Schneider-Adams, T.; Immel, S. Practical Synthesis of β-D-Xyl-(l$\rightarrow$2)-β-D-Man-(1$\rightarrow$4)-α-D-Glc-OMe, a Trisaccharide Component of the *Hyriopsis schlegelii* Glycosphingolipid. *J. Org. Chem.* **1994**, *59*, 6735–6738.

[23] Fletcher, H. G.; Hudson, C. S. 1,5-Anhydro-xylitol. *J. Am. Chem. Soc.* **1947**, *69*, 921–923.

[24] (a) Crich, D.; Dai, Z. Direct Synthesis of β- D- Xyl- (1$\rightarrow$2) - β-D-Man-(1$\rightarrow$4)-α-D-Glc-OMe: A Trisaccharide Component of the Hyriopsis Schlegelii Glycosphingolipid. *Tetrahedron Lett.* **1998**, *39*, 1681–1684. (b) Crich, D.; Dai, Z. Direct Synthesis of β-Mannosides. Synthesis of β-D-xyl-(1$\rightarrow$2)-β-D-man-(1$\rightarrow$4)-α-D-Glc-OMe: A Trisaccharide Component of the Hyriopsis Schlegelii Glycosphingolipid. Formation of an Orthoester from a Xylopyranosyl Sulfoxide. *Tetrahedron.* **1999**, *55*, 1569–1580.

[25] Takeda, T.; Hada, N.; Ogihara, Y. Synthetic Studies On Oligosaccharide Of A Glycolipid From the Spermatozoa of Bivalves. VII. The synthesis of di-, tri-, Tetrasaccharides Related to Glycosphingolipid. *Chem. Pharm. Bull.* **1992**, *40*, 1930–1933.

[26] Takeda, T.; Hada, N.; Ogihara, Y. Total Synthesis of Octasaccharide Related To Glycosphingolipid From the Spermatozoa Of Bivalves. *Chem. Pharm. Bull.* **1993**, *41*, 2058–2060.

[27] Krekgyarto, J.; van der Ven, J. G. M.; Kamerling, J. P.; Liptak, A.; Vliegenthart, J. F. G. Synthesis of a Selectively Protected Trisaccharide Building Block That is Part of Xylose-Containing Carbohydrate Chains From N-Glycoproteins. *Carbohydr. Res.* **1993**, *238*, 135–145.

[28] Jonke, S.; Liu, K.-G.; Schmidt, R. R. Solid-Phase Oligosaccharide Synthesis Of A Small Library of N-Glycans. *Chem. Eur. J.* **2006**, *12*, 1274–1290. doi:10.1002/chem.200500707.

[29] Doboszewski, B.; Hay, G. W.; Szarek, W. A. The Rapid Synthesis Of Deoxyfluoro Sugars Using Tris(dimethylamino) Sulfonium Difluorotrimethylsilicate (TASF). *Can. J. Chem.* **1987**, *65*, 412–419.