Formation of β-Mannose and β-Glucosamine Linkages Using Glycosyl Phosphates

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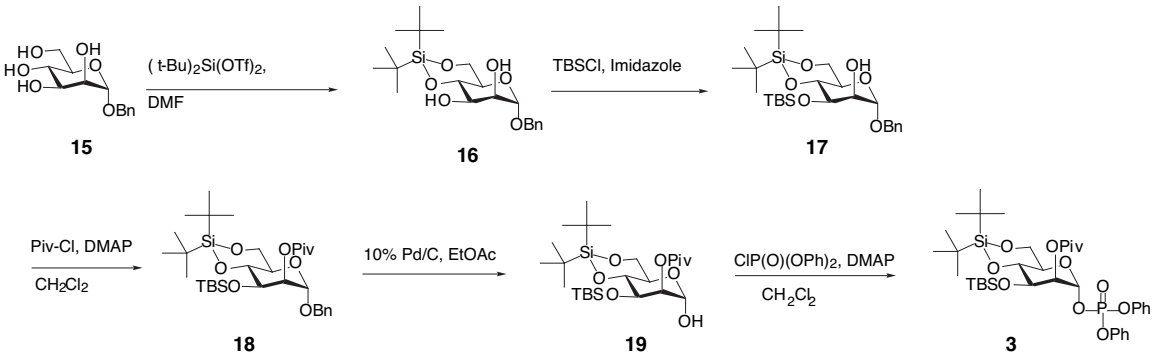
Supplementary Material

Supporting Information Available: Detailed experimental procedures and compound characterization data, including ^{1}H, ^{13}C, ^{31}P NMR, spectral data for all described compounds. This material is available free of charge via the internet at http://pubs.acs.org.

Scheme A. Synthesis of differentially protected mannosyl phosphate **3**.



Experimental Section

General Methods. All chemicals used were reagent grade and used as supplied except where noted. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Liquid column

chromatography was performed using forced flow of the indicated solvent on Sigma H-type silica (10-40 μm). ^{1}H NMR spectra were obtained on a Varian VXR-300 (300 MHz) or Varian VXR-500 (500 MHz) and are reported in parts per million (δ) relative to $CHCl_3$ (7.27 ppm). Coupling constants (J) are reported in Hertz. ^{13}C NMR spectra were obtained on a VXR-300 (75 MHz) or VXR-500 (125 MHz) and are reported in δ relative to $CDCl_3$ (77.23 ppm) as an internal reference. ^{31}P NMR spectra were obtained on a VXR-300 (120 MHz) and are reported in δ relative to H_3PO_4 (0.0 ppm) as an external reference.

Synthesis of Dibutyl 2-azido-3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranoside phosphate. (2) 2-Azido-3,4,6-tri-O-benzyl-2-deoxy-α-D-glucopyranosyl trichloroacetimidate (0.107 g, 0.172 mmol) was dried azeotropically with toluene and taken up in toluene (4 mL). Dibutyl phosphate (0.04 mL, 0.224 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 2h and the solvent was removed in vacuo to afford a yellow oil. The crude product was purified by column chromatography (10:1→5:1 hexanes:EtOAc) to yield **2** as a clear oil (0.103 g, 84%). $[\alpha]^{24}_{D}$: -2.4° (c 0.70, CH_2Cl_2); IR (thin film) 2960, 2111, 1729 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37-7.17 (m, 15H), 5.02 (t, J = 7.9 Hz, 1H), 4.85 (d, J = 10.4 Hz, 1H), 4.81 (d, J = 10.7 Hz, 1H), 4.79 (d, J = 10.7 Hz, 1H) 4.58 (m, 2H), 4.49 (d, J = 11.9 Hz, 1H), 4.10 (m, 4H), 3.73 (m, 2H), 3.70 (dd, J = 2.1, 11.0 Hz, 1H), 3.50 (m, 3H), 1.66 (m, 4H), 1.40 (m, 4H), 0.91 (m, 6H); ^{31}P-NMR (120 MHz, $CDCl_3$) δ -2.10; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 137.8, 137.7, 137.7, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 128.0, 127.9, 97.6, 97.6, 83.0, 75.9, 75.7, 75.3, 73.7, 68.3, 68.2, 66.8, 66.7, 32.4, 32.3, 32.3 18.9, 13.9, 13.9; FAB MS m/z (M+Na) calcd 690.2920, obsd 690.2915.

Synthesis of Diphenyl 3-O-tert-butyldimethylsilyl-4,6-di-O-(tert-butyl)silanediyl-2-O-pivaloyl-α-D-mannopyranoside phosphate. (3) 3-O-tert-

Butyldimethylsilyl-4,6-di-O-(tert-butyl)silanediyl-2-O-pivaloyl-α-D-mannopyranose **19** (0.339 g, 0.653 mmol) was azeotropically dried with toluene and dissolved in CH_2Cl_2 (5 mL). DMAP (0.199 g, 1.633 mmol) and freshly distilled diphenyl chlorophosphate (0.271 mL, 1.305 mmol) were added and the reaction was stirred at room temperature for 4 h. CH_2Cl_2 (100 mL) was then added and washed with 50 mL each: saturated $NaHCO_3$, H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to provide a clear oil. The crude material was purified by column chromatography (10% EtOAc/Hexanes) to afford pure **3** (0.415 g, 85%). $[\alpha]^{24}_D$: -8.3° (c 1.55, CH_2Cl_2); IR (thin film) 2932, 2858, 1739, 1591, 1489 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (m, 4H), 7.29-7.21 (m, 6H), 5.72 (dd, J = 1.5, 6.4 Hz, 1H), 5.13-5.11 (m, 1H), 4.04 (t, J = 9.2 Hz, 1H), 3.90 (dd, J = 3.4, 9.2 Hz, 1H) 3.84-3.73 (m, 4H), 1.21 (s, 9H), 1.04 (s, 9H), 0.97 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 176.9, 150.5, 130.2, 130.1, 126.0, 125.9, 120.2, 120.1, 120.0, 97.3, 74.3, 71.1, 71.0, 69.7, 66.6, 39.1, 27.7,27.3, 27.2, 25.8, 23.0, 20.1, 18.3, -4.5, -4.8; ^{31}P-NMR (120 MHz, $CDCl_3$) δ -14.2; FAB MS m/z (M^+) calcd 750.3384, obsd 750.3388.

Synthesis of Dibutyl 3,4,6-tri-O-benzyl-2-O-pivaloyl-α-D-mannopyranoside phosphate. (4) 1,2-Anhydro-3,4,6-tri-O-benzyl-β-D-mannopyranose (0.100 g, 0.232 mmol) was dried azeotropically with toluene and taken up in CH_2Cl_2 (2 mL). The reaction mixture was cooled to -78°C and dibutyl phosphate (0.05 mL, 0.232 mmol) was added. The solution was stirred for 15 min at -78°C after which the reaction flask was placed in an ice bath and warmed to 0°C. Pivaloyl chloride (0.060 mL, 0.464 mmol) and N,N- dimethylamino pyridine (0.112 g, 0.928 mmol) were added and the solution was allowed to reach room temperature over a period of 1.5 h. A solution of 3:1 hexanes:EtOAc (10 mL) was added to the flask and the white precipitate was filtered and discarded. The solvent was removed in vacuo to afford a yellow oil. The crude product was purified by column chromatography (3:1 hexanes:EtOAc) to yield pure **4** as a clear oil (43.0 mg, 27%). IR (thin film) 2961, 1737 cm^{-1}. $[\alpha]^{24}_D$: +30.0° (c 1.00, CH_2Cl_2); ^{1}H-NMR

(500 MHz, $CDCl_3$) δ 7.34-7.19 (m, 17H), 5.67 (dd, J = 2.1, 6.4 Hz, 1H), 5.44 (app t, J = 2.8 Hz, 1H), 4.85 (d, J = 10.7 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.55 - 4.50 (m, 3H), 4.10 - 3.96 (m, 6H), 3.93 (d, J = 9.5 Hz, 1H), 3.82 (dd, J = 4.0, 11.0 Hz, 1H), 3.71 (dd, J = 1.5, 11 Hz, 1H), 1.70 - 1.60 (m, 4H), 1.42-1.35 (m, 5H), 1.2 (s, 9H), 0.95-0.89 (m. 6H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.4, 138.2, 138.0, 128.4, 128.4, 128.4, 128.2, 128.2, 127.9, 127.9, 95.8, 95.8, 77.6, 75.5, 73.6, 73.6, 73.5, 71.8, 68.8, 68.1, 68.1, 67.8, 67.7, 33.1, 32.4, 32.4, 27.3, 18.8, 18.8, 13.8; ^{31}P-NMR (120 MHz, $CDCl_3$) δ -2.28; FAB MS m/z (M+Na) calcd 749.3431, obsd 749.3416.

Synthesis of Disaccharides 6 - 8 in CH_2Cl_2. General Procedure. Diphenyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside phosphate **1** (0.120 mmol) and acceptor **5** or **7** (0.100 mmol) were combined and azeotropically dried with toluene (3 x 5 mL). CH_2Cl_2 (1 mL) was added and the reaction mixture was cooled to -78°C for 15 min. Upon addition of trimethylsilyl triflate (0.130 mmol), the reaction turned green and was stirred for 30 min. Triethylamine (0.130 mmol) was added and the solvent was removed under vacuum. Column chromatography (20-25% EtOAc/Hexanes) afforded disaccharides **6** and **8** in 62% and 88% respectively as a mixture of anomers.

Synthesis of Disaccharides 6 - 8 in CH_3CN. General Procedure. Diphenyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside phosphate **1** (0.120 mmol) and acceptor **5** or **7** (0.100 mmol) were combined and azeotropically dried with toluene (3 x 5 mL). CH_2Cl_2 (1 mL) was added and the reaction mixture was cooled to -40°C for 15 min. Upon addition of trimethylsilyl triflate (0.130 mmol), the reaction turned green and was stirred for 30 min. Triethylamine (0.130 mmol) was added and the solvent was removed under vacuum. Column chromatography (20-25% EtOAc/Hexanes) afforded disaccharides **6** and **8** in 80% and 83% respectively as a mixture of anomers.

Methyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside-(1→2)-3,4,6-tri-O-benzyl-β-D-glucopyranoside. (6α) $[\alpha]^{24}_{D}$: +30.6° (c 0.77, CH_2Cl_2); IR (thin film) 3029, 2863, 1495, 1453 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.45-7.10 (m, 35H), 5.52 (d, J = 1.5 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 4.84-4.51 (m, 13H), 4.36 (d, J = 11.9 Hz, 1H), 4.18-4.13 (m, 2H), 3.97-3.90 (m, 2H), 3.86-3.84 (m, 1H), 3.78-3.44 (m, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 139.2, 138.8, 138.7, 138.3, 138.1, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 104.7, 97.6, 83.7, 79.9, 78.5, 76.1, 75.2, 74.9, 74.3, 73.7, 73.4, 72.2, 72.1, 68.9, 68.8, 57.0; FAB MS m/z (M^+) calcd 986.4065, obsd 986.4069.

Methyl 2,3,4,6-tetra-O-benzyl-β-D-mannopyranoside-(1→2)-3,4,6-tri-O-benzyl-β-D-glucopyranoside. (6β) $[\alpha]^{24}_{D}$: -24.2° (c 0.67, CH_2Cl_2); IR (thin film) 3029, 2864, 1490, 1453, 1362 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.43-7.17 (m, 35H), 4.90-4.88 (m, 3H), 4.79-4.74 (m, 2H), 4.69-4.55 (m, 8H), 4.44 (d, J = 7.3 Hz, 1H), 4.41-4.34 (m, 2H), 3.93 (t, J = 9.5 Hz, 1H), 3.84-3.64 (m, 8H), 3.56-3.52 (m, 4H), 3.44-3.42 (m, 1H), 3.33 (dd, J = 2.8, 9.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 139.1, 138.9, 138.5, 138.4, 138.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.1, 102.9, 101.8, 85.5, 83.2, 80.6, 78.3, 76.3, 75.4, 75.3, 75.1, 75.0, 74.5, 74.0, 71.8, 69.7, 69.0, 56.9; FAB MS m/z (M^+) calcd 986.4065, obsd 986.4067.

Synthesis of Disaccharides 9 - 10 in CH_2Cl_2. General Procedure. Dibutyl 2-azido-3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranoside phosphate **2** (0.120 mmol) and acceptor **5** or **7** (0.100 mmol) were combined and azeotropically dried with toluene (3 x 5 mL). CH_2Cl_2 (1 mL) was added and the reaction mixture was cooled to -40°C. Upon addition of trimethylsilyl triflate (0.130 mmol), the reaction turned yellow and was stirred for 2 h. Upon warming to -20°C for 1 h, the yellow solution was quenched with triethylamine (0.02 mL). Solvent was removed under vacuum and the residue was purified by column chromatography (5:1 hexanes:EtOAc) to afford pure disaccharides **9** and **10** in 77% and 60% yield respectively as a mixture of anomers.

Synthesis of Disaccharides 9 - 10 in CH_3CN. General Procedure. Dibutyl 2-azido-3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranoside phosphate **2** (0.120 mmol) and acceptor **5** or **7** (0.100 mmol) were combined and azeotropically dried with toluene (3 x 5 mL). CH_3CN (1 mL) was added and the reaction mixture was cooled to -30°C. Upon addition of trimethylsilyl triflate (0.130 mmol), the reaction turned yellow and was stirred for 2 h. Upon warming to -20°C for 1 h, triethylamine (0.02 mL) was added and the solvent was removed under vacuum. Column chromatography (5:1 hexanes:EtOAc) afforded disaccharides **9** and **10** in 61% and 60% yield respectively as a mixture of anomers.

Methyl 2-azido-3,4,6-tri-O-benzyl-2-deoxy-α-D- glucopyranoside-(1→2)-3,4,6-tri-O-benzyl-β-D-glucopyranoside. (9α) $[\alpha]^{24}_D$: +54.0° (c 0.30, CH_2Cl_2); IR (thin film) 3029, 2863, 2108, 1727, 1496 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.37-7.06 (m, 30H), 5.58 (d, J = 3.6 Hz, 1H), 4.92 (d, J = 10.7 Hz, 1H), 4.87 (app s, 2H), 4.80 (d, J = 10.7 Hz, 1H), 4.76 (d, J = 11.0 Hz, 1H), 4.73 (d, J = 11.0 Hz, 1H), 4.65 (d, J = 12.2 Hz, 1H), 4.56 (m, 3H), 4.43 (d, J = 11.0 Hz, 1H), 4.39 (d, J = 7.3 Hz, 1H), 4.29 (d, J = 12.2 Hz, 1H), 3.99 (app d, J = 10.4 Hz, 1H), 3.92 (app t, J = 9.2 Hz, 1H), 3.75 - 3.61 (m, 7H), 3.57 (s, 3H), 3.50 (m, 1H), 3.35 (dd, J = 3.7 Hz, 10.4, 1H), 3.25 (app d, J = 1.8 Hz, 2H); FAB MS m/z (M+Na) calcd 944.4098 obsd 944.4120.

Methyl 2-azido-3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranoside-(1→2)-3,4,6-tri-O-benzyl-β-D-glucopyranoside. (9β) $[\alpha]^{24}_D$: -32.7° (c 0.60, CH_2Cl_2); IR (thin film) 3029, 2863, 2108, 1727, 1496 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40 -7.20 (m, 30H), 4.96 (d, J = 10.7 Hz, 1H), 4.90 (d, J = 10.7 Hz, 1H), 4.87 (d, J = 10.7 Hz, 1H), 4.84-4.78 (m, 3H), 4.73 (d, J = 8.2 Hz, 1H), 4.68-4.63 (m, 2H), 4.60-4.54 (m, 4H), 4.38 (d, J = 7.0 Hz, 1H), 3.81-3.67 (m, 8H), 3.52-3.40 (m, 4H), 3.50 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 139.0, 139.0, 138.8, 138.6, 138.6, 138.6, 129.2, 129.1, 128.8, 128.7, 128.7, 128.6, 128.6 128.5, 128.4, 128.3, 128.3 103.1, 101.8, 85.8, 84.1, 79.7, 79.0, 78.5, 76.2, 76.2,

75.9, 75.5, 74.4, 74.2, 69.5, 69.0, 67.2, 57.1; FAB MS m/z (M+Na) calcd 944.4098 obsd 944.4120.

2-azido-3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranoside-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside. (10α/β)

IR (thin film) 2917, 2110, 1643, 1070 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 38H), 7.20 – 7.18 (m, 2H), 5.56 (d, J = 5.2 Hz, 1H), 5.53 (d, J = 5.1 Hz, 0.2H), 5.01 (d, J = 4.3 Hz, 0.2H), 4.90 (app t, J = 10.7 Hz, 2H), 4.81 (d, J = 10.7 Hz, 1H), 4.80 (d, J = 10.7 Hz, 1H), 4.68 – 4.60 (m, 3H), 4.58 – 4.51 (m, 2H), 4.44 – 4.42 (m, 1H), 4.34 (dd, J = 2.4, 4.9 Hz, 1H), 4.28 (dd, J = 1.2, 7.9 Hz, 1H), 4.10 – 4.00 (m, 3H), 3.84 – 3.61 (m, 6H), 3.45 – 3.40 (m, 3H), 1.68 (s, 1.3H), 1.58 (s, 3H), 1.57 (s, 1.3H), 1.47 (s, 3H), 1.45 (s, 1.3H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.2, 138.2, 138.1, 128.6, 128.6, 128.5, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 109.5, 108.9, 102.6, 96.5, 83.3, 77.8, 77.5, 75.7, 75.2, 75.1, 73.7, 71.4, 70.8, 70.0, 68.6, 67.7, 66.6, 26.2, 26.2, 25.2, 24.5; FAB MS m/z (M+H) calcd 717.3261, obsd 718.3290.

Synthesis of 3-O-tert-Butyldimethylsilyl-4,6-di-O-(tert-butyl)silanediyl-2-O-pivaloyl-α-D-mannopyranoside-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside. (11) Donor **3** (0.111 g, 0.148 mmol) and acceptor **7** (0.042 g, 0.163 mmol) were combined and dried (3 x 5 mL toluene). CH_2Cl_2 (1.5 mL) was added and the reaction vessel was cooled to -78°C for 15 min. Trimethylsilyl triflate (30 μL, 0.162 mmol) was added dropwise and the reaction was stirred for 1 h at -78°C. Upon warming to -50°C over 30 min, the yellow solution was quenched with triethylamine (30 μL). Solvent was removed under vacuum and the residue was purified by column chromatography (10% EtOAc/Hexanes) to afford pure disaccharide **11** (95.6 mg, 85 %). $[\alpha]^{24}_D$: -16.3° (c 1.20, CH_2Cl_2); IR (thin film) 2933, 2859, 1737, 1474, 1383 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.49 (d, J = 4.9 Hz, 1H), 5.05 (dd, J = 1.8, 3.4 Hz, 1H), 4.68 (d, J = 1.5 Hz, 1H), 4.62 (dd, J = 2.4, 7.9 Hz, 1H), 4.31 (dd, J = 2.4, 4.9 Hz, 1H), 4.23

(dd, J = 1.8, 7.9 Hz, 1H), 4.12 (dd, J = 4.6, 9.5 Hz, 1H), 4.02 (t, J = 9.2 Hz, 1H), 3.98-3.86 (m, 3H), 3.84-3.74 (m, 2H), 3.67 (dd, J = 6.1, 10.4 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.21 (s, 9H), 1.05 (s, 9H), 1.00 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.5, 109.5, 108.8, 98.2, 96.5, 75.3, 72.3, 71.1, 70.9, 70.8, 70.7, 67.8, 67.2, 66.4, 66.3, 39.1, 27.8, 27.3, 27.2, 26.2, 26.1, 25.9, 25.2, 24.6, 23.0, 20.1, 18.3, 0.3, -4.4, -4.8; FAB MS m/z (M^+) calcd 760.4249, obsd 760.4248.

Synthesis of Methyl 3-O-tert-butyldimethylsilyl-4,6-di-O-(tert-butyl)silanediyl-2-O-pivaloyl-α-D-mannopyranoside-(1→2)-3,4,6-tri-O-benzyl-β-D-glucopyranoside. (12) Donor **3** (54.3 mg, 0.072 mmol) and acceptor **5** (35.3 mg, 0.79 mmol) were combined and dried azeotropically (3 x 5 mL toluene). CH_2Cl_2 (1 mL) was added and the reaction vessel was cooled to -78°C for 15 min. Trimethylsilyl triflate (15.3 μL, 0.162 mmol) was added dropwise and the reaction was stirred for 30 min at -78°C. Upon warming to -50°C for 1 h, the yellow solution was quenched with triethylamine (15 μL). Solvent was removed under vacuum and the residue was purified by column chromatography (10% EtOAc/Hexanes) to afford pure disaccharide **12** (53.0 mg, 75 %). $[\alpha]^{24}_D$: +22.7° (c 1.11, CH_2Cl_2); IR (thin film) 2932, 2858, 1737, 1473, 1362 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 13H), 7.08-7.06 (m, 2H), 5.21 (dd, J = 1.8, 3.1 Hz, 1H), 5.09 (d, J = 1.5 Hz, 1H), 4.97 (d, J = 11.6 Hz, 1H), 4.81 (d, J = 1.3 Hz, 1H), 4.70 (d, J = 10.7 Hz, 1H), 4.63 (d, J = 12.2 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 10.7 Hz, 1H), 4.23 (d, J = 7.6 Hz, 1H), 4.08-3.98 (m, 3H), 3.92-3.83 (m, 2H), 3.76-3.57 (m, 8H), 3.49-3.46 (m, 1H), 1.23 (s, 9H), 1.05 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.2, 138.6, 138.3, 128.6, 128.1, 128.0, 127.9, 127.8, 127.4, 104.4, 99.9, 83.6, 81.0, 78.0, 75.2, 75.1, 74.9, 73.7, 72.3, 70.6, 68.9, 68.8, 67.3, 57.5, 39.0, 27.8, 27.4, 27.1, 25.9, 23.0, 19.9, 18.4, -4.4, -4.7; FAB MS m/z (M^+) calcd 978.5344, obsd 978.5341.

Synthesis of Ethyl 3,4,6-tri-O-benzyl-2-pivaloyl-α-D-mannopyranoside-(1→2)-3,4,6-tri-O-benzyl-β-D-glucopyranoside. (14) Dibutyl 3,4,6-tri-O-benzyl-2-O-pivaloyl-α-D-mannopyranoside phosphate **4** (0.120 mmol) and acceptor **13** (0.100 mmol) were combined and azeotropically dried with

toluene (3 x 5 mL). CH_2Cl_2 (1 mL) was added and the reaction mixture was cooled to -50°C. Upon addition of trimethylsilyl triflate (0.130 mmol), the reaction turned yellow and was stirred for 1 h. Triethylamine (0.02 mL) was added and the solvent was removed under vacuum. Column chromatography (5:1 hexanes:EtOAc) afforded disaccharide **14** in 82% yield. $[\alpha]^{24}_D$: +3.8° (c 0.90, CH_2Cl_2); IR (thin film) 2852, 1731, 1462 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 7.34 - 7.06 (m, 30H), 5.46 (d, J = 1.8 Hz, 1H), 5.42 (app t, J = 2.4 Hz, 1H), 4.84-4.76 (m, 3H), 4.74 (d, J = 11.3 Hz, 1H), 4.68 (d, J = 10.8 Hz, 1H), 4.62 (d, J = 11.9 Hz, 2H), 4.58-4.53 (m, 3H), 4.46 (d, J = 11.0 Hz, 1H), 4.34 (d, J = 7.9 Hz, 1H), 4.32 (d, J = 12.2 Hz, 1H), 3.91-4.00 (m, 4H), 3.74 (dd, J = 1.8, 11.0 Hz, 1H), 3.70-3.62 (m, 2H), 3.62-3.56 (m, 2H), 3.54-3.48 (m, 2H), 3.48 - 3.42 (m, 2H), 1.21 - 1.19 (m, 12 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.9, 139.1, 138.9, 138.5, 138.1, 138.0, 128.6, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.7, 127.6, 127.6, 127.5, 127.4, 103.7, 97.4, 83.7, 78.6, 78.3, 76.6, 76.1, 75.2, 75.2, 74.4, 73.7, 73.2, 71.6, 71.4, 69.0, 68.7, 68.2, 65.9, 39.2, 29.9, 27.4, 15.2; FAB MS m/z (M+Na) calcd 1017.4765, obsd 1017.4787.

Synthesis of Benzyl 4,6-di-O-(tert-butyl)silanediyl-α-D-mannopyranoside. (16) Benzyl α-D-mannopyranoside **15** (0.519 g, 1.92 mmol) was azeotropically dried with toluene (3 x 10 mL) and taken up in DMF (10 mL). The reaction vessel was cooled to -40°C and stirred for 30 min. Addition of di-tert-butylsilyl ditriflate (0.70 mL, 1.92 mmol) over 15 min afforded a clear solution that was further stirred at -40°C for 30 min. Upon warming to room temperature the reaction mixture was diluted with 100 mL diethyl ether and washed with 50 mL each: saturated $NaHCO_3$, H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to provide a white solid. The crude product was purified b y column chromatography (35% EtOAc/Hexanes) to afford the pure **16** (0.767 g, 97%). $[\alpha]^{24}_D$: +54.8° (c 1.59, CH_2Cl_2); IR (thin film) 3516, 3284, 2930, 2855, 1474 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 7.36-7.30 (m, 5H), 4.91 (s, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.55 (d, J = 11.9 Hz, 1H), 4.07-4.01 (m, 3H), 3.95 (t, J = 10.4 Hz, 1H), 3.90-3.87 (m, 1H), 3.73 (dt, J = 4.9, 10.1 Hz, 1H), 2.96 (d, J = 2.1 Hz, 1H), 2.93 (d, J =

2.1 Hz, 1H), 1.06 (s, 9H), 0.98 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 137.4, 128.8, 128.7, 128.4, 128.2, 99.5, 74.9, 72.0, 70.7, 69.8, 67.2, 66.6, 27.7, 27.2, 22.8, 20.1; FAB MS m/z (M^+) calcd 410.2124, obsd 410.2127.

Synthesis of Benzyl 3-O-tert-butyldimethylsilyl-4,6-di-O-(tert-butyl)silanediyl-α-D-mannopyranoside. (17) Benzyl 4,6-di-O-(tert-butyl)silanediyl-α-D-mannopyranoside **16** (0.560 g, 1.36 mmol) was azeotropically dried with toluene (3 x 10 mL) and taken up in DMF (15 mL). Imidazole (0.231 g, 3.40 mmol) and tert-butyldimethylsilyl chloride (0.247 g, 1.64 mmol) were added and the reaction mixture was stirred for 18 h. Diethyl ether (150 mL) was added and washed with 75 mL each: saturated $NaHCO_3$, H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to provide **17** as a clear liquid (0.696 g, 98%) that was used in the next step without purification. $[\alpha]^{24}_D$: +46.4° (c 1.49, CH_2Cl_2); IR (thin film) 3565, 2932, 2858, 1472 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 4.93 (s, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.03-3.98 (m, 2H), 3.93 (t, J = 10.4 Hz, 1H), 3.89-3.86 (m, 1H), 3.84-3.82 (m, 1H), 3.73 (dt, J = 4.9, 10.1 Hz, 1H), 2.82 (s, 1H), 1.06 (s, 9H), 1.00 (s, 9H), 0.93 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 137.5, 128.7, 128.3, 128.2, 98.9, 75.1, 72.9, 72.1, 69.7, 67.2, 66.9, 27.8, 27.3, 26.0, 22.9, 20.1, 18.3, -4.0, -4.6; FAB MS m/z (M^+) calcd 524.2989, obsd 524.2991.

Synthesis of Benzyl 3-O-tert-butyldimethylsilyl-4,6-di-O-(tert-butyl)silanediyl-2-O-pivaloyl-α-D-mannopyranoside. (18) Benzyl 3-O-tert-butyldimethylsilyl-4,6-di-O-(tert-butyl)silanediyl-α-D-mannopyranoside **17** (0.577 g,

1.10 mmol) was azeotropically dried with toluene (3 x 10 mL) and taken up in CH_2Cl_2 (10 mL). DMAP (0.403 g, 3.30 mmol) and pivaloyl chloride (0.203 mL, 1.55 mmol) were added and the reaction was stirred for 2 h. CH_2Cl_2 was added and washed with 50 mL each: saturated $NaHCO_3$, H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (5% EtOAc/Hexanes) to afford **18** as a clear oil (0.561 g, 84%). $[\alpha]^{24}_D$: +21.0° (c 0.93, CH_2Cl_2); IR (thin film) 2933, 2859, 1738, 1474, 1132 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.38-7.34 (m, 5H), 5.10 (dd, J = 1.5, 3.1 Hz, 1H), 4.76 (d, J = 1.5 Hz, 1H), 4.67 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 12.2 Hz, 1H), 4.05-3.97 (m, 3H), 3.87 (t, J = 10.1 Hz, 1H), 3.70 (dt, J = 4.3, 10.1 Hz, 1H), 1.22 (s, 9H), 1.06 (s, 9H), 0.99 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.5, 137.5, 128.7, 128.5, 128.2, 128.1, 127.6, 98.3, 75.4, 72.3, 70.8, 68.0, 67.2, 39.1, 27.8, 27.4, 27.2, 25.9, 23.0, 20.1, 18.3, -4.3, -4.7; FAB MS m/z (M^+) calcd 608.3564, obsd 608.3560.

Synthesis of 3-O-tert-Butyldimethylsilyl-4,6-O-di-(tert-butyl)silanediyl-2-O-pivaloyl-α-D-mannopyranose. (19) Benzyl mannoside **18** (0.558 g, 0.917 mmol) was dissolved in EtOAc (15 mL). 10% Pd/C (0.500 g) were added and the flask was purged with H_2. The mixture was stirred under an atmosphere of H_2 for 15 h at room temperature. The reaction mixture was purified by passing through a fritted funnel containing celite (2 g). After rinsing the celite with EtOAc (150 mL) the organics were concentrated to afford pure **19** as a clear oil (0.460 g, 97%). $[\alpha]^{24}_D$: -12.9° (c 1.09, CH_2Cl_2); IR (thin film) 3428, 2933, 2859, 1738, 1715 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.06-5.03 (m, 2H), 4.10 (dd, J = 4.6, 9.5 Hz, 1H), 4.05-4.03 (m, 2H), 3.96-3.93 (m, H), 3.89 (t, J = 9.8 Hz, 1H), 3.26 (s, 1H), 1.21 (s, 9H), 1.06 (s, 9H), 1.00 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.9, 93.1, 75.3, 72.7, 70.2, 67.9,

67.2, 39.1, 27.7, 27.3, 27.2, 25.9, 23.0, 20.1, 18.3, -4.4, -4.8; FAB MS m/z (M^+) calcd 518.3095, obsd 518.3096.