Route from Glycals to Mannose β-Glycosides

Kevin K.-C. Liu* and Samuel J. Danishefsky

Department of Chemistry, Yale University, New Haven, Connecticut 06511, and Laboratory for Bioorganic Chemistry, The Memorial Sloan Kettering Cancer Institute, New York, New York 10021

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Although impressive progress has been realized in the synthesis of O-glycosides, the difficulties associated with a highly stereoselective synthesis of β-mannosides have continued to be formidable. Such mannosides are found in asparagine linked high-mannose oligosaccharides and are implicated in cell-surface receptors, cell adhesion molecules, immunoglobulins, serum proteins, and tumor antigens.[1] Recently, this pattern has been found in the viral coat of GP-120.[2]

The two classical strategies which have been used so successfully in the synthesis of β- and α-glucosides,[3,4] i.e., neighboring group participation of a resident 2α-substituent[3] or *in situ* anomerization,[4] are not appropriate to the β-mannoside problem. The problem has been addressed in three ways. One method involves the use of a mannose donor which reacts with an acceptor via displacement of an α-disposed anomeric leaving group, with inversion of configuration.[5] In this strategy, the β-disposed resident oxy function does not provide neighboring group participation in the glycosidation. A more recent approach involves migration of a nucleophile originally tethered to a C2β-oxy function to form a glycoside at C1.[6] The third type of solution starts with a β-glucoside (for which many synthetic protocols are available) and requires inversion at C2. This inversion can be accomplished, though only with some difficulty, by nucleophilic displacement of a uniquely placed α-disposed leaving group at C2 with inversion of configuration.[7] Since this inversion would usually require attack of nucleophile from an axial trajectory, the difficulties are not surprising. A recent report of Kunz, wherein this displacement is achieved via a β-participating group at C3, points the way to a promising variation.[8] Alternatively, net inversion at C2 can be accomplished by oxidation to a 2-keto-β-glucoside followed by stereoselective reduction to the 2β-alcohol.[9]

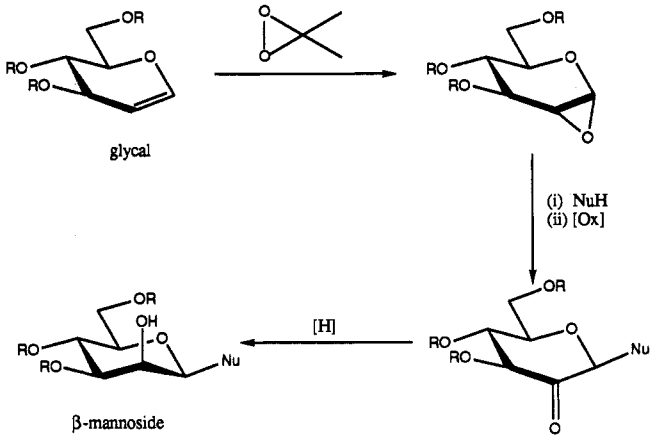

Figure 1.

For any of these gluco → manno inversion protocols, it is necessary to uniquely expose a 2-hydroxyl group in the β-glucoside (which may be part of an oligosaccharide array). The need for this differential unveiling, which would traditionally be accomplished by position-specific protections and deprotections, is clearly a complication in the third approach.

Recently, we have been focusing on the use of glycals in the synthesis of oligosaccharides.[10] A key resource in this strategy is the direct and stereospecific epoxidation of glycals with 3,3-dimethyldioxirane to produce 1α,2α-oxiranes. These epoxides function as donors to produce β-glucosides with high margins of stereoselectivity (Figure 1). Since the process *per force* generates a unique free 2-hydroxyl group in the β-glycoside,[11] an excellent opportunity presents itself for the synthesis of the target β-mannosides by inversion of this center. To reduce this prospect to operational reality we focused on an oxidation reduction sequence to achieve net inversion at C2. Our results are summarized below.

Starting with known glucals the 1α,2α-oxiranes **1**–**3** were generated via direct epoxidation as reported.[10,12] Following previously described protocols **1**–**3** were converted to β-glycosides **4**–**8** (see Figure 2 and Experimental Section). Glycosides **4**–**8** were oxidized by the method of Moffett and Pfitzner.[13] The resultant 2-ulose variants were used in crude form. The difficulty associated with full purification of these 2-ketosaccharides is their tendency to exist, to varying extents, as hydrates. Rather, the ketones directly from the reaction were reduced with sodium borohydride in methylene chloride–methanol.[14] For purposes of optimal characterization, the resultant mannosides (**9**–**13**) were acetylated under standard conditions to produce **9a**–**13a** (Figure 3).[15] Only in one case could we find β-glucoside (**12a**:**7a** = 67:5) following this sequence.Thus, glucals and their derived α-1,2-oxiranes, in addition to serving as starting materials for β-glucosides,[10] also serve as precursors for β-mannopyranosides (cf. **9a**–

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(14) The oxidation was checked with TLC until no starting material was presence.

0022-3263/94/1959-1892$04.50/0

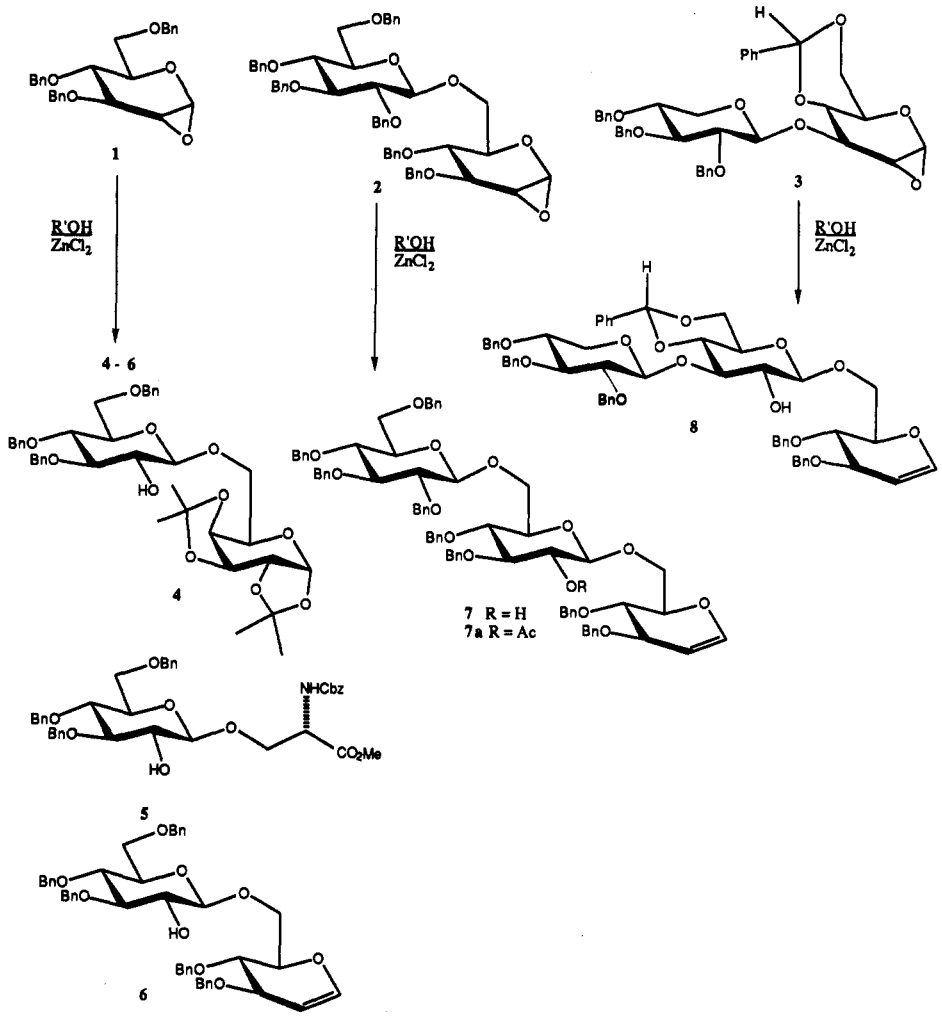

Figure 2.

13a). We note that in the cases of 11a–13a, the glycal linkages, present in the product, can be exploited for further development of the ensembles.[16]

Experimental Section

General Procedure for Glycal Epoxidation and Preparation of β-Glucosides.[10] The glycal (0.1 mmol) was dissolved in 1 mL of dry CH_2Cl_2, and cooled to 0 °C in a nitrogen atomsphere. A solution of dimethyldioxirane in acetone (2 equiv, ca 0.07 M) was added. The reaction mixture was stirred at 0 °C for 30 min. The anhydro sugar thus obtained was concentrated to dryness by passing a stream of nitrogen over the reaction mixture and placing it under vacuum for 1 h. A solution of the acceptor sugar or *N*-Cbz-L-serine methyl ester (1.5 equiv) in dry THF (2 mL) was added to the 1,2-anhydro sugar and cooled to −78 °C. Zinc chloride (1.5 equiv of a 1 M solution in diethyl ether) was added to the reaction mixture slowly. The reaction was allowed to warm to rt of its own accord and stirred overnight. The reaction mixture was then diluted with H_2O and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified with silica gel column chromatography.

***O*-(3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl)-*N*-Cbz-L-serine methyl ester (5):** 46% yield as a colorless liquid; $[\alpha]^{25}_D$ +7.67 (c 0.6, $CHCl_3$); FTIR (neat) 3510, 3489, 2840, 1722, 1550, 1249, 1069, 725, 697 cm^{-1}; ^1H NMR (300 MHz, $CHCl_3$) δ 7.40–7.10 (m, 20 H), 5.87 (s, br, 1 H), 5.11 (s, 2 H), 4.91 (d, 1 H, *J* = 11.4 Hz), 4.82 (d, 1 H, *J* = 4.5 Hz), 4.78 (d, 1 H, *J* = 4.2 Hz), 4.58–4.45 (m, 5 H), 4.24 (d, 1 H, *J* = 5.7 Hz), 4.22 (d, 1 H, *J* = 6.3, 9.6 Hz), 3.87 (dd, 1 H, *J* = 4.5, 8.1 Hz), 3.72 (s, 3 H), 3.69–3.66 (m, 2 H), 3.61–3.45 (M, 3 H); HRMS (FAB) calcd for (M + Na^+) 722.7951, found (M + Na^+) 722.3428.

***O*-(3,4-Di-*O*-benzyl-β-D-xylopyranosyl)-(1→3)-*O*-(4,6-*O*-benzylidene-2-hydroxy-β-D-glucopyranosyl)-(1→6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (8):** 40% yield as a colorless liquid; $[\alpha]^{25}_D$ −5.03 (c 2.9, $CHCl_3$); FTIR (neat) 3479, 2873, 1731, 1650, 1496, 1454, 1372, 1097, 913, 750, 698 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 7.59–7.23 (m, 30 H), 6.40 (dd, 1 H, *J* = 0.9, 6 Hz), 5.6 (s, 1 H), 5.02–4.98 (m, 4 H), 4.96–4.81 (m, 4 H), 4.72 (s, 1 H), 4.68 (s, 1 H), 4.63–4.54 (m, 5 H), 4.25 (dd, 1 H, *J* = 4.8, 10.2 Hz), 4.20 (d, 1 H, *J* = 8.4), 4.15 (dd, 1 H, *J* = 2.4, 10.8 Hz), 4.05–3.98 (m, 2 H), 3.95–3.89 (m, 3 H), 3.76 (t, 1 H, *J* = 10.2 Hz), 3.69–3.52 (m, 4 H), 3.50 (dd, 1 H, *J* = 4.8, 10.2 Hz), 3.35 (t, 1H, *J* = 9.8 Hz), 3.20–3.14 (m, 1 H), 2.85 (s, 1 H); HRMS (FAB) calcd for (M + Na^+) 1001.1260, found (M + Na^+) 1001.2400.

General Procedure for Preparation of β-Mannopyranosides. A solution of the β-glucoside (20 mg) in 1:2 acetic anhydride–dimethyl sulfoxide (1 mL) was kept for 48 h at room temperature and then evaporated to dryness.

The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$ and evaporated. The crude 2-ulose and its hydrate were dissolved in 1:1 CH_2Cl_2–MeOH (2 mL) solution and cooled to 0 °C. $NaBH_4$ (10 mg) was added to the reaction mixture in one portion, and the ice bath was removed after the addition. After 6 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, successively washed with water, 1% citric acid solution, $NaHCO_3$ (sat), and NaCl (sat), and evaporated in vacuum. Acetic anhydride (0.5 mL) was added to a solution of crude 2-hydroxy-β-mannopyranoside in dry pyridine (1 mL). The mixture was stirred at rt for 12 h, after

(15) In these acetates the C2 α-protons appear as tight doublet (*J* = 3 Hz) for δ 5.4–5.6 ppm.

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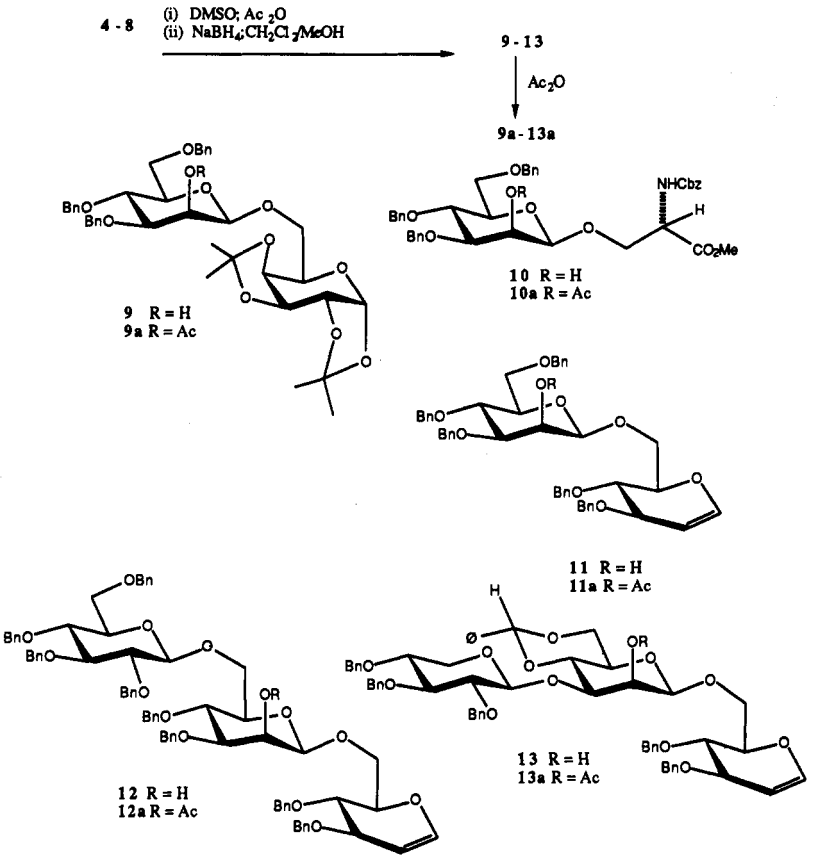

Figure 3.

which it was slowly added to 10 mL of saturated $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel gave the β-mannopyranoside acetate.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-(1→6)-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose (9a)**: 61% yield (from compound 4) as a colorless liquid; $[\alpha]^{25}_D$ −54.3 (*c* 0.14, $CHCl_3$); FTIR (neat) 2931, 1745, 1652, 1453, 1372, 1237, 1068, 804, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.10 (m, 15 H), 5.66 (d, 1 H, *J* = 2.7 Hz), 5.48 (d, 1 H, *J* = 4.8 Hz), 4.84 (d, 1 H, *J* = 10.8 Hz), 4.74 (d, 1 H, *J* = 11.1 Hz), 4.67 (s, 1 H), 4.64 (d, 1 H, *J* = 12.3 Hz), 4.56 (dd, 1 H, *J* = 2.4, 8.1 Hz), 4.52 (d, 1 H, *J* = 11.2 Hz), 4.48 (d, 1 H, *J* = 11.2 Hz), 4.27 (dd, 1 H, *J* = 2.4, 4.8 Hz), 4.19 (dd, 1 H, *J* = 1.2, 8.1 Hz), 4.07 (dd, 1 H, *J* = 3.50, 11.2 Hz), 3.94 (m, 1 H), 3.77–3.65 (m, 4 H), 3.63 (dd, 1 H, *J* = 11.3, 7.21 Hz), 3.48 (m, 1 H), 2.05 (s, 3 H), 1.54 (s, 3 H), 1.48 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H); HRMS (FAB) calcd for (M + Na^+) 757.8382, found (M + Na^+) 757.3233.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-*N*-Cbz-L-serine methyl ester (10a)**: 68% yield (from compound 5) as a colorless liquid; $[\alpha]^{25}_D$ −25.5 (*c* 0.54, $CHCl_3$); FTIR (neat) 3320, 2890, 2353, 1742, 1237, 1099, 697, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.11 (m, 20 H), 5.57 (d, 1 H, *J* = 3 Hz), 5.19 (s, br, 1 H), 5.10 (s, br, 2 H), 4.84 (d, 1 H, *J* = 10.8 Hz), 4.70 (d, 1 H, *J* = 11.1 Hz), 4.60 (d, 1 H, *J* = 12 Hz), 4.52–4.45 (m, 3 H), 4.19–4.05 (m, 4H), 3.96 (dd, 1H, *J* = 2.4, 10.2 Hz), 3.75 (s, 3H), 3.62 (dd, 1H, *J* = 3, 9.3 Hz), 3.49–3.42 (m, 1 H), 2.00 (s, 3 H); HRMS (FAB) calcd for (M + Na^+) 764.8328, found (M + Na^+) 764.3079.

***O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl)-(1→6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (11a)**: 89% yield (from compound 6) as a colorless liquid; $[\alpha]^{25}_D$ −17 (*c* 1.6, $CHCl_3$); FTIR (neat) 2898, 2310, 1742, 1236, 1099, 710, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.12 (m, 25 H), 6.36 (d, 1 H, *J* = 6 Hz), 5.55 (d, 1 H, *J* = 3.3 Hz), 4.87–4.84 (m, 1 H), 4.81 (d, 1 H, *J* = 7.5 Hz), 4.73 (d, 1H, *J* = 11.1 Hz), 4.66–4.44 (m, 8 H), 4.15–4.09 (m, 4 H), 3.81 (dd, 1H, *J* = 6.9, 11.7 Hz), 3.69–3.76 (m, 4 H), 3.58 (dd, 1H, *J* = 3.3, 9.3 Hz), 3.45–3.37 (m, 1H), 2.01 (s, 3 H); HRMS (FAB) calcd for (M + Na^+) 823.1678, found (M + Na^+) 823.3468.

***O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-*O*-(2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-mannopyranosyl)-(1→6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (12a)**: 67% yield (from compound 7) as a colorless liquid; $[\alpha]^{25}_D$ −10.32 (*c* 0.31, $CHCl_3$); FTIR (neat) 3012, 2867, 1745, 1454, 1366, 1236, 1069, 736, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.16 (m, 40H), 6.33 (d, 1H, *J* = 6 Hz), 5.50 (d, 1H, *J* = 3 Hz), 4.94 (d, 1H, *J* = 10.8 Hz), 4.88 (d, 1H, *J* = 10.8 Hz), 4.82–4.71 (m, 8H), 4.60–4.45 (m, 6H), 4.33 (s, 1H), 4.22 (d, 1H, *J* = 10.5 Hz), 4.15–4.07 (m, 2H), 3.99–3.93 (m, 1H), 3.79–3.35 (m, 14H); HRMS (FAB) calcd for (M + Na^+) 1255.4578, found (M + Na^+) 1255.5402.

***O*-(2,3,4-Tri-*O*-benzyl-β-D-xylopyranosyl)-(1→3)-*O*-(2-*O*-acetyl-4,6-benzylidene-β-D-mannopyranosyl)-(1→6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (13a)**: 54% yield (from compound 8) as a colorless liquid; $[\alpha]^{25}_D$ −31 (*c* 0.62, $CHCl_3$); FTIR (neat) 2798, 1746, 1644, 1453, 1371, 1232, 1093, 735, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.19 (m, 30H), 6.36 (d, 1H, *J* = 6 Hz), 5.55 (s, br, 2H), 4.86 (dd, 1H, *J* = 3.3, 6.8 Hz), 4.83 (d, 1H, *J* = 11.2 Hz), 4.80 (d, 1H, *J* = 11.2 Hz), 4.75–4.72 (m, 3H), 4.68–4.62 (m, 3H), 4.58 (d, 1H, *J* = 12.5 Hz), 4.56 (d, 1H, *J* = 12.5 Hz), 4.48 (d, 1H, *J* = 7.5 Hz), 4.43 (d, 1H, *J* = 12.5 Hz), 4.29 (dd, 1H, *J* = 5.8, 11.8 Hz), 4.15 (m, 1H), 4.09–4.02 (m, 3H), 3.98–3.79 (m, 4H), 3.71 (dd, 1H, *J* = 7.5, 9.5 Hz), 3.61–3.58 (m, 2H), 2.41–3.32 (m, 2H), 3.25–3.15 (m, 1H), 1.98 (s, 3H); HRMS (FAB) calcd for (M + Na^+) 1043.1636, found (M + Na^+) 1043.4200.

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Supplementary Material Available: ^1H-NMR spectra of compounds 5, 8, 9a, 10a, 11a, 12a, and 13a (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.