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Note

Synthesis of partially protected 1,5-anhydroalditols by hydroboration of glycals

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Synthesis of rare sugars continues to be a topic of active interest. 1,5-Anhydroalditols, of which many are biologically active, are among such rarely occurring sugars and several methods for their syntheses are known. The available methods include: (a) reductive dehalogenation of glycosyl halides using lithium aluminium hydride [1], tributyltin hydride [2] and hydrogenolysis [3]; (b) hydrogenation of hydroxyglycals [3]; (c) reductive desulfurization of thioglycosides [4] and (d) silylation/reductive cleavage of glycosides [5]. All these methods have certain disadvantages. Glycosyl halides give clean reactions but their utility is limited because differentially protected glycosyl halides are not readily available. Also, the tin method is known to give both 1,5-anhydroalditols and 2-deoxyglycosides depending on the reaction conditions [6]. Catalytic hydrogenation of hydroxyglycals gives mixtures and hence is not useful for synthetic purposes. The yields of reductive desulfurization with Raney nickel are not high and useful protecting groups such as benzyl ethers do not survive under the reaction conditions. Therefore, there is a need for synthetic methodologies leading to differentially protected anhydroalditols. We reasoned that hydroboration of glycals, which are readily available, would furnish 1,5-anhydroalditols. The rationale behind this was that enol ethers undergo highly regioselective hydroboration with the boron attached almost exclusively to the β-carbon, resulting in β-hydroxy ethers [7]. We were particularly interested in the directing effect of the C-3 substituent on the outcome of hydroboration of glycals. Our results are presented in the following paragraphs.

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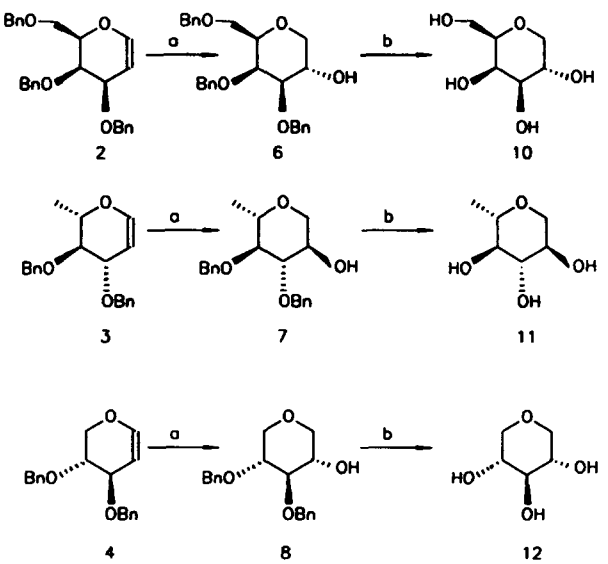
Four glycals, namely 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol (**1**), 1,5-anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-*lyxo*-hex-1-enitol (**2**), 1,5-anhydro-3,4-di-*O*-benzyl-2,6-dideoxy-L-*arabino*-hex-1-enitol (**3**) and 1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*threo*-pent-1-enitol (**4**), were selected as representative examples. The glycals, when treated with an excess of diborane in tetrahydrofuran, underwent clean hydroboration 3 resulting in single products **5**–**8** in very good yields after 1 oxidative workup. Examination of the crude ^{1}H-NMR spectra of these products revealed that they were virtually pure and contained only one diastereomer. The crude products were 1 characterized by their ^{1}H-NMR spectra.

In order to firmly establish the identity of the products, the benzyl ether protecting groups were cleaved by hydrogenolysis. Compounds **5**, **6** and **8** gave products which were identified as 1,5-anhydro-D-glucitol (**9**), 1,5-anhydro-D-galactitol (**10**) and 1,5-anhydroxylitol (**12**) respectively, by comparing their physical properties with those reported in the literature. Compound **7** gave a product **11** whose melting point was nearly identical with that reported for 1,5-anhydro-6-deoxy-D-glucitol, but the optical rotation values were of opposite sign with same magnitude [8]. A direct comparison was not possible as 1,5-anhydro-6-deoxy-L-glucitol is not reported in the literature. The melting points of **10** and **12** differ from that reported in the literature. However, the specific rotation of **10** (+80°) is very close to that reported for 1,5-anhydro-D-galactitol (+76.7°) [9]. Incidentally, the C-2 epimer of **10**, 1,5-anhydro-D-talitol [10], is a syrup and has a negative specific rotation ($[\alpha]_D$ −11.4°). Furthermore, the ^{13}C-NMR spectrum of **10** agrees very well with that reported in the literature [5]. In the case of 1,5-anhydroxylitol **12**, the compound, as expected, showed no rotation and gave only three lines in its ^{13}C-NMR spectrum, in keeping with its symmetry.



Scheme 1. (a) i) BH_3:THF, 0 °C; ii) H_2O_2, aq NaOH. (b) 20% $Pd(OH)_2$, H_2, MeOH, rt.

The formation of compounds **9–12** from **5–8** clearly indicated that hydroboration of the glycal double bond had taken place from the side opposite to the C-3 benzyloxy substituent. We believe that steric reasons are responsible for this selectivity. In summary, an efficient method for the synthesis of partially protected 1,5-anhydroalditols has been developed. The advantage of the present method is that it allows for differential protection of 1,5-anhydroalditols. Further research on the utility of organoboranes derived from glycals in asymmetric synthesis is in progress.

1. Experimental

General methods.—The glycals **1–4** [11] and $Pd(OH)_2$ [12] catalyst were prepared according to lit. IR spectra were recorded on JASCO FT-IR model 5300 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded at 200 and at 50.32 MHz respectively, on a Bruker AC200 instrument. $CDCl_3$ and D_2O were used as solvents and Me_4Si (in $CDCl_3$) and dioxane (in D_2O) were employed as internal standards. THF was distilled over sodium-benzophenone just before use. Chromatography was performed using ACME 100–200 mesh silica gel using appropriate mixtures of hexane and EtOAc as eluent.

Hydroboration of glycals: General procedure.—To a stirred solution of glycals **1–4** respectively (1 mmol), in THF (5 mL) cooled in an ice bath, was added an excess of borane:THF complex in THF. After stirring for 2 h at 0 °C, excess borane was destroyed by careful addition of water (0.5 mL). Sodium hydroxide solution (3 M, 2 mL) was then added all at once, followed by dropwise addition of aq hydrogen peroxide (30%, 5 mL). After 1 h, the solution was diluted with ether (10 mL), the layers separated and the aqueous layer extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over anhyd $MgSO_4$ and concentrated. The products were purified by chromatography.

*1,5-Anhydro-3,4,6-tri-*O*-benzyl-*D*-glucitol* (**5**).—0.250 g (69%), colorless gum; $[\alpha]_D$ +53° (*c* 1, $CHCl_3$); IR (neat) cm^{-1} 3449, 3030, 2865, 1497, 1454, 1362, 1209, 1092, 739, 698; ^{1}H-NMR ($CDCl_3$) δ 1.60 (br, 1 H, OH), 3.11 (t, *J* 11 Hz, 1 H), 3.27–3.64 (m, 6 H), 3.91 (dd, *J* 11.0, 5.5 Hz, 1 H), 4.38–4.88 (m, 6 H), 7.0–7.24 (m, 15 H); ^{13}C-NMR ($CDCl_3$) δ 68.94, 69.59, 70.22, 73.62, 74.86, 75.18, 78.03, 79.49, 86.93, 127.85, 127.93, 128.43, 128.65, 137.92, 138.05, 138.63. Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.71; H, 7.00.

*1,5-Anhydro-3,4,6-tri-*O*-benzyl-*D*-galactitol* (**6**).—0.235 g (65%), colorless gum; $[\alpha]_D$ +22° (*c* 1, $CHCl_3$); IR (neat) cm^{-1} 3449, 2865, 1497, 1454, 1364, 1209, 1088, 1028, 737, 698; ^{1}H-NMR ($CDCl_3$) δ 2.20 (br, 1 H), 3.10 (t, *J* 10.2 Hz, 1 H), 3.26 (dd, *J* 9, 2.5 Hz, 1 H), 3.41–3.51 (m, 3 H), 3.89–4.06 (m, 3 H), 4.36–4.79 (m, 6 H), 7.10–7.25 (m, 15 H); ^{13}C-NMR ($CDCl_3$) δ 66.75, 69.08, 69.92, 71.86, 73.15, 73.59, 74.60, 77.99, 84.46, 127.74, 127.97, 128.12, 128.28, 128.43, 128.61, 137.92, 138.45. Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.63; H, 6.96. Found: C, 74.61; H, 7.05.

*1,5-Anhydro-3,4-di-*O*-benzyl-6-deoxy-*L*-glucitol* (**7**).—0.210 g (64%), mp 75–76 °C (from hexane), $[\alpha]_D$ −44.5° (*c* 1.6, $CHCl_3$); IR (KBr) cm^{-1} 3291, 3030, 2917, 1497, 1454, 1377, 1358, 1098, 1036, 752, 692, 660; ^{1}H-NMR ($CDCl_3$) δ 1.20 (d, *J* 6.4 Hz, 3

H), 2.0 (br, 1 H), 3.08 (m, 2 H), 3.27 (m, 2 H), 3.60 (m, 1 H), 3.82 (dd, *J* 11, 5 Hz, 1 H), 4.75 (m, 4 H), 7.24 (m, 10 H); ^{13}C-NMR ($CDCl_3$) δ 18.24, 69.43, 70.65, 75.27, 76.34, 83.91, 86.88, 127.93, 128.01, 128.56, 138.13, 138.20, 138.74. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.25; H, 7.41.

*1,5-Anhydro-3,4-di-*O*-benzyl-*D*-xylitol* (**8**).—0.188 g (60%), mp 50–52 °C (from hexane/EtOAc), $[\alpha]_D$ −9.2° (*c* 1.3, $CHCl_3$); IR (KBr) cm^{-1} 3439, 3063, 2861, 1497, 1454, 1069, 739, 698; ^{1}H-NMR ($CDCl_3$) δ 3.20 (br, 1 H), 3.50–3.70 (m, 5 H), 3.80–4.0 (m, 2 H), 4.64–4.74 (m, 4 H), 7.35 (m, 10 H); ^{13}C-NMR ($CDCl_3$) δ 66.70, 68.31, 69.45, 72.01, 73.38, 76.03, 78.28, 127.79, 127.96, 128.55, 137.71, 138.32. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.49; H, 7.13.

Debenzylation of partially benzylated 1,5-anhydroalditols: General procedure.—The partially benzylated 1,5-anhydroalditols (1 mmol) were dissolved in methanol (5 mL) and hydrogenated in a Parr hydrogenator with 20% $Pd(OH)_2/C$ at 45 psi for 4 h. The catalyst was filtered off and the filtrate concentrated to furnish the 1,5-anhydroalditols.

*1,5-Anhydro-*D*-glucitol* (**9**).—0.133 g (81%), mp 138–140 °C; $[\alpha]_D$ +40° (*c* 1, H_2O); IR (KBr) cm^{-1} 3410, 3329, 2980, 1466, 1370, 1107, 1007, 874, 658; ^{1}H-NMR (D_2O) δ 3.04–3.26 (m, 4 H), 3.36–3.54 (m, 2 H), 3.68–3.85 (m, 2 H); ^{13}C-NMR (D_2O) δ 61.75, 69.56, 70.15, 70.53, 78.29, 81.03; lit. [1] mp 142–143 °C, lit. [2] $[\alpha]_D$ +42.3° (*c* 0.84, H_2O).

*1,5-Anhydro-*D*-galactitol* (**10**).—0.148 g (90%), mp 126–128 °C; $[\alpha]_D$ +80° (*c* 0.8, H_2O); ^{1}H-NMR (D_2O) δ 3.06 (t, *J* 10.3 Hz, 1 H), 3.41–3.46 (m, 2 H), 3.56–3.71 (m, 3 H), 3.82–3.91 (m, 2 H); ^{13}C-NMR (D_2O) δ 62.2, 67.4, 69.9, 74.9, 80.2 (one signal around 60 ppm obscured by dioxane signal); lit. [9] mp 114–115 °C, $[\alpha]_D$ +76.6° (*c* 1.08, H_2O).

*1,5-Anhydro-6-deoxy-*L*-glucitol* (**11**).—0.140 g (94%), mp 144–146 °C; $[\alpha]_D$ −30° (*c* 1, MeOH); IR (KBr) cm^{-1} 3343, 2901, 2853, 1100, 1069, 1030, 858; ^{1}H-NMR (D_2O) δ 1.11 (d, *J* 6.1 Hz, 3 H), 3.00 (t, *J* 9.2 Hz, 1 H), 3.05–3.27 (m, 3 H), 3.35–3.5 (m, 1 H), 3.78 (dd, *J* 11.0, 5.2 Hz, 1 H); ^{13}C-NMR (D_2O) δ 17.70, 69.48, 70.39, 75.79, 77.20, 77.99; lit. [8] mp 149–150 °C, $[\alpha]_D$ +29° (*c* 1, MeOH).

1,5-Anhydroxylitol (**12**).—0.109 g (81%), mp 90–91 °C; ^{1}H-NMR (D_2O) δ 3.09 (t, *J* 10.6 Hz, 2 H), 3.27 (d, *J* 8.7 Hz, 1 H), 3.46 (m, 1 H), 3.80 (dd, *J* 11, 5 Hz); ^{13}C-NMR (D_2O) δ 56.76, 59.55, 59.70; lit. [13] mp 116–117 °C.

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