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Hydride Addition to 1,2-Anhydrosugars: A Highly Stereoselective Route to Anhydroalditols

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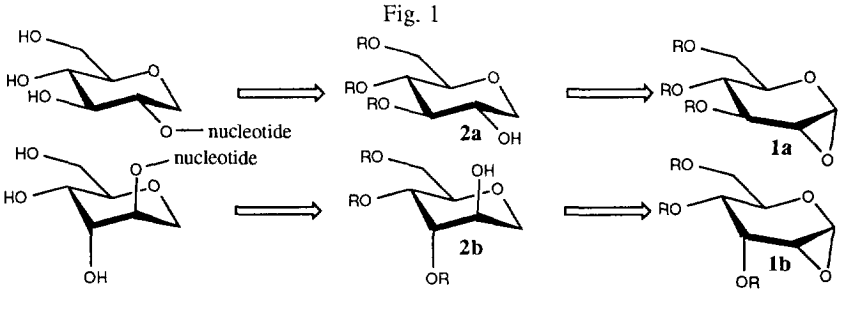
Abstract: Stereoselective hydride addition to endocyclic 1,2-anhydrosugars has been achieved providing an efficient route to differentially protected anhydroalditols.

As part of a program directed toward the synthesis of glycosyl transferase inhibitors, we required a method for producing anhydroalditols with differentially protected hydroxyl centers. Several routes to anhydrosugars are documented in the literature[1] and the more efficient methods involve reductive cleavage of methyl glycosides[2] and anomeric acetates.[3] However, these protocols do not lend themselves to the production of selectively protected substrates, such as **2a** and **2b** (Fig. 1), without elaborate protecting group schemes. It occurred to us that hydride addition to 1,2-anhydrosugars **1a** and **1b** could provide ready access to our target compounds through stereoselective addition to the anomeric center, leaving a selectively unprotected hydroxyl group available for further elaboration.[4] Reported herein is the highly stereoselective hydride addition to 1,2-anhydrosugars.

Fig. 1



1,2-Anhydro-tri-3,4,6-*O*-benzyl-D-glucose **3** was prepared by stereospecific addition of dimethyldioxirane to 3,4,6-tri-*O*-benzyl-D-glucal.[4] Table 1 lists the results of our hydride addition survey, using various reagents and conditions. To our surprise, Lewis acid catalyzed addition of triethylsilane did not provide acceptable yields of the desired material (**4**). In fact, only the diol **5** was obtained from trimethylsilyl triflate activation of **3** in the

presence of triethylsilane (entries 1 and 2). Low yields were obtained using borane with either triethylsilane or lithium borohydride (entry 3) and activation with boron trifluoride etherate provided **4** in only 36% yield (entry 4). Since care was taken in assuring anhydrous conditions, it appears that lithium borohydride and triethylsilane are not appropriate hydride donors for reduction of **3**. The best yield of **4**, under Lewis acid catalyzed conditions, was achieved using borane and Super Hydride (entry 6). However, as in all the Lewis acid catalyzed reactions, the diol **5** was a major component of the reaction mixture.[5]

In order to prevent formation of **5** we decided to explore the possibility of effecting direct hydride addition to **3** using lithium aluminum hydride. We were encouraged by the 50% yield of **4** obtained at room temperature because, contrary to Lewis acid catalyzed conditions, no diol formation was observed during the course of the reaction. Only the anhydrosugar (**3**) and the reduced product (**4**) appeared in the TLC analysis of the reaction mixture. This reaction was further improved when performed at reflux, providing **4** as the only observed product in an isolated yield of 74%.[6]

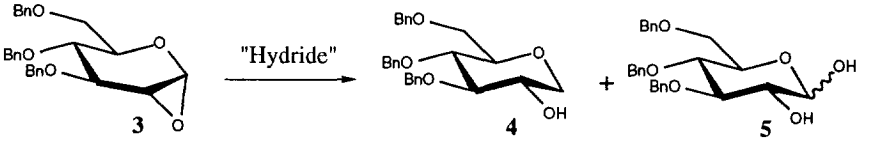
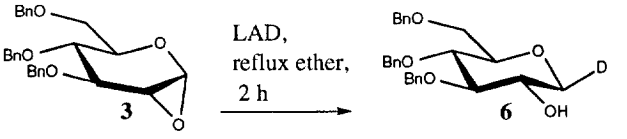


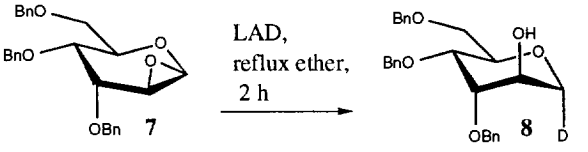
Table 1: Hydride, Deuteride Addition to 1,2-Anhydro-3,4,6-Tri-*O*-Benzyl-D-Glucose.

Entry	Reagents and Conditions	Reaction Time	(%) Yield of **4**
1	TMSOTf, Et_3SiH, THF, -78°C to r.t.	18 h	0
2	TMSOTf, Et_3SiH, CH_3CN, -30°C to r.t.	18 h	0
3	BH_3, Et_3SiH, THF, 0°C	3 h	26
4	BH_3, $LiBH_4$, THF, 0°C	3 h	26
5	BF_3OEt_2, Et_3SiH, THF, 0°C	3 h	36
6	BH_3, $LiEt_3BH$, 0°C	2 h	60
7	LAH, Et_2O, 25°C	1 h	50
8	LAH, Et_2O, reflux	2 h	74

In order to determine the stereochemical outcome of the hydride addition, **3** was treated with $LiAlD_4$ to yield **6**. The proton NMR clearly showed that equatorial hydride addition had occurred, evidenced by the collapse of the anomeric doublet of doublet in **4** to a doublet with a coupling constant of 10.4 Hz, indicating that the two hydrogen atoms were *trans*-diaxial.



The stereospecificity of this reaction was determined by subjecting 3,4,6-tri-*O*-benzyl-D-allal to epoxidation providing **7**, and lithium aluminum deuteride addition at reflux afforded a single product in 58% yield. The 1-D proton spectrum was complicated by spectral overlap; however two-dimensional NMR analysis indicated that the upfield anomeric proton was replaced by deuterium, suggesting that axial attack had occurred to give **8**.



In conclusion, we have shown that hydride addition to endocyclic 1,2-anhydrosugars is essentially stereospecific and can be achieved in high yield, providing an efficient route to differentially protected anhydroalditols.

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5. A typical experiment proceeded as follows: To a solution of borane (240 mL, 1.0 M, 0.24 mmol) and lithium triethylborohydride (240 mL, 1.0 M, 0.24 mmol) cooled to 0°C in THF (2 mL) was added dropwise a solution of 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose (0.24 mmol) in THF (2 mL). The reaction was quenched after 2 h by the addition of water (1 mL). Ethyl acetate (25 mL) was added. The organic phase was collected, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (1:1 hexanes: ethyl acetate) to yield 62.7 mg of **4** (60.2%) as a colorless oil.

R_f = 0.5 (50% EtOAc/hexanes). ^1H NMR (250 MHz, $CDCl_3$) δ 1.88 (br s, 1 H, OH), 3.20 (t, *J* = 10.9, 1 H, H-1_{ax}), 3.37-3.47 (m, 2 H), 3.58 (t, *J* = 9.0, 1 H), 3.62 - 3.76 (m, 3 H), 4.01 (dd, *J* = 11.0, 5.3, 1 H, H-1_{eq}), 4.48-4.97 (m, 6 H, OCH_2Ar), 7.13-7.35 (m, 15 H, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 68.3, 69.0, 69.6, 73.1, 74.4, 74.7, 77.0, 77.5, 86.4, 127.2, 127.3, 127.5, 127.8, 127.9, 128.2, 137.3; IR ($CDCl_3$) cm^{-1} 603, 638, 698, 735, 910, 1028, 1084, 1209, 1323, 1361, 1454, 1496, 2864, 3030, 3063, 3447. Anal. Calcd for $C_{27}H_{30}O_5$: C, 74.62; H, 6.96. Found: C, 74.63; H, 6.93.

6. A typical experiment proceeded as follows: To a stirred solution of lithium aluminum hydride LAH (46 mg, 1.2 mmol) in Et_2O (2 mL) was slowly added a solution of 1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose (0.24 mmol) dissolved in Et_2O (2 mL). The solution was refluxed for 2 h. The reaction was quenched by sequential addition of H_2O (0.6 mL), 10% NaOH (0.6 mL), and H_2O (1.8 mL). The solution was filtered and dichloromethane (50 mL) was added. The organic phase was collected, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed (1:1 hexanes: ethyl acetate) to yield 77 mg (74%) of **4** as a colorless oil.

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