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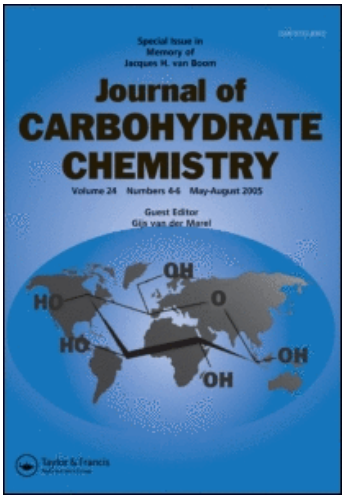

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COMMUNICATION

REDUCTIONS OF CARBOHYDRATE VICINAL DIACETATES WITH LITHIUM ALUMINUM HYDRIDE.

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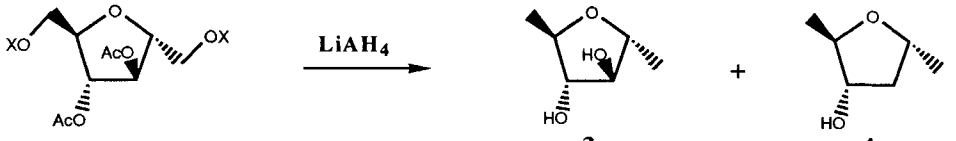
As part of a study of stereoselective carbohydrate synthesis via the palladium hydroxide catalyzed epoxide hydrogenolysis reported recently by our group,[1] we planned the synthesis of several compounds, such as **3**, which bear only the 1,2-diol functionality. Lithium aluminum hydride ($LiAlH_4$) reduction is a general method for the conversion of hydroxymethyl groups (through their sulfonate esters) to methyl groups with concomitant removal of acetate protecting groups.[2] Results of a limited study of an unexpected $LiAlH_4$ reaction are presented below.



	3		4	
	R.T.	0 °C	R.T.	0 °C
1 : X = Ts	70	100	30	0
2 : X = Ms	90	100	10	0

The room temperature $LiAlH_4$ reduction of **1** or **2** produced a mixture of **3** and a more reduced compound (**4**) in good yield. In contrast to these results, if the reaction was performed at 0 °C, the predominant product was **3**. Thus, 3,4-di-*O*-acetyl-2,5-anhydro-1,6-di-*O*-tosyl-D-mannitol (**1**)[3] and 3,4-di-*O*-acetyl-2,5-anhydro-1,6-di-*O*-mesyl-D-mannitol (**2**)[4] react with $LiAlH_4$ at 0 °C to

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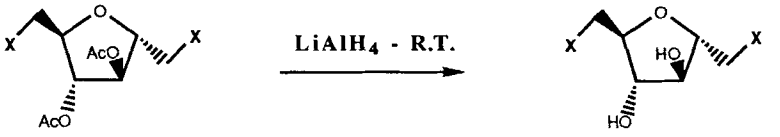
produce 66% and 71% isolated yields[5] of 2,5-anhydro-1,6-dideoxy-D-mannitol (**3**)[6]. Traces of 2,5-anhydro-1,3,6-trideoxy-D-*arabino*-hexitol (**4**)[7] were detected by ^{1}H NMR. The same reactions at room temperature afford a mixture of **3** and **4**, in 70:30 and 90:10 ratios from **1** and **2**, in 64 and 61% yields,[5] respectively.[8] The stereochemistry of **3** and **4** was determined by ^{1}H NMR (500 MHz) spectroscopy.[9]

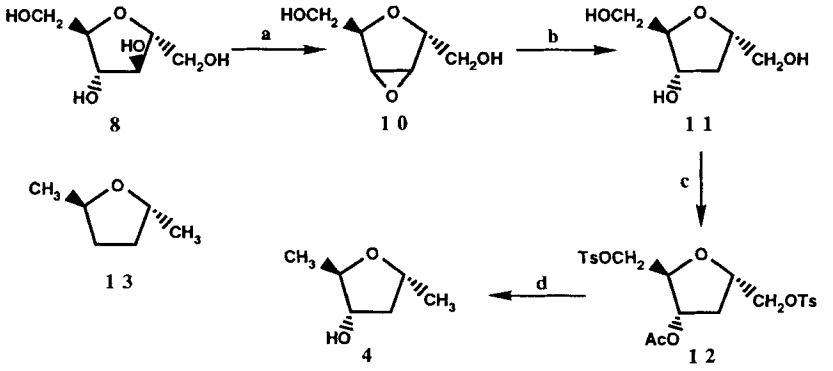
Attempted reduction of the related compounds **5**,[10] **6**[11] and **7**[12] gave only the corresponding expected products **8**,[13] **9**[3,14] and **3**[6] in 76, 84 and 66% yield as shown below. It is apparent from these results that the sulfonyl group is a critical structural element for reduction of the vicinal diacetates at room temperature.



5: X = OAc
6: X = OTr
7: X = H

8: X = OH
9: X = OTr
3: X = H

An independent synthesis of **4** confirmed the structure obtained from compounds **1** and **2**. Epoxidation of **8** gave compound **10**[3,15] and selective epoxide hydrogenolysis afforded the trihydroxy compound **11**.[1] Tandem tosylation of the primary hydroxy groups and acetylation of the secondary hydroxy group[16] of **11** gave **12**.[17] Reduction of **12** with $LiAlH_4$ gave **4** with no 2,5-dimethyltetrahydrofuran (**13**) being observed.[18]



a: $(CH_3)_2CHOCON{=}NCOOCH(CH_3)_2$ / $(Ph)_3P$ / DMF / 0 °C;[3]
b: H_2 / $Pd(OH)_2$ / Ethanol;[1]
c: 1) TsCl / Pyridine / 0 °C, 2) $(Ac)_2O$ / Pyridine / 0 °C / 85%;
d: $LiAlH_4$ / Ethyl Ether / R.T. / 52%.

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The mechanism for the formation of **3** from **1** and **2** and the formation of **4** from **12** is probably predominantly S_N2. The formation of **4** from **1** and **2** and the failure to observe **13** from **1**, **2** and **12** requires a mechanism utilizing both acetyl groups either directly or indirectly through an inductive effect. One possibility is the single-electron-transfer reaction of $LiAlH_4$ which has been extensively studied.[19] It was reported that this reaction does not occur in simple open chain alkyl (and alkenyl) tosyl compounds but the arrangement of groups in **1** and **2** may extend this interesting reaction mechanism. The reaction may involve a single-electron-transfer to the sulfonyl group which transfers the electron to the acetyl ester bond with subsequent loss of this group and hydrogen atom transfer to complete the unusual reduction. The sulfonyl groups may then be reduced by another single-electron-transfer reaction or by an S_N2 process. The second acetate must have an inductive effect on the first acetate which allows the reaction to occur with **1** and **2** but not with **12**. Therefore, these results indicate that the vicinal diacetate functionality is, in addition to the sulfonyl group, a critical structural requirement for the unexpected $LiAlH_4$ reduction reaction reported here, and the formation of unanticipated reduction products should be carefully monitored when utilizing $LiAlH_4$. Some of these carbohydrate analogues are being tested as part of a study of the anomeric, tautomeric and epimeric specificities of the regulatory enzyme phosphofructokinase.[20]

In summary, 3,4-di-*O*-acetyl-2,5-anhydro-1,6-di-*O*-tosyl(or -mesyl)-D-mannitol (**1** or **2**) reacts with lithium aluminum hydride at room temperature to produce a 70:30 or 90:10 mixture, respectively, of 2,5-anhydro-1,6-dideoxy-D-mannitol (**3**) and 2,5-anhydro-1,3,6-trideoxy-D-*arabino*-hexitol (**4**). However, when **1** or **2** reacts with lithium aluminum hydride at 0 °C, the expected compound **3** is formed with traces of compound **4**. The stereochemistry of the alcohols has been determined by NMR spectroscopy. An independent synthesis of **4** confirmed its structure. The critical functionality for this unexpected reaction seems to be, in addition to the sulfonyl group, the vicinal diacetate structure.

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gratefully acknowledged. Also, we thank Dr. David Vargas for help with the decoupling experiments performed with the 500 MHz instrument and Professor Mark L. McLaughlin for helpful discussions.

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2. H. C. Brown and S. Krishnamurthy, *Tetrahedron*, **35**, 567 (1979); E. R. H. Walker, *Chem. Soc. Rev.*, **5**, 23 (1976).

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4. **2**: ^{1}H NMR ($CDCl_3$) δ 5.19 (d, 2H), 4.38 (d, 4H), 4.36-4.28 (m, 2H), 3.09 (s, 6H), 2.11 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 170.24, 81.28, 77.58, 68.14, 37.86, 20.81.

5. General experimental procedure: Reactions are performed by treating a suspension of $LiAlH_4$ in dry ethyl ether at 0 °C (or room temperature) with the reactant overnight, quenching with ice until a white paste is formed, followed by filtration through a celite pad. The celite pad is washed with ethyl ether and the filtrate concentrated.

6. Compound **3** was characterized as its diacetate (**7**) by Guthrie et al.[3] **3**: ^{1}H NMR ($CDCl_3$) δ 3.87-3.94 (m, H_a), 3.74 (d, H_b), 1.31 (d, $[CH_3]_g$); ^{13}C NMR ($CDCl_3$) δ 83.65, 77.52, 19.04.

7. Compound **4** was reported by Bats et al.[21] No spectroscopic data were given. **4**: ^{1}H NMR ($CDCl_3$) δ 3.94-3.99 (m, H_a), 4.00 (ddd, H_b), 2.38 (ddd, H_c), 1.53 (ddd, H_d), 4.21 (ddd, H_e), 1.31 (d, $[CH_3]_f$), 1.20 (d, $[CH_3]_g$); ^{13}C NMR ($CDCl_3$) δ 80.65, 78.24, 72.81, 42.24, 22.31, 18.41; FT-IR 3713-3095 (broad), 2973.9, 2930.4, 2878.3, 1730.4, 1652.2, 1382.6 cm^{-1}. Acetylated **4** (Ac_2O in pyridine at 0 °C): ^{1}H NMR ($CDCl_3$) δ 4.88 (ddd, 1H), 4.24 (ddd, 1H), 4.22-4.11 (m, 1H), 2.48 (ddd, 1H), 2.06 (s, 3H), 1.67-1.53 (m, 1H), 1.30 (d, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2, 80.1, 79.0, 73.2, 38.8, 21.7, 18.6.

8. The ratio of both compounds was determined based upon the integration of the signals H_b of **3** vs. H_c, H_d and H_e of **4**.

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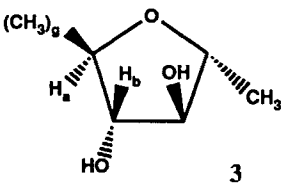

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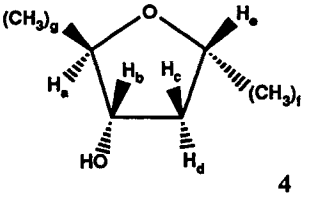

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9. When H_c or H_d signals are decoupled, H_a signal remains unaffected. Decoupling the $(CH3)_g$ signal affected greatly H_a. H_e is assigned to the ddd signal at 4.21 δ, which is neither coupled to H_a nor to H_b, as determined by COSY experiment (200 MHz). Decoupling H_e affects greatly both the signals assigned to H_c and H_d. Distinction between H_c and H_d was made by comparison to the parent compound 2,5-anhydro-3-deoxy-D-*arabino*-hexitol (**11**),[1] and NOE experiments confirmed the *arabino*- stereochemistry.

10. T. A. W. Koerner, Jr., Ph.D. Dissertation, Louisiana State University, Baton Rouge, La. USA (1975).

11. Prepared by a standard acetylation procedure using **9**.[3]

12. Compound **7** was prepared by a standard acetylation procedure using **3**. Previously, **7** was prepared by a different route by A. C. Cope and T. Y. Shen, *J. Am. Chem. Soc.*, **78**, 5912 (1956).

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14. Structure **9** was verified by NMR. No reduction products were observed.. **9**: ^1H NMR ($CDCl_3$) δ 7.52-7.18 (30H), 4.19 (2H), 4.04 (2H), 3.48 (4H); ^{13}C NMR ($CDCl_3$) δ 143.38, 128.78, 127.97, 127.24, 87.69, 84.32, 80.05, 64.99.

15. X-ray crystal structure determination: J. G. Garcia, R. J. Voll, F. R. Fronczek, and E. S. Younathan, *Acta Cryst.*, in press (1992).

16. Tosylation was performed by adding 2.2 eq. of tosyl chloride to 1 eq. of **11** in pyridine at 0 °C and allowing the reaction mixture to stir for 4 h at R.T. Acetylation followed by adding excess acetic anhydride to the reaction mixture at 0 °C (ice bath) in pyridine. Subsequent DCM extraction and washing of the organic layer with cold 1N HCl until pH of the aqueous layer remained acidic afforded **12** upon concentration.

17. Compound **12**: ^1H NMR ($CDCl_3$) δ 7.59 (q, 4H), 7.60 (q, 4H), 5.08 (dd, 1H), 4.20-4.36 (m, 1H), 3.97-4.16 (m, 4 H), 3.99-3.90 (m, 1H), 2.48 (s, 6H), 2.38 (ddd, 1H), 2.02 (s, 3H), 1.88 (ddd, 1H); ^{13}C NMR ($CDCl_3$) δ 170.39, 129.93, 127.97, 81.86, 76.67, 75.16, 70.46, 69.54, 33.84, 21.65, 20.26.

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18 As determined by ^1H NMR and GC of the reaction mixture, compared to the *cis/trans* mixture available from Aldrich.

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