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Note

Preparation of methyl 3,6-dideoxy-α-D-*xylo*-hexopyranoside (methyl α-abequoside) and its α-L-*lyxo* isomer by reduction of epoxides with lithium triethylborohydride

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We have recently described[1] the reductive desulfonyloxylation of some secondary *p*-toluenesulfonates of glycosides by lithium triethylborohydride (Super Hydride®, LTBH), which afforded high yields of deoxy sugars. The glycosides used were 4,6-*O*-benzylidenated glycopyranoside 2- and 3-tosylates, and the reactions were demonstrated to proceed *via* 2,3-anhydroglycoside intermediates. In continuation[2] of these studies, a number of non-benzylidenated hexopyranoside tosylates, *e.g.*, **1** and **2**, were treated with LTBH in the same way, and, although desulfonyloxylation occurred with equal ease, it was accompanied by ring contraction, to give *C*-(hydroxymethyl)pentofuranosides (*e.g.*, **3** from **2**). For an assessment of the mechanism involved in this rearrangement of the glycose skeleton, it was necessary to decide whether or not there were formed intermediary epoxides in these instances, too, as in those of the benzylidenated series previously studied. Consequently, by independent routes, we prepared the known epoxides **4** and **7**, and allowed them to react with LTBH under the conditions employed for the desulfonyloxylations mentioned. The epoxides underwent clean and facile reduction to the dideoxyhexopyranosides **5** and **8**; isolated yields were >90%, and no products of ring contraction were detectable.

We now describe the preparative aspects of, and record some new data for, **5** and **8**, which are glycosides of considerable interest.

Methyl 3,6-dideoxy-α-D-*xylo*-hexopyranoside (**5**) is derived from abequose, a component of pyrogenic lipopolysaccharides isolated from *Salmonella* species[3]. Early syntheses[4] of abequose departed from derivatives of 3-deoxy-D-*xylo*-hexose. Later on, Siewert and Westphal[5] synthesized the glycoside **5** by reduction of methyl 3,4-anhydro-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside (**4**) with lithium aluminum hydride in oxolane solution, which afforded a 61% yield. Similar reduction of the 6-deoxy analog of **4** gave **5** in 76% yield[5], or almost quantitatively[6]. The syrupy

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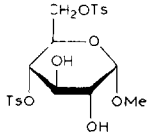

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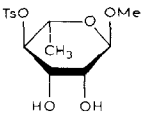

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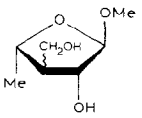

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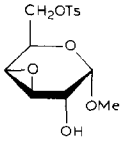

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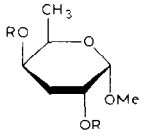
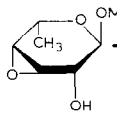


5 R = H

6 R = $COC_6H_4NO_2$-*p*



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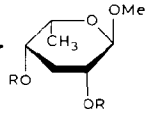

8 R = H

9 R = Ms

abequoside was characterized[5] as the crystalline 2,4-bis(*p*-nitrobenzoate) **6** and[6] the crystalline 2,4-dimesylate. In the present work, reduction of tosylated epoxide **4** with LTBH furnished **5** in 94% yield. The n.m.r. data for **5** and its diester **6** (see Table I), which do not appear to have been previously recorded in the literature, are in full accord with the structures assigned.

Syntheses of β-anomeric methyl and benzyl abequosides have also been reported[7].

By contrast with the naturally occurring 3,6-dideoxyhexoses having the D- and L-*xylo*, D- and L-*arabino*, and D-*ribo* configurations (abequose, colitose, tyvelose, ascarylose, and paratose, respectively), the D- and L-*lyxo* isomers, which have not thus far been encountered in Nature, have received comparatively little attention with regard to synthesis. Ferrier and Sankey[8] isolated the α-D-*lyxo* sugar as its 1,2,4-triacetate in 5% yield upon catalytic hydrogenation of 1,2,4-tri-*O*-acetyl-3,6-dideoxy-α-D-*threo*-hex-2-enopyranose, whereas Percival[9] as well as Lederer[10], and their co-workers, produced the free L enantiomer by reduction of methyl 3,4-anhydro-α-L-talopyranoside (**7**) with lithium aluminum hydride, followed by acid hydrolysis. Yields were not stated[9], or were very low[10], and the intermediate methyl glycoside **8** was not isolated. Jarý and co-workers[11] obtained **8** in 13.5% yield (together with 51.5% of the 4,6-dideoxy isomer) by Raney nickel hydrogenation of **7**, and characterized the syrupy product by its crystalline 2,4-dimesylate **9**. More recently, the four racemic 3,6-dideoxyhexoses were prepared by reduction of the corresponding DL-hexonolactones obtained through total synthesis[12], but the yields were not indicated. We have now prepared **8** from **7**, in 93% yield, by reduction with LTBH. The n.m.r. data for **8** and its diester **9** are listed in Table I.

EXPERIMENTAL

For general comments on the performance of reactions with LTBH (Super

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR METHYL 3,6-DIDEOXYHEXOPYRANOSIDES[a]

Compound	*^{1}H-Chemical shifts (δ), with multiplicities*[b]								
	H-1	*H-2*	*H-3a*	*H-3e*	*H-4*	*H-5*	*C-Me*	*OMe*	*Others*
5	4.68d	3.97ddd	1.81dt	2.12dddd[c]	3.73nt	3.89dq	1.21d	3.45s	
6	5.07d	5.43m	2.50dt	2.32dt	5.37nt	4.24dq	1.26d	3.50s	8.34–8.19m (aromatic)
8	4.62s	3.69nm[d]	2.02nm (2 H)		3.62nm[d]	3.91q	1.26d	3.41s	
9	4.79s	4.66nm[g]	2.30dt	2.60dt	4.66nm[g]	4.08m	1.33d	3.43s	3.11s (Ms)

Compound	*Coupling constants (Hz)*								
	$J_{1,2}$	$J_{1,3e}$	$J_{2,3a}$	$J_{2,3e}$	$J_{3a,3e}$	$J_{3a,4}$	$J_{3e,4}$	$J_{4,5}$	$J_{5,6}$
5	3.7	1.3	12.2	4.6	13.0	2.9	3.5	1.4	6.6
6	3.2		12	4	13	3	4	1.4	6.6
8	~0		*e*	*e*	0	*e*	*e*	*f*	6.6
9	~0		3.5	~2.5	16.1	3.5	~2.5	*f*	6.6

Compound	*^{13}C-Chemical shifts (p.p.m. from tetramethylsilane)*								
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OMe*	*Ms*	*Acyl*
5	99.4	69.0	34.9	63.6	65.9	16.3	55.1		
6	96.7	72.6	28.7	68.2	64.7	16.4	55.5		164.1, 150.8, 135.2, 135.1, 130.9, (2) 123.7, 123.6
8	101.1	68.0	31.3	66.2[h]	66.6[h]	17.0	54.9		
9	98.0	74.1	29.6	71.1	64.4	16.8	55.3	38.8	

[a]From solutions in $CDCl_3$ containing tetramethylsilane as the internal standard. [b]From 200-MHz spectra. Assignments were verified by spin–spin decoupling experiments. Signal multiplicities: d, doublet; m, multiplet; n, narrow; q, quartet; s, singlet; and t, triplet. [c]Visible after D_2O exchange. [d]H-2 and H-4 assignments may have to be reversed. [e]Small. [f]Very small. [g]H-2 and H-4 signals coincided. [h]C-4 and C-5 assignments may have to be reversed.

Hydride®, purchased as a M solution in oxolane from Aldrich Chemical Co.), see ref. 1.

*Methyl 3,6-dideoxy-α-*D-xylo-*hexopyranoside* (**5**). — An ice-cooled solution of methyl 3,4-anhydro-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside[13] (**4**; 1.65 g, 5 mmol) in dry oxolane[1] (20 mL) was magnetically stirred under a nitrogen atmosphere, and a M LTBH solution (50 mL, 10 mol. equiv.) was added dropwise by syringe. The ice bath was removed, and the solution boiled under reflux for 15 min. T.l.c. with ethyl acetate then indicated the disappearance of all of the **4** (R_F 0.65), and formation of a single spot for **5** (R_F 0.28). The mixture was cooled, the excess

of reductant was decomposed by careful addition of small amounts of methanol until gas evolution ceased, and the mixture was poured into ice water (400 mL), with which it was stirred for 2 h. Some fresh ice was then added, followed by 30% hydrogen peroxide (19 mL), which was introduced cautiously, and stirring was continued at ambient temperature for several hours (or overnight). The alkaline solution was evaporated almost to dryness under diminished pressure, the residue was taken up in saturated, aqueous potassium carbonate solution (50 mL), and the mixture extracted with chloroform (7 × 100 mL). The extracts were combined, dried ($MgSO_4$), and evaporated, to give **5** as an almost colorless oil (760 mg, 94% vacuum-dried), homogeneous in t.l.c.; $[\alpha]_D$ +139.1° (*c* 0.9, chloroform) and +146.7° (*c* 1, methanol) [lit.[6] +143 ±3° (methanol)]; (*m/z*): f.a.b. mode, 131 [$M^+ - OCH_3$], 161 [$M^+ - H$], and 261 [dimerized fragments, 2 $M^+ - OCH_3 - HOCH_3$]; d.c.i. mode, 131, 163 [$M^+ + H$], and 261.

A sample of **5** was *p*-nitrobenzoylated[5], to give the crystalline diester **6**, which was recrystallized from ethanol–acetone; m.p. 89–90° (sintering at 80–83°); lit.[5] m.p. 80–83; and $[\alpha]_D$ +155.5° (*c* 1, chloroform).

*Methyl 3,6-dideoxy-α-*L*-lyxo-hexopyranoside* (**8**). — Methyl 3,4-anhydro-6-deoxy-α-L-talopyranoside[9] (**7**) (2.0 g, 12.5 mmol) in dry oxolane (50 mL) was allowed to react with LTBH (42 mL, 3.4 mol.equiv.), and the mixture subsequently processed as described for the preparation of **5**. Compound **8** was obtained as a pale-yellow syrup (1.90 g, 94%) whose t.l.c. (1:1 ethyl acetate–hexane) showed the main product, R_F 0.25, plus a trace of a slower-moving impurity. The material was purified by chromatography on a column of silica gel, using ethyl acetate as the eluant, and the colorless syrup then had $[\alpha]_D$ −100° (*c* 1, chloroform); lit.[11] −103.3 ±1°; *m/z*: f.a.b. mode, 131 [$M^+ - OCH_3$], 161 [$M^+ - H$], 163 [$M^+ + H$], 325 [dimer, 2 $M^+ + H$]; d.c.i. mode, 131, 163, and 261 [dimerized fragment, 2 $M^+ - OCH_3 - CH_3OH$].

A sample of **8** was mesylated[11] to give the crystalline diester **9**, which was recrystallized from chloroform–petroleum ether; m.p. 153–155°, $[\alpha]_D$ −47.0° (*c* 1, chloroform); lit.[11] m.p. 153–154°, $[\alpha]_D$ −48.5 ±0.6°.

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