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Note

An improved synthesis of 1,6-anhydro-2,4-dideoxy-β-D-*threo*-hexopyranose

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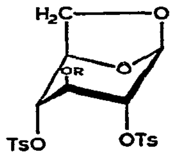
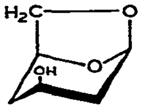
In connexion with syntheses starting from 2,4-dideoxyhexopyranoses[1], a short and efficient route to 1,6-anhydro-2,4-dideoxy-β-D-*threo*-hexopyranose and its derivatives was required. A previous synthesis[2] of this alcohol was multistage with a low overall yield. We now report a simple, high-yielding synthesis of the title compound.

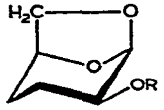
Treatment of 1,6-anhydro-2,4-di-*O*-toluene-*p*-sulphonyl-β-D-glucopyranose[3] (**1**) with lithium triethylborohydride[4] gave 90% of a mixture of **2** and **3** in the ratio of 5.25:1. Reaction of the mixture with diethyltrimethylsilylamine[5] resulted in selective trimethylsilylation of **3** to give **5**. Aqueous extraction of the reaction mixture, followed by back-extraction, then gave **2**.



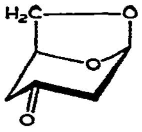
1 R = H
10 R = $CH_2OCH_2CH_2OMe$



2



3 R = H
5 R = $SiMe_3$



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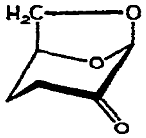

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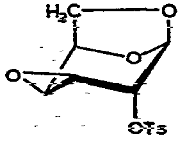

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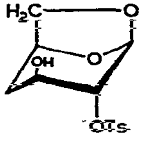
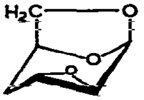


8



9

The same steric effects which retard silylation of **2** also permit its selective oxidation in the presence of **3**. Thus, on treatment with pyridinium chlorochromate[6] **2** was quantitatively oxidised in 1 h, whereas **3** required 24 h. Separation of **3** and **4** was effected by column chromatography.

The reduction of **1** with lithium triethylborohydride was monitored by t.l.c., and the intermediates were isolated by p.l.c. In this way, **7–9** were isolated, and identified by comparison with authentic samples[7,8]. The absence of tosylate displacement by hydride ion in the conversion **1**→**8** was proved by the failure of the protected derivative **10** to react under the usual reduction conditions. Reduction of the epoxide[8] **9** with lithium triethylborohydride yielded **2** and **3** in the ratio 4.56:1 (*cf.* 5.25:1 for the reduction of **1**). This finding demonstrates that **8** undergoes little or no direct tosylate displacement by hydride ion.

The foregoing results contrast with those of Černý *et al.*[9] who reported that reduction of **8** with lithium aluminium hydride gave a mixture of **2** and **3** in the ratio 4:1. The ratio changed to 1.7:1 for the reduction of **9**.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. Optical rotations were measured with a Perkin–Elmer PE 141 polarimeter. N.m.r. spectra ($CDCl_3$, internal Me_4Si) were recorded with a Perkin–Elmer R32 90-MHz spectrometer. G.l.c. was performed with a Perkin–Elmer F11 instrument equipped with flame-ionization detection and a column (50 ft) of SCOT Carbowax 20M. Peak areas were calculated with a Supergrator computing integrator.

*Reduction of 1,6-anhydro-2,4-di-*O*-toluene-*p*-sulphonyl-β-*D*-glucopyranose* (**1**) *with lithium triethylborohydride.* — To a solution of **1** (3.5 g, 7.5 mmol) in dry tetrahydrofuran (50 ml) under dry nitrogen and at 0° was added, dropwise with stirring, a solution of lithium triethylborohydride (45 mmol) in tetrahydrofuran during 2 h. After 18 h, water (7 ml) was added dropwise at 0° followed by a mixture of 3M sodium hydroxide (25 ml) and 30% hydrogen peroxide (20 ml). The solution was warmed to room temperature and stirred for 1 h. Dichloromethane (150 ml) was added, and the aqueous layer was saturated with potassium carbonate, separated, and then extracted continuously with dichloromethane for 10 h. The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was extracted with hot ether. Concentration of the extract yielded an oil (0.86 g) which was shown by g.l.c. to be 90% pure, and to contain **2** and **3** in the ratio 5.25:1.

To a solution of the mixture (0.78 g) in dry acetone (10 ml) at 0° was added diethyltrimethylsilylamine (0.29 g), and the solution was stirred for 45 min at 0°. G.l.c. then showed that the conversion **3**→**5** was complete. Water (10 ml) was added, the acetone was evaporated, and the aqueous solution was extracted with dichloromethane (10 ml) and then continuously with dichloromethane for 20 h. The extract was dried ($MgSO_4$) and concentrated to give 1,6-anhydro-2,4-dideoxy-β-D-*threo*-hexopyranose (**2**; 0.62 g, 80%), $[\alpha]_D^{25}$ −80° (*c* 1, water); lit.[2] $[\alpha]_D^{25}$ −81°. N.m.r.

data: δ 5.65 (s, 1 H, H-1), 4.52 (m, 1 H, H-5), 4.33 (d, 1 H, H-6*endo*), 4.04 (m, 1 H, H-3), 3.72 (m, 1 H, H-6*exo*), and 1.6–2.4 (m, 4 H, H-2*exo,endo*, H-4*exo,endo*).

Selective oxidation of the mixture **2** *and* **3**. — A solution of the mixture (0.13 g) in dichloromethane (2 ml) at 25° was slowly added to a stirred suspension of pyridinium chlorochromate (0.43 g) in dichloromethane (5 ml). After 1 h, the solvent was evaporated and the residue was extracted with ether. The extract was concentrated and the residue was eluted from silica gel (10 g) with benzene–ethanol (98:2) to give, first, 1,6-anhydro-2,4-dideoxy-β-D-*glycero*-hexopyranos-3-ulose[10] (**4**, 0.078 g), $[\alpha]_D^{25}$ −99° (*c* 3, chloroform); lit.[10] $[\alpha]_D$ −98°.

1,6-Anhydro-3,4-dideoxy-β-D-*threo*-hexopyranose (**3**, 0.011 g) was eluted in the later fractions. N.m.r. data: δ 5.27 (s, 1 H, H-1), 4.47 (m, 1 H, $w_{\frac{1}{2}h}$ ~9 Hz, H-5), 3.7–3.9 (m, 2 H, H-2*endo*,6*endo*), 3.55 (dd, 1 H, $J_{6endo,6exo}$ ~9, $J_{6exo,5}$ ~5 Hz, H-6*exo*), and 2.5–1.3 (m, 4 H, H-3*exo,endo*,4*exo,endo*).

A solution of **3** (0.13 g) in dichloromethane (2 ml) was slowly added to a stirred suspension of pyridinium chlorochromate (0.43 g) in dichloromethane (5 ml). After 24 h, the solvent was evaporated and the residue was extracted with ether. Concentration of the extract gave pure 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hexopyranos-2-ulose[2] (**6**; 0.104 g, 80%).

*1,6-Anhydro-3-*O*-(2-methoxyethoxymethyl)-2,4-di-*O*-toluene-*p*-sulphonyl-β-*D*-glucopyranose* (**10**). — To a solution of **2** (2.75 g) in dry acetonitrile (50 ml) was added triethyl(2-methoxyethoxymethyl)ammonium chloride (2.64 g). The solution was boiled under reflux for 48 h, and then cooled, poured into ice–water (300 ml), and extracted with dichloromethane (100 ml). The extract was washed with water, aqueous ammonium chloride, and water, dried ($MgSO_4$), and concentrated. The resulting oil (4.2 g) was eluted from silica gel (300 g) with light petroleum–ether–ethyl acetate (5:3.5:1.5). The later fractions contained **10** (1.94 g, 60%), m.p. 98.5–99.5°, $[\alpha]_D^{25}$ −33° (*c* 1, chloroform).

Anal. Calc. for $C_{24}H_{30}O_{11}S_2$: C, 51.60; H, 5.41; S, 11.48. Found: C, 51.77; H, 5.43; S, 11.66.

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REFERENCES

1 J. Jurczak, M. Chmielewski, and A. Zamojski, *Rocz. Chem.*, 52 (1978) 743–749.
2 J. Pecka, J. Staněk, Jr., and M. Černý, *Collect. Czech. Chem. Commun.*, 39 (1974) 1192–1209.
3 M. Černý, L. Kalvoda, and J. Pacak, *Collect. Czech. Chem. Commun.*, 33 (1967) 1143–1156.
4 S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, 41 (1976) 3064–3066.
5 I. Weiz, K. Felfoldi, and K. Kovacs, *Synthesis*, (1970) 26–27.
6 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, (1975) 2647–2650.
7 M. Černý, V. Gut, and J. Pacak, *Collect. Czech. Chem. Commun.*, 26 (1961) 2542–2550.
8 M. Černý and J. Pacak, *Collect. Czech. Chem. Commun.*, 26 (1961) 94–105.
9 J. Halbych, T. Trnka, and M. Černý, *Collect. Czech. Chem. Commun.*, 38 (1973) 2151–2166.
10 M. Černý, J. Pacak, and J. Staněk, *Carbohydr. Res.*, 15 (1970) 379–389.