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Note

A convenient synthesis of methyl 4,6-*O*-benzylidene-α- and β-D-allopyranosides

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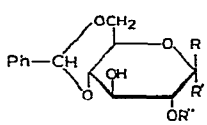
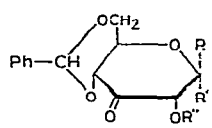
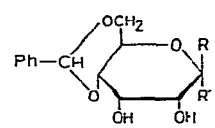
The sequential oxidation and reduction of suitably protected monosaccharide derivatives are useful for the synthesis of the epimers of the starting sugar derivatives[1–4]. Baker *et al.*[2] first synthesized methyl 4,6-*O*-benzylidene-α-D-allopyranoside *via* methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-allopyranoside obtained by sequential oxidation and reduction of methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside. In their procedure, however, it is necessary to remove the blocking tosyl ester group. This removal requires a prolonged treatment with lithium aluminum hydride and causes formation of by-products*. This communication describes a direct synthesis of methyl 4,6-*O*-benzylidene-α- and β-D-allopyranosides from mono-acylated derivatives of D-glucose by reduction with sodium borohydride, and the factors determining the stereoselectivity of the reduction are discussed.

Methyl 2-*O*-acetyl- and 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranosides[5] (**1** and **2**) were treated with dimethyl sulfoxide and acetic anhydride to afford the corresponding ketones[6,7] **4** and **5**. Reduction of these ketones with sodium borohydride in methanol–*N*,*N*-dimethylformamide, which is accompanied by cleavage of the acyl groups, gave methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**8**) in good yields with no by-product. The t.l.c. examination showed that the addition of sodium borohydride immediately causes cleavage of the acyl ester group, indicating that deacylation and reduction occurs simultaneously. The same product was obtained

1 R = H, R′ = OMe, R″ = Ac
2 R = H, R′ = OMe, R″ = Bz
3 R = OMe, R′ = H, R″ = Ac
4 R = H, R′ = OMe, R″ = Ac
5 R = H, R′ = OMe, R″ = Bz
6 R = H, R′ = OMe, R″ = H
7 R = OMe, R′ = H, R″ = Ac
8 R = H, R′ = OMe
9 R = OMe, R′ = H

*T.l.c. showed the presence of three components other than the starting material.

from the borohydride reduction of methyl 4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose[6] (**6**), which obtained by the dimethyl sulfoxide oxidation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside. These results suggest that the hydride ion, without regard to neighboring groups, attacks stereoselectively the carbonyl group at C-3 from an equatorial position to afford the axial hydroxyl group.

To obtain methyl 4,6-*O*-benzylidene-β-D-allopyranoside (**9**), methyl 2-*O*-acetyl-4,6-*O*-benzylidene-β-D-*ribo*-hexopyranosid-3-ulose (**7**), obtained by oxidation of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**3**), was similarly treated with sodium borohydride. However, it was found that the reduction of **7** yielded the *allo* and *gluco* epimers in a 1:1 ratio. After column chromatography, methyl 4,6-*O*-benzylidene-β-D-allopyranoside was obtained in 48% yield.

The present method allows a convenient synthesis of methyl 4,6-*O*-benzylidene-D-allopyranosides, although the yield of the β-D anomer is comparatively low because of formation of the *gluco* epimer. It is evident that the configuration of the methoxyl group at C-1 has a definite effect on the stereoselectivity of the borohydride reduction. The high stereoselectivity of the attack of the α-D-anomer by the hydride ion may be due to the axial methoxyl group which hinders an approach of the hydride ion from the axial position.

EXPERIMENTAL

General methods. — Melting points were determined on a Yanagimoto hot-stage microscope and are uncorrected. The optical rotations were measured with a Yanagimoto OR-20 polarimeter, and n.m.r. spectra were taken on a Hitachi–Perkin–Elmer 90 MHz instrument at 35° with tetramethylsilane as an internal standard. T.l.c. was carried out on silica gel G (Merck) with 4:1, v/v, benzene–acetone.

Methyl 4,6-O-*benzylidene*-α-D-*allopyranoside* (**8**). — *A.* To a solution of **4** (200 mg) in methanol (30 ml) and *N*,*N*-dimethylformamide (2 ml) was added sodium borohydride (400 mg). The solution was stirred for 35 min at room temperature, and then heated for 10 min under reflux to decompose the excess of sodium borohydride. After concentration, the syrupy residue was extracted with chloroform, and the extract washed with water until neutral, dried (Na_2SO_4), and evaporated. The resulting syrup was crystallized from ethanol–water to give **8** (168 mg, 90%) as dihydrate*, m.p. 60°, $[\alpha]_D^{30}$ +110.0° (*c* 0.9, *N*,*N*-dimethylformamide); n.m.r. data (dimethyl sulfoxide-d_6): τ 2.56 (s, 5 H, phenyl), 4.38 (s, 1 H, benzylic), 5.38 (d, 1 H, OH, *J* 4.6 Hz), 5.43 (d, 1 H, OH, *J* 9.5 Hz), 5.66 (d, 1 H, H-1, $J_{1,2}$ 5.1 Hz), 6.69 (s, 3 H, OMe).

Anal. Calc. for $C_{14}H_{18}O_6 \cdot 2H_2O$: C, 52.89; H, 6.97. Found: C, 52.64; H, 7.00.

Recrystallization twice from chloroform–petroleum ether gave fine needles of anhydrous **8**, m.p. 148–149°, $[\alpha]_D^{28}$ +126.0° (*c* 1, *N*,*N*-dimethylformamide); lit.[2]:

*Compound **8** prepared by the method of Baker *et al.*[2] is crystallized from ethanol and water to give crystals having m.p. 65 °C, and its i.r. and n.m.r. spectral properties are in good agreement with those of dihydrate obtained by the present method.

m.p. 175–177° (from ethanol–petroleum ether), $[\alpha]_D^{25}$ +117 ±2° (*N,N*-dimethylformamide).

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.70; H, 6.54.

The substancial difference between the observed melting points may be due to different crystalline forms, and the apparent discrepancy between the observed specific rotations to different temperatures of the measurement.

B. Compound **5** (280 mg) was treated with sodium borohydride (560 mg) as just described. The dihydrate of **8** was obtained in 55% yield (114 mg), m.p. 63°, $[\alpha]_D^{28}$ +121.6° (*c* 1.1, *N,N*-dimethylformamide).

C. A similar treatment of **6** (110 mg) with sodium borohydride (110 mg) gave **8** as dihydrate (41 mg, 30%), m.p. 62°, $[\alpha]_D^{30}$ +114.0° (*c* 0.5, *N,N*-dimethylformamide).

Oxidation of methyl 2-O-acetyl-4,6-O-benzylidene-β-D-glucopyranoside (**3**). — A solution of the 2-acetate[8] **3** (800 mg) in dimethyl sulfoxide (40 ml) and acetic anhydride (8 ml) was stirred for 24 hr at room temperature. The mixture was extracted with chloroform, and the extract washed with a saturated sodium hydrogen carbonate solution, water, and dried (Na_2SO_4) to give methyl 2-*O*-acetyl-4,6-*O*-benzylidene-β-D-*ribo*-hexopyranosid-3-ulose (**7**) (550 mg, 69%), m.p. 210–211°; $[\alpha]_D^{23}$ −95.0° (*c* 1, chloroform); i.r. data: ν_{max}^{KBr} 1760 (C=O), and 1748 cm^{-1} (C=O, ester); n.m.r. data (chloroform-*d*): τ 4.45 (s, 1 H, benzylic), 4.50 (q, 1 H, $J_{1,2}$ 8.0, $J_{2,4}$ 1.4 Hz, H-2), 5.38 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 6.44 (s, 3 H, OMe), and 7.82 (s, 3 H, OAc).

Anal. Calc. for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.86; H, 5.57.

Reduction of methyl 2-O-acetyl-4,6-O-benzylidene-β-D-ribo-hexopyranosid-3-ulose (**7**). — Compound **7** (200 mg) in *N,N*-dimethylformamide (2 ml) and methanol (30 ml) was treated with sodium borohydride (400 mg) as described for the α-D anomer. The resulting syrup was applied to a silicic acid column (30 g) and eluted stepwise with benzene–ethyl acetate (4:1 and 1:1, v/v). Methyl 4,6-*O*-benzylidene-β-D-allopyranoside (**9**) (85 mg, 48%) was first eluted, m.p. 176°; $[\alpha]_D^{16}$ −40.0° (*c* 0.8, chloroform); n.m.r. data (dimethyl sulfoxide-d_6): τ 4.40 (s, 1 H, benzylic), 4.94 (d, 1 H, *J* 3.9 Hz, OH), 5.03 (d, 1 H, *J* 6.5 Hz, OH), 5.53 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), and 6.62 (s, 3 H, OMe).

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.54; H, 6.52.

Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (78 mg, 45%) was next eluted, m.p. 209–211°, $[\alpha]_D^{24}$ −63.0° (*c* 1, chloroform); lit.[9]: m.p. 203–204°, $[\alpha]_D^{24}$ −62.4 ±2° (*c* 1.15, chloroform). The i.r. and n.m.r. spectra were in good agreement with those of an authentic sample.

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