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Note

Use of the benzyl group during Purdie methylation: a synthesis of 2-*O*-methyl-D-mannose

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The benzyl function is useful as a protecting group during Purdie methylation (methyl iodide, silver oxide) as it does not migrate under these conditions and it may be removed concurrently with other groups, such as benzylidene acetals, that are susceptible to hydrogenolysis. The *p*-tolyl-sulfonyl group, which does not migrate, has been used[1], but its direct removal is not simple, as epoxide formation or elimination may also occur.

The aim of this work was a useful synthesis of 2-*O*-methyl-D-mannose, which has previously been obtained by way of methyl 4,6-*O*-ethylidene-3-*O*-*p*-tolylsulfonyl-α-D-mannopyranoside[1], from 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose by using diazomethane-boron trifluoride[2], and from methyl 4,6-*O*-benzylidene-3-*O*-(2,6-dimethoxybenzoyl)-α-D-mannopyranoside[3]. The present synthesis is similar to the former ones, but the benzyl group is used in place of ester groups for protecting O-3. Removal of the *O*-benzyl and 4,6-*O*-benzylidene groups is effected in one step.

Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside, when treated with 1.1 mol of benzyl bromide and sodium hydride in dimethyl sulfoxide[4] gave, after column chromatography, methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (66%), methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (20%), and small amounts of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside and starting material. Benzylation was, therefore, selective at the equatorial 3-hydroxyl group, as in the esterification reactions[1]. Higher molar proportions of benzyl bromide gave more of the dibenzyl derivative.

Methylation of the 3-ether gave the syrupy 2-*O*-methyl derivative (80%), and hydrogenolysis of the latter yielded methyl 2-*O*-methyl-α-D-mannopyranoside, acid hydrolysis of which gave crystalline 2-*O*-methyl-D-mannose, characterized by conversion into D-*arabino*-hexulose phenylosazone.

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EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were determined for solutions in chloroform, unless stated otherwise, at ambient temperature within the concentration range of 0.6–1.0%. N.m.r. spectra were obtained with a Varian HA-60 instrument, with tetramethylsilane as the internal reference. Column chromatography was conducted with silica gel 60 (Merck) and 3:2 hexane–ethyl acetate.

Methyl 3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside. — Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[5] (10 g) was dissolved in dimethyl sulfoxide (50 ml) and added slowly under nitrogen to a stirred suspension of sodium hydride (10 g) in dimethyl sulfoxide (25 ml). Benzyl bromide (5.1 g, 1.1 mol equiv.) was added dropwise, and the mixture was vigorously stirred for 2 h at room temperature. It was then poured onto crushed ice (300 g), and the product was extracted with ether (3 × 100 ml). The ether extract was washed with ice-cold water, dried, and evaporated to a syrup (12.5 h) that was resolved on a column of silica gel (300 g). The main fraction (R_F 0.58), on crystallization from methanol, gave methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (7.6 g, 66% based on diol reacted), m.p. 68–69°, $[\alpha]_D$ +67°; n.m.r. data ($CDCl_3$): τ 2.65 (m, 10 H, Ph), 4.46 (1 H, s, PhC*H*), 4.56 (1 H, d, *J* 4 Hz, H-3), 5.04–5.12 (3 H, m, CH_2-benzyl plus H-2), 5.26 (1 H, d, $J_{1,2}$ 2 Hz, H-1), 6.68 (3 H, s, CH_3O), and 7.72 (1 H, s, OH); *m/e* M^+ 372.

Anal. Calc. for $C_{21}H_{24}O_6$: C, 67.7; H, 6.5; OCH_3, 8.3. Found: C, 67.5; H, 6.2; OCH_3, 8.7.

The second main fraction (R_F 0.86) was the 2,3-diether, obtained as a glass (2.3 g), $[\alpha]_D$ +8.8°. The i.r. spectrum showed no absorption in the hydroxyl region; the methoxyl content corresponded to the molecular formula $C_{28}H_{30}O_6$.

The third, minor fraction (R_F 0.42), obtained as a syrup, $[\alpha]_D$ +4.2°, was not investigated in detail, but was probably methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside; lit.[7] m.p. 42–44°, $[\alpha]_D$ +2° (*c* 1, chloroform).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-mannopyranoside. — The benzylated compound (2 g) was dissolved in boiling methyl iodide (20 ml), and silver oxide (4 g, prepared by the method of Helferich and Klein[6]) was added during 5 h with stirring. Stirring and heating was continued until all starting material had reacted (19 h). The silver residues were filtered off and washed with chloroform, and the organic solution was evaporated to dryness. The residue (1.65 g, 80%), $[\alpha]_D$ +24.6°, failed to crystallize, even after purification by column chromatography; n.m.r. data ($CDCl_3$): τ 2.68 (10 H, m, Ph), 4.42 (1 H, s, PhC*H*), 4.55 (1 H, d, *J* 4 Hz, H-3), 5.06–5.18 (4 H, CH_2-benzyl protons, plus H-1 and H-2), and 6.66 (6 H, 2 CH_3O).

Anal. Calc. for $C_{22}H_{26}O_6$. C, 68.4; H, 6.8; OCH_3, 16.1. Found: C, 68.2; H, 6.9; OCH_3, 15.6.

Methyl 2-O-methyl-α-D-mannopyranoside. — Catalytic hydrogenolysis of the methyl ether (1.0 g) gave a syrup that was homogeneous by t.l.c. Purification by column chromatography (silica gel, 70 g, 10:1 chloroform–methanol) afforded a chromatographically homogeneous syrup (0.46 g, 85%), $[\alpha]_D$ +48.5° (lit.[3] $[\alpha]_D$ +51° in chloroform); n.m.r. data ($CDCl_3$): τ 5.27 (1 H, d, $J_{1,2}$ 2 Hz, H-1), 6.58 (3 H, s, H-2, CH_3O), 6.65 (3 H, CH_3O), and 7.56 (3 H, OH).

2-O-Methyl-α-D-mannose. — Methyl 2-*O*-methyl-α-D-mannopyranoside (0.35 g) was hydrolyzed with hydrochloric acid (5 ml, 0.5M) for 6 h at 100° (to constant rotation). The solution was diluted with water (5 ml), neutralized with silver carbonate and the mixture was filtered, hydrogen sulfide was passed through the filtrate, and the solution was evaporated. The residue was extracted with boiling ethanol (3 × 20 ml), and the combined extracts were filtered. Concentration yielded a chromatographically homogeneous syrup (0.22 g) which, on crystallisation from ethanol (in a desiccator containing calcium chloride), afforded the free sugar (0.15 g, 47%), m.p. 137–138°, $[\alpha]_D$ +14.2 → +4.8° (24 h, *c* 0.7, water) in accord with reported values[3]. M_G 0.28. The n.m.r. data indicated a mixture of α and β anomers: τ 4.46 (d, $J_{1,2}$ 2 Hz, H-1α); 5.18 (d, $J_{1,2}$ 4 Hz, H-1β), and 6.64 (3 H, s, CH_3O).

Anal. Calc. for $C_7H_{14}O_6$: C, 43.3; H, 7.2; OCH_3, 16.0. Found: C, 43.2, H, 7.2; OCH_3, 15.6.

The 2-*O*-methyl-D-mannose was characterized by conversion into D-*arabino*-hexulose phenylosazone, m.p. 205–206°, $[\alpha]_D$ −63 → 32 (24 h, *c* 0.52, 3:2 ethanol–pyridine), in accord with reported values[3].

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