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Note

Hydrogenolysis of some methyl 4,6-*O*-benzylidene-α-D-mannopyranoside derivatives: unambiguous synthesis of the 2,4- and 3,4-dimethyl ethers of methyl α-D-mannopyranoside

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The reductive ring-opening[1–7] of benzylidene acetals to monobenzyl ethers is a useful synthetic reaction. The benzyl group, readily removed by catalytic hydrogenolysis, may be utilized as a protecting group in a wide variety of synthetic processes. The previous reports were related to the reductive cleavage of benzylidene acetals of fully protected hexopyranosides, and the cleavage of the acetals of hexopyranosides having isolated hydroxyl groups has received little attention. We now describe the preparation of methyl 2,4- and 3,4-di-*O*-methyl-α-D-mannopyranoside *via* hydrogenolysis of methyl 2- and 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside.

Application of hydrogenolytic ring-cleavage of the 4,6-benzylidene acetals to hexopyranosides has been reported mainly by two research groups. Nánási *et al.*[2–5] described reduction using lithium aluminum hydride–aluminum chloride, to give the 4-benzyl ethers with the free hydroxyl group on C-6, whereas Garegg *et al.*[6,7] reported the reverse stereoselectivity, giving the 6-benzyl ethers with the free hydroxyl group on C-4, on reduction of the 4,6-benzylidene acetals with sodium cyanoborohydride–hydrogen chloride. In order to prepare the 2,4- and 3,4-dimethyl ethers of methyl α-D-mannopyranoside, HO-6 should be protected by the benzyl group, and therefore, we selected the cyanoborohydride reduction giving the 6-benzyl ether.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) was hydrogenolyzed with sodium cyanoborohydride–hydrogen chloride in oxolane (tetrahydrofuran) at 0°, to give methyl 3,6-di-*O*-benzyl-α-D-mannopyranoside (**5**), which was identical with an authentic sample prepared from methyl *exo*-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**4**) according to the procedure of Garegg *et*

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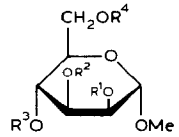

	R^1	R^2	R^3	R^4
1	H	Bzl	—PhCH—	
2	Bzl	H	—PhCH—	
3	Bzl	Bz	—PhCH—	
4	—PhCH—		—PhCH—	
5	H	Bzl	H	Bzl
6	Me	Bzl	Me	Bzl
7	Me	H	Me	H
8	Bzl	H	Bzl	H
9	Bzl	H	H	Bzl
10	Bzl	Bz	Bz	Bzl
11	Bzl	Me	Me	Bzl
12	H	Me	Me	H

Bz = PhCO

Bzl = $PhCH_2$

al.[6,7]. Similar treatment of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**2**) with sodium cyanoborohydride gave a mixture which was fractionated by column chromatography on silica gel, to afford methyl 2,4- (**8**; ref. 8) and 2,6-di-*O*-benzyl-α-D-mannopyranoside (**9**) in 30 and 32% yield, respectively.

The position of the benzyl groups in **9** was determined by ^{1}H-n.m.r. spectroscopy of its dibenzoate **10**. The signals of H-3 and H-4 respectively appeared as a one-proton quartet and a one-proton triplet at lower field than the other ring-proton resonances, because of the deshielding effect, on the same methine protons attached to C-3 and C-4, of the two benzoyl groups. On the other hand, hydrogenolysis of methyl 3-*O*-benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**3**) with sodium cyanoborohydride, followed by *O*-debenzoylation, gave only the 2,6-dibenzyl ether **9**, which was also prepared by cyanoborohydride reduction of methyl *endo*-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (**4**).

The foregoing results indicate that the direction of the reductive opening of the 2,3-benzylidene acetal with sodium cyanoborohydride–hydrogen chloride is similar to that with lithium aluminum hydride–aluminum chloride[4]. This observation agrees with a suggestion by Garegg *et al.*[7]. In the opening of the 4,6-benzylidene acetals, the stereoselectivity of the cleavage by sodium cyanoborohydride reduction is quite different from that by lithium aluminum hydride reduction[1–5], but the direction of opening with sodium cyanoborohydride seems to depend on the steric requirements of the substituents on C-3. A similar dependence on the C-3

substituents was reported by Nánási *et al.* for the lithium aluminum hydride reduction of 4,6-*O*-benzylidene-D-galacto-[2] and -gluco-pyranoside[5].

The 3,6-dibenzyl ether **5** resulting from cleavage of the acetals was methylated with methyl iodide, to give methyl 3,6-di-*O*-benzyl-2,4-di-*O*-methyl-α-D-mannopyranoside (**6**), which, on debenzylation with palladium-on-charcoal, gave methyl 2,4-di-*O*-methyl-α-D-mannopyranoside (**7**). Methyl 3,4-di-*O*-methyl-α-D-mannopyranoside (**12**) was similarly prepared from methyl 2,6-di-*O*-benzyl-3,4-di-*O*-methyl-α-D-mannopyranoside (**11**) *via* methylation of the 2,6-dibenzyl ether **9**.

EXPERIMENTAL

General. — Optical rotations were measured with a Jasco DIP-181 digital polarimeter. ^{1}H-N.m.r. spectra were recorded at 60 MHz with a Hitachi R-24 spectrometer for solutions in $CDCl_3$ (internal Me_4Si) or in D_2O (internal sodium 4,4-dimethyl-4-silapentane-1-sulfonate).

Methyl 3,6-di-O-benzyl-α-D-mannopyranoside (**5**). — (*a*) *From methyl* exo-*2,3:4,6-di-O-benzylidene-α-D-mannopyranoside* (**4**). Diethyl ether presaturated with hydrogen chloride was added dropwise during 3 h at 0° to a stirred suspension of **4** (ref. 9; 1.5 g) and sodium cyanoborohydride (10.2 g, 40 mol. equiv.) in dry oxolane (110 mL) containing 3A molecular sieves (1.5 g). After 3 h, t.l.c. indicated the presence of one preponderant component. The mixture was diluted with chloroform, shaken with saturated sodium hydrogencarbonate, and filtered. The filtrate was washed with water, dried (sodium sulfate), and evaporated to a syrup. T.l.c. with 2:1 benzene–acetone showed the presence of one major component (R_F 0.65) and a trace of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (R_F 0.35). Purification by chromatography on a column of silica gel gave **5** (752 mg, 50%); $[\alpha]_D^{26}$ +24.9° (*c* 1.1, chloroform); lit.[7] $[\alpha]_D^{22}$ +25° (*c* 1.3, chloroform).

(*b*) *From methyl 3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside* (**1**). Hydrogenolysis of **1** (ref. 10; 133 mg) with sodium cyanoborohydride (449 mg, 20 mol. equiv.), as described in (*a*), gave **5** (81 mg, 61%).

Methyl 2,6-di-O-benzyl-α-D-mannopyranoside (**9**). — (*a*) *From methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside* (**2**). Compound **2** (ref. 10; 100 mg) was reduced with sodium cyanoborohydride (337 mg, 20 mol. equiv.) as described for the preparation of **5**. The resultant syrup was fractionated on silica gel with 4:1 benzene–acetone. The first fraction gave the 2,4-dibenzyl ether **8** (30 mg, 30%); $[\alpha]_D^{24}$ +23.7° (*c* 0.85, chloroform); lit.[8] $[\alpha]_D$ +23.5° (*c* 0.77, chloroform).

The second fraction afforded compound **9** (32 mg, 32%) as a syrup, $[\alpha]_D^{26}$ −4.9° (*c* 1.0, chloroform).

Anal. Calc. for $C_{21}H_{26}O_6 \cdot 0.5\ H_2O$: C, 65.78; H, 7.09. Found: C, 65.88; H, 7.06.

The 2,6-dibenzyl ether **9** (95 mg) was treated with benzoyl chloride (0.1 mL) in pyridine, to give methyl 3,4-di-*O*-benzoyl-2,6-di-*O*-benzyl-α-D-mannopyranoside (**10**) as a syrup (146 mg, 99%); $[\alpha]_D^{25}$ −19.2° (*c* 0.6, chloroform); ^{1}H-

n.m.r. (in $CDCl_3$): δ 5.97 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 5.43 (q, 1 H, $J_{2,3}$ 3 Hz, H-3), 4.83 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 4.62 and 4.52 (2 s, 4 H, 2 PhCH_2), and 3.45 (s, 3 H, CH_3O).

(*b*) *From methyl 3-*O*-benzoyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-*D*-mannopyranoside* (**3**). Cyanoborohydride reduction of **3** (ref. 10; 149 mg) as described in (*a*), followed by *O*-debenzoylation, yielded **9** (84 mg, 66%).

(*c*) *From methyl* endo*-2,3:4,6-di-*O*-benzylidene-α-*D*-mannopyranoside* (**4**). Hydrogenolysis of **4** (ref. 9; 500 mg) with sodium cyanoborohydride (3.4 g, 40 mol. equiv.) afforded **9** (323 mg, 64%).

*Methyl 2,4-di-*O*-methyl-α-*D*-mannopyranoside* (**7**). — Compound **5** (520 mg) was methylated by treatment with methyl iodide (0.5 mL) in *N,N*-dimethylformamide (2 mL) in the presence of barium oxide (670 mg) and barium hydroxide octahydrate (265 mg). The usual processing, followed by chromatography on a column of silica gel, gave methyl 3,6-di-*O*-benzyl-2,4-di-*O*-methyl-α-D-mannopyranoside (**6**) (522 mg, 93%); a syrup; $[\alpha]_D^{19}$ +57.9° (*c* 0.78, chloroform); ^{1}H-n.m.r. (in $CDCl_3$): δ 7.31 (m, 10 H, 2 Ph), 5.08 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.68 and 4.62 (2 s, 4 H, 2 PhCH_2), and 3.45, 3.43, and 3.32 (3 s, 9 H, 3 CH_3O).

To a solution of compound **6** (102 mg) in glacial acetic acid (5 mL) was added 10% palladium-on-charcoal (102 mg), and the mixture was stirred under hydrogen for 22 h at room temperature. Removal of the catalyst, and evaporation of the solvent, gave syrupy compound **7** (51 mg, 91%); $[\alpha]_D^{32}$ +48.1° (*c* 2.0, water); lit.[11] $[\alpha]_D^{25}$ +51° (*c* 1.1, water); ^{1}H-n.m.r. (in $CDCl_3$): δ 4.76 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), and 3.55, 3.47, and 3.34 (3 s, 9 H, 3 CH_3O); (in D_2O): δ 4.83 (d, $J_{1,2}$ 2 Hz, H-1), and 3.48, 3.42, and 3.37 (3 s, 9 H, 3 CH_3O); lit.[11] ^{1}H-n.m.r. spectrum ($CDCl_3$): δ 3.55, 3.46, and 3.33 (3 s, 9 H, 3 CH_3O).

*Methyl 3,4-di-*O*-methyl-α-*D*-mannopyranoside* (**12**). — Methylation of **9** (81 mg) with methyl iodide (0.1 mL), as described for the preparation of **6**, yielded methyl 2,6-di-*O*-benzyl-3,4-di-*O*-methyl-α-D-mannopyranoside (**11**) (78 mg, 90%); a syrup; $[\alpha]_D^{18}$ +15.3° (*c* 3.9, chloroform); ^{1}H-n.m.r. (in $CDCl_3$): δ 7.30 (m, 10 H, 2 Ph), 4.8–4.4 (m, 5 H, H-1, 2 PhCH_2), and 3.52, 3.43, and 3.37 (3 s, 9 H, 3 CH_3O).

O-Debenzylation of **11** (78 mg) by hydrogenolysis in the presence of palladium-on-charcoal gave syrupy compound **12** (32 mg, 74%); $[\alpha]_D^{31}$ +75.6° (*c* 1.6, chloroform), +65.0° (*c* 1.4, ethanol); lit.[12] $[\alpha]_D^{25}$ +86° (*c* 1.4, chloroform); ^{1}H-n.m.r. (in $CDCl_3$): δ 4.70 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), and 3.50, 3.43, and 3.37 (3 s, 9 H, 3 CH_3O); (in D_2O): δ 4.73 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), and 3.52, 3.43, and 3.38 (3 s, 9 H, 3 CH_3O); lit.[12] ^{1}H-n.m.r. spectrum ($CDCl_3$): δ 4.73 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), and 3.50, 3.44, and 3.36 (3 s, 9 H, 3 CH_3O).

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