Carbohydrate Research, 59 (1977) 268–273

Note

Synthesis of β-D-mannopyranosides

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(Received November 8th, 1976; accepted for publication in revised form, February 21st, 1977)

Previous reports[1] from this laboratory described the synthesis of some α-D-mannopyranosides. The less readily available β-D-mannopyranosides have been prepared[2] by using 4,6-di-*O*-acetyl-α-D-mannopyranosyl bromide 2,3-carbonate and by the stereoreduction of methyl β-D-*arabino*-hexopyranosidulose[3,4]. We now report the synthesis of some synthetically useful β-D-mannopyranosides from methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**2**) and the 3-*O*-benzyl (**6**) and 3-*O*-methyl (**10**) derivatives of benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside, and an improved procedure for the preparation of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside[5].

Methyl 3-*O*-benzyl-β-D-glucopyranoside[6] was converted into methyl 2-*O*-acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**1**, 64%) by condensation with benzal chloride in pyridine at reflux temperature[7] and subsequent acetylation. Deacetylation of **1** afforded methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**2**, 90%). Treatment of 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide[6] with benzyl alcohol and silver oxide yielded crystalline benzyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranoside (**3**, 61%). Deacetylation of **3** afforded crystalline benzyl 3-*O*-benzyl-β-D-glucopyranoside (**4**, 88%), which was converted into benzyl 2-*O*-acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**5**, 56%) by condensation with benzal chloride in pyridine followed by acetylation. Deacetylation of **5** yielded benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**6**, 93%).

In an analogous manner, crystalline benzyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**10**, 36%) was prepared from 2,4,6-tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranosyl bromide[8].

Oxidation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside with methyl sulphoxide–phosphorus pentoxide[9] gave crystalline methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-*arabino*-hexopyranosid-2-ulose (**11**, 50%), and subsequent reduction with sodium borohydride in methanol–*N*,*N*-dimethylformamide[9,10] gave a product mixture from which methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside[11] (**12**, 57%) was isolated by chromatography.

Analogous oxidation and reduction procedures applied to **6** and **10** gave the corresponding, crystalline carbonyl compounds **13** (81%) and **15** (54%), and the

crystalline 3-*O*-benzyl (**14**, 65%) and 3-*O*-methyl (**16**, 70%) derivatives of benzyl 4,6-*O*-benzylidene-β-D-mannopyranoside.

The stereospecificity of the reduction of **11**, **13**, and **15** accords with expectations[12].

Work on the synthesis of (1→2)-linked oligosaccharides from the above glycosides is in progress.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. Solutions were concentrated under diminished pressure below 50°. T.l.c. was performed on Silica gel F-254 (Merck) with benzene–methanol (96:4–9:1), and detection with ferric hydroxamate or charring with sulphuric acid. Column chromatography was carried out on silica gel (Grace, mesh 50–100). N.m.r. spectra were measured with a HA-100 spectrometer, and optical rotations with a Perkin–Elmer Model-241 polarimeter.

Methyl 2-O-acetyl-3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside (**1**). — A solution of methyl 3-*O*-benzyl-β-D-glucopyranoside[6] (9 g) in dry pyridine (100 ml) and benzal chloride (8 ml) was boiled under reflux[7] for 8.5 h. After cooling to room temperature, acetic anhydride (25 ml) was added and the mixture was stored overnight. Excess of water was added, the mixture extracted with benzene, and the extract washed with ice-cold M sulphuric acid, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated. T.l.c. of the syrupy residue showed two products, and elution of the mixture from a column (25 × 4 cm) of silica gel with benzene followed by ether–benzene (2:98) gave **1** (8.6 g), m.p. 128–129° (from ethanol), $[\alpha]_D$ −20° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): τ 2.68–3.02 (m, 10 H, 2 Ph), 4.62 (s, 1 H, PhC*H*), 5.16 (t, 1 H, H-2), 5.28 and 5.48 ($J_{H,H}$ 12 Hz, PhCH_2O), 5.78 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 5.70–5.86 (m, 1 H, H-5), 6.20–6.76 (m, 4 H, H-3,4,6,6'), 6.64 (s, 3 H, OMe), and 8.06 (3 H, AcO).

Anal. Calc. for $C_{23}H_{26}O_7$: C, 66.67; H, 6.28. Found: C, 66.48; H, 6.41.

Methyl 3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside (**2**). — A solution of **1** (500 mg) in methanol (6 ml) was treated with 0.1M methanolic sodium methoxide (1.5 ml) for 5 h at room temperature. Cations were removed with Amberlite IR-120(H^+) resin, and the solution was concentrated to a syrup (150 mg) which crystallised from ethanol to give **2**, m.p. 182–183°, $[\alpha]_D$ −51° (*c* 0.86, chloroform).

Anal. Calc. for $C_{21}H_{24}O_6$: Calc. C, 67.74; H, 6.45. Found: C, 67.42; H, 6.48.

Benzyl 2,4,6-tri-O-acetyl-3-O-benzyl-β-D-glucopyranoside (**3**). — To a solution of 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide[6] (syrup, 7.5 g) in dry ether (30 ml), benzyl alcohol (30 ml), silver oxide (2.5 g), and Drierite (2.5 g) were added[13]. The mixture was stirred in the dark for 18 h at room temperature, then filtered through Celite, and concentrated, with the repeated addition of water, to give a syrup that crystallised from ethanol to yield **3** (5.1 g), m.p. 102–104°, $[\alpha]_D$ −55.5° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): τ 2.6–3.2 (10 H, 2 Ph), 4.92–5.12 (bm,

H-2,4), 5.24 and 5.53 (dd, 2 H, $J_{H,H}$ 12 Hz, PhCH_2O-1), 5.54 (s, 2 H, PhCH_2O-3), 5.66 (d, $J_{1,2}$ 8 Hz, H-1), 5.84–5.98 (bs, H-6,6'), and 7.98–8.10 (9 H, 3 AcO).

Anal. Calc. for $C_{26}H_{30}O_9$: C, 64.20; H, 6.17. Found: C, 64.64; H, 6.21.

Benzyl 3-O-benzyl-β-D-glucopyranoside (**4**). — Deacetylation of **3** (2 g), as described above for **2**, gave **4** (1.5 g), m.p. 88.5–90° (from isopropyl ether–ethanol), $[\alpha]_D$ −67° (*c* 0.89, chloroform).

Anal. Calc. for $C_{20}H_{24}O_6$: C, 66.67; H, 6.67. Found: C, 66.53; H, 6.44.

Benzyl 2-O-acetyl-3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside (**5**). — A solution of **4** (9 g) in dry pyridine (100 ml) and benzal chloride (10 ml) was boiled under reflux for 8 h. The mixture was acetylated and worked up as described above for **1**. T.l.c. of the crude crystalline product showed one major and two minor components, and elution from a column (40 × 2.5 cm) of silica gel, with benzene, yielded **5** (6 g, 53%), m.p. 150°, $[\alpha]_D$ −49° (*c* 1, chloroform).

Anal. Calc. for $C_{29}H_{30}O_7$: C, 71.02; H, 6.12. Found: C, 71.13; H, 6.05.

Benzyl 3-O-benzyl-4,6-O-benzylidene-β-D-glucopyranoside (**6**). — Deacetylation of **5** (5.9 g), as described above for **2**, gave **6** (5 g, 90%), m.p. 130–132° (from ethanol), $[\alpha]_D$ −64° (*c* 1, chloroform).

Anal. Calc. for $C_{27}H_{28}O_6$: C, 72.32; H, 6.25. Found: C, 72.20; H, 6.36.

Benzyl 3-O-methyl-β-D-glucopyranoside (**8**). — A solution of benzyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-β-D-glucopyranoside (**7**, 18 g) in dry methanol (180 ml) was deacetylated, as described above, and the product was crystallised from isopropyl ether–ethanol to give **8** (9.8 g), m.p. 111–113°, $[\alpha]_D$ −66° (*c* 1, ethanol); lit.[1b] $[\alpha]_D$ −58° (ethanol).

Anal. Calc. for $C_{14}H_{20}O_6$: C, 59.15; H, 7.04. Found: C, 58.98; H, 6.91.

Benzyl 2-O-acetyl-4,6-O-benzylidene-3-O-methyl-β-D-glucopyranoside (**9**). — A solution of **8** in dry pyridine (100 ml) and benzal chloride (6 ml) was boiled under reflux for 8.5 h. The mixture was acetylated and worked up as described above for **1**. T.l.c. of the crystalline product showed three components, and elution from a column (24 × 4 cm) of silica gel with benzene gave **9** (5.5 g), m.p. 158–160°, $[\alpha]_D$ −95° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): τ 2.7–3.1 (10 H, 2 Ph), 4.66 (s, 1 H, PhC*H*), 5.16 (t, 1 H, $J_{1,2} = J_{2,3} = 8$ Hz, H-2), 5.30 and 5.58 (dd, 2 H, $J_{H,H}$ 12 Hz, PhCH_2O), 5.64 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 5.68–5.90 (dd, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 5, $J_{5,6'}$ <1 Hz, H-5), 6.2–6.7 (m, 4 H, H-3,4,6,6'), 6.62 (s, 3 H, OMe), and 8.03 (s, 3 H, AcO).

Anal. Calc. for $C_{23}H_{26}O_7$: C, 66.67; H, 6.28. Found: C, 66.56; H, 6.55.

Benzyl 4,6-O-benzylidene-3-O-methyl-β-D-glucopyranoside (**10**). — Deacetylation of **9** (5.2 g), as described above for **2**, gave **10** (4 g), m.p. 128–130° (from ethanol), $[\alpha]_D$ −74° (*c* 0.95, chloroform).

Anal. Calc. for $C_{21}H_{24}O_6$: C, 67.74; H, 6.45. Found: C, 67.75; H, 6.24.

Methyl 2-O-acetyl-4,6-O-benzylidene-3-O-methyl-β-D-glucopyranoside. — A solution of methyl 3-*O*-methyl-β-D-glucopyranoside[14] (9 g) in dry pyridine (100 ml) and benzal chloride (6 ml) was boiled under reflux for 8.5 h. The mixture was acetylated and worked up as described above for **1**. T.l.c. of the product showed three components, and elution from a column (21 × 3.5 cm) of silica gel with benzene gave

the title compound (3.4 g, 24%), m.p. 130–132° (from ethanol), $[\alpha]_D$ −68° (*c* 1.1, chloroform). N.m.r. data: τ 2.7–3.1 (5 H, Ph), 4.68 (1 H, PhC*H*), 5.24 (t, 1 H, $J_{1,2} = J_{2,3} = 8$ Hz, H-2), 5.64–5.9 (m, 2 H, H-1,5; d for H-1 distinguishable at τ 5.74, $J_{1,2}$ 8 Hz), 6.2–6.8 (m, 10 H, H-3,4,6,6′, 2 MeO), and 7.98 (3 H, AcO).

Anal. Calc. for $C_{17}H_{22}O_7$: C, 60.36; H, 6.51. Found: C, 60.51; H, 6.63.

Methyl 4,6-O-benzylidene-3-O-methyl-β-D-glucopyranoside. — Deacetylation of the foregoing compound (3.3 g), as described for **2**, and crystallisation of the product from ethanol gave the title compound (2.5 g, 86%), m.p. 165–170°, $[\alpha]_D$ −51.5° (chloroform); lit.[5,14] m.p. 174°, $[\alpha]_D$ −50°.

Methyl 3-O-benzyl-4,6-O-benzylidene-β-D-arabino-hexopyranosid-2-ulose (**11**). — To a solution of **2** (1.2 g) in *N*,*N*-dimethylformamide (22 ml), methyl sulphoxide (11 ml) and phosphorus pentoxide (1.2 g) were added. After stirring for 26 h at 40°, the mixture was extracted with chloroform, and the extract washed with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated to a small volume. Addition of cold ethanol yielded **11** (600 mg, 50%) which, when recrystallised from 1:1 isopropyl ether–acetone, had m.p. 175–178°, $[\alpha]_D$ −81° (*c* 1, chloroform), ν_{max} 1753 (strong, C=O) and 3600 cm^{-1} (v. weak, OH). N.m.r. data ($CDCl_3$): τ 2.52–2.84 (m, 10 H, 2 Ph), 4.50 (s, 1 H, PhC*H*), 5.08 and 5.32 ($J_{H,H}$ 12 Hz, PhCH_2O), 5.30 (s, 1 H, H-1), 5.52–6.32 (m, 5 H, H-3,4,5,6,6′), and 6.46 (s, 3 H, OMe).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.11; H, 5.95. Found: C, 67.93; H, 6.09.

Methyl 3-O-benzyl-4,6-O-benzylidene-β-D-mannopyranoside (**12**). — To a solution of **11** (350 mg) in methanol (55 ml) and *N*,*N*-dimethylformamide (7 ml), sodium borohydride (700 mg) was added. After stirring for 35 min at room temperature, the solution was heated for 10 min at ~95° to decompose excess of sodium borohydride, concentrated, and extracted with chloroform, and the extract was worked up in the usual manner. T.l.c. of the syrupy product revealed a major and a minor component. The mixture was eluted from a column (24 × 2 cm) of silica gel (100-ml fractions).

Ether–benzene (5:95) (fractions 1–4) gave **2** (12 mg), and fractions 5–8 contained a mixture of **2** and **12**. Fractions 9–10, eluted with ether–benzene (1:9), contained **2** and a trace of **12**.

Elution with ether–benzene (1:9) (fractions 11–24), followed by ether–benzene (15:85) (fractions 25–32) and ether–benzene (1:4) (fractions 33–40), gave **12** (200 mg), which crystallised from ethanol and had m.p. 119–120°, $[\alpha]_D$ −33° (*c* 0.89, chloroform); lit.[11] m.p. 119–120°, $[\alpha]_D$ −32° (chloroform).

3-O-Benzyl-D-mannose. — Compound **12** (90 mg) was hydrolysed with 0.35M sulphuric acid (10 ml) for 6 h at 100°. The hydrolysate was neutralised (barium carbonate) and centrifuged, and the supernatant solution was concentrated to dryness. Concentration of an ethanol extract of the residue yielded the syrupy title compound (30 mg), $[\alpha]_D$ −16° (equil.; *c* 0.99, chloroform), R_{GLC} 2.14, R_F 0.80 (p.c., 1-butanol–pyridine–water, 6:4:3); M_G 0.44 (*cf.* Ref. 11).

Benzyl 3-O-benzyl-4,6-O-benzylidene-β-D-arabino-hexopyranosid-2-ulose (**13**). — Compound **6** (250 mg) was oxidised, as described above for **2**, to give **13** (200 mg), m.p. 176–178.5° (from 1:1 isopropyl ether–acetone), $[\alpha]_D$ −104° (*c* 1, chloroform), ν_{max} 1760 (strong, C=O) and 3600 cm^{-1} (weak, HO). N.m.r. data ($CDCl_3$): τ 2.62–2.98 (m, 15 H, 3 Ph), 4.49 (s, 1 H, PhC*H*), 5.06–5.46 (4 H, 4 overlapping d, $J_{H,H}$ 12 Hz, 2 PhCH_2O), 5.28 (s, 1 H, H-1), and 5.54–6.74 (m, 5 H, H-3,4,5,6,6′).

Anal. Calc. for $C_{27}H_{26}O_6$: C, 72.65; H, 5.83. Found: C, 72.18; H, 6.04.

Benzyl 3-O-benzyl-4,6-O-benzylidene-β-D-mannopyranoside (**14**). — Compound **13** (200 mg) was reduced as described above for **11**. The product mixture was eluted from a column (23 × 2 cm) of silica gel (100-ml fractions). Elution with ether–benzene (5:95) (fractions 1–3) gave benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (10 mg). Elution with ether–benzene (5:95) (fractions 4–9) gave a *gluco–manno* mixture.

Fractions 10–15 (eluted with ether–benzene, 1:9), 16–21 (eluted with ether–benzene, 15:85), and 22–27 (eluted with ether–benzene, 1:4) gave **14** (130 mg), m.p. 150–152° (from ethanol), $[\alpha]_D$ −70° (*c* 0.93, chloroform). N.m.r. data ($CDCl_3$): τ 2.42–2.78 (m, 15 H, 3 Ph), 4.39 (s, 1 H, PhC*H*), 5.0–5.40 (4 H, 2 overlapping d of $J_{H,H}$ 12 Hz, at 5.06 and 5.34, 2 PhCH_2O), 5.48 (d, 1 H, $J_{1,2}$ <1 Hz, H-1), 5.60–6.80 (m, 6 H, H-2,3,4,5,6,6′), and 7.40 (bs, 1 H, O*H*),

Anal. Calc. for $C_{27}H_{28}O_6$: C, 72.32; H, 6.25. Found: C, 72.02; H, 6.42.

Benzyl 4,6-O-benzylidene-3-O-methyl-β-D-arabino-hexopyranosid-2-ulose (**15**). — Compound **10** (3 g) was oxidised, as described above for **2**, to give **15** (1.5 g), m.p. 168–169° (from isopropyl ether–acetone, 1:1), $[\alpha]_D$ −104° (*c* 1, chloroform), ν_{max} 1756 (strong, C=O) and 3600 cm^{-1} (weak, HO). N.m.r. data ($CDCl_3$): τ 2.64–3.0 (m, 10 H, 2 Ph), 3.60 (s, 1 H, PhC*H*), 5.16 and 5.42 (4 H, $J_{H,H}$ 12 Hz, PhCH_2O), 5.61 (s, 1 H, H-1), 5.64–5.88 (m, 1 H, H-5), and 6.1–6.8 (m, 7 H, H-3,4,6,6′, MeO).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.11; H, 5.95. Found: C, 67.79; H, 5.89.

Benzyl 4,6-O-benzylidene-3-O-methyl-β-D-mannopyranoside (**16**). — Compound **15** (1.5 g) was reduced as described above for **11**. The product mixture was eluted from a column (22 × 2.5 cm) of silica gel (100-ml fractions). Elution with benzene (fractions 1–6) and ether–benzene (2:98) (fractions 7–10) gave the *gluco* epimer and a *gluco–manno* mixture.

Fractions 11–18 (eluted with ether–benzene, 2:98), 19–26 (eluted with ether–benzene, 5:95), and 27–33 (eluted with ether–benzene, 1:9) gave **16** (1.1 g), m.p. 113–115° (from ethanol), $[\alpha]_D$ −107° (*c* 1.25, chloroform). N.m.r. data ($CDCl_3$): τ 2.46–2.82 (m, 10 H, 2 Ph), 4.48 (s, 1 H, PhC*H*), 5.08 and 5.36 (4 H, $J_{H,H}$ 12 Hz, PhCH_2O), 5.46 (d, 1 H, $J_{1,2}$ <1 Hz, H-1), 5.56–6.24 (m, 4 H, H-2,3,4,5), 6.42–6.80 (m, 5 H, H-6,6′, OMe), and 7.46 (s, 1 H, OH).

Anal. Calc. for $C_{21}H_{24}O_6$: C, 67.74; H, 6.45. Found: C, 67.79; H, 6.58.

ACKNOWLEDGMENT

The authors thank the National Science Council of Ireland for a grant and for a scholarship (G.K.).

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