Note

Alternative syntheses of methylated sugars Part IX[1]. A simple, unambiguous synthesis of 2,4-di-*O*-methyl-D-glucose

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The title compound has been obtained previously from methylated laminarin[2], and also from phenyl 2,4-di-*O*-methyl-6-*O*-trityl-β-D-glucopyranoside, one of the products of partial methylation of phenyl 6-*O*-trityl-β-D-glucopyranoside[3,4]. Methyl 2,4-di-*O*-methyl-α-D-glucopyranoside has been prepared by partial methylation of methyl 6-*O*-trityl-α-D-glucopyranoside[5,6].

The starting material for the present synthesis of 2,4-di-*O*-methyl-D-glucose (**6**) was methyl 3-*O*-benzyl-α-D-glucopyranoside (**1**), the 6-*O*-trityl derivative **2** of which, isolated through the diacetate **3**, was methylated to give crystalline methyl 3-*O*-benzyl-2,4-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (**4**). The protecting benzyl and trityl groups in **4** were removed simultaneously by reductive cleavage with sodium in liquid ammonia[7] to give methyl 2,4-di-*O*-methyl-α-D-glucopyranoside **5** which was subsequently hydrolysed to give **6**.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. Optical rotations were measured on a Bendix–Ericsson automatic polarimeter. Thin-layer chromatography (t.l.c.) on Silica Gel G and column chromatography on silica gel (0.05–0.1 mm) were performed with *A* hexane–ethyl acetate (4:1), and *B* chloroform–methanol (6:1); detection was by charring with 5% sulphuric acid in ethanol. 1,2-Dimethoxyethane was dried as described by Perrin *et al.*[8] and stored over sodium hydride. Solvents were removed under diminished pressure at <40°.

*Methyl 2,4-di-*O*-acetyl-3-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside* (**3**). — A solution of 3-*O*-benzyl-D-glucose[5] (20 g) in 2% methanolic hydrogen chloride (300 ml) was boiled under reflux for 18 h, with the exclusion of moisture. The cooled solution was neutralized ($PbCO_3$) and then evaporated. A solution of the resulting, thick syrup in dry acetone (20 ml) was diluted with ether (200 ml) and, after standing at room temperature for 2–3 h, the small amount of insoluble material was removed by filtration. Concentration of the filtrate gave a syrup which, having stood overnight,

partially crystallized. Recrystallisation from ethyl acetate–ether, with seeding, gave the crude product (14.5 g, in three crops; 70%). Recrystallization from ethyl acetate–ether (1:5) and then from ethyl acetate gave methyl 3-*O*-benzyl-α-D-glucopyranoside (**1**), m.p. 91.5–92.5°, which was sufficiently pure for the next step; lit.[9] m.p. 96°.

A solution of **1** (1 g) and chlorotriphenylmethane (1.1 g) in dry pyridine (30 ml) was heated for 2 h at 100°. The solution was cooled and, after addition of acetic anhydride (1.4 ml), left at room temperature overnight. The product **3** (2 g, 93%), isolated in the usual manner and crystallized from chloroform–methanol, had m.p. 202–202.5°, $[\alpha]_D^{24}$ +60° (*c* 1.06, chloroform) (Found: C, 72.69; H, 6.17; OMe, 5.25. $C_{37}H_{38}O_8$ calc.: C, 72.77; H, 6.27; OMe, 5.08%).

Methyl 3-O-*benzyl-2,4-di*-O-*methyl-6*-O-*trityl*-α-D-*glucopyranoside* (**4**). — Compound **3** (1 g) was heated under reflux in a mixture of dry methanol (10 ml) and M methanolic potassium hydroxide (6.5 ml) for 40 min. The mixture was then deionized with a mixed-bed ion-exchange resin (Ionenaustauscher V, Merck, Darmstadt) and evaporated to dryness to afford the deacetylated product **2** as a white, solid foam (0.85 g, 98.5%), $[\alpha]_D^{24}$ +55.7° (*c* 0.97, chloroform); the i.r. spectrum showed no acetyl absorption (Found: C, 75.27; H, 6.97; OMe, 5.5 $C_{33}H_{34}O_6$ calc.: C, 75.26; H, 6.50; OMe, 5.89%).

To a solution of **2** (3.7 g) in 1,2-dimethoxyethane (35 ml), cooled in an ice bath, sodium hydride (0.65 g) was added and the mixture was stirred for 20 min with the exclusion of moisture. Methyl iodide (2.5 ml) was added and the stirring was continued for an additional 30 min. T.l.c. (solvent *A*) then showed complete conversion of the starting material into a single product (R_F 0.3, *cf.* 0.1 for the starting material). The mixture was poured into ten volumes of ice–water, and the semisolid mass that separated was dissolved in chloroform. The chloroform solution was washed (water), dried (Na_2SO_4), and evaporated to give a syrup which crystallized from heptane; yield 3.5 g (90%). Recrystallization from heptane containing a few drops of chloroform afforded **4**, m.p. 107.5–109.5°, $[\alpha]_D^{24}$ +71.3° (*c* 1.03, chloroform) (Found: C, 75.85; H, 7.04; OMe, 16.49. $C_{35}H_{38}O_6$ calc.: C, 75.78; H, 6.91; OMe, 16.79%).

2,4-Di-O-*methyl*-D-*glucose* (**6**). — A solution of compound **4** (9.5 g) in 1,2-dimethoxyethane (25 ml) was slowly added with stirring to a mixture of liquid ammonia (400 ml) and 1,2-dimethoxyethane (50 ml), followed by addition of sodium (1.75 g) cut into small pieces. The colour of the reaction mixture changed from slight turbidity through wine-red to dark blue, indicating that the reaction was complete. The mixture was worked-up as described[7] to give chromatographically homogeneous (R_F 0.5, solvent *B*) methyl 2,4-di-*O*-methyl-α-D-glucopyranoside (**5**) (2.7 g, 71%), m.p. 78–80° (from acetone–ether), $[\alpha]_D^{24}$ +177° (*c* 1.02, acetone); lit.[5,6] m.p. 79°, $[\alpha]_{5461}^{20}$ +172.5° (*c* 0.41, methanol).

A solution of the glycoside **5** (6.5 g) in 5% hydrochloric acid (70 ml) was heated at reflux for 2.5 h, after which time t.l.c. showed almost complete disappearance of the starting material. The acid was removed with Ionenaustauscher II (HO^-) resin (Merck, Darmstadt), and the solution was concentrated. Elution of the residue from a column (3 × 30 cm) of silica gel afforded chromatographically homogeneous (R_F 0.3,

cf. 0.5 for the starting material; solvent *B*) **6** (5.8 g, 96%) which readily crystallized from ethyl acetate. Recrystallization from the same solvent or from butanone gave 2,4-di-*O*-methyl-D-glucose having m.p. 124–128° (slow heating) and $[\alpha]_D^{24}$ +37° (initial) → +75.8° (equil. 3 h; *c* 1.03, water); lit.[3] m.p. 124–129° (slow heating), $[\alpha]_D^{25}$ +37.3° (initial) → +76.5° (equil.; *c* 1.6, water).

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