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Note

An improved preparation of benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate

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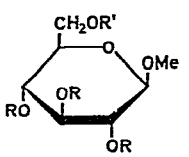
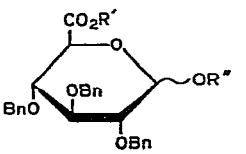
The title compound (**8**) is a suitably protected intermediate for the synthesis[1–4] of 1-esters of D-glucuronic acids. It has been prepared[5] previously in this laboratory by a multistep reaction procedure that involved, *inter alia*, catalytic oxidation of methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**3**) to methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosiduronic acid (**4**); the preparation of **3** comprised six reaction-steps, starting from 1,6-anhydro-β-D-glucopyranose. We now report a shorter and simpler route to **3** that starts from methyl β-D-glucopyranoside and involves its tritylation to **1**, followed by benzylation to **2** and *O*-detritylation to give **3** in an overall yield of 27–31%.

In a series of experiments, it was established that the platinum-catalyzed oxidation method[6], performed under conditions already described[5], is more convenient for the conversion of **3** into **4** than the chromium trioxide–dilute sulfuric acid[7–9] oxidation in acetone. Using the former method, chromatographically pure **4** has been isolated in yields ranging from 65 to 75%, and the unreacted **3** could be recovered almost quantitatively from the reaction mixture. In the second procedure, although the yield *a priori* seemed high (~75%), the oxidation product, as shown by t.l.c., was not homogeneous, and it was necessary to resort to chromatography on silica gel, and crystallization, in order to obtain pure **4** in ~30–40% yield.

Esterification of **4**, and hydrolysis of the methyl glycosidic group of the resulting





1 R = H, R' = Tr
2 R = Bn, R' = Tr
3 R = Bn, R' = H

4 R' = H, R" = Me
5 R' = Bn, R" = Me
8 R' = Bn, R" = H

Bn = $PhCH_2$

5, performed *via* the 1-*O*-acetyl derivative (**6**) and the bromide (**7**), to give **8**, were achieved by procedures previously described[5]; some of experimental conditions used in the original synthesis of **8** have been slightly modified, and are described in the Experimental part. Attempts to convert **5** in a single reaction-step into **8**, by treating[10] the former with acetic acid–aqueous hydrochloric acid were unsuccessful, because, under the conditions required, partial cleavage of the benzyl ester bond at C-6 also took place.

EXPERIMENTAL

General. — Melting points are uncorrected. Column chromatography was performed on Merck silica gel (0.05–0.2 mm); t.l.c. was conducted on Kieselgel G (Merck), and detection was effected with 10% sulfuric acid and heating. Optical rotations were determined for 1% solutions in chloroform, unless otherwise stated. I.r. spectra were recorded with a Perkin–Elmer Model 137 spectrometer, and n.m.r. spectra with a Varian A-60-A spectrometer, with chloroform-*d* as the solvent, unless otherwise stated, and tetramethylsilane as the internal standard.

Deacetylation of methyl tetra-*O*-acetyl-β-D-glucopyranoside, prepared (73% yield) from tetra-*O*-acetyl-α-D-glucopyranosyl bromide, was accomplished with methanolic sodium methoxide, enough of which was added to the sample in dry methanol to make it ~3mM in sodium methoxide. The solution was kept overnight at room temperature, and then passed through a column of Dowex-50 X-8 (H^+) resin, followed by elution with methanol; evaporation of the eluate afforded pure methyl β-D-glucopyranoside in 96–98% yield.

Methyl 6-O-trityl-β-D-glucopyranoside (**1**). — Compound **1** was prepared by a modification of the procedures given by Helferich and Becker[11] and Casinovi and co-workers[12]. To a suspension of methyl β-D-glucopyranoside (12 g) in dry pyridine (46 mL) was added trityl chloride (17.8 g, freshly crystallized from petroleum ether) in one portion, and the mixture was vigorously stirred at 100° until dissolution was complete (~20 h; t.l.c. in 8:1 chloroform–methanol). The mixture was cooled, poured into ice–water (~100 mL), and extracted with chloroform; the extracts were combined, washed successively with saturated, aqueous potassium hydrogensulfate (6 ×), water (3 ×), saturated aqueous hydrogencarbonate (3 ×), and water, dried (Na_2SO_4), and evaporated. The residue was dissolved in methanol (~50 mL) at room temperature, whereupon crystals of triphenylmethanol (m.p. 162–164°) were deposited after several minutes; they were filtered off after ~30 min, the filtrate was evaporated to dryness, and the residue (a solid foam) was dissolved in ether (~50 mL). After standing overnight at room temperature, the precipitated **1** (13 g, 46.5%), m.p. 104–106°, was filtered off; the product, still containing traces of triphenylmethanol, was used without purification in the next step. A sample was recrystallized from 1:1 methanol–water; m.p. 108–109°, $[\alpha]_D$ −36.3° (pyridine); lit.[11] 108–109° and 148° (dimorphous), $[\alpha]_D$ −37.6° (pyridine).

Anal. Calc. for $C_{26}H_{28}O_5$: C, 71.54; H, 6.47. Found: C, 71.32; H, 6.78.

Methyl 2,3,4-tri-O-benzyl-6-O-trityl-β-D-glucopyranoside (**2**). — Sodium hydride (3.3 g, 60% dispersion in oil), dry *N,N*-dimethylformamide (50 mL, distilled over sodium hydride), and **1** (8 g) were stirred at room temperature, and α-chlorotoluene (benzyl chloride) (12.6 mL) was added dropwise during ~30 min. The mixture was then slowly heated to ~70°, whereupon a vigorous, exothermic reaction (foaming) took place; heating was discontinued, and after 10–15 min, t.l.c. (1:2 ether–petroleum ether) showed almost quantitative conversion of **1** (R_F 0.0) into **2** (R_F ~0.7). After cooling, the unreacted sodium hydride was decomposed by cautious addition of 2:1 ethanol–water (~10 mL) and water (~20 mL), and the mixture was poured onto ice, whereupon the product was deposited as a brown resinous, precipitate. The supernatant liquor was decanted off, the residue was dissolved in 1,4-dioxane (50 mL), and the benzyl chloride was removed by distillation with steam until a clear distillate (at ~6 L) appeared. The nonvolatile material was extracted with ether, and the extracts were combined, washed with water, dried (Na_2SO_4), and evaporated. The residue (12.7 g, 97%) was used in the next step without purification. A sample (458 mg) was passed through a column of silica gel (8 g), with benzene, to give analytically pure **2** (370 mg, 81%) as a solid foam; $[\alpha]_D$ +7.1°; i.r. data: ν_{max}^{KBr} 1070 (C-O-C), 738, and 700 cm^{-1} (Ph); n.m.r. data: τ 2.17–2.78 (m, 30 H, 6 Ph), 5.65 (d, $J_{1,2}$ 7 Hz, H-1), and 6.31 (s, OMe).

Anal. Calc. for $C_{47}H_{46}O_6$: C, 79.85; H, 6.56. Found: C, 79.85; H, 6.72.

Methyl 2,3,4-tri-O-benzyl-β-D-glucopyranoside (**3**). — Compound **3** was prepared by a modification of the procedure described by Eby and Schuerch[13] for the α anomer. To a solution of crude **2** (12.7 g) in acetic acid (50 mL) was added, in one portion, 40% hydrogen bromide in acetic acid (2.6 mL) with cooling (ice–water) and vigorous stirring, and, after ~0.5 min, the mixture was filtered (to remove the precipitated trityl bromide) into an ice-cooled, aqueous solution of sodium hydrogencarbonate (~100 mL). The solid deposited was extracted with chloroform, and the extracts were combined, washed with aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and evaporated. Crystallization of the residue from ether–benzene afforded **3** (5.2 g, 61.2%), m.p. 91–92°, $[\alpha]_D$ +9.9°, indistinguishable from the product obtained by the procedure already described[5]; n.m.r. data: τ 2.50–2.76 (m, 15 H, 3 Ph), 5.63 (d, $J_{1,2}$ 7.5 Hz, H-1), and 6.40 (s, OMe).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.21; H, 7.01.

The residue left after evaporation of the mother liquor was passed through a column of silica gel, with 6:1 benzene–ether, to give methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (100 mg, 3%), m.p. 60–62° (methanol), $[\alpha]_D$ +25.4°; (lit.[5] m.p. 61–63°, $[\alpha]_D$ +26°); n.m.r. data: τ 2.65–2.85 (m, 30 H, 6 Ph), 6.49 (s, OMe), and 8.05 (s, OAc).

Methyl 2,3,4-tri-O-benzyl-β-D-glucopyranosiduronic acid (**4**), *and its subsequent conversion into benzyl 2,3,4-tri-O-benzyl-D-glucopyranuronate* (**8**). — The sequence of reactions from **3** to **4**, and thence to **8**, was conducted as described[5], but with some modifications. Catalytic oxidation of **3** was modified as follows: (*a*) to ensure a fine suspension, **3** (4 g, previously powdered in a mortar) was added in small portions to

vigorously agitated sodium carbonate–sodium hydrogencarbonate buffer solution (600 mL) before addition of the platinum-on-carbon catalyst (4 g; 10%, Fluka) and introduction of a well-dispersed stream of oxygen, and (*b*) the reaction (performed at 76–78°) was extended from 9 to ~20 h to give, after processing, chromatographically pure **4** in 65–75% yield. The progress of the reaction was monitored by t.l.c. (8:1 chloroform–methanol) of the precipitate obtained from samples (0.3 mL) of the reaction mixture after filtration, and acidification of the filtrate with dilute hydrochloric acid (R_F of **3** and **4**, ~0.9 and ~0.5, respectively). Esterification of **4** was performed in the presence of dicyclohexylcarbodiimide, as described, except that a 20% excess of benzyl alcohol was used; after processing and crystallization (ethanol), **5** was obtained in 72–75% yield.

It was found that the acetolysis reaction of **5** to give **6** could be accomplished in higher yield when performed on a small scale; thus, 1-g samples of **5** were treated with sulfuric acid in acetic acid–acetic anhydride in parallel experiments (3–4), and the reaction time was shortened from 24 to ~16 h (t.l.c. in 1:1 ether–petroleum ether; R_F of **5** and **6**, ~0.8 and ~0.7, respectively). Each lot was poured onto ice-water, the mixture was extracted with ether, and the extracts were pooled, and processed, to give **6** (73–77% yield) as a thick oil which was used directly for the preparation of **7**. The α configuration of **6** (previously passed through a column of silica gel, with 1:1 benzene–petroleum ether) was established from the n.m.r. data: τ 2.70–2.80 (m, 20 H, 4 Ph), 3.77 (d, $J_{1,2}$ 3 Hz, H-1), and 8.0 (s, OAc). The conversion of **6** into the bromide **7**, and hydrolysis of the latter to **8** were conducted as already described, except that the final product was not purified on a column of alumina, but passed through a column of silica gel, with 10:1 benzene–ethyl acetate, to give, in 40–44% yield (based on **5**), chromatographically homogeneous (R_F in the same solvent, 0.4) benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronate (**8**) that was identical in all respects with the sample prepared by the original procedure; lit.[5] 42% yield, m.p. 124–125° (ethanol), $[\alpha]_D$ −12°.

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