Note

Alternative syntheses of methylated sugars
Part VIII. Methyl (methyl 3,4-di-*O*-methyl-α-D-galactopyranosid)uronate

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The title compound was previously synthesized by Edington and Percival[2] from methyl (methyl 3,4-*O*-isopropylidene-α-D-galactopyranosid)uronate (**1**) *via* the 2-toluene-*p*-sulphonate. Although the final product was obtained in good yield, the procedure[2] is tedious in its last step since removal of the tosyl group under alkaline conditions must be followed by re-esterification. A more-convenient synthesis is now described, involving benzylation of **1** followed by hydrolysis of the 3,4-*O*-isopropylidene group in the resulting 2-benzyl ether **2** to give methyl (methyl 2-*O*-benzyl-α-D-galactopyranosid)uronate (**3**). Methylation of **3** followed by catalytic hydrogenolysis of the methyl ether **4** gave methyl (methyl 3,4-di-*O*-methyl-α-D-galactopyranosid)uronate (**5**).

Although **4** was obtained in excellent yield, the conversion was accompanied by a side-reaction. The i.r. spectrum of the minor by-product, isolated by silica gel chromatography, indicated unsaturation. That the minor product was formed by a β-elimination reaction and was methyl (methyl 2-*O*-benzyl-4-deoxy-3-*O*-methyl-β-L-*threo*-hex-4-enopyranosid)uronate, was further substantiated by mass[3] and n.m.r. spectrometry. The fact that methylation of a uronic acid derivative under mild conditions may be accompanied by β-elimination should be taken into account in evaluating the results of methylation analysis of acidic polysaccharides.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. Optical rotations were measured on a Bendix–Ericsson automatic polarimeter. I.r. spectrometry was carried out with a double-beam Zeiss UR-10 instrument. N.m.r. spectra were measured at 80 MHz. 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*) benzene–ethyl acetate (4:1), (*B*) benzene–ethyl acetate (6:1), (*C*) chloroform–acetone (9:4), and (*D*) carbon tetrachloride–acetone (5:1), and detection by charring with 5% sulphuric acid in ethanol. Solvents were removed under diminished pressure at <40°.

Methyl (methyl 2-O-benzyl-3,4-O-isopropylidene-α-D-galactopyranosid)uronate (**2**). — Benzyl bromide (11 ml) and silver oxide (4 g) were added to a solution of **1**[4] (5 g) in dry benzene (50 ml), and the mixture was shaken at room temperature for 8 h. Additional portions of the reagents (5 ml of benzyl bromide and 4 g of silver oxide) were then added, and shaking was continued overnight, whereafter t.l.c. (solvent *D*) showed the disappearance of starting material. The mixture was filtered, the solid was washed with chloroform, and the combined filtrate and washings were evaporated. The syrupy product was purified on a column (40×3 cm) of silica gel in system *A* which gave 5.95 g (88.5%) of chromatographically homogeneous **2** (R_F 0.7 and 0.4 in solvents *D* and *A*, respectively); **2** crystallized spontaneously and had m.p. 80.5–81.5° (from benzene–hexane), $[\alpha]_D^{27}$ +70.2° (*c* 0.97, chloroform) (Found: C, 61.37; H, 6.88; OMe, 17.64. $C_{18}H_{24}O_7$ calc.: C, 61.35; H, 6.86; OMe, 17.61%).

Methyl (methyl 2-O-benzyl-α-D-galactopyranosid)uronate (**3**). — A solution of **2** (5 g) in 90% methanol (100 ml) containing methanol-washed, air-dried Dowex-50W x8 (H^+) resin (10 g) was heated at 60° with stirring for 40 min, after which time t.l.c. (system *A*) showed the absence of starting material. The resin was filtered off and washed with a little methanol, and the combined filtrate and washings were evaporated to dryness. Recrystallisation of the residue (4.2 g, 95%) from methyl acetate gave **3**, m.p. 133–134°, $[\alpha]_D^{27}$ +73.3° (*c* 0.84, chloroform), R_F 0.4 (solvent *C*) (Found: C, 57.92; H, 6.46; OMe, 19.80. $C_{15}H_{20}O_7$ calc.: C, 57.68; H, 6.45; OMe, 19.85%).

Methyl (methyl 2-O-benzyl-3,4-di-O-methyl-α-D-galactopyranosid)uronate (**4**). — To a solution of **3** (0.9 g) in a small volume of 1,2-dimethoxyethane, methyl iodide (10 ml), silver oxide (3 g), and two drops of methyl sulphide were added, and the mixture was shaken at room temperature. After 48 h, during which time fresh portions (3×1 g) of silver oxide were added, the reaction was complete and two products (R_F 0.4 and 0.8, *cf.* 0.05 for the starting material) were detected by t.l.c. (solvent *A*). The reaction mixture was worked up in the usual manner and the product was chromatographed on a column (20×2 cm) of silica gel in system *B*.

The slower-moving component **4** (0.9 g, 91%) was distilled (b.p. 161°/0.05 mmHg) to give a colourless syrup, $[\alpha]_D^{27}$ +44° (*c* 0.72, chloroform) (Found: C, 59.82; H, 7.12; OMe, 36.35. $C_{17}H_{24}O_7$ calc.: C, 59.99; H, 7.10; OMe, 36.47%).

The faster-moving component was identified by mass spectrometry[3] as methyl (methyl 2-*O*-benzyl-4-deoxy-3-*O*-methyl-β-L-*threo*-hex-4-enopyranosid)uronate and had ν_{max} (film) 710, 1500, 3030 (aryl); 1740 (C=O); 1260 (ester); 1655 cm^{-1} (C=C, olefinic unsaturation). The integrated n.m.r. spectrum ($CDCl_3$) showed twenty protons, five of which are aromatic (τ 2.7). The other signals appeared as follows (τ): H-4, 3.89 (doublet); H-1, 5.13 (doublet); CH_2, 5.19 and 5.33 (doublet of doublets); H-3, 5.87 (quartet); $COCH_3$, 6.21 (singlet); H-2, 6.40 (quartet); OCH_3, 6.53 (singlet); $J_{1,2}$ 2.4, $J_{2,3}$ 7.6, $J_{3,4}$ 2.7, J_{CH_2} 12.5 Hz.

Methyl (methyl 3,4-di-O-methyl-α-D-galactopyranosid)uronate (**5**). — The 3,4-dimethyl ether **4** (1 g) in methanol–acetic acid (9:1, 100 ml) was hydrogenated at room temperature over 5% palladium-on-charcoal (0.5 g) until the starting material disappeared from the reaction mixture, as shown by t.l.c. (system *C*). The product

(R_F 0.5, *cf.* 0.95 for the starting material) was isolated, in the usual manner, as a crystalline residue (0.75 g, ~100%). Recrystallisation from ether afforded **5**, m.p. 114–115°, $[\alpha]_D^{27}$ +168° (*c* 0.49, chloroform); lit.[2] m.p. 113–114°, $[\alpha]_D^{16}$ +165° (*c* 0.4, chloroform) (Found: C, 48.01; H, 7.06; OMe, 49.97. $C_{18}H_{18}O_7$ calc.: C, 48.0; H, 7.25; OMe, 49.61%).

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