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Note

Preparation of α-ethoxyethyl-protected D-glucopyranuronic acid having HO-1 unsubstituted

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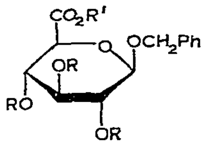
The synthesis of 1-*O*-acyl-D-glucopyranuronic acids requires the use of easily removable protecting-groups. Benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranuronic acid has been utilised as an intermediate for introduction of saturated acyl groups[1–3]. The chloroacetyl group can be removed at neutral pH by thiourea; hence, the reported[4] synthesis of benzyl 2,3,4-tri-*O*-(chloroacetyl)-β-D-glucopyranosiduronic acid indicates a possible route to 1-*O*-acyl-D-glucopyranuronic acids. Allyl 2,3,4-tri-*O*-allyl-D-glucopyranuronic acid[5] has been used in the preparation of 1-*O*-acyl-D-glucopyranuronic acids, *e.g.*, 1-methacrylates, but the method failed for the synthesis of bilirubin or biliverdin 1-*O*-acyl-D-glucopyranuronic acids[5].

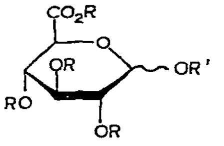
A derivative (**4**) of D-glucopyranuronic acid is now described, in which the carboxyl group and HO-2,3,4 are protected by α-ethoxyethyl groups, and which is an intermediate suitable for the synthesis of 1-*O*-acyl-D-glucopyranuronic acids.

Treatment of the glycosyl bromide[6] of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranuronate with benzyl alcohol and silver carbonate gave the crystalline glycoside **1**, which, on saponification, gave benzyl β-D-glucopyranosiduronic acid (**2**). The carboxyl group and HO-2,3,4 of **2** were substituted on treatment with ethyl vinyl ether and trifluoroacetic acid in tetrahydrofuran, to give **3**, which was a mixture of stereoisomers. The electron-impact mass spectrum of **3** contained the characteristic ion $[M - \alpha\text{-ethoxyethyl}]^+$ at *m/e* 499. Hydrogenolysis of **3**, in the presence of triethylamine to prevent partial loss of acetal groups, yielded the derivative **4** having HO-1 unsubstituted.

Acid-catalysed hydrolysis of the acetate **5** of **4** gave 1-*O*-acetyl-αβ-D-glucopyranuronic acid (**6**), for which an αβ-ratio of 2:1 was established by n.m.r. spectroscopy and by g.l.c.–m.s. of the trimethylsilyl derivatives. The mild conditions (4:1 acetic acid–0.1M hydrochloric acid, 22°, 30 min) used for the hydrolysis of **5**→**6** demonstrate the potential of **4** as an intermediate for the synthesis of 1-*O*-acyl-D-glucopyranuronic acids.



1 R = Ac, R' = Me
2 R = R' = H



3 R = EtO(Me)CH, R' = PhCH$_2$
4 R = EtO(Me)CH, R' = H
5 R = EtO(Me)CH, R' = Ac
6 R = H, R' = Ac

EXPERIMENTAL

For general methods, see ref. 5.

Methyl (benzyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (**1**). — To a solution of the glycosyl bromide prepared[6] from methyl 1,2,3,4-tetra-*O*-acetyl-α- or -β-D-glucopyranuronate (8 g) in benzyl alcohol (30 ml) were added molecular sieve (5 g) and silver carbonate (8 g), and the mixture was stirred in the dark for 6 h. T.l.c. (15:1 chloroform–acetonitrile) revealed the formation of **1** (R_F ~0.35; *cf.* ~0.4 for the bromide). Small amounts of the 1,2,3,4-tetra-acetate (R_F ~0.3) and 2,3,4-triacetate (R_F ~0.1) were also detected. Dichloromethane (200 ml) was added, the solution was filtered and concentrated, and benzyl alcohol was removed *in vacuo*. Elution of the product from silica gel (using, in sequence, 30:1, 20:1, and 15:1 chloroform–acetonitrile), followed by crystallisation from ether at —5°, gave **1** (3.7–4.6 g), m.p. 137–138°, $[\alpha]_D$ —67° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): δ 2.04 (s, 9 H, 3 OAc), 3.80 (s, COOMe), 4.05 (d, $J_{4,5}$ 9 Hz, H-5), 4.60 (d, $J_{1,2}$ 7 Hz, H-1), 4.62 and 4.94 (d, J 12 Hz, OCH_2Ph), 5.0–5.4 (m, 3 H, H-2,3,4), and 7.31 (s, Ph). Mass spectrum: *m/e* 424 (M^+, 0.005%), 423 (0.01), 393 (0.03), 365 (0.2), 333 (0.7), 317 (2), 258 (2.5), 257 (2), 245 (6), 231 (8), 215 (2.5), 203 (3), 198 (7), 157 (5), 155 (8), 144 (5), 143 (15), 139 (25), and 91 (100).

Anal. Calc. for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70. Found: C, 56.65; H, 5.81.

Benzyl β-D-glucopyranosiduronic acid (**2**). — A mixture of **3** (500 mg) with methanol (30 ml), triethylamine (15 ml), and water (15 ml) was stirred at 0° until dissolution was complete (~3 h). After 2–3 days at 22°, t.l.c. (9:2 1-propanol–water) showed conversion into **2** (R_F ~0.5). The solution was concentrated *in vacuo*, and a solution of the residue in water was passed over Dowex-50 (H^+) resin and then concentrated *in vacuo*, to yield **2** (0.31 g) as a colorless syrup, $[\alpha]_D$ —74° (*c* 0.5, water). Mass spectrum of trimethylsilyl derivative: *m/e* 557 ($[M - Me]^+$, 0.1%), 467 (0.5), 449 (0.4), 392 (1.0), 391 (0.8), 377 (1.0), 375 (1.5), 323 (4), 305 (8), 233 (10), 217 (50), 204 (30), 91 (70), and 73 (100). G.l.c. (3% OV-101, 4°/min): elution temperature, 201°.

α-Ethoxyethyl 2,3,4-tri-O-(α-ethoxyethyl)-D-glucopyranuronate (**4**). — To a solution of **2** (0.31 g) in dry tetrahydrofuran (30 ml) at 0° were added ethyl vinyl ether (5 ml) and trifluoroacetic acid (0.3 ml). The mixture was kept at 0° for 3 days and then at 22° for 3 h. Triethylamine (5 ml), dichloromethane (50 ml), and water (50 ml) were added in sequence, and the organic layer was washed with water (4 × 50 ml), dried over molecular sieves, and concentrated, to yield syrupy **3**, $[\alpha]_D$ −20° (*c* 1, chloroform). Mass spectrum: *m/e* 499 ($[M - \alpha\text{-ethoxyethyl}]^+$, 25%), 453 (7), 427 (5), 409 (30), 381 (15), 365 (15), 337 (25), 321 (10), 319 (15), 303 (25), 293 (20), 275 (30), 217 (100), 91 (>100), and 73 (>100).

Compound **3** was dissolved immediately in ethyl acetate (30 ml), triethylamine (0.2 ml) and 10% palladium-on-carbon (500 mg) were added, and the mixture was shaken with hydrogen (2 atm.) at 22° for 3–6 h until complete disappearance of the peak at *m/e* 499 in the mass spectrum. The solution was filtered, and then concentrated *in vacuo*, to yield **4** (0.55 g) as an oil, $[\alpha]_D$ +22° (*c* 1, chloroform). Mass spectrum: *m/e* 409 ($[M - \alpha\text{-ethoxyethyl}]^+$, 31%), 391 (12), 363 (18), 347 (25), 337 (17), 319 (69), 303 (28), 291 (38), 275 (100), 247 (62), 217 (92), and 73 (>100).

1-O-Acetyl-D-glucopyranuronic acid (**6**). — A solution of **4** (150 mg) in pyridine (1 ml) and acetic anhydride (0.5 ml) was kept for 2 h at 22° and then concentrated *in vacuo*, to give **5**. Mass spectrum: *m/e* 451 ($[M - \alpha\text{-ethoxyethyl}]^+$, 100%), 421 (8), 391 (8), 380 (15), 379 (20), 350 (10), 361 (50), 347 (25), 333 (25), 320 (10), 319 (15), 317 (25), 308 (25), 303 (24), 290 (20), 275 (50), 262 (55), 245 (45), and 73 (>100).

To a solution of **5** in acetic acid (1 ml) was added 0.1M hydrochloric acid (0.25 ml). After 30 min, the solution was concentrated *in vacuo* at 20–30°, to give **6**, $[\alpha]_D$ +25° (*c* 1, water). N.m.r. data (D_2O): δ 2.14 (s, AcO-1β), 2.24 (s, AcO-1α), 3.5 (m, 3 H, H-2,3,4), 4.25 (d, $J_{4,5}$ 8 Hz, H-5), 5.62 (d, $J_{1,2}$ 7 Hz, H-1β), and 6.17 (d, $J_{1,2}$ 3 Hz, H-1α). G.l.c.–m.s. was performed on the trimethylsilyl derivatives prepared by reaction of **6** (1 mg) with *N,O*-bistrimethylsilylacetamide (20 μl) and then pyridine (50 μl) for 30 min. Columns of 3% OV-101 were used (150°, 4°/min). Only the peaks for the 1-*O*-acetyl derivatives were significant; elution temperatures, 172.5 and 174° for the α and β anomers (ratio, 2:1). Mass spectrum for β anomer: *m/e* 524 (M^+, 0.2%), 509 (2), 465 (0.7), 464 (1.5), 449 (1.7), 419 (2.5), 392 (2), 391 (0.7), 377 (3), 375 (2), 359 (2), 333 (6), 305 (10), 217 (53), 204 (19), 147 (25), and 73 (100). Incomplete hydrogenolysis of **3**→**4** was revealed by a peak corresponding to trimethylsilylated **2**, eluted at 201° (3% OV-101).

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