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Note

A simplified synthesis of α-D-galactopyranose 1,3,4,6-tetraacetate

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The title tetraacetate **1** has been used[1–10] in syntheses of D-galactose-containing di- and oligo-saccharides and, *inter alia,* for the preparation of D-galactose 2-phosphate[11] and 2-sulfate[12], partially methylated[13,14] and benzylated[15] derivatives of D-galactose, and kojic acid diacetate[16]. It is usually prepared by the method of Helferich and Zirner[1], involving three stages from D-galactose with a modest overall yield (32–36%).

A simplified route to **1** in good yield (68–72%) from β-D-galactopyranose pentaacetate (**2**) resulted from other studies. When a solution of **2** in trifluoroacetic acid–water (10:1) was maintained at room temperature for 5 h, t.l.c. revealed one major component, and ~70% of **1** could be isolated and identified[12] by its ^{1}H-n.m.r. spectrum.

Treatment of β-D-glucopyranose pentaacetate (**4**) with aqueous trifluoroacetic acid, as for **2**, gave a syrupy ~2:1 (n.m.r. data) mixture of 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**5** and **6**) characterised[17] as the 2,4-dinitrophenyl β-D-glycoside **7**.

The pentaacetates of α-D-galactopyranose (**3**) and α-D-glucopyranose (**8**), which are 1,2-*cis* compounds, were recovered unchanged when treated with aqueous trifluoroacetic acid as for **2**.

The formation of **1** from **2** and the mixture of **5** and **6** from **4** must occur *via* the 1,2-acetoxonium ions **9** and **10**, respectively, since AcO-1 is good leaving group in solvolyses with neighbouring-group participation[18]. The ions **9** and **10** behave differently on hydrolysis. The expected[19,20] *cis* pathway is followed by **9**, probably *via* the ortho acid and participation of AcO-4, yielding mainly **1** as the kinetic product. With **10**, the ortho-acid intermediate could react with water to give the α-product **5** or by *trans* opening[20,21] to give the β-product **6**. Mutarotation then occurs to give the observed mixture of **5** and **6**. These compounds are known[22] to equilibrate in the presence of trifluoroacetic acid.

The presence of water in the reaction of **2** with trifluoroacetic acid is essential

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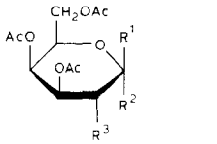
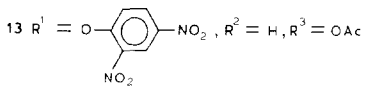
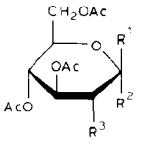
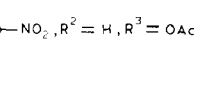


1 $R^1 = H, R^2 = OAc, R^3 = OH$
2 $R^1 = R^3 = OAc, R^2 = H$
3 $R^1 = H, R^2 = R^3 = OAc$
11 $R^1 = H, R^2 = OH, R^3 = OAc$
12 $R^1 = OH, R^2 = H, R^3 = OAc$

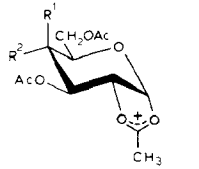




4 $R^1 = R^3 = OAc, R^2 = H$
5 $R^1 = H, R^2 = OH, R^3 = OAc$
6 $R^1 = OH, R^2 = H, R^3 = OAc$



8 $R^1 = H, R^2 = R^3 = OAc$



9 $R^1 = OAc, R^2 = H$
10 $R^1 = H, R^2 = OAc$

for the formation of **1** since, in its absence, an α,β-mixture of the 2,3,4,6-tetraacetates (**11** and **12**) was formed and characterised[17] as the 2,4-dinitrophenyl β-D-glycoside **13**. The peracetate **4** reacted in an analogous manner. These reactions probably involve displacement of AcO-1 by a trifluoroacetoxy group, followed by hydrolysis and mutarotation. Various 1,2-*trans* acetates undergo direct replacement reactions with formic acid[23].

The observed unreactivity of the 1,2-*cis* pentaacetates **3** and **8** reflects the lack of neighbouring assistance in the expulsion of AcO-1, and front-side participation is to be expected only in the presence of strong organic acids[24].

Trifluoroacetic acid–water (9:1) has been recommended[25] for the cleavage of isopropylidene and benzylidene acetals and is said to be compatible with other substituents, including esters. This compatibility may be valid only for relatively short reaction periods.

EXPERIMENTAL

Optical rotations were determined with a Perkin–Elmer Model 241 automatic polarimeter on 1% solutions in chloroform. T.l.c. was performed (Kieselgel 60, Merck) with 1,2-dimethoxyethane–cyclohexane (3:2) and detection by charring with sulphuric acid. ^{1}H-N.m.r. spectra were recorded with a Varian EM 2940 (90 MHz) spectrometer on solutions in $CDCl_3$ (internal Me_4Si).

Reactions of trifluoroacetic acid–water.—*(a) With β-D-galactopyranose pentaacetate* (**2**). A solution of **2**[26] (10 g) in trifluoroacetic acid (35 mL) containing water (3.5 mL) was stirred at room temperature for 5 h, then concentrated *in vacuo* at 35°, and toluene (3 x 40 mL) was distilled *in vacuo* from the residue. The residue, which contained one major component, R_F 0.52 (t.l.c.), was recrystallised from isopropyl ether to give 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**1**; 6.01–6.42 g, 68–72%), m.p. 145–147°, $[\alpha]_D^{20}$ +145°; lit. [1]m.p. 151°, $[\alpha]_D^{18}$ +142.7°. ^{1}H-N.m.r. data ($CDCl_3$): δ 6.3 (d, $J_{1,2}$ 4.0 Hz, H-1), 5.45 (m, H-4), 5.15 (dd, J 4 and 4 Hz, H-3),

3.95–4.45 (m, H-2,5,6), 2.18, 2.15, 2.05, 2.02 (4 s, 4 Ac).

A solution of **2** (2.0 g) in trifluoroacetic acid (7.5 mL) was kept for 5 h at room temperature, water (1.0 mL) was then added, and the mixture was concentrated *in vacuo* at 35°. Toluene (4 x 30 mL) was distilled *in vacuo* from the residue, to leave 2,3,4,6-tetra-*O*-acetyl-α,β-D-galactopyranose (**11** + **12**) as a colourless syrup (1.76 g), $[\alpha]_D^{20}$ +43°.

A mixture of above product, 1-fluoro-2,4-dinitrobenzene (1.0 g), and DABCO (2.0 g) was dissolved in *N*,*N*-dimethylformamide (15 mL) and stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* to leave an oil which was dissolved in dichloromethane (200 mL) and then washed with saturated aqueous sodium hydrogencarbonate (100 mL) and water (2 x 100 mL). The dried (Na_2SO_4) extract was concentrated *in vacuo* to leave a glass which was crystallised from ethanol to give 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**13**) as pale-yellow needles (2.05 g, 78%), m.p. 172–176°, $[\alpha]_D^{20}$ +66.5°; lit.[27] m.p. 174–176°, $[\alpha]_D$ +68°.

(*b*) *With α-D-galactopyranose pentaacetate* (**3**). When **3**[26] (3.0 g) was treated as in (*a*), **3** (2.67 g, 89%) was recovered; m.p. 94–96° (from ethanol), $[\alpha]_D^{21}$ +106°; lit.[26] m.p. 95.5°, $[\alpha]_D$ +107°.

(*c*) *With β-D-glucopyranose pentaacetate* (**4**). Treatment of **4**[26] (5.0 g) as in (*a*) yielded syrupy 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranose (**5** + **6**). A portion (1.0 g) of the product was characterised[17], *vide supra*, as 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**7**; 1.08 g, 72%), m.p. 176–178° (from ethanol), $[\alpha]_D^{20}$ +34°; lit.[27] m.p. 177–179°, $[\alpha]_D$ +33°.

A solution of **4** (3.0 g) in trifluoroacetic acid (10 mL) was kept for 5 h at room temperature, water (1.4 mL) was then added, and the mixture was concentrated *in vacuo* at 35°. Toluene (4 x 40 mL) was distilled *in vacuo* from the residual syrup to give a clear glass (2.63 g), $[\alpha]_D^{21}$ +67°. The product was treated as described above, to give **7** (3.3 g, 74%), m.p. 174–176°, $[\alpha]_D^{20}$ +32.6°.

(*d*) *With α-D-glucopyranose pentaacetate* (**8**). After treatment of **8**[26] (2.0 g) as described in (*a*), **8** (1.78 g, 89%) was recovered; m.p. 110–112° (from ethanol), $[\alpha]_D^{20}$ +101°; lit.[26] m.p. 112–113°, $[\alpha]_D^{20}$ +102°.

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