FLUORINATED CARBOHYDRATES

PART IV. 4-DEOXY-4-FLUORO-D-GALACTOSE

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ABSTRACT

A slow displacement of the equatorial mesyloxy group by fluoride occurred, with Walden inversion, when methyl 2,3-di-*O*-benzyl-4-*O*-mesyl-6-*O*-trityl-α-D-glucopyranoside (**2**) was treated with tetra-n-butylammonium fluoride in boiling acetonitrile to yield the corresponding 4-deoxy-4-fluoro-D-galactose derivative (**3**). Application, in sequence, of hydrogenolysis and acid hydrolysis to **3** gave 4-deoxy-4-fluoro-D-galactose.

INTRODUCTION

The introduction of a fluorine atom into naturally occurring compounds involved in biochemical processes has, in several cases, produced analogues having significant biological activity, and in some cases of therapeutic value[2]. The anti-tumour activity of fluorinated sugars and their use in probing the mechanism of certain biochemical and immunochemical reactions is being evaluated in these laboratories. The present paper reports the synthesis of 4-deoxy-4-fluoro-D-galactose (**6**) and thereby completes the series of fluorogalactopyranose derivatives[3,4].

The tetra-n-butylammonium fluoride–acetonitrile system has been used[4,5] for the fluoride displacement, in furanoid derivatives, of secondary sulphonate groups attached in an *endo* position to a trioxabicyclo [3.3.0]octane ring-system. Recently, the displacement of a pyranoid axial sulphonate in a 4-*O*-mesyl-D-galactose derivative provided a route to 4-deoxy-4-fluoro-D-glucose[6]. We now report the displacement of a pyranoid equatorial sulphonate in a synthesis of 4-deoxy-4-fluoro-D-galactose.

RESULTS AND DISCUSSION

Methyl 2,3-di-*O*-benzyl-4-*O*-mesyl-6-*O*-trityl-α-D-glucopyranoside (**2**) was selected as the substrate for fluoride displacement in a synthetic approach to 4-deoxy-4-fluoro-D-galactose, since the ether blocking groups at positions 2, 3, and 6, should

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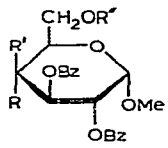
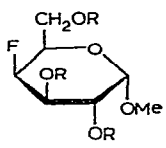
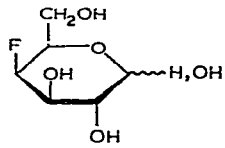
subsequently, be removable in a single hydrogenolysis step to give methyl 4-deoxy-4-fluoro-α-D-galactopyranoside (**4**).



1 R = OH, R′ = R″ = H
2 R = OMs, R′ = H, R″ = Tr
3 R = H, R′ = F, R″ = Tr



4 R = H
5 R = Ac



6

Bz = benzyl

Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**1**) was prepared from methyl α-D-glucopyranoside by application, in sequence, of conventional benzylidenation[7], benzylation (benzyl bromide–sodium hydride–*N*,*N*-dimethylformamide[8]), and debenzylidenation. Treatment of compound **1** with trityl chloride–pyridine under forcing conditions (75° for 16 h), followed by mesylation, without isolation of the trityl ether, gave methyl 2,3-di-*O*-benzyl-4-*O*-mesyl-6-*O*-trityl-α-D-glucopyranoside (**2**). The location of the mesyl group at position 4 in **2**, anticipated on the basis of analogy with similar reaction sequences[6], was confirmed by the behaviour of **2** in the subsequent fluoride displacement reaction. Thus, when the methanesulphonate **2** was treated with 8–15 mol. of tetra-n-butylammonium fluoride in boiling acetonitrile a slow, presumably S_N2, displacement occurred to yield methyl 2,3-di-*O*-benzyl-4-deoxy-4-fluoro-6-*O*-trityl-α-D-galactopyranoside (**3**); no other product could be detected (t.l.c.). That the reaction required one week for completion (~90% displacement after 5 days) contrasts with the relatively rapid reaction (<9 h) of methyl 4-*O*-mesyl-2,3-di-*O*-methyl-6-*O*-trityl-α-D-galactopyranoside under similar reaction conditions[6]; the latter compound was converted, in part (~30%), into olefinic products. This marked difference in the rate of fluoride displacement is probably not due entirely to the difference in the blocking groups at positions 2 and 3, since methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-iodo-α-D-galactopyranoside reacts with radioactive iodide in acetone at 80°, at a rate that is 2.4-times greater than that for the D-*gluco* analogue[9]. The rate difference may be rationalised in terms of the steric and polar factors [10] which influence the nucleophilic displacement of carbohydrate sulphonates. Thus, although the transition states for the two displacements would not seem to be appreciably different, the incoming nucleophile would have a less-hindered access to the galactose methanesulphonate than to the glucose methanesulphonate, where it has to approach over the sugar ring and consequently interacts with the ring-oxygen dipole.

The benzyl and trityl protecting groups were smoothly removed from the fluoride **3**, by hydrogenolysis over palladised charcoal, to give methyl 4-deoxy-4-fluoro-α-D-galactopyranoside (**4**). The n.m.r. and mass-spectral data for the triacetate (**5**) of **4** confirmed the 4-deoxy-4-fluoro-D-*galacto* structure. The ^{19}F n.m.r. spectrum

of **5** contained a five-line pattern, composed of two triplets, the inner lines of which overlapped. The spectrum contained the following coupling constants: $J_{F,4}$ 50 and $J_{F,3} \sim J_{F,5} \sim 26$ Hz. Some smaller splittings were detected and were presumably due to long-range F–H couplings. The magnitudes of the vicinal F–H couplings clearly indicate *trans*-diaxial relationships and are consistent with a *C1*(D) conformation of a 4-deoxy-4-fluoro-D-galactopyranoid system (*cf.* $J_{F,3}$ 15, $J_{F,5}$ <2 Hz for 4-deoxy-4-fluoro-D-*gluco* derivatives[6]). Loss of the mesyloxy group, with participation of a benzyloxy or trityloxy group, could not yield a product containing a secondary fluorine atom and vicinal protons in *trans*-diaxial relationship.

The ^{1}H n.m.r. spectrum ($CDCl_3$) of **5** showed H-1 as a doublet (τ 5.0, $J_{1,2}$ 3.2 Hz) with no detectable long-range coupling to the fluorine atom, in contrast to derivatives of 4-deoxy-4-fluoro-α-D-glucopyranose which have[6] $J_{F,1}$ 3.4–4 Hz. The H-1 resonance of **5** was unaffected by irradiation of F-4. The signal for H-4 appeared as a widely spaced (due to gemical F–H coupling) pair of broad peaks, the broadening being due to the smaller values (~1 Hz) of $J_{3,4}$ and $J_{4,5}$. Similar small couplings have been observed[11] in galactopyranose derivatives. Irradiation of F-4 caused the H-4 resonance to collapse to a single, broad peak.

The fragmentation pattern of **5** under electron impact would be expected to resemble that of the other 4-fluorohexopyranoses[6,12]. Thus, Fig. 1 represents the expected routes of fragmentation and, indeed, the ions derived from pathways *A*, *D*,

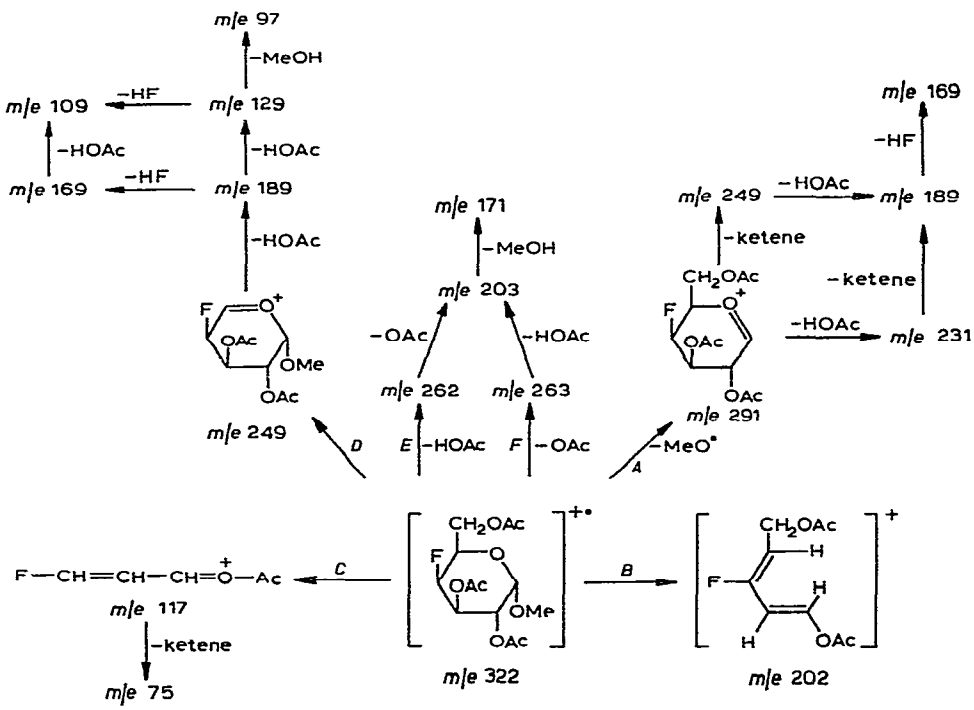


Fig. 1. Mass-spectral fragmentation pattern of methyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-galactopyranoside.

E, and *F* are all seen in the mass spectrum of **5**. According to the Biemann–Heyns scheme[13,14] of fragmentation of acetylated hexopyranose derivatives, pathway *C* would normally (*e.g.*, in a penta-*O*-acetylhexopyranose) provide two prominent peaks in the spectrum. However, the presence of a fluorine atom on C-4 makes the cleavage of the C-4–C-5 (and the C-4–C-3) bond an unfavourable process[12], resulting, in this case, in small peaks at *m/e* 117 and *m/e* 75. For two 4-deoxy-4-fluoro-D-glucopyranose derivatives[6,12], pathway *B* produced an intense ion, but instead of the expected peak at *m/e* 202 in the spectrum of **5**, a large peak appears at *m/e* 203 with a much smaller one at *m/e* 202. Although *m/e* 203 is obtained from pathways *E* and *F*, there appears to be an anomalous situation in this case, which at the moment cannot be explained.

Hydrolysis of methyl 4-deoxy-4-fluoro-α-D-galactopyranoside with 2M hydrochloric acid gave crystalline 4-deoxy-4-fluoro-D-galactose, m.p. 148–149.5°. When the mutarotation of an aqueous solution of the fluoro sugar was complete (+68°), the ratio of α:β froms was ~1:2, as inferred by integration of the ^{19}F resonances; the corresponding ratio[15] for D-galactose is 1:4. The anomeric composition of fluoro sugars in aqueous solution is readily determined, as a rule, from the ^{19}F resonances.

EXPERIMENTAL

Thin-layer chromatography (t.l.c.) was performed on Kieselgel (Merck, 7731) and column chromatography on Kieselgel (Merck, 7734.) Optical rotations were measured by using a Perkin–Elmer 141 polarimeter. Melting points are uncorrected. N.m.r. spectra were recorded on solutions in deuteriochloroform with tetramethylsilane as internal standard, using Perkin–Elmer R-10 and Varian HA-100 instruments.

Methyl 2,3-di-O-benzyl-4-O-mesyl-6-O-trityl-α-D-glucopyranoside (**2**). — A solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[16] {11.5 g, m.p. 73.5–75°, $[\alpha]_D$ +21° (*c* 1.8, chloroform)} and trityl chloride (9.5 g, 1.1 mol.) in dry pyridine (50 ml) was heated at 75° for 16 h with the exclusion of moisture. T.l.c. (ether–ethyl acetate, 3:1) then showed the reaction to be complete, and mesyl chloride (3.6 ml, 1.5 mol.) was added with stirring to the cooled (4°) reaction mixture. After stirring had been continued for 4 h at room temperature, the reaction was complete (t.l.c., light petroleum–ether, 2:1) and the mixture was poured into ice–water (500 ml). The product was extracted with chloroform, in the usual manner, to give, after crystallisation from ethanol–chloroform, **2** (16.3 g, 79%), m.p. 137.5–138.5°, $[\alpha]_D$ +26° (*c* 1.5, chloroform) (Found: C, 71.4; H, 6.1; S, 4.6. $C_{41}H_{42}O_8S$ calc.: C, 70.9; H, 6.1; S, 4.6%).

Methyl 2,3-di-O-benzyl-4-deoxy-4-fluoro-6-O-trityl-α-D-galactopyranoside (**3**). — A solution of **2** (1.8 g) and tetra-n-butylammonium fluoride (16 g) in dry acetonitrile (30 ml) was boiled for 5 days with the exclusion of moisture. The reaction mixture was concentrated to dryness in the presence of a small amount of Kieselgel, and the residue was applied to a column of dry Kieselgel. Elution with light petroleum–ether (4:1) yielded **3** (950 mg, 57%), m.p. 71–74° (from ether–light petroleum), $[\alpha]_D$ +9°

(*c* 1.1, chloroform) (Found: C, 77.6; H, 6.4; F, 3.1. $C_{40}H_{39}FO_5$ calc.: C, 77.4; H, 6.8; F, 3.0%).

Methyl-4-deoxy-4-fluoro-α-D-galactopyranoside (**4**). — A solution of **3** (970 mg) in ethanol (50 ml) was shaken in the presence of hydrogen and palladised charcoal at room temperature for 40 h, and the reaction was monitored by t.l.c. (ethyl acetate–methanol, 8:1). The reaction mixture was filtered through Celite, Kieselgel was added, and, after concentration under reduced pressure, the residue was placed on a column of dry Kieselgel. Elution with ethyl acetate–methanol (10:1) gave **4** (260 mg, 86%), m.p. 99–101° (methanol–ethyl acetate), $[\alpha]_D$ +148° (*c* 1, methanol) (Found: C, 42.5; H, 6.6; F, 9.6. $C_7H_{13}FO_5$ calc.: C, 42.8; H, 6.6; F, 9.7%).

Treatment of **4** with pyridine–acetic anhydride at room temperature in the usual manner gave methyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-galactopyranoside (**5**) which was eluted from a column of dry Kieselgel with ether–light petroleum (1:1) to give material having m.p. 91–92° (ethanol–light petroleum), $[\alpha]_D$ +150° (*c* 1.2, chloroform) (Found: C, 48.6; H, 5.7; F, 5.7. $C_{13}H_{19}FO_8$ calc.: C, 48.5; H, 5.9; F, 5.9%). The mass spectrum of **5** (recorded at 70 eV, using direct introduction of the sample and a source temperature of 75°) contained the following peaks expressed as *m/e* (% abundance, using *m/e* 203 as the base peak): 28(34), 29(8), 31(5), 32(12), 41(5), 42(11), 43(⩾100), 44(28), 45(5), 53(5), 61(5), 69(18), 70(21), 72(7), 73(7), 74(4), 75(4), 81(23), 85(6), 87(4), 97(10), 98(13), 99(28), 100(33), 101(30), 102(62), 103(63), 104(4), 109(9), 112(4), 117(7), 118(17), 129(13), 131(4), 139(7), 144(20), 145(31), 159(6), 160(25), 161(18), 169(14), 182(4), 189(7), 202(4), 203(100), 231(27).

4-Deoxy-4-fluoro-D-galactose (**6**). — A solution of **4** (380 mg) in 2M hydrochloric acid (5 ml) was heated at 100° for 4 h, and the reaction was monitored by t.l.c. (ethyl acetate–methanol, 5:1). After neutralisation with aqueous barium hydroxide and addition of Kieselgel, the reaction mixture was concentrated to dryness under reduced pressure, and the residue was placed on a column of dry Kieselgel. Elution with ethyl acetate–methanol (8:1) gave **6**, m.p. 148–149.5° (methanol–ethyl acetate), $[\alpha]_D$ +104 (5 min) → +68° (16 h, equil., *c* 1.32, water), R_G 1.37 on Whatman No. 1 paper with butyl alcohol–acetic acid–water (5:2:3) (Found: C, 39.9; H, 5.8; F, 10.3. $C_6H_{11}FO_5$ calc.: C, 39.5; H, 6.0; F, 10.4%).

The ^{19}F n.m.r. spectrum of a solution of **6** in D_2O (external reference C_6F_6) which had been allowed to reach equilibrium contained two resonances corresponding to the α- and β-pyranose forms of the sugar. The following data were obtained from the spectrum: α-D anomer +4990, β-D anomer +4746 Hz upfield of C_6F_6:$J_{F,4}$ 50, $J_{F,3} \sim J_{F,5} \sim 30$ Hz for both anomers.

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