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FLUORINATED CARBOHYDRATES

PART II. ALTERNATIVE SYNTHESES OF 4-DEOXY-4-FLUORO-D-GLUCOSE[1]

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ABSTRACT

Treatment of methyl 4-*O*-mesyl-2,3-di-*O*-methyl-6-*O*-trityl-α-D-galactopyranoside (**2**) with tetrabutylammonium fluoride–boiling acetonitrile and of methyl 4-*O*-mesyl-2,3-di-*O*-methyl-α-D-galactopyranoside (**4**) with caesium fluoride–boiling ethane-1,2-diol resulted in fluoride displacements to give derivatives (**5** and **6**, respectively) of 4-deoxy-4-fluoro-D-glucopyranose. These reactions constitute the first examples of the direct fluoride displacement of pyranose secondary sulphonates.

Demethylation of methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**6**) with boron trichloride afforded 4-deoxy-4-fluoro-D-glucose.

The n.m.r. data for **6** (and structurally closely related compounds) reveal a novel type of long-range (^5J) coupling (3–4 Hz) between F-4 and H-1. Comment is made on the mass-spectral fragmentation pattern of the acetate of **6**.

INTRODUCTION

In seeking an improved route to 4-deoxy-4-fluoro-D-glucose[2], the fluoride displacement of derivatives of 4-*O*-mesyl-D-galactopyranose has been investigated. Cholestan-3-α- and -3-β-yl toluene-*p*-sulphonate are converted[3] into fluorides, in good yield and with inversion of configuration, by treatment with tetrabutylammonium fluoride in a dipolar, aprotic solvent (acetone, butanone), but the response to this type of reagent of secondary sulphonates attached to pyranoid rings has not hitherto been reported. Tetrabutylammonium fluoride–acetonitrile has been effectively used in the conversion of a carbohydrate primary sulphonate[1] and of 3-*O*-toluene-*p*-sulphonyl derivatives of allofuranose[1,4] and gulofuranose[5] into the corresponding fluorides. We now report on the fluoride displacement of two 4-*O*-mesyl-D-galactopyranose derivatives[6].

RESULTS AND DISCUSSION

Methyl 4-*O*-mesyl-2,3-di-*O*-methyl-6-*O*-trityl-α-D-galactoside (**2**) was readily obtained from methyl 2,3-di-*O*-methyl-α-D-galactopyranoside[7] (**1**) by sequential application of conventional tritylation and mesylation procedures. Attempted tosyl-

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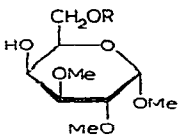
ation of the intermediate trityl compound **3** failed, even under vigorous conditions (tosyl chloride–pyridine, 100°, 4 h). Compound **1** is obtainable from D-galactose in 4 stages, two of which [D-galactose → methyl α-D-galactopyranoside[8] and methyl 4,6-*O*-benzylidene-α-D-galactopyranoside → 2,3-di-*O*-methyl derivative[9]] can be significantly improved by the use of procedures described more recently.



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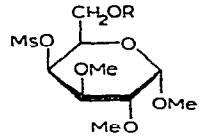
3 R = Tr



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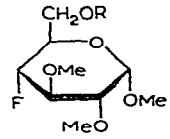


5 R = Tr
6 R = H
7 R = Ac

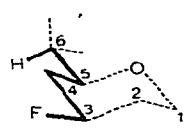
Attempts to detritylate **2** by hydrogenolysis over palladised charcoal were unsuccessful, but smooth conversion into methyl 4-*O*-mesyl-2,3-di-*O*-methyl-α-D-galactopyranoside (**4**) was effected with ethanolic hydrogen chloride at room temperature. The reaction sequence **1**→**2**→**4** can be conveniently telescoped. Surprisingly vigorous conditions (pyridine–trityl chloride, 20 h, 70°) were necessary to retritylate **4**.

When a solution of the methanesulphonate **2** in acetonitrile containing an 8.5-molar excess of tetrabutylammonium fluoride was boiled for 9 h, the product apparently contained two components (t.l.c.) of which the major (71%) was methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (**5**). The minor component, which was not rigorously identified, appeared to be unsaturated. The formation of at least one unsaturated product is not surprising, since the sulphonyloxy group in **2** is in *trans*-diaxial relation with H-3 and H-5.

Detritylation of **5** with chloroform–hydrogen chloride at room temperature afforded methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**6**). That **6** had the *gluco* configuration and, therefore, that the fluoride displacement of the methanesulphonate **2** had proceeded with the anticipated Walden inversion, was indicated by the n.m.r. data (100 MHz for ^{1}H and 94.1 MHz for ^{19}F resonances). The signal for H-4 appeared as a widely spaced pair of triplets centred at τ 5.70, and the magnitude ($J_{3,4} = J_{4,5} = 8.8$ Hz) of the vicinal ^{1}H–^{1}H coupling constants for H-3, H-4, and H-5 is consistent with a *trans*-diaxial orientation of H-3–H-4 and of H-4–H-5 and therefore indicative of an equatorial F-4. The signal for F-4 was a quartet of broadened peaks ($J_{F,4}$ 49.5, $J_{F,3}$ 15 Hz, with other small unresolved couplings) and that for H-1 was a triplet (τ 5.24, $J_{1,2}$ 3.8, $J_{F,1}$ 3.8 Hz). The long-range (^5J) coupling between F-4 and H-1 was verified by irradiation of F-4 which caused the signal for H-1 to collapse to a doublet ($J_{1,2}$ 3.8 Hz).

Similar long-range couplings have been observed in the n.m.r. spectra of methyl 6-*O*-acetyl-4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**7**; $CDCl_3$, $J_{F,1}$ ~3.5 Hz) and 4-deoxy-4-fluoro-α-D-glucopyranose (D_2O, $J_{F,1}$ 3.8 Hz). No such coupling occurs in the β-D-anomer of the fluoro sugar or in 1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-fluoro-β-D-glucopyranose[2].

The stereochemical requirements for $^{1}H-^{19}F$ spin–spin coupling over five bonds have not yet been clearly defined[10]. The ^{5}J coupling ($J_{F,6}$ 1.5 Hz) observed[11] for 3-deoxy-3-fluoro-β-D-glucopyranose tetra-acetate involves a geometrical arrangement (**8**) of F-3 and the relevant H-6, which is formally quite different from that (**9**) of F-4 and H-1 in **6**.



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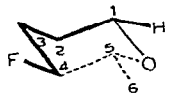

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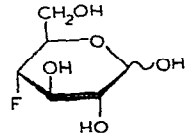

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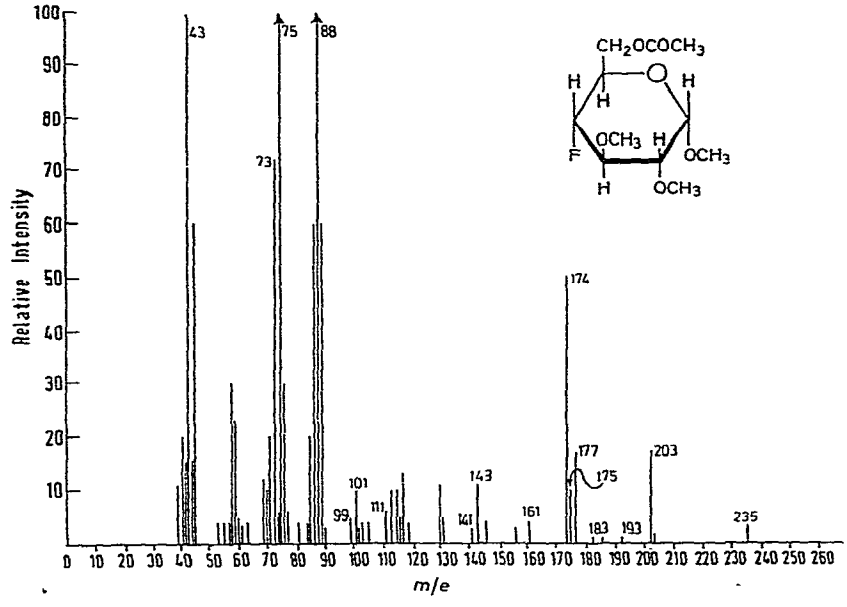
However, neither of these ^{5}J couplings appears to conform to the converging vector[12] or proximity[13] rules which have been used to explain ^{5}J, $^{1}H-^{19}F$ couplings in fluorosteroids and other compounds[10]. A full analysis of the n.m.r. spectra of **6**, **7**, and related compounds will be published elsewhere.

A single treatment of methyl-4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**6**) with boron trichloride did not effect complete demethylation. Two products were isolated, of which the first (~20%) was a reducing sugar (positive reaction with aniline hydrogen phthalate) probably containing a single *O*-methyl group (n.m.r.) and the second (~20%) was 4-deoxy-4-fluoro-D-glucose[2] (**10**). The above conversion of D-galactose into 4-deoxy-4-fluoro-D-glucose involves nine stages. This fact, coupled with the formation of mixtures and the consequent need for column chromatography in the purification of products in the stages 2→5 and 6→8, largely deprives the route of convenience for the synthesis of 4-deoxy-4-fluoro-D-glucose on a scale adequate to permit a thorough evaluation of biological properties. However, when this work was essentially complete, an alternative synthesis was worked out which satisfied the above requirement, and a preliminary report has been published[14].

The direct displacement by fluoride ion of secondary sulphonate groups attached to pyranoid rings has, apparently, not hitherto been reported. It is clear, from Richardson's analysis[15] of the steric and polar factors which may inhibit the nucleophilic displacement of pyranoid secondary sulphonates, that 4-sulphonate derivatives of D-galactopyranose and D-glucopyranose should be relatively susceptible to displacement, and several examples are known[16]. The conversion of methyl 4-*O*-mesyl-2,3-di-*O*-methyl-6-*O*-trityl-α-D-galactopyranoside (**2**) into the 4-fluoro-D-glucose derivative **5**, by using tetrabutylammonium fluoride–acetonitrile, proceeds in good yield (>70%). Under comparable conditions, methyl 2,3-di-*O*-benzyl-4-*O*-mesyl-6-*O*-trityl-α-D-glucopyranoside reacts less rapidly[17] (5–10% of starting material remained after 5 days), but 70% of the corresponding 4-fluoro-D-galactose derivative was ultimately obtained. The rate of reaction of methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-iodo-α-D-galactopyranoside with radioactive iodide in acetone at 80° is 2.4 times that of the D-*gluco* analogue[18].

The displacement of pyranoid secondary sulphonates by charged nucleophiles usually requires a dipolar, aprotic solvent[15]. It is therefore of interest to note that



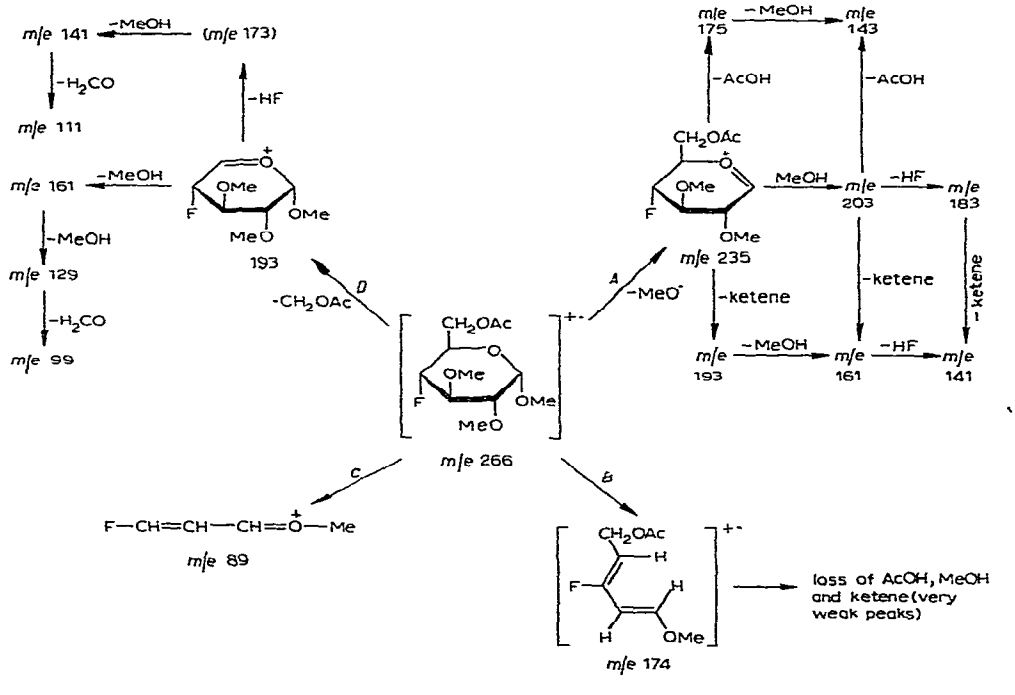


Fig. 1. Mass spectrum (AEI, MS-12, 70eV, direct insertion, ion source temperature 80°) and fragmentation pattern of methyl 6-*O*-acetyl-4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside.

treatment of methyl 4-*O*-mesyl-2,3-di-*O*-methyl-α-D-galactopyranoside (**4**) with caesium fluoride in boiling ethane-1,2-diol for 5 min, afforded the corresponding 4-fluoro-D-glucose derivative **6** in moderate yield (23–44%).

In the course of establishing the structure of **6**, the acetate **7** was subjected to mass spectrometry. The fragmentation pattern of **7** (Fig. 1) is closely related to that established[19] for acetylated and methylated hexopyranose derivatives, but with modifications that can be correlated with the location of the fluorine atom. Pathways *A* and *D* show that the fluorine atom is attached directly to the pyranoid ring. The intense peak at *m/e* 174 can be assigned to the fragment derived from pathway *B*. The formation of this apparently stable fragment, which requires cleavage of the C-1–C-2 bond and loss of the C-3 substituent, indicates that the fluorine atom is not attached to C-3 and probably not at C-2, since cleavage of a C–C bond when one of the carbon atoms carries a fluorine atom is an unfavourable process[20]. For this reason, cleavage of the C-3–C-4 bond should also not be favoured, and the fragment of *m/e* 89 arising from pathway *C* (Fig. 1) should not occur to any extent. However, the peak at *m/e* 88, which is assigned to the fragment $(CH_3O–CH=CH–OCH_3)^{+\bullet}$, is the most intense in the spectrum and consequently will give rise to a large "isotope peak" at *m/e* 89.

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography (t.l.c.) was performed on Kieselgel (Merck, 7731), and detection was effected with conc. sulphuric acid. Column chromatography was performed on Kieselgel, 7734. Light petroleum refers to the fraction of b.p. 60–80°. Optical rotations were determined with a Perkin–Elmer 141 polarimeter on 1–2% solutions in chloroform unless stated otherwise. N.m.r. spectra were obtained on solutions in deuteriochloroform (internal tetramethylsilane) by using Perkin–Elmer R-10 and Varian HA-100 instruments.

Methyl 4-O-mesyl-2,3-di-O-methyl-6-O-trityl-α-D-galactopyranoside (**2**). — Methyl 2,3-di-*O*-methyl-α-D-galactopyranoside[7] (**1**, 3.8 g) was dissolved in pyridine (80 ml) and treated with trityl chloride (5.3 g, 1.1 mol.). The reaction, which was monitored by t.l.c. (9:1 benzene–methanol), proceeded slowly at room temperature. After 6 days, the mixture was poured into ice–water (1 litre), and the sticky residue was filtered off and dried azeotropically by repeated distillation of toluene under diminished pressure. The resulting syrup was eluted from Kieselgel with chloroform to give the 6-*O*-trityl compound **3** (6.2 g, 78%) as an amorphous solid, m.p. 77–80°, $[\alpha]_D^{25}$ +68°, R_F *ca.* 0.3 (t.l.c., 9:1 benzene–methanol) which was chromatographically homogeneous but could not be satisfactorily recrystallised.

A solution of the trityl ether **3** (4.2 g) in pyridine (40 ml) was treated with mesyl chloride (2.04 g, 2 mol.) at room temperature. The reaction was essentially complete in 2 h (t.l.c., 9:1 benzene–methanol). After a further 14 h, the mixture was poured into ice–water (500 ml), and the product, which was extracted with chloroform (2 × 300 ml) in the usual manner, was eluted from Kieselgel with 4:1 ether–light petroleum. Recrystallisation of the crude product (4.5 g, 91%) from ethanol–light petroleum

gave the title compound **2**, m.p. 159–160.5°, $[\alpha]_D^{25}$ +76°, R_F *ca.* 0.5 (t.l.c., 9:1 benzene–methanol) (Found: C, 64.2; H, 6.0; S, 6.0. $C_{29}H_{34}O_8S$ calc.: C, 64.2; H, 6.2; S. 5.9%).

Methyl 4-O-mesyl-2,3-di-O-methyl-α-D-galactopyranoside (**4**). — (*a*) Dry hydrogen chloride was bubbled for 15 min into a solution of the trityl compound **2** (1.9 g) in ethanol (500 ml) at room temperature. Reaction was complete (t.l.c., ether) after 3 h. The solution was then neutralised with anhydrous sodium carbonate and concentrated under diminished pressure, and the residue was extracted with chloroform (2 × 50 ml) in the usual manner to give material which was eluted from Kieselgel with chloroform. The purified product (920 mg, 87%) was recrystallized from ethanol–light petroleum to give the title compound **4**, m.p. 143–144°, $[\alpha]_D^{25}$ +145° (Found: C, 40.2; H, 6.5; S, 10.3. $C_{10}H_{20}O_8S$ calc.: C, 40.0; H, 6.7; S, 10.7%).

(*b*) A solution of methyl 2,3-di-*O*-methyl-α-D-galactopyranoside (9.4 g) in pyridine (200 ml) was treated with trityl chloride (13 g, 1.1 mol.) for 8 h at 95–100°, after which time only traces of starting material remained (t.l.c.). Mesyl chloride (9 g) was added to the cooled solution, which, after storage for 16 h at room temperature, was poured into ice–water (3 l) and then extracted with chloroform (3 × 500 ml). The combined extracts were dried ($MgSO_4$) and concentrated under diminished pressure. Dry hydrogen chloride was passed for 30 min into a stirred solution of the residue in ethanol (500 ml) at room temperature. After a further 2.5 h, the mixture was neutralised (K_2CO_3) and concentrated, and the product was extracted as described in (*a*). Elution of the product from Kieselgel (250 g) with chloroform gave the title compound **4** (9.3 g, 72%, after recrystallisation), m.p. 145–146°.

Tritylation of methyl 4-O-mesyl-2,3-di-O-methyl-α-D-galactopyranoside (**4**). — A solution of **4** (1.5 g) and trityl chloride (1.68 g, 1.2 mol.) in dry pyridine (6 ml) was heated for 20 h at 70° and then left for 1 week at room temperature; no starting material remained after this time (t.l.c.). Kieselgel (10 g) was added to the reaction mixture which was concentrated *in vacuo*, and toluene was distilled several times from the residue which was then added to the top of a column of Kieselgel and eluted with 3:1 ether–light petroleum. The purified product (2.88 g, ~100%) was recrystallised from ethanol–light petroleum to give methyl 4-*O*-mesyl-2,3-di-*O*-methyl-6-*O*-trityl-α-D-galactopyranoside (**2**), m.p. 160–161°, $[\alpha]_D^{22}$ +81°.

Treatment of methyl 4-O-mesyl-2,3-di-O-methyl-6-O-trityl-α-D-galactopyranoside (**2**) *with tetrabutylammonium fluoride.* — A solution of **2** (1.2 g) and tetrabutylammonium fluoride[21] (4.85 g, 8.5 mol.) in acetonitrile was heated under reflux for 9 h. T.l.c. (6:4 ether–light petroleum) then showed the presence of traces of starting material (R_F *ca.* 0.25) and two products having R_F values 0.5 (major) and 0.4 (minor). The reaction mixture was concentrated under diminished pressure, and the syrupy residue was eluted from Kieselgel with 1:1 ether–light petroleum. The major component (730 mg, 71%) was recrystallised from ethanol–light petroleum to give methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-6-*O*-trityl-α-D-glucopyranoside (**5**), m.p. 129–133°, $[\alpha]_D^{22}$ +85° (Found: C, 72.85; H, 6.7; F, 3.9. $C_{28}H_{31}FO_5$ calc: C, 72.2; H, 6.7; F, 4.1%).

The weak i.r. band at *ca.* 1685 cm^{-1} shown by the crystalline fluoride **5** suggested the presence of a small amount of olefinic impurity. Hydrogenation of **5** over

palladised carbon, however, gave only material (68%) having an R_F value (t.l.c., ether) and i.r. spectrum indistinguishable from those of the starting material.

The minor component (160 mg), which did not crystallise, had $[\alpha]_D^{25}$ +16° (*c* 1.4, chloroform), and showed an i.r. band (medium intensity) at 1660 cm^{-1}, indicative of unsaturation, was not investigated further.

*Methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-*D*-glucopyranoside* (**6**). – The fluoride **5** (446 mg) was dissolved in a 0.5% solution of hydrogen chloride in chloroform (22 ml) and stored at room temperature. After 30 min, t.l.c. (4:1 ether–light petroleum) showed that detritylation was complete. The solution was concentrated (<40°) under diminished pressure, and the residue was submitted directly to column chromatography by using 4:1 ether–light petroleum. The major product (130 mg, 61%, R_F *ca.* 0.1) which was eluted was distilled to give methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**6**, 71 mg), b.p. 115–120° (bath)/0.2 mm, $[\alpha]_D^{22}$ +133° (Found: C, 48.1; H, 7.1. $C_9H_{17}FO_5$ calc: C, 48.2; H, 7.6%).

The i.r. spectrum of this material showed a band (3460 cm^{-1}) for hydroxyl group, but no absorption indicative of unsaturation. The n.m.r. spectral data are reported in the Discussion.

*4-Deoxy-4-fluoro-*D*-glucose.* — Undistilled, but chromatographically homogeneous methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**6**, 214 mg) was treated[22] with boron trichloride (25 ml) for 1 h at −70°. Boron trichloride was evaporated from the reaction mixture at room temperature to leave a residue which was dissolved in a small volume of water. Methanol was added, and the mixture was concentrated to dryness. The residue was dissolved in methanol, and the solution was concentrated under diminished pressure. Several repetitions of this process gave a product which contained two components, *A* (R_F *ca.* 0.45) and *B* (R_F *ca.* 0.4) (t.l.c., 5:1 ethyl acetate–methanol). Elution of the mixture from Kieselgel with ethyl acetate gave *A* (41 mg), a reducing sugar (brown spot with aniline hydrogen phthalate[23]) which did not crystallise and which still contained a methoxyl group as indicated by the n.m.r. spectrum (D_2O, sharp singlet, 1.55 p.p.m. downfield from the signal for acetonitrile). Further elution gave *B* (35 mg, 20%) which crystallised from ethanol to give 4-deoxy-4-fluoro-D-glucose (**10**), m.p. 182–186° alone and 180–184° in admixture with the authentic compound[2] (m.p. 180–185°), $[\alpha]_D^{22}$ +45° (equil., *c* 0.5, water), M_G 0.27 (ionophoresis[24] in borate buffer, pH 10), R_G 1.59 (Whatman No. 1 paper, 10:3:6 butyl alcohol–ethanol–water). The i.r. spectrum was identical with that of authentic[2] **10**.

*Action of caesium fluoride on methyl 4-*O*-mesyl-2,3-di-*O*-methyl-α-*D*-galactopyranoside* (**4**). — A solution of sulphonate **4** (1 g) and caesium fluoride (5 g) in dry ethane-1,2-diol (25 ml) was boiled under reflux for 5 min. Kieselgel and methanol were then added to the reaction mixture, and after concentration, the residue was added to a column of Kieselgel. Elution with ether gave a product (331 mg) which appeared to be homogeneous on t.l.c. (ether) but which had an i.r. band at *ca.* 1685 cm^{-1} indicative of contamination by an olefinic impurity. Hydrogenation of an ethanolic solution of the mixture (0.3 g) over palladised charcoal for 5 h at room

temperature resulted in the loss of the i.r. band at 1685 cm^{-1}. Examination of the product by t.l.c. (5:1 ether–ethyl acetate) showed one major and several minor products. Elution of the mixture from Kieselgel with 5:1 ether-ethyl acetate gave the major component (168 mg) as a colourless liquid (131 mg), b.p. 130–140° (bath), 0.3 mm, $[\alpha]_D^{22}$ +133°. The product had an R_F value 0.3 (t.l.c., 5:1 ether–ethyl acetate), i.r. spectrum, and n.m.r. spectrum which were indistinguishable from those of methyl 4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**6**).

Acetylation (pyridine–acetic anhydride) of **6** gave, after elution from Kieselgel with 3:1 ether–light petroleum, methyl 6-*O*-acetyl-4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside (**7**) as a colourless liquid, b.p. 120–130° (bath)/0.25 mm, $[\alpha]_D^{22}$ +115°, ν_{max} 1745 cm^{-1} (C=O) (Found: C, 49.3; H, 7.2; F, 6.9. $C_{11}H_{19}FO_6$ calc.: C, 49.6; H, 7.1; F, 7.1%). The i.r. spectrum of **7** contained no bands assignable to OH or C=C. The n.m.r. spectrum, which was consistent with the assigned structure, contained, *inter alia*, the following signals: τ 5.19, triplet ($J_{1,2}$ ~3.5, $J_{F,1}$ ~3.5 Hz), H-1; 7.91 singlet, AcO; 6.40, 6.50, and 6.58, singlets, OMe.

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