FLUORINATED CARBOHYDRATES*

PART XII[1]. 4-DEOXY-4-FLUORO-D-GLUCOSE: AN IMPROVED SYNTHESIS AND THE GLYCOSYL FLUORIDE DERIVATIVES

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(Received January 26th, 1971; accepted for publication, February 22nd, 1971)

ABSTRACT

4-Deoxy-4-fluoro-D-glucose (**5**) has been synthesised by two routes. Treatment of 1,6-anhydro-4-*O*-tosyl-β-D-glucopyranose (**1**) or 1,6:3,4-dianhydro-β-D-galactopyranose (**2**) with potassium hydrogen fluoride in boiling ethane-1,2-diol affords 1,6-anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (**3**). Acid hydrolysis effects the conversion **3** → **5**. The dianhydride **2** was readily obtained by photolysis of its 2-*O*-tosyl derivative. N.m.r. data are given for **5** and the 3-fluoro analogue, and for 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α- and -β-D-glucopyranosyl fluoride. Numerous long-range (^4J and ^5J) F–H and F–F couplings were observed for these compounds. Treatment of the 2-toluene-*p*-sulphonate of **3** with base gave 1,6:2,3-dianhydro-4-deoxy-4-fluoro-β-D-mannopyranose (**10**), which was converted into 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (**11**) by reaction with potassium hydrogen fluoride.

INTRODUCTION

In seeking a synthesis of 4-deoxy-4-fluoro-D-glucose convenient for the production of quantities of material adequate for a thorough evaluation of antitumour and other biological activities[2], two approaches have been investigated involving, as key stages, (*1*) fluoride displacement reactions on 4-sulphonate derivatives of D-galactopyranose and (*2*) cleavage of 3,4-anhydro-D-galactopyranose derivatives with potassium hydrogen fluoride. The former approach yields 4-deoxy-4-fluoro-D-glucose but, since it involves a sequence of 9 stages[3] (starting from D-galactose), certain of which are poor yielding, the route is largely deprived of convenience. We now report in detail on the latter approach[4].

*This paper also constitutes Part XIV of a series from U. B. C. entitled "Studies of Specifically Fluorinated Carbohydrates".

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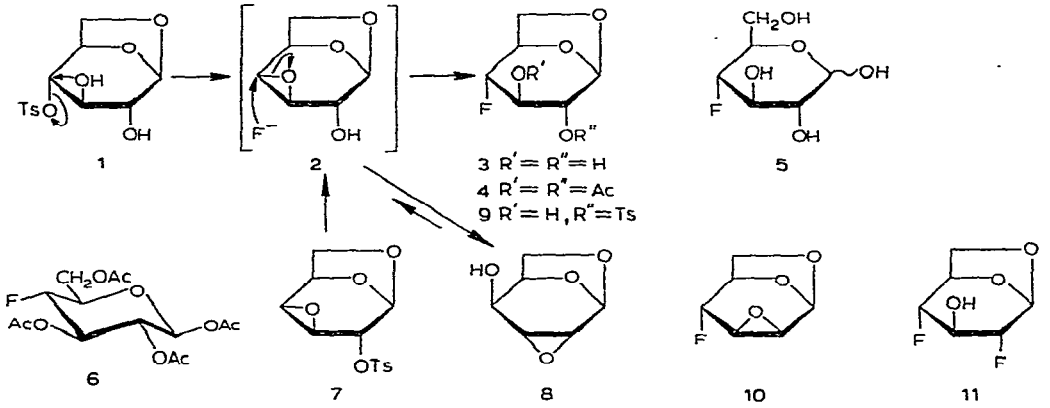
RESULTS AND DISCUSSION

Treatment[5] of 1,6-anhydro-β-D-glucopyranose with 1 mol. of toluene-p sulphonyl chloride in pyridine at 0° affords, *inter alia*, 29% of a mixture of the 2- an 4-toluene-*p*-sulphonates. The monosulphonates are not easily separable by colum chromatography, and only poor yields of the pure compounds are obtainable. Th 4-sulphonate **1** reacted with potassium hydrogen fluoride in boiling ethane-1,2-dic to give 1,6-anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (**3**), presumably via th epoxide **2**. No evidence was obtained which would indicate the occurrence of epoxid migration (*cf.* ref. 6).

Hydrolysis of the anhydride **3** with boiling M hydrochloric acid or with 0.5 sulphuric acid at 100° gave 4-deoxy-4-fluoro-D-glucose (**5**). Alternatively, the anhy dride **3** could be acetolysed at room temperature (reaction complete in 10 min; c Ref. 7) and the resulting αβ-tetra-acetate saponified with methanolic sodium metho ide. The fluoro sugar **5** was converted into the β-tetra-acetate **6** by sodium acetate acetic anhydride.



The structure of 4-deoxy-4-fluoro-D-glucose was unequivocally established[4] o the basis of n.m.r. data for the β-tetra-acetate **6**, for which the relevant couplin constants were as follows: $J_{1,2}$ 8.1, $J_{2,3}$ 9.5, $J_{3,4}$ 8.8, $J_{4,5}$ 10.0, $J_{5,6'}$ 2.5, $J_{5,6''}$ 4.4 $J_{6',6''}$ 12.4, $J_{F,3}$ 14.5, $J_{F,4}$ 49.5; $J_{F,5}$ ~2.6, $J_{F,6'}$ ~1.6, $J_{F,6''}$ ~1.5 Hz. The magnitud (8.1–10 Hz) of the vicinal H–H coupling for H-1,2,3,4,5 is indicative[8] of *trans* diaxi relationships and therefore of the *gluco* configuration.

Although F/H-3 and F/H-5 are in *gauche* relationship, the relatively sma magnitude (~2.6 Hz) of $J_{F,5}$ may be ascribed[9] to an electronegativity effect of th ring oxygen atom which is manifest because the C-4–F/C-5–O-5 bonds are antiplana A similar, steric situation is present in derivatives of 2-deoxy-2-fluoro-D-glucopyrar ose for which values of $J_{F,1}$ <0.5 and 2.5 Hz have been observed[10] for the α an β anomers, respectively. In the absence of this electronegativity effect, *J* values fc vicinal, *gauche* F–H are typically[11] in the range 12–14.5 Hz.

The low yield in the conversion of 1,6-anhydro-β-D-glucopyranose into the 4-sulphonate **1** largely deprives the above synthesis of convenience as a route for the large-scale preparation of 4-deoxy-4-fluoro-D-glucose.

Because HO-3 is markedly sterically hindered, reaction[5] of 1,6-anhydro-β-D-glucopyranose with an excess of toluene-*p*-sulphonyl chloride in pyridine affords mainly the 2,4-disulphonate, which is converted by treatment[12] with sodium methoxide–chloroform–methanol into 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (**7**, 48% overall yield). Compound **7** is therefore an attractive intermediate for the synthesis of 4-deoxy-4-fluoro-D-glucose. Detosylation of **7**, without cleavage of the epoxide, has been effected[13] with sodium amalgam in aqueous methanol. However, there appears to be a balance in this reaction between detosylation to give 1,6:3,4-dianhydro-β-D-galactopyranose (**2**) and the epoxide migration **2** → 1,6:2,3-dianhydro-β-D-gulopyranose (**8**). Base-catalysed equilibration[14] of **2** and **8** revealed the *gulo* compound to be thermodynamically the more stable. We did not discover conditions that would allow extensive detosylation of **7** without significant epoxide migration (**2** → **8**).

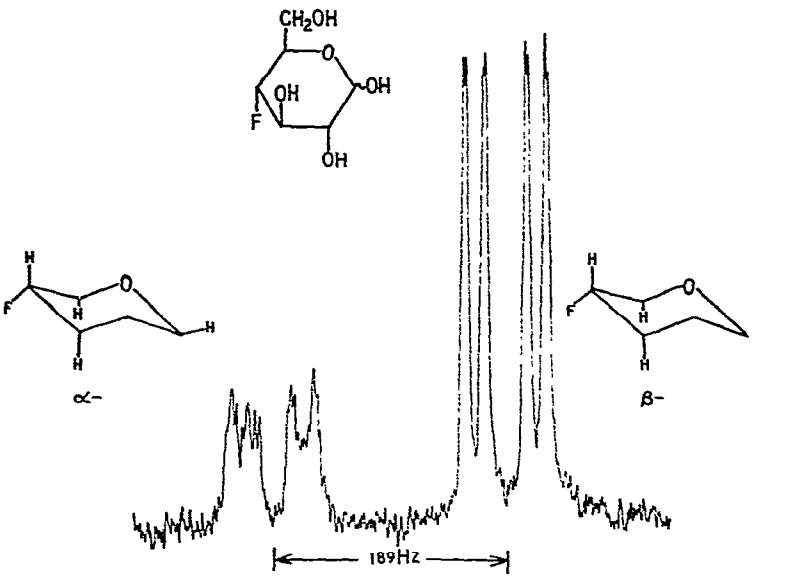
Zen *et al.*[15] have described a photochemically induced desulphonylation of the toluene-*p*-sulphonates of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. This reaction, which is still largely unexploited, was applied to **7** by irradiation (quartz vessel, 450-watt, high-pressure Hg lamp, 3 h, ~35°) of a 0.3% solution containing an equimolar amount of sodium methoxide. Smooth detosylation occurred to give, in small-scale (~1 g) reactions, acceptable (~80%) yields of 1,6:3,4-dianhydro-β-D-galactopyranose (**2**). Somewhat lower yields were obtained with a circulating system designed for larger scale (10–50 g) reactions.

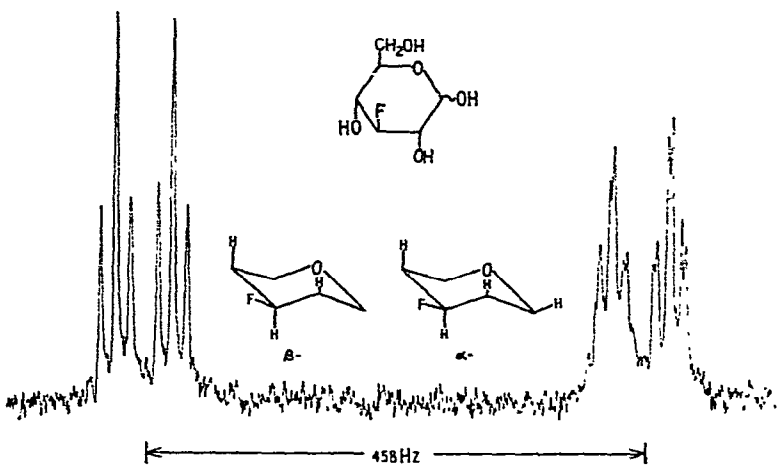
Irradiation of 1,6-anhydro-2,4-di-*O*-tosyl-β-D-glucopyranose, under conditions similar to those noted above, resulted in non-selective detosylation.

Treatment of the dianhydride **2** with potassium hydrogen fluoride in boiling ethane-1,2-diol gave 1,6-anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (**3**). The reaction sequence 1,6-anhydro-di-*O*-tosyl-β-D-glucopyranose → **7** → **2** → **3** → **5** offers a route of reasonable convenience for the synthesis of 4-deoxy-4-fluoro-D-glucose on a decagram scale.

In the preceding paper[1], it was noted that ^{19}F n.m.r. spectroscopy can be used to probe the configuration and/or conformation of fluoro sugars in molecular situations for which ^{1}H spectral data would be difficult to obtain. Thus, the n.m.r. spectrum of an aqueous solution of 4-deoxy-4-fluoro-D-glucose at mutarotational equilibrium showed (Fig. 1) ^{19}F resonances (p.p.m. upfield relative to external CCl_3F) at Φ_c 193.5 (α anomer) and 195.6 (β anomer). Long-range (^5J) coupling of F-4 to H-1 occurs only in the α anomer (see below), resulting in a complex ^{19}F resonance. The αβ-ratio (integrated intensities of ^{19}F resonances) of ~1:1.38 may be compared with that[16] (1:1.8) for D-glucose and indicates that the fluorine atom has only a small effect on the mutarotational equilibrium.

A somewhat greater effect on the mutarotational equilibrium was found for





Figs. 1 and 2. ^{19}F n.m.r. spectra of ~10% aqueous solutions of 4-deoxy-4-fluoro-D-glucose (Fig. 1) and 3-deoxy-3-fluoro-D-glucose (Fig. 2) measured using a Varian HA-100 spectrometer operating at 94.1 MHz in the frequency-sweep mode. The conformational formulae indicate those protons in the respective α and β anomer which are significantly coupled to the fluorine substituent.

3-deoxy-3-fluoro-D-glucose[11], an aqueous solution of which showed ^{19}F resonances (Fig. 2) at Φ_c 195.4 (α anomer) and 190.5 (β anomer) with an $\alpha\beta$-ratio of 1:1. The more-complex ^{19}F resonance of the α anomer is due to the ^4J coupling of F-3 and H-1 which requires[17] a planar W arrangement of the intervening bonds.

4-Deoxy-4-fluoro-D-glucose is exceptional, in that the ^{19}F resonance for the α anomer occurs to lower field than that of the β anomer. The reverse situation obtains for the corresponding 2- (Φ_c^α 194.8, Φ_c^β 194.6)[18], 3- (Φ_c values noted above), and 6-fluoro analogues (Φ_c^α 230.6, Φ_c^β 229.9)[1].

In methyl sulphoxide (internal Me_4Si), the form of 4-deoxy-4-fluoro-D-glucopyranose which crystallised from ethanol–light petroleum showed resonances for the protons of pyranose anomeric hydroxyl groups[19], principally at δ 6.75 ($J \sim 7$ Hz, HO-1, β anomer) with a much weaker ($\sim 10\%$) resonance at 6.42 (HO-1, α anomer). Likewise, the form of 3-deoxy-3-fluoro-D-glucopyranose crystallising from ethanol[11] showed resonances at δ 6.50 (J 4.5 Hz, HO-1, α anomer) and 6.82 (J 6.3 Hz, HO-1, β anomer); $\alpha\beta$-ratio $\sim$ 1:1. A similar ratio was observed (based on ^{19}F resonances) for an aqueous solution, and for which no mutarotation was detected.

The availability of 1,6-anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (**3**) offers a route to 2,4-dideoxy-2,4-difluoro-D-glucose. Treatment of **3** with an excess of toluene-*p*-sulphonyl chloride in pyridine at 55–60° gave the 2-sulphonate **9** which was converted, at room temperature with methanolic sodium methoxide, into 1,6:2,3-dianhydro-4-deoxy-4-fluoro-β-D-mannopyranose (**10**). The fluoro-epoxide **10** yielded 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (**11**) on reaction with potassium hydrogen fluoride in boiling ethane-1,2-diol. This reagent also converted the 2-sulphonate **9** into the difluoride **11**, but in very poor yield. The difluoride **11** has also been synthesised from 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose[20] by 4-tosylation, followed by treatment in sequence with base and potassium hydrogen fluoride, and converted[21] into 2,4-dideoxy-2,4-difluoro-D-glucose by acid hydrolysis.

A full analysis of the n.m.r. data of the acetates of 1,6-anhydro-β-D-glucopyranose and the 2-, 4-, and 2,4-di-fluoro derivatives will be published elsewhere, but the observation of a zero $J_{F,F}$ value for 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (**11**) may be noted here. In the light of published data[22] on ^4J F–F couplings for carbohydrate derivatives (*ax,ax* +10.4, *ax,eq*, +1.0, *eq,eq*, −3.0 Hz), a zero value requires that the fluorine substituents be nearer to a di-equatorial than to a di-axial orientation. Clearly, in **11** there must be considerable distortion of the chair form of the pyranoid ring towards a boat form. Such distortion of the molecule exists in the crystalline form of 1,6-anhydro-β-D-glucopyranose[23].

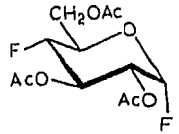
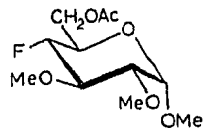
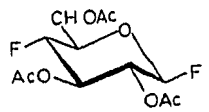
In extending the utilisation of carbohydrate derivatives for studying long-range F–H and F–F couplings, 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-(**12**) and -β-D-glucopyranosyl fluoride (**14**) were investigated. The n.m.r. data for **12** and **14**, which were prepared by conventional procedures (see Experimental), are recorded in Tables I and II, together with those for methyl 6-*O*-acetyl-4-deoxy-4-fluoro-2,3-di-*O*-methyl-α-D-glucopyranoside[3] (**13**).

The spectral assignments were confirmed in all cases by continuous-waves ^1H–^{19}F heteronuclear decoupling experiments[24]. The ^{19}F–^{19}F couplings were unequivocally identified by observing the ^{19}F resonances with simultaneous irradiation of the entire ^1H spectrum, using the noise-modulated ^{19}F–^1H heteronuclear decoupling technique[24]. The relative signs of some of the ^1H–^{19}F couplings and of the ^{19}F–^{19}F couplings of **12** and **14** were determined by an off-resonance ^1H–^{19}F decoupling method[25], and the signs were then placed on an *absolute* basis following previously established criteria[26].

The data given in Table I are unexceptional, but confirm that the derivatives

TABLE I

^1H–^1H COUPLING AND ^1H CHEMICAL SHIFT DATA FOR COMPOUNDS **12–14**

		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*
	**12**[b]	+2.8	10.2	8.9	~9.5	[a]	[a]	[a]	4.32	5.13	4.40	5.48	←5.50–5.88——→		
	**13**[c]	+3.6	+9.5	8.4	9.9	2.7	4.7	12.0	5.19	6.79	6.35	5.71	6.11	5.66	5.77
	**14**[d]	+5.8	7.4	+8.6	9.4	2.9	4.9	12.1	4.63	4.98	4.70	5.35	6.04	5.52	5.76

[a]Indeterminate. [b]AcO 7.894(1), 7.904(2). [c]OMe 6.40, 6.49, 6.57; OAc 7.922. [d]OAc 7.897, 7.908, 7.917.

TABLE II

^{19}F–^{1}H AND ^{19}F–^{19}F COUPLINGS AND ^{19}F CHEMICAL-SHIFT DATA FOR COMPOUNDS **12–14**

		F-1							*F-4*							
	$J_{1,F}$	$J_{F,1}$	$J_{F,2}$	$J_{1,3}$	$J_{F,4}$	$J_{F,5}$	$J_{F,6}$	$J_{F,6'}$	$J_{F,1}$	$J_{F,2}$	$J_{F,3}$	$J_{F,4}$	$J_{F,5}$	$J_{F,6}$	$J_{F,6'}$	J_{F,OCH_3}[d]
12	−0.6	+52.0	+23.7	[a]	[a]	[a]	[a]	[a]	+3.0	−0.8	14.6	48.5	[e]	[e]	[e]	—
13	—	—	—	—	—	—	—	—	+3.3	−0.9[b]	+16.0[b]	51.2[c]	3.6[c]	1.9	1.3	0.8
14	+3.1	+50.7	+10.2	−0.8	0.8	0.9	0.6	0.6	+0.5	0	15.8	+49.5	4.9	1.6	1.9	—

Data in Tables I and II for solutions in $CDCl_3$–CCl_3F–Me_4Si (16:3:1, v/v) measured with a modified Varian HA-100 spectrometer operating in the locked, frequency-sweep mode at 94 MHz for ^{19}F resonances and at 100 MHz for ^{1}H resonances. **12** Φ_c F-1 150.0, F-4 199.5; **13** Φ_c F-4 196.1; **14** Φ_c F-1 137 (temperature dependent), F-4 199.4 p.p.m.

[a]Irradiation at the F-1 resonance frequency caused no detectable changes in the line-widths of the H-3 and H-4 resonances, indicating that any ^{19}F–^{1}H couplings present must be of very small magnitude. [b]Corrected values; splittings, 0.7, 15.8. [c]Corrected values; splittings 50.2, 4.6. [d]OCH_3 at τ 6.40. [e]Indeterminate.

have the assigned structures. For derivatives **12** and **13**, the ^1H–^1H couplings indicate that the pyranose ring has an essentially undeformed $^4C_1$-(D) conformation; the somewhat smaller magnitude of $J_{3,4}$ does not appear to reflect a conformational distortion, since the value of $J_{4,5}$ is normal[1,11]. However, for the β-D-glucosyl fluoride **14**, the small magnitudes of $J_{1,2}$ and $J_{2,3}$ are significant and arise from the known[27] effect of a β-D-fluorine substituent attached to C-1, which causes distortion and/or time-averaging of the normal $^4C_1$-(D) conformation.

In like fashion, the ^{19}F–^1H couplings listed in Table II accord well with the values anticipated, although the profusion of long-range couplings across four (^4J) and five (^5J) bonds is particularly noteworthy. A detailed discussion of long-range ^{19}F–^1H couplings for a wide range of fluoro sugar derivatives will be published elsewhere, but it is pertinent to comment here on three particular sets of J values. The $^5J_{e,e}$ couplings between F-4 and H-1 of derivatives **12** and **13** are larger (+3.0 and +3.3 Hz, respectively) than the $^5J_{e,a}$ couplings between F-1 and H-4 and F-4 and H-1 (0.8 and +0.5 Hz) of **14**. With the minor proviso that this latter derivative may have a slightly distorted $^4C_1$-(D) conformation, these values clearly indicate a partial stereospecificity for ^5J couplings, which must await further data for completion. If the couplings are transmitted through the bonds, it will be important to establish the individual contributions in the pathway F-4, C-4, C-5, O-5, C-1, H-1, compared with those in the pathway F-4, C-4, C-3, C-2, C-1, H-1.

Similar considerations apply to the ^5J ^{19}F–^{19}F couplings of **12** and **14**. Here also the $^5J_{e,a}$ coupling (+3.1 Hz for **14**) is considerably larger than the $^5J_{e,a}$ coupling (−0.6 Hz for **12**). The significant magnitude of the $^5J_{e,a}$ coupling clearly indicates the danger of assigning structures on the basis of ^{19}F–^{19}F couplings unless both the source and the sign of the coupling have been determined. For example, the $^4J_{F-1,F-3}$ coupling of 2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-β-D-glucopyranosyl fluoride has[22] a magnitude (3.0 Hz) similar to that of the $^5J_{e,e}$ coupling noted above for **14**, but is negative in sign.

A small (0.8 Hz) coupling in the lowest-field (τ 6.40) methoxyl resonance of compound **13** was observed. Although an unequivocal assignment of the MeO resonances cannot be simply made, it is possible that it is MeO-3 which is involved in ^5J coupling with F-4. Further information on this type of coupling should be provided by a study of 2-*O*-methylglycopyranosyl fluoride derivatives and methyl 2-deoxy-2-fluorohexopyranosides. The synthesis of these compounds is in hand.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were obtained for 0.5–2% solutions in chloroform (unless stated otherwise), using a Perkin–Elmer 141 polarimeter. Thin-layer chromatography (t.l.c.) was performed on Kieselgel (Merck, 7731), and detection was effected with conc. sulphuric acid. Column chromatography was effected on Kieselgel 7734.

1,6-Anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (**3**). — A solution of 1,6-

anhydro-4-*O*-tosyl-β-D-glucopyranose[5] (**1**, 2.77 g, m.p. 123–124°, $[\alpha]_D$ −57°) and potassium hydrogen fluoride (6 g) in ethane-1,2-diol (10 ml) was heated under reflux. Monitoring by t.l.c. (ether–ethyl acetate, 3:1) showed that the reaction was complete in 75 min. The mixture was then poured into saturated, aqueous sodium hydrogen carbonate (50 ml). Kieselgel (~25 g) was added, the mixture was concentrated, and the residue was placed on top of a short, dry column of Kieselgel. Elution with ether–ethyl acetate (5:1) gave the product contaminated with ethane-1,2-diol, so that further chromatography over Kieselgel (200 g) was necessary to give the uncontaminated product as a pale-yellow syrup (670 mg, 47%) which crystallised from ether. Two recrystallisations from acetone–ether gave **3**, m.p. 118–120°, $[\alpha]_D$ −53° (water) (Found: C, 44.35; H, 5.45; F, 11.3. $C_6H_9FO_4$ calc.: C, 43.9; H, 5.5; F, 11.7%).

Treatment of **3** (153 mg) with acetic anhydride–pyridine, in the usual manner, gave the 2,3-diacetate **4** (196 mg, 85%) as a thick, colourless syrup, b.p. 120–140° (bath)/ 0.15 mmHg, $[\alpha]_D$ −49° (Found: C, 48.35; H, 5.25; F, 7.35. $C_{10}H_{13}FO_6$ calc.: C, 48.4; H, 5.25; F, 7.65%).

4-Deoxy-4-fluoro-D-glucose (**5**). — (*a*) The anhydride **3** (407 mg) was treated with boiling M hydrochloric acid (4.5 ml) for 16 h (t.l.c. monitoring, ether–ethyl acetate, 5:1), The cooled hydrolysate was diluted with water (50 ml), neutralized with silver carbonate, and filtered. Kieselgel (~2 g) was added to the filtrate which was then concentrated. The residue was added to the top of a column of dry Kieselgel (100 g) and eluted with ethyl acetate–methanol (10:1). Concentration of the eluate gave a syrup which crystallised from methanol; recrystallisation of the product (252 mg, 56%) from ethanol–light petroleum gave **5**, m.p. 187–189°, $[\alpha]_D$ +26 (9 min) → +49° (76 h, equil., water), R_G 2.53 (Whatman No. 1 paper, butyl alcohol–acetic acid–water, 5:2:3; detection with alkaline silver nitrate[28]) (Found: C, 39.85; H, 5.95; F, 10.3. $C_6H_{11}FO_5$ calc.: C, 39.55; H, 6.05; F, 10.45%).

Subsequently, it was found better to effect the hydrolysis of **3** with 0.5M sulphuric acid for 70 h at 100°, followed by neutralisation (pH meter) with saturated, aqueous barium hydroxide.

(*b*) A solution of **3** (280 mg) in acetic anhydride (4 ml) containing conc. sulphuric acid (0.1 ml) was stored at room temperature for 10 min; t.l.c. (ether–light petroleum, 2:1) then showed the absence of starting material. Water was then added cautiously, the excess of acid was neutralised with sodium hydrogen carbonate, Kieselgel (~1 g) and acetone were added, and the mixture was concentrated to dryness. The residue was added to a column of dry Kieselgel (50 g) and eluted with ether–light petroleum (2:1) to give syrupy 1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-fluoro-αβ-D-glucopyranose (550 mg, 92%).

A solution of the αβ-tetra-acetate (1.2 g) in methanol (40 ml) was treated with methanolic sodium methoxide [prepared from sodium (60 mg) and methanol (10 ml)] at ~5° for 16 h. T.l.c. (ethyl acetate–methanol, 5:1) then showed that only the free sugar was present. The reaction mixture was concentrated to dryness in the presence of Kieselgel (~2 g), and the residue was added to a column of dry Kieselgel (~30 g). After elution with ethyl acetate–methanol (10:1), the appropriate fractions were

combined and concentrated to give 4-deoxy-4-fluoro-D-glucose (440 mg, 70%), which, after recrystallisation from ethanol–light petroleum, had m.p. 186–189° and $[\alpha]_D$ +48° (equil., water).

1,2,3,6-Tetra-O-acetyl-4-deoxy-4-fluoro-β-D-glucopyranose (**6**). — 4-Deoxy-4-fluoro-D-glucose (250 mg) was acetylated with sodium acetate (500 mg) and boiling acetic anhydride (10 ml), in the usual manner. Elution of the syrupy product from Kieselgel (30 g) with ether–light petroleum (2:1), with combination and evaporation of the appropriate fractions, gave a syrup which crystallised from ether. Recrystallisation from ethanol gave **6** (149 mg, 31%), m.p. 127–129°, $[\alpha]_D$ −32° (Found: C, 48.3; H, 5.65; F, 5.7. $C_{14}H_{19}FO_9$ calc.: C, 48.0; H, 5.5; F, 5.4%).

1,6:3,4-Dianhydro-β-D-galactopyranose (**2**). — A solution of 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose[12] (**7**, 0.5 g) in methanol (150 ml) containing sodium methoxide derived from sodium (0.04 g) was irradiated in a quartz vessel with a 450-watt, high-pressure Hg lamp for 3 h. Nitrogen was bubbled through the solution during the reaction. The white precipitate was then removed, and the filtrate was concentrated. The syrupy residue was eluted from a column of dry Kieselgel (30 g) with ether–light petroleum (4:1). The appropriate fractions were combined and concentrated to give a syrup (229 mg, 95%) which crystallised on seeding. Recrystallisation from ether–light petroleum gave **2**, m.p. 69–71°, $[\alpha]_D$ −76° (water); lit.[14] m.p. 67–69°, $[\alpha]_D$ −80° (water).

On scaling up the reaction to 5-g quantities and using a 100-watt lamp, it was found that a 15-h reaction time was required. In the subsequent work-up, the use of a short column of silica gel and elution with chloroform gave a mixture of starting material and product. Recrystallisation of the mixture from chloroform–ethanol gave starting material (0.9 g, 18%). The mother liquors were concentrated to a syrup (1.1 g, 48%) which crystallised on seeding with **2**, but which contained a small amount of impurity. The material, however, was suitable for conversion into the fluoride **3**.

Treatment of **2** (25 mg) with pyridine (1 ml) and tosyl chloride (50 mg) at room temperature for 23 h, in the usual manner, regenerated **7** (35 mg, 68%), m.p. 148–150° (from chloroform–methanol), $[\alpha]_D$ −42°; lit.[10] m.p. 148–150°, $[\alpha]_D$ −42°.

Action of sodium amalgam on 1,6:3,4-dianhydro-2-O-tosyl-β-D-galactopyranose (**7**). — 10% Sodium amalgam (250 mg) was added to a stirred solution of **7** (50 mg) in methanol (10 ml) and water (2 ml). Monitoring by t.l.c. (ether–light petroleum, 4:1) revealed mostly starting material, along with some detosylated epoxide, after 2.25 h; mainly the starting material, as well as the 3,4-*galacto* (**2**) and 2,3-*gulo* epoxide (**8**) in approximately equal proportion, after 5.75 h; and mainly the 2,3-*gulo* epoxide after 3 days.

In a second experiment with methanol as solvent, the *galacto* epoxide was detectable within 30 min, but after 5.5 h the 2,3-*gulo* epoxide was detectable and much starting material remained.

1,6-Anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (**3**). — The dianhydride **2** (500 mg) was heated under reflux with a solution of potassium hydrogen fluoride (1.25 g) in ethane-1,2-diol (5 ml) for 1 h. The reaction mixture was poured into

saturated, aqueous sodium hydrogen carbonate (50 ml), Kieselgel was added, and the mixture was concentrated to dryness. The residue was added to a column of dry Kieselgel (100 g) and eluted with chloroform–methanol (25:1). The appropriate fractions were combined and concentrated to a syrup (254 mg, 45%) which crystallised on seeding. Recrystallisation from acetone–light petroleum gave **3**, m.p. 120–122° alone and in admixture with the product described above, $[\alpha]_D$ −53° (water).

Later fractions containing the product contaminated by ethane-1,2-diol were combined and concentrated to give material which was purified on a second column to yield a further crop (116 mg, 20%) of **3**. No satisfactory solvent alternative to ethane-1,2-diol was encountered. With solvents such as, for example, Methyl Cellosolve and hexanol, reaction proceeded very slowly.

1,6-Anhydro-4-deoxy-4-fluoro-2-O-tosyl-β-D-glucopyranose (**9**). — A solution of 1,6-anhydro-4-deoxy-4-fluoro-β-D-glucopyranose (**3**, 240 mg) and toluene-*p*-sulphonyl chloride (700 mg) in dry pyridine (6 ml) was kept at 55–60° and monitored by t.l.c. (chloroform–methanol, 25:1). After 5 days, only a small amount of starting material remained, and the reaction mixture was then concentrated to dryness in the presence of toluene. The syrupy residue was dissolved in acetone, Kieselgel (1 g) was added, and, after concentration, the residue was added to a column of dry Kieselgel (30 g). Elution with chloroform–methanol (25:1) gave **9** (370 mg, 80%), m.p. 114–116° (from ethanol–light petroleum), $[\alpha]_D$ −52° (Found: C, 49.1; H, 4.6; F, 6.3. $C_{13}H_{15}FO_6S$ calc.: C, 49.1; H, 4.7; F, 6.0%).

1,6:2,3-Dianhydro-4-deoxy-4-fluoro-β-D-mannopyranose (**10**). — A solution of **9** (298 mg) in methanol (10 ml) containing sodium methoxide (from 64 mg of sodium) was stored at room temperature and monitored by t.l.c. (ether–light petroleum, 4:1). After 20 h, only a small amount of starting material remained, and the reaction mixture, after neutralisation with 5% sulphuric acid, was concentrated to dryness in the presence of Kieselgel (~1 g). The residue was added to a column of dry Kieselgel (30 g) and eluted with ether–light petroleum to give material (120 mg, 88%) which was crystallised from ethanol–light petroleum to yield **10** (65 mg, 48%), m.p. 46–47.5°, $[\alpha]_D$ −61° (Found: C, 49.6; H, 4.9; F, 13.6. $C_6H_7FO_3$ calc.: C, 49.3; H, 4.8; F, 13.0%).

1,6-Anhydro-2,4-dideoxy-2,4-difluoro-β-D-glucopyranose (**11**). — (*a*) The fluoroepoxide **10** (60 mg) was treated with potassium hydrogen fluoride (130 mg) in boiling ethane-1,2-diol (2 ml) for 1 h; t.l.c. [ether–light petroleum (4:1)] then showed that the reaction was complete. The mixture was poured into aqueous sodium hydrogen carbonate and Kieselgel (5 g) was added. After concentration to dryness, the residue was added to a column of Kieselgel (~100 g). Elution with ether–light petroleum (4:1) gave material (40 mg, 59%) which was recrystallised from chloroform–light petroleum to give **11**, m.p. 99–100°, $[\alpha]_D$ −70° (water). Pacák *et al.*[21] recorded m.p. 99–100° and $[\alpha]_D$ −62° (water) for **11** synthesised by a different route.

(*b*) When the toluene-*p*-sulphonate **9** (4 g) was treated with potassium hydrogen fluoride (5 g) in boiling ethane-1,2-diol (10 ml) for 1 h, t.l.c. (ether–light petroleum, 4:1) indicated reaction to be complete. The reaction mixture was poured into saturated, aqueous sodium hydrogen carbonate (150 ml); Kieselgel (~10 g) was added,

and the mixture was concentrated to dryness. The residue was added to a column of dry Kieselgel (200 g), and elution with ether–light petroleum (2:1) gave material (179 mg, 8%) which was recrystallised from chloroform–light petroleum to give a product having m.p. 98.5–100° alone or in admixture with the product described in (*a*), $[\alpha]_D$ −70° (water).

2,3,6-Tri-O-acetyl-4-deoxy-4-fluoro-α (**12**) *and -β-D-glucopyranosyl fluoride* (**14**). — (*a*) A solution of syrupy 1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-fluoro-αβ-D-glucopyranose (2.3 g, described above) in liquid hydrogen fluoride (~4 ml) was stored at *ca.* −10° for 20 min and then poured into a vigorously stirred mixture of chloroform (40 ml) and saturated, aqueous sodium hydrogen carbonate (400 ml). The separated aqueous layer was washed twice with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and concentrated on to Kieselgel (10 g). The residue was added to a column of dry Kieselgel (~200 g) and eluted with ether–light petroleum (1:1). The appropriate fractions were combined and concentrated to give the syrupy α-difluoride **12** (79 mg, 48%), b.p. 145–155° (bath)/0.15 mmHg, $[\alpha]_D$ +54° (Found: C, 46.2; H, 5.2; F, 12.0. $C_{12}H_{16}F_2O_7$ calc.: C, 46.4; H, 5.2; F, 12.3%).

(*b*) The foregoing αβ-mixture of tetra-acetates (578 mg) was treated at room temperature with a 45% solution (6 ml) of hydrogen bromide in glacial acetic acid until dissolution was complete (~15 min). Evaporation was effected first at 50°/~15 mmHg and then at 50°/~0.3 mmHg. The resulting syrup was dissolved in dry acetonitrile (10 ml) and stirred vigorously at room temperature for 24 h with silver fluoride (1.2 g). The reaction mixture was diluted with a little acetone and then concentrated in the presence of Kieselgel. The residue was added to a column of dry Kieselgel (15 g) and eluted with ether–light petroleum (1:1). The appropriate fractions were combined and concentrated, and the residue (152 mg) was recrystallised from ether–light petroleum to give the β-difluoride **14** (109 mg), m.p. 82–83°, $[\alpha]_D$ −26° (Found: C, 46.1; H, 5.1; F, 12.2%).

ACKNOWLEDGMENTS

This investigation was supported by grants to the Chester Beatty Research Institute (Institute of Cancer Research: Royal Cancer Hospital) from the Medical Research Council and the Cancer Research Campaign, from the National Research Council of Canada (to L.D.H.), and from N.A.T.O. The authors are indebted to Dr. V. Wray (Imperial College, University of London) for determination of the n.m.r. spectra of the free sugars.

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