2-Deoxy-2-fluoro-D-glucose

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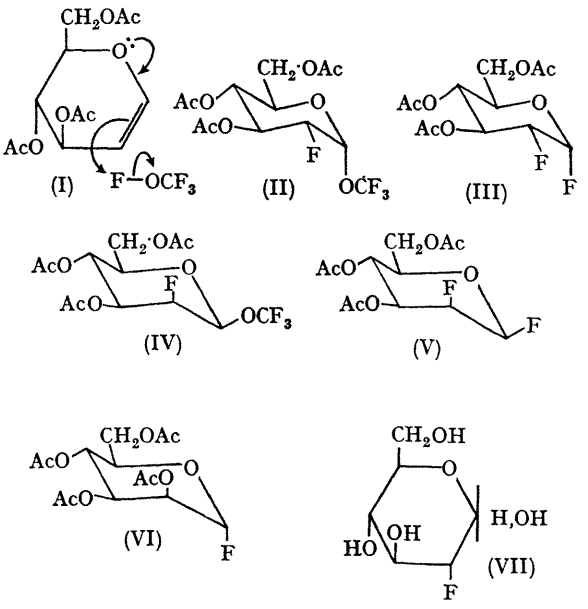
Summary 2-Deoxy-2-fluoro-D-glucose has been synthesized in a four-stage reaction sequence from D-glucose.

OF particular interest in a study of structure–activity relationships[1] involving substrates of hexokinase isozymes[2] are the fluorodeoxy-D-glucoses and their glycosyl fluorides, especially[3] compounds fluorinated at C-2. Until recently, only the 3- and 6-fluoro-derivatives were known.[4] A synthesis of 2-deoxy-2-fluoro-D-glucose,[5] prompts us to describe an alternative route.

Reaction of 3,4,6-tri-*O*-acetyl-D-glucal (I) in trichlorofluoromethane at −78° with fluoro-oxytrifluoromethane[6] gave a mixture of four products which could be resolved by t.l.c. [Kieselgel (Merck) 7731, light petroleum–ether (1 : 1), detection with conc. H_2SO_4] and g.l.c. (Pye 104 Chromatograph, SE 30, 170°, flame ionization detection). Elution of the mixture from Kieselgel (Merck, 7734) gave [in order of elution and after crystallisation, in each case, from ether–light petroleum (b.p. 100—120°)] trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranoside {(II), 26%, m.p 84—85°, $[\alpha]_D$ +158° ($CHCl_3$)}, 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride {(III), 34%, m.p. 91—92°, $[\alpha]_D$ +138° ($CHCl_3$)}, trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranoside {(IV), 5·5%, m.p. 96—97°, $[\alpha]_D$ − 21° ($CHCl_3$)}, and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride {(V), 7·6%, m.p. 113—114°, $[\alpha]_D$ −3·5° ($CHCl_3$)}. Compounds (II) and (III) were eluted with light petroleum–ether (4 : 1), and compounds (IV) and (V) with a solvent ratio of 2 : 1.



Coupling constants[a] (J *Hz.*) *for the products arising by the reaction of* 3,4,6-*tri*-O-*acetyl*-D-*glucal with* CF_3OF

	H(1)–H(2)	H(2)–H(3)	H(3)–H(4)	H(4)–H(5)	F(1)–H(2)	F(2)–H(1)	F(2)–H(3)
(II)	3·9	9·7	9·4	9·4		< 0·5	11·5
(III)	2·9	9·5	9·5	9·5	23·8	< 0·5	12·0
(IV)	~1·0	2·5	9·7	9·0		16	~25
(V)	1·0	2·6	8·7	7·5	7·6	12·8	21·4

[a] Data for $CDCl_3$ solutions at 100 MHz using a modified Varian HA-100 spectrometer operating in the frequency-sweep mode.

The structures of compounds (II)—(V), which gave satisfactory elemental analyses, were established by n.m.r. spectroscopy. The essential data are included in the Table. The α-D-*gluco*-configuration of compounds (II) and (III) is unequivocally established by the magnitude of the ^1H–^1H coupling constants[7] and the close similarity between the respective *J* values strongly suggests that both derivatives have the same conformation (*C*1). The value (23·8 Hz) of *J* [F(1)–H(2)] for compound (III) is close to that for other derivatives of α-D-glucopyranosyl fluoride[8] and the values of *J* [F(2)–H(3)] (11·5, 12·0 Hz) are similar to those[9] (12·8 Hz in each case) for *J* [F(3)–H(2)] and *J* [F(3)–H(4)] in 3-deoxy-3-fluoro-β-D-glucopyranose tetra-acetate.[4,10] The small magnitude (< 0·5 Hz) of *J* [F(2)–H(1)] for compounds (II) and (III) reflects the high total electronegativity of the substituents attached to C-1 and C-2 and, in particular, the antiplanar relationship between the C-2–F(2) and C-1–O(5) bonds.[11]

Likewise the magnitude of the ^1H–^1H *J* values for compounds (IV) and (V) unequivocally establishes the *manno*-configuration and the *C*1 conformation and confirmation is provided by the magnitude (20—25 Hz) of *J* [F(2)–H(3)] which is characteristic [8,12] of *trans*-diaxial orientation.

The suggested mechanism[13] favours *cis*-addition and hence the products should have the established α-D-*gluco*- and also the β-D-*manno*-configurations, the latter also being supported by n.m.r. data. The low value (*ca.* 2 Hz) for *J*[F(1)–H(2)] for 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl fluoride (VI) has been ascribed[12] to the antiplanar arrangement of the C-2–O(2)/C-1–F(1) and C-2–H(2)/C-1–O(5) bonds. Thus, the relatively high (7·6 Hz) value of *J*-[F(1)–H(2)] for compound (V) suggests that the C-1–F(1)

bond is not antiplanar to an electronegative substituent. Moreover, the vicinal coupling constants between nuclei which are nominally *trans*-diaxial in the mannosyl fluoride (V) are significantly smaller than in the trifluoromethyl analogue (IV). This difference is consistent with the presence of an equatorial fluorine atom at the anomeric centre in compound (V) and would be expected on the basis of the known[14] large anomeric effect[15] of a glycosidic fluorine atom causing a time-averaged decrease in the coupling constants.

The preponderance of products (II) and (III) having the *gluco*-configuration parallels observations on the reactions of 3,4,6-tri-*O*-acetyl-D-glucal with chlorine[16] and nitrosyl chloride[17] which have been rationalised in stereo-electronic terms.[16]

Hydrolysis of the trifluoromethyl glucoside (II) in boiling 5N-hydrochloric acid was complete in 4 hr. [t.l.c., Kieselgel (Merck, 7731), ethyl acetate–ether, 1 : 1] to give a single product (R_F *ca.* 0·9). After neutralisation (Ag_2CO_3) and elution of the product from Kieselgel (Merck, 7734), 2-deoxy-2-fluoro-D-glucose (VII) (91%) was obtained, m.p. 160—165° (from ethyl acetate), $[\alpha]_D$ + 56° (H_2O), which had the same mobility in t.l.c. and the same i.r. spectrum as the product {m.p. 170—176°, $[\alpha]_D$ + 62° (H_2O)} described by Pacák *et al.*[5] The wide and variable m.p. range of the fluoro-sugar (VII) probably reflects variations in the proportions of α- and β-anomers under different conditions of crystallisation.

Hydrolysis of the glucosyl fluoride (III) in boiling 3·5N-hydrochloric acid containing 33% ethanol appeared (t.l.c.) to be complete after 5 hr. but only 26·5% of crystalline 2-deoxy-2-fluoro-D-glucose could be isolated.† The other product(s) of hydrolysis remain to be identified.

Although only *ca.* 25% of the product mixture obtained by the action of CF_3OF on 3,4,6-tri-*O*-acetyl-D-glucal can be used efficiently at present for the synthesis of 2-deoxy-2-fluoro-D-glucose, the total reaction sequence involves four stages starting from D-glucose whereas the alternative synthesis[5] involves eight stages starting from starch as a precursor of 1,6-anhydro-D-glucose.

The glycosyl fluorides (III) and (V) are the first examples of a third type of difluorinated sugar derivative; geminal difluorides[18] (*e.g.*, 2,5-anhydro-1-deoxy-1,1-difluoro-D-mannitol) and 3,5-dideoxy-3,5-difluoro-D-xylose[19] exemplify the other types.

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† *Added in proof.* The yield was raised to 85% after hydrolysis with boiling N-HCl for 30 min.; *ca.* 60% of the product mixture (II)–(V) can therefore be converted efficiently into 2-deoxy-2-fluoro-D-glucose.

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