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FLUOROCARBOHYDRATES—XXVII[1]

2-DEOXY-2-FLUORO-L-FUCOSE: SYNTHESIS AND STRUCTURE

C. G. BUTCHARD and P. W. KENT*
Glycoprotein Research Unit, Durham University, U.K.

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Abstract—Addition of CF_3OF to 3,4-di-O-acetyl-L-fucal gave a 95% yield of two di-O-acetyl-2-deoxy-2-fluoro-L-fucosyl derivatives separable by column chromatography, both in crystalline form. The derivatives were identified by ^1H and ^{19}F-NMR to be the α-fluoride and the α-trifluoromethyl-glycoside. Acidic hydrolysis of either derivative gave the free sugar 2-deoxy-2-fluoro-L-fucose (non-crystalline), further characterised as the crystalline 1,3,4-tri-O-α-acetate.

The ease of addition of CF_3OF to readily available peracetylated glycals of pentoses[2,3,16,17] and hexoses[4-7] provides a convenient route to the synthesis of 2-deoxy-2-fluorosugars. In general, pairs of epimeric products result as *cis* glycosyl fluorides and trifluoromethyl glycosides.

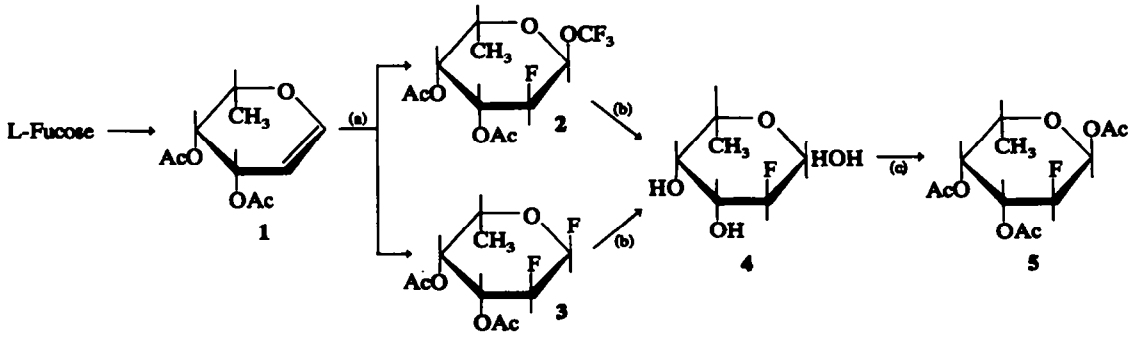
The mechanism of the addition reaction proposed by Barton *et al*[8] follows the stero-electronic explanation proposed for the addition of nitrosyl chloride to glycals,[9] accounting for the exclusively *cis* adducts with the fluorine at C-2 predominantly *trans* to substituent at C-3. Recently however, a similar addition to hexa-O-acetyl-D-lactal[10] has given products with F predominantly *cis* to the substituent at C-3, believed to be due to reduced conformation flexibility arising from presence of the second sugar in the disaccharide.

Fluoro-derivatives of L-fucose may be expected to be of some biochemical and immunological significance because of the distinctive role of the parent sugar as a component of antigenic determinant sites. Winterbourne *et al.*[11] have shown that 2-deoxy-2-fluoro-L-fucose appears to be taken up by mammalian fibroblasts in culture where it competes with L-fucose in glycoprotein biosynthesis.

Reviews of the methods of synthesis and chemical properties of fluorosugars have been published.[12,13]

DISCUSSION

Di-O-acetyl-L-fucal (**1**) can be readily synthesized from L-fucose by a two stage reaction.[14,15] Addition of CF_3OF to **1** proceeded smoothly and quantitatively at −70° under rigorously anhydrous conditions (see Scheme). Tlc and glc analysis show the presence of two major products with traces of two further products which were not further investigated. The major products were separated chromatographically on a silica column, and both were obtained in crystalline form from ether-petroleum. The first product was shown to be trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-L-fucoside (**2**) on the basis of proton and ^{19}F-NMR spectra. The compound **2** displayed two ^{19}F signals, $\phi_c(CF_3)+58.8$ ppm as a doublet (J, 1.25 Hz) which, as decoupling experiments (kindly performed by Dr. R. A. Dwek) showed, arose from OCF_3 coupling to F-2e. Similar couplings have



(a) CF_3OF in $CFCl_3$
(b) aq. HCl
(c) $(CH_3CO)_2O+HClO_4$

SCHEME—SYNTHESIS OF 2-DEOXY-2-FLUORO-L-FUCOSE

Table 1. ^{1}H and ^{19}F-Nuclear magnetic Resonance Data for 2-deoxy-2-fluoro-L-fucose (2,6-Dideoxy-2-fluoro-L-galactose) and Derivatives.

	Observed Coupling Constants (J, Hz.)											
Compound	[(H1)–(H2)]	[(H2)–(H3)]	[(H3)–(H4)]	[(H4)–(H5)]	[(H5)–(H6)]	[(F1)–(H1)]	[(F1)–(F2)]	[(F1)–(H2)]	[(F2)–(H1)]	[(F2)–(H2)]	[(F2)–(H3)]	[(F2)–(H4)]
2	3.9	9.5	3.5	~2	6.6		1.25*		<0.2	48.5	13.0	3.5
3	3.0	9.5	3.5	2.0	6.4	54.0	18.5	23.5	<0.2	49.0	11.5	4.3
4(β)									4.0	50.5	14.5	4.0
4(α)									<0.2	50.0	14.0	4.0
5	4.0	10.5	3.5		6.5				<0.5	49.5	11.5	3.8

been reported[7] in trifluoromethyl 2-deoxy-2-fluoro-α-D-galactoside. The further ^{19}F signals were assigned to F-2, $\phi_c(F_{2e})+209.9$ ppm, a multiplet J[F(2e)–H(2a)] 48.5 Hz, J[F(2e)–H(3a)] 13.0 Hz, J[F(2e)–H(4e)] 3.5 Hz, J[F(2e)–CF_3] 1.4 Hz.

The second product was identified as 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-L-fucosyl fluoride (**3**), having two sets of ^{19}F-NMR signals. The axial conformation of F-1 was shown from the signal $\phi(F_{1a})+148.1$ ppm, J[F(1a)–H(1e)] 54.0 Hz, J[F(1a)–H(2a)] 23.5 Hz, J[F(1a)–F(2e)] 18.5 Hz. The equatorial conformation of F-2 was shown by the results $\phi_c(F_{2e})+211.7$ ppm J[F(2e)–H(2a)] 49.0 Hz, J[F(2e)–F(1a)] 19.0 Hz, J[F(2e)–H(3a)] 11.5 Hz and J[F(2e)–H(4e)] 4.3 Hz.

Acidic hydrolysis of either product (**2, 3**) gave 2-deoxy-2-fluoro-L-fucose (**4**) as a chromatographically pure syrup. NMR measurements in D_2O showed it to be as mixture of anomers with a ratio α:β of 1:2.5. The fluorine NMR signals were $\phi_c(F_{2e}, \alpha)+205.8$ ppm. J[F(2e)–H(2a)] 50.0 Hz, J[F(2e)–H(3a)] 14.0 Hz, J[F(2e)–H(4e)] 4.0 Hz and $\phi_c(F_{2e}, \beta)+206.1$ ppm., J[F(2e)–H(2a)] 50.5 Hz, J[F(2e)–H(3a)] 15.5 Hz, J[F(2e)–H(4e)] 4.0 Hz. By glc measurements of the trimethylsilyl derivative, **4** showed a ratio of anomers of 1:4(α/β).

Peracetylation of **4** with acetic anhydride-perchloric acid gave the corresponding α-tri-O-acetate (**5**) as a crystalline derivative having $\phi_c(F_{2e})+209.9$ ppm., J[F(2e)–H(2a)] 49.5 Hz, J[F(2e)–H(3a)] 11.5 Hz, J[F(2e)–H(4e)] 3.8 Hz and J[F(2e)–H(1e)] 0.5 Hz. The ^{19}F-spectra of **5** showed second order coupling caused by the similarity of the shifts possessed by H_{3a} (4.61τ) and H_{4e}(4.67τ). Similar second order coupling of F_{2e} can be observed in spectra of **2** and **3** and is present in the corresponding D-*galacto* derivatives.[7,16].

It is of interest that, unlike pentose glycals,[2,17] where complex products results, only two significant products are present in the CF_3OF addition to peracetyl fucal.

EXPERIMENTAL

Chromatographic separations and analytical methods were carried out as described by Butchard and Kent.[17]

NMR measurements were carried out using a Bruker MFX-90 spectrometer operating at 27° and at 90 MHz for ^1H spectra or 84.67 MHz for ^{19}F. Fluorine chemical shifts (ϕ_c) are quoted with reference to $CFCl_3$. Results are summarized in the Table.

Addition of CF_3OF *to* 3,4-*di*-O-*acetyl*-L-*fucal* (**1**). The acetylated fucal (5 g) was dissolved in dry $CFCl_3$ (80 ml) and cooled to −70°. After flushing the apparatus with dry N_2, fluoroxytrifluoromethane (CF_3OF, ca 3g, 20% excess) was slowly (2 bubbles per second) passed into the stirred soln until no starting material remained (as detected externally by $KMnO_4$). The mixture was purged with dry N_2 and allowed to warm to room temp. Dry $CHCl_3$ (100 ml) was added and $CFCl_3$ was removed under diminished pressure. After addition of further $CHCl_3$ (400 ml), sat $NaHCO_3$ aq (400 ml, twice) and water (400 ml) and was finally dried (Na_2SO_4). Removal of $CHCl_3$ gave the products (6.8 g) containing 18.2% of fluorine. Glc showed two major products R_T (120°) 5.6 min and 6.8 min and two trace products (<2%) at 8.1 and 9.4 min. (cf R_T (120°) for **1**, 6.3 min) Tlc (in ether:petroleum 2:3 (v/v) on plates of Kieselgel PF245) showed two compounds R_f 0.42 and 0.39 (cf R_f 0.40 for **1**).

The major products were separated by preparative chromatography on a silica column (4.0 cm × 95 cm) by elution with ether/petroleum (2:13 v/v).

Trifluoromethyl 3,4-*di*-0-*acetyl*-2-*deoxy*-2-*fluoro*-α-L-*fucopyranoside* (**2**). This compound (3.1 g, 42%) was obtained first as a colourless syrup from column fractions between 1,860 and 2,040 ml of eluate. On storage (−20°) **2** crystallised from ether-petroleum, m.p. 58°, $[\alpha]_{546}^{22}$ −198.2° (*c*0.50, $CHCl_3$) (Found: C, 41.7: H, 4.5; F, 24.2 Calc. for $C_{11}H_{14}F_4O_6$: C. 41.5; H, 4.4; F, 23.9%). Tlc in ether-petroleum (2:3 v/v) gave one spot, R_f 0.42; and glc a single peak R_T (120° const) 4.6 min.

3,4-*Di*-0-*acetyl*-2-*deoxy*-2-*fluoro*-α-L-*fucopyranosyl fluoride* (**3**). The product **3**, (2.8 g; 48%) was obtained in column fractions eluting between 2,100 ml and 2,360 ml, which crystallised from the eluting solvent on storage at −20° m.p. 46°$[\alpha]_{546}^{22}$ −187.6°(*c* 0.48, $CHCl_3$) (Found: C, 48.0; H, 5.4; F, 15.4 Calc. for $C_{10}H_{14}F_2O_5$: C, 47.6; H, 5.6; F, 15.1%). Tlc in the above solvent gave a single spot R_f 0.39 and glc a single peak R_T (120°) 6.8 min.

2-*Deoxy*-2-*fluoro*-L-*fucose* (**4**). Treatment of either **2** or **3** (1g) with 2M HCl (50 ml) at 100° for 2 hr, gave the reducing sugar **4**. The soln, neutralised ($PbCO_3$) filtered and de-ionized on Amberlite MB3 resin, was evaporated under reduced pressure to furnish **4** as a colourless glass. (0.35g. from **2**, 67%; 0.49 g from **3**, 74%; $[\alpha]_{546}^{22}$ −91.2° (*c* 0.35, H_2O) (Found: C, 42.6; H, 6.9; F, 11.1 Calc. for $C_6H_{11}FO_4$: C, 43.4; H, 6.6; F, 11.5%). Paper chromatography on Whatman No. 1 paper in water-poor phase of ethyl acetate/pyridine/water 8:2:1 (v/v) gave a single component R_f 0.39 and glc showed two components R_T (120°) 5.2 and 6.0 min (as the trimethylsilyl derivative) *cf* L-fucose gave R_T (150°) 10.7 and 12.8 min).

1,3,4-*Tri*-*O*-*acetyl*-2-*deoxy*-2-*fluoro*-α-L-*fucopyranose* (**5**). The fluorosugar **4**, (0.4 g) was dissolved in cooled dry Ac_2O (15 ml, 10°) containing perchloric acid (0.1 ml) and stirred for 10 min. CH_2Cl_2 (80 ml) was added and the soln washed thoroughly with water and $NaHCO_3$ aq. Finally it was dried ($MgSO_4$), filtered and evaporated to dryness. The acetylated product **5** (0.31 g; 45%) was crystallised from ether/dry EtOH m.p. 105° $[\alpha]_{546}^{22}$ −218.7°(*c* 0.45, $CHCl_3$). (Found: C, 49.3; H, 5.7; F, 6.9 Calc. for $C_{12}H_{17}FO_7$: C, 49.3, H, 5.8; F, 6.5%). Tlc (conditions as for **2**) gave a single component R_f 0.29 and glc a single component R_T (150°) 5.1 min. Proton NMR measurements (in $CDCl_3$) confirmed the α-anomeric structure, H_{1e} at 35.8τ, J[H(1e)–H(2a)] 4.0 Hz.

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