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FLUOROCARBOHYDRATES—XXVIII[1]

SYNTHESIS AND CHARACTERISATION OF 2-DEOXY-2-FLUORO-DERIVATIVES OF L-RHAMNOSE AND L-EPIRHAMNOSE

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Abstract—Addition of CF_3OF to 3,4-di-O-acetyl-L-rhamnal gave four products separable by fractional crystallisation and column chromatography. The two principal products were in the epirhamnose series, i.e. trifluoromethyl 3,4-di-O-acetyl-2,6-dideoxy-2-fluoro-α-L-glucoside and 3,4-di-O-acetyl-2,6-dideoxy-2-fluoro-α-L-glucosyl fluoride. The lesser products were in the rhamnose series *viz.* trifluoromethyl 3,4-di-O-acetyl-2,6-dideoxy-2-fluoro-β-L-mannoside and 3,4-di-O-acetyl-2,6-dideoxy-2-fluoro-β-L-mannosyl fluoride. The structures were confirmed by ^1H and ^{19}F NMR spectral measurements. Deacylation and acidic hydrolysis gave the free 2-deoxy-2-fluoro sugars of both series.

Previous studies[1] showed that diacetyl - L - fucal underwent a ready addition reaction with CF_3OF gave a large predominance of 2 - deoxy - 2 - fluorofucose derivatives. The biochemical interest in such compounds arises from the possibilities which they offer of metabolically influencing the incorporation of L-fucose into key antigenic determinant sites in animal systems.[2] In bacterial and plant systems, L-rhamnose (6 - deoxy - L - mannose) is distinctive and is known to contribute to antigenicity eg. in the pneumococcal Type II polysaccharide.[3,4].

Comparable addition reactions have been carried out in the pentose[5-7] and hexose[8-11] series and with the disaccharide glycal, hexa - O - acetyllactal.[12]

DISCUSSION

Di - O - acetyl - L - rhamnal (1), readily obtainable via the corresponding peracetylated glycosyl bromide[13,14] was found to undergo quantitative addition of CF_3OF at $-70°$ giving four chief products, detectable by glc (Scheme). In this respect, the reaction is notably more complex than that with the corresponding L-fucal derivative.[1] The major products were separable after favourable conditions for column chromatography on silica had been established since the separation was particularly sensitive to the rate of column elution. No satisfactory separation could be achieved by tlc. Fortunately, on concentration of the mixed products, one component crystallised spontaneously and this proved to be 3, 4 - di - O - acetyl - 2 - deoxy - 2 - fluoro - α - L - epirhamnosyl fluoride (3). Preparative chromatography of the mother liquors on a silica column then furnished a further major product which crystallised on concentration of the eluate, and this was shown to be trifluoromethyl 3, 4 - di - O - acetyl - 2 - deoxy - 2 - fluoro - α - L - epirhamnoside (2). The lesser products trifluoromethyl 3, 4 - di - O - acetyl - 2 - deoxy - 2 - fluoro - β - L - rhamnoside (4) and 3, 4 - di - O - acetyl - 2 - deoxy - 2 - fluoro - β - L - rhamnosyl fluoride (5) were obtained crystalline from the corresponding column fractions.

The structure of the products was established by elemental analysis and by ^1H and ^{19}F NMR spectral measurements as summarised in Table 1.

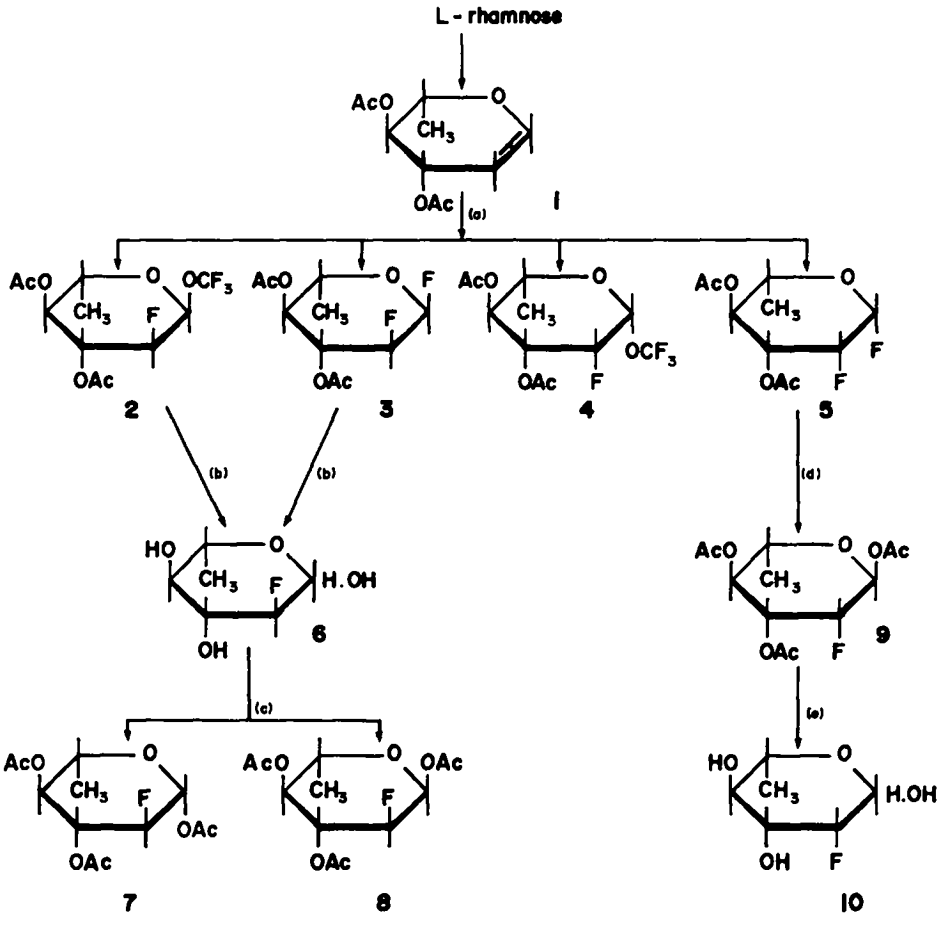
The α - epirhamnoside (2) had a characteristic chemical shift $\phi_c(CF_3) + 58.9$ ppm originating from the aglycone. This was a doublet, J = 0.8Hz, comparable with the coupling constant J = 0.5Hz found for the corresponding trifluoromethyl 2 - deoxy - 2 - fluoro - D - glucoside.[15] By contrast, the ^{19}F NMR signal from OCF_3 in the fluoro - β - L - rhamnoside (4) was a sharp singlet, as has been reported also for the corresponding fluoro - β - D - mannoside derivative.[15]

Deacylation of 2 or 3 with methanolic ammonia, followed by mild acidic hydrolysis cleaved the fluorine or glycosidic group respectively and gave the free reducing sugar 6; 2 - deoxy - 2 - fluoro - L - epirhamnose (2, 6 - dideoxy - 2 - fluoro - L - glucose). Glc analysis of the trimethylsilyl derivative of 6, showed two anomeric components $\beta:\alpha$ in the ratio 3:2 similar to the ratio determined from NMR spectra. The fluorine signal consisted of overlapping multiplets with ϕ_c(F2, β) + 197.2 ppm, J[F(2e) − H(1a)] 2.5Hz and ϕ_c(F2, α) + 197.0 ppm, J[F(2e) − H(1e)] 0.1 Hz.

Acetylation of the epirhamnose (6) with acetic anhydride and perchoric acid gave a mixture of α and β-triacetates not separable by tlc or even by glc. A crystalline product was a mixture of α and β isomers (8, 7) in the ratio of 1:2, respectively as indicated by ^1H and ^{19}F NMR measurements. Repeated recrystallisation of the mixed crystals did not appear to change their composition, the m.p. remained sharp and constant and the optical rotation was not affected. The main adducts (2 and 3) showed signals with J[F(2e) − H(3a)] 12Hz and J[F(2e) − H(1e)] 0.2Hz confirming the α-L-*gluco* configuration for these fluoroepirhamnose derivatives.

The axial anomeric F in 3 and the OCF_3 group in 2 and the $-OCF_3$ group in the rhamnose adduct 4 all resisted displacement by acetolysis.

Chromatography and crystallisation furnished pure specimens of the fluororhamnose adducts 4 and 5. NMR spectra measurements (summarised in Table 1) of the



(a) CF_3OF in $CFCl_3$ (b) NH_3-MeOH; 2M-HCl (c) $Ac_2O/HClO_4$ (d) Ac_2O/NaAc (e) NH_3-MeOH

Scheme 1. Synthesis of 2-deoxy-2-fluoro-L-rhamnose and -epirhamnose.

trifluoromethyl 3, 4 - di - O - acetyl - 2 - deoxy - 2 - fluoro - β - L - rhamnoside (4) showed a signal from OCF_3 having $\phi_3(CF_3)+54.3$ ppm and from F-2a of 220.8 ppm (J [F(2a)-H(1a)] 17Hz, J [F(2a)-H(3a)] 30.0Hz. The fluororhamnosyl fluoride 5 had fluorine signals ϕ_c(F1e)+148.3 ppm) with coupling constants J [F(1e)-F(2a)] 13.0 Hz and J [F(1e)-H(2e)] 4.2Hz. The F-2 signals had a chemical shift ϕ_c(F2a)+221.6 ppm with J [F(2a)-H(3a)] 28.0Hz, J [F(2a)-H(1a)] 17.0Hz and J [F(2a)-F(1e)] 13.0Hz.

Acetolysis of the fluororhamnosyl fluoride (5) gave 1, 3, 4 - tri - O - acetyl - 2 - deoxy - 2 - fluoro - α - L - rhamnose (9) as a crystalline derivative in 85% yield. De-acylation of 9 with methanolic ammonic yield the free sugar, 2 - deoxy - 2 - fluoro - L - rhamnose (10) as a non-crystalline syrup. In D_2O, this was an anomeric mixture of α/β forms in the ratio 3:1 respectively. The sugar (10) exhibited F-signals, ϕ_c(F2a, β-anomer)+221.2 ppm having J [F(2a)-H(1a)] 20Hz and ϕ_c (F2a, α-anomer)+202.7 ppm, with J [F(2a)-H(1e)] 8.0Hz. Glc analysis indicated an anomeric ratio α/β of 4:1. In principle the ^1H and ^{19}F responses for these 2-fluororhamnose derivatives closely resembled those reported in corresponding 2 - deoxy - 2 - fluoro - D - *manno* series.[8,15]

In comparing the outcome of CF_3OF addition to diacetyl - L - fucal and diacetyl - L - rhamnal, it is apparent that the axially directed acetoxy group at C-4 in the former exerts a marked influence on the steric electrophilic attack at C-2 and strongly favours the *galacto*-configuration in the products as the yield of the *galacto* pair is near quantitative. Further in these products the anomeric F or OCF_3 substituent is axial *and trans* to the C-4 substituent. In the rhamnal reaction, the acetoxy groups at C-4 and C-3 are both equatorially directed and allow easier access of the fluoroxytrifluoromethane at $\Delta^{1,2}$ and thus the *gluco* configuration is found in the predominating products (53%). Nevertheless a significant amount (23%) of the *manno*-adducts is present. The extracylic methyl group at C-6 appears to exert little influence on the outcome of the reaction since similar results are obtained[5,7] with diacetylxylal where the two *lyxo* products greatly preponderate and also have trans diaxial substituents at C-1 and C-4. In contrast to this, addition to diacetylarabinal leads to the more complex mixture of products.[5]

EXPERIMENTAL

Chromatographic procedures and analytical techniques were as used previously.[1,7]

NMR measurements. Spectra were measured on a Bruker MFX-90 instrument operating at 27°. Measurements were made at 90 MHz for ^1H and 84.76 MHz for ^{19}F. For acetylated derivatives $CDCl_3$ was used as solvent and for free sugars, D_2O. Fluorine chemical shifts were determined with reference to $CFCl_3$. Other details are as previously described.[16].

Table 1. ^{1}H and ^{19}F NMR data for 2,6-dideoxy-2-fluror-L-hexoses and derivatives

Compound	Observed Coupling Constants (J, Hz.)											
	H(1)–H(2)	H(2)–H(3)	H(3)–H(4)	H(4)–H(5)	H(5)–H(6)	F(1)–H(1)	F(1)–F(2)	F(1)–H(2)	F(2)–H(1)	F(2)–H(2)	F(2)–H(3)	F(2)–H(4)
2	4.0	9.5	9.5	9.5	6.2		0.8*		< 0.5	48.0	12.0	
3	3.2	9.8	9.8	9.8	6.2	53.5	19.0	24.0	0.2	48.0	12.5	
4	< 0.5	2.2	9.8	8.5	6.2		0*		17.0	50.5	30.0	~ 2
5	< 0.5	2.3	9.5	7.5	6.2	48.5	13.0	4.2	17.0	52.0	28.0	
6 (α)									2.5	50.5	16.0	
6 (β)									< 0.1	49.5	14.5	
7	8.0	9.5	9.5	9.5	6.5				3.5	51.5	14.5	
8	4.0	9.5	9.5	9.5	6.5				< 0.5	49.0	12.5	
10 (α)									20.0	51.0	30.0	
10 (β)									8.0	49.5	30.5	
9									7.5	49.0	30.0	

* anomeric $-OCF_3$ group

Addition of CF_3OF to 3, 4 - *di* - O - *acetyl* - L - *rhamnal* (1). The diacetate (1, 5g) dissolved in dry trichlorofluoromethane (80 ml) and cooled to −70°, was treated with fluoroxytrifluoromethane (~3g, 30% excess) under the same conditions as reported for diacetylfucal.[1] The progress of the reaction was monitored until complete, i.e. until test samples no longer reacted with alkaline $KMnO_4$. The mixture was diluted with dry $CHCl_3$ (100 ml), purged with dry N_2, and the mixed products (5g) isolated.[1] Glc analysis showed the presence of four compounds R_T(120°) 3.9 min and 4.8 min with lesser products R_T(120°) 5.7 and 7.4 min (cf starting material 1, 5.3 min).Tlc on Kieselgel PF254 with ether/petroleum (2:3, v/v) as solvent showed one major component R_f 0.4 and minor components R_f 0.24 and 0.18 (*cf* R_f of 1, 0.46). During the removal of the solvent from the mixed products, 3, 4 - *di* - O - *acetyl* - 2 - *deoxy* - 2 - *fluoro* - *α* - L - *epirhamnosyl fluoride* (3) crystallised spontaneously; having, after recrystallisation, m.p. 152°, yield 1.35 g, (22%), $[\alpha]_{546}^{22}$ − 188° (*c* 0.46 $CHCl_3$). (Found: C, 47.6; H, 6.6; F, 14.6. Calc. for $C_{10}H_{14}F_2O_5$: C, 47.6; H, 6.6; F, 15.1%).Tlc (in preceding conditions) showed one spot R_f 0.39, and glc a single peak, R_t (120°) 4.8 min.

The collected mother liquors were passed down a silica column (type SO/tlc; 4.0 cm × 40 cm) with ether–petroleum (2:3, v/v) as solvent. The emergence of the separated products was followed by repeated glc analysis, the extent of the overlaps which illustrates the difficulty of the separation being shown in Fig. 1.

Trifluoromethyl 3, 4 - *di* - O - *acetyl* - 2 - *deoxy* - 2 - *fluoro* - *α* - L - *epirhamnoside* (2). The first eluted fraction (2010 to 2130 ml of elutant) provided the 2 as shown in Fig. 1. The product (2.3g, 31%) crystallised on concentration of the soln and had, after recrystallisation from ether/petroleum, m.p. 115° $[\alpha]_{546}^{22}$ -201.8° (*c* 0.50, $CHCl_3$). (Found: C, 41.3; H, 4.3; F, 24.6: Calc. for $C_{11}H_{14}F_4O_6$: C, 41.5; H, 4.4; F, 23.9%). Tlc (conditions as above) gave a single spot, R_f 0.41 and glc a single peak R_t (120°) 3.9 min.

Trifluoromethyl 3, 4 - *di* - O - *acetyl* - 2 - *deoxy* - 2 - *fluoro* - *β* - L - *rhamnoside* (4). This product was isolated from the column fractions when between 2280 ml and 2510 ml of elutant had been obtained. The product (3, 595 mg, 11%) after recrystallisation from ether/petroleum had m.p. 94°, $[\alpha]_{546}^{22}$ + 22.0° (*c* 0.47, $CHCl_3$) (Found: C, 41.9; H, 4.3; F, 24.4. Calc. for $C_{11}H_{14}F_4O_6$: C, 41.5; H, 4.4; F, 23.9%). Tlc (as before) showed one spot R_f 0.24 and glc a single peak, R_t (120°) 5.7 min.

3,4-*Di*-O-*acetyl*-2-*deoxy*-2-*fluoro*-2-*β*-L-*rhamnosyl fluoride* (5). This compound was isolated from the column effluent, 2650–2940 ml and crystallised spontaneously on removal of the solvent. The product 5 after recrystallisation from dry ether had m.p. 87° $[\alpha]_{546}^{22}$ + 7.1° (*c* 0.48, $CHCl_3$) yield 710 mg (12%) (Found: C, 47.5; H, 5.4; F, 14.6. Calc. for $C_{10}H_{14}F_2O_5$: C, 47.6; H, 5.6; F, 15.1%). The product was homogenous by tlc (R_f 0.18, condition as above) and by glc analysis (R_t(120°) 7.4 min).

2 - *Deoxy* - 2 - *fluoro* - L - *epirhamnose* (2, 6 - *dideoxy* - 2 - *fluoro* - L - *glucose* (6). Treatment of either epirhamnose derivative 2 or 3 (1g) with dry methanolic ammonia (saturated, 20 ml) for 30 min brought about quantitative deacetylation, as determined by glc. After removal of ammonia and solvent under reduced pressure, the material was dissolved in 2M HCl (20 ml) and kept at room temp for 3 hr. The neutralised ($PbCO_3$) soln was passed through an Amberlite MB3 column and then was concentrated to dryness *in vacuo*. The resulting reducing sugar (6) was obtained as a colourless glass (420 mg, 82% from 2 and 450 mg, 86% from 3). The products $[\alpha]_{546}^{22}$ − 49.6° (*c* 0.52, H_2O) was homogeneous by paper chromatography R_g 8.0 (Whatman No. paper; EtOAc/pyridine/water (8:2:1, v/v/v) as solvent. Glc of the silylated derivative, revealed two peaks R_t (150°) 5.6 and 7.1 min, in the ratio 2:3.

1, 2, 4 - *Tri* - O - *acetyl* - 2 - *deoxy* - 2 - *fluoro* - *α*/*β* - L - *epirhamnoses* (7, 8). The fluoroepirhamnose 6 (0.1 g) was treated with Ac_2O-perchloric acid[1] gave mixed *β* and *α*-acetates (7 and 8) yield 113 mg, 86% having m.p. 126° after several recrystallisations, $[\alpha]_{546}^{22}$ − 152° (*c* 0.4, $CHCl_3$). The mother liquors from the recrystallisation were found by ^{19}F NMR to contain predominant the *α*-triacetate though this was not crystallised. Tlc of the mixed crystals showed a single spot R_f 0.29 and glc a single peak R_t (150°) 5.1 min. The evidence for the presence of *α* and *β* anomers in the ratio of 1:2 rests on ^1H and ^{19}F NMR measurements as set out in the Discussion and the Table.

1, 3, 4 - *Tri* - O - *acetyl* - 2 - *fluoro* - *α* - L - *rhamnose* (9). Displacement of the anomeric fluorine in 5 was achieved when that compound (0.4 g) was treated with Ac_2O (5 ml) glacial AcOH (0.5 ml) and anhyd NaOAc (1 g) in a sealed tube at 140° for 24 h. The mixture, poured into water, was extracted with CH_2Cl_2 repeatedly and the organic soln was washed in the usual manner. The product was purified on a silica column (4 cm × 95 cm) being eluted with ether/petroleum (2:3, v/v). Concentration of the eluted soln (between 1870 ml and 2030 ml) gave the crystalline 9, which after recrystallisation from dry ether had m.p. 136° $[\alpha]_{546}^{22}$ − 121.4° (*c*, 0.2, $CHCl_3$) yield 350 mg (69%). Some starting material (48 mg, 12%) was recovered from later column fractions. (Found: C, 49.5; H, 5.9. Calc. for $C_{12}H_{17}FO_7$: C, 49.3; H, 5.8%). The product was homogeneous by tlc (preceding conditions) R_f 0.21 and by glc, R_t (150°) 5.1 min. The presence of fluorine was established by ^{19}F NMR and the coupling J [F(2a)-H(1e)] 7.5Hz confirmed the *α*-configuration.

2 - *Deoxy* - 2 - *fluoro* - L - *rhamnose* (2, 6 - *dideoxy* - 2 - *fluoro*

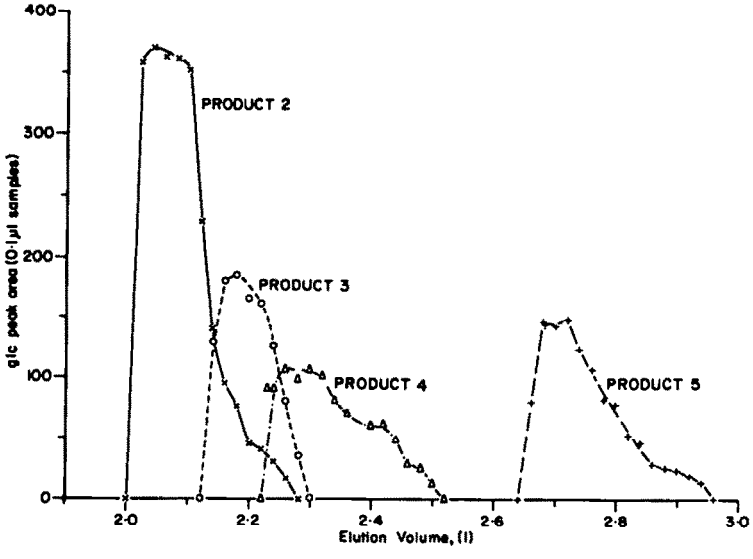


Fig. 1. Chromatographic separation of reaction products of addition of CF_3OF to 3,4-di-*O*-acetyl-L-rhamnal. Column fractions were individually analysed by glc. Products designated as in Scheme.

- L - *mannose*) **10**. The free sugar was obtained by deesterification of the triacetate (**9**, 250 mg) using MeOH–NH_3 (saturated, 20 ml) for 30 min, when the reaction was observed to be complete by glc measurements. Removal of the solvent under reduced pressure gave **10** as a colourless glass, yield 153 mg (95%), $[\alpha]_{546}^{22}$ + 2.5 (*c* 0.18, H_2O) (Found: C, 42.8; H, 6.9. Calc. for $C_6H_{11}FO_4$: C, 43.4; H, 6.6%). Paper chromatographic analysis (conditions as above) gave a single spot, R_g 7.8 (*cf* L-rhamnose, R_g 3.6) and glc of the trimethylsialated derivative showed two peaks, R_t (150°) 5.8 and 8.2 min in ratio 4:1 (*cf* values for L-rhamnose, R_t (150°) 8.8 and 12.1 min in ratio 2:1). The presence of F was confirmed by ^{19}F NMR measurements (Table).

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