FLUORINATED CARBOHYDRATES

PART XIII[1]. 2-DEOXY-2-FLUORO-D-GALACTOSE

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ABSTRACT

Reaction of trifluoro(fluoroxy)methane at *ca.* −80° with 3,4,6-tri-*O*-acetyl-D-galactal affords trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranoside (**2**, 39%), 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl fluoride (**3**, 37%), trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-talopyranoside (**4**, 3%), and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-talopyranosyl fluoride (**5**, 2%). The structures of compounds **2**–**5** have been established by n.m.r. spectroscopy. Acid hydrolysis of **2** or **3** affords 2-deoxy-2-fluoro-D-galactose.

INTRODUCTION

Terminal, non-reducing D-galactopyranosyl residues occur in many antigens of biological interest, and lactose has been employed as a hapten in numerous immunochemical studies[2]. The replacement of a hydroxyl group in a galactose residue by a fluorine substituent may offer a means to use ^{19}F n.m.r. spectroscopy to probe the conformations of galactose residues (in, for example, lactose and galactosides) involved in binding to antibodies and enzymes, thereby, enabling structure–activity relationships to be defined. It is now established[3–5] that, for deoxyfluoro-D-glucoses, the extensive vicinal and long-range (^4J, ^5J) F–H coupling permits the conformation of a major part, if not the whole, of the molecule to be assessed from the ^{19}F-resonance. The complete series of deoxyfluoro-D-galactopyranoses was, therefore, required. The 3-, 4-, and 6-fluoro derivatives have been described[6–8], and we now report in detail the synthesis of 2-deoxy-2-fluoro-D-galactose[9]. Methods for the condensation of the deoxyfluoro-D-galactopyranoses with D-glucose derivatives are at present being evaluated. These data, the series of *p*-nitrophenyl galactosides, and the biochemical results will be reported elsewhere.

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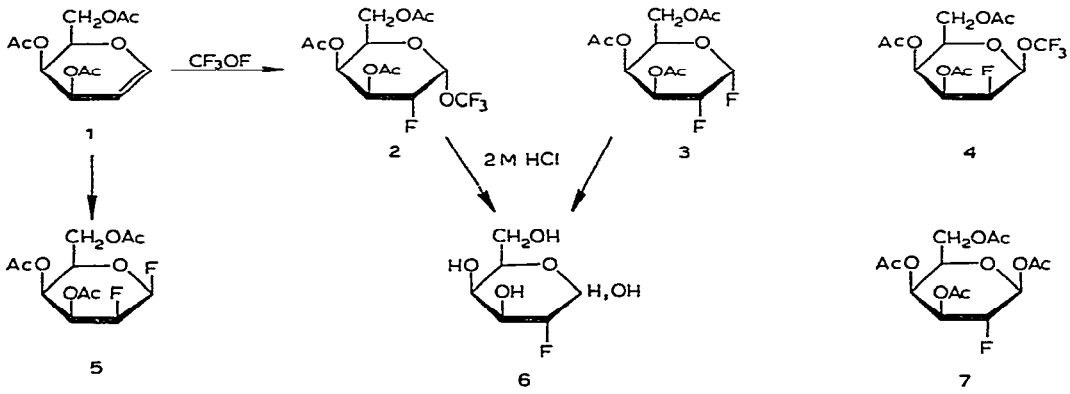
RESULTS AND DISCUSSION

The general background to the reaction of trifluoro(fluoroxy)methane[10,11] with glycals, some mechanistic considerations, and points of special practical importance have been described[12].

Reaction of tri-*O*-acetyl-D-galactal (**1**) in chlorotrifluoromethane at *ca.* −80° with trifluoro(fluoroxy)methane (1.2 mol.) was complete within 2 h and gave a mixture of four products which could be separated by chromatography on Kieselgel, to afford, in order of elution, trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranoside (**2**, 39%), 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl fluoride (**3**, 37%), trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-talopyranoside (**4**, 3%), and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-talopyranosyl fluoride (**5**, 2%).



The yields of the *galacto* compounds are for recrystallised products, and could, undoubtedly, be improved by re-chromatography of the mother liquors. Yields of the *talo* compounds are after re-chromatography and distillation. The *galacto–talo* ratio (13:1) is somewhat greater than the *gluco–manno* ratio reported[12] (4:1), and may be taken as a measure of the steric influence exerted by the quasi-axial 4-acetyl group above the ring in **1**, resulting in the attack of the double bond from above the ring being even less favoured. This has been reported previously and discussed in detail in stereo-electronic terms[13], with particular reference to the chloromethoxylation of tri-*O*-acetyl derivatives of D-glucal and D-galactal.

The structures of compounds **2**–**5** were established by n.m.r. spectroscopy, and the essential data are given in Table I. The α-D-*galacto* configuration of **2** and **3** follows from the magnitude of the vicinal ^1H–^1H coupling constants[14]. This is confirmed by the vicinal ^1H–^{19}F coupling constants[14], and the ^4J coupling (3.5 Hz) between F-2 and H-4 is consistent with a planar-W relationship[3] inherent in the D-galactopyranoid configuration in the *C1*(D) conformation. The fluorines ubstituents of the $-OCF_3$ group were coupled (J 1.5 Hz) to F-2 as shown by decoupling exper-

TABLE I

COUPLING CONSTANTS[a] J (IN Hz) FOR THE PRODUCTS FROM THE REACTION OF 3,4,6-TRI-*O*-ACETYL-D- GALACTAL WITH CF_3OF

Compound	*H−1/H−2*	*H−2/H−3*	*H−3/H−4*	*H−4/H−5*	*F−1/H−1*	*F−1/H−2*	*F−1/F−2*	*F−2/H−1*	*F−2/H−2*	*F−2/H−3*	*F−2/H−4*
2	3.7	10.5	3.5	1.0				0.5	48.5	11.0	3.5
3	2.7	9.7	3.2	1.0	52.5	23.0	18.0	0.5	48.0	11.0	3.5
4	1.0	3.0	3.5	1.0				16.5	51	29	
5	1.0	3.0	3.0	1.0	48	6.0	12.0	14.5	51	25	

[a]Data refer to solutions in $CDCl_3$; they were obtained with a modified Varian HA-100 spectrometer operating in the field-sweep mode at 100 MHz for ^1H spectra and in the frequency-sweep mode at 94.1 MHz for ^{19}F spectra.

TABLE II

COUPLING CONSTANTS J (IN Hz) FOR 2-DEOXY-2-FLUORO-D-GALACTOSE

Solvent	*Anomer*	*H−1/H−2*	*H−2/H−3*	*H−3/H−4*	*H−4/H−5*	*F−2/H−2*	*F−2/H−1*	*F−2/H−3*	*F−2/H−4*	*H−1/OH−1*
Me_2SO-d_6	α	4.0	10			50	<0.5	11.2	4.5	
Me_2SO-d_6	β	7.5	7.5	3.5	3.5	51	3.5	14	3.5	7.0
D_2O	α	4.0	10.5	3.5		50.5	<0.5	13.3	2.8	
D_2O	β	7.3	7.5	3.2		51.5	3.0	14.5	2.8	

iments. Removal of the total proton coupling resulted in a sharpening of the $-OCF_3$ doublet; decoupling F-2 simultaneously with irradiation of the proton region afforded a sharp singlet; decoupling F-2 from the $-OCF_3$ gave a broad singlet. The residual coupling of the ring protons with the $-OCF_3$ fluorine substituents was estimated[16] as 0.5 Hz. A similar coupling is seen in the analogous *gluco* compound, but is not present in the *manno* and *talo* compounds. The reason for this difference is not understood. The small magnitude (<0.5 Hz) of J (F-2/H-1) for **2** and **3** 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. This is seen in the *gluco* analogues, and has been discussed in detail[15].

Similarly, the D-talo configuration in the *C1* conformation is suggested by the magnitude of the vicinal ^1H–^1H coupling constants, although the *1C*(D) conformation is also consistent with these data. The *C1*(D) conformation is confirmed by the magnitude (25–30 Hz) of J (F-2/H-3) which is characteristic[15] of the *trans*-diaxial orientation. The H-1/H-2 coupling does not unequivocally establish, but is consistent with, the β-D orientation at the anomeric centre. The H-1/F-2 coupling constant (14–17 Hz) is not inconsistent with the β-D orientation, having the same approximate magnitude as the β-D-manno analogues[15]. However, doubt has been expressed[5] as to the validity of using such equatorial–axial H/F coupling constants in defining the anomeric configuration of fluorohexoses.

The configurations of products **2**–**5** would be expected on mechanistic grounds[13,17], since *cis*-addition of the reagent to activated double bonds is very strongly favoured.

Hydrolysis of **2** or **3** in boiling 2M hydrochloric acid afforded 2-deoxy-2-fluoro-D-galactose (63–79%). The β-pyranose form crystallised from ethyl acetate–methanol. The ^{19}F n.m.r. spectrum (Table II, 94.1 MHz) of a solution of the β-anomer in Me_2SO-d_6 showed one fluorine signal (+3,952 Hz relative to C_6F_6) as a quartet of triplets, with $J_{F,2}$ 51, $J_{F,3}$ 14, $J_{F,4}$ 3.5, and $J_{F,1}$ 3.5 Hz (*cf.* $J_{F,1}$ <0.5 Hz in **2** and **3**). The ^1H n.m.r. spectrum (100 MHz) showed the anomeric hydroxyl proton at δ 6.83 (doublet, J 7 Hz) (acetonitrile at δ 2.0) and this coupling is characteristic[18] of an equatorial hydroxyl group. One other hydroxyl proton was tentatively assigned to HO-3, δ 5.00 (doublet, J 5 Hz), the coupling constant suggesting[18] an equatorial hydroxyl group, and HO-3 would be expected to occur at low field due to deshielding by the neighbouring fluorine atom. The remainder of the spectrum was too complex to assign. Decoupling the ^{19}F resulted in the collapse of H-2 to δ 4.10 (triplet, $J_{2,3} = J_{1,2} = 7.5$ Hz). Addition of D_2O removed the hydroxyl protons, and decoupling of ^{19}F then allowed assignment of H-1 (δ 4.59, doublet, $J_{1,2}$ 7.5 Hz) and of a complex band at δ 3.6–3.5 to H-3. Irradiating this band and the ^{19}F simultaneously gave H-4 as a doublet at δ 3.75 ($J_{4,5}$ 3.5 Hz). Comparison with the initial spectrum then allowed estimation of $J_{3,4}$ as 3.5 Hz.

The ^{19}F n.m.r. spectrum (94.1 MHz) of the anomeric mixture of sugars in Me_2SO-d_6 showed two fluorine resonances, β anomer +3991 Hz; α anomer +4091 Hz (multiplet, $J_{F,2}$ 50, $J_{F,1}$ <0.5, $J_{F,3}$ 11.2, $J_{F,4}$ 4.5 Hz). The chemical shifts were obtained by irradiation of the proton region, removing all the coupling, and leaving two sharp

singlets. The ^1H n.m.r. spectrum (100 MHz) in D_2O showed two anomeric protons: β anomer, δ 4.94 (quartet, $J_{F,1}$ 3.0, $J_{1,2}$ 7.3 Hz); α anomer, δ 5.56 (doublet, $J_{1,2}$ 4.0 Hz); in a ratio of 3:2.

The ^{19}F n.m.r. spectrum (94.1 MHz) of the free sugar in D_2O showed a very complex band which was not amenable to a first-order treatment. Decoupling the protons from this band gave two singlets, with chemical shifts of +3082 and +3882.5 Hz relative to C_6F_6 as external standard, with an integrated ratio of 3:2 assigned to the β and α anomers, respectively. The problem was treated as a five-spin system; the interactions of H-5 and H-6 were ignored, and the coupling constants obtained in the previous spectra were used. In a spectral simulation[19] with the appropriate weighting for each signal, a fit was obtained with the experimental spectrum. The coupling constants given in Table II are estimated to be accurate to better than 0.5 Hz, and afford unequivocal proof that the free sugar crystallises in the β-D configuration.

Mutarotation of the β anomer in water [+78.5 → +92° (equilibrium ratio α:β, 2:3)] may be compared with an aqueous solution of β-D-galactose[20] [+52 → +77° (equilibrium ratio α:β, 3:8)].

Acetylation of 2-deoxy-2-fluoro-β-D-galactopyranose with acetic anhydride–pyridine afforded the β-tetra-acetate, as expected, since this reagent is known to acetylate hexoses without changing the anomeric configuration. The ^1H n.m.r. spectrum (100 MHz) showed the anomeric proton at τ 4.30 (quartet, $J_{F,1}$ 4.0, $J_{1,2}$ 8.0 Hz); H-2 at 5.53 (octet, $J_{F,2}$ 51.1, $J_{2,3}$ 9.6, $J_{1,2}$ 8.0 Hz); H-3 at 4.90 (septet, $J_{F,3}$ 13.1, $J_{2,3}$ 9.6, $J_{3,4}$ 3.5 Hz); H-4 at 4.66 (triplet $J_{3,4}$ 3.5, $J_{4,5}\sim0$, $J_{F,4}$ 2.7 Hz); H-5, H-6, and H-6′ appeared as a singlet at 6.00, and four acetyl resonances appeared at 7.93, 7.96, 8.06, and 8.08. The ^{19}F n.m.r. spectrum (94.1 MHz) showed one fluorine resonance, +4314 Hz relative to C_6F_6, with $J_{F,2}$ 51.1, $J_{F,3}$ 13.2, $J_{F,1}$ 4.1, $J_{F,4}$ 2.8 Hz.

TABLE III

CHEMICAL SHIFTS (IN HZ) FOR ^{19}F RELATIVE TO C_6F_6

Compound	*Solvent*	*F-1*	*OCF_3*	*F-2*
2	$CDCl_3$		−9753	+4408
3	$CDCl_3$	−925		+4603
4	$CDCl_3$		−9697	+5376
5	$CDCl_3$	−1567		+5295
6	α } Me_2SO-d_6			+4091
	β } Me_2SO-d_6			+3991
	α } D_2O			+3821
	β } D_2O			+3802
7				+4314

EXPERIMENTAL

General. — Thin-layer chromatography (t.l.c.) was performed on Kieselgel (Merck, 7731) and column chromatography on Kieselgel (Merck, 7734). Optical

rotations were measured with a Perkin–Elmer 141 polarimeter. Melting points a uncorrected. ^{1}H n.m.r. spectra were recorded on 10–15% solutions with Perkin–Elm R-10 and Varian HA-100 instruments. ^{19}F n.m.r. spectra were recorded on a modifi Varian HA-100 instrument operating in the frequency sweep mode. Gas–liqu chromatography (g.l.c.) was performed on a Pye 104 chromatograph, using an SE column at 200°, with nitrogen as carrier gas at 15 p.s.i.

*Reaction of 3,4,6-tri-*O*-acetyl-*D*-galactal* (**1**) *with trifluoro(fluoroxy)methane.* - A solution of **1** (16.3 g) in chlorotrifluoromethane (Freon 11, 500 ml) at *ca.* −8 was stirred with calcium oxide to remove hydrogen fluoride during the reaction a purged with nitrogen. Trifluoro(fluoroxy)methane (1.2 equiv.), diluted with nitroge was passed into the solution during 6 h [the reaction can be monitored by observi the disappearance of the i.r. band at 1650 cm^{-1} (C=C) and by diminution in intensi of the olefin on t.l.c. (ether–light petroleum, 2:1)] followed by nitrogen for 30 min remove excess reagent. The reaction mixture was filtered into 5% aqueous sodiu hydrogen carbonate (300 ml), the residue was washed with dichloromethane, and t combined organic layers were washed with water and dried (Na_2SO_4). A solution the mixture in chloroform was evaporated under reduced pressure in the presence dry Kieselgel, and the residue was placed on a column of dry Kieselgel (200 g Elution with light petroleum–ether (2:1) gave first, trifluoromethyl 3,4,6-tri-*O*-acety 2-deoxy-2-fluoro-α-D-galactopyranoside (**2**, 39%), m.p. 67–68° (from light petroleu ether), $[\alpha]_D$ +151° (*c* 3.2, chloroform) (Found: C, 42.2; H, 4.4; F, 20.5. $C_{13}H_{16}F_4C$ calc.: C, 41.5; H, 4.3; F, 20.2%); closely followed by 3,4,6-tri-*O*-acetyl-2-deoxy- fluoro-α-D-galactopyranosyl fluoride (**3**, 37%), m.p. 71–72° (from light petroleu ether), $[\alpha]_D$ +136° (*c* 2.8, chloroform) (Found: C, 46.8; H, 5.3; F, 12.5. $C_{12}H_{16}F_2C$ calc.: C, 46.4; H, 5.2; F, 12.3%).

Further elution of the column with light petroleum–ether (1:1), with monitori

TABLE IV

CHEMICAL SHIFTS (τ) FOR ^{1}H RELATIVE TO INTERNAL TETRAMETHYLSILANE

Compound	*H−1*	*H−2*	*H−3*	*H−4*	*H−5*	*H−6,6′*	*OAc*
2	4.25	5.23	4.68	4.54	5.65	5.97	7.93 8.03
3	4.24	5.32	4.66	4.52	5.64	5.94	7.92 8.02
4	4.83	5.33	5.01	4.75	— 5.77 to 6.03 —		7.94, 7.98, 8.03, 8.04
5	4.67	5.31	4.93	4.81	— 5.72 to 6.10 —		7.95 8.01
7	4.30	5.53	4.90	4.66	— 6.00 —		7.93, 7.96, 8.06, 8.08

CHEMICAL SHIFTS (δ) FOR ^{1}H, INTERNAL ACETONITRILE AT δ 2.00

	H−1	*H−2*	*H−3*	*H−4*	*HO−1*	*HO−3*	
6	β 4.59	4.10	3.60 to 3.50	3.75	6.83	5.00	Me_2SO-d_6
	4.94						D_2O
	α 5.56						D_2O

by g.l.c., yielded trifluoromethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-talopyranoside (**4**, 3%), b.p. 148–150°/0.15 mmHg, $[\alpha]_D$ +1.9° (Found: C, 41.9; H, 4.3; F, 20.0%), closely followed by 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-talopyranosyl fluoride (**5**, 2%), b.p. 168–170°/0.17 mmHg, $[\alpha]_D$ +19.0° (Found: C, 46.6; H, 5.1; F, 12.4%).

2-Deoxy-2-fluoro-β-D-galactopyranose (**6**). — Hydrolysis of **2** (7.8 g) with boiling 2M hydrochloric acid (100 ml) was complete in 2.5 h (t.l.c.; ethyl acetate–ethanol, 8:1) to give a single product (R_F 0.65). Dilution with ethanol, neutralisation ($PbCO_3$), evaporation on to Kieselgel, and elution of the product from a column of Kieselgel (200 g) with ethyl acetate–methanol (10:1) gave **6** (79%), m.p. 131–135° (from ethyl acetate–methanol), $[\alpha]_D$ +78.5 (*5 min*) → +92° (*c* 2.3, water) (Found: C, 39.8; H, 6.3; F, 10.7. $C_6H_{11}FO_5$ calc.: C, 39.5; H, 6.0; F, 10.4%).

Hydrolysis of **3** (6.2 g) with 2M hydrochloric acid (100 ml) was complete in 1 h, and **6** (63%), m.p. 131–135°, was isolated as described above.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-fluoro-β-D-galactopyranose (**7**). — Acetylation of **6** (1.4 g) with acetic anhydride and pyridine in the usual manner, followed by elution of the product from Kieselgel (75 g) with ether–light petroleum (2:1), yielded **7** (80%), m.p. 141–143° (from ether–light petroleum), $[\alpha]_D$ +47.6° (*c* 1.5, chloroform) (Found: C, 48.0; H, 5.3; F, 5.3. $C_{14}H_{19}FO_9$ calc.: C, 48.0; H, 5.4; F, 5.4%).

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