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SYNTHESIS OF 2-DEOXY-2-FLUOROHEXOSES BY FLUORINATION OF GLYCALS IN AQUEOUS MEDIA*

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ABSTRACT

1,5-Anhydro-2-deoxy-D-*arabino*- (D-glucal), 1,5-anhydro-2-deoxy-D-*lyxo*- (D-galactal), and 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (3,4,6-tri-*O*-acetyl-D-galactal) (**3**) were fluorinated in water and organic solvent–water with molecular fluorine and, for ^{18}F-labelled compounds, with [^{18}F]fluorine. Chemical yields of 40 and 10% were obtained for 2-deoxy-2-fluoro-D-glucose and 2-deoxy-2-fluoro-D-mannose, respectively, and 35 and 5% for 2-deoxy-2-fluoro-D-galactose (**12**) and 2-deoxy-2-fluoro-D-talose (**13**), respectively. In the fluorination of **3**, the chemical yields of **12** and **13** were 38 and 6%, respectively. An l.c. separation of 2-deoxy-2-fluoro-D-hexoses is described.

INTRODUCTION

O-Acetyl derivatives of glycals have been fluorinated with fluorine[2], acetyl hypofluorite[3–9], trifluoromethyl hypofluorite[10–13], and xenon difluoride[14–16] in organic solvents, often at subambient temperatures. 2-Deoxy-2-fluoro-D-glucose has also been prepared by nucleophilic substitution[17–20]. After the work described herein had been completed, a paper describing the fluorination of D-glucal in water with acetyl hypo[^{18}F]fluorite and [^{18}F]fluorine was published; however, the separation of 2-deoxy-2-[^{18}F]fluoro-D-glucose, a tracer in great demand for PET medical research[22–24], and 2-deoxy-2-[^{18}F]fluoro-D-mannose was not reported.

The fluorination of tri-*O*-acetylglycals with trifluoromethyl hypofluorite and xenon difluoride gave a mixture of many fluorinated compounds which required an elaborate purification procedure[10–12,14]. Furthermore, these two reagents are not convenient for the synthesis of ^{18}F-labelled compounds as they are not easily labelled with ^{18}F. The fluorination of two glycals (**1** and **2**) and 3,4,6-tri-*O*-acetyl-D-galactal (**3**) in aqueous media is described herein.

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RESULTS AND DISCUSSION

The fluorination of the glycals was performed in water with F_2–N_2 (Method *A*) and in methyl cyanide–water and *N*,*N*-dimethylformamide–water (Method *B*), and in the same solvent mixtures with F_2–Ne (Method *C*). The products of the reactions were studied by ^{19}F-n.m.r. spectrometry of the crude reaction mixture and of the fractions of mono- and di-fluoro compounds isolated by flash chromatography, t.l.c. (for nonradioactive compounds), and thin-layer radiochromatography (t.l.r.c.) (for radioactive compounds). ^{19}F-N.m.r. spectrometry was also used for the identification of the purified compounds.

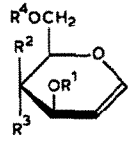
In the fluorination of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (D-glucal)[25] (**1**) by Method *A*, t.l.c. and t.l.r.c. of the crude reaction mixture showed the presence of two spots, each corresponding to two compounds (from ^{19}F-n.m.r. data). The first spot corresponded to 2-deoxy-2-fluoro-D-glucopyranosyl fluoride (**4**) and 2-deoxy-2-fluoro-D-mannopyranosyl fluoride (**5**) in the ratio of 4.5:1. The compounds giving the second spot were identified as 2-deoxy-2-fluoro-D-glucose (**10**) (α and β anomers in the ratio of 1:1.2) and 2-deoxy-2-fluoro-D-mannose (**11**) (α and β anomers in the ratio of 1.3:1) by ^{19}F-n.m.r. spectrometry (Table I) and by comparison with the n.m.r. data of samples prepared by an independent procedure[2] or from a commercial sample. In the crude reaction mixtures, the ratio between **10** and the corresponding 1,2-difluoro compound **4** was 7:1; and between the corresponding *manno* compounds (**5** and **11**) ~17:1. The F-1 of **4** and **5** was easily

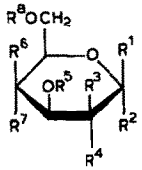
TABLE I

^{19}F-N.M.R. SPECTRAL DATA FOR COMPOUNDS **4–6** AND **10–13**

Compound	*Chemical shifts (δ)*[a]	*Coupling constant (Hz)*					
		$J_{F,F}$	$J_{F\text{-}1,H\text{-}1}$	$J_{F\text{-}1,H\text{-}2}$	$J_{F\text{-}2,H\text{-}1}$	$J_{F\text{-}2,H\text{-}2}$	$J_{F\text{-}2,H\text{-}3}$
4	−151.3 (F-1)	19.5	53.8	24.5[b]			
4	−205.1 (F-2)	19.5				48.8	14.6
5	−150.0 (F-1)	12.4	48.8	9.8			
5	−222.0 (F-2)	12.4				48.8	24.0
6	−153.4 (F-1)	19.6	54.1	24.4			
6[c]	−213.0 (F-2)	19.6				48.9	14.6
10 (α)	−200.57			0.8	48.3	15.0	
10 (β)	−200.41			2.9	51.6	14.7	
11 (α)	−206.0			7.7	51.7	32.8	
11 (β)	−224.5			20.0	52.0	32.0	
12 (α)	−208.74			2.9	51.3	14.6	
12 (β)[d]	−208.93				46.4	12.2	
13 (α)	−203.43			12.2	44.0	34.2	
13 (β)	−223.51			19.7	51.2	32.9	

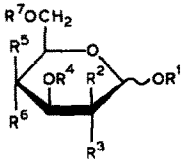
[a]Relative to the signal of CCl_3CF_3 (δ −82.204). The absolute values of the chemical shifts changed from experiment to experiment; however, the relative difference between them was always very close. [b]*Trans* orientation. [c]Additional coupling $J_{F\text{-}2,H\text{-}4}$ 4.9 Hz. [d]Additional coupling $J_{F\text{-}2,H\text{-}4}$ 4.8 Hz.





1 $R^1 = R^2 = R^4 = H; R^3 = OH$
2 $R^1 = R^3 = R^4 = H; R^2 = OH$
3 $R^2 = H; R^1 = R^4 = Ac; R^3 = OAc$

4 $R^1 = R^3 = R^5 = R^6 = R^8 = H; R^2 = R^4 = F; R^7 = OH$
5 $R^2 = R^4 = R^5 = R^6 = R^8 = H; R^1 = R^3 = F; R^7 = OH$
6 $R^1 = R^3 = R^5 = R^7 = R^8 = H; R^2 = R^4 = F; R^6 = OH$
7 $R^2 = R^4 = R^5 = R^7 = R^8 = H; R^1 = R^3 = F; R^6 = OH$
8 $R^1 = R^3 = R^7 = H; R^5 = R^8 = Ac; R^6 = OAc; R^2 = R^4 = Au$
9 $R^2 = R^4 = R^7 = H; R^5 = R^8 = Ac; R^6 = OAc; R^1 = R^3 = Au$



10 $R^1 = R^2 = R^4 = R^5 = R^7 = H; R^3 = F; R^6 = OH$
11 $R^1 = R^3 = R^4 = R^5 = R^7 = H; R^2 = F; R^6 = OH$
12 $R^1 = R^2 = R^4 = R^6 = R^7 = H; R^3 = F; R^5 = OH$
13 $R^1 = R^3 = R^4 = R^6 = R^7 = H; R^2 = F; R^5 = OH$
14 $R^1 = R^2 = R^6 = H; R^4 = R^7 = Ac; R^5 = OAc; R^3 = F$
15 $R^1 = R^3 = R^6 = H; R^4 = R^7 = Ac; R^5 = OAc; R^2 = F$
16 $R^2 = R^6 = H; R^1 = R^4 = R^7 = Ac; R^5 = OAc; R^3 = F$
17 $R^3 = R^6 = H; R^1 = R^4 = R^7 = Ac; R^5 = OAc; R^2 = F$

hydrolyzed to give **10** and **11** in the ratio of 2.2:1 (see Table II). ^{19}F-N.m.r. spectrometry of the fluorosugars purified by l.c. (recycling mode) showed <4% of **11** in **10** and <6% of **10** in **11**. The overall chemical yields for the purified compounds were 40% for **10** and 10% for **11** owing to a substantial loss of **11** during l.c. purification.

Fluorination in water–methyl cyanide or water–*N*,*N*-dimethylformamide (Method *B*) affected the ratio of **10** to **11**. At the end of the reaction, the difluoro compounds (**4** and **5**) were preponderant, only 5% of **11** and 10% of **10** being present. After hydrolysis of the crude mixture to remove F-1, the ratio of **10** to **11** was 2:1. The availability of a method of fluorination in water–organic solvent is of interest for compounds of low water-solubility.

Labelling with ^{18}F by Method *C* or a combination of Methods *A* to *C* increased the sensitivity of the detection and, thus, the possibility of obtaining purer fractions. The flash-chromatography fractions were examined for radioactivity and the fractions corresponding to the two spots found by t.l.r.c. (di- and mono-fluoro compounds) were combined. The difluoro compounds were hydrolyzed and ^{19}F-n.m.r. spectrometry showed the presence of **10** and **11** in the ratio of 4.5:1. The

TABLE II

RATIOS OF YIELDS OF VARIOUS 2-DEOXY-2-FLUORO-D-HEXOSES[a]

Starting compound	*Method*	*Present work, detection by*		*Previous work, detection by ^{19}F-n.m.r. sp.*
		^{19}F-n.m.r. sp.	*L.c.*	
1	*A*	2.2:1	3:1	1.9:1[b]
1	*B*[c]	2:1	2.7:1	
2	*A*	5.4:1	6.1:1	
2	*B*	5.2:1	6:1	
3	*A*	3.9:1	4.5:1	

[a]As estimated by ^{19}F-n.m.r. spectrometry and l.c. separation. [b]See ref. 21. [c]The ratio was not changed by performing the reaction in methyl cyanide–water or *N,N*-dimethylformamide–water.

pure, radioactively-labelled **10** and **11** were isolated from the hydrolyzate by semi-preparative l.c.

In the fluorination of 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol[25] (D-galactal) (**2**) by Methods *A* and *B*, ^{19}F-n.m.r. spectrometry of the crude reaction product showed the presence of three different compounds, but t.l.c. and t.l.r.c. showed only two spots. Flash chromatography gave two fractions. The first contained only 2-deoxy-2-fluoro-D-galactopyranosyl fluoride (**6**) and the second a mixture of 2-deoxy-2-fluoro-D-galactose (**12**) and 2-deoxy-2-fluoro-D-talose (**13**). The assignments of the pure compounds were made by[19] F-n.m.r. spectrometry (Table I). Hydrolysis of the crude reaction product gave only two compounds, 2-deoxy-2-fluoro-D-galactopyranose (**12**) (α and β anomers in the ratio of 1.6:1) and 2-deoxy-2-fluoro-D-talopyranose (**13**) (α and β anomers in the ratio of 1.8:1). The ratio of 2-deoxy-2-fluoro-D-galactose (**12**) to 2-deoxy-2-fluoro-D-talose (**13**) obtained by Method *A* was 5.4:1. Purification by l.c. gave pure **12** and **13** in average chemical yields of 35 and 5%, respectively (Method *A*), and average radiochemical yields (Method *C*) relative to [^{18}F]fluorine of 15 and 2%, respectively, the latter low figure resulting from loss during the purification.

Fluorination of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol[25] (3,4,6-tri-*O*-acetyl-D-galactal) (**3**) by Method *A* gave a mixture of 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranosyl fluoride (**8**), 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranose (**14**), and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-talopyranose (**15**). T.l.c. (and t.l.r.c. when [^{18}F]F_2 was used) of tetraacetates **16** and **17**, prepared from triacetates **14** and **15**, showed two spots corresponding to the two fractions that were separated by flash chromatography. ^{19}F-N.m.r. spectrometry after hydrolysis indicated that the first fraction contained **12** and the second **13** in the chemical yields of 38 and 6%, respectively.

The fluorination of glycals in water described herein yields preponderantly 2-fluoro compounds. Since the ratios of **12** to **13** (fluorination products of **1**) and **14** to **15** (fluorination products of **2**) are approximately the same, the orientation at

C-4 did not influence the stereoselectivity of the reaction. Formation of *cis*-difluoro compounds with F_2 in trichlorofluoromethane was explained[2] by the addition of F_2 to the double bond in a manner similar to that of other halogens[26]. This mechanism could also explain the results obtained in methyl cyanide– or *N,N*-dimethylformamide–water, indicating that the rate of the reaction between fluorine and glycal is higher than that between fluorine and water. The formation of fluorides in 9:1 *N,N*-dimethylformamide–water could be explained by the reaction of HOF (assuming the polarization suggested by Appelman and Thompson[27]). If this is indeed the case, as fluorides were not found when the fluorination was done in water, the fluorinating agent in water is apparently not HOF.

The syntheses described herein gave chemical and radiochemical yields comparable with those of other syntheses using electrophilic substitutions for the preparation of nonlabelled 2-deoxy-2-fluoro sugars[2,4,10–14] and of ^{18}F-labelled 2-deoxy-2-fluoro-D-glucose (**10**)[3,5–9,15,16,21]. The yield of ^{18}F-**10** was also similar to that recently reported by Bida *et al.*[21] for the fluorination of D-glucal with [^{18}]fluorine in water.

EXPERIMENTAL

General methods. – ^{19}F-N.m.r. spectra were recorded at a frequency of 280 (Varian XL-200) or 75.386 MHz (Bruker WP-80SY), and ^{1}H-n.m.r. spectra at 300 MHz (Varian XL-200), trichlorotrifluoroethane being the external reference standard (δ −82.204). I.r. and m.s. spectra were recorded with a Perkin–Elmer 297 spectrometer on thin-film compounds and with a HP 5980 A spectrometer, respectively. Thin-layer chromatography (t.l.c.) and radiochromatography (t.l.r.c.) were performed on hard-layer silica gel plates (Analtech Cart. No. 42571) containing a u.v.-indicator in 5:1 ethyl acetate–methanol. Nonradioactive compounds were detected by spraying the plates with 10% H_2SO_4 in ethanol, drying for 10 min at 110°, and examining under u.v. light. Plates containing ^{18}F-labelled compounds were scanned with a windowless, gas-flow proportional detector having an opening of 1 mm. Flash chromatography was performed on silica gel (40–140 mesh) by collecting 0.3–0.5 mL fractions.

All reaction mixtures were analyzed by t.l.c., t.l.r.c., or both. In several experiments, the crude reaction mixture was analyzed by t.l.c., t.l.r.c., and by ^{19}F-n.m.r. on separate fractions. All chemical and radiochemical yields are expressed relative to fluorine and [^{18}F]F_2, respectively, the reactant being in less than equimolar concentration. 2-Deoxy-2-fluoro-D-glucose (**10**) was purchased from Calbiochem–Behring Corporation, La Jolla, California.

Fluorination of glycals. — Method A. Compound **1, 2** or **3** (0.15–0.3 mmol) dissolved (or emulsified for **3**) in water (8 mL) in a narrow, Teflon test tube, was fluorinated by bubbling through 1:19 F_2–N_2, at room temperature and a flow rate of 50 mL/min, for a total of 0.1–0.2 mmol of fluorine.

Method B. The glycal (**1, 2** or **3**; 0.15 mmol) was fluorinated in 9:1 CH_3CN–water or 19:1 *N,N*-dimethylformamide–water.

Method C. The glycal (**1, 2** or **3**; ~0.1 mmol) was fluorinated by Method *A* or *B* with $[^{18}F]F_2$ (~0.07 mmol of 0.5% F_2 in Ne).

Reaction of **1** *with* F_2 *and* $[^{18}F]F_2$. — The reaction mixture was evaporated and the residue separated by flash chromatography on silica gel in 8:1 ethyl acetate–methanol to give **10** and **11** (R_F 0.32) and **4** and **5** (R_F 0.87) for a total yield of 90%. The difluoro compounds **4** and **5** were converted into the respective 2-fluoro compounds **10** and **11** by hydrolysis with 2M HCl for 5 min at 130° (bath temperature) in quantitative yield (^{19}F-n.m.r. spectrometry). In experiments with F_2, the product of hydrolysis was evaporated, the residue taken up into 4:1 CH_3CN–water (2 mL) and Ag_2O (50 mg) added. The solution was chromatographed in a PAC column (25 × 0.6 cm) of Partisil-5 with 9:41 2.5mM sodium acetate–acetonitrile as eluent at a flow of 0.3 mL. The capacity factors[28] (k') were 1.02 and 1.26 for **10** and **11**, respectively, and the resolution factor[28] (R_s) 1.05 after a single passage through the column, which was used in a recycling mode. The combined recovery of **10** and **11** (ratio 4:1) was ~95% and the overall chemical yields (based on the amount of F_2) ~40% for **10** and ~10% for **11**. A successful separation was greatly dependent on the ionic strength of the solution. The ^{19}F-n.m.r. data for **10** and **11** are given in Table I.

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.56; H, 6.09; F, 10.43. Found for **10**: C, 39.45; H, 6.18; F, 10.00. Found for **11**: C, 39.39; H, 6.00; F, 9.90.

In the reaction with $[^{18}F]F_2$ (Method *C*), ^{18}F-**10** was isolated by l.c. as just described to give a radiochemical yield of ~18% relative to $[^{18}F]F_2$ (not corrected for radioactive decay). The synthesis of ^{18}F-**10** required about 45–55 min.

Reaction of **2** *with* F_2 *and* $[^{18}F]F_2$. — The reaction mixture obtained after fluorination by Methods *A* or *B* was analyzed by t.l.c. which showed two spots having R_F 0.7 and 0.24. The corresponding fractions were separated by flash chromatography. ^{19}F-N.m.r. spectrometry of the crude mixture showed the presence of 2-deoxy-2-fluoro-D-galactose (**12**), 2-deoxy-2-fluoro-D-talose (**13**) (second chromatographic fraction), and 2-deoxy-2-fluoro-D-galactopyranosyl fluoride (**6**) (first chromatographic fraction). L.c. as described earlier, after hydrolysis[18] with 2M HCL at 130° for 10 min[18], gave the pure 2-deoxy-2-fluoro-D-hexoses in overall-chemical yields (based on F_2) of 35 for **12** and 5% for **13**. The overall radiochemical yield was 15% for ^{18}F-**13** when Method *C* was used; the ^{19}F-n.m.r. data for **6, 12,** and **13** are given in Table I.

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.56; H, 6.09. Found for **12**: C, 39.62; H, 6.14. Found for **13**: C, 39.40; H, 6.00.

Reaction of **3** *with* F_2. — The compounds obtained by Method *A* were extracted into CH_2Cl_2 or $CHCl_3$ and identified by ^{19}F-n.m.r. and H-decoupled ^{19}F-n.m.r. spectrometry as **8, 9, 14,** and **15**. The compounds extracted into CH_2Cl_2 (5 mL) were acetylated[20] for 15 min at room temperature with 4-dimethylaminopyridine (100 mg) and acetic anhydride (1 mL) to transform **14** and **15** into **16** and

17, respectively. Flash chromatography in 9:11 ether–hexane gave **14** and **16** in the first fraction, and **17** in the second fraction, identified by ^{19}F-n.m.r. spectrometry. After hydrolysis[12] with 4M HCl, the first fraction (R_F 0.60) gave **12** and the second fraction (R_F 0.30) **13** in the chemical yields of 38 and 6%, respectively. The ^{19}F-n.m.r. data for **12** and **13** are given in Table I.

Anal. Calc. for $C_6H_{11}FO_5$: C, 39.56; H, 6.09; F, 10.43. Found for **12**: C, 39.45; H, 6.10; F, 10.30. Found for **13**: C, 39.50; H, 6.15.

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