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A CONVENIENT SYNTHESIS OF 1, 2-DIFLUORO-1, 2-DIDEOXYHEXOSES USING XENON FLUORIDE

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Abstract—A method for the addition of fluorine to the double bond in acetylated glycals using XeF_2 in the presence of BF_3 has been shown to provide a convenient route for the synthesis of acetylated 1, 2-dideoxy-1, 2-difluorosugars. The reagent attacks the double bond predominantly from the least hindered side to give a *cis* adduct, but the reaction also provided other isomers which have been separated by chromatography and their stereo-chemistry determined by ^{19}F NMR spectroscopy. The proposed mechanism of the reaction involves an initial electrophilic attack by the reagent on C-2 followed by a nucleophilic attack on C-1. Deacetylation of the adducts gave 1, 2-dideoxy-1, 2-difluorosaccharides, which are of interest in biochemical studies. A crystalline 2-deoxy-2-L-fucose was prepared by selective hydrolysis of the anomeric fluorine atom of 1, 2-dideoxy-1, 2-difluoro-L-fucose.

There has been considerable interest in the synthesis and properties of fluorinated carbohydrates.[1] Our primary interest in the area is related to their potential as inhibitors or modifiers of cell surface glycoconjugates.[2] In this connection we have been developing methods for the substitution of hydroxyl groups with fluoride, and in particular, those on the anomeric carbon atom and the carbon adjacent to it. Fluorinations of acetylglycals such as **1** (Scheme 1) has been achieved using fluorine gas, but the reaction requires specialized equipment and considerable precautions.[3] Another, milder method, involves an additional reaction of CF_3OF to peracetylated glycals.[4-7] Although this method is regarded as being more convenient, it often gives rise to complex reaction mixtures, consisting of trifluoromethylglycosides in addition to the desired fluorosugar. Both methods involve the use of toxic and corrosive gases.

Xenon difluoride has been applied to the fluorination of organic compounds and can be handled without taking special precautions.[8] Recently, it has been labeled with ^{18}F, and hence it is of potential use for the synthesis of fluorinated chemicals for emission tomography.[9] XeF_2 has also been applied to the fluorination of alkenes, the reaction being usually catalyzed by HF or CF_3 COOH.[10] In our attempts to affect fluorination of acetylglycals, we have used BF_3-etherate as the catalyst because of its mildness.[11] Nevertheless, acetylglycals were found to undergo rearrangement and dimer formation with catalytic amounts of BF_3.[12] Hence it was necessary to control the reaction by slowly adding BF_3-etherate solution in benzene to a solution of acetylglycal (**1**, **5** or **9**) in ether containing an equilmolar amount of XeF_2. Solvent composition of the reaction mixture was also found to be critical. When the reaction was carried out in ether, it slowed down considerably. In the benzene–ether mixture the total yield of the fluorinated isomers was 78%, which were separated by chromatography on silica gel. The main product was identified as 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride (**2**, 61%), accompanied by 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-2-β-D-glucopyranosyl fluoride (**3**, 12%) and 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride (5%). Two minor additional spots on the tlc plate have not been identified.

When 3, 4, 6-tri-O-acetyl-D-galactal **5** was subjected to similar reaction conditions, there was some increase of the *cis* isomer **6** (69%) at the expense of the other isomers (**7** 11% and **8**, 3%). Thus, the presence of a pseudoaxial acetoxy group in the 4 position of **5** hinders the attack of the fluorinating reagent from the less hindered side.

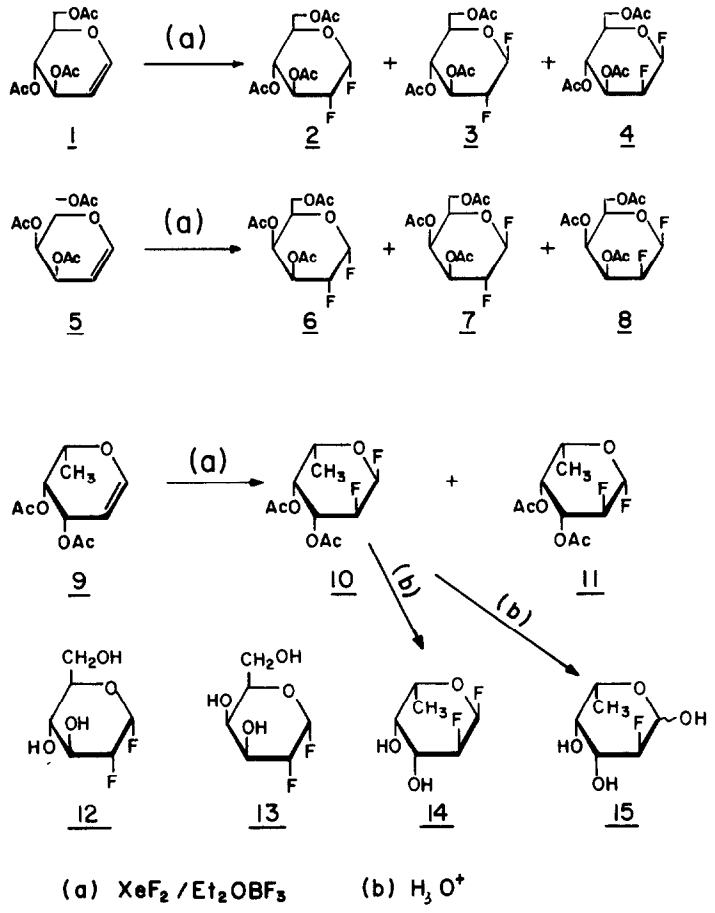
We have also subjected 3, 4, -di-O-acetyl-L-fucal **9**[13] to the fluorination reaction. The product consisted almost excusively of the *cis*-addition product **10** with only a minor amount of *trans*-isomer **11**.

Both ionic and free radical mechanisms have been proposed for fluorinations with XeF_2.[10] In order to make the free radical mechanisms less likely, we have carried out the fluorination of 3, 4-di-O-acetyl-L-fucal **9** in the presence of oxygen, which was expected to suppress the formation of free radicals during fluorination reaction. The yield and the product composition of the reaction were similar to those obtained when the reaction was carried out under the nitrogen atmosphere, thus indicating an ionic mechanism.

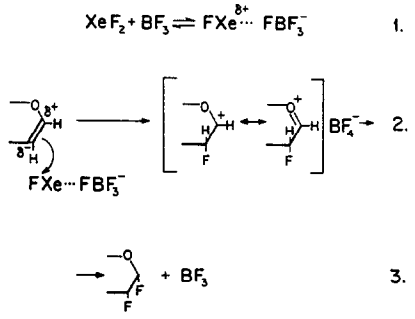
The presence of anomeric fluorides (e.g. **2** and **3**) in the product mixture could be due to the establishment of an equilibrium after the initial fluorination has taken place. In order to eliminate this possibility, we have subjected **2** to the fluorination conditions, resulting in complete recovery of **2** with no other products formed. This indicates that the three isomers are formed directly during the fluorination reaction.

Hence, we are proposing the following reaction mechanism (Scheme 2).

In the first step, complex formation between XeF_2 and BF_3 induces a partial positive charge on the fluorine, which is followed by an electrophilic attack of the complex on C-2 of the double bond to form the 2-fluorocarbocation (reaction 2). In the last step (reaction 3), nucleophilic attack by F^- gives rise to an anomeric mixture of fluorides. The attack on the double bond occurs from both sides and hence, theoretically, should give rise to four products. The preferred attack is from the less hindered side, with the *cis*-adducts clearly predominating. This explains the apparent absence of the fourth isomer in the reaction mixtures we have examined, as the amounts were too small for detection.



Scheme 1.



Scheme 2.

We have subjected several other unsaturated sugar derivatives to this fluorination reaction. Thus benzyl 2-acetamido-2, 3, 4-trideoxy-6-O-acetyl-α-D-hexy-3-enopyranoside, a protected D-glucosamine derivative with a 3, 4-double bond,[14] resisted fluorination. Surprisingly, 3, 4, 6-tri-O-acetyl-5-thio-D-glucal, a close analogue of **1** in which the ring oxygen is replaced with sulphur,[15] was also found to be unreactive. This is attributable to the inadequate activation of the double bond by the less electronegative sulfur, particularly since the conformation of both **1** and the sulphur analogue, were found to be similar by ^{1}H-NMR spectrocopy.[16]

Unprotected 1, 2-dideoxy-1, 2-difluorosaccharides are of biochemical and biological interest. We have obtained representative examples of this class of fluorinated carbohydrates by Zemplen deacetylation (i.e. using catalytic amounts of NaOMe) of **2**, **6** and **10**, to give the free fluorinated sugars **12**, **13** and **14**, respectively, mostly in a crystalline form. This new class of fluorinated sugars proved to be stable on storage as solids as well as in neutral or alkaline aqueous solutions. Recently, Butchard and Kent[1] have described the synthesis of 2-deoxy-2-fluoro-L-fucose **15** as a non-crystalline material. We have succeeded in obtaining the sugar as a crystalline derivative by acid hydrolysis of either **10** or **14** with 0.1N H_2SO_4. It crystallized as an α-anomer in two crystalline forms and mutarotated to a mixture consisting of 34% α- and 66% β-anomers. It should be mentioned that L-fucose analogs are of interest as inhibitors or modifiers of cell surface glycoproteins,[18] and that it has been shown that 2-deoxy-2-fluoro-L-fucose **15** competes with L-fucose in glycoprotein biosynthesis.[19] Biological and biochemical studies on these fluorinated derivatives are in progress and will be reported elsewhere.

Of particular value in the characterization and in the configurational assignments of the fluorinated carbohydrates were their ^{19}F-NMR spectra, which are summarized in Table 1. They were determined in $CDCl_3$ for the acetylated derivatives (compounds **2–11**). 1, 2-Dideoxy-1, 2-difluoro-hexoses are characterized by the most deshielded F-1 multiplet from which F-2 is shifted upfield by 60–70 ppm. For compounds **2–4** the positions of the peaks are similar to those determined earlier

Table 1. ^{19}F Chemical shifts[a] and coupling constants (J, Hz) of 2-deoxy-2-fluorohexopyranosyl fluorides

Compounds	Shifts (ppm)[a]		Coupling Constants, J, Hz						
	F-1	F-2	(F1)-(F2)[c]	(F1)-(H-2)	(F-1)-(H-2)	(F-2)-(H-1)	(F-2)-(H-1)	(F2)-(H-1)	(F-2) (H-4)
2	151.6 (151.5)[b]	204.7 (204.5)[b]	-18.8	53.3	23.8	48.3	0	12.3	0
3	140.4 (140.3)[b]	200.9 (200.9)[b]	-15.8	51.7	11.2	49.0	4.0	15.0	0
4	146.4 (146.4)[b]	220.1 (277.0)[b]	-13.5	48.5	8.0	49.0	13.5	22.4	2.0
6	152.8	211.5	-18.0	52.5	23.0	48.0	0.5	11.0	3.5
7	142.3	209.4	-14.5	52.5	14.3	51.3	5.0	14.8	2.5
8	145.8	218.4	-12.8	48.0	6.0	51.0	14.5	25.0	d
10	152.1	211.9	-18.3	53.5	23.2	48.8	0.5	11.3	3.8
11	142.7	210.4	-15.4	52.8	14.5	51.5	2.9	13.3	4.9
12	71.6	125.5	-20.8	54.1	23.8	47.7	d	13.8	d
13	73.7	133.4	-19.5	54.3	24.5	d	d	d	d
14	73.1	133.7	-19.5	54.4	24.5	48.2	0.6	13.4	4.2
15α	—	129.75	--	--	--	49.4	<0.5	13.0	4.0
15β	--	129.5	--	--	--	51.0	3.5	14.5	4.0

[a] For compounds 2 to 11 upfield from $CFCl_3$ solution (ϕ_c values); for compounds 12 to 15 upfield from trifluoroacetic acid in D_2O solution.

[b] Values in parenthesis are those reported in ref. 20.

[c] Negative values of the coupling constant were determined in ref. 21.

[d] Not determined.

(given in parenthesis),[20] with the exception of the F-2 shift for the β-D-manno-isomer 4, the anomalous value of which has been commented upon.[1] The reason for the discrepancy is not readily apparent, but our value is more in line with other shifts, such as that for the F-2 of the β-D-talo isomer 8. The F1–F2 coupling constant has been determined to have a negative value by Hall *et al.*[21] for 2 or 4 and are assumed to be so in the whole series. No clear angular dependency for these coupling constants could be established.[21] Although a $^4C_1$-(D) conformation is assumed for components 2–8, its preponderance is most strongly manifest if F-1 is axial, because of its strong anomeric effect, as is the case in the α-D-gluco 2 and α-D-galacto 6 isomers. The coupling constants of fluorinated sugars with an equatorial F-1 (e.g. 3 and 7) exhibit greater dissimilarity, indicating that they may have appreciable amounts of the $^1C_4$ (D) conformer in the equilibrium mixture.

EXPERIMENTAL

General methods. Melting points were performed on a Meltemp apparatus and are uncorrected. ^{19}F NMR spectra were carried out using a Varian XL-100 spectrometer in the Fourier-transform mode at 94.1 MHz. Optical rotation was measured with a Perkin–Elmer 141 polarimeter. Tlc was performed on silica gel and, if not otherwise stated, benzene–ether (1:1) as the eluent and sulphuric acid spray at 100° for visualization. Evaporations were carried out on a rotary evaporator under reduced pressure. Open column chromatography was performed using silica gel 60 (E. Merck, Darmstadt).

Reaction of 3, 4, 6-*tri*-O-*acetyl*-D-*glucal* 1 *with* XeF_2. It suggested that work be conducted under N_2 (glove bag) on humid days and climates, but in most cases we were able to work without this precaution. To solid XeF_2 (157 mg, 0.93 mmole) in a dry flask was added a solution of 1 (253 mg, 0.93 mmole) in 5 ml of dry ether. To the stirred suspension, a solution of BF_3-etherate (21 μl, 0.18 mmole) in dry benzene (5 ml) was added dropwise for 5–10 min, and the reaction mixture was stirred overnight. The reaction time can be reduced to 30 min [see 3, 4-di-O-acetyl-L-fucal 9 experiment below]. After washing with saturated aqueous $NaHCO_3$ solution, the aqueous layer was extracted with ether, and the combined organic layers were washed with water and dried (Na_2SO_4). Solvent was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (20g). Elution with ether-petroleum (1:1) gave the following three fractions: (a) 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride (2, 177 mg, 61%), m.p. 90–92° (from ether–petroleum), $[\alpha]_D^{20}+135°$ (c 1, $CDCl_3$); lit.[23] m.p. 91–92° $[\alpha]_D+138°$ ($CDCl_3$); (b) 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl fluoride (3, 35 mg, 12%); m.p. 104–105° (from ether–petroleum); $[\alpha]_D^{20}+82°$ (c 1, $CDCl_3$); lit.[18] m.p. 99–101°; $[\alpha]_D^{20}+75°$ ($CHCl_3$); (c) 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride (15 mg, 5%), m.p. 109–111° from ether–petroleum, $[\alpha]_D-2.5°$ ($CHCl_3$); lit.[17] m.p. 113–114°, $[\alpha]_D-3.5°$ ($CDCl_3$). The total yield of fluorinated compounds was 225 mg (78%).

Reaction of 3, 4, 6-*tri*-O-*acetylgalactal* 5 *with* XeF_2. XeF_2 (135 mg, 0.80 mmole) reacted with 5 (218 mg. 0.80 mmole) as described in the preceding experiment. Progress of the reaction was followed by tlc (ether–petroleum ether 2:1; after spraying with sulphuric acid and heating, compounds containing a double bond charred black; saturated fluorine-containing compounds charred brown). It was found that the reaction was complete within 4 h. The work-up and chromatography was carried out as

described in the preceding experiment. The three compounds obtained were: (a) 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl fluoride **6** (172 mg, 69%), m.p. 69–70° (from ether–petroleum ether), $[\alpha]_D$ + 148.5° (c 1, $CDCl_3$); lit.[24] m.p. 69–79°, $[\alpha]_D$ + 136°(b)3, 4, 6 - tri - O - acetyl -2- deoxy - 2 - fluoro- β -D-galactopyranosyl fluoride **7** (27 mg, 12%) m.p. 79.5–80° (from ether–petroleum ether, needles); $[\alpha]_D^{22}$ + 84.5° (c 1, $CHCl_3$). Found: C, 46.48; H, 5.27; F, 12.09. Calc. for $C_{12}H_{16}F_2O_7$,:C, 46.45; H, 5.20; F, 12.25, (c) 3, 4, 6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-talopyranosyl fluoride (8 mg, 3%) was an oil, the identity of which was shown by ^{19}F NMR; lit.[24] m.p. 168–170° (0.17 mm Hg, $[\alpha]_D$ + 19.0 $CHCl_3$)]. The total yield was 207 mg (83%).

Reaction of 3, 4, *-di-O-acetyl-L-fucal* **9** *with* XeF_2. When the XeF_2 reaction was carried out on **9**, as described for **1** and **5**, the yield of **10** was 53%. The following modification improved the yield. A solution of **9**,[13] (500 mg, 2.3 mmoles) in benzene (10 ml) was added dropwise to a stirred and cooled (dry ice-acetone bath) solution containing XeF_2 (320 mg, 2.57 mmole and BF_3-etherate (200 μl). During the addition, the reaction mixture was gradually allowed to reach room temperature. Reaction was complete in 20 min, as indicated by tlc (ether–dichloromethane, 2:98). Work-up and chromatography was carried out as described for **1**. Elution with dichloromethane–ether (98:2) gave 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-L-fucopyranosyl fluoride (366 mg, 62%); R_F 0.8, m.p. 46.5–49° (from ether–petroleum, $[\alpha]_D^{25}$ – 182° (c 0.5, $CHCl_3$); lit.[17] m.p. 46°; $[\alpha]_D^{22}$ – 187.6° (c 0.5, $CHCl_3$). (Found: C, 47.90; H, 5.85; F, 14.79. Calc. for $C_{10}H_{14}F_2O_5$:C, 47.62, H, 5.59, F, 15.07). The second fraction consisted of 3, 4-di-O-acetyl-2-deoxy-fluoro-β-L-fucopyranosyl fluoride **11**, which was crystallized from ether–pectroleum (1:10) yielding 8.5 mg (1.4%), m.p. 85–86°, $[\alpha]_D^{22}$ – 110° (c 0.1, $CHCl_3$), R_F 0.75, (Found: C, 47.71; H, 5.58; F, 15.27. Calc. for $C_{10}H_{14}F_2O_5$: C, 47.62: H, 5.59, F, 15.07%).

2-Deoxy-2-fluoro-α-D-glucopyranosyl fluoride **12**. To a solution of **2** (31 mg, 0.1 mmole) in methanol (10 ml), 0.1N sodium methoxide solution in methanol (4 ml) was added and the combined solution allowed to stand at room temperature overnight. After treatment with Amberlite IR–120 (H+) and concentration *in vacuo*, an oil (18 mg, 100%) was obtained, which could not be crystallized, $[\alpha]_D^{20}$ 91.7° (c 2, methanol). (Found: C, 38.89, H, 5.22; F, 20.43. Calc. for $C_6H_{10}F_2O_4$: C, 39.13; H, 5.47; F, 20.64%).

2-Deoxy-2-fluoro-α-D-galactopyranosyl fluoride **13**. To a solution of **6** (155 mg, 0.5 mmole) in methanol (10 ml), 0.1N NaOMe in methanol (1 ml) was added and the solution was allowed to stand for 1 h at room temperature and then treated with Amberlite IR 120 (H^+). After concentration *in vacuo*, the compound crystallized. Recrystallization from isopropyl alcohol-ether yielded 2-deoxy-2-fluoro-α-D-galactopyranosyl fluoride (71 mg, 77%), m.p. 163°, $[\alpha]_D^{22}$ + 105° (c 1.0; methanol) (Found: C, 39.25; H. 5.45; F, 20.44. Calc. for $C_6H_{10}F_2O_4$: C, 39.13; H, 5.47; F, 20.64%).

2-Deoxy-2-fluoro-α-L-fucopyranosyl fluoride **14**. A solution of **10** (174 mg) in methanol (25 ml) was neutralized by dropwise addition of NaOMe (1N). After 15 min the mixture was filtered through Amberlite IR–120 (H^+) resin, and then evaporated to dryness. The residue was dissolved in a minimum volume of ether to which petroleum ether was added until turbid. Cooling induced crystal formation; yield 107 mg (99%) m.p. 120° (decomposition) $[\alpha]_D^{22}$ – 135° (c 1, methanol) (Found; C, 43.07: H, 5.92; F, 22.45. Calc. for $C_6H_{10}F_2O_3$: C, 42.86; H, 5.99; F, 22.60%).

2-Deoxy-2-fluoro-L-fucose **15**. *Method A.* The preceding difluoro compound **14** (366 mg) was hydrolyzed in 1N H_2SO_4 solution (15 ml) at 100° for 1 h. The solution was filtered through Dowex-1-formate column and evaporated to dryness yielding 227 mg (94%) of **15**. Crystallization was achieved by dissolving in a minimum amount of water, adding acetonitrile (2–3 ml) and then a few drops of ether to turbidity. After chilling the solution to −10°, 130 mg (54%) of needles formed; m.p. 180–181°, $[\alpha]_D^{20}$ – 83.1 to −82.9° (8 h) (c 0.35, H_2O). After several days in the cold, 88 mg (36%) of additional crystals (cubes) have formed: m.p. 146°–147° $[\alpha]_D^{20}$ – 84.0° to 83.4° (8 h) (c 0.35, H_2O). A mixture of two forms was analyzed. (Found: C, 43.49; H, 6.90; F, 11.20. Calc. for $C_6H_{11}F0_4$: C, 43.47; H, 6.67; F, 11.44%. *Method B.* A solution of **10** (75 mg) was hydrolyzed with 0.1N H_2SO_4 (5 ml) on heating at 100° for 15 min. After passing through a Dowex-1-formate resin, the material was evaporated to dryness to yield 47 mg (71%) of **15**, which was recrystallized from acetonitrile as described above.

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