THE SYNTHESIS OF CERTAIN DERIVATIVES OF 2-FLUORO-D-RIBOSE, 2-DEOXY-2-FLUORO-D-RIBOSE, AND 2-DEOXY-2-FLUORO-D-ARABINOSE

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ABSTRACT

Addition of trifluoromethyl hypofluorite to 3,4-di-*O*-acetyl-D-arabinal (**1**) gave three crystalline products. The reaction products (one F,OCF_3 adduct and two F,F adducts) were determined, by spectroscopic and chemical methods, to be trifluoromethyl 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-β-D-arabinopyranoside (**2**), 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-β-D-arabinopyranosyl fluoride (**3**), and 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-α-D-ribopyranosyl fluoride (**4**). Acid hydrolysis of **2** and **3** furnished 2-deoxy-2-fluoro-D-arabinose (**5**); the reaction sequence is particularly well-suited for large-scale preparation of this fluoro sugar. Similarly, hydrolysis of **4** gave 2-deoxy-2-fluoro-D-ribose (**6**). Crystalline 2,3,4-tri-*O*-acetyl-1,5-anhydro-D-*erythro*-pent-1-enitol (**8**) was prepared from tri-*O*-acetyl-β-D-arabinopyranosyl bromide; it gave two adducts on treatment with trifluoromethyl hypofluorite in the presence of calcium oxide; the structures assigned to them, namely, trifluoromethyl 2,3,4-tri-*O*-acetyl-2-fluoro-β-D-ribopyranoside (**9**) and 2,3,4-tri-*O*-acetyl-2-fluoro-β-D-ribopyranosyl fluoride (**10**), were confirmed by 90-MHz n.m.r. spectral studies and spin-decoupling experiments.

INTRODUCTION

The high bond-energy of C–F bonds, the comparable Van der Waals radii of fluorine and hydrogen, and the similar electronegativities of fluorine and oxygen (–OH) make fluoro-sugars of considerable biological interest, as evidenced by the number of recent advances in the preparation and study of them. It was the goal of this study to investigate the addition of trifluoromethyl hypofluorite[1] to a pentose glycal and 2-hydroxyglycal. In the literature, there are very few examples of addition to 2-hydroxyglycals.

RESULTS AND DISCUSSION

The addition of trifluoromethyl hypofluorite to 3,4-di-*O*-acetyl-D-arabinal (**1**) gave three products: one F,OCF_3 adduct and two F,F adducts. The configuration and conformation of the products[2] was established by n.m.r. spectroscopy, and by hydrolysis.

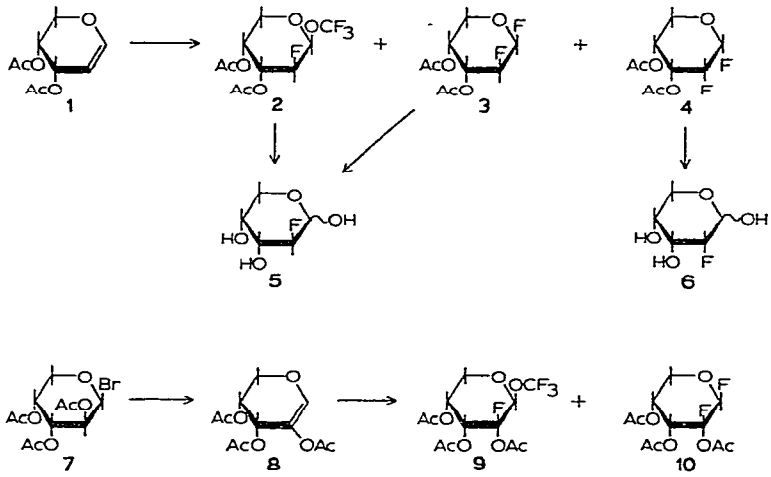
The F,OCF_3 adduct was assigned the structure of trifluoromethyl 3,4-di-*O*-

acetyl-2-deoxy-2-fluoro-β-D-arabinopyranoside (**2**) in the *1C* (D) conformation. The H-5 and H-5′ signals appeared as a pair of quartets showing $J_{4,5}$ 1.5 Hz and $J_{4,5'}$ 1.5 Hz, and hence, H-4 must be equatorially attached. Were compound **2** in the *C1* (D) conformation, H-5 would appear as a wide triplet or wide quartet. In a study of acetylated aldopentopyranoses, Durette and Horton[3] gave values of 1.5–1.8 Hz for $J_{4e,5e}$ and $J_{4e,5a}$, and 11.0 Hz for $J_{4a,5a}$. Similarly, in a study of fluorinated pentopyranosyl compounds, Hall and Manville[4] gave values of 2–3.5 Hz for $J_{4e,5e}$, 1.8–4.3 for $J_{4e,5a}$, 8–11 Hz for $J_{4a,5a}$, and 3.9–6.2 Hz for $J_{4a,5e}$. In the p.m.r. spectrum of **2**, H-1 appeared as a doublet at δ 5.80, showing $J_{1,2}$ 3.5 Hz and $J_{1,F\text{-}2}$ ~0 Hz. Irradiation of F-2 produced no change in the signals; this indicated an equatorial–axial arrangement for H-1 and H-2 (not a diequatorial arrangement, which would[5] show $J_{1,2}$ ~1.5 Hz, or a *trans*-diaxial arrangement, which would give a large coupling). The absence of an F-2,H-1 coupling shows that the bonds are diequatorially situated[1]; hence, H-2 must be axially attached. The zero (or very small) coupling is indicative of an anti-planar C-2–F-2 and C-1–O-5 arrangement[6]; this is further substantiated by the H-2 signal, which appeared as a pair of quartets ($J_{2,F\text{-}2}$ 48 Hz) that collapsed to a quartet on irradiation of F-2, and showed $J_{2,3}$ 9.0 Hz. The large coupling of H-2 with H-3 indicated a *trans*-diaxial arrangement. The *arabino* configuration was further confirmed by acid hydrolysis to 2-deoxy-2-fluoro-D-arabinose (**5**), identical in spectral and chromatographic properties with an authentic sample[7].

The major difluoro adduct was assigned the structure of 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-β-D-arabinopyranosyl fluoride (**3**). The H-5 and H-5′ signals were similar to those of the first product, and hence, by the same argument, it must be present as the *1C* (D) conformer. The H-1 resonance appeared as a pair of doublets that collapsed to a narrow doublet after irradiation of F-1 ($J_{1,F\text{-}1}$ 53 Hz, $J_{1,2}$ 3.0 Hz, $J_{1,F\text{-}2}$ ~0.5 Hz). Using arguments similar to the foregoing, H-1,H-2 must be equatorial–axial and H-1,F-2 must be diequatorial. The geminal coupling between H-1 and F-1 confirms this assignment. According to Hall and Manville[4,6,8], $J_{1,F\text{-}1}$ coupling constants are dependent on the orientation of the substituent at C-2. If the compound has a substituent axially attached to C-2, $J_{1,F\text{-}1}$ has values of ~49 Hz, and, for compounds having equatorially attached substituents at C-2, $J_{1,F\text{-}1}$ has values of ~53 Hz for a series of aldohexopyranosyl and aldopentopyranosyl fluorides. Compound **3** was also hydrolyzed to 2-deoxy-2-fluoro-D-arabinose (**5**), thus confirming the structure proposed.

On the basis of the n.m.r. data and the *cis* mechanism proposed by Barton *et al.*[9,10], the (minor) difluoro adduct is assigned the structure of 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-α-D-ribopyranosyl fluoride (**4**). In contrast to the other two products, compound **4** assumes the *C1* (D) conformation. The H-5 signal appeared as a wide triplet indicative of axial H-4 ($J_{4,5}$ 10.0 Hz). The proton on C-1 gave a pair of doublets ($J_{1,F\text{-}1}$ 53.5 Hz, $J_{1,2}$ 3.5 Hz) and the H-2 signal appeared as a quadruplet of triplets ($J_{2,F\text{-}2}$ 44 Hz, $J_{2,3}$ 3.5 Hz, and $J_{2,F\text{-}1}$ 24.5 Hz). The large coupling between H-2 and F-1 indicates a *trans*-diaxial arrangement[1,4]. The structure proposed was further confirmed by hydrolysis to 2-deoxy-2-fluoro-D-ribose[11] (**6**).

The reaction is very useful for the synthesis of 2-deoxy-2-fluoro-D-arabinose in a 4-step sequence from D-arabinose, because both of the major products of the addition reaction give the desired sugar in ~80% yield after hydrolysis.



The synthesis of 2-acetoxy-2-fluoro sugars was also accomplished by use of the trifluoromethyl hypofluorite reagent. Attempts to prepare the starting material, namely, 2,3,4-tri-*O*-acetyl-1,5-anhydro-D-*erythro*-pent-1-enitol (**8**), by the method of Lemieux and Lineback[12] failed. However, application of the general method of Ferrier and Sankey[13] for the preparation of 2-acetoxy glycals was successful. Treatment of 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl bromide (**7**) with sodium iodide in acetone, followed by treatment of the iodide with anhydrous diethylamine, gave crystalline **8**. The identity of the compound was confirmed by elemental analysis, the presence of a band in the i.r. spectrum at 1680 cm^{-1} (C=C), and n.m.r. spectroscopic evidence.

The addition of trifluoromethyl hypofluorite to **8** gave two products, to which were assigned the structures of trifluoromethyl 2,3,4-tri-*O*-acetyl-2-fluoro-β-D-ribopyranoside (**9**) and 2,3,4-tri-*O*-acetyl-2-fluoro-β-D-ribopyranosyl fluoride (**10**) on the basis of the n.m.r. data and the elemental analyses. Both compounds were shown to exist in the *1C* (D) conformation, as with **2** and **3**. The n.m.r. spectrum of compound **9** showed a singlet at δ 6.44 that was assigned to H-1. The absence of splitting between H-1 and F-2 again showed a diequatorial arrangement for H-1 and F-2. The data are compatible only with the structure proposed. The equatorial attachment of F-2 is further substantiated by the $J_{3,F-2}$ coupling of 6.5 Hz. A *trans*-diaxial H-3,F-2 system would show[1,4] a splitting of ~25 Hz. The alternative, namely, the diequatorial H-3,F-2 orientation, is not compatible with the rest of the data, because H-4 must be equatorially attached and $J_{3,4}$ 4.0 Hz indicates that H-3 is axially attached (see the Experimental section).

The fluoride **10** gave a spectrum very similar to that of **9**, except that H-1 had

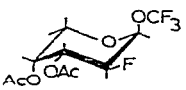
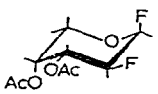
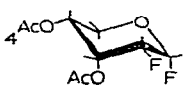
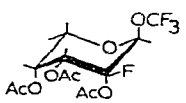
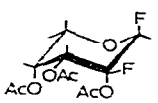
a large, geminal H-1,F-1 coupling that collapsed to a sharp singlet on irradiation of F-1. The H-1 signal did not show any splitting with F-2, and hence, by the same arguments used for compounds **2**, **3**, and **9**, the compound must have the *β*-D-*ribo* configuration.

The addition of trifluoromethyl hypofluorite to the 2-acetoxy glycal **8** proceeded more slowly, and at a higher temperature, than that of the glycal, and it was necessary to add calcium oxide to prevent decomposition of the acid-sensitive starting-material.

The existence of the compounds investigated in that chair conformation that has the F or OCF_3 substituent on C-1 axially attached may be attributed to the anomeric effect[14]. This effect has been used to explain the all-axial, *1C* (D) conformation favored by tri-*O*-acetyl-*β*-D-xylopyranosyl chloride[15] and its fluoro[4,16] analog. The H-5,H-5′ coupling-constants of 13.5 and 13.0 Hz for compounds **2**, **3**, **9**, and **10**, and of 10.0 Hz for **4**, are respectively compatible with the values of 14–13 Hz reported for the *1C* (D) conformation, and 10–11 Hz reported for the *C1* (D) conformation[3,17].

TABLE I

^{19}F CHEMICAL SHIFTS (p.p.m. RELATIVE TO CCl_3F STANDARD)

		$\phi_{F(1)}$	$\phi_{F(2)}$	$\phi_{OCF_3(1)}$
2			+208	+59
3		+156	+210	
4		+151	+206	
9			+133	+60
10		+153	+133	

The formation of all of the products is in accord with the *cis* mechanism originally proposed by Barton *et al.*[9,10] and found to apply to addition to glycals[1]. The reagent attacks the more nucleophilic center, and forms an ion pair that collapses and immediately combines with the counter-ion (OCF_3^- or F^-). It was postulated that the fluoride anion arises from the equilibrium: $CF_3O^- \rightleftarrows COF_2 + F^-$. The preponderant products arise from attack of the reagent from the less-hindered side of the olefin.

EXPERIMENTAL

General. — Melting points were determined with a Thomas–Hoover melting-point apparatus and are uncorrected. Specific rotations were determined with a Perkin–Elmer Model 141 polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 257 grating infrared spectrophotometer. N.m.r. spectra were recorded at 60 MHz with a Hitachi Model R-20A n.m.r. spectrometer, and at 90 MHz with a Bruker Model B-90 n.m.r. spectrometer. Chemical shifts were measured relative to tetramethylsilane as the internal standard, and are recorded as δ values. Column chromatography was performed with Silica Gel 7734 (E. Merck). Paper chromatograms were obtained on Whatman No. 1 paper with 8:2:1 ethyl acetate–pyridine–water, 2:1:1 butyl alcohol–ethanol–water, 18:3:1:4 ethyl acetate–acetic acid–formic acid–water, 5:1:2 butyl alcohol–acetic acid–water, and 6:4:3 butyl alcohol–pyridine–water, with detection with silver nitrate–sodium hydroxide spray reagent[18].

Trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-β-D-arabinopyranoside (**2**); *3,4-di-O-acetyl-2-deoxy-2-fluoro-β-D-arabinopyranosyl fluoride* (**3**); *and 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-ribopyranosyl fluoride* (**4**). — A solution of **1** (21.3 g, 106 mmoles) in trichlorofluoromethane (150 ml) was cooled in a Dry Ice–acetone bath (−78°), and trifluoromethyl hypofluorite was slowly bubbled into the solution; t.l.c. revealed that all of **1** had reacted after ~4 h. The solution was then evaporated to a syrup which was dissolved in the minimal volume of dichloromethane. The solution was passed through a column of silica gel (500 g), with dichloromethane as the eluant, to give, on evaporation of fractions, **2** as a syrup (6.91 g, 21.4%), **3** as a syrup (6.41 g, 25.6%), **4** as colorless crystals (0.40 g, 1.7%), and a mixture of **2** and **3** in ~20% yield.

The glycoside **2** was distilled at 0.5 torr/ 85–90° (bath), affording a syrup that crystallized after cooling. It was recrystallized from chloroform–petroleum ether (b.p. 60–90°), to give analytically pure **2**, m.p. 51–52°; $[\alpha]_D^{25}$ −195° (*c* 1, chloroform); n.m.r. data: δ 5.80 (1-proton doublet, $J_{1,2}$ 3.5 Hz, $J_{1,F-2}$ ~0 Hz, H-1); 5.23–5.53 (2-proton multiplet, H-3,4); 5.13, 4.60 [1-proton pair of quartets, $J_{2,F-2}$ 48 Hz, $J_{2,3}$ 9.0 Hz, (collapsed to quartet centered at δ 4.90 on irradiation of F-2), H-2]; 4.13 (1-proton pair of doublets, $J_{5,5'}$ 13.5 Hz, $J_{4,5}$ 1.5 Hz, H-5); 3.82 [1-proton pair of triplets, $J_{4,5'}$ 1.5 Hz, $J_{5',F-2}$ 1.5 Hz, (collapsed to a pair of doublets on irradiation of F-2), H-5']; and 2.08, 2.15 (two 3-proton singlets, 2 OAc).

Anal. Calc. for $C_{10}H_{12}F_4O_6$: C, 39.48; H, 3.97; F, 24.98. Found: C, 39.50; H, 4.00; F, 24.91.

The fluoride **3** was distilled at 0.5 torr/ 72–76° (bath) to give a syrup that crystallized after refrigeration. Recrystallization from ether–petroleum ether (b.p. 60–90°) gave analytically pure **3**, m.p. 75–76°; $[\alpha]_D^{22}$ −191.6° (*c* 1, chloroform); n.m.r. data: δ 6.14, 5.54 [1-proton pair of doublets, $J_{1,F-1}$ 53 Hz, $J_{1,2}$ 3.0 Hz, $J_{1,F-2}$ 0.5 Hz (collapsed to a doublet centered at δ 5.86 on irradiation of F-1; showed sharpening of signals on irradiation of F-2), H-1]; 4.31–5.50 (3-proton multiplets, H-2, 3, 4); 4.16 (1-proton pair of doublets, $J_{5,5'}$ 13.5 Hz, $J_{4,5}$ 1.5 Hz, H-5); 3.85 [1-proton pair of

triplets, $J_{4,5'}$ 2.0 Hz, $J_{5',F-2}$ 2.0 Hz (irradiation of F-2 caused collapse into a pair of doublets), H-5']; and 2.05, 2.15 (two 3-proton singlets, 2 OAc).

Anal. Calc. for $C_9H_{12}F_2O_5$: C, 45.38; H, 5.07; F, 15.95. Found: C, 45.43; H, 5.05; F, 15.91.

The fluoride **4** was purified by sublimation; m.p. 87–88°; $[\alpha]_D^{22}$ +82.80° (*c* 0.9, chloroform); n.m.r. data: δ 5.30, 5.90 (1-proton pair of doublets, $J_{1,F-1}$ 53.5 Hz, $J_{1,2}$ 3.5 Hz, H-1; 5.78 (1-proton multiplet), 4.97 (1-proton multiplet); 4.13, 4.41, 4.63, 4.90 (1-proton quadruplet of triplets, $J_{2,F-2}$ 44 Hz, $J_{2,3}$ 3.5 Hz, $J_{2,F-1}$ 24.5 Hz, H-2), 4.00 (1-proton triplet, $J_{4,5}$ 10.0 Hz, $J_{5,5'}$ 10.0 Hz, H-5); 3.67 (1-proton quartet with fine splittings, $J_{4,5'}$ 5.0 Hz, H-5'); and 1.94, 2.02 (two 3-proton singlets, 2 OAc).

Anal. Calc. for $C_9H_{12}F_2O_5$: C, 45.38; H, 5.07; F, 15.95. Found: C, 45.48; H, 5.13; F, 15.63.

*2-Deoxy-2-fluoro-*D*-arabinose* (**5**) *from glycoside* **2**. — A suspension of the glycoside **2** (1.00 g, 3.2 mmoles) in 5 M hydrochloric acid (20 ml) was boiled for 5 h under reflux, cooled, and made neutral with Amberlite IR-45 (OH^-) ion-exchange resin (30 g); the suspension was filtered, and the filtrate was evaporated. The resulting syrup was chromatographed on silica gel (20 g), with 1:1 methanol–ethyl acetate as the eluant, to give pure **5**, yield 0.394 g (81%); identical by paper chromatography (in five solvent-systems) and by i.r. spectrum with an authentic sample*.

*2-Deoxy-2-fluoro-*D*-arabinose* (**5**) *from fluoride* **3**. — A suspension of the fluoride **3** (1.00 g, 4.2 mmoles) in M hydrochloric acid (15 ml) was boiled for 30 min under reflux, cooled, and made neutral with Amberlite IR-45 (OH^-) ion-exchange resin (10 g). The suspension was filtered, and the filtrate was evaporated *in vacuo*. Column chromatography on silica gel (20 g) with 1:1 methanol–ethyl acetate as the eluant gave pure **5**, yield 0.512 g (85%), identical by paper chromatography and by i.r. spectrum with **5** obtained in the previous experiment and with an authentic sample*.

*2-Deoxy-2-fluoro-*D*-ribose* (**6**) *from fluoride* **4**. — A suspension of the fluoride **4** (20 mg) in M hydrochloric acid (10 ml) was boiled for 30 min under reflux, cooled, and made neutral with Amberlite IR-45 (OH^-) ion-exchange resin. The suspension was filtered, and the filtrate was evaporated to a syrup, yield 9 mg (70%). Paper chromatography on Whatman No. 1 paper in five solvent-systems showed that it was identical with an authentic sample of 2-deoxy-2-fluoro-D-ribose**.

*2,3,4-Tri-*O*-acetyl-1,5-anhydro-*D*-erythro-pent-1-enitol* (**8**). — A mixture of **7** (6.50 g, 147 mmoles), sodium iodide (25 g), and dry acetone (250 ml) was stirred for 15 min. Dry diethylamine (50 ml) was added, and the resulting mixture was stirred for 2 h, and then diluted with dichloromethane (300 ml) and water (500 ml), and shaken. The layers were separated, and the organic layer was washed successively with 2 M hydrochloric acid (50 ml), saturated aqueous sodium hydrogen carbonate solution (50 ml), and water (100 ml), dried (magnesium sulfate), and evaporated

* Kindly supplied by Dr. J. J. Fox[7].
**Kindly supplied by Dr. J. J. Fox[11].

to a syrup. Column chromatography on silica gel (500 g) with 10:1 dichloromethane–ether as the eluant gave **8**, which crystallized after being kept for several days at 5°; yield, 17.25 g (46%). Recrystallization from chloroform–petroleum ether (b.p. 60–90°) gave pure **8**, m.p. 59–60°; $[\alpha]_D^{25}$ +223.6° (*c* 1, chloroform); ν_{max}^{KBr} 1780, 1745, 1740 (OAc), and 1680 cm^{-1} (C=C); n.m.r. data: δ 6.65 (1-proton, sharp singlet, H-1); 5.70 (1-proton doublet, $J_{3,4}$ 4.0 Hz, H-3); 5.25 (1-proton quintet, $J_{4,5}$ 4.0 Hz $J_{4,5'}$ 8.0 Hz, H-4); 4.13–3.80 (2-proton multiplet, H-5,5'); and 2.03, 2.07, 2.10 (three 3-proton singlets, 3 OAc).

Anal. Calc. for $C_{11}H_{14}O_7$: C, 51.16; H, 5.46. Found: C, 51.43; H, 5.58.

*Trifluoromethyl 2,3,4-tri-*O*-acetyl-2-fluoro-β-*D*-ribopyranoside* (**9**) *and 2,3,4-tri-*O*-acetyl-2-fluoro-β-*D*-ribopyranosyl fluoride* (**10**). — A solution of **8** (4.20 g, 16.2 mmoles) in trichlorofluoromethane (100 ml) was cooled to 0°, calcium oxide (5 g) was added, and trifluoromethyl hypofluorite was slowly bubbled through the suspension for 5 h. The solids were then filtered off, and the filtrate was evaporated to a syrup which was chromatographed on silica gel (100 g), with 100:1 dichloromethane–ether as the eluant, to give **9** as a syrup that crystallized on standing (1.60 g, 27%) and **10** as crystals (0.64 g, 13%).

The glycoside **9** was recrystallized from ether–petroleum ether (b.p. 60–90°), m.p. 71–73°; $[\alpha]_D^{30}$ −56.7 (*c* 1, chloroform); ν_{max}^{KBr} 1780, 1767, and 1760 cm^{-1} (OAc); n.m.r. data: δ 6.44 (1-proton singlet, $J_{1,F-2}$ ~0 Hz, H-1); 5.58 [1-proton quartet, $J_{3,4}$ 4.0 Hz, $J_{3,F-2}$ 6.5 Hz (collapsed to a doublet on irradiation of F-2), H-3]; 5.44 (1-proton multiplet, H-4), 4.26 (1-proton pair of doublets, $J_{4,5}$ 2.5 Hz, $J_{5,5'}$ 13.5 Hz, H-5), 3.86 [1-proton pair of quartets, $J_{4,5'}$ 2.5 Hz, $J_{5',F-2}$ 1.2 Hz (collapsed to a pair of doublets on irradiation of F-2), H-5']; and 2.22, 2.17 (3-proton singlet, 6-proton singlet, 3 OAc).

Anal. Calc. for $C_{12}H_{14}F_4O_8$: C, 39.78; H, 3.89; F, 20.98. Found: C, 39.91; H, 3.95; F, 21.03

The fluoride **10** was recrystallized from chloroform–petroleum ether (b.p. 60–90°) to give pure **10**, m.p. 125–126°; $[\alpha]_D^{25}$ −22.7° (*c* 1, chloroform); ν_{max}^{KBr} 1785, 1760, and 1745 cm^{-1} (OAc); n.m.r. data: δ 6.74, 6.18 [1-proton doublet, $J_{1,F-1}$ 51 Hz $J_{1,F-2}$ ~0 Hz (irradiation of F-1 showed a singlet at δ 6.47), H-1]; 5.31–5.61 (2-proton multiplet, H-3, H-4), 4.22 (1-proton pair of doublets, $J_{4,5}$ 2.0 Hz, $J_{5,5'}$ 13.0 Hz, H-5), 3.83 [1-proton pair of triplets, $J_{4,5'}$ 1.5 Hz, $J_{5',F-2}$ 1.5 Hz (irradiation of F-2 gives a pair of doublets), H-5'], and 2.15, 2.20 (3-proton singlet, 6-proton singlet, 3 OAc).

Anal. Calc. for $C_{11}H_{14}F_2O_7$: C, 44.59; H, 4.76; F, 12.82. Found: C, 44.80; H, 4.83; F, 12.76.

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