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Note

Nucleosides from fluorinated branched-chain sugars: some reactions of 3-deoxy-3-fluoro-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose

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Fluorinated carbohydrates have attracted considerable interest in recent years, mainly due to the fact that the introduction of a fluorine atom onto the carbohydrate ring can result in a dramatic change in biological activity[1,2]. Unlike the naturally occurring, fluoro-sugar, nucleoside-antibiotic nucleocidin[3], which inhibits protein synthesis by the prevention of peptide elongation[4], the majority of synthetically prepared fluoro-sugar nucleosides are inhibitors of DNA and RNA synthesis[5,6]. These compounds are potential antiviral and antitumour agents, and in some cases have shown a marked growth-inhibitory effect on experimental tumours[7].

In a previous paper[8], we described the use of trifluoro(fluoroxy)methane for the stereospecific introduction of fluorine at the branching point of branched-chain sugars, and we now report the synthesis of pyrimidine nucleosides from these sugars. We also describe the use of the elegant reaction scheme developed by Reichman *et al.*[9] to transform the 3-fluoro-glucofuranose derivative **9**[*] into the 2-fluoro-arabinofuranose derivative **14**. Our interest in the synthesis of compounds such as **14** stems from the observation that 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine[7] inhibits the growth of L-1210 lymphoid leukemia in mice.

Acetolysis of the fluoro sugar **1**[8] with acetic anhydride–acetic acid–sulphuric acid gave an anomeric mixture of the acetates **2** and **3**. This mixture behaved as a single compound on t.l.c., but the anomers were separated by fractional crystallization and identified by n.m.r. spectroscopy. For compound **2**, H-1 appeared as a doublet ($J_{1,2}$ 5 Hz) at τ 3.50; for **3**, H-1 appeared at much higher field (τ 3.90) as a singlet. Assignment of the anomeric configurations for **2** and **3** was based on the observation[10,11] that, for a pair of anomers, H-1 resonates at lower field when the 1,2-

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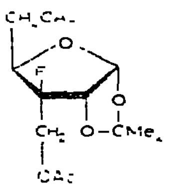
[*] For naming these sugars which bear unequal geminal substituents, the substituent having the highest priority according to the Sequence Rule is regarded as replacing the hydroxyl group at the carbon atom concerned.

substituents are *cis* than when they are *trans*. The very small $J_{1,2}$ value observed for **3** also established[12] that the 1,2-substituents of **3** are *trans*



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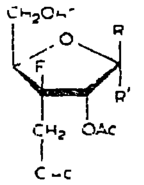
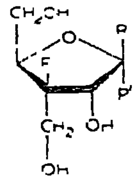


2 R = H, R' = OAc
3 R = OAc, R' = H
4 R = H, R' = Uracil
5 R = Uracil, R' = H



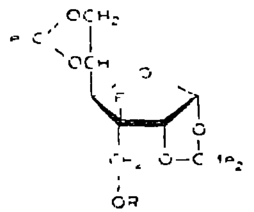
6 R = H, R' = Uracil
7 R = Uracil, R' = H

A mixture of **2** and **3** was used for the preparation of a mixture of the protected α- and β-nucleosides **4** and **5** by the modified Hilbert–Johnson procedure[13] The mixture of nucleosides was fractionated by chromatography on silica gel, and each anomer was identified from its n m r spectrum For the α-nucleoside **4**, H-1' appeared as a doublet ($J_{1,2}$ 6 Hz) at τ 3.76, whereas H-1' of the β-nucleoside **5** also resonated as a doublet ($J_{1,2}$ 3 Hz) but at higher field (τ 3 98) These anomeric assignments were supported by the observation, first noticed for pyrimidine nucleosides by Cushley *et al* [14], that, due to the shielding effect of the 5,6-double bond, two of the *O*-acetyl signals of the 1',2'-*cis* nucleoside **4** are slightly upfield in comparison with the *O*-acetyl signals of the 1',2'-*trans* nucleoside **5**.

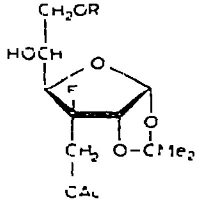
The unprotected nucleosides **6** and **7** were prepared from **4** and **5**, respectively by hydrolysis with sodium methoxide in methanol Compounds **6** and **7** showed the expected difference between the chemical shifts of their anomeric protons, and in addition, the o r d spectrum of **6** exhibited a negative Cotton effect characteristic of the α-D configuration of furanosylpyrimidines[15], whereas the spectrum of **7** exhibited a positive Cotton effect consistent with the β-D configuration

To effect the transformation of the 3-deoxy-3-fluoro-compound **8** into the 2-deoxy-2-fluoro-compound **14**, the hydroxymethyl group of **8** was protected by acetylation and the 5,6-*O*-isopropylidene group was then selectively removed by treatment with 75% aqueous acetic acid, to give the diol **10** in high yield. The selective benzoylation of the primary hydroxyl group of **10** was conducted at low temperature to afford compound **11**, and the 1,2-*O*-isopropylidene group of **11** was then removed by treatment with Amberlite IR-120(H^+) resin to give **12**, which was oxidized with sodium metaperiodate to give the 2-fluoro-arabinofuranose **13** Without further purification, **13** was acetylated to give **14** as a 1 3 mixture of the α and β anomers, respectively The pure anomers were separated by chromatography and identified by use of Hudson's isorotation rules[16]

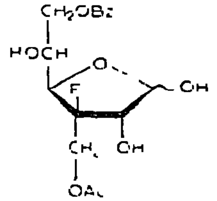
It could be seen from the n.m r spectra of **9**, **10**, and **11** (and by inspection of Dreiding models) that the bulky 1,2-*O*-isopropylidene group caused restriction of



8 R = H
9 R = Ac



10 R = H
11 R = Bz



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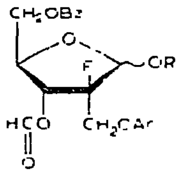

13 R = H
14 R = Ac

rotation of the branched chain around the C-3–C-1′ bond, leading to non-equivalence of H-1′ and H-1″. For all three compounds, coupling constants $J_{1',F}$ *gauche* = ~13 Hz and $J_{1',F}$ *trans* = 34 Hz were observed. These values were similar to those obtained[17] for $J_{H,F}$ *trans* and $J_{H,F}$ *gauche* of 1,2,2-trichloro-1-fluoroethane (37 Hz and ~13 Hz, respectively). A vicinal $J_{H,F}$ of 30.6 Hz has also been reported[18] for 2-fluoroethanol.

The nucleoside 7 showed no activity against L-1210 lymphoid leukemia in mice.

As the reagent trifluoro(fluoroxy)methane is no longer commercially available, we have not been able to prepare enough of the 2-deoxy-2-fluoro-derivative **14** for use in nucleoside synthesis. The use of bases such as cytosine and chloropurine for the synthesis of other potentially interesting nucleosides from compounds **2** and **3** has also not been possible due to lack of reagent.

EXPERIMENTAL

General methods. — All solvent extracts were dried (Na_2SO_4), filtered, and evaporated below 50° *in vacuo*. T.l.c. and column chromatography were performed on silica gel (Merck GF_{254}) [100 g of silica gel per g of residue for column separations][6]. M.p.s. were determined on a hot-stage apparatus. I.r. spectra were measured with a Perkin–Elmer 237 spectrophotometer for solutions in chloroform unless otherwise stated. Optical rotations were measured for solutions in chloroform with a Bendix-NPL automatic polarimeter type 143 (*c* 1.0 ±0.3). U.v. spectra were recorded on a Unicam S.P. 800 instrument, and o.r.d. spectra on a Jasco J-20 automatic recording spectropolarimeter. Mass spectra were determined with an A.E.I. MS9 spectrometer, by direct insertion and with an ionizing voltage of 70 eV. N.m.r. spectra were recorded on a Varian HA-100 instrument for solutions in $CDCl_3$, with tetramethylsilane as internal standard, unless otherwise stated. For syrups, microanalytical figures are only given when a syrup could be distilled under high vacuum by use of a Kugelröhr. For unstable syrups, accurate mass measurements were made on the detectable ions of highest mass.

3-C-Acetoxymethyl-1,2,5-tri-O-acetyl-3-deoxy-3-fluoro-α-D-xylofuranose (**2**) *and its β anomer* **3**. — A solution of **1** (1.12 g) in a mixture of glacial acetic acid (45 ml) and acetic anhydride (5 ml) was stirred in an ice-bath, and conc. sulphuric acid (1.5 ml) was added dropwise. The ice-bath was removed, and the mixture was kept at 20° for 48 h and then poured into ice-water (500 ml). The mixture was made alkaline by the addittion of a slight excess of saturated, aqueous sodium hydrogen carbonate. Extraction of the mixture with chloroform (3 × 100 ml) and removal of solvent gave a semi-crystalline mixture (1.16 g) of **2** and **3**. Fractional crystallization from ethyl acetate–hexane gave pure **2**, m.p. 103–104°, $[\alpha]_D^{22}$ +89°, ν_{max} 1745 cm^{-1} (acetate) Mass spectrum: *m/e* 291 ($M^+ - CH_3CO_2$). N.m.r. data: τ 3.50 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 4.54 (q, 1 H, $J_{2,F}$ 24, $J_{2,1}$ 5 Hz, H-2), 5.30–6.00 (m, 5 H, H-4,5,5′,1′,1″), 7.83 (s, 3 H, OAc), 7.89 (s, 6 H, 2 OAc), 7.92 (s, 3 H, OAc).

Anal. Calc. for $C_{14}H_{19}FO_9$: C, 48.0; H, 5.5. Found: C, 48.0; H, 5.3.

The mother liquors from the fractional crystallization of **2** were combined, and the solvent was removed to leave an oil consisting of the β anomer **3** and traces of the α anomer **2** (n.m.r. evidence). Compound **3** had ν_{max} 1745 cm^{-1} (acetate) Mass spectrum: *m/e* 291 ($M^+ - CH_3CO_2$). N.m.r. data: τ 3.90 (s, 1 H, H-1), 4.66 (d, 1 H, $J_{2,F}$ 14 Hz, H-2), 5.40–5.90 (m, 5 H, H-4,5,5′,1′,1″), 7.80–8.00 (m, 12 H, 4 OAc).

1-[3-C-Acetoxymethyl-2,5-di-O-acetyl-3-deoxy-3-fluoro-α-D-xylofuranosyl]uracil (**4**) *and its β anomer* **5**. — To a solution of an anomeric mixture of **2** and **3** (700 mg, 2 mmol) in dry 1,2-dichloroethane (60 ml), bis(trimethylsilyl)uracil (1.12 g, 5 mmol) and tin(IV) chloride (0.5 ml) were added under anhydrous conditions. The mixture was stirred at 20° for 24 h and then poured into saturated, aqueous sodium hydrogen carbonate (400 ml). The mixture was filtered through Celite, and the aqueous phase was extracted with chloroform (5 × 50 ml). The extracts were combined and the solvent was removed to give a crude mixture (810 mg) of **4** and **5**. Chromatography of this mixture on silica gel, with elution by ethyl acetate, gave **5** as an oil (507 mg), $[\alpha]_D^{22}$ +24°; ν_{max} 3390 (NH), 1745 (acetate), and 1695 cm^{-1} (amide). N.m.r. data: τ 2.56 (d, 1 H, $J_{6,5}$ 8 Hz, H-6), 3.98 (d, 1 H, $J_{1',2'}$ 3 Hz, H-1′), 4.19 (d, 1 H, $J_{5,6}$ 8 Hz, H-5), 4.52 (q, 1 H, $J_{2',1'}$ 3, $J_{2',F}$ 18 Hz, H-2′), 5.50–5.90 (m, 5 H, H-4′,5′,5″,1″,1‴), 7.86 (s, 3 H, OAc), 7.88 (s, 3 H, OAc), 7.89 (s, 3 H, OAc).

Anal: Acc. mass calc. for $C_{14}H_{15}FN_2O_7$ ($M^+ - 60$): 342.086. Found: 342.08

Further elution gave **4** as an oil (266 mg), $[\alpha]_D^{22}$ +42°; ν_{max} 3420 (NH), 1740 (acetate), and 1690 cm^{-1} (amide). N.m.r. data: τ 2.80 (d, 1 H, $J_{6,5}$ 8 Hz, H-6), 3.63 (q, 1 H, $J_{2',1'}$ 6, $J_{2',F}$ 24 Hz, H-2′), ~3.76 (H-1′, obscured by H-2′), 4.29 (d, 1 H $J_{5,6}$ 8 Hz, H-5), 5.20–6.00 (m, 5 H, H-4′,5′,5″,1″,1‴), 7.85 (s, 3 H, OAc), 7.91 (s, 6 H, 2 OAc).

Anal: Acc. mass calc. for $C_{14}H_{15}FN_2O_7$ ($M^+ - 60$): 342.086 Found: 342.085

1-[3-Deoxy-3-fluoro-3-C-hydroxymethyl-α-D-xylofuranosyl]uracil (**6**). — A mixture of **4** (160 mg) and 0.1M methanolic sodium methoxide (10 ml) was boiled under reflux for 1 h. The solution was cooled, and the pH was adjusted to 7 with glacial acetic acid. After removal of the solvent, the residue was chromatographed on silica gel with 1:1 ethanol–ethyl acetate to give **6** as an oil, $[\alpha]_D^{22}$ −23° (methanol), ν_{max}^{KBr} 3800 (broad, NH, OH) and 1650 cm^{-1} (amide). N.m.r. data (D_2O): τ 2.49 (d, 1 H, $J_{6,5}$ 8 Hz, H-6), 3.83 (d, 1 H, $J_{1',2'}$ 7 Hz, H-1′), 4.16 (d, 1 H, $J_{5,6}$ 8 Hz, H-5), 4.70 (q, 1 H, $J_{2',1'}$ 7, $J_{2',F}$ 24 Hz, H-2′), 5.60–6.30 (m, 5 H, H-4′,5′,5″,1″,1‴). Electronic spectrum (methanol): log ε_{262} 3.83, log ε_{212} 3.68. O.r.d. data (c 1.1 × 10^{-3}, methanol) $[\Phi]_{320}$ +300, $[\Phi]_{283}$ −700, $[\Phi]_{273}$ 0, $[\Phi]_{260}$ +1300, $[\Phi]_{250}$ 0, a = −20.

Anal: Calc. for $C_{10}H_{13}FN_2O_6$: C, 43.5; H, 4.7; N, 10.1. Found: C, 42.9; H, 5.1; N, 9.9.

1-[3-Deoxy-3-fluoro-3-C-hydroxymethyl-β-D-xylofuranosyl]uracil (**7**). — Compound **5** (1.02 g) was treated as described for the preparation of **6** from **4**. The β-nucleoside **7** was obtained as a foam (420 mg, 60%) which crystallized from ethanol as colourless needles, m.p. 209–211°, $[\alpha]_D^{22}$ +45° (methanol); ν_{max}^{KBr} 3350 (broad, NH, OH) and 1660 cm^{-1} (amide).N.m.r. data (D_2O): τ 2.16 (d, 1 H, $J_{6,5}$ 8 Hz, H-6), 4.12 (d, 1 H, $J_{5,6}$ 8 Hz, H-5), 4.12 (d, 1 H, $J_{1',2'}$ 2 Hz, H-1'), 5.50 (q, 1 H, $J_{2',1'}$ 2, $J_{2',F}$ 16 Hz, H-2'), 5.80–6.30 (m, 5 H, H-4',5',5'',1'',1'''). Electronic spectrum (methanol): log ε_{261} 3.99, log ε_{210} 3.83. O.r.d. data (*c* 8.0×10^{-4}, methanol): $[\Phi]_{320}$ +8500, $[\Phi]_{278}$ +14300, $[\Phi]_{260}$ 0, $[\Phi]_{246}$ −4100, $[\Phi]_{234}$ 0, a = +184.

Anal: Calc. for $C_{10}H_{13}FN_2O_6$: C, 43.5: H, 4.7; N, 10.1. Found: C, 43.9; H, 5.0, N, 10.3.

3-C-Acetoxymethyl-3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**9**). — To a solution of 3-deoxy-3-fluoro-3-C-hydroxymethyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose[8] (**8**) (4.4 g) in dry pyridine (50 ml), acetic anhydride (25 ml) was added and the mixture was left at room temperature for 18 h. The mixture was poured into ice–water (200 ml) and was then extracted with chloroform (4 × 100 ml). The combined extracts were successively washed with ice-cold 0.5M hydrochloric acid (3 × 100 ml), saturated, aqueous sodium hydrogen carbonate (100 ml), and water (100 ml). Removal of the solvent left **9** (4.6 g, 91.4%) as a chromatographically pure syrup, $[\alpha]_D^{21}$ +27°, ν_{max} 1745 cm^{-1} (acetate). N.m.r. data: τ 4.12 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.30 (q, 1 H, $J_{1',1''}$ 13, $J_{1',F}$ 13 Hz, H-1'), 5.37 (q, 1 H, $J_{2,F}$ 11 Hz, H-2), 5.76 (q, 1 H, $J_{1'',1'}$ 13, $J_{1'',F}$ 34 Hz, H-1''), 5.70–6.30 (m, 4 H, H-4,5,6,6'), 7.89 (s, 3 H, OAc), 8.50, 8.59, and 8.67 (3 s, 12 H, 4 Me).

Anal: Acc mass calc. for $C_{14}H_{20}O_7F$ ($M^+ - 15$). 319.119. Found: 319.119.

3-C-Acetoxymethyl-3-deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (**10**). — A solution of **9** (4.5 g) in 75% aqueous acetic acid (100 ml) was kept at 70°: the reaction was monitored by t.l.c. and was complete within 1 h. Solvent was removed *in vacuo* (bath temp., <45°) to give **10** as an oil (3.50 g, 88%) which crystallized on standing. Recrystallization from ethanol–hexane gave needles, m.p. 124–125°, $[\alpha]_D^{21}$ +47°, $\nu_{max}^{CHCl_3}$ 3500 (OH) and 1750 cm^{-1} (acetate). Mass spectrum: *m/e* 279 ($M^+ - 15$). N.m.r. data: τ 4.11 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.16 (q, 1 H, $J_{1',1''}$ 13, $J_{1',F}$ 14 Hz, H-1'), 5.36 (q, 1 H, $J_{2,1}$ 4, $J_{2,F}$ 11 Hz, H-2), 5.73 (q, 1 H, $J_{1'',1'}$ 13, $J_{1'',F}$ 34 Hz, H-1''), 5.85–6.24 (m, 5 H, H-4,5,6,6', OH), 7.05 (1 H, disappears on addition of D_2O, OH), 7.88 (s, 3 H, OAc), 8.50 and 8.64 (2 s, 6 H, 2 Me).

Anal: Calc. for $C_{12}H_{19}FO_7$: C, 49.0: H, 6.5. Found: C, 49.1; H, 6.1.

3-C-Acetoxymethyl-6-O-benzoyl-3-deoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (**11**). — To a stirred solution of **10** (1.646 g, 5.6 mmol) at 0°, a solution of benzoyl chloride (845 mg, 6 mmol) in dichloromethane (20 ml) was added dropwise. The mixture was stirred for 1 h at 0°, kept at room temperature for 18 h, and then poured into ice–water (300 ml). Cold 0.5M hydrochloric acid was added until the mixture was slightly acidic and the mixture was then extracted with chloroform

(3 × 100 ml) The combined extracts were successively washed with saturated aqueous sodium hydrogen carbonate (100 ml) and water (100 ml), and the solvent was removed to give **11** as a chromatographically homogeneous syrup (2 04 g, 92%), $[\alpha]_D^{21}$ +33°, $\nu_{max}^{CHCl_3}$ 3450 (OH) and 1740 cm^{-1} (ester) Mass spectrum *m/e* 383 ($M^+ - 15$) N m r. data τ 1 94–2 71 (m. 5 H, aromatic protons), 4.09 (d, 1 H, $J_{1,2}$ 3 8 Hz, H-1), 5 16 (q, 1 H, $J_{1',1}$ 13, $J_{1',F}$ 14 Hz, H-1′), 5 36 (q, 1 H, $J_{2,F}$ 10 Hz, H-2), 5 45 (q, 1 H, $J_{4,5}$ 8, $J_{4,F}$ 25 Hz, H-4), 5 71 (q, 1 H, $J_{1'',1}$ 13, $J_{1'',F}$ 34 Hz, H-1″), 5 68–6 15 (m, 3 H, H-5,6,6′), 6 87 (s, 1 H, OH), 7.90 (s, 3 H, OAc), 8 52 and 8.66 (2 s, 6 H, 2 Me)

Anal Acc mass calc for $C_{18}H_{20}FO_8$ ($M^+ - 15$) 383.114 Found 383.113.

3-C-Acetoxymethyl-6-O-benzoyl-3-deoxy-3-fluoro-D-glucofuranose (**12**). — Compound **11** (2.20 g) was dissolved in a mixture of *p*-dioxane–water (1 1, 80 ml) Amberlite IR-120(H$^+$) resin (16 g) was added and the mixture was heated with stirring at 80° for 22 h. The mixture was filtered and the filtrate was evaporated to leave an oil (1.8 g), which was chromatographed with ethanol–chloroform (1.4) to give **12** (1 17 g, 59%) as a 1 1 mixture of anomers, ν_{max}^{KBr} 3300 (OH) and 1700 cm^{-1} (benzoate and acetate). N m r data (Me$_2$SO-d_6). τ 5 02 (d, 0 5 H, $J_{1,2}$ 8.0 Hz, αH-1), 5.14 (s, 0 5 H, βH-1). Mass spectrum *m/e* 285 ($M^+ - CH_2OAc$)

Anal Calc for $C_{16}H_{19}FO_8$: C, 53.6, H, 5 3. Found C, 53.3, H, 5 3

1,2-Di-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-3-O-formyl-α-D-arabinofuranose (**14α**) *and its β anomer* (**14β**). — To a solution of **12** (500 mg, 1.4 mmol) in methanol (30 ml), a solution of sodium metaperiodate (342 mg, 1 6 mmol) in water (20 ml) was added and the mixture was stirred at room temperature for 2 h. A drop of ethylene glycol was added and the solvent was evaporated The residue was taken up in chloroform (50 ml), the solution was filtered through Celite, and the solvent was removed to give syrupy **13** as a mixture of anomers (484 mg) Without further purification, the syrup was dissolved in a mixture of pyridine (8 ml) and acetic anhydride (4 ml) The mixture was kept at room temperature for 16 h and was then worked-up in the usual manner to give a mixture of **14α** and **14β** Chromatographic separation of the anomers was achieved on silica gel, with ethyl acetate–hexane (1 1), to give **14α** (134 mg, 24%) and **14β** (365 mg, 66%)

The α anomer **14α** was obtained as an oil, $[\alpha]_D^{20}$ −14 9°, *m/e* 339 ($M^+ - CH_3CO_2$) N.m r data τ 1 90 (s, 1 H, C*H*O), 1 88–2.70 (m, 5 H, aromatic protons), 3.64 (s, 1 H, H-1), 4.29 (q, 1 H, $J_{3,4}$ 5 5, $J_{3,F}$ 16 Hz, H-3), 5 02–5 88 (m, 5 H. H-1′,1″,4,5,5′), 7 94 (s, 6 H, 2 OAc).

Anal Acc. mass calc. for $C_{16}H_{16}FO_7$ ($M^+ - CH_3CO_2$) 339 088. Found 339 092

The β anomer **14β** was also obtained as an oil, $[\alpha]_D^{20}$ −38.2°, *m/e* 339 ($M^+ - CH_3CO_2$) N m.r data τ 1.90–2.70 (m, 5 H, aromatic protons), 1 92 (s, 1 H, C*H*O), 3 56 (d, 1 H. $J_{1,F}$ 10 Hz, H-1), 4 65 (q, 1 H, $J_{3,4}$ 3, $J_{3,F}$ 21 Hz, H-3), 5 30–5.65 (m, 5 H, H-1′,1″,4,5,5′). 7 86 and 7.87 (2 s, 6 H, 2 OAc)

Anal Acc mass calc for $C_{16}H_{16}FO_7$ ($M^+ - CH_3CO_2$) 339 088 Found 339 092

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