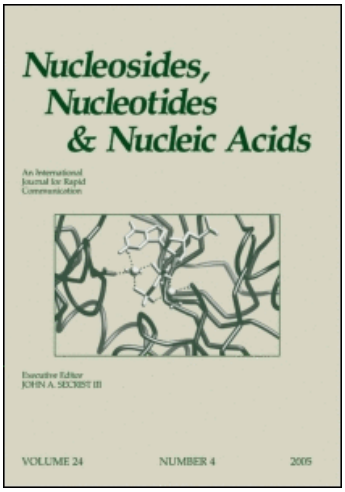

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Synthesis of Novel Fluorinated 2',3'-Dideoxynucleosides

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SYNTHESIS OF NOVEL FLUORINATED 2',3'-DIDEOXYNUCLEOSIDES

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ABSTRACT: The synthesis of various 2',3'-dideoxypyrimidine nucleosides, starting from 5-(2,2,2-trifluoroethoxymethyl) (10) and 5-(bis-2,2,2-trifluoroethoxy)methyl-2'-deoxyuridine (11), is described. These compounds were synthesized for screening against herpes simplex virus type-1 and type-2, and HIV virus.

INTRODUCTION

A number of sugar-modified nucleosides show antiviral activity.[1] These compounds may interfere with viral-encoded enzymes which catalyze reactions that occur specifically in virus-infected cells.[2] 2',3'-Dideoxynucleoside analogues[3] have attracted considerable attention as anti-HIV compounds, and several congeners of this class are currently under clinical trial. 3'-Fluoro-2',3'-dideoxythymidine (FddThD) (1) is the most potent anti-HIV nucleoside reported so far.[4] Another promising congener which is under clinical trial is 1-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl)thymine (D4T;2).[5] These compounds along with their respective analogues, azidothymidine (AZT;3) and 2',3'-

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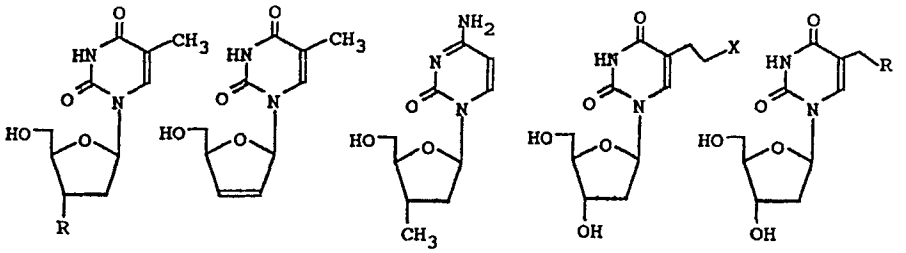
This paper is dedicated to the memory of a scholar and friend, Professor T. Ueda.

dideoxythymidine (4) in their 5′-triphosphate forms, interfere with HIV reverse transcriptase,[6,7] an enzyme specific to retroviruses.



1,R=F
3,R=N$_3$
4,R=H

2

5

6,X=F
7,X=Cl
8,X=CF$_3$

9,R=OCH$_3$

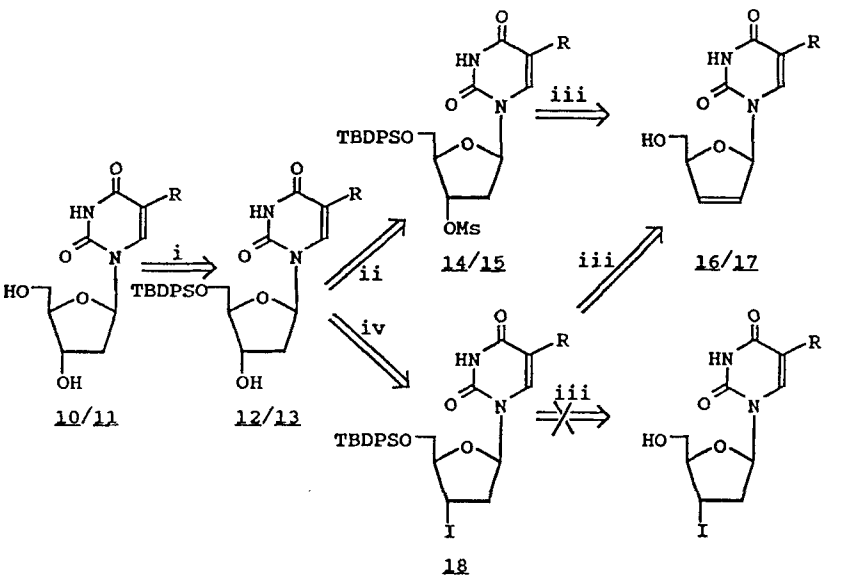
3′-*C*-Methylcytidine (5) has been shown to be effective against vaccinia in mice[8] and to inhibit the growth of KB cells *in vitro*.[9] 5-(2-Fluoroethyl)-2′-deoxyuridine (FEDU, 6) was found to inhibit HSV-1 replication at the same or slightly higher concentration than 5-(2-chloroethyl)-2′-deoxyuridine (CEDU, 7); however it is more active against HSV-2 in comparison to CEDU.[10]

Derivatives of 2′-deoxyuridine with C-5 substituents no longer than *n*-butyl and with a C atom attached to C-5 are of particular interest as chemotherapeutic agents.[11-14] Bergstrom et al[15] recently described 5-(3,3,3-trifluoropropyl)-2′-deoxyuridine (TFPDU, 8) to be potent and unusually selective against HSV-1. 5-Methoxymethyl-2′-deoxyuridine[16] (MMdU, 9) has also been shown to exhibit antiviral activity against strains of HSV-1 in primary rabbit kidney cell culture. In our present work, both features, the 2′,3′-dideoxy sugars and the pyrimidine base with a side chain at C-5 no longer than C-4, are combined. We now report the synthesis of novel fluorinated 2′,3′-dideoxy pyrimidine nucleosides which were designed to extend our search for a better antiviral agent in comparison to the corresponding non-fluorinted MMdU.

CHEMISTRY

5-(2,2,2-Trifluoroethoxymethyl)-2′-deoxyuridine (10) and 5-(bis-2,2,2-trifluoroethoxy)methyl-2′-deoxyuridine (11) were synthesized by a method described earlier.[17] Compounds 10 and 11, on reaction with 1.1

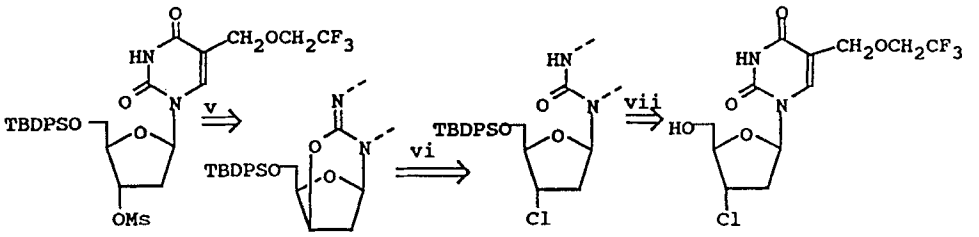
equivalents of t.butylchlorodiphenylsilane (TBDPS-Cl) in anhydrous pyridine, yielded 5-(2,2,2-trifluoroethoxymethyl)-5'-O-TBDPS-2'-deoxyuridine (12) and 5-(bis-2,2,2-trifluoroethoxy)methyl-5'-O-TBDPS-2'-deoxyuridine (13), respectively, in 87% and 96% yields. Methanesulfonation of 12 and 13 in pyridine gave 5-(2,2,2-trifluoroethoxymethyl)-3'-O-methanesulfonyl-5'-O-TBDPS-2'-deoxyuridine (14) (93%) and 5-(bis-2,2,2-trifluoroethoxy)methyl-3'-O-methanesulfonyl-5'-O-TBDPS-2'-deoxyuridine (15) (89%), respectively. Each compound (14 and 15) was refluxed in anhydrous tetrahydrofuran with a total of 5 equivalents of tetrabutylammonium fluoride solution for 48 h, which after purification, afforded 5-(2,2,2-trifluoroethoxymethyl)-1-(2,3-dideoxy-β-D-glycero-pent-2-eno)furanose (16) and 5-(bis-2,2,2-trifluoroethoxy)methyl-1-(2,3-dideoxy-β-D-glycero-pent-2-eno)furanose (17) in 48% and 40% yields, respectively. The conversion of 14 to 16, and 15 to 17, probably proceeds via the formation of the 3',5'-anhydro intermediate, since the starting materials are initially converted to more polar products, which, upon addition of additional equivalents of TBAF, disappear to give the desired products. It was observed that conversion of the 3'-methanesulfonyl derivatives 14 and 15 to their corresponding 2',3'-dideoxy-β-D-glycero-pent-2-enofuranose products 16 and 17 affected the magnetic environment of the fluorine substituents significantly; the ^{19}F spectrum of 16 was upfield by 1.8 ppm, and a similar trend was seen in ^{19}F NMR spectrum of 17 where the spectrum shifted upfield by 2.2 ppm. This effect was substantiated by the ^{13}C spectra of 16 and 17. Shielding the fluorine atoms in 16 and 17 should deshield the carbon atom of the CF_3 moiety, and thus cause a downfield chemical shift of the CF_3 carbon. In fact, the carbon spectra of 16 and 17 showed that these carbons were deshielded by ≈2.8 and ≈2.0 ppm, respectively. Introduction of a double bond between the C-2' and C-3' positions of the furanose ring was confirmed by the fact that the C-2' resonance appeared at 136.18 ppm and C-3' was present at 127.11 ppm in the spectrum of 16; this is within the expected limits for vinylic carbons. Similarly, for 17, the C-2' signal was found at 136.40 ppm while the C-3' signal appeared at 126.79 ppm. The ^{19}F spectrum of 16 displayed a triplet ($J_{H,F}$=8.7 Hz) at 89.49 ppm due to coupling of the neighboring methylenic protons with fluorines. The ^{13}C spectrum of the same compound contained



where, i= TBDPS-Cl/Pyridine, 25°C, ii= CH_3SO_2Cl/Pyridine, 25°C, iii= n-TBAF/THF, 25°C; iv= methyltriphenoxyphosphonium iodide/DMF, 25°C.
R= $CH_2OCH_2CF_3$ (10, 12, 14, 16, 18); R= $CH(OCH_2CF_3)_2$ (11, 13, 15, 17).

SCHEME I

two quartets, specific for fluorine-carbon coupling, one at 63.87 ppm ($J_{F,C}$=34.4 Hz) for the methylenic carbon of OCH_2CF_3 and the other at 123.44 ppm ($J_{F,C}$=278.3 Hz) for the tertiary carbon of the CF_3 moiety. In the case of 17, a triplet was observed at 89.60 ppm ($J_{H,F}$=8.8 Hz) in the ^{19}F NMR spectrum, while the ^{13}C NMR spectrum showed two quartets at 63.86 ppm ($J_{F,C}$=35 Hz) and 64.61 ppm ($J_{F,C}$=34.8 Hz) for the methylenic carbons of two OCH_2CF_3 groups; another quartet at 125.39 ppm ($J_{F,C}$=277 Hz) represented trifluoromethyl carbon. In an attempt to synthesize the 3′-iodo derivative of 10, compound 12 was treated with methyltriphenoxyphosphonium iodide in anhydrous dimethylformamide. This, after chromatographic purification, gave 5-(2,2,2-trifluoroethoxymethyl)-3′-iodo-2′-deoxyuridine (18) in 84% yield, as a white foam. Substitution of the 3′-position with an iodo group significantly shifts the C-3′ resonance upfield as is evident by its ^{13}C NMR spectrum, which shows the C-3′ carbon signal at 13.77 ppm. Deprotection of 18 to form



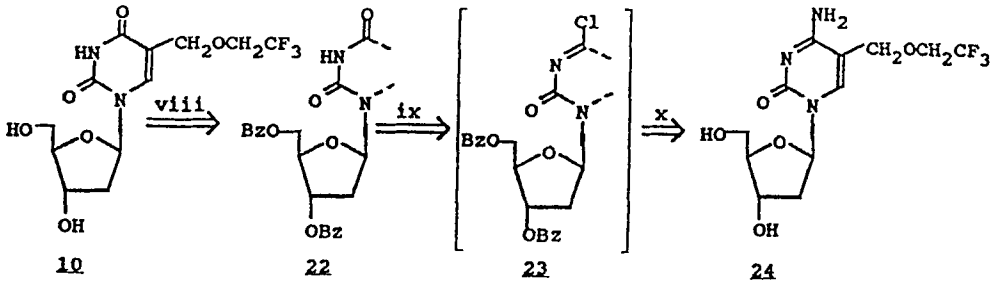
14 19 20 21

where, v= 1 N.NaOH/Ethanol, 80°C, vi= Lithium chloride/DMF, 110°C; vii= Ammonium Fluoride/Methanol, reflux.

SCHEME II

5-(2,2,2-trifluoroethoxymethyl)-3'-iodo-2'-deoxyuridine was not successful; this reaction yielded only the elimination product 16. (Scheme I).

When 14 was heated under reflux in ethanolic 1 N NaOH solution, 5-(2,2,2-trifluoroethoxymethyl)-5'-O-TBDPS-2,3'-anhydro-2',3'-dideoxyuridine (19) was obtained in 59% yield. The formation of the 2,3'-anhydro linkage in 19 resulted in a downfield chemical shift of C-3' to 76.83 ppm, deshielded by ≈38.4 ppm in comparison to its starting material 14. The reaction of 19 with lithium chloride in anhydrous dimethylformamide at 110°C afforded 5-(2,2,2-trifluoroethoxymethyl)-3'-chloro-5'-O-TBDPS-2',3'-dideoxyuridine (20) (50%). The ^{19}F NMR spectrum of 20 exhibited a triplet ($J_{H,F}$=8.7 Hz) at 87.27 ppm. The position of C-3' in ^{13}C NMR spectrum was shifted slightly upfield (by ≈15.7 ppm) as compared to its starting material 19. Compound 20 could be easily desilylated by refluxing in methanolic solution with 4 equivalents of ammonium fluoride, to give 21 in ≈67% yield. Ammonium fluoride has several advantages over tetrabutylammonium fluoride for desilylation; first, the solvent does not need to be anhydrous, and second, it crystallizes out on cooling and can be easily removed by filtration. A triplet was observed at 89.34 ppm ($J_{H,F}$=8.8 Hz) in the ^{19}F NMR spectrum of 21. Desilylation of 20 caused a 2.0 ppm downfield shift in the position of the trifluoromethyl carbon, which appeared as a quartet at 125.71 ppm ($J_{F,C}$=278.8 Hz) in the ^{13}C NMR spectrum (Scheme II).



where, viii= Benzoylchloride/Pyridine, 25°C; ix= Thionyl chloride/Chloroform/DMF, reflux; x= NH_3/Methanol

SCHEME III

The synthesis of 4-amino-5-(2,2,2-trifluoroethoxy)methyl-2'-deoxyuridine (24) started from 10, which was dibenzoylated at the 3' and 5'-positions of the furanose moiety, to give 5-(2,2,2-trifluoroethoxy-methyl)-3',5'-di-O-benzoyl-2'-deoxyuridine (22) in 97% yield. Upon reaction of 22 with thionyl choride in anhydrous chloroform and subsequent treatment with methanolic ammonia, 24 was obtained in 43% yield. The ^1H NMR spectrum of this product in dimethyl sulfoxide-d_6 showed two broad singlets at 7.46 ppm and 6.80 ppm, which disappeared upon exchange with deuterium oxide, indicating that the 4-NH_2 group was present. A quartet ($J_{F,H}$=9.0) also appeared at 4.04 ppm for the two methylenic protons of the -OCH_2CF_3 moiety. The ^{19}F NMR spectrum of 24 showed a triplet ($J_{H,F}$=9.0) at 89.69 ppm due to coupling of methylenic protons with fluorines. The ^{13}C NMR spectrum of the same product showed the desired fluorine-carbon couplings for both carbons of the -OCH_2CF_3 group. The fluorine-carbon coupling constants are in accordance with the values reported in the literature[18]. (Scheme III).

EXPERIMENTAL

Melting points were determined on a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra (^1H-NMR, ^{13}C-NMR and ^{19}F-NMR) were recorded on a Bruker AM 300 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane (^1H-NMR) and hexafluorobenzene (^{19}F-NMR) as internal standards. ^1H-NMR assignments

were confirmed by double irradiation experiments. ^{13}C-NMR resonances were assigned by using the J spin echo modulation (Jmod) technique to determine the number of attached hydrogens. Thin-layer chromatography was performed on Whatman MK6F silica gel microslides (250-μm thickness). The TLC solvent systems employed were A: chloroform/methanol (9.5:0.5, v/v), B: chloroform/methanol (9:1, v/v). Silica gel column chromatography was carried out using Merck 7734 silica gel (100-200 mesh particle size). Pyridine and carbon tetrachloride were distilled over calcium hydride and used fresh at the time of reaction. Dimethoxyethane and tetrahydrofuran were dried over sodium/benzophenone and distilled fresh at the time of reaction.

5-(2,2,2-Trifluoroethoxymethyl)-5'-O-t.butyldiphenylsilyl-2'-deoxyuridine 12. Compound 10 (0.25 g; 0.74 mmol) was dissolved in anhydrous pyridine (2 mL), and *t*.butylchlorodiphenylsilane (0.23 mL, 0.81 mmol) was added to this solution under a nitrogen atomsphere. The contents were stirred overnight at 25°C. Pyridine was evaporated, *in vacuo*, and the viscous mass was extracted with chloroform/water (30:10 mL x 2). The organic phase was dried over anhyrous sodium sulfate, filtered and evaporated to recover a foamy material which was purified on a silica gel column. The elution started with toluene and ended with 20% ethyl acetate to give 0.37 g (87%) of pure 12; mp 193°C; ^1H NMR ($CDCl_3$)-δ 8.36 (s, broad, exchanges with D_2O, ^1H, NH), 7.74-7.34 (m, 11H, 10H of two phenyls, and 1H of H-6), 6.30 (d, $J_{2',1'}$=6.0 Hz of d, $J_{2'',1'}$=8.3 Hz, 1H, H-1'), 4.62 (m, 1H, H-3'), 4.12 (d, J_{gem}=12.0 Hz, 1H of $C\underline{H}_2OCH_2CF_3$), 4.06 (d, J_{gem}=12.0 Hz, 1H of $C\underline{H}_2OCH_2CF_3$), 4.0 (d, $J_{5',4'}$=3.6 Hz of d, $J_{3',4'}$=8.4 Hz, 1H, H-4'), 3.90 (d, $J_{4',5'}$=3.6 Hz of d, J_{gem}=12 Hz, 2H, H-5'), 3.75 (q, $J_{F,H}$=9.0 Hz, 2H, OCH_2CF_3), 2.42 (d, $J_{1',2'}$=6.0 Hz of d, $J_{3',2''}$=3.0 Hz of d, J_{gem}=13.5 Hz, 1H, H-2'), 2.17 (septet, $J_{1',2''}$=8.3 Hz, $J_{3',2''}$=6.6 Hz, J_{gem}=13.5 Hz, 1H, H-2") and 1.06 (s, 9H, *t*.butyl group); ^{19}F NMR ($CDCl_3$ + C_6F_6) -δ 87.65 (t, J_{H-F}=9.0 Hz); ^{13}C NMR ($CDCl_3$)-δ 162.01 (C-4), 149.64 (C-2), 138.86 (C-6), 135.53-127.90 (phenyl carbons), 123.91 (q, $J_{F,C}$=276.3 Hz, $\underline{C}F_3$), 110.86 (C-5), 86.79 (C-1'), 85.13 (C-4'), 72.20 (C-3'), 68.37 (q, $J_{F,C}$=34.33 Hz, $O\underline{C}H_2CF_3$), 66.57 ($\underline{C}H_2OCH_2CF_3$), 63.97 (C-5'), 40.95 (C-2'), 26.95 (methyl carbons of *t*.butyl group) and 19.28 (*t*. carbon of *t*.butyl group); anal. calcd. for $C_{28}H_{33}F_3N_2O_6Si$ (578.64); C, 58.11; H, 5.75; N, 4.84; found; C, 57.95; H, 5.71; N, 4.82.

5-(Bis 2,2,2-trifluoroethoxy)methyl-5'-O-t.butyldiphenylsilyl-2'-deoxyuridine (13). Compound 11 (0.29 g, 0.67 mmol) was dissolved in anhydrous pyridine (2 mL) and *t*.butylchlorodiphenylsilane (0.21 mL, 0.74 mmol) was added at 25°C under N_2 atomsphere. The reaction mixture was stirred overnight. The crude content was worked up and purified as described for 12, to yield 0.43 g (96%) of pure 13; mp 203°C (dec.); ^{1}H NMR ($CDCl_3$)-δ 7.68 (s, 1H, H-6), 7.58-7.28 (m, 10H of phenyl groups), 6.12 (t, $J_{2',1'}$=6.3 Hz, 1H, H-1'), 5.56 (s, 1H, $CH(OCH_2CF_3)_2$), 4.36 (m, 1H, H-3'), 3.96 (m, 1H, H-4'), 3.92-3.66 (m, 6H, 4H of two OCH_2CF_3's and 2H of H-5'), 2.40 and 2.04 (m, 2H, H-2') and 1.01 (s, 9H, *t*.butyl group); ^{19}F NMR ($CDCl_3$ + C_6F_6)-δ 87.29 (t, $J_{H,F}$=8.4 Hz, 3F of one OCH_2CF_3) and 87.20 (t, $J_{H,F}$=7.8 Hz, 3F of other OCH_2CF_3 group); ^{13}C NMR ($CDCl_3$)-δ 161.03 (C-4), 149.34 (C-2), 139.12 (C-6), 135.51-127.90 (phenyl carbons), 123.47 (q, $J_{F,C}$=278 Hz, CF_3's), 109.95 (C-5), 97.52 ($CH(OCH_2CF_3)_2$), 86.65 (C-1'), 85.95 (C-4'), 72.49 (C-3'), 64.12 (quintet, $J_{F,C}$=35.4 Hz, methylenic carbons of two OCH_2CF_3 groups), 52.40 (C-5'), 40.39 (C-2') 26.88 (methyl carbons of *t*.butyl group) and 20.21 (*t*.carbon of *t*.butyl group); anal. calcd. for $C_{30}H_{34}F_6N_2O_7Si$ (676.68); C, 53.24; H, 5.02; N, 4.14; found; C, 53.43; H, 5.20; N, 4.51.

5-(2,2,2-Trifluoroethoxymethyl)-5'-O-t.butyldiphenylsilyl-3'-O-methanesulfonyl-2'-deoxyuridine (14). 5-(2,2,2-Trifluoroethoxymethyl)-5'-O-TBDPS-2'-deoxyuridine (12) (0.17 g, 0.29 mmol) was taken in anhydrous pyridine (2 mL) and methanesulfonyl chloride (0.04 mL, 0.33 mmol) added to it at 0°C while stirring. After 1 h, the contents were warmed to 25°C and the stirring was continued for an additional 30 min. The solvent was evaporated *in vacuo*, the residue was taken up in chloroform/water (25:10 mL x 2), and the organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to produce a foam which was purified on a silica gel column using toluene/ethyl acetate (5%), to give pure 14; yield 0.18 g (93%); mp 62°C (softened); ^{1}H NMR ($CDCl_3$)-δ 8.82 (s, 1H, exchanges with D_2O, NH), 7.68-7.60 (m, 5H, 1H of H-6 and 4H of phenyls), 7.50-7.36 (m, 6H of phenyls), 6.32 (d, $J_{2',1'}$=5.7 Hz of d, $J_{2'',1'}$=9.5 Hz, 1H, H-1'), 5.35 (d, $J_{2'',3'}$=6.4 Hz, 1H, H-3'), 4.32 (m, 1H, H-4'), 4.12 (d, J_{ab}=11.6 Hz, 1H of $CH_2OCH_2CF_3$), 4.06 (d, J_{ab}=11.6 Hz, 1H, $CH_2OCH_2CF_3$) 3.99 (d, $J_{4',5'}$=2.9 Hz of d, J_{gem}=12.2 Hz, 2H, H-5'), 3.77 (q, $J_{F,H}$=8.7 Hz, 2H, OCH_2CF_3), 3.04 (s, 3H, SO_2CH_3), 2.70 (d,

$J_{1',2'}$=5.7 Hz of d, J_{gem}=14.8 Hz, 1H, H-2') and 2.30 (d, $J_{1',2''}$=9.5 Hz of d, $J_{3',2''}$=6.4 Hz of d, J_{gem}=14.8 Hz, 1H, H-2") and 1.11 (s, 9H, *t*.butyl group); ^{19}F NMR ($CDCl_3$ + C_6F_6)-δ 87.69 (t, $J_{H,F}$=8.7 Hz). ^{13}C NMR ($CDCl_3$)-δ 161.80 (C-4), 149.60 (C-2), 138.28 (C-6), 135.55-128.07 (phenyl carbons), CF_3 merged in the basal line, 111.44 (C-5), 85.02 (C-1'), 79.43 (C-4'), 68.51 (q, $J_{F,C}$=34 Hz, $\underline{C}H_2CF_3$), 66.54 ($\underline{C}H_2OCH_2CF_3$), 63.40 (C-5'), 38.80 (C-2'), 38.66 ($SO_2\underline{C}H_3$), 38.41 (C-3'), 27.01 ($CH_{3's}$ of *t*.butyl group), 19.31 (*t*.carbon of *t*.butyl group); anal. calcd. for $C_{29}H_{35}F_3N_2O_7SSi$ (656.74); C, 53.03; H, 5.37; N, 4.26; found; C, 53.01; H, 5.17; N, 4.19.

5-(Bis-2,2,2-trifluoroethoxy)methyl-5'-O-t.butyldiphenylsilyl-3'-O-methanesulfonyl-2'-deoxyuridine (15). Methanesulfonyl chloride (0.08 mL; 0.95 mmol) was added dropwise to a precooled solution of 13 (0.42 g, 0.63 mmol) in anhydrous pyridine (2 mL) at 0°C. The contents were allowed to warm to 25°C, stirred for 2 h, and then worked up as described for 14. The chromatographic purification of the crude product gave 0.43 g (89%) pure 15; mp 64°C (softened); ^{1}H NMR ($CDCl_3$)-δ 8.49 (broad, 1H, N$\underline{H}$, exchanges with D_2O), 7.74 (s, 1H, H-6), 7.62=7.28 (m, 10H, aromatic protons), 6.10 (d, $J_{2',1'}$=5.0 Hz of d, $J_{2'',1'}$=8.0 Hz, 1H, H-1'), 5.15 (d, $J_{2'',3'}$=6.0 Hz, 1H, H-3'), 4.24 (m, 1H, H-4'), 3.94-3.75 (m, 6H, 2H of H-5' and 4H of two $OC\underline{H}_2CF_3$ groups), 2.93 (s, 3H, $SO_2C\underline{H}_3$), 2.66 (d, $J_{1',2'}$=5.0 Hz of d J_{gem}=14.0 Hz; 1H, H-2'), 2.16 (d, $J_{1',2''}$=8.0 Hz of d, $J_{3',2''}$=6.0 Hz of d J_{gem}=14.0 Hz, 1H, H-2") and 1.02 (s, 9H of CH_3 of *t*.butyl group); ^{19}F NMR ($CDCl_3$ + C_6F_6)-δ 87.39 (t, $J_{H,F}$=8.7 Hz); ^{13}C NMR ($CDCl_3$)-δ 161.39 (C-4), 149.55 (C-2), 138.73 (C-6), 135.52-127.95 (aromatic carbons), 123.44 (q, $J_{F,C}$=278.3 Hz, $\underline{C}F_3$'s), 110.44 (C-5), 97.45 ($\underline{C}H(OCH_2CF_3)_2$), 85.90 (C-1'), 85.04 (C-4'), 79.68 (C-3'), 64.35 (q, $J_{F,C}$=34.4 Hz, one $O\underline{C}H_2CF_3$ carbon), 63.87 (q, $J_{F,C}$=34.4 Hz, second $O\underline{C}H_2CF_3$ carbon), 63.07 (C-5'), 38.41 ($SO_2\underline{C}H_3$), 29.66 (C-2'), 26.83 ($\underline{C}H_3$ of *t*.butyl group) and 19.10 (*t*.carbon of *t*.butyl group); anal. calcd. for $C_{31}H_{36}F_6N_2O_9SSi$ (754.71); C, 49.32; H, 4.81; N, 3.71; found; C, 49.35; H, 4.71; N, 3.91.

5-(2,2,2-Trifluoroethoxymethyl)-1-[(2,3-dideoxyβ-D-glycero-pent-2-eno)furanosyl]pyrimidine-2,4-dione (16). Compound 14 (0.19 g; 0.26 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and tetrabutyl-

ammonium fluoride solution (TBAF) (0.65 mL, 0.65 mmol of 1M solution in THF) was added under a nitogren atmosphere. The reaction mixture was refluxed for 24 h, after which an additional 2.5 equivalents of TBAF solution were added and the refluxing was continued for another 24 h. The solvent was evaporated *in vacuo*, and the crude product was purified on a silica gel column, using chloroform/methanol (50:1 v/v) as eluent to recover 40 mg (48%) of pure 16 as a gum; ^{1}H NMR (CD_3OD)-δ 7.76 (s, 1H, H-6), 6.70 (m, 1H, H-1′), 6.14 (m, 1H, H-2′), 5.67 (m, 1H, H-3′), 4.63 (m, 1H, H-4′), 4.08 (d, J_{gem}=12 Hz, 1H, $C\underline{H}_2OCH_2CF_3$), 4.04 (d, J_{gem}=12 Hz, 1H, $C\underline{H}_2OCH_2CF_3$), 3.68 (q, $J_{F,H}$=9.0 Hz, 2H, $OC\underline{H}_2CF_3$) and 3.49 (m, 2H, H-5′); ^{19}F NMR (CD_3OD + C_6F_6)-δ 89.48 (t, $J_{H,F}$=9.0 Hz); ^{13}C NMR (CD_3OD)-δ 165.19 (C-4), 153.20 (C-2), 142.39 (C-6), 136.18 (C-2′), 127.11 (C-3′), 126.80 (q, $J_{F,C}$=279.2 Hz, $\underline{C}F_3$), 111.33 (C-5), 91.39 (C-1′), 89.22 (C-4′), 68.57 (q, $J_{F,C}$=34.0 Hz, $O\underline{C}H_2CF_3$), 67.80 ($\underline{C}H_2OCH_2CF_3$), 63.82 (C-5′); HRMS for $C_{12}H_{11}F_3N_2O_4$ (M^+-H_2O), calcd., 304.0665; found, 304.0667, abundance (0.26%).

5-(Bis-2,2,2-trifluoroethoxy)methyl-1-[(2,3-dideoxy-β-D-glycero-pent-2-eno)furanosyl]pyrimidine-2,4-dione (17). TBAF solution (0.65 mL, 0.65 mmol of 1M solution in THF) was added to a solution of 15 (0.2 g, 0.26 mmol) in anhydrous tetrahydrofuran (10 mL) under an atmosphere of nitrogen. The reaction mixture was refluxed for 24 h, after which an additional 2.5 equivalents of TBAF solution were added and the refluxing was continued for another 24 h. Evaporation of the solvent and purification of the crude mixture, following the procedure as described for 16, gave 45 mg (40%) of pure 17 as a gum; ^{1}H NMR (CD_3OD)-δ 8.07 (s, 1H, H-6), 6.96 (m, 1H, H-1′), 6.43 (m, 1H, H-2′), 5.94 (m, 1H, H-3′), 5.71 (s, 1H, $C\underline{H}(OCH_2CF_3)_2$), 4.18 (m, 5H, 1H of H-4′ and 4H of two $OC\underline{H}_2CF_3$'s), 3.74 (d, $J_{4',5'}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5′) and 3.69 (d, $J_{4',5''}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5"); ^{19}F NMR (CD_3OD + C_6F_6)-δ 89.60 (t, $J_{H,F}$=8.8 Hz, 3F, one CF_3 group) and 89.50 (t, $J_{H,F}$=8.7 Hz, 3F, other CF_3 group); ^{13}C NMR (CD_3OD)-δ 163.84 (C-4), 152.29 (C-2), 142.04 (C-6), 136.40 (C-2′), 126.79 (C-3′), 125.39 (q, $J_{F,C}$=270.9 Hz, CF_3), 110.31 (C-5), 98.50 ($\underline{C}H(OCH_2CF_3)_2$), 91.63 (C-1′), 89.38 (C-4′), 64.61 (q, $J_{F,C}$=34.8 Hz, one $O\underline{C}H_2CF_3$), 63.92 (C-5′), 63.86 (q, $J_{F,C}$=35.0 Hz, other $O\underline{C}H_2CF_3$); HRMS for $C_{14}H_{12}F_6N_2O_5$ (M^+-H_2O), calcd., 402.0650; found, 402.0650, abundance (0.37%).

5-(2,2,2-Trifluoroethoxymethyl)-5'-O-t.butyldiphenylsilyl-3'-iodo-2',3'-dideoxyuridine (18). Methyltriphenoxyphosphonium iodide (0.24 g, 0.46 mmol) was added to a solution of 12 (0.133 g, 0.23 mmol) in anhydrous dimethylformamide (2.5 mL) and the contents were stirred at 25°C for 20 h. Afterwards, the solvent was evaporated *in vacuo*, the contents dissolved in chloroform (25 mL) and extracted with a 5% aqueous solution of sodium thiosulfate (10 mL). The organic layer was washed with cold water (10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to get a crude viscous mass which after silica gel column chromatography, starting with toluene and ending with 10% ethyl acetate, gave pure 18; yield, 0.17 g (84%); m.p. 60°C (softened); ^{1}H NMR ($CDCl_3$)-δ 7.80 (s, 1H, H-6), 7.78-7.40 (m, 10H of two phenyl groups), 6.16 (d, $J_{2',1'}$=5.0 Hz of d, $J_{2'',1'}$=7.0 Hz, 1H, H-1'), 4.50 (d, $J_{4',3'}$=8.0 Hz of d, $J_{2',3'}$=16 Hz, 1H, H-3'), 4.33 (d, $J_{3',4'}$=8.0 Hz of t, $J_{5',4'}$=3.0 Hz, 1H, H-4'), 4.14 (d, $J_{4',5'}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5'), 4.06 (two d, $J_{a,b}$=10.0 Hz, 2H of $C\underline{H}_2OCH_2CF_3$), 3.88 (d, $J_{4',5''}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5"), 3.72 (q, $J_{F,H}$=9.0 Hz, 2H, $OC\underline{H}_2CF_3$), 2.82 (m, 2H, H-2') and 1.10 (s, 9H, *t.* butyl group). ^{19}F NMR (CD_3OD + C_6F_6)-δ 89.49 (t, $J_{H,F}$=9.0 Hz). ^{13}C NMR (CD_3OD)-δ 164.89 (C-4), 151.82 (C-2), 141.10 (C-6), 136.65-128.95 (phenyl carbons), 126.60 (q, $J_{F,C}$=277 Hz, $\underline{C}F_3$), 111.54 (C-5), 90.87 (C-1'), 87.20 (C-4'), 68.69 (q, $J_{F,C}$=33.9 Hz, $O\underline{C}H_2CF_3$), 67.48 ($\underline{C}H_2OCH_2CF_3$), 62.92 (C-5'), 44.95 (C-2'), 27.52 (CH_3's of *t.*butyl group), 20.21 (*t.*carbon of *t.*butyl group) and 13.77 (C-3'). HRMS for $C_{24}H_{23}N_2O_5F_3ISi$ (M^+-Bu), calcd., 631.0742; found, 631.0332, abundance (1.61%).

2,3'-Anhydro-5-(2,2,2-trifluoroethoxymethyl)-5'-O-t.butyldiphenylsilyl-2'-deoxyuridine (19). A solution of 14 (0.29 g, 0.46 mmol) in ethanol (10 mL) was refluxed and 1 N NaOH solution (0.25 mL) was added dropwise under stirring. Refluxing was continued for another 15 min until tlc indicated complete conversion of starting material to product. The solvent was evaporated *in vacuo* to dryness and the residue chromatographed on a silica gel column using chloroform-methanol (20:1 v/v) as eluent to yield 0.15 g (59%) of pure 19 as a foam; mp 67°C (softened); ^{1}H NMR ($CDCl_3$)-δ 7.66-7.28 (m, 10H, aromatic protons), 7.08 (s, 1H, H-6), 5.64 (d, $J_{2'',1'}$=3.5 Hz, 1H, H-1'), 5.23 (broad m, 1H, H-3'), 4.47 (d, J_{gem}=15 Hz, 1H, $C\underline{H}_2OCH_2CF_3$), 4.41 (d, J_{gem}=15 Hz, 1H,

$C\underline{H}_2OCH_2CF_3$), 4.31 (d, $J_{3',4'}$=3 Hz of t, $J_{5',4'}$=7.0 Hz, 1H, H-4'), 3.94 (q, $J_{F,H}$=8.5 Hz, 2H, $OC\underline{H}_2CF_3$), 3.78 (d, $J_{4',5''}$=7.0 Hz, 2H, H-5'), 2.53 (d, J_{gem}=13 Hz, 1H, H-2'), 2.42 (d, $J_{1',2''}$=3.5 Hz of d, $J_{3',2''}$=4.0 Hz of d J_{gem}=13.0 Hz, 1H, H-2") and 1.00 (s, 9H, *t*.butyl group); ^{19}F NMR ($CDCl_3$ + C_6F_6)-δ 86.30 (t, $J_{H,F}$=8.5 Hz, 3F, $C\underline{F}_3$); ^{13}C NMR ($CDCl_3$)-δ 169.74 (C-4), 153.69 (C-2), 136.34 (H-6), 135.44-127.71 (aromatic carbons), 123.79 (q, $J_{F,C}$=279.9 Hz, CF_3), 117.62 (C-5), 87.89 (C-1'), 85.61 (C-4'), 76.83 (C-3'), 68.55 (q, $J_{F,C}$=34.5 Hz, $O\underline{C}H_2CF_3$), 67.51 ($\underline{C}H_2OCH_2CF_3$), 62.05 (C-5'), 33.47 (C-2'), 26.62 (methyl carbons of *t*.butyl group), 19.04 (*t*. carbon of *t*.butyl group); anal. calcd. for $C_{28}H_{31}F_3N_2O_5Si$ (560.646); C, 59.98; H, 5.57; N, 5.00; found; C, 60.26; H, 5.59; N, 5.06.

5-(2,2,2-Trifluoroethoxymethyl)-5'-O-t.butyldiphenylsilyl-3'-chloro-2'3'-dideoxyuridine (20). Lithium chloride (69 mg, 1.62 mmol) was added to a solution of 19 (0.18 g, 0.32 mmol) in anhydrous dimethylformamide (3 mL) and the mixture was stirred and heated at 110°C for 24 h. DMF was evaporated, *in vacuo*, and the contents were extracted in CH_2Cl_2 (2x20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to produce a viscous mass which, after purification on a silica gel column using toluene:ethyl acetate (80:20 v/v) as eluent, gave 70 mg (50%) of oily 20; ^1H NMR ($CDCl_3$)-δ 8.78 (s, broad, exchanges with D_2O, 1H, NH), 7.68-7.21 (m, 11H, 1H, H-6; 10H, phenyl carbons), 6.09 (t, $J_{2',1'}$=$J_{2'',1'}$=6.0 Hz, 1H, H-1'), 4.19 (d, $J_{4',3'}$=4.2 Hz of d, $J_{2',3'}$=3.6 Hz of d, $J_{2'',3'}$=7.2 Hz, 1H, H-3'), 4.07 (d, J_{gem}=12.0 Hz, 1H, $C\underline{H}_2OCH_2CF_3$), 4.01 (d, J_{gem}=12.0 Hz, 1H, $C\underline{H}_2OCH_2CF_3$), 3.91 (m, 1H, H-4'), 3.88 (d, J_{gem}=12.0 Hz of d, $J_{4',5'}$=3.6 Hz, 1H, H-5'), 3.76 (d, J_{gem}=12.0 Hz of d, $J_{4',5''}$=3.6 Hz, 1H, H-5"), 3.68 (q, $J_{F,H}$=8.4 Hz, 2H, $OC\underline{H}_2CF_3$), 2.40 (d, $J_{3',2'}$=3.6 Hz of d, $J_{1',2'}$=6.0 Hz of d, J_{gem}=13.8 Hz, 1H, H-2'), 2.19 (d, $J_{3',2''}$=7.2 Hz of d, $J_{1',2''}$=6.0 Hz of d, J_{gem}=13.8 Hz, 1H, H-2") and 1.03 (s, 9H, methyl protons of *t*.butyl chain); ^{19}F NMR ($CDCl_3$ + C_6F_6)-δ 87.27 (t, $J_{H,F}$=8.7 Hz, $C\underline{F}_3$); ^{13}C NMR ($CDCl_3$)-δ 162.19 (C-4), 149.67 (C-2), 138.47 (C-6), 135.52-127.71 (aromatic carbons), 123.7 (q, $J_{F,C}$=286.8 Hz, $\underline{C}F_3$), 111.09 (C-5), 85.06 (C-1'), 84.54 (C-4'), 68.45 (q, $J_{F,C}$=34.1 Hz, $\underline{C}H_2CF_3$), 66.52 ($\underline{C}H_2OCH_2CF_3$), 63.49 (C-5'), 60.56 (C-3'), 37.91 (C-2') 26.83 ($\underline{C}H_3$'s of *t*.butyl group) and 19.28 (*t*.carbon of *t*.butyl group); HRMS for $C_{24}H_{22}F_3N_2O_5Si$ (M^+-butyl group and HCl), calcd., 503.1262; found, 503.1261; abundance (22.95%).

5-(2,2,2-Trifluoroethoxymethyl)-3'-chloro-2',3'-dideoxyuridine (21). Ammonium fluoride (111 mg, 0.3 mmol) was added to a solution of 20 (60 mg, 0.1 mmol) in methanol (4 mL) and the mixture was refluxed for 30 min. The contents were cooled to 25°C, filtered and the filtrate was evaporated *in vacuo*. The crude mixture was chromatographed on a silica gel column using chloroform-methanol (98:2 v/v) to give pure 21 (24 mg, 67%) as a semi-solid; ^{1}H NMR (CD_3OD)-δ 8.01 (s, 1H, H-6), 6.06 (t, $J_{2',1'}$=6.0 Hz, 1H, H-1'), 4.28 (s, 2H, $C\underline{H}_2OCH_2CF_3$), 4.06 (m, 1H, H-3'), 3.90 (q, $J_{F,H}$=8.8 Hz, 2H, $OC\underline{H}_2CF_3$), 3.84 (d $J_{3',4'}$=8.0 Hz of d, $J_{3',4'}$=3.0 Hz, 1H, H-4'), 3.76 (d, $J_{4',5''}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5"), 3.64 (d, $J_{4',5'}$=3.0 Hz of d, J_{gem}=12.0 Hz, 1H, H-5') and 2.34 (t, $J_{1',2'}$=$J_{3',2'}$=6.0 Hz, 2H, H-2'); ^{19}F NMR (CD_3OD + C_6F_6)-δ 89.34 (t, $J_{H,F}$=8.8 Hz, $C\underline{F}_3$); ^{13}C NMR (CD_3OD)-δ 165.10 (C-4), 152.03 (C-2), 141.77 (C-6), 125.71 (q, $J_{F,C}$=278.8 Hz, $\underline{C}F_3$), 111.49 (C-5), 86.60 (C-1'), 86.35 (C-4'), 67.83 (q, $J_{F,C}$=34.0 Hz, $O\underline{C}H_2CF_3$), 67.33 (s, $\underline{C}H_2OCH_2CF_3$), 62.27 (C-5'), 61.48 (C-3'), 38.57 (C-2'); HRMS for $C_{12}H_{11}F_3N_2O_4$ (M^+-H_2O, Cl), calcd., 304.0660; found, 304.0663, abundance (0.46%).

5-(2,2,2-Trifluoroethoxymethyl)-3'-5'-di-O-benzoyl-2'-deoxyuridine (22). 5-(2,2,2-Trifluoroethoxymethyl)-2'-deoxyuridine 10 (0.115 g, 0.34 mmol) was dissolved in anhydrous pyridine (2mL), cooled to 0°C and benzoyl chloride (0.10 mL, 0.86 mmol) added dropwise. The contents were warmed to 25°C and stirred for 4 h. The solvent was evaporated *in vacuo*, the residue was dissolved in chloroform (30 mL) and the organic solution was washed sequentially with cold water (10 mL), 5% aqueous sodium bicarbonate solution (10 mL) and water (10 mL x 2). The chloroform phase was dried over anhydrous sodium sulfate, filtered and evaporated to obtain the impure product which was chromatographed on a silica gel column using toluene/ethyl acetate (10%) to get 0.18 g (97%) of pure 22; mp 68°C; ^{1}H NMR ($CDCl_3$)-δ 8.2-7.44 (m, 11H, 10H of phenyls and 1H of H-6), 6.43 (d, $J_{2',1'}$=5.5 Hz of d, $J_{2'',1'}$=9.0 Hz, 1H, H-1'), 5.66 (d, $J_{2'',3'}$=6.5 Hz of d, $J_{2',3'}$=1.5 Hz of d, $J_{4',3'}$=4.5 Hz, 1H, H-3'), 4.73 (d, $J_{4',5'}$=3.5 Hz of d, J_{gem}=12.5 Hz, 2H, H-5'), 4.58 (d, $J_{3',4'}$=4.5 Hz of d, $J_{5',4'}$=3.5 Hz, 1H, H-4'), 4.19 (s, 2H of $C\underline{H}_2OCH_2CF_3$), 3.76 (q, $J_{F,H}$=9.0 Hz, 2H, $OC\underline{H}_2CF_3$), 2.78 (d, $J_{3',2'}$=1.5 Hz of d, $J_{1',2'}$=5.5 Hz of d, J_{gem}=14 Hz, 1H, H-2') and 2.36 (septet, $J_{3',2''}$=6.5 Hz, $J_{1',2''}$=9.0 Hz, J_{gem}=14.0 Hz, 1H, H-2"); ^{19}F NMR ($CDCl_3$ + C_6F_6)-δ 87.652 (t, $J_{F,H}$=9.0 Hz).

^{13}C NMR ($CDCl_3$)-δ 165.96 (C-4), 162.21 (C=O of benzoyls), 149.90 (C-2), 137.80 (C-6), 133.70-128.37 (m, carbons of phenyls), 123.80 (q, $J_{F,C}$=278.3 Hz, $\underline{C}F_3$), 111.44 (C-5), 85.68 (C-1′), 83.01 (C-3′), 74.93 (C-4′), 68.42 (q, $J_{F,C}$=34.3 Hz, $O\underline{C}H_2CF_3$), 66.66 ($\underline{C}H_2OCH_2CF_3$), 64.29 (C-5′), 38.30 (C-2′); anal. calcd. for $C_{26}H_{23}F_3N_2O_8$ (548.46); C, 56.93; H, 4.23; N, 5.11; found C, 57.18; H, 4.33; N, 5.16.

4-Amino-5-(2,2,2-trifluoroethoxy)methyl-2′-deoxyuridine (24). A solution of 22 (0.15 g, 0.27 mmol) in anhydrous chloroform (2 mL), in a 25 mL round bottom flask equipped with a reflux condenser, was treated successively with thionyl chloride (0.22 mL, 2.7 mmol) and dimethylformamide (100μL) and the mixture refluxed for 14.5 h. The content was cooled and evaporated to dryness under diminished pressure. The resulting crude intermediate 23, which was not isolated or characterized, was dissolved in hot benzene (2 mL). This solution was added dropwise to a stirred saturated solution of ammonia in methanol (10 mL). The mixture was stirred overnight at 25°C, after which, the solvent was evaporated *in vacuo* and the crude material was purified on a silica gel column to yield 40 mg (43%) of pure 24 as a foam; m.p. 178°C (dec.); ^1H NMR (DMSO-d_6)-δ 7.94 (s, 1H, H-6), 7.46 and 6.80 (two broad s, exchangeable with D_2O 2H, NH_2), 6.14 (t, $J_{2',1'}=J_{2'',1'}$=6.8 Hz, 1H, H-1′), 5.22 (d, $J_{3',OH}$=3.8 Hz, exchanges with D_2O, 1H, 3′-OH), 5.04 (t, $J_{5',OH}$=5.3 Hz, exchanges with D_2O, 1H, 5′-OH), 4.39 (d, $J_{a,b}$=11.3 Hz, 1H of $C\underline{H}_2OCH_2CF_3$), 4.32 (d, $J_{a,b}$=11.3 Hz, 1H of $C\underline{H}_2OCH_2CF_3$), 4.21 (m, 1H, H-3′), 4.04 (q, $J_{F,H}$=9.0 Hz, 2H, $OC\underline{H}_2CF_3$), 3.78 (m, 1H, H-4′), 3.77 (m, 2H, H-5′), 2.11 (m, 1H, H-2′) and 2.0 (m, 1H, H-2"); ^{19}F NMR (CD_3OD + C_6F_6) δ 89.69 (t, $J_{H,F}$=9.0 Hz); ^{13}C NMR (CD_3OD)-δ 143.24 (C-6), CF_3 embedded in the base line, 110.40 (C-5), 89.08 (C-1′), 87.70 (C-3′), 71.76 (C-4′), 69.02 ($\underline{C}H_2OCH_2CF_3$), 67.64 (q, $J_{F,C}$=34.0 Hz, $O\underline{C}H_2CF_3$), 62.54 (C-5′) and 42.13 (C-2′). HRMS for $C_{12}H_{16}F_3N_3O_5$, calcd., 339.2760; found, 339.2761; abundance (4.1%).

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