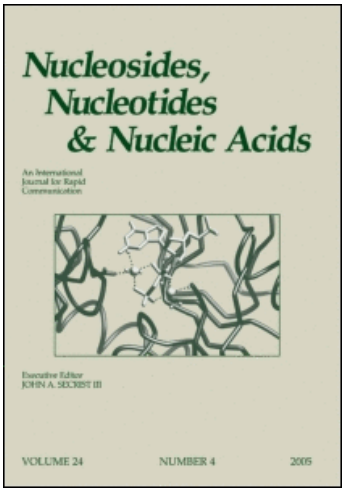

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Pawan K. Sharma[a]; Vasu Nair[a]
[a] Department of Chemistry, University of Iowa, Iowa City, Iowa, U. S. A

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SYNTHESIS OF 3′-TRIFLUOROMETHYL NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS

Pawan K. Sharma and Vasu Nair*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, U.S.A.

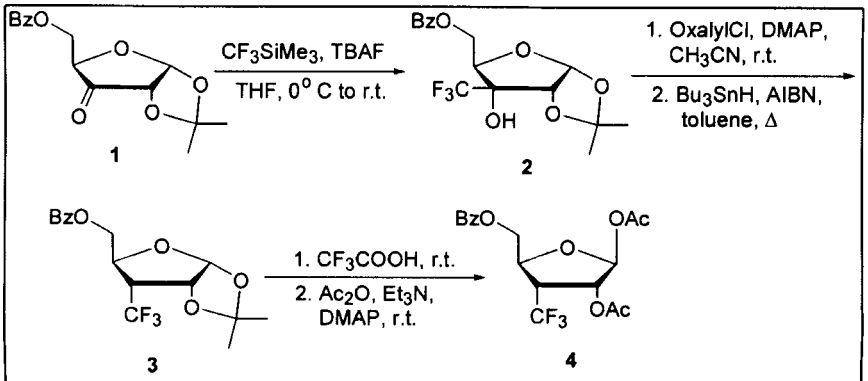
ABSTRACT: 1,2-Di-*O*-acetyl-3-deoxy-3-trifluoromethyl-5-*O*-benzoyl-β-D-ribofuranose was synthesized from the precursor keto sugar by the use of Ruppert's reagent (CF_3SiMe_3) as the source of a nucleophilic trifluoromethyl group. Coupling of this trifluoromethyl sugar with nucleobases and elaboration gave novel deoxy and dideoxynucleosides. A single crystal X-ray analysis confirmed the structure and stereochemistry. The deoxynucleosides were converted through an elimination reaction to their dideoxydidehydro derivatives.

Introduction

Novel nucleoside analogues occupy the centerstage in our present armamentarium to fight against HIV-1 infection. Amongst the nucleoside derivatives, the 2′,3′-dideoxy family has produced the maximum number of anti HIV agents.[1,2] Due to specific properties of the fluorine atom, a large number of 2′- or 3′-fluoro derivatives of 2′,3′-dideoxynucleosides have been prepared recently and evaluated. Some of these fluorinated analogs possess significant anti HIV activity.[3-6] For example, 3′-fluoro-2′,3′-dideoxyuridine (3′-FddU)[6] has strong inhibitory activity against HIV-1 (IC_{50} 0.06 μM, CC_{50} 1.1 μM, MT-4 cells). Owing to the comparatively close inductive effects of F and CF_3 (σ, F = 0.50, CF_3 = 0.45), coupled with the fact that the presence of a sterically demanding trifluoromethyl group in strategical positions of bioactive compounds often causes reduced metabolism, enhanced bioavailability and increased lipophilicity,[7] we thought it of interest to synthesize 3′-trifluoromethyl nucleosides as potential antiviral agents. We report herein the synthesis and antiviral assessment of trifluoromethyl derivatives of 2′,3′-dideoxy- and 2′-3′-dideoxy-2′,3′-didehydronucleosides.

Results and Discussion

The initial approach to these target compounds involved the direct introduction of the trifluoromethyl group at the 3′-position of 3′-keto deoxynucleosides. However, these attempts were not only unsuccessful, but also resulted in decomposition of the starting material. The second approach involved preparation of the appropriate carbohydrate precursor and subsequent coupling with various nucleobases. The carbohydrate precursor was **4** and it was synthesized from D-xylose as shown in Scheme 1. Initially, ketosugar **1** was prepared by initial formation of the *bis*-isopropylidene derivative of D-xylose, selective deprotection of the six-membered isopropylidene ring,[8] selective benzoylation of the primary 5-hydroxyl group[9] followed by Moffatt oxidation. Compound **1** was then converted to the trifluoromethyl derivative **2** in 63% yield in a stereocontrolled manner by reaction with Ruppert's reagent (CF_3SiMe_3).[10] Stereochemical control of this reaction arises from the presence of the adjacent isopropylidene group which prevents the trifluoromethyl group from approaching from α-face of the sugar ring. Radical deoxygenation of **2** to **3** under Barton conditions using the imidazole-1-thiocarbonyl or the phenoxythiocarbonyl derivative of **2** was unsuccessful. However, when a modification of the Barton reaction as described by



[OxalylCl: monomethyloxalyl chloride; DMAP: dimethylaminopyridine; AIBN: α,α'-azobisisobutyronitrile]

Scheme 1

Dolan and MacMillan was attempted,[11] **2** underwent stereospecific deoxygenation and hydrogen atom abstraction from Bu_3SnH occurred from the β-face, to give **3** with the desired 3*R* configuration as the sole product in 79% yield. The α-stereochemistry of the trifluoromethyl group was established from the observed *cis*-coupling between H_2 and H_3 (Figure 1).

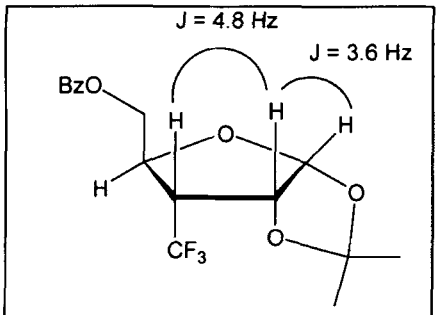
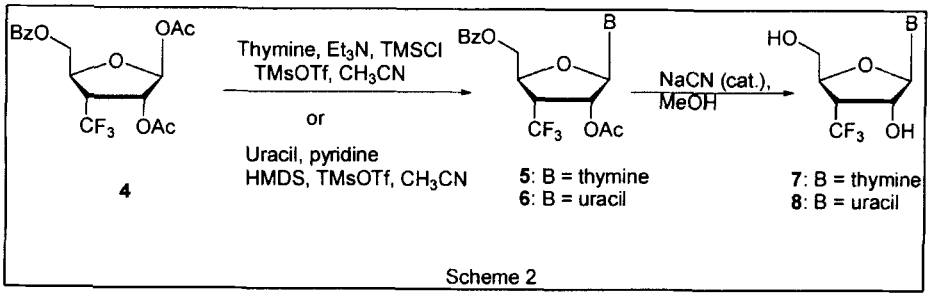


Figure 1: Coupling constant data from the ^1H NMR spectrum of **3**

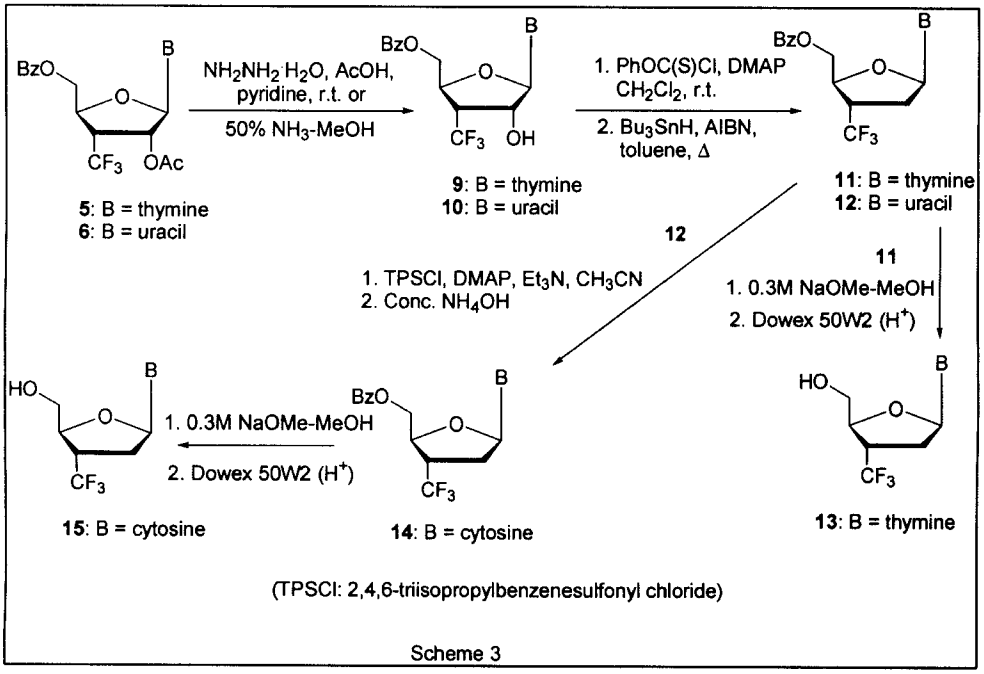
Compound **3** was deprotected with 80% trifluoroacetic acid to generate the diol which was immediately treated with acetic anhydride and triethylamine in the presence of catalytic 4-dimethylaminopyridine (DMAP) in dichloromethane to give the diacetate **4** in 74% yield. The β-stereochemistry of the 1-OAc group was confirmed by the small *trans*-coupling constant observed between H_1 and H_2 (J = ~0 Hz). Condensation of **4** with thymine and uracil (Scheme 2) by the Vorbrüggen procedure[12] gave products **5** (76%) and **6** (73%). Nucleosides **5** and **6** were exclusively the β-anomers due to the



Scheme 2

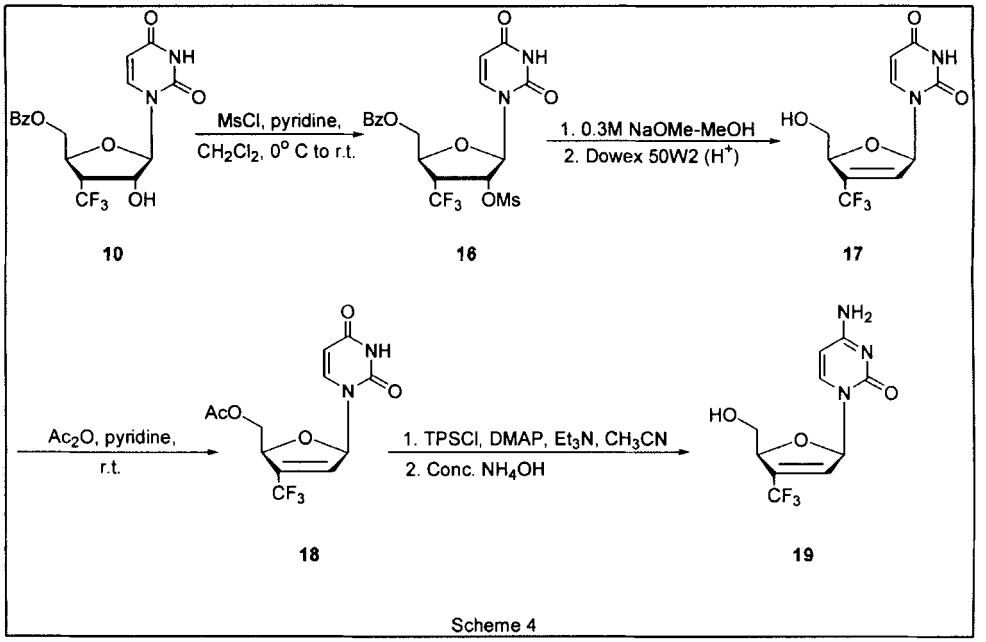
participation of the acetate group at C-2. Deprotections of **5** and **6** were carried out with catalytic NaCN in methanol to give the corresponding products **7** (91%) and **8** (93%).

Synthesis of the dideoxy derivatives from compounds **5** and **6** is described in Scheme 3. Selective deprotection of the hydroxyl group at C-2 was carried out by the procedure described by Ishido *et al*[13] as well as by using 50% NH_3-MeOH to afford **9** and **10**. It was found that the former procedure was advantageous with respect to yield and selectivity, but not in terms of reaction time (5 days). On the other hand, deprotection with 50% NH_3-MeOH was complete in 1 h: however, the yield was low because fully deprotected product was also obtained. Radical deoxygenation at C-2 of compounds **9** and **10** was performed by the Barton reaction[14-16] *via* the thionocarbonates to afford **11** and **12**. Basic hydrolysis of the deoxygenated compound **11** gave the desired nucleoside **13** in 81% yield (Scheme 3). The uracil derivative **12** was converted into cytosine congener **14** by the conventional method followed by debenzoylation with NaOMe giving the desired nucleoside **15** in 64% yield (two steps).



Scheme 3

Synthesis of the didehydro derivatives **17** and **19** was achieved as depicted in Scheme 4. Compound **10** was converted to its methanesulfonate **16** in 84% yield. Subsequent elimination reactions using lithium cyanide[17] or potassium *tert*-butoxide[18] failed. However, conversion of **16** to the desired product **17** was conveniently carried out in quantitative yield by treating **16** with sodium methoxide in methanol resulting in elimination as well as debenzoylation. The uracil derivative **17** was acetylated with an excess of acetic anhydride in pyridine to afford **18** which was converted into the cytosine nucleoside **19** in a single step as described for compound **14**. However, in the case of compound **18**, the reaction mixture was stirred overnight after the addition of conc. NH_4OH resulting in subsequent deacetylation to yield compound **19** in one step from **18**.



Scheme 4

The configuration and conformation of the target structures were further confirmed by single crystal X-ray diffraction analysis. For example, for compound **13**, the crystal structure data established the absolute configuration, the preferred glycosidic bond conformation, and the puckering of the sugar moiety (Figure 2).

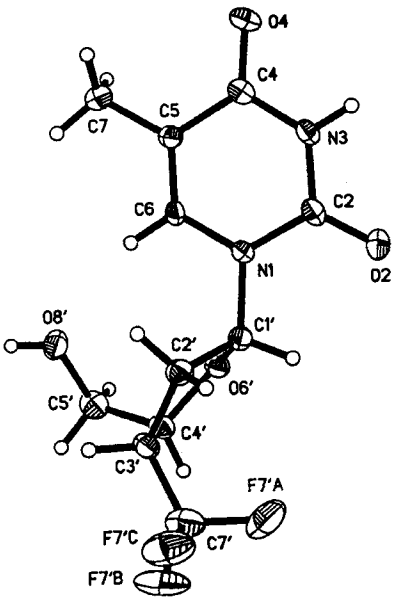


Figure 2. ORTEP plot of single-crystal X-ray structure of compound **13**

In summary, synthesis of the trifluoromethyl derivatives of deoxynucleosides has been achieved starting from an inexpensive precursor material, D-xylose. Furthermore, the method has been used to prepare 2′,3′-dideoxy- or 2′,3′-dideoxy-2′,3′-didehydro derivatives as well as both ribo- and 2′-deoxyribonucleosides with various nucleobases. As the work towards the synthesis and biological evaluation of these nucleoside derivatives was nearing completion, there appeared an article[19] reporting one of the compounds (**13**) described in this paper with a different strategy that involved starting from diacetone D-glucose and involving many more steps than our synthesis. Of the compounds for which data have been obtained so far, none has shown significant anti-HIV activity *in vitro* in infected CEM-SS cells. Further biological studies are in progress.

Experimental

Melting points reported are uncorrected and were determined on a Thomas Hoover apparatus fitted with a microscope. NMR spectra were recorded on a Bruker AC-300 pulse Fourier transform spectrometer. Mass spectra were determined on a VG ZAB-HF instrument. Preparative layer chromatography used plates prepared with E. Merck PF_{254}

silica gel. Flash chromatography was carried out on columns packed with 240-400 mesh silica gel.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-3-deoxy-3-trifluoromethyl-α-D-ribofuranose (3)

5-O-Benzoyl-1,2-O-isopropylidene-3-trifluoromethyl-α-D-ribofuranose (2): To a solution of **1** (979 mg, 3.35 mmol) and (trifluoromethyl)trimethylsilane (0.64 mL, 4.36 mmol) in THF (8 mL) was added dropwise a solution of TBAF in THF (1M, 4.35 mL, 4.36 mmol) under nitrogen at 0° C. The reaction mixture was brought to room temperature and stirred for 2 h. THF was removed under vacuo, dichloromethane (15 mL) was added and the mixture was washed with water (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated to give the crude product which was flash chromatographed (8 : 2 petroleum ether : EtOAc) to afford **2** (0.77 g, 63.2%) as a white crystalline solid: mp 128.9-129.6° C; lit.[20] mp 127-129 ° C; R_f = 0.70 (7 : 3 petroleum ether : EtOAc); ^1H NMR ($CDCl_3$): δ 8.15-8.00 (m, 2H, arom ortho), 7.65-7.35 (m, 3H, arom para and meta), 6.00 (d, 1H, H-1), 4.83-4.72 (dd, 1H, H-4), 4.63 (d, 1H, H-2), 4.60-4.28 (m, 2H, H-5 and H-5'), 3.42 (s, 1H, OH), 1.63 (s, 3H, CH_3), 1.45 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$): δ -75.07 (s, CF_3).

5-O-Benzoyl-1,2-O-isopropylidene-3-deoxy-3-trifluoromethyl-α-D-ribofuranose (3): Compound **2** (760 mg, 2.10 mmol) was dissolved in CH_3CN (15 mL) and 4-(DMAP) (769 mg, 6.30 mmol) was added followed by dropwise addition of monomethyloxalyl chloride (0.48 mL, 5.25 mmol) at 10°C. The reaction mixture was stirred at room temperature for 1 h and poured onto H_2O and EtOAc. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and H_2O, dried over Na_2SO_4 and concentrated under vacuum. The oil was coevaporated with toluene and dissolved in the same solvent (15 mL). To the above refluxing solution, a nitrogen purged solution of Bu_3SnH (0.79 mL, 2.94 mmol) and AIBN (241 mg, 1.47 mmol) in toluene (10 mL) was added dropwise over a period of 45 min. The mixture was stirred at reflux for 2 h and then concentrated under reduced pressure. The residue was purified by flash chromatography (eluent: gradient of EtOAc 0% to 6.5% in petroleum ether) to give **3** as a colorless viscous oil (571 mg, 78.6%): R_f = 0.70 (7 : 3 petroleum ether : EtOAc); ^1H NMR ($CDCl_3$): δ 8.10-8.00 (m, 2H, arom ortho), 7.62-7.52 (m, 1H, arom para), 7.49-7.38 (m, 2H, arom meta), 5.91 (d, 1H, H-1, J_{H1-H2}=3.6

Hz), 4.90 (dd, 1H, H-2, J_{H2-H1}=3.6 Hz, J_{H2-H3}=4.8 Hz), 4.74 (dd, 1H, H-5', $J_{H5'-H5}$=12.5 Hz, $J_{H5'-H4}$=2.6 Hz), 4.66 (ddd, 1H, H-4, J_{H4-H5}=4.2 Hz, $J_{H4-H5'}$=2.6 Hz, J_{H4-H3}=10.2 Hz), 4.38 (dd, 1H, H-5, $J_{H5-H5'}$=12.5 Hz, J_{H4-H5}=4.2 Hz), 2.86 (m, 1H, H-3, J_{H3-H2}=4.8 Hz, J_{H3-H4}=10.2 Hz, J_{H3-F}=8.4 Hz), 1.57 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 165.60 (CO), 132.98 (arom para), 129.39 (arom ortho), 129.35 (arom ipso), 128.15 (arom meta), 124.11 (q, CF_3, J_{C-F}=275.4 Hz), 113.091 (Cq isopropylidene), 104.63 (C-1), 78.75 (C-4), 74.35 (C-2), 62.89 (C-5), 48.54 (q, C-3, J_{C-F}=27.4 Hz), 26.06 and 26.17 (2 × CH_3); ^{19}F NMR ($CDCl_3$): δ -62.29 (d, CF_3, J_{F-H}=7.9 Hz); HRMS (FAB) calcd for $C_{16}H_{17}F_3O_5$: $(M + Na)^+$ 369.0926, found: 369.0938.

1-(3-Deoxy-3-trifluoromethyl-β-D-ribofuranosyl)thymine (7)

1,2-Di-O-acetyl-3-deoxy-3-trifluoromethyl-5-O-benzoyl-β-D-ribofuranose (4): A solution of **3** (4.98 g, 14.39 mmol) in 80% trifluoroacetic acid (80 mL) was stirred at room temperature for 15 h. Trifluoroacetic acid was removed under vacuo, and then coevaporated with toluene (2 × 50 mL) to give the crude diol. The diol was dissolved in dichloromethane (125 mL) to which was added DMAP (50 mg), triethylamine (12.03 mL, 86.34 mmol) and acetic anhydride (6.78 mL, 71.95 mmol) dropwise under nitrogen. The mixture was stirred for 2 h, dichloromethane (150 mL) was added and the mixture was washed with water (2 × 200 mL), saturated aqueous $NaHCO_3$ (2 × 200 mL) and then again with water (2 × 200 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuo to give crude **4** which was flash chromatographed (9:1, petroleum ether: AcOEt) to give **4** (4.18 g, 74.5%): mp 126.4-126.6°C (recrystallized from EtOAc and petroleum ether); R_f = 0.70 (7 : 3 petroleum ether : EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.15-8.04 (m, 2H, arom ortho), 7.64-7.54 (m, 1H, arom para), 7.51-7.41 (m, 2H, arom meta), 6.15 (s, 1H, H-1), 5.55 (d, 1H, H-2), 4.91-4.80 (m, 1H, H-4), 4.75 (dd, 1H, H-5'), 4.37 (dd, 1H, H-5), 3.52-3.33 (m, 1H, H-3), 2.14 (s, 3H, CH_3), 1.89 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 169.02, 168.54, 165.65 (3 CO), 133.32 (arom para), 129.61 (arom ortho), 129.38 (arom ipso), 128.38 (arom meta), 124.30 (q, CF_3, J_{C-F}=275.8 Hz), 98.35 (C-1), 77.57 (C-4), 74.43 (C-2), 63.89 (C-5), 45.36 (q, C-3, J_{C-F}=28.8 Hz), 20.62 and 20.42 (2 × CH_3); ^{19}F NMR ($CDCl_3$): δ -63.41 (d, CF_3, J_{F-H}=8.5 Hz).

1-(2-O-Acetyl-3-deoxy-3-trifluoromethyl-5-O-benzoyl-β-D-ribofuranosyl)thymine (5): To a well stirred suspension of thymine (1.29 g, 10.26 mmol) and TMSCl (2.60 mL, 20.51

mmol) in dry benzene (30 mL) was added dropwise triethylamine (2.86 mL, 20.51 mmol) under anhydrous conditions at room temperature. After the addition, stirring was continued for 15 h. The precipitated mixture of triethylamine hydrochloride and thymine was filtered off and washed with dry benzene (3 × 15 mL), the filtrate and washings were collected and the solvent removed under vacuo to give a viscous oily silylated thymine which was then treated with a solution of **4** (1.0 g, 2.56 mmol) in dry acetonitrile (25 ml) followed by TMSOTf (1.86 mL, 10.26 mmol) to give a clear solution. The reaction mixture was stirred at room temperature for 20 h and then saturated aqueous $NaHCO_3$ (50 mL) and dichloromethane (50 mL) were added. The organic layer was washed with water (2 × 50 mL), dried over $MgSO_4$ and concentrated under vacuo to give the crude product which was flash chromatographed (gradient of MeOH 0 to 0.5% in $CHCl_3$) to give **5** (1.0 g, 85.5%): mp 143.6-143.8°C (recrystallized from with EtOAc and petroleum ether); R_f = 0.55 (19 : 1 $CHCl_3$: MeOH); ^{1}H NMR ($CDCl_3$): δ 9.70 (s, 1H, NH), 8.14-8.04 (m, 2H, arom ortho), 7.64-7.56 (m, 1H, arom para), 7.55-7.42 (m, 2H, arom meta), 7.02 (d, 1H, H-6, $J_{H5\text{-}H6}$=1.4 Hz), 5.78-5.67 (m, 2H, H-1′ and H-2′), 4.85-4.68 (m, 2H, H-5″ and H-4′), 4.46 (dd, 1H, H-5′, $J_{H5'\text{-}H5''}$=12.3 Hz, $J_{H5'\text{-}H4'}$=4.5 Hz), 3.78-3.63 (m, 1H, H-3′), 2.16 (s, 3H, OAc), 1.70 (d, 3H, CH_3, $J_{H6\text{-}H5}$=1.4 Hz); ^{13}C NMR ($CDCl_3$): δ 169.85, 165.85, 163.78, 150.07 (4 CO), 136.27 (C-6), 133.57 (arom para), 129.61 (arom ortho), 129.13 (arom ipso), 128.64 (arom meta), 124.33 (q, CF_3, $J_{C\text{-}F}$=278.0 Hz), 111.79 (C-5), 91.18 (C-1′), 76.29 (C-4′), 73.34 (C-2′), 63.96 (C-5′), 45.16 (q, C-3′, $J_{C\text{-}F}$=26.8 Hz), 20.50 (CH_3 acetyl), 12.11 (CH_3); ^{19}F NMR ($CDCl_3$): δ -64.52 (d, CF_3, $J_{F\text{-}H}$=10.2 Hz).

1-(3-Deoxy-3-trifluoromethyl-β-D-ribofuranosyl)thymine (7): To a solution of **5** (120 mg, .26 mmol) in methanol (5 mL) were added several crystals of NaCN and the reaction mixture was stirred at room temperature for 30 h. The solvent was removed under vacuo and the crude residue was flash chromatographed (gradient of MeOH 0 to 3.0% in $CHCl_3$) to give **7** as a white solid (74 mg, 90.7%): mp 103.7-104.0° C; R_f = 0.20 (9 : 1 $CHCl_3$: MeOH); ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.93 (d, 1H, H-6, $J_{H5\text{-}H6}$=1.2 Hz), 5.76 (d, 1H, H-1′, $J_{H1'\text{-}H2'}$=2.7 Hz), 4.56-4.44 (m, 2H, H-2′ and H-4′), 4.02 (dd, 1H, H-5″, $J_{H5''\text{-}H5'}$=12.2 Hz, $J_{H5''\text{-}H4'}$=1.8 Hz), 3.69 (dd, 1H, H-5′, $J_{H5''\text{-}H5'}$=12.2 Hz, $J_{H5'\text{-}H4'}$=3.2 Hz), 3.12 (m, 1H, H-3′), 1.85 (d, 3H, CH_3, $J_{H6\text{-}H5}$=1.2 Hz); ^{13}C NMR ($CDCl_3$ + CD_3OD): δ 164.51, 150.51 (2 CO), 136.15 (C-6), 124.65 (q, CF_3, $J_{C\text{-}F}$=276.7 Hz), 109.62 (C-5), 90.97 (C-1′),

78.98 (C-4′), 73.77 (C-2′), 59.98 (C-5′), 43.91 (q, C-3′, $J_{C\text{-}F}$=26.5 Hz), 11.06 (CH_3); ^{19}F NMR ($CDCl_3$ + CD_3OD): δ -60.21 (d, CF_3, $J_{F\text{-}H}$=8.5 Hz). HRMS (FAB) calcd for $C_{11}H_{13}F_3N_2O_5$: $(M + H)^+$ 311.0856, found: 311.0846.

1-(3-Deoxy-3-trifluoromethyl-β-D-ribofuranosyl)uracil (8):

1-(2-O-Acetyl-3-deoxy-3-trifluoromethyl-5-O-benzoyl-β-D-ribofuranosyl)uracil (6): A mixture of uracil (517 mg, 4.62 mmol), 1,1,1,3,3,3-hexamethyldisilazane (6 mL) and dry pyridine (6 mL) was refluxed under anhydrous conditions for 3 h. The solvents were evaporated under vacuo and then coevaporated with toluene (2 × 10 mL) to give a viscous silylated uracil, which was then treated with a solution of **4** (450 mg, 1.15 mmol) in dry acetonitrile (8 mL) followed by TMSOTf (0.84 mL, 4.62 mmol) to give a clear solution. The reaction mixture was stirred at room temperature for 24 h and then saturated aqueous $NaHCO_3$ (15 mL) and dichloromethane (15 mL) were added. The organic layer was washed with water (2 × 15 mL), dried over $MgSO_4$ and concentrated under vacuo to give the crude product which was flash chromatographed (gradient of MeOH 0 to 0.3% in $CHCl_3$) to give **6** (373 mg, 73%) as white solid: mp 116.0-116.9° C (recrystallized with $CHCl_3$); R_f = 0.65 (9 : 1 $CHCl_3$: MeOH); ^1H NMR ($CDCl_3$): δ 10.06 (s, 1H, NH), 8.10-8.00 (m, 2H, arom ortho), 7.65-7.55 (m, 1H, arom para), 7.52-7.42 (m, 2H, arom meta), 7.30 (d, 1H, H-6, $J_{H5\text{-}H6}$=8.1 Hz), 5.74 (dd, 1H, H-2′, $J_{H2'\text{-}H3'}$=7.2 Hz, $J_{H1'\text{-}H2'}$=3.6 Hz), 5.69 (d, 1H, H-1′, $J_{H1'\text{-}H2'}$=3.6 Hz), 5.64 (d, 1H, H-5, $J_{H5\text{-}H6}$=8.1 Hz), 4.88-4.68 (m, 2H, H-5″ and H-4′), 4.51 (dd, 1H, H-5′, $J_{H5'\text{-}H5''}$=12.3 Hz, $J_{H5'\text{-}H4'}$=4.5 Hz), 3.85-3.60 (m, 1H, H-3′), 2.15 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$): δ 169.68, 165.84, 163.43, 149.95 (4 CO), 140.91 (C-6), 133.49 (arom para), 129.54 (arom ortho), 129.06 (arom ipso), 128.53 (arom meta), 124.16 (q, CF_3, $J_{C\text{-}F}$=277.8 Hz), 102.94 (C-5), 92.04 (C-1′), 76.64 (C-4′), 73.70 (C-2′), 63.71 (C-5′), 45.18 (q, C-3′, $J_{C\text{-}F}$=28.8 Hz), 20.44 (CH_3 acetyl); ^{19}F NMR ($CDCl_3$): δ -64.13 (d, CF_3, $J_{F\text{-}H}$=9.0 Hz).

1-(3-Deoxy-3-trifluoromethyl-β-D-ribofuranosyl)uracil (8): The synthesis of **8** was carried out by the same reaction and work up procedure used for **7** starting from **6** (88 mg, 0.20 mmol). The nucleoside **8** was obtained as white foam (55 mg, 93%): mp 98.0-100.0° C; R_f = 0.20 (9 : 1 $CHCl_3$: MeOH); ^1H NMR (CD_3OD): δ 8.09 (d, 1H, H-6, $J_{H5\text{-}H6}$=8.1 Hz), 5.79 (d, 1H, H-1′, $J_{H1'\text{-}H2'}$=2.7 Hz), 5.67 (d, 1H, H-5, $J_{H5\text{-}H6}$=8.1 Hz), 4.58 (dd,

1H, H-2', $J_{H1''-H2'}$=2.7 Hz, $J_{H2''-H3'}$=6.0 Hz), 4.48 (m, 1H, H-4'), 3.99 (dd, 1H, H-5'', $J_{H5''-H5'}$=12.5 Hz, $J_{H5''-H4'}$=1.8 Hz), 3.68 (dd, 1H, H-5', $J_{H5''-H5'}$=12.5 Hz, $J_{H5'-H4'}$=2.7 Hz), 3.30-3.07 (m, 1H, H-3'); ^{13}C NMR (CD_3OD): δ 166.20, 152.22 (2 CO), 142.31 (C-6), 126.65 (q, CF_3, J_{C-F}=277.6 Hz), 102.34 (C-5), 92.90 (C-1'), 80.90 (C-2'), 75.46 (C-4'), 61.81 (C-5'), 45.85 (q, C-3', J_{C-F}=26.4 Hz); ^{19}F NMR ($CDCl_3$ + CD_3OD): δ -60.67 (d, CF_3, J_{F-H}=11.0 Hz). HRMS (FAB) calcd for $C_{10}H_{11}F_3N_2O_5$: $(M + H)^+$ 297.0699, found: 297.0710.

1-(3-Deoxy-3-trifluoromethyl-5-*O*-benzoyl-β-D-ribofuranosyl)thymine (9): Hydrazine monohydrate (1.48 mmol) in solution in acetic acid and pyridine (22 mmol of $NH_2NH_2.H_2O$ for 66 mL of mixture pyridine-acetic acid, proportions v/v 4/1) was added to **5** (450 mg, 0.99 mmol). After stirring for 24 h at room temperature, acetone (10 mL) was added and the stirring was continued for 2 h. The solution was evaporated and partitioned between H_2O and AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated. Flash chromatography (gradient of MeOH 0 to 1.5% in $CHCl_3$) gave **9** (338 mg, 82.8%) as a foam: mp 90.3-90.6°C (recrystallized with AcOEt); ^{1}H NMR ($CDCl_3$): δ 10.89 (s, 1H, NH), 8.15-8.00 (m, 2H, arom ortho), 7.70-7.56 (m, 1H, arom para), 7.55-7.42 (m, 2H, arom meta), 7.40 (d, 1H, H-6), 5.77 (d, 1H, H-1'), 5.46 (d, 1H, OH), 5.04-4.76 (m, 3H, H-5'', H-4' and H-2'), 4.54 (dd, 1H, H-5'), 3.25-3.05 (m, 1H, H-3'), 1.48 (d, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 165.74, 163.90, 151.22 (3 CO), 134.54 (C-6), 133.45 (arom para), 129.34 (arom ortho), 129.08 (arom ipso), 128.55 (arom meta), 124.59 (q, CF_3, J_{C-F}=278.5 Hz), 110.70 (C-5), 91.79 (C-1'), 74.49 (C-4'), 74.49 (C-2'), 63.38 (C-5'), 45.27 (q, C-3', J_{C-F}=27.2 Hz), 11.92 (CH_3); ^{19}F NMR ($CDCl_3$): δ -62.98 (d, CF_3, J_{F-H}=7.1 Hz); HRMS (FAB) calcd for $C_{18}H_{17}F_3N_2O_6$: $(M + Na)^+$ 437.0937, found: 437.0927.

1-(3-Deoxy-3-trifluoromethyl-5-*O*-benzoyl-β-D-ribofuranosyl)uracil (10): The synthesis of **10** was carried out by the same reaction and work up procedure used for **9** starting from **6** (373 mg, 0.84 mmol). The nucleoside **10** was obtained as white foam (202 mg, 59.8%): mp 177.0-178.5° C (recrystallized with MeOH); R_f= 0.50 (9 : 1 $CHCl_3$: MeOH); ^{1}H NMR ($CDCl_3$): δ 10.64 (s, 1H, NH), 8.10-8.00 (m, 2H, arom ortho), 7.68 (d, 1H, H-6, J_{H5-H6}=8.1 Hz), 7.65-7.55 (m, 1H, arom para), 7.50-7.40 (m, 2H, arom meta),

5.79 (d, 1H, H-1′, $J_{H1'-H2'}$=1.8 Hz), 5.42 (d, 1H, H-5, J_{H5-H6}=8.1 Hz), 5.22 (d, 1H, OH), 5.00-4.75 (m, 3H, H-5″, H-4′ and H-2′), 4.57 (dd, 1H, H-5′, $J_{H5''-H5'}$=13.2 Hz, $J_{H5'-H4'}$=3.6 Hz), 3.25-3.05 (m, 1H, H-3′); ^{13}C NMR ($CDCl_3$): δ 165.82, 163.37, 151.30 (3 CO), 138.99 (C-6), 133.76 (arom para), 129.55 (arom ortho), 129.12 (arom ipso), 128.67 (arom meta), 124.47 (q, CF_3, J_{C-F}=278.2 Hz), 102.45 (C-5), 92.24 (C-1′), 77.41 (C-4′), 74.93 (C-2′), 63.23 (C-5′), 45.31 (q, C-3′, J_{C-F}=29.6 Hz); ^{19}F NMR ($CDCl_3$): δ -63.06 (d, CF_3, J_{F-H}=8.7 Hz). HRMS (FAB) calcd for $C_{17}H_{15}F_3N_2O_6$: $(M + Na)^+$ 423.0780, found: 423.0775.

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-ribofuranosyl)thymine (13):

1-(2,3-Dideoxy-3-trifluoromethyl-5-O-benzoyl-β-D-ribofuranosyl)thymine (11): To a solution of **9** (322 mg, 0.78 mmol) in dichloromethane (8 mL) were added phenyl chlorothionoformate (0.43 mL, 1.56 mmol) and 4-(DMAP) (380 mg, 3.11 mmol). After stirring for 1 h at room temperature the reaction mixture was diluted with dichloromethane. The organic phase was washed successively with H_2O, 1N aqueous HCl, H_2O, saturated aqueous $NaHCO_3$ and H_2O, then dried over $MgSO_4$ and evaporated to dryness. The residue was coevaporated with toluene and dissolved in the same solvent (5 mL). To the above refluxing solution, a nitrogen purged solution of Bu_3SnH (0.29 mL, 1.09 mmol) and AIBN (89 mg, 0.55 mmol) in toluene (5 mL) was added dropwise over a period of 45 min. The mixture was stirred at reflux for 2 h and then concentrated under reduced pressure. The residue was purified by flash chromatography (eluent: gradient of MeOH 0% to 0.5% in $CHCl_3$) to give **11** as a foam (235 mg, 75.9%): mp 87.5-87.8°C (recrystallized with AcOEt); R_f= 0.60 (9 : 1 $CHCl_3$: MeOH); ^{1}H NMR ($CDCl_3$): δ 10.46 (s, 1H, NH), 8.10-7.98 (m, 2H, arom ortho), 7.65-7.55 (m, 1H, arom para), 7.55-7.40 (m, 2H, arom meta), 7.26 (s, 1H, H-6), 6.14 (m, 1H, H-1′), 4.85-4.70 (m, 1H, H-4′), 4.60-4.45 (m, 2H, H-5″ and H-5′), 3.45-3.22 (m, 1H, H-3′), 2.80-2.60 (m, 1H, H-2′), 2.50-2.30 (m, 1H, H-2″) 1.65 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 165.60, 163.96, 150.23 (3 CO), 134.89 (C-6), 133.28 (arom para), 129.16 (arom ortho), 128.88 (arom ipso), 128.34 (arom meta), 125.91 (q, CF_3, J_{C-F}=277.7 Hz), 110.96 (C-5), 85.46 (C-1′), 76.49 (C-4′), 64.20 (C-5′), 43.30 (q, C-3′, J_{C-F}=29.7 Hz), 31.91 (C-2′), 11.77 (CH_3); ^{19}F NMR ($CDCl_3$): δ -70.57 (d, CF_3, J_{F-H}=10.2 Hz).

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-ribofuranosyl)thymine (13): A solution of **11** (60 mg, 0.15 mmol) in 0.3M NaOMe (in MeOH) (1.5 mL) was stirred at room temperature for 35 min. Excess of NaOMe was neutralized with Dowex 50W2 resin (H^+). The reaction mixture was filtered and the resin was washed with MeOH. The combined filtrate was evaporated to dryness and flash chromatographed (gradient of MeOH 0 to 1.5% in $CHCl_3$) to give **13** which was recrystallized from ethanol to yield long needles like crystals (36 mg, 81.2%): mp 197.6-198.0°C; R_f = 0.40 (9 : 1 $CHCl_3$: MeOH); ^1H NMR (CD_3OD): δ 7.79 (s, 1H, H-6), 6.09 (m, 1H, H-1′), 4.18 (m, 1H, H-4′), 3.87 (dd, 1H, H-5″, $J_{H5'-H5''}$=12.2 Hz, $J_{H5''-H4'}$=1.8 Hz), 3.65 (dd, 1H, H-5′, $J_{H5'-H5''}$=12.2 Hz, $J_{H5'-H4'}$=3.2 Hz), 3.36-3.16 (m, 1H, H-3′), 2.58-2.43 (m, 1H, H-2′), 2.38-2.21 (m, 1H, H-2″) 1.83 (s, 3H, CH_3); ^{13}C NMR (CD_3OD): δ 166.35, 152.26 (2 CO), 138.03 (C-6), 127.97 (q, CF_3, J_{C-F}=277.7 Hz), 111.61 (C-5), 86.39 (C-1′), 81.12 (C-4′), 63.14 (C-5′), 43.67 (q, C-3′, J_{C-F}=28.1 Hz), 33.18 (C-2′), 12.43 (CH_3); ^{19}F NMR (CD_3OD): δ -68.17 (d, CF_3, $J_{F-,H}$= 10.7 Hz). HRMS (FAB) calcd for $C_{11}H_{13}F_3N_2O_4$: $(M + H)^+$ 295.0906, found: 295.0911.

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-ribofuranosyl)cytosine (15):

1-(2,3-Dideoxy-3-trifluoromethyl-5-O-benzoyl-β-D-ribofuranosyl)uracil (12): The synthesis of **12** was carried out by the same reaction and work up procedure used for **11** starting from **10** (240 mg, 0.60 mmol). The nucleoside **12** was obtained as white solid (176 mg, 76.4%): mp 80.0-82.0° C (recrystallized with EtOAc); R_f = 0.45 (9 : 1 $CHCl_3$: MeOH); ^1H NMR ($CDCl_3$): δ 10.10 (s, 1H, NH), 8.05-7.95 (m, 2H, arom ortho), 7.65-7.55 (m, 1H, arom para), 7.52-7.42 (m, 3H, arom meta and H-6), 6.09 (m, 1H, H-1′), 5.59 (d, 1H, H-5, J_{H5-H6}=7.9 Hz), 4.72 (dd, 1H, H-5″, $J_{H5''-H5'}$=13.7 Hz, $J_{H5''-H4'}$=4.3 Hz), 4.59-4.50 (m, 2H, H-4′ and H-5′), 3.25-3.05 (m, 1H, H-3′), 2.80-2.65 (m, 1H, H-2″), 2.45-2.30 (m, 1H, H-2′); ^{13}C NMR ($CDCl_3$): δ 165.86, 163.54, 150.16 (3 CO), 139.43 (C-6), 133.63 (arom para), 129.44 (arom ortho), 129.04 (arom ipso), 128.60 (arom meta), 125.90 (q, CF_3, J_{C-F}=277.6 Hz), 102.58 (C-5), 86.21 (C-1′), 77.31 (C-4′), 64.22 (C-5′), 43.43 (q, C-3′, J_{C-F}=29.2 Hz), 32.68 (C-2′); ^{19}F NMR ($CDCl_3$): δ -70.38 (d, CF_3, J_{F-H}=9.3 Hz).

1-(2,3-Dideoxy-3-trifluoromethyl-5-O-benzoyl-β-D-ribofuranosyl)cytosine (14): Et_3N (78 μL, 0.56 mmol) was added to a solution of **12** (107 mg, 0.28 mmol) in CH_3CN (10 mL)

containing 2,4,6-triisopropylbenzenesulfonyl chloride (169 mg, 0.56 mmol) and DMAP (68 mg, 0.56 mmol) at 0° C. The mixture was stirred for 3.5 h at room temperature under nitrogen and then concentrated NH_4OH (28%, 5 mL) was added to the mixture, which was further stirred for 1.5 h at room temperature. The mixture was concentrated to dryness and the residue was purified on a silica gel column (gradient of MeOH 1 to 3% in $CHCl_3$) to give **14** (84 mg, 78.7%) as white paste: R_f = 0.80 (8 : 2 $CHCl_3$: MeOH); ^1H NMR ($CDCl_3$): δ 8.05-7.95 (m, 2H, arom ortho), 7.65-7.53 (m, 2H, arom para and H-6), 7.52-7.42 (m, 2H, arom meta), 6.07 (m, 1H, H-1′), 5.87 (d, 1H, H-5, $J_{H5\text{-}H6}$=7.2 Hz), 4.75-4.45 (m, 3H, H-5′, H-5″ and H-4′), 3.25-3.02 (m, 1H, H-3′), 2.84-2.70 (m, 1H, H-2″), 2.42-2.30 (m, 1H, H-2′); ^{19}F NMR ($CDCl_3$): δ -70.34 (d, CF_3, $J_{F\text{-}H}$=9.0 Hz).

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-ribofuranosyl)cytosine (15): The synthesis of **15** was carried out by the same reaction and work up procedure used for **13** starting from **14** (84 mg, 0.22 mmol). The nucleoside **15** was obtained as white solid (50 mg, 81.7%): mp 214.8-216.0° C (recrystallized with EtOH); R_f = 0.35 (8 : 2 $CHCl_3$: MeOH); ^1H NMR (CD_3OD): δ 8.02 (d, 1H, H-6, $J_{H5\text{-}H6}$=7.8 Hz), 6.10 (m, 1H, H-1′), 5.89 (d, 1H, H-5, $J_{H5\text{-}H6}$=7.8 Hz), 4.25 (dt, 1H, H-4′, $J_{H4'\text{-}H3'}$=6.3 Hz, $J_{H4'\text{-}H5'}$= $J_{H4'\text{-}H5''}$=2.4 Hz), 3.91 (dd, 1H, H-5″, $J_{H5'\text{-}H5''}$=12.3 Hz, $J_{H5''\text{-}H4'}$=2.4 Hz), 3.69 (dd, 1H, H-5′, $J_{H5'\text{-}H5''}$=12.3 Hz, $J_{H5'\text{-}H4'}$=3.3 Hz), 3.25 (m, 1H, H-3′), 2.63 (dt, 1H, H-2″, $J_{H2'\text{-}H2''}$=14.1 Hz, $J_{H2''\text{-}H1'}$= $J_{H2''\text{-}H3''}$=6.3 Hz), 2.27 (ddd, 1H, H-2′, $J_{H2'\text{-}H2''}$=14.1 Hz, $J_{H2'\text{-}H3'}$=9.6 Hz, $J_{H2'\text{-}H1'}$=5.7 Hz); ^{13}C NMR (CD_3OD): δ 167.71, 158.12 (C-4 and C-2), 142.59 (C-6), 126.75 (q, CF_3, $J_{C\text{-}F}$=278.2 Hz), 96.00 (C-5), 87.69 (C-1′), 81.48 (d, C-4′, $J_{C\text{-}F}$=2.7 Hz), 63.08 (C-5′), 43.55 (q, C-3′, $J_{C\text{-}F}$=27.4 Hz), 34.11 (d, C-2′, $J_{C\text{-}F}$=3.0 Hz); ^{19}F NMR (CD_3OD): δ -68.02 (d, CF_3, $J_{F\text{-},H}$=8.8 Hz); HRMS (FAB) calcd for $C_{10}H_{12}F_3N_3O_3$: $(M + Na)^+$ 302.0729, found: 302.0727.

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-glyceropent-2-enofuranosyl)uracil (17):

1-(2-O-Methanesulfonyl-3-deoxy-3-trifluoromethyl-5-O-benzoyl-β-D-ribofuranosyl)-uracil (16): Pyridine (240 μL, 3.00 mmol) followed by methanesulfonyl chloride (116 μL, 1.5 mmol) were added to a solution of **10** (200 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) at 0° C. The reaction mixture was stirred for 24 h at room temperature. Water (5 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated

under vacuo. The residue was purified by flash chromatography (eluent: gradient of MeOH 0% to 0.5% in $CHCl_3$) to afford **16** as a white crystalline solid: mp 181.0-181.5°C (crystallized with methanol); R_f = 0.65 (9 : 1 $CHCl_3$: MeOH); ^1H NMR ($CDCl_3$): δ 9.05 (s, 1H, NH), 8.10-8.00 (m, 2H, arom ortho), 7.65-7.55 (m, 1H, arom para), 7.50-7.40 (m, 2H, arom meta), 7.30 (d, 1H, H-6, J_{H5-H6}=8.4 Hz), 5.72-5.55 (m, 3H, H-1′, H-2′ and H-5), 4.90-4.70 (m, 2H, H-5″ and H-4′), 4.50 (m, 1H, H-5′), 3.95-3.80 (m, 1H, H-3′), 3.18 (s, 3H, SO_2CH_3); ^{19}F NMR ($CDCl_3$): δ -62.83 (d, CF_3, J_{F-H}=7.9 Hz).

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-glyceropent-2-enofuranosyl)uracil (17): A solution of **16** (150 mg, 0.31 mmol) in 0.3M NaOMe (in MeOH) (3.5 mL) was stirred at room temperature for 2 h. Excess of NaOMe was neutralized with Dowex 50W2 resin (H^+). The reaction mixture was filtered and the resin was washed with MeOH. The combined filtrate was evaporated to dryness and flash chromatographed (eluent: gradient of MeOH 0 to 2.0% in $CHCl_3$) to give **17** which was recrystallized from ethanol to yield a white solid (85 mg, 97.4%): mp 123.8-124.7°C; R_f = 0.50 (9 : 1 $CHCl_3$: MeOH); ^1H NMR (CD_3OD): δ 7.93 (d, 1H, H-6, J_{H5-H6}=7.9 Hz), 7.01 (m, 1H, H-1′), 6.66 (d, 1H, H-2′, $J_{H2'-H1'}$=1.5 Hz), 5.67 (d, 1H, H-5, J_{H5-H6}=7.9 Hz), 5.05 (m, 1H, H-4′), 3.83 (m, 2H, H-5′ and H-5″); ^{13}C NMR (CD_3OD): δ 166.13 (C-4), 152.39 (C-2), 143.08 (C-6), 137.51 (q, C-3′, J_{C-F}=34.9 Hz), 132.93 (q, C-2′, J_{C-F}=4.4 Hz), 122.35 (q, CF_3, J_{C-F}=269.3 Hz), 102.85 (C-5), 89.87 (C-1′), 86.45 (C-4′), 62.31 (C-5′); ^{19}F NMR (CD_3OD): δ -61.23 (s, CF_3); HRMS (FAB) calcd for $C_{10}H_9F_3N_2O_4$: $(M + H)^+$ 279.0593, found: 279.0599.

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-glyceropent-2-enofuranosyl)cytosine (19):

1-(2,3-Dideoxy-3-trifluoromethyl-5-O-acetyl-β-D-glyceropent-2-enofuranosyl)uracil (18): A solution of **17** (80 mg, .29 mmol) and acetic anhydride (136 μL, 1.44 mmol) in anhydrous pyridine (5 mL) was stirred at room temperature for 24 h. The reaction mixture was then quenched with water and the solvent was evaporated under vacuo and coevaporated with toluene (2 × 10 mL). The residue was purified by flash chromatography (eluent: gradient of MeOH 0 to 1.0% in CH_2Cl_2) to give **18** which was recrystallized from ethanol to yield a colorless solid (88 mg, 95.6%): R_f = 0.60 (9 : 1 CH_2Cl_2 : MeOH); ^1H NMR (CD_3OD): δ 7.61 (d, 1H, H-6, J_{H5-H6}=7.9 Hz), 7.01 (m, 1H, H-1′), 6.77 (d, 1H, H-2′, $J_{H2'-H1'}$=1.5 Hz), 5.75 (d, 1H, H-5, J_{H5-H6}=7.9 Hz), 5.27 (m, 1H,

H-4′), 4.33 (m, 2H, H-5′ and H-5″); ^{13}C NMR (CD_3OD): δ 171.76 (*C*OMe), 165.79 (C-4), 152.15 (C-2), 142.20 (C-6), 136.44 (q, C-3′, $J_{C\text{-}F}$=35.1 Hz), 133.62 (q, C-2′, $J_{C\text{-}F}$=4.3 Hz), 122.14 (q, CF_3, $J_{C\text{-}F}$=269.6 Hz), 103.38 (C-5), 90.15 (C-1′), 82.91 (C-4′), 64.56 (C-5′), 20.59 (CH_3); ^{19}F NMR (CD_3OD): δ -61.26 (s, CF_3).

1-(2,3-Dideoxy-3-trifluoromethyl-β-D-glyceropent-2-enofuranosyl)cytosine ***(19)****:* The synthesis of **19** was carried out by the same reaction and work up procedure used for **14** starting from **18** (80 mg, 0.25 mmol). However in this case, after adding concentrated NH_4OH, the reaction mixture was stirred for 15 h. The nucleoside **19** was obtained as white plates (38 mg, 69.7%): mp 221.3-221.7° C (recrystallized with MeOH); R_f = 0.15 (9 : 1 CH_2Cl_2 : MeOH); ^{1}H NMR (CD_3OD): δ 7.96 (d, 1H, H-6, $J_{H5\text{-}H6}$=7.5 Hz), 7.06 (m, 1H, H-1′), 6.65 (d, 1H, H-2′, $J_{H1'\text{-}H2'}$=1.8 Hz), 5.86 (d, 1H, H-5, $J_{H5\text{-}H6}$=7.5 Hz), 5.06 (m, 1H, H-4′), 3.83 (m, 2H, H-5′ and H-5″); ^{13}C NMR (CD_3OD): δ 167.88, 158.36 (C-4 and C-2), 143.51 (C-6), 136.84 (q, C-3′, $J_{C\text{-}F}$=36.4 Hz), 133.66 (d, C-2′, $J_{C\text{-}F}$=4.8 Hz), 122.49 (q, CF_3, $J_{C\text{-}F}$=268.4 Hz), 96.33 (C-5), 90.91 (C-1′), 86.40 (C-4′), 62.43 (C-5′); ^{19}F NMR (CD_3OD): δ -61.29 (s, CF_3); HRMS (FAB) calcd for $C_{10}H_{10}F_3N_3O_3$: $(M + Na)^+$ 300.0572, found: 300.0565.

Single Crystal X-ray Structure Determination of Compound 13. A colorless needle (0.07 x 0.08 x 0.66mm) was isolated from the sample and mounted with grease on the tip of a glass capillary epoxied to a brass pin and placed on the diffractometer with the long crystal dimension (c-axis) approximately parallel to the diffractometer ϕ-axis. Data were collected on an Enraf-Nonius CAD4 diffractometer (Mo K-α radiation, graphite monochromator) at 213K (cold N2 gas cooling) using θ-2θ scans. Intensity standards were measured at 2 h intervals. Net intensities were obtained by profile analysis of the 7467 data. Lorentz and polarization corrections were applied. No changes in the intensity standards were noted. Absorption was minimal and no correction was applied. Equivalent data were averaged yielding 2184 unique data [R-int = 0.053, 1749 > 4 *σ (F)]. Based on preliminary examination of the data, the space group P6(3) was assigned (no exceptions to the 001, l=odd systematic absence were noted). The computer programs from the MoLEN package were used for data reduction. The preliminary model

of the structure was obtained using XS, a direct methods program. Least-squares refining of the model vs. the data was done with the XL computer program. Illustrations were made with the XP program and tables were made with the XCIF program. All are in the SHELXTL v5.0 package. Thermal ellipsoids are drawn at the 35% level unless otherwise noted. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were included with a riding model using default values. The structure has an open channel along the c-axis that is partially occupied by disordered water molecules. Attempts to model the disordered water molecules were unsatisfactory. To correct for the contribution from the disordered water molecules, the data were treated with the SQUEEZE option[21] in the PLATON program package. The program calculated the occupancy of the disordered water to be 0.57.

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