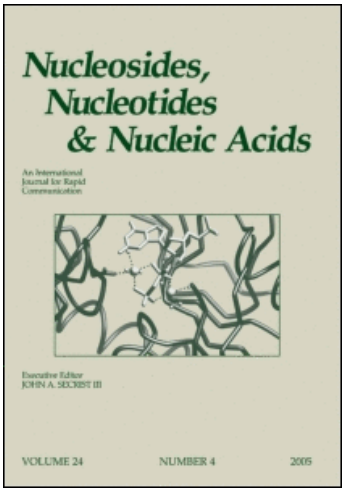

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Socrates C. H. Cavalcanti[a]; Yuejun Xiang[a]; M. Gary Newton[a]; Raymond F. Schinazi[b]; Yung-Chi Cheng[c]; Chung K. Chu[a]
[a] Center for Drug Discovery, Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy and Department of Chemistry, The University of Georgia, Athens, Georgia [b] Department of Pediatrics, Emory University School of Medicine Veterans Affairs Medical Center Decatur, Georgia [c] Department of Pharmacology, Yale School of Medicine, New Haven, Connecticut, USA

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SYNTHESIS OF 2',3'-DIDEOXY-2'-FLUORO-L-*threo*-PENTOFURANOSYL NUCLEOSIDES AS POTENTIAL ANTIVIRAL AGENTS

Sócrates C. H. Cavalcanti,[†] Yuejun Xiang,[†] M. Gary Newton,[†] Raymond F. Schinazi,[#] Yung-Chi Cheng,[‡] and Chung K. Chu[†*]

[†]*Center for Drug Discovery, Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy and Department of Chemistry, The University of Georgia, Athens, Georgia 30602;*
[#]*Department of Pediatrics, Emory University School of Medicine /Veterans Affairs Medical Center Decatur, Georgia 30033;*
and
[‡]*Department of Pharmacology, Yale School of Medicine, New Haven, Connecticut, 06510 USA.*

ABSTRACT: A series of 2',3'-dideoxy-2'-fluoro-L-*threo*-pentofuranosyl nucleosides has been synthesized as potential antiviral agents. The synthesized compounds were evaluated against HIV-1, HBV, HSV-1, and HSV-2. Among the synthesized analogues, only the cytosine derivative showed moderate antiviral activity against HIV and HBV.

Little attention had been given to unnatural L-nucleosides until the finding that (-)-β-L-1-[(2-hydroxymethyl)oxathiolan-5-yl]cytosine (3TC)[1,2] and (-)-β-L-2',3'-dideoxy-5-fluoro-2'-thiacytidine (FTC)[3,4] were found to be more active and less toxic than their (+)-D-isomers[4,5] against HIV-1 and hepatitis B virus (HBV).[6,7] Biochemically, some L-nucleosides are substrates for cellular kinases[8,9] and also have greater stability for catabolizing enzymes such as cytidine and adenosine deaminase,[10] thereby, providing higher anti-HIV and anti-HBV activities.[1] In addition to 3TC and FTC, (-)-β-L-dioxolanecytosine [(-)-OddC],[11,12] 2'-fluoro-5-methyl-β-arabinofuranosyl uridine (L-FMAU),[13,14] 2',3'-dideoxy-β-L-cytosine (L-ddC),[4,7] and 2',3'-dideoxy-β-L-5-fluorocytosine (L-FddC)[15,16] have demonstrated potent anti-HIV and anti-HBV activities. As 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (2'-F-Ara-ddA),[17] and 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (2'-F-Ara-ddC)[18] have shown to be potent against HIV, it was of interest to synthesize the corresponding L-nucleosides. In our preliminary studies we found that the 9-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine derivative was moderately active against HIV and HBV.[19] Therefore, herein we wish to report the comprehensive structure-activity relationships of 2',3'-dideoxy-2'-fluoro-L-*threo*-pentofuranosyl nucleosides.

CHEMISTRY

Synthesis of the key intermediate **7** was accomplished by a similar procedure reported for the preparation of D-isomer (Scheme I).[20] Compound **1** was synthesized according to the procedure published by Ma *et al.*[21] The reaction of **1** under Wolff-Kishner conditions gave the 3-deoxy derivative **4**.[22] The tosyl hydrazone derivative **2** was prepared by the reaction of **1** with *p*-toluenesulfonylhydrazide in EtOH in 71% yield. Reduction of **2** with $NaCNBH_3$ in methanol at pH 3 gave the reduced compound **3**, which was refluxed with $NaOAc.3H_2O$ in ethanol to obtain the deoxygenated compound **4** in 69% yield. Selective deprotection of the isopropylidene of compound **4** using 80% acetic acid at 100 °C for 4 h gave the diol **5** in 80% yield. Since the direct condensation of difluoro sugar **6** with a base gave low yield,[23] the compound **6** was brominated with 45% HBr/HOAc to the key intermediate **7**, which was condensed with bases. Once **7** is unstable, it was synthesized before the condensation step and readily used.

Pyrimidine nucleosides were prepared by the Hilbert-Johnson method (cytosine and thymine derivatives) or Vorbrüggen method (uracil derivatives) using TMSOTf as catalyst.[24] The 5'-benzoylated uracil derivatives **8-17** were synthesized by condensation of **7** with silylated 5-substituted uracil bases in dichloroethane (DCE) and catalytic amounts of TMSOTf to give an α, β-mixture, which was purified by silica gel column chromatography followed by separation by fractional recrystallization (uracil and fluorouracil). The anomers were individually deprotected by methanolic ammonia to afford the final uracil derivatives **25-34** (Scheme I). The condensation of **7** with silylated cytosine in dry CH_3CN gave the protected cytosine **18**, which was purified by silica gel column chromatography. Higher yields were obtained when DCE was used, instead of CH_3CN, for the preparation of 5-substituted cytosine derivatives **19-23**. Compounds **18-23** were then treated with methanolic ammonia to give the nucleoside derivatives **35-40** (Scheme I). Synthesis of the thymine derivative was accomplished by the condensation of **7** with silylated thymine in CH_3CN, followed by deprotection in methanolic ammonia yielding **41** as white crystals.

In order to prepare purine derivatives, silylated 6-chloropurine was condensed with **7** in the presence of TMSOTf to give an α, β mixture of **42** and **43**, which was separated by silica gel column chromatography (Scheme I). The inosine derivatives **46** and **47** were synthesized by refluxing compounds **42** and **43** with NaOMe and mercaptoethanol in methanol. The α- and β-6-chloropurine derivatives were also converted to adenine derivatives **48** and **49** by treatment with methanolic ammonia at 100 °C. Treatment of **42** and **43** with methylamine in methanol at 90 °C yielded N^6-methyladenine analogues **50** and **51**.

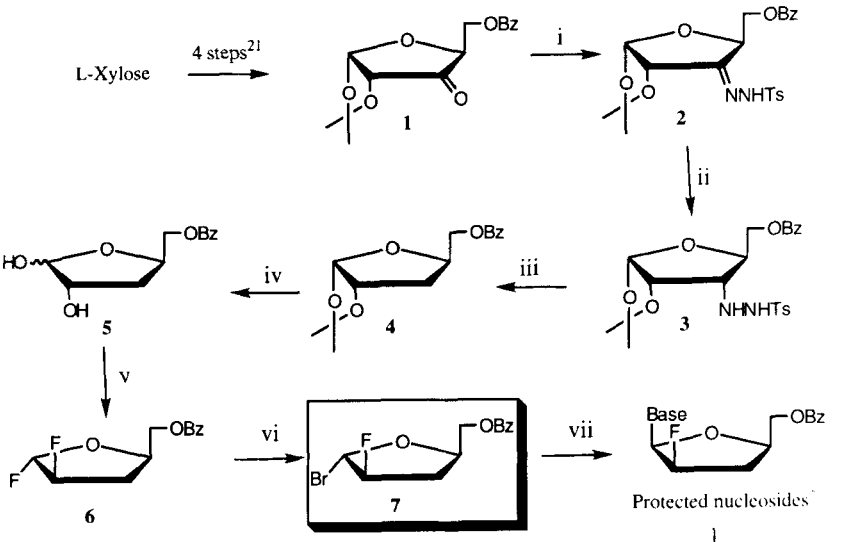
The key intermediate **7** was also used for the synthesis of the guanosine derivative. Condensation of **7** with 2-isobutyrylamino-6-chloropurine in the presence of TMSOTf gave an α, β-mixture **44** and **45**, which was readily separated by silica gel column chromatography. The guanosine derivatives were obtained by refluxing compounds **44** and **45** in similar conditions as for the inosine derivatives, to afford the β-isomer **52** as a white foam and the α-isomer **53** as white crystals.

The structure and stereochemistry of 5-fluoro-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (**19**) was also confirmed by X-ray crystallography (Figure I).[25]

ANTIVIRAL ACTIVITY

The synthesized nucleosides **25-41** and **46-53** were evaluated against HIV-1, HBV, HSV-1, and HSV-2. The antiviral activity was expressed by the concentration (μM) that inhibits

SCHEME 1



* Base = **8**: β-uracil
9: α-uracil
10: β-5-fluorouracil
11: α-5-fluorouracil
12: β-5-bromouracil
13: α-5-bromouracil
14: β-5-iodouracil
15: α-5-iodouracil
16: β-5-chlorouracil
17: α-5-chlorouracil
18: cytosine
19: 5-fluorocytosine
20: 5-bromocytosine
21: 5-iodocytosine
22: 5-methylcytosine
23: 5-chlorocytosine
24: thymine
42: β-6-chloropurine
43: α-6-chloropurine
44: β-2-isobutyrylamino-6-chloropurine
45: α-2-isobutyrylamino-6-chloropurine

** Base = **25**: β-uracil
26: α-uracil
27: β-5-fluorouracil
28: α-5-fluorouracil
29: β-5-bromouracil
30: α-5-bromouracil
31: β-5-iodouracil
32: α-5-iodouracil
33: β-5-chlorouracil
34: α-5-chlorouracil
35: cytosine
36: 5-fluorocytosine
37: 5-bromocytosine
38: 5-iodocytosine
39: 5-methylcytosine
40: 5-chlorocytosine
41: thymine
46: β-hypoxanthine
47: α-hypoxanthine
48: β-adenine
49: α-adenine
50: β-N^6-methyladenine
51: α-N^6-methyladenine
52: β-guanine
53: α-guanine

i) NH_2NHTs, EtOH; ii) $NaCNBH_3$, MeOH; iii) $NaOAc{\cdot}3H_2O$, EtOH; iv) OHAc (80 %, 100 °C); v) DAST, CH_2Cl_2; vi) 45 % HBr/OHAc, CH_2Cl_2; vii) Silylated base; viii) Deprotection.

50% of viral replication (Table I). Among these analogues, only the cytosine analogue **35** exhibited moderate anti-HIV-1 and anti-HBV activity *in vitro* with EC_{50} values of 16.2 and 4.0 μM in PBM cells and 2.2.15 cells, respectively. Other derivatives show neither significant antiviral activity nor cytotoxicity.

EXPERIMENTAL

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker 250 and AMX 400 MHz

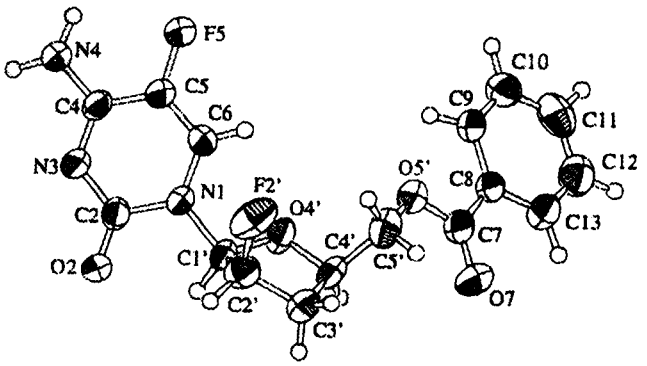


Figure I. Ortep plot of compound **19**.

spectrometers with tetramethylsilane as the internal reference; chemical shifts are reported in parts per million (δ), and the signals are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), dm (doublet of multiplet), and m (multiplet). UV spectra were obtained on a Beckman DU 650 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Low and high resolution mass spectra were obtained by Dr. Dennis R. Phillips and Dr. Michael Bartlett on a Ribermag R10-10C and a Micromass Inc. Autospec High Resolution double focusing sector (EBE) MS spectrometers. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. All reactions were monitored using thin layer chromatography on Analtech, 200 mm silica gel GF plates.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-*p*-toluenesulfonylhydrazone-α-L-*erythro*-pentofurano-3-ulose (2). A solution of **1** (30.00 g, 102.00 mmol) and *p*-toluenesulfonyl-hydrazide (21.00 g, 112.00 mmol) in absolute ethanol (150 mL) was refluxed for 2 h and then cooled to 0 °C. The white crystalline needles were filtered and washed with diethyl ether to give pure product **2** (33.50 g, 71%). mp 174-175 °C; IR (KBr) 1722, 1070 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.19 (s, 1H, NH, D_2O exch.); 7.70-7.05 (m, 9H, Ar-H); 5.98 (d, 1H, H-1, J = 4.6 Hz); 5.05-5.00 (m, 2H, H-2 and H-4); 4.68-4.28 (m, 2H, H-5); 2.35 (s, 3H, CH_3-Ar); 1.39 (s, 3H, CH_3); 1.18 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.5, 154.6, 143.6, 135.8, 133.7, 129.5, 129.4, 129.4, 128.9, 127.4, 112.9, 104.7, 76.5, 73.3, 65.7, 27.5, 27.3, 21.2; *Anal.* Calcd. for $C_{22}H_{24}N_2O_7S$: C, 57.38; H, 5.28; N, 6.08. Found: C, 57.49; H, 5.26; N, 6.06.

5-*O*-Benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*p*-toluenosulfonylhydrazino-α-L-ribofuranose (3). To a stirred solution of **2** (33.50 g, 72.80 mmol) in a mixture of THF and MeOH (400 mL, 1:1) was added a trace of methyl orange and sodium cyanoborohydride (4.41 g, 70.00 mmol). Saturated methanolic HCl was added dropwise keeping the color of the solution red yellow transition point during all the reaction time (pH = 3). The mixture was stirred at rt for 1 h. A second portion of $NaCNBH_3$ (2.52 g, 40.00 mmol) was added followed by dropwise addition of methanolic HCl to maintain pH at 3. The solution was stirred at rt for another hour, then neutralized with sat $NaHCO_3$, and concentrated to dryness. The residue was dissolved in H_2O (150 mL) and extracted with CH_2Cl_2 (3 X 150 mL). The organic layer was washed with brine (3

TABLE I. Antiviral activities and cytotoxicities of 2',3'-dideoxy-2'-fluoro-L-*threo*-pentofuranosyl nucleosides.

Number	HBV	HIV-1	HSV (I+II)	Cytotoxicity		
	EC_{50} (μM) (2.2.15)	EC_{50} (μM) (PBM)	IC_{50} (μM)	IC_{50} (μM) PBM	IC_{50} (μM) CEM	IC_{50} (μM) Vero
25	>10	155.0	>100	>100	>100	>100
26	>10	>100	>100	>100	>100	>100
27	>50	>100	>100	>100	>100	>100
28	>10	>100	>100	>100	>100	>100
29	>50	>100	>100	>100	>100	>100
30	>100	>100	>100	>100	>100	>100
31	>50	>100	>100	>100	>100	>100
32	>50	>100	>100	>100	>100	>100
33	>50	>100	>51	>100	>100	>100
34	>50	>100	>40	>100	61.1	>100
35	4.0	16.4	ND	>100	>100	>100
36	>10	48.0	>100	>100	>100	>100
37	>10	>100	>100	>100	>100	>100
38	>10	>100	>100	>100	>100	>100
39	>100	>100	>100	>100	>100	>100
40	>50	>100	>100	>100	>100	>100
41	>10	190	>100	>100	>100	>100
46	>10	>100	>100	>100	>100	>100
47	>10	>100	>100	>100	>100	>100
48	>10	>100	ND	>100	>100	>100
49	>100	ND*	>100	>100	>100	ND
50	>10	>100	>100	>100	>100	>100
51	>10	>100	>100	>100	>100	>100
52	ND	>100	>100	>100	>100	>100
53	>10	>100	>100	ND	>100	>100
AZT	>100	0.004	ND	>100	14.3	29.0

* Not determined

X 100 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to obtain the product **3** as a white solid, which was crystallized in methanol (31.50 g, 94%). mp 148-150 °C; IR (KBr) 1691, 1072 cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.18 (s, 1H, NH-Ar, D_2O exch.); 9.98 (s, 1H, NH, D_2O exch.); 7.74-7.06 (m, 9H, Ar-H); 5.99 (d, 1H, H-1, J = 3.7 Hz); 5.36-5.35 (m, 1H, H-2); 5.07 (s, 1H, H-4); 4.38-4.34 and 4.08-4.04 (m, 2H, H-5); 3.23-3.20 (m, 1H, H-3); 2.38 (s, 3H, CH_3-Ar); 2.09 (s, 3H, CH_3); 1.79 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 165.5, 143.3, 135.8, 133.7, 129.7, 129.5, 129.4, 128.9, 127.6, 127.4, 112.9, 104.6, 76.5, 73.3, 65.7, 27.5, 27.3, 25.1; *Anal.* Calcd. for $C_{22}H_{26}N_2O_7S$: C, 57.13; H, 5.67; N, 6.06. Found: C, 57.01; H, 5.61; N, 6.05.

5-*O*-Benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-L-*erythro*-pentofuranose (4). A mixture of **3** (31.10 g, 65.00 mmol) and sodium acetate trihydrate (35.50 g, 264.00 mmol) in absolute ethanol (700 mL) was refluxed for 1 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (300 mL), washed with brine (3 X 100 mL) and dried over Na_2SO_4. After concentration, the crude mixture was purified by silica gel column chromatography (20% EtOAc/hexanes) to give pure compound **4** as a clear syrup (13.00 g, 69%). $[\alpha]_D^{25}$ +10.5° (c 0.50, MeOH); IR (neat) 1720, 1068 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05 (d, 2H, Ar-

H, J = 8.3 Hz); 7.56 (t, 1H, Ar-H, J = 7.1 Hz); 7.43 (t, 2H, Ar-H, J = 7.5 Hz); 5.85 (d, 1H, H-1, J = 3.6 Hz); 4.76 (t, 1H, H-2, J = 4.2 Hz); 4.59-4.53 (m, 1H, H-4); 4.59-4.53 (m) and 4.40 (dd, 2H, H-5, J = 6.0 and 12.2 Hz); 2.19 (dd, 1H, H-3, J = 6.1 and 13.3 Hz) and 1.80 (m, 1H, H-3); 1.51 (s, 3H, CH_3); 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.6, 133.4, 130.1, 130.0, 128.7, 111.6, 106.0, 80.6, 76.1, 65.6, 35.7, 27.1, 26.4; *Anal.* Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.48; H, 6.54.

5-*O*-Benzoyl-3-deoxy-L-*erythro*-pentose (5). The mixture of **4** (10.00 g, 42.00 mmol) in 50 mL 80% HOAc was heated at 100 °C for 4 h. The solvent was removed under reduced pressure and coevaporated with toluene (2 X 30 mL). The syrup was purified by silica gel column chromatography (10% MeOH/$CHCl_3$) to give **5** as a white solid (6.80 g, 28.00 mmol, 68%), which was recrystallized from EtOAc and hexanes. mp 73-74 °C; IR (KBr) 3383, 3254, 1711, 1080 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.99 (d, 2H, Ar-H, J = 7.2 Hz); 7.64 (t, 1H, Ar-H, J = 6.7 Hz); 7.52 (d, 2H, Ar-H, J = 7.1 Hz); 6.17 (d, 1H, H-1, J = 4.5 Hz); 5.05 (bs, 2H, 3-OH, 2-OH, D_2O exch.); 4.33-4.22 (m, 3H, H-4 and H-5); 3.98-3.96 (m, 1H, H-2); 1.96-1.83 (m, 2H, H-3); ^{13}C NMR (DMSO-d_6) δ 166.0, 133.7, 130.0, 129.5, 129.0, 103.2, 76.1, 75.5, 68.5, 34.3; *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.43; H, 5.90.

5-*O*-Benzoyl-2,3-dideoxy-1,2-difluoro-α-L-*threo*-pentofuranosyl (6). To a solution of the sugar **5** (2.00 g, 8.80 mmol) in anhydrous CH_2Cl_2 (50 mL), DAST (6 mL, 45.40 mmol) was slowly added at -20 °C, and the reaction mixture was stirred at rt for 10 h, then the reaction mixture was cooled to 0 °C and quenched with methanol. The solvent was evaporated to dryness and the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to yield **6** (0.95 g, 46%) as a clear oil. $[\alpha]_D^{25}$ -46.8° (c 0.61, MeOH); IR(neat) 1724 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.07 (d, 2H, Ar-H, J = 7.3 Hz); 7.57 (t, 1H, Ar-H, J = 5.3 Hz); 7.43 (t, 2H, Ar-H, J = 7.6 Hz); 5.94 (dd, 1H, H-1, J = 5.2 and 59.5 Hz); 5.16 (ddd, 1H, H-2, J = 51.8, 2.4 and 5.1 Hz); 4.78 (m, 1H, H-4); 4.51-4.35 (m, 2H, H-5); 2.22-2.02 and 2.62-2.43 (m, 2H, H-3); ^{13}C NMR ($CDCl_3$) δ 166.7, 133.6, 130.1, 130.0, 120.8, 112.7 (dd, J = 220.8 and 34.2 Hz), 94.15 (dd, J = 180.0 and 40.7 Hz), 79.2, 66.2, 31.5 (d, J = 20.5 Hz); *Anal.* Calcd. for $C_{12}H_{12}F_2O_3$: C, 59.50; H, 4.99. Found: C, 59.33; H, 4.92.

5-*O*-Benzoyl-1-bromo-2,3-dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl (7). To a solution of **6** (0.36 g, 1.59 mmol) in CH_2Cl_2 (10.4 mL), was added 45% HBr/HOAc (1.73 mL, 9.61 mmol). The reaction mixture was stirred at rt for 1 h. After evaporation of the solvent and co-evaporation with toluene (2 X 26 mL), the crude mixture obtained was not purified and used directly for the next reaction.

General procedure for condensation of bromide 7 with 5-substituted uracils. A mixture of silylated uracil (2.10 g, 18.73 mmol), hexamethyldisilazane (HMDS) and a catalytic amount of $(NH_4)_2SO_4$ was refluxed for 4 h. The clear solution obtained was concentrated to dryness *in vacuo*. The residue of the brominated sugar **7**, which was prepared from bromination of **6** (1.34 g, 5.88 mmol) was taken up into dry DCE (35 mL) and added to the base, followed by addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.27 mL, 6.57 mmol) at 0 °C. Then the reaction mixture was refluxed for 20 h under nitrogen. After completion, the reaction mixture was washed with sat $NaHCO_3$ solution (100 mL), dried (Na_2SO_4), filtered through Celite pad and concentrated *in vacuo*. The crude mixture was purified by flash silica gel column chromatography (50% EtOAc/hexanes) to yield a mixture of α and β (0.73 g, 37%), which were separated by fractional recrystallization in DCE to afford **8** (0.24 g) and **9** (0.48 g).

1-(5-*O*-Benzoyl-2,3-dideoxy-2-fluoro-(β and α)-L-*threo*-pentofuranosyl)uracil (8

and **9**). **8**: mp 158-159 °C; $[\alpha]_D^{25}$ -122.5° (c 0.30, MeOH); UV (MeOH) λ_{max} 257.0 nm; IR (KBr) 3105, 3013, 1724, 1709, 1687, 1076 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.89 (bs, 1H, NH); 8.07 (d, 2H, Ar-H, *J* = 7.7 Hz); 7.63-7.45 (m, 4H, Ar-H and H-5); 6.07 (dd, 1H, H-1', *J* = 19.8 and 2.6 Hz); 5.71 (d, 1H, H-6, *J* = 8.1 Hz); 5.29 (d, 1H, H-2', *J* = 53.5 Hz); 4.60-4.51 (m, 3H, H-4' and H-5'); 2.71-2.32 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 165.0, 163.2, 149.8, 141.2, 133.8, 130.1, 129.7, 128.9, 102.2, 90.8 (d, *J* = 188.0 Hz), 86.7 (d, *J* = 16.1 Hz), 75.7, 65.9, 33.9 (d, *J* = 21.0 Hz); *Anal.* Calcd. for $C_{16}H_{15}FN_2O_5$: C, 57.51; H, 4.48; N, 8.38. Found: C, 57.32; H, 4.55; N, 8.43. **9**: mp 194-195 °C; $[\alpha]_D^{25}$ +41.1° (c 0.19, MeOH); UV (MeOH) λ_{max} 257.0 nm; IR (KBr) 3049, 1718, 1676, 1066 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.40 (bs, 1H, NH, D_2O exch.); 8.01 (d, 2H, Ar-H, *J* = 7.8 Hz); 7.68 (t, 1H, Ar-H, *J* = 7.2 Hz); 7.60 (d, 1H, H-5, *J* = 8.1 Hz); 7.55 (t, 2H, Ar-H, *J* = 7.7 Hz); 5.99 (d, 1H, H-6, *J* = 16.3 Hz); 5.59 (d, 1H, H-1', *J* =8.1 Hz); 5.51 (d, 1H, H-2', *J* = 52.9 Hz); 4.96-4.95 (m, 1H, H-4'); 4.42-4.35 (m, 2H, H-5'); 2.71-2.15 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 165.9, 163.7, 150.7, 141.5, 133.8, 129.7, 129.6, 129.1, 101.8, 96.6 (d, *J* = 178.4 Hz), 92.5 (d, *J* = 36.4 Hz), 80.0, 66.7, 32.9 (d, *J* = 20.4 Hz); *Anal.* Calcd. for $C_{16}H_{15}FN_2O_5$: C, 57.51; H, 4.48; N, 8.38. Found: C, 57.49; H, 4.51; N, 8.45.

5-Fluoro-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-(β and α)-L-*threo*-pentofuranosyl)uracil (10 and 11). 5-Fluorouracil (1.00 g, 7.68 mmol), **7** (0.55 g, 2.41 mmol), and TMSOTf (0.5 mL, 2.60 mmol) were reacted for 16 h to give a mixture of **10** and **11**, which was purified by flash silica gel column chromatography (50% EtOAc/hexanes) and separated by fractional recrystallization in EtOAc/MeOH (4:1) to yield **10** (0.12 g, 14%), and **11** (0.26 g, 30%) as white solids. **10**: mp 154-156 °C; $[\alpha]_D^{25}$ -91.9° (c 0.29, EtOAc); UV (EtOAc) λ_{max} 263.5 nm; IR (KBr) 1720, 1670, 1072 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.01 (s, 1H, NH, D_2O exch.); 7.98 (d, 2H, Ar-H, *J* = 8.3 Hz); 7.80 (dd, 1H, H-6, *J* = 7.0 and 1.7 Hz); 7.66 (t, 1H, Ar-H, *J* = 7.3 Hz); 7.52 (t, 2H, Ar-H, *J* = 7.6 Hz); 6.04 (d, 1H, H-1', *J* = 17.5 Hz); 5.30 (dd, 1H, H-2', *J* = 54.6 and 2.7 Hz); 4.58-4.47 (m, 3H, H-4' and H-5'); 2.76-2.60 and 2.26-2.15 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 166.0, 157.2 (d, *J* = 27.4 Hz), 149.0, 139.8 (d, *J* = 230.3 Hz), 133.9, 129.6, 129.5, 129.1, 125.7 (d, *J* = 34.6 Hz), 91.5 (d, *J* = 186.0 Hz), 85.6 (d, *J* = 14.6 Hz), 75.3, 66.1, 33.2 (d, *J* = 19.9 Hz); *Anal.* Calcd. for $C_{16}H_{14}F_2N_2O_5$: C, 54.57; H, 3.97; N, 7.95. Found: C, 54.50; H, 4.05; N, 7.92. **11**: mp 190-191 °C; $[\alpha]_D^{25}$ +28.3° (c 0.39, EtOAc); UV (EtOAc) λ_{max} 265.0 nm; IR (KBr) 1732, 1707, 1682, 1074 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.91 (s, 1H, NH, D_2O exch.); 7.99 (d, 2H, Ar-H, *J* = 8.3 Hz); 7.93 (d, 1H, H-6, *J* = 6.9 Hz); 7.66 (t, 1H, Ar-H, *J* = 8.2 Hz); 7.53 (t, 2H, Ar-H, 7.8 Hz); 5.94 (d, 1H, H-1', *J* = 15.6 Hz); 5.46 (dd, 1H, H-2', *J* = 52.7 and 5.1 Hz); 5.03-4.98 (m, 1H, H-4'); 4.39-4.30 (m, 2H, H-5'); 2.67-2.48 and 2.22-2.12 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 171.3, 162.4 (d, *J* = 26.2 Hz), 154.3, 145.0 (d, *J* = 230.6 Hz), 139.1, 134.9, 134.8, 134.4, 130.9 (d, *J* = 35.4 Hz), 96.8 (d, *J* = 185.0 Hz), 90.8 (d, *J* = 15.7 Hz), 80.5, 71.3, 38.4 (d, *J* = 20.0 Hz); *Anal.* Calcd. for $C_{16}H_{14}F_2N_2O_5$: C, 54.57; H, 3.97; N, 7.95. Found: C, 54.65; H, 4.03; N, 7.87.

5-Bromo-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-(β and α)-L-*threo*-pentofuranosyl)uracil (12 and 13). 5-Bromouracil (1.00 g, 5.23 mmol), **7** (0.53 g, 2.32 mmol), and TMSOTf (0.5 mL, 2.60 mmol) were reacted for 16 h to give a mixture of **12** and **13**, which was separated by flash silica gel column chromatography (50% EtOAc/hexanes) and recrystallized in EtOAc to afford **12** (0.15 g, 15%), and **13** (0.30 g, 31%) as white solids. **12**: mp 122-124 °C; $[\alpha]_D^{25}$ -51.6° (c 0.33, EtOAc); UV (EtOAc) λ_{max} 273.5 nm; IR (KBr) 1718,1070 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.01 (s, 1H, NH, D_2O exch.); 8.00 (d, 2H, Ar-H, *J* = 8.1 Hz);

7.89 (s, 1H, H-6); 7.67 (t, 1H, Ar-H, J = 8.3 Hz); 7.53 (t, 2H, Ar-H, J = 7.6 Hz); 6.04 (dd, 1H, H-1', J = 19.3 and 2.9 Hz); 5.28 (d, 1H, H-2', J = 54.6 Hz); 4.57-4.50 (m, 3H, H-4' and H-5'); 2.77-2.61 and 2.29-2.17 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 166.0, 159.3, 149.7, 140.5, 133.9, 129.7, 129.5, 129.1, 95.6, 91.5 (d, J = 185.8 Hz), 86.0 (d, J = 14.8 Hz), 75.5, 65.7, 33.1 (d, J = 20.1 Hz); *Anal.* Calcd. for $C_{16}H_{14}BrFN_2O_5$: C, 46.52; H, 3.38; N, 6.77. Found: C, 46.60; H, 3.44; N, 6.75. **13**: mp 158-160 °C; $[\alpha]_D^{25}$ +12.9° (c 0.43, EtOAc); UV (EtOAc) λ_{max} 274.0 nm; IR (KBr) 1714, 1072 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.90 (s, 1H, NH, D_2O exch.); 8.01 (d, 2H, Ar-H, J = 6.8 Hz); 7.98 (s, 1H, H-6); 7.66 (t, 1H, Ar-H, J = 7.5 Hz); 7.53 (t, 2H, Ar-H, J = 7.7 Hz); 5.94 (d, 1H, H-1', J = 16.4 Hz); 5.52 (dd, 1H, H-2', J = 53.0 and 5.3 Hz); 5.02-4.97 (m, 1H, H-4'); 4.40-4.30 (m, 2H, H-5'); 2.72-2.48 and 2.21-2.11 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 165.9, 159.7, 150.1, 141.0, 133.8, 129.7, 129.6, 129.1, 96.6 (d, J = 177.92 Hz), 96.2, 93.1 (d, J = 38.4 Hz), 80.2, 66.7, 32.4 (d, J = 20.5 Hz); *Anal.* Calcd. for $C_{16}H_{14}BrFN_2O_5$: C, 46.52; H, 3.38; N, 6.77. Found: C, 46.48; H, 3.45; N, 6.77.

5-Iodo-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-(β and α)-L-*threo*-pentofuranosyl)uracil (14 and **15**). 5-Iodouracil (1.50 g, 6.30 mmol), **7** (1.12 g, 4.90 mmol), and TMSOTf (0.25 mL, 1.30 mmol) were reacted for 16 h to give a mixture of **14** and **15**, which was separated by flash silica gel column chromatography (40% EtOAc/hexanes) and recrystallized in EtOAc to afford **14** (0.33 g, 14%), and **15** (0.39 g, 17%) as white solids. **14**: mp 160-162 °C; $[\alpha]_D^{25}$ -23.0° (c 0.23, MeOH); UV (MeOH) λ_{max} 280.5 nm; IR (KBr) 1701, 1072 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.86 (s, 1H, NH, D_2O exch.); 8.03 (d, 2H, Ar-H, J = 9.3 Hz); 7.92 (s, 1H, H-6); 7.67 (t, 1H, Ar-H, J = 7.3 Hz); 7.54 (t, 2H, Ar-H, J = 7.7 Hz); 5.27 (d, 1H, H-2', J = 57.9 Hz); 6.02 (dd, 1H, H-1', J = 19.7 and 2.9 Hz); 4.57-4.49 (m, 3H, H-4' and H-5'); 2.77-2.62 and 2.28-2.17 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 166.0, 160.7, 150.1, 145.3, 133.8, 129.7, 129.6, 129.2, 91.5 (d, J = 187.0 Hz), 85.9 (d, J = 15.9 Hz), 75.5, 69.2, 65.6, 33.1 (d, J = 20.1 Hz); *Anal.* Calcd. for $C_{16}H_{14}FIN_2O_5$: C, 41.76; H, 3.07; N, 6.09. Found: C, 41.64; H, 3.08; N, 6.10. **15**: 172-174 °C; $[\alpha]_D^{25}$ +4.3° (c 0.75, MeOH); UV (EtOAc) λ_{max} 277.5 nm; IR (KBr) 1709, 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.85 (s, 1H, NH, D_2O exch.); 8.10 (s, 1H, H-6); 8.09 (d, 2H, Ar-H, J = 7.7 Hz); 7.76 (t, 1H, Ar-H, J = 7.4 Hz); 7.62 (t, 2H, Ar-H, J = 7.6 Hz); 6.03 (d, 1H, H-1', J = 17.0 Hz); 5.62 (dd, 1H, H-2', J = 53.1 and 5.5 Hz); 5.08-5.02 (m, 1H, H-4'); 4.49-4.40 (m, 2H, H-5'); 2.83-2.67 and 2.29-2.18 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 165.9, 161.1, 150.5, 145.8, 133.8, 129.7, 129.6, 129.1, 96.6 (d, J = 179.0 Hz), 93.2 (d, J = 37.3 Hz), 80.2, 69.8, 66.6, 33.1 (d, J = 20.9 Hz); *Anal.* Calcd. for $C_{16}H_{14}FIN_2O_5$: C, 41.78; H, 3.07; N, 6.07. Found: C, 41.43; H, 3.10; N, 6.11.

5-Chloro-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-(β and α)-L-*threo*-pentofuranosyl)uracil (16 and **17**). 5-Chlorouracil (2.00 g, 13.60 mmol), **7** (0.93 g, 4.06 mmol), and TMSOTf (0.25 mL, 1.30 mmol) were reacted for 16 h to give a mixture of **16** and **17**, which was separated by flash silica gel column chromatography (40% EtOAc/hexanes) and recrystallized in EtOAc to afford **16** (0.30 g, 20%) and **17** (0.40 g, 26%) as white solids. **16**: mp 181-182 °C; $[\alpha]_D^{25}$ -69.1° (c 0.32, EtOAc); UV (EtOAc) λ_{max} 271.5 nm; IR (KBr) 1718, 1678, 1626, 1076 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.86 (s, 1H, NH, D_2O exch.); 7.82 (d, 2H, Ar-H, J = 8.1 Hz); 7.65 (d, 1H, H-6, J = 1.4 Hz); 7.49 (t, 1H, Ar-H, J = 7.2 Hz); 7.35 (t, 2H, Ar-H, J = 7.7 Hz); 5.87 (dd, 1H, H-1', J = 19.1 and 3.2 Hz); 5.12 (d, 1H, H-2', J = 58.1 Hz); 4.41-4.33 (m, 3H, H-4' and H-5'); 2.60-2.44 and 2.12-2.00 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 166.0, 159.1, 149.5, 138.2, 133.9, 129.7, 129.5, 129.1, 107.2, 91.5 (d, J = 186.1 Hz), 85.9 (d, J = 14.9 Hz), 75.5, 65.7, 33.1 (d, J = 19.4 Hz); *Anal.* Calcd. for $C_{16}H_{14}ClFN_2O_5$: C, 52.12; H,

3.83; N, 7.60. Found: C, 52.25; H, 3.87; N, 7.57. **17**: mp 170-171 °C; $[\alpha]_D^{25}$ +4.3° (c 0.34, EtOAc); UV (EtOAc) λ_{max} 272.5 nm; IR (KBr) 1709, 1072 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.94 (s, 1H, NH, D_2O exch.); 8.00 (d, 2H, Ar-H, *J* = 8.3 Hz); 7.97 (s, 1H, H-6); 7.67 (t, 1H, Ar-H, *J* = 8.3 Hz); 7.53 (t, 2H, Ar-H, *J* = 7.6 Hz); 5.95 (d, 1H, H-1', *J* = 16.2 Hz); 5.50 (dd, 1H, H-2', *J* = 52.8 and 5.2 Hz); 5.01-4.99 (m, 1H, H-4'); 4.40-4.31 (m, 2H, H-5'); 2.71-2.48 and 2.21-2.11 (m, 2H, H-3'); ^{13}C NMR (DMSOd_6) δ 165.3, 159.0, 149.3, 138.0, 133.2, 129.2, 129.0, 128.5, 107.1, 96.0 (d, *J* = 178.9 Hz), 92.4 (d, *J* = 37.1 Hz), 79.7, 66.1, 32.2 (d, *J* = 20.5 Hz); *Anal.* Calcd. for $C_{16}H_{14}ClFN_2O_5$: C, 52.12; H, 3.83; N, 7.60. Found: C, 52.09; H, 3.85; N, 7.60.

General procedure for condensation of bromide 7 with 5-substituted cytosines and thymine.

Method A: Cytosine (0.33 g, 3.00 mmol) was suspended in dry CH_3CN (20 mL), treated with *N,O-bis*(trimethylsilyl)trifluoroacetamide (BSTFA, 6 mL), and stirred at rt for 30 min. Volatiles were distilled from the homogeneous mixture and the resultant solid was dried under vacuum. The residue of the brominated sugar **7** (0.21 g, 0.86 mmol) was taken up into dry DCE (15 mL) and added to the base, then the reaction mixture was refluxed for 16 h under N_2. After cooling, the solvent was removed and the residue was purified by preparative TLC (10% MeOH/$CHCl_3$) to provide **18** as a solid (0.13 g, 45%) after coevaporation with hexanes.

1-(5-*O*-Benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (18). UV (MeOH) λ_{max} 271.5 nm; ^1H NMR ($CDCl_3$): δ 8.25 (d, 2H, Ar-H, *J* =5.9 Hz); 7.75 (d, 1H, H-6, *J* = 7.4 Hz); 7.61 (t, 1H, Ar-H, *J* = 7.3 Hz); 7.48 (t, 2H, Ar-H, *J* = 7.4 Hz); 6.06 (d, 1H, H-1', *J* = 19.4 Hz); 5.82 (d, 1H, H-5, *J* = 7.5 Hz); 5.78 (s, 2H, NH_2, D_2O exch.); 5.31 (dm, 1H, H-2', *J* = 54.0 Hz); 4.59 (m, 3H, H-4' and H-5'); 2.80-2.23 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 166.8, 161.9, 163.8, 145.2, 133.7, 130.1, 129.9, 129.0, 96.8, 90.8 (d, *J* = 189.1 Hz), 88.0 (d, *J* = 16.3 Hz), 75.0, 65.5, 34.0 (d, *J* = 21.0 Hz); *Anal.* Calcd. for $C_{16}H_{16}FN_3O_4 \cdot 0.13CHCl_3$: C, 55.56; H, 4.62; N, 12.04. Found: C, 55.90; H, 4.98; N, 11.68.

Method B: A mixture of 5-fluorocytosine (0.90 g, 6.97 mmol), hexamethyldisilazane (20 mL), and a catalytic amount of $(NH_4)_2SO_4$ was refluxed for 2 h under nitrogen. The clear solution obtained was concentrated to dryness *in vacuo*. The residue of the brominated sugar **7** (0.90 g, 3.73 mmol) was taken up into dry DCE (20 mL) and added to the base. The reaction mixture was refluxed for 6 h under nitrogen, washed with sat $NaHCO_3$ solution (30 mL), dried (Na_2SO_4), filtered through Celite pad and concentrated *in vacuo*. The crude mixture was purified by flash silica gel column chromatography (3% MeOH/$CHCl_3$) and recrystallized in hexanes/EtOAc/MeOH (2:1:1) to obtain **19** (0.96 g, 73%) as white crystals.

5-Fluoro-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl) cytosine (19). mp 167-168 °C; $[\alpha]_D^{25}$ -35.3° (c 0.70, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 284.0 nm; IR (KBr) 3437, 1722, 1680, 1066 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.08 (dd, 2H, Ar-H, *J* = 7.9 and 1.3 Hz); 7.72 (dd, 1H, H-6, *J* = 6.3 and 1.4 Hz); 7.59 (t, 1H, Ar-H, *J* = 7.3 Hz);7.46 (t, 3H, Ar-H and NH_2, *J* = 7.6 Hz, D_2O exch.); 6.07 (dt, 1H, H-1', *J* = 19.9 and 1.9 Hz); 5.53 (s, 1H, NH_2, D_2O exch.); 5.33 (dm, 1H, H-2', *J* = 53.5 Hz); 4.63-4.49 (m, 3H, H-4' and H-5'); 2.68-2.29 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 166.7, 158.5 (d, *J* = 13.7 Hz), 154.1, 136.5 (d, *J* = 241.3 Hz), 133.7, 130.1, 129.9, 128.9, 126.9 (d, *J* = 33.1 Hz), 90.5 (d, *J* = 187.8 Hz), 87.8 (d, *J* = 16.3 Hz), 75.7, 66.1, 34.0 (d, *J* = 21.0 Hz); *Anal.* Calcd. for $C_{16}H_{15}F_2N_3O_4$: C, 54.73; H, 4.27; N, 11.96. Found: C, 54.74; H, 4.28; N, 12.06.

5-Bromo-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl) cytosine (20). 5-Bromocytosine (0.90 g, 4.74 mmol), hexamethyldisilazane (20 mL) and a

catalytic amount of $(NH_4)_2SO_4$ were refluxed for 2 h under nitrogen. The crude mixture was purified by flash silica gel column chromatography (3% MeOH/CH_2Cl_2) and recrystallized in EtOAc:CH_2Cl_2:hexanes (2:1:1) to obtain (0.72 g, 75%) of **20** as white crystals. mp 124-125 °C; $[\alpha]_D^{25}$ -75.2° (c 0.66, $CHCl_3$); UV ($CHCl_3$) λ_{max} 289.0 nm; IR (KBr) 3414, 1716, 1633, 1074 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.41 (s, 1H, NH_2, D_2O exch.); 8.09 (d, 2H, Ar-H, *J* = 8.6 Hz); 7.91 (d, 1H, H-6, *J* = 1.2 Hz); 7.58 (t, 1H, Ar-H, *J* = 7.4 Hz); 7.46 (t, 2H, Ar-H, *J* = 9.5 Hz); 6.09 (dd, 1H, H-1', *J* = 19.8 and 2.6 Hz); 5.78 (s, 1H, NH_2, D_2O exch.); 5.33 (dm, 1H, H-2', *J* = 53.5 Hz); 4.62-4.51 (m, 3H, H-4' and H-5'); 2.70-2.30 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 166.8, 162.9, 154.7, 142.7, 133.7, 130.1, 129.9, 128.9, 89.9 (d, *J* = 188.4 Hz), 88.1, 87.8 (d, *J* = 23.0 Hz), 75.9, 66.0, 34.0 (d, *J* = 20.9 Hz) *Anal.* Calcd. for $C_{16}H_{15}BrFN_3O_4$: C, 46.63; H, 3.64; N, 10.19. Found: C, 46.73; H, 3.65; N, 10.24.

5-Iodo-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (21). 5-Iodocytosine (1.20 g, 5.06 mmol), hexamethyldisilazane (20 mL), and a catalytic amount of $(NH_4)_2SO_4$ were refluxed for 2 h under nitrogen. The crude mixture was purified by flash silica gel column chromatography (3% MeOH/EtOAc) and recrystallized in EtOAc to obtain (0.76 g, 58%) of **21** as a white foam. mp 104-106 °C; $[\alpha]_D^{25}$ -50.5° (c 0.64, $CHCl_3$); IR (KBr) 3453, 1722, 1651, 1070 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.10 (dd, 3H, Ar-H and NH_2, *J* = 8.7 and 1.4 Hz, D_2O exch.); 7.99 (d, 1H, H-6, *J* = 1.5 Hz); 7.59 (t, 1H, Ar-H, *J* = 7.4 Hz); 7.47 (t, 2H, Ar-H, *J* = 7.5 Hz); 6.08 (dd, 1H, H-1', *J* = 19.8 and 2.6 Hz); 5.68 (s, 1H, NH_2, D_2O exch.); 5.33 (dm, 1H, H-2', *J* = 53.5 Hz); 4.62-4.51 (m, 3H, H-4' and H-5'); 2.70-2.31 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 166.8, 164.2, 154.8, 148.3, 133.7, 130.2, 129.9, 129.0, 90.4 (d, *J* = 189.0 Hz), 88.0 (d, *J* = 16.9 Hz), 75.9, 65.9, 56.3, 34.0 (d, *J* = 20.6 Hz); *Anal.* Calcd. for $C_{16}H_{15}FIN_3O_4$: C, 41.86; H, 3.26; N, 9.15. Found: C, 41.82; H, 3.37; N, 9.08.

5-Methyl-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl) cytosine (22). 5-Methylcytosine (1.00 g, 7.99 mmol), hexamethyldisilazane (20 mL), and a catalytic amount of $(NH_4)_2SO_4$ were refluxed for 2 h under nitrogen. The crude mixture was purified by preparative TLC (10% MeOH/CH_2Cl_2) and recrystallized in EtOAc to obtain **22** (0.29 g, 40%) as white crystals. mp 98-100 °C; $[\alpha]_D^{25}$ -99.5° (c 0.31, $CHCl_3$); UV ($CHCl_3$) λ_{max} 282.5 nm; IR (KBr) 1718, 1660, 1070 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.09 (d, 2H, Ar-H, *J* = 8.1 Hz); 7.59 (m, 1H, Ar-H); 7.48 (s, 1H, H-6); 7.46 (t, 2H, Ar-H, *J* = 9.5 Hz); 6.14 (dd, 1H, H-1', *J* = 20.6 and 2.6 Hz); 5.32 (dm, 1H, H-2', *J* = 53.6 Hz); 5.25 (s, 2H, NH_2, D_2O exch.); 4.61-4.49 (m, 3H, H-4' and H-5'); 2.67-2.29 (m, 2H, H-3'); 1.90 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 165.9, 156.1, 140.0, 133.7, 130.1, 130.0, 128.9, 101.3, 91.1 (d, *J* = 187.0 Hz), 87.7 (d, *J* = 16.0 Hz), 75.4, 66.2, 34.1 (d, *J* = 20.6 Hz), 13.5; *Anal.* Calcd. for $C_{17}H_{18}FN_3O_4$: C, 56.73; H, 5.43; N, 11.67. Found: C, 56.60; H, 5.45; N, 11.67.

5-Chloro-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl) cytosine (23). 5-Chlorocytosine (1.00 g, 6.86 mmol), hexamethyldisilazane (20 mL), and a catalytic amount of $(NH_4)_2SO_4$ were refluxed for 2 h under nitrogen. The crude mixture was purified by flash silica gel column chromatography (1% MeOH/EtOAc) and recrystallized in EtOAc to obtain **23** (0.26 g, 33%) as white crystals. mp 84-86 °C; $[\alpha]_D^{25}$ -97.8° (c 0.45, EtOAc); UV ($CHCl_3$) λ_{max} 283.0 nm; IR (KBr) 1720, 1645, 1070 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.99 (dd, 2H, Ar-H, *J* = 8.4 and 1.3 Hz); 7.97 (s, 1H, NH_2, D_2O exch.); 7.73 (s, 1H, H6); 7.66 (t, 1H, Ar-H, *J* = 6.2 Hz); 7.54 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.33 (s, 1H, NH_2, D_2O exch.); 5.99 (dd, 1H, H-1', *J* = 19.5 and 2.9 Hz); 5.26 (dd, 1H, H-2', *J* = 54.6 and 3.3 Hz); 4.54-4.49 (m, 3H, H-4' and H-5'); 2.77-2.16 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 166.1, 161.8, 153.4, 139.6, 133.9, 129.7,

129.5, 129.1, 99.0, 91.2 (d, J = 185.3 Hz), 86.8 (d, J = 15.3 Hz), 75.3, 65.9, 33.3 (d, J = 20.7 Hz); *Anal.* Calcd. for $C_{16}H_{15}ClFN_3O_4 \cdot 0.7H_2O$: C, 50.52; H, 4.35; N, 11.05. Found: C, 50.45; H, 4.34; N, 11.07.

1-(5-*O*-Benzoyl-2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)thymine (24). Thymine (0.65 g, 5.19 mmol) was suspended in dry CH_3CN (34.6 mL), treated with BSTFA (6 mL), and stirred at rt for 30 min under nitrogen. The crude mixture was purified by preparative TLC (5% MeOH/$CHCl_3$) to yield **24** (0.20 g, 36%) as a white solid. mp 152-153 °C; $[\alpha]_D^{25}$ -104.9° (c 0.07, MeOH); UV (MeOH) λ_{max} 265 nm; IR (KBr) 3190, 1718, 1662, 1070 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.40 (bs, 1H, NH, D_2O exch.); 8.02 (d, 2H, Ar-H, J = 8.0 Hz); 7.68 (t, 1H, Ar-H, J = 8.0 Hz); 7.55 (t, 2H, Ar-H, J = 8.0 Hz); 7.39 (s, 1H, H-6); 6.06 (dd, 1H, H-1', J = 20.0 and 4.0 Hz); 5.29 (d, 1H, H-2', J = 64.0 Hz); 4.57-4.48 (m, 3H, H-4' and H-5'); 2.79-2.19 (m, 2H, H-3'); 1.63 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 163.7, 161.5, 148.1, 134.5, 131.6, 127.4, 127.2, 126.8, 106.4, 89.3 (d, J = 186.5 Hz), 83.0 (d, J = 15.4 Hz), 72.6, 63.5, 31.0 (d, J = 19.9 Hz), 9.99; *Anal.* Calcd. for $C_{17}H_{17}FN_2O_5$: C, 58.65; H, 4.88; N, 8.04. Found: C, 58.34; H, 4.95; N, 7.99.

General procedure for debenzoylation.

A solution of **8** (0.15 g, 0.45 mmol) was stirred in sat methanolic ammonia in a steel bomb at rt for 48 h, the solvent was removed under vacuum and the residue was purified by preparative TLC (10% MeOH/$CHCl_3$) to yield white crystals **25** (0.09 g, 89%), which was recrystallized from a mixture of ethyl acetate and hexanes (2:1).

1-(2,3-Dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)uracil (25). mp 140-141 °C; $[\alpha]_D^{25}$ -110.7° (c 0.09, MeOH); UV (H_2O) λ_{max} 260.5 nm (ε 7570) (pH 2); 260.5 nm (ε 9980) (pH 7); 260.5 nm (ε 5800) (pH 11); IR (KBr) 3439, 3190, 1713, 1686, 1051, 1039 cm^{-1}; MS (ESI) *m/e* 230.8 $(MH)^+$; ^1H NMR (DMSO-d_6): δ 11.42 (s, 1H, NH, D_2O exch.); 7.75 (d, 1H, H-5, J = 8.1 Hz); 5.96 (dd, 1H, H-1', J = 16.8 and 3.6 Hz); 5.62 (dd, 1H, H-6, J = 8.1 and 1.86 Hz); 5.28 (dm, 1H, H-2', J = 54.9 Hz); 5.02 (bs, 1H, OH); 4.12-4.06 (m, 1H, H-4'); 3.59-3.48 (m, 2H, H-5'); 2.53-1.98 (m, 2H, H-3'); ^{13}C NMR (D_2O) δ 143.0, 135.6, 127.8, 101.6, 91.6 (d, J = 186.0 Hz), 86.2 (d, J = 16.0 Hz), 78.5, 63.6, 32.7 (d, J = 20.3 Hz); *Anal.* Calcd. for $C_9H_{11}FN_2O_4$: C, 46.98; H, 4.78; N, 12.17. Found: C, 47.02; H, 4.83; N, 12.11.

1-(2,3-Dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)uracil (26). 9 (0.22 g, 0.66 mmol) was debenzoylated and the residue was purified by preparative TLC (10% MeOH/$CHCl_3$) to yield **26** (0.09 g, 89%) as a hygroscopic amorphous powder, which was triturated with diethyl ether. $[\alpha]_D^{25}$ +40.1° (c 0.11, MeOH); UV (H_2O) λ_{max} 260.5 nm (ε 8200) (pH 2); 261.5 nm (ε 10300) (pH 7); 260.5 nm (ε 7750) (pH 11); IR (KBr) 3258, 2966, 1705, 1664, 1059 cm^{-1}; MS (ESI) *m/e* 230.8 MH^+; ^1H NMR (DMSO-d_6): δ 11.38 (s, 1H, NH, D_2O exch.); 7.53 (d, 1H, H-5, J = 7.76 Hz); 5.88 (d, 1H, H-1', J = 15.32 Hz); 5.58 (d, 1H, H-6, J = 7.75 Hz); 5.40 (d, 1H, H-2', J = 52.7 Hz); 4.94 (s, 1H, OH, D_2O exch.); 4.53 (s, 1H, H-4'); 3.59-3.38 (m, 2H, H-5'); 2.44-1.99 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 163.7, 150.6, 141.2, 101.8, 96.6 (d, J = 177.7 Hz), 91.83 (d, J = 35.9 Hz), 82.9, 63.9, 32.4 (d, J = 19.9 Hz); *Anal.* Calcd. for $C_9H_{11}FN_2O_4$: C, 46.90; H, 4.70; N, 12.11. Found: C, 47.08; H, 4.77; N, 12.05.

5-Fluoro-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)uracil (27). 10 (0.04 g, 0.11 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (10% MeOH/$CHCl_3$) to yield **27** (0.03 g, 90%) which was recrystallized from methanol. mp 156-157 °C; $[\alpha]_D^{25}$ -147.3° (c 0.14, MeOH); UV (H_2O) λ_{max} 266.5 nm (ε 9460) (pH 2); 267.0 nm (ε 8950) (pH 7); 266.5 nm (ε 7060) (pH 11); IR (KBr) 1709 cm^{-1}; MS (FAB)

m/e 249 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 11.79 (s, 1H, NH, D_2O exch.); 7.95 (dd, 1H, H-6, *J* = 7.1 and 1.0 Hz); 5.77 (dm, 1H, H-1', *J* = 15.1 Hz); 5.13 (dm, 1H, H-2', *J* = 54.8 Hz); 4.95 (t, 1H, OH, D_2O exch.); 3.94-3.89 (m, 1H, H-4'); 3.46-3.29 (m, 2H, H-5'); 2.33-2.19 and 1.95-1.82 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 157.3 (d, *J* = 26.2 Hz), 149.0, 139.7 (d, *J* = 229.3 Hz), 126.0 (d, *J* = 34.6 Hz), 91.6 (d, *J* = 186.8 Hz), 85.0 (d, *J* = 16.1 Hz), 78.3, 62.4, 32.1 (d, *J* = 19.9 Hz); *Anal.* Calcd. for $C_9H_{10}F_2N_2O_4$: C, 43.56; H, 4.06; N, 11.29. Found: C, 43.47; H, 4.06; N, 11.19.

5-Fluoro-1-(2,3-dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)uracil (28). 11 (0.09 g, 0.25 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (10% MeOH/$CHCl_3$) to yield **28** (0.06 g, 96%) as a hygroscopic amorphous powder, which was triturated with EtOAc. $[\alpha]_D^{25}$ +2.4° (c 0.54, MeOH); UV (H_2O) λ_{max} 268.0 nm (ε 7700) (pH 2); 267.0 nm (ε 5200) (pH 7); 268.0 nm (ε 8300) (pH 11); IR (KBr) 1716 cm^{-1}; MS (FAB) *m/e* 249 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 11.92 (s, 1H, NH, D_2O exch.); 7.88 (d, 1H, H-6, *J* = 6.9 Hz); 5.88 (d, 1H, H-1', *J* = 15.0 Hz); 5.41 (dd, 1H, H-2', *J* = 52.7 and 5.1 Hz); 4.97 (t, 1H, OH, D_2O exch.); 4.63-4.60 (m, 1H, H-4'); 3.50-3.33 (m, 2H, H-5'); 2.48-2.32 and 2.12-2.01 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 157.6 (d, *J* = 26.3 Hz), 149.2, 140.4 (d, *J* = 229.7 Hz), 125.4 (d, *J* = 34.7 Hz), 96.5 (d, *J* = 179.0 Hz), 91.6 (d, *J* = 35.7 Hz), 82.9, 63.9, 32.1 (d, *J* = 19.8 Hz); *Anal.* Calcd. for $C_9H_{10}F_2N_2O_4 \cdot 0.4EtOAc$: C, 44.92; H, 4.69; N, 9.88. Found: C, 45.07; H, 4.74; N, 9.99.

5-Bromo-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)uracil (29). 12 (0.10 g, 0.24 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (10% MeOH/$CHCl_3$) to yield **29** (0.07 g, 91%) which was recrystallized from methanol/EtOAc (2:1). mp 154-156 °C; $[\alpha]_D^{25}$ -93.9° (c 0.24, MeOH); UV (H_2O) λ_{max} 278.0 nm (ε 8770) (pH 2); 278.0 nm (ε 8120) (pH 7); 275.0 nm (ε 5840) (pH 11); IR (KBr) 1714, 1674 cm^{-1}; MS (FAB) *m/e* 309 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 12.04 (s, 1H, NH, D_2O exch.); 8.32 (s, 1H, H-6); 6.03 (dd, 1H, H-1', *J* = 15.0 and 3.8 Hz); 5.39 (dm, 1H, H-2', *J* = 54.9 Hz); 5.25 (t, 1H, OH, D_2O exch.); 4.19-4.15 (m, 1H, H-4'); 3.73-3.53 (m, 2H, H-5'); 2.56-2.45 and 2.21-2.05 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 159.4, 149.8, 140.9, 127.8, 91.6 (d, *J* = 186.0 Hz), 85.2 (d, *J* = 16.0 Hz), 78.4, 62.2, 32.0 (d, *J* = 20.2 Hz); *Anal.* Calcd. for $C_9H_{10}BrFN_2O_4 \cdot 0.1EtOAc$: C, 35.52; H, 3.42; N, 8.81. Found: C, 35.48; H, 3.32; N, 9.06.

5-Bromo-1-(2,3-dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)uracil (30). 13 (0.12 g, 0.29 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (5% MeOH/$CHCl_3$) to yield **30** (0.08 g, 86%) as a white solid. mp 148-149 °C; $[\alpha]_D^{25}$ -12.2° (c 0.24, MeOH); UV (H_2O) λ_{max} 279.0 nm (ε 9220) (pH 2); 278.5 nm (ε 8620) (pH 7); 275.0 nm (ε 7000) (pH 11); IR (KBr) 1697 cm^{-1}; MS (FAB) *m/e* 309 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 11.90 (s, 1H, NH, D_2O exch.); 7.96 (s, 1H, H-6); 5.87 (d, 1H, H-1', *J* = 15.7 Hz); 5.46 (dd, 1H, H-2', *J* = 53.1 Hz); 4.95 (t, 1H, OH, D_2O exch.); 4.62-4.56 (m, 1H, H-4'); 3.50-3.38 (m, 2H, H-5'); 2.51-2.37 and 2.09-1.98 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 159.7, 150.1, 140.7, 132.9, 96.8 (d, *J* = 137.2 Hz), 92.4 (d, *J* = 36.8 Hz), 83.2, 63.8, 32.4 (d, *J* = 20.3 Hz); *Anal.* Calcd. for $C_9H_{10}BrFN_2O_4$: C, 34.97; H, 3.26; N, 9.06. Found: C, 35.08; H, 3.28; N, 8.99.

5-Iodo-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)uracil (31). 14 (0.17 g, 0.36 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (5% MeOH/$CHCl_3$) to yield **31** (0.09 g, 69%) as a white solid, which was recrystallized from methanol. mp 176-178 °C; $[\alpha]_D^{25}$ -67.0° (c 0.31, MeOH); UV (H_2O) λ_{max}

285.0 nm (ε 6100) (pH 2); 286.5 nm (ε 5950) (pH 7); 276.5 nm (ε 5310) (pH 11); IR (KBr) 1714 cm^{-1}; MS (ESI) *m/e* 357 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 11.83 (s, 1H, NH, D_2O exch.); 8.25 (s, 1H, H-6); 5.97 (dd, 1H, H-1', *J* = 15.2 and 3.9 Hz); 5.33 (dm, 1H, H-2', *J* = 54.9 Hz); 5.18 (t, 1H, OH, *J* = 5.6 Hz, D_2O exch.); 4.15-4.10 (m, 1H, H-4'); 3.67-3.48 (m, 2H, H-5'); 2.53-2.39 and 2.15-2.02 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 160.7, 150.2, 145.6, 91.6 (d, *J* = 187.2 Hz), 85.1 (d, *J* = 15.7 Hz), 78.3, 68.9, 62.2, 32.1 (d, *J* = 19.8 Hz); *Anal.* Calcd. for $C_9H_{10}FIN_2O_4$: C, 30.36; H, 2.83; N, 7.87. Found: C, 30.46; H, 2.90; N, 7.72.

5-Iodo-1-(2,3-dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)uracil (32). 15 (0.16 g, 0.34 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (5% MeOH/$CHCl_3$) to yield **32** (0.10 g, 82%) as a white solid. mp 156-158 °C; $[\alpha]_D^{25}$ -23.8° (c 0.31, MeOH); UV (H_2O) λ_{max} 287.0 nm (ε 7100) (pH 2); 286.5 nm (ε 6680) (pH 7); 278.5 nm (ε 5370) (pH 11); IR (KBr) 1714, 1664, 1068 cm^{-1}; MS (ESI) *m/e* 357 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 11.74 (s, 1H, NH, D_2O exch.); 7.92 (s, 1H, H-6); 5.85 (d, 1H, H-1', *J* = 16.1 Hz); 5.44 (dd, 1H, H-2', *J* = 53.2 and 4.6 Hz); 4.92 (s, 1H, OH, D_2O exch.); 4.56-4.51 (m, 1H, H-4'); 3.44-3.42 (m, 2H, H-5'); 2.51-2.36 and 2.07-1.95 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 161.1, 150.5, 145.4, 96.6 (d, *J* = 178.7 Hz), 92.5 (d, *J* = 36.7 Hz), 83.2, 69.7, 63.8, 32.6 (d, *J* = 20.1 Hz); *Anal.* Calcd. for $C_9H_{10}FIN_2O_4$: C, 30.36; H, 2.83; N, 7.87. Found: C, 30.85; H, 2.81; N, 7.74.

5-Chloro-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)uracil (33). 16 (0.13 g, 0.35 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (10% MeOH/$CHCl_3$) to yield **33** (0.09 g, 97%) as white crystals, which was recrystallized from methanol. mp 160-162 °C; $[\alpha]_D^{25}$ -101.7° (c 0.20, MeOH); UV (H_2O) λ_{max} 275.5 nm (ε 9350) (pH 2); 274.5 nm (ε 8540) (pH 7); 273.0 nm (ε 6110) (pH 11); IR (KBr) 1714, 1682 cm^{-1}; MS (FAB) *m/e* 265 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 12.02 (s, 1H, NH, D_2O exch.); 8.20 (s, 1H, H-6); 5.98 (dd, 1H, H-1', *J* = 15.0 Hz); 5.34 (dm, 1H, H-2', *J* = 54.9 Hz); 5.19 (t, 1H, OH, D_2O exch.); 4.13-4.12 (m, 1H, H-4'); 3.67-3.49 (m, 2H, H-5'); 2.54-2.40 and 2.16-2.03 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 159.2, 149.6, 138.6, 107.0, 91.6 (d, *J* = 187.2 Hz), 85.2 (d, *J* = 15.7 Hz), 78.4, 62.3, 32.0 (d, *J* = 20.2 Hz); *Anal.* Calcd. for $C_9H_{10}ClFN_2O_4$: C, 40.85; H, 3.81; N, 10.59. Found: C, 40.95; H, 3.80; N, 10.52.

5-Chloro-1-(2,3-dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)uracil (34). 17 (0.10 g, 0.27 mmol) was debenzoylated and the residue was purified by flash silica gel column chromatography (10% MeOH/$CHCl_3$) to yield **34** (0.05 g, 66%) as a white solid. mp 60-62 °C; $[\alpha]_D^{25}$ -0.8° (c 0.21, MeOH); UV (H_2O) λ_{max} 277.0 nm (ε 8670) (pH 2); 276.0 nm (ε 9200) (pH 7); 273.5 nm (ε 6110) (pH 11); IR (KBr) 1707 cm^{-1}; MS (FAB) *m/e* 265 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 11.95 (s, 1H, NH, D_2O exch.); 7.90 (s, 1H, H-6); 5.88 (d, 1H, H-1', *J* = 15.4 Hz); 5.45 (dd, 1H, H-2', *J* = 52.7 and 5.0 Hz); 4.96 (s, 1H, OH, D_2O exch.); 4.63-4.60 (m, 1H, H-4'); 3.49-3.40 (m, 2H, H-5'); 2.51-2.36 and 2.10-2.00 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 159.6, 149.8, 138.3, 107.6, 96.6 (d, *J* = 178.4 Hz), 92.3 (d, *J* = 35.6 Hz), 83.2, 63.8, 32.3 (d, *J* = 19.3 Hz); *Anal.* Calcd. for $C_9H_{10}ClFN_2O_4$: C, 40.85; H, 3.81; N, 10.59. Found: C, 40.75; H, 3.81; N, 10.64.

1-(2,3-Dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (35). 18 (0.09 g, 0.27 mmol) was debenzoylated and the residue was purified by silica gel column chromatography (15% MeOH/$CHCl_3$) to provide **35** as white crystals (0.05 g, 90%), which was recrystallized from a mixture of MeOH and ether (1:1). mp 142-144 °C; $[\alpha]_D^{25}$ -210.7° (c 0.12, MeOH); UV (H_2O) λ_{max} 272.0 nm (ε 8140) (pH 2), 271.5 nm (ε 8680) (pH7), 271.5 nm (ε 9860) (pH 11); ^1H NMR

(DMSO-d_6): δ 7.67 (d, 1H, H-6, J = 7.6 Hz); 7.32 (bs, 2H, NH_2, D_2O exch.); 5.94 (dd, 1H, H-1', J = 18.5 and 2.6 Hz); 5.72 (d, 2H, H-5', J = 7.6 Hz); 5.21 (dm, 1H, H-2', J = 58.0 Hz); 4.95 (t, 1H, 5'-OH, J = 3.0 Hz, D_2O exch.); 4.09 (m, 1H, H-4'); 3.51 (m, 1H, H-5); 1.99-2.60 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 165.5, 154.9, 139.8, 94.8, 92.1 (d, J = 185.8 Hz), 85.8 (d, J = 16.1 Hz), 77.3, 63.5, 33.5 (d, J = 19.0 Hz); *Anal.* Calcd. for $C_9H_{12}FN_3O_3$: C, 47.18; H, 5.24; N, 18.34. Found: C, 46.89; H, 5.27; N, 18.07.

5-Fluoro-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (36). **19** (0.23 g, 0.71 mmol) was debenzoylated and the residue purified by silica gel column chromatography (5% MeOH/$CHCl_3$) to obtain **36** (0.17 g, 96%) as colorless crystals. mp 192-194 °C; $[\alpha]_D^{25}$ -166.5° (c 1.00, MeOH); UV (H_2O) λ_{max} 285.5 nm (ε 9050) (pH 2); 280.0 nm (ε 7490) (pH 7); 279.5 nm (ε 7730) (pH 11); IR (KBr) 3364, 1686, 1060 cm^{-1}; HRMS (FAB): calculated *m/e* 248.0846. Found: 248.0846 $(MH)^+$; ^1H NMR (DMSO-d_6): δ 7.94 (d, 1H, H-6, J = 7.1 Hz); 7.82 (s, 1H, NH_2, D_2O exch.); 7.58 (s, 1H, D_2O exch.); 5.88 (dm, 1H, H-1', J = 17.2 Hz); 5.20 (dm, 1H, H-2', J = 54.8 Hz); 5.04 (t, 1H, 5'-OH, J = 5.8 Hz, D_2O exch.); 4.12-4.06 (m, 1H, H-4'); 3.59-3.46 (m, 2H, H-5'); 2.51-2.36 and 2.10-1.97 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 157.9 (d, J = 13.3 Hz), 153.3, 136.0 (d, J = 240.0 Hz), 126.6 (d, J = 32.2 Hz), 91.4 (d, J = 185.8 Hz), 86.1 (d, J = 16.1 Hz), 78.1, 62.9, 32.6 (d, J = 20.2 Hz); *Anal.* Calcd. for $C_9H_{11}F_2N_3O_3 \cdot 0.4MeOH$: C, 43.44; H, 4.84; N, 16.16. Found: C, 43.55; H, 4.88; N, 16.12.

5-Bromo-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (37). **20** (0.17 g, 0.42 mmol) was debenzoylated and the residue purified by flash silica gel column chromatography (7% MeOH/$CHCl_3$) to obtain **37** (0.11 g, 88%). mp 198-200 °C; $[\alpha]_D^{25}$ -115.7° (c 0.32, MeOH); UV (H_2O) λ_{max} 294.5 nm (ε 8350) (pH 2); 286.5 nm (ε 6590) (pH 7); 286.5 nm (ε 6360) (pH 11); IR (KBr) 1658, 1631, 1078 cm^{-1}; MS (FAB) *m/e* 308 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 8.12 (s, 1H, H-6); 8.01 (s, 1H, NH_2, D_2O exch.); 7.16 (s, 1H, NH_2, D_2O exch.); 5.99 (dd, 1H, H-1', J = 17.0 and 3.5 Hz); 5.33 (dm, 1H, H-2', J = 54.8 Hz); 5.17 (t, 1H, OH, J = 5.8 Hz, D_2O exch.); 4.21-4.15 (m, 1H, H-4'); 3.69-3.52 (m, 2H, H-5'); 2.59-2.05 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 162.3, 163.7, 142.6, 132.9, 91.3 (d, J = 191.1 Hz), 86.2 (d, J = 14.0 Hz), 76.1, 62.7, 32.5 (d, J = 20.0 Hz); *Anal.* Calcd. for $C_9H_{11}BrFN_3O_3$: C, 35.00; H, 3.50; N, 13.60. Found: C, 35.14; H, 3.59; N, 13.38.

5-Iodo-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (38). **21** (0.09 g, 0.20 mmol) was debenzoylated and the residue purified by preparative TLC (7% MeOH/$CHCl_3$) to obtain **38** (0.06 g, 84%). mp 220-222 °C; $[\alpha]_D^{25}$ -99.0° (c 0.41, MeOH); UV (H_2O) λ_{max} 305.5 nm (ε 7790) (pH 2); 292.0 nm (ε 5910) (pH 7); 292.0 nm (ε 5690) (pH 11); IR (KBr) 1651, 1072 cm^{-1}; MS (FAB) *m/e* 356 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 8.05 (s, 1H, H-6); 7.89 (s, 1H, NH_2, D_2O exch.); 6.69 (s, 1H, NH_2, D_2O exch.); 5.90 (dd, 1H, H-1', J = 17.2 and 3.5 Hz); 5.24 (dm, 1H, H-2', J = 54.9 Hz); 5.08 (t, 1H, OH, D_2O exch.); 4.12-4.06 (m, 1H, H-4'); 3.60-3.44 (m, 2H, H-5'); 2.51-2.36 and 2.09-1.96 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 163.4, 153.1, 147.1, 90.5 (d, J = 186.1 Hz), 85.2 (d, J = 16.1 Hz), 77.2, 61.9, 55.6, 31.7 (d, J = 20.2 Hz); *Anal.* Calcd. for $C_9H_{11}FIN_3O_3$: C, 30.45; H, 3.09; N, 11.83. Found: C, 30.58; H, 3.05; N, 11.78.

5-Methyl-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (39). **22** (0.08 g, 0.23 mmol) was debenzoylated and the residue purified by flash silica gel column chromatography (10% MeOH/$CHCl_3$) to obtain **39** (0.05 g, 87%). mp 192-194 °C; $[\alpha]_D^{25}$ -146.0° (c 0.32, MeOH); UV (H_2O) λ_{max} 285.5 nm (ε 11100) (pH 2); 276.5 nm (ε 7230) (pH 7); 276.0 nm (ε 7510) (pH 11); IR (KBr) 1670 cm^{-1}; MS (FAB) *m/e* 244 $(MH)^+$; ^1H NMR ($CDCl_3$): δ

7.51 (s, 1H, H-6); 7.34 (s, 1H, NH_2, D_2O exch.); 6.85 (s, 1H, NH_2, D_2O exch.); 5.94 (dd, 1H, H-1', J = 18.6 and 3.3 Hz); 5.22 (dt, 1H, H-2', J = 55.0 and 2.4 Hz); 4.98 (t, 1H, OH, J = 5.8 Hz, D_2O exch.); 4.12-4.06 (m, 1H, H-4'); 3.59-3.50 (m, 2H, H-5'); 2.54-2.43 and 2.03-2.01 (m, 2H, H-3'); 1.86 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.8, 155.1, 139.3, 100.6, 91.4 (d, J = 185.8 Hz), 85.9 (d, J = 16.2 Hz), 77.6, 63.2, 33.1 (d, J = 20.0 Hz), 13.6; *Anal.* Calcd. for $C_{10}H_{14}FN_3O_3$: C, 49.38; H, 5.80; N, 17.28. Found: C, 49.38; H, 5.77; N, 17.14.

5-Chloro-1-(2,3-dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)cytosine (40). **23** (0.11 g, 0.31 mmol) was debenzoylated and the residue purified by flash silica gel column chromatography (10% MeOH/$CHCl_3$) to obtain **40** (0.07 g, 90%). mp 180-181 °C; $[\alpha]_D^{25}$ -153.0° (c 0.28, MeOH); UV (H_2O) λ_{max} 292.0 nm (ε 10800) (pH 2); 284.5 nm (ε 7840) (pH 7); 284.5 nm (ε 7680) (pH 11); IR (KBr) 1666, 1082 cm^{-1}; MS (FAB) *m/e* 264 $(MH)^+$; ^1H NMR ($CDCl_3$): δ 8.02 (s, 1H, H-6); 7.94 (s, 1H, NH_2, D_2O exch.); 7.32 (s, 1H, NH_2, D_2O exch.); = 52.0 and 4.0 Hz); 5.00-4.99 (m, 1H, H-4'); 4.54-4.53 (m, 2H, H-5'); 3.05-2.36 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 165.9, 152.1, 151.4, 149.6, 146.0, 133.8, 131.8, 129.7, 129.6, 129.1, 96.4 (d, J = 179.8 Hz), 90.2 (d, J = 35.4 Hz), 79.8, 66.4, 33.2 (d, J = 20.1 Hz); *Anal.* Calcd. for $C_{17}H_{14}ClFN_4O_3$: C, 54.21; H, 3.71; N, 14.87. Found: C, 54.37; H, 3.73; N, 14.64.

2-Isobutyrylamino-6-chloro-9-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-(β and α)-L-*threo*-pentofuranosyl)purine (44 and 45). A mixture of 2-isobutyrylamino-6-chloropurine (1.50 g, 6.26 mmol), hexamethyldisilazane (50 mL) and $(NH_4)_2SO_4$ (catalytic amount) was refluxed for 2 h under nitrogen. The clear solution obtained was evaporated to dryness *in vacuo*. The residue of the brominated sugar **7** (prepared from bromination of **6** (0.90 g, 3.93 mmol)) was taken up into DCE (25 mL) and added to the base, after that TMSOTf (1.2 mL, 6.26 mmol) was added and the reaction mixture was refluxed for 20 h under nitrogen. The reaction was worked up and purified as described for compounds **42** and **43** to obtain **44** (0.21 g, 12%) as white crystals and **45** (0.42 g, 24%) as white crystals, after recrystallized in a mixture of EtOAc and hexanes (1:2). **44**: mp 168-170 °C; $[\alpha]_D^{25}$ +42.9° (c 0.54, $CHCl_3$); UV (EtOAc) λ_{max} 252.0 nm; IR (KBr) 3190, 1724, 1026 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25 (s, 1H, H-8); 8.15 (s, 1H, NH, D_2O exch.); 8.09 (d, 2H, Ar-H, J = 7.5 Hz); 7.62 (t, 1H, Ar-H, J = 7.5 Hz); 7.51 (t, 2H, Ar-H, J = 7.8 Hz); 6.51 (dd, 1H, H-1', J = 19.5 and 2.1 Hz); 5.50 (d, 1H, H-2', J = 53.1 Hz); 5.09-5.06 (m, 1H, H-4'); 4.54-4.44 (m, 2H, H-5'); 2.81-2.70 (m, 2H, H-3' and CH); 2.46-2.32(m, 1H, H-3'); 1.31 (s, 3H, CH_3); 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.7, 164.6, 152.1, 152.6, 140.3, 132.5, 131.6, 131.1, 128.4, 128.2, 127.8, 90.1 (d, J = 184.0 Hz), 73.8, 82.8 (d, J = 23.7 Hz), 65.1, 33.3, 32.1 (d, J = 20.7 Hz), 17.9, 17.0; *Anal.* Calcd. for $C_{21}H_{21}ClFN_5O_4$: C, 54.63; H, 4.54; N, 15.16. Found: C, 54.33; H, 4.53; N, 14.96. **45**: mp 142-143 °C; $[\alpha]_D^{25}$ +52.1° (c 1.00, EtOAc); UV (EtOAc) λ_{max} 257.5 nm; IR (KBr) 3285, 1714, 1075; ^1H NMR ($CDCl_3$): δ 8.06 (s, 1H, H-8); 8.02-8.00 (m, 3H, NH and Ar-H); 7.50 (t, 1H, Ar-H, J = 7.4 Hz); 7.37 (t, 2H, Ar-H, J = 7.6 Hz); 6.20 (d, 1H, H-1', J = 16.64 Hz); 5.86 (dd, 1H, H-2', J = 52.6 and 5.3 Hz); 5.05-4.99 (m, 1H, H-4'); 4.49-4.41 (m, 2H, H-5'); 2.67-2.60 and 2.42-2.36 (m, 1H, H-3'); 1.23 (d, 3H, CH_3, J = 2.0 Hz); 1.21 (d, 3H, CH_3, J = 1.6 Hz); 2.67-2.60 (m, 2H, H-3' and CH); ^{13}C NMR ($CDCl_3$) δ 175.2, 165.9, 152.1, 149.6, 145.6, 133.8, 129.8, 129.6, 129.4, 129.1, 128.0, 97.1 (d, J = 175.1 Hz), 90.3 (d, J = 22.4 Hz) 80.5, 66.5, 35.1, 33.9 (d, J = 24.0 Hz), 19.6, 19.5; *Anal.* Calcd. for $C_{21}H_{21}ClFN_5O_4$: C, 54.63; H, 4.54; N, 15.16. Found: C, 54.35; H, 4.60; N, 14.99.

9-(2,3-Dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)hypoxanthine (46). A mixture of **42** (0.59 g, 1.42 mmol), 2-mercaptoethanol (0.4 mL, 5.70 mmol), and NaOMe (0.31 g, 5.74

mmol) in MeOH (75 mL) was refluxed for 5 h. The reaction mixture was cooled, neutralized with glacial HOAc and evaporated to dryness under vacuum. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) (9:1 and 17:3) to obtain **46** (0.30 g, 83%) as white foam. mp 138-140 °C; $[\alpha]_D^{25}$ -54.1° (c 0.35, H_2O); UV (H_2O) λ_{max} 247.5 nm (ε 9120) (pH 2); 247.0 nm (ε 9380) (pH 7); 252.0 nm (ε 9800) (pH 11); IR (KBr) 3389, 1701, 1086; MS (FAB) *m/e* 255 5.92 (dd, 1H, H-1', *J* = 17.0 and 3.3 Hz); 5.28 (d, 1H, H-2', *J* = 54.8 Hz); 5.10 (t, 1H, OH, *J* = 5.9 Hz, D_2O exch.); 4.13-4.12 (m, 1H, H-4'); 3.63-3.47 (m, 2H, H-5'); 2.54-2.39 and 2.12-1.99 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 161.8, 153.6, 140.0, 98.9, 91.4 (d, *J* = 185.9 Hz), 86.2 (d, *J* = 16.4 Hz), 78.1, 62.7, 32.5 (d, *J* = 19.9 Hz); *Anal.* Calcd. for $C_9H_{11}ClFN_3O_3$: C, 41.00; H, 4.20; N, 15.94. Found: C, 40.94; H, 4.18; N, 15.88.

1-(2,3-Dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)thymine (41). **24** (0.07 g, 0.22 mmol) was debenzoylated and the residue was purified by preparative TLC (5% MeOH/$CHCl_3$) to yield **41** (0.03 g, 68%) as white crystals, which was recrystallized from a mixture of diethyl ether and methanol (1:1). mp 140-142 °C; $[\alpha]_D^{25}$ -145.3° (c 0.09, MeOH); UV (H_2O) λ_{max} 266.0 nm (ε 9340) (pH 2); 266.5 nm (ε 9400) (pH 7); 266.0 nm (ε 7120) (pH 11); IR (KBr) 2843, 1690, 1660, 1059 cm^{-1}; MS (ESI) *m/e* 244.9 $(MH)^+$; ^1H NMR (DMSO-d_6): δ 11.36 (bs, 1H, NH, D_2O exch.); 7.61 (s, 1H, H-6); 5.96 (dd, 1H, H-1', *J* = 16.6 and 3.76 Hz); 5.36-5.20 (dm, 1H, H-2', *J* = 55.1 Hz); 5.08-5.05 (m, 1H, H-4'); 5.01 (s, 1H, OH, D_2O exch.); 3.62-3.52 (m, 2H, H-5'); 2.49-2.01 (m, 2H, H-3'); 1.76 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 161.6, 148.1, 130.5, 106.1, 89.2 (d, *J* = 186.6 Hz), 82.3 (d, *J* = 16.3 Hz), 75.4, 60.2, 30.1 (d, *J* = 20.4 Hz), 10.1; *Anal.* Calcd. for $C_{10}H_{13}FN_2O_4$: C, 49.21; H, 5.32; N, 11.47. Found: C, 49.04; H, 5.44; N, 11.31.

6-Chloro-9-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-(β and α)-L-*threo*-pentofuranosyl)purine (42 and 43). A mixture of 6-chloropurine (3.00 g, 19.40 mmol), hexamethyldisilazane (50 mL) and $(NH_4)_2SO_4$ (catalytic amount) was refluxed for 2 h under argon. The clear solution obtained was concentrated to dryness under vacuum. The residue of the brominated sugar **7** (prepared from the bromination of **6** (1.05 g, 4.38 mmol)) was taken up into dry DCE (50 mL) and added to the base. TMSOTf (3.8 mL, 19.40 mmol) was added then the reaction mixture was refluxed for 24 h under argon. The solution was then washed with sat $NaHCO_3$ solution (100 mL), dried (Na_2SO_4), filtered through a Celite pad, and concentrated *in vacuo* to give a yellowish residue, which was purified by flash silica gel column chromatography (EtOAc:hexanes) (1:1) to obtain **42** (0.33 g, 18%) and **43** (0.32 g, 17%) as white crystals, which were recrystallized from a mixture of EtOAc and hexanes (3:1). **42**: mp 125-127 °C; $[\alpha]_D^{25}$ -28.4° (c 0.60, $CHCl_3$); UV (MeOH) λ_{max} 263.5 nm; ^1H NMR ($CDCl_3$): δ 8.74 (s, 1H, H-2); 8.46 (s, 1H, H-8); 8.09 (d, 2H, Ar-H, *J* = 7.4 Hz); 7.59 (t, 1H, Ar-H, *J* = 7.7 Hz); 7.46 (t, 2H, Ar-H, *J* = 7.6 Hz); 6.44 (dd, 1H, H-1', *J* = 19.7 and 2.6 Hz); 5.25 (dm, 1H, H-2', *J* = 53.5 Hz); 4.65 (m, 3H, H-4' and H-5'); 2.86-2.48 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 165.3, 151.1, 151.0, 150.1, 143.6, 143.5, 132.4, 128.7, 128.4, 126.1, 90.0 (d, *J* = 181.0 Hz), 84.4 (d, *J* = 11.0 Hz), 74.59, 64.55, 32.7 (d, *J* = 20.0 Hz); *Anal.* Calcd. for $C_{17}H_{14}ClFN_4O_3 \cdot 0.25H_2O$: C, 53.55; H, 3.81; N, 14.69. Found: C, 53.61; H, 3.90; N, 14.69. **43**: mp 106-108 °C; $[\alpha]_D^{25}$ -2.0° (c 0.90, $CHCl_3$); UV (MeOH) λ_{max} 264.0 nm; IR (KBr) 1720, 1718, 1560, 1070 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.76 (s, 1H, H-2); 8.22 (s, 1H, H-8); 8.08 (d, 2H, Ar-H, *J* = 8.0 Hz); 7.57 (t, 1H, Ar-H, *J* = 7.4 Hz); 7.46 (t, 2H, Ar-H, *J* = 8.0 Hz); 6.40 (d, 1H, H-1', *J* = 12.0 Hz); 5.95 (dd, 1H, H-2', *J* $(MH)^+$; ^1H NMR (DMSO-d_6): δ 8.14 (s, 1H, H-2); 8.25 (d, 1H, H-8, *J* = 3.0 Hz); 7.33 (bs, 1H, NH, D_2O exch.); 6.30 (dd, 1H, H-1', *J* = 16.1 and 3.8 Hz); 5.42 (dm, 1H, H-2', *J* = 54.5 Hz);

5.05 (t, 1H, 5'-OH, J = 5.5 Hz); 4.16 (m, 1H, H-4'); 3.59 (m, 2H, H-5'); 2.61-2.14 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 157.0, 148.2, 146.6, 139.3, 123.9, 91.6 (d, J = 187.0 Hz), 84.1 (d, J = 16.5 Hz), 78.3, 63.0, 32.4 (d, J = 19.5 Hz); *Anal.* Calcd. for $C_{10}H_{11}FN_4O_3$: C, 47.20; H, 4.33; N, 21.93. Found: C, 47.32; H, 4.33; N, 21.93.

9-(2,3-Dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)hypoxanthine (47). A mixture of **43** (0.47 g, 1.13 mmol), 2-mercaptoethanol (0.32 mL, 4.56 mmol), and NaOMe (0.25 g, 4.62 mmol) in MeOH (60 mL) was refluxed for 5 h. The reaction mixture was worked up and purified as described for compound **46** to obtain **47** (0.22 g, 76%) as white crystals. mp 230-232 °C; $[\alpha]_D^{25}$ -55.0° (c 0.57, H_2O); UV (H_2O) λ_{max} 248.5 nm (ε 10800) (pH 2); 248.5 nm (ε 10800) (pH 7); 253.5 nm (ε 11700) (pH 11); IR (KBr) 3273, 1711, 1674 cm^{-1}; MS (ESI) *m/e* 255 $(MH)^+$; ^{1}H NMR (DMSO-d_6): δ 8.26 (s, 1H, H-8); 8.17 (s, 1H, H-2); 7.34 (s, 1H, NH, D_2O exch.); 6.34 (d, 1H, H-1', J = 15.9 Hz); 5.81 (dd, 1H, H-2', J = 52.9 and 4.2 Hz); 5.02 (bs, 1H, 5'-OH, D_2O exch.); 4.57-4.54 (m, 1H, H-4'); 3.53-3.52 (m, 2H, H-5'); 2.86-2.71 and 2.21-2.10 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 156.8, 147.8, 146.4, 138.7, 124.9, 96.7 (d, J = 178.7 Hz), 89.2 (d, J = 35.3 Hz), 82.2, 63.6, 33.0 (d, J = 19.8 Hz); *Anal.* Calcd. for $C_{10}H_{11}FN_4O_3$: C, 47.27; H, 4.32; N, 22.04. Found: C, 47.02; H, 4.27; N, 21.90.

9-(2,3-Dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)adenine (48). A solution of **42** (0.08 g, 0.26 mmol) in sat methanolic ammonia (30 mL) was heated at 100 °C in a steel bomb for 20 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (10% MeOH/$CHCl_3$) to give a white solid **48** (0.05 g, 70%). mp 225-226 °C; $[\alpha]_D^{25}$ -94.6° (c 0.11, MeOH); UV (H_2O) λ_{max} 258.9 nm (ε 12700) (pH 2); 258.5 nm (ε 13600) (pH 7); 258.0 nm (ε 12200) (pH 11); ^{1}H NMR (DMSO-d_6): δ 8.14 (s, 1H, H-2); 8.25 (d, 1H,H-8, J = 3.0 Hz); 7.33 (bs, 2H, NH_2, D_2O exch.); 6.30 (dd, 1H, H-1', J =3.8 and 16.1 Hz); 5.42 (dm, 1H, H-2', J = 54.5 Hz); 5.05 (t, 1H, OH, J = 5.5 Hz, D_2O exch.); 4.16 (m, 1H, H-4'); 3.65-3.59 (m, 2H, H-5'); 2.14-2.61 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 155.3, 153.1, 149.1, 139.3, 118.6, 91.7 (d, J = 181.2 Hz), 83.9 (d, J = 16.5 Hz), 78.2, 63.0, 32.7 (d, J = 19.5 Hz); *Anal.* Calcd. for $C_{10}H_{12}N_5O_2 \cdot 0.25H_2O$: C, 46.60; H, 4.88; N, 27.17. Found: C, 46.80; H, 4.78; N, 27.03.

9-(2,3-Dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)adenine (49). A solution of **43** (0.15 g, 4.00 mmol) in sat methanolic ammonia (30 mL) was heated at 100 °C in a steel bomb for 20 h. The solvent was evaporated and the residue was purified by silica gel column chromatography (5% MeOH:$CHCl_3$) to give a white solid **49** (0.06 g, 57%). mp 60-62 °C; $[\alpha]_D^{25}$ -42.0° (c 0.30, MeOH); UV (H_2O) λ_{max} 256.5 nm (ε 13900) (pH 2); 260.0 nm (ε 14000) (pH 7); 259.5 nm (ε 14000) (pH 11); IR (KBr) 1691, 1647, 1062 cm^{-1}; MS (FAB) *m/e* 254 $(MH)^+$; ^{1}H NMR ($CDCl_3$): δ 8.26 (s, 1H, H-8); 8.17 (s, 1H, H-2); 7.34 (s, 2H, NH_2, D_2O exch.); 6.34 (d, 1H, H-1', J =15.8 Hz); 5.80 (dd, 1H, H-2', J =52.9 and 4.2 Hz); 5.02 (s, 1H, 5'-OH, D_2O exch.); 4.57-4.54 (m, 1H, H-4'); 3.53-3.52 (m, 2H, H-5'); 2.86-2.71 and 2.21-2.10 (m, 2H, H-3'); ^{13}C NMR ($CDCl_3$) δ 156.4, 153.1, 149.1, 139.6, 119.4, 96.6 (d, J = 179.3 Hz), 89.0 (d, J = 35.6 Hz), 82.2, 63.7, 33.4 (d, J = 19.9 Hz); *Anal.* Calcd. for $C_{10}H_{12}N_5O_2 \cdot 0.54MeOH$: C, 46.79; H, 5.28; N, 25.89. Found: C, 46.73; H, 5.08; N, 26.01.

***N*^{6}-methyl-9-(2,3-Dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)adenine (50).** A solution of **42** (0.30 g, 0.79 mmol) and methylamine (40% solution in H_2O, 20 mL) in MeOH (20 mL) was heated at 90 °C in a steel bomb for 15 h. After cooling, the solvents were removed under vacuum. The residue was purified by preparative TLC (7% MeOH:$CHCl_3$) to give **50** (0.15 g, 77%). mp 58-60 °C; $[\alpha]_D^{25}$ -40.2° (c 0.23, MeOH); UV (H_2O) λ_{max} 261.5 nm (ε 14200) (pH 2);

265.0 nm (ε 13400) (pH 7); 264.5 nm (ε 12900) (pH 11); IR (KBr) 3385, 1628, 1070 cm^{-1}; MS (EI) *m/e* 268.0 $(MH)^+$; ^1H NMR (DMSO-d_6): δ 8.27 (s, 1H, H-8); 8.26 (s, 1H, H-2); 7.84 (s, 1H, NH); 6.33 (dd, 1H, H-1', *J* = 16.0 and 3.9 Hz); 5.43 (dm, 1H, H-2', *J* = 58.3 Hz); 5.07 (s, 1H, 5'-OH, D_2O exch.); 4.20-4.14 (m, 1H, H-4'); 3.65-3.56 (m, 2H, H-5'); 2.95 (s, 3H, CH_3); 2.63-2.50 and 2.32-2.19 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 155.2, 153.1, 148.3, 139.6, 119.0, 91.6 (d, *J* = 187.2 Hz), 83.9 (d, *J* = 16.5 Hz), 78.1, 63.1, 32.5 (d, *J* = 19.5 Hz), 27.3; *Anal.* Calcd. for $C_{11}H_{14}FN_5O_2 \cdot 0.5MeOH$: C, 48.76; H, 5.69; N, 24.72. Found: C, 48.97; H, 5.55; N, 24.70.

N^6-methyl-9-(2,3-Dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)adenine (51). A solution of **43** (0.20 g, 0.53 mmol) and methylamine (40% solution in H_2O, 15 mL) in MeOH (15 mL) was heated at 90 °C in a steel bomb for 15 h. After cooling, the solvents were removed under vacuum. The residue was purified by preparative TLC (7% MeOH:$CHCl_3$) to give **51** (0.10 g, 74%). mp 42-43 °C; $[\alpha]_D^{25}$ -35.2° (c 0.30, MeOH); UV (H_2O) λ_{max} 262.0 nm (ε 15800) (pH 2); 265.5 nm (ε 12000) (pH 7); 265.5 nm (ε 15000) (pH 11); IR (KBr) 3372, 1630, 1072 cm^{-1}; MS (EI) *m/e* 268.0 (MH^+); ^1H NMR (DMSO-d_6): δ 8.74 (s, 2H, H-8 and H-2); 8.32 (s, 1H, NH_2, D_2O exch.); 6.84 (d, 1H, H-1', *J* = 15.6 Hz); 6.29 (dd, 1H, H-2', *J* = 52.8 and 4.8 Hz); 5.46 (t, 1H, 5'-OH, *J* = 5.6 Hz, D_2O exch.); 5.07-5.033 (m, 1H, H-4'); 4.05-3.96 (m, 2H, H-5'); 3.45 (s, 3H, CH_3); 3.33-3.24 and 2.70-2.62 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 155.3, 155.1, 148.0, 139.3, 119.8, 96.5 (d, *J* = 179.6 Hz), 89.0 (d, *J* = 35.6 Hz), 82.1, 63.6, 33.2 (d, *J* = 20.2 Hz), 27.3; *Anal.* Calcd. for $C_{11}H_{14}FN_5O_2 \cdot 0.5H_2O \cdot 0.1EtOAc$: C, 48.06; H, 5.54; N, 24.57. Found: C, 48.08; H, 5.56; N, 24.28.

9-(2,3-Dideoxy-2-fluoro-β-L-*threo*-pentofuranosyl)guanine (52). A mixture of **44** (0.15 g, 0.32 mmol), 2-mercaptoethanol (0.2 mL, 2.35 mmol) and NaOMe (0.05 g, 0.92 mmol) in methanol (20 mL) was refluxed for 24 h under nitrogen. The reaction mixture was cooled neutralized with glacial HOAc, and evaporated to dryness under vacuum. The residue was taken up in hot methanol, filtered, washed with H_2O, and triturated in a mixture of MeOH and $CHCl_3$ (1:1) to give **52** (0.04 g, 45%) as a white foam. mp >300 °C; $[\alpha]_D^{25}$ -14.1° (c 0.47, DMSO); UV (H_2O) λ_{max} 253.5 nm (ε 6520) (pH 2); 251.0 nm (ε 7130) (pH 7); 256.5 nm (ε 5720); IR (KBr) 3427, 1693 cm^{-1}; HRMS (FAB): calculated *m/e* 270.1002. Found: 270.1007 $(MH)^+$; ^1H NMR (DMSO-d_6): δ 11.00 (s, 1H, NH); 7.76 (d, 1H, H-8, *J* = 2.3 Hz); 6.75 (s, 2H, NH_2, D_2O exch.); 5.98 (dd, 1H, H-1', *J* = 16.5 and 3.8 Hz); 5.34 (dm, 1H, H-2', *J* = 54.3 Hz); 5.01 (s, 1H, 5'-OH, D_2O exch.); 4.12-4,06 (m, 1H, H-4'); 3.61-3.54 (m, 2H, H-5'); 2.59-2.43 and 2.24-2.12 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 155.7, 151.4, 135.7, 132.9, 116.3, 91.5 (d, *J* = 186.1 Hz), 83.3 (d, *J* = 16.3 Hz), 77.7, 63.2, 32.7 (d, *J* = 19.4 Hz); *Anal.* Calcd. for $C_{10}H_{12}FN_5O_3 \cdot 0.4CHCl_3$: C, 39.41; H, 3.94; N, 22.09. Found: C, 39.41; H, 4.21; N, 22.15.

9-(2,3-Dideoxy-2-fluoro-α-L-*threo*-pentofuranosyl)guanine (53). A mixture of **45** (0.22 g, 0.47 mmol), 2-mercaptoethanol (0.2 mL, 2.35 mmol) and NaOMe (0.06 g, 1.11 mmol) in methanol (30 mL) was refluxed for 16 h under nitrogen. The reaction mixture was cooled neutralized with glacial HOAc, and evaporated to dryness under vacuum. The residue was taken up in hot methanol, filtered, washed with H_2O, and crystallized in MeOH to give **53** (0.06 g, 57%) as white crystals. mp >300 °C; $[\alpha]_D^{25}$ -52.6° (c 0.27, DMSO); UV (H_2O) λ_{max} 255.5 nm (ε 12500) (pH 2); 251.5 nm (ε 13100) (pH 7); 262.0 nm (ε 15800) (pH 11); IR (KBr) 3182, 1701, 1072 cm^{-1}; MS (FAB) *m/e* 270 $(MH)^+$; ^1H NMR (DMSO-d_6): δ 10.67 (s, 1H, NH); 7.62 (s, 1H, H-8); 7.02 (s, 2H, NH_2); 6.09 (d, 1H, H-1', *J* = 16.03 Hz); 5.66 (dd, 1H, H-2', *J* = 52.8 and 4.8 Hz); 4.93 (s, 1H, 5'-OH, D_2O exch.); 4.50-4.44 (m, 1H, H-4'); 3.51-3.39 (m, 2H, H-5');

2.81-2.00 (m, 2H, H-3'); ^{13}C NMR (DMSO-d_6) δ 163.2, 158.4, 151.4, 134.1, 117.4, 96.7 (d, J = 177.5 Hz), 88.3 (d, J = 34.5 Hz), 81.7, 63.8, 33.3 (d, J = 20.3 Hz); *Anal.* Calcd. for $C_{10}H_{12}FN_5O_3$: C, 44.60; H, 4.40; N, 26.00. Found: C, 44.53; H, 4.48; N, 26.08.

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REFERENCES

1. Chang, C. N., Doong, S. L., Zhou, J. H., Beach, J. W., Jeong, L. S., Chu, C. K., Tsai, C. H., Cheng, Y.-C., Liotta, D. and Schinazi, R. *J. Biol. Chem.* **1992** ***267***, 13938-13942.
2. Belleau, B., Dixit, D., Nguyen-Ga, N. and Kraus, J.-L. **1990**, 515.
3. Furman, P. A., Davis, M., Liotta, D. C., Paff, M., Frick, L. W., Nelson, D. J., Dornsife, R. E., Wurster, J. A., Wilson, L. J., Fyfe, J. A., Tuttle, J. V., Miller, W. H., Condreay, L., Avereet, D. R., Schinazi, R. F. and Painter, G. R. *Antimicrob. Agents Chemother.* **1992** ***36***, 2686-2692.
4. Schinazi, R. F., Gosselin, G., Faraj, A., Korba, B. E., Liotta, D. C., Chu, C. K., Mathe, C., Imbach, J.-L. and Sommadossi, J.-P. *Antimicrob. Agents Chemother.* **1994** ***38***, 2172-2174.
5. Coates, J. A., Cammack, N. S., Jenkinson, H. J., Jowett, M. I., Pearson, B. A., Penn, C. R., Rouse, P. L., Viner, K. C. and Cameron, J. M. *Antimicrob. Agents Chemother.* **1992** ***36***, 733-739.
6. Doong, S. L., Tsai, C. H., Scinazi, R. F., Liotta, D. C. and Cheng, Y.-C. *Proc. Natl. Acad. Sci. U.S.A.* **1991** ***88***, 8495-8499.
7. Chang, C. N., Skalski, V., Zhou, J. H. and Cheng, Y.-C. *J. Biol. Chem.* **1992** ***267***, 22414-22420.
8. Grove, K. L., Guo, X., Liu, S. H., Gao, Z., Chu, C. K. and Cheng, Y.-C. *Cancer Res.* **1995** ***55***, 3008-3011.
9. Pai, S. B., Liu, S. H., Zhu, Y. L., Chu, C. K. and Cheng, Y.-C. *Antimicrob. Agents Chemother.* **1996** ***40***, 380-386.
10. Pelicano, H., Pierra, C., Eriksson, S., Gosselin, G., Imbach, J.-L. and Maury, G. *J. Med. Chem.* **1997** ***40***, 3969-3973.
11. Kim, H. O., Shanmuganathan, K., Alves, A. J., Jeong, L. S., Beach, J. W., Schinazi, R. F., Chang, C. N., Cheng, Y.-C. and Chu, C. K. *Tetrahedron Lett.* **1992** ***33***, 6899-6902.
12. Kim, H. O., Schinazi, R. F., Shanmuganathan, K., Jeong, L. S., Beach, J. W., Nampalli, S., Cannon, D. L. and Chu, C. K. *J. Med. Chem.* **1993** ***36***, 519-528.
13. Chu, C. K., Ma, T., Shanmuganathan, K., Wang, C., Xiang, Y., Pai, S. B., Yao, G. Q., Sommadossi, J.-P. and Cheng, Y.-C. *Antimicrob. Agents Chemother.* **1995** ***39***, 979-981.
14. Wright, J. D., Ma, T. W., Chu, C. K. and Boudinot, F. D. *Pharm. Res.* **1995** ***12***, 1350-1353.

15. Lin, T. S., Luo, M. Z., Liu, M. C., Pai, S. B., Dutschman, G. E. and Cheng, Y.-C. *J. Med. Chem.* **1994** ***37***, 798-803.
16. Gosselin, G., Schinazi, R. F., Sommadossi, J.-P., Mathe, C., Bergone, M. C., Aubertin, A. M., Kirn, A. and Imbach, J.-L. *Antimicrob. Agents Chemother.* **1994** ***38***, 1292-1297.
17. Marquez, V. E., Tseng, C. K., Mitsuya, H., Aoki, S., Kelly, J. A., Ford, H. J., Roth, J. S., Broder, S., John, D. G. and Driscoll, J. S. *J. Med. Chem.* **1990** ***33***, 978-985.
18. Siddiqui, M. A., Driscoll, J. S., Marquez, V. E., Roth, J. S., Shirasaka, T., Mitsuya, H., Barchi, J. J. J. and Kelley, J. A. *J. Med. Chem.* **1992** ***35***, 2195-2201.
19. Xiang, Y., Cavalcanti, S., Chu, C. K., Schinazi, R. F., Pai, S. B., Zhu, Y. L. and Cheng, Y.-C. *Bioorg. & Med. Chem. Lett.* **1995** ***5***, 877-880.
20. Misra, S., Jain, S., Avasthi, K. and Bhakuni, D. S. *Nucleosides & Nucleotides* **1990** ***9***, 837-846.
21. Ma, T., Pai, B., Zhu, Y. L., Lin, J. S., Shanmuganathan, K., Du, J., Wang, C., Kim, H., Newton, G., Cheng, Y.-C. and Chu, C. K. *J. Med. Chem.* **1996** ***39***, 2835-2843.
22. Nair, V. and Sinhababu, A. K. *J. Org. Chem.* **1977** ***43***, 5013-5017.
23. Shanmuganathan, K., Koudriakova, T., Nampalli, S., Du, J., Gallo, J. M., Schinazi, R. F. and Chu, C. K. *J. Med. Chem.* **1994** ***37***, 821-827.
24. Townsend, L. B. *Chemistry of Nucleosides and Nucleotides*; Plenum Press: New York, 1988; Vol. 1.
25. Collorless prism crystal of orthorhombic system with the lattice parameters: a = 8.812 Å, b = 11.159 Å, c = 16.392 Å, V = 1611.984; space group P212121.

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