Structure−Activity Relationships of 2′-Deoxy-2′,2′-difluoro-L-*erythro*-pentofuranosyl Nucleosides

Lakshmi P. Kotra,[†] Yuejun Xiang,[†] M. Gary Newton,[‡] Raymond F. Schinazi,[§] Yung-C. Cheng,[||] and Chung K. Chu*,[†]

Department of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry, The University of Georgia, Athens, Georgia 30602-2352, Georgia Research Center for AIDS and HIV Infections, Veterans Affairs Medical Center, and Department of Pediatrics, Emory University School of Medicine, Decatur, Georgia 30033, and Department of Pharmacology, School of Medicine, Yale University, New Haven, Connecticut 06510

Received April 28, 1997[⊗]

Following the recent discoveries that some L-nucleosides are more or equal potent than their D-counterparts, we synthesized 2′-deoxy-2′,2′-difluoro-L-*erythro*-pentofuranosyl nucleosides as potential antiviral agents. The target compounds were synthesized via the key intermediates **7a** or **7b** from L-gulono γ-lactone. Compound **2** was oxidatively cleaved and coupled with ethyl bromodifluoroacetate in the presence of activated zinc under Reformatsky conditions to obtain a diastereomeric mixture of **4(R)** and **4(S)**, in a 4:1 ratio. The major **4(R)** isomer was cyclized and treated appropriately to obtain the mesylate **8a** or **8b**, which was condensed with various silyl-protected pyrimidines. Condensation of the alcohol **7a** or **7b** with 6-chloropurine under Mitsunobu conditions afforded the 6-chloropurine analogs **53a** or **53b** and **54a** or **54b**. Further treatment of the compounds **53a**, **54a** and **53b**, **54b** afforded the inosine and adenine derivatives **57**−**60**, respectively. The condensation of 2-amino-6-chloropurine with compound **8a** and subsequent treatment with 2-mercaptoethanol/sodium methoxide afforded the guanine analogs **63** and **64**. All of the synthesized nucleosides **31**−**52**, **57**−**60**, **63**, and **64** were evaluated for antiviral activity and for cellular toxicity. Adenine derivative **57** showed a moderate activity against HIV-1 in PBM cells (3.4 μM). None of the other compounds showed any significant activities against HIV-1, HBV, HSV-1, HSV-2, and toxicity in Vero, CEM, and PBM cell lines up to 100 μM. The X-ray structure of the 5-iodocytosine analog showed a 2′-exo/3′-endo conformation for the carbohydrate moiety, which is different from those of the biologically active compounds (−)-FTC and L-FMAU.

Introduction

Nucleoside analogs have played an important role in the treatment of various cancers and viral infections, including human immunodeficiency virus (HIV) infection.[1,2] However, the toxicities associated with certain nucleoside analogs[3,4] and the emergence of resistant viral strains[5,6] warrant the search for further novel and structurally diverse compounds with minimally overlapping resistance profile and toxicity. Most of the currently available nucleosides in the clinical use *viz*. AZT, ddI, ddC, and d4T have the same D-configuration as those of the natural nucleosides. Recently, the synthesis and antiviral activities of a new class of nucleosides *viz*. oxathiolanyl and dioxolanyl nucleosides have drawn a significant attention.[7,8] Among these classes of nucleosides, certain L-nucleosides like 3TC (Lamivudine)[9,10] and its 5-fluorocytosine analog, (−)-FTC,[11] exhibit either equal or more potent activities compared to their D-counterparts while exhibiting less toxicity.

This sparked the interest to explore the L-nucleosides as potential antiviral agents, including β-L-arabinofuranosyl and β-L-2′,3′-dideoxyribofuranosyl nucleosides[12−15] and 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine nucleosides.[16] Among these compounds, 2′-fluoro-5-methyl-β-L-arabinofuranosyluracil (L-FMAU, Figure 1) was synthesized in our laboratories and has shown potent antihepatitis B virus (anti-HBV) and anti-Epstein−Barr virus (anti-EBV) activities[17] with a favorable toxicity profile.[18] Recently, L-FMAU has demonstrated outstanding *in vivo* efficacy in chronically infected woodchucks with woodchuck hepatitis virus.[19] L-FMAU is currently undergoing preclinical toxicological studies.

Among the other classes of nucleosides, 2′-deoxy-2′,2′-difluoro-D-nucleosides have shown various antiviral and antineoplastic activities.[20,21] 2′-Deoxy-2′,2′-difluorocytidine (Gemcitabine, Gemzar, Figure 1) was recently approved by FDA for inoperable pancreatic cancer and for 5-fluorouracil resistant pancreatic cancer. Gemcitabine showed an interesting mechanism of action by inhibiting the DNA and RNA synthesis and/or by inhibiting ribonucleotide reductase.[22] Gemcitabine also showed activity against ovarian, small cell lung, breast cancer, and colon cancer after being activated to its triphosphate form.[23] The guanine derivative 2′-deoxy-2′,2′-difluoroguanosine also exhibited a similar mechanism of action in the inhibition of DNA synthesis in Chinese hamster ovary cell line with a promising antimetabolite characteristics.[24]

As part of our efforts to develop novel antiviral agents, recently we reported the preliminary accounts of the synthesis and anti-HIV activities of 2′-deoxy-2′,2′-difluoro-β-L-*erythro*-pentofuranosyl nucleosides.[25] These nucleosides were designed to take advantage of the characteristics of L-nucleosides and the potential activi-

* Corresponding Author: Tel: (706) 542-5379. Fax: (706) 542-5381. E-mail: dchu@rx.uga.edu.
[†] Department of Medicinal Chemistry, College of Pharmacy, The University of Georgia.
[‡] Department of Chemistry, The University of Georgia.
[§] Veterans Affairs Medical Center and Emory University School of Medicine.
[||] Yale University.
[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

S0022-2623(97)00275-6 CCC: $14.00

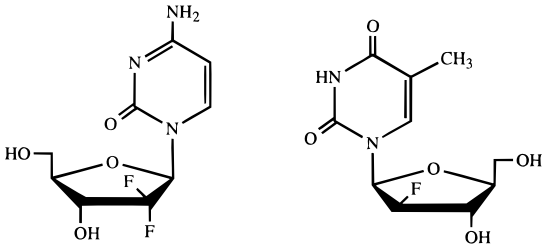


Figure 1.

ties of 2′-deoxy-2′,2′-difluoro nucleosides. Among these nucleosides, 9-(2′-deoxy-2′,2′-difluoro-β-L-*erythro*-pentofuranosyl)adenine exhibited moderate activity (EC_{50} 3.4 μM) against HIV-1 in PBM cells, without cytotoxicity up to 100 μM in PBM and Vero cells. These findings have prompted us to explore the structure−activity relationships of other 2′-deoxy-2′,2′-difluoro-L-nucleosides. We report herein the full accounts of the synthesis and anti-HIV, anti-HBV, and anti-HSV activities of several pyrimidine and purine derivatives of 2′-deoxy-2′,2′-difluoro-L-nucleosides.

Synthesis

Compound **7a** or **7b** was the key intermediate in the synthesis of various 2′-deoxy-2′,2′-difluoro-L-*erythro*-pentofuranosylpurine and pyrimidine nucleosides (Scheme 1). Compound **7a** or **7b** was conveniently prepared from L-gulono γ-lactone (**1**).[25] L-Gulono γ-lactone was selectively protected at the 5,6-positions by isopropylidene to obtain compound **2** in 80% yield. Compound **2** was subjected to oxidative cleavage with $NaIO_4$ at pH 5−6 to obtain compound **3**.[26] Compound **3** was coupled with ethyl bromodifluoroacetate in the presence of activated zinc using Reformatsky conditions to obtain a diastereomeric mixture of **4(R)** and **4(S)** in a ratio of 4:1 (35% and 8%, respectively).[27] It was important to use freshly distilled compound **3** to obtain higher yields of **4** and avoid complication. Diastereomers **4(R)** and **4(S)** were separated by column chromatography to obtain the major isomer **4(R)**. The compound **4(R)** was either treated with Dowex-50 (H^+) resin in methanol/water for 4 days or treated with 5% HCl in ethanol for 4 h and then refluxed in benzene at 90 °C for 25 h in Dean−Stark apparatus to obtain compound **5**. Compound **5** was treated with imidazole and *tert*-butylchlorodimethylsilane in DMF at 40 °C for 16 h to obtain compound **6b** in 54% yield. However, later the benzoyl protecting group was used to conveniently monitor the reactions and to avoid column chromatography for purification. Thus, compound **5** was treated with benzoyl chloride and 2,6-lutidine in dichloromethane to obtain compound **6a**. The salts from the reaction mixture were removed by repeated precipitation from EtOAc. Without further purification, compound **6a** was treated with lithium tri(*tert*-butoxy)alumino hydride in THF at −78 °C to obtain the key intermediate **7a**. Compound **7a** was stable and could be stored for extended periods of time. Similarly, compound **6b** was treated with DIBAL-H in toluene at −85 °C for 2 h to give compound **7b** in 96% yield. For the synthesis of various uracil and cytosine derivatives, either compound **7a** or **7b** was mesylated by the treatment with mesyl chloride and triethylamine in dichloromethane and the crude mesylate **8a** or **8b** was condensed with various silyl-protected uracil and cytosine derivatives (Scheme 1). The temperature for the condensation was very critical and was maintained at 80−100 °C. Ambient temperatures resulted in either no reaction or lower yields. In general, 3′,5′-benzoyl-protected uracil derivatives (**9**−**20**) gave anomeric mixtures which were inseparable by chromatographic methods at the protected stage. However, the anomeric mixture was able to be separated into individual anomers by flash column chromatography after deprotecting the benzoyl group by methylamine or methanolic ammonia. Cytosine analogs (**21**−**30**) could be separated at the protected stage into α and β anomers by silica gel column chromatography. Thus, various 5-substituted uracil derivatives (**31**−**42**) and 5-substituted cytosine derivatives (**43**−**52**) were prepared. Condensation of compound **7a** or **7b** with 6-chloropurine under Mitsunobu conditions afforded the 6-chloropurine analogs (**53a** and **54a**) or (**53b** and **54b**), respectively (Scheme 2).[28] Compounds **53b** and **54b** were desilylated separately and treated with ammonia under pressure at 100 °C to obtain the adenine analogs **57** and **58**, respectively. The anomeric mixture of **53a** and **54a** was treated with 2-mercaptoethanol and sodium methoxide in methanol to afford the mixture of compounds **59** and **60**. Compounds **59** and **60** were separated by HPLC using a reverse phase C-18 preparative column using 5% methanol:water as the eluting solvent. 2-Amino-6-chloropurine derivatives **61** and **62** (Scheme 2) were obtained by the condensation of silyl-protected 2-amino-6-chloropurine with compound **8a** using TMSOTf as a catalyst in DCE followed by chromatographic separation (Scheme 2). Compounds **61** and **62** were treated separately with 2-mercaptoethanol and sodium methoxide in methanol at 80 °C to afford the guanine analogs **63** and **64**, respectively. The anomeric configuration was assigned by either H-4′ chemical shift or by 2D NOESY experiments. The single-crystal X-ray structure of 5-iodocytosine derivative **51** was obtained (Figure 2).[29] The crystal structure shows a water molecule present in the close proximity of O-3′ within the hydrogen-bonding distance (2.84 Å). The hydrogen bonding of these nucleosides to a water molecule seems to be a general

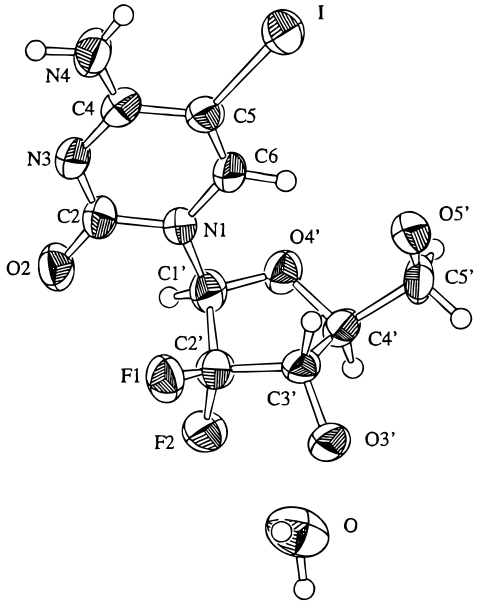
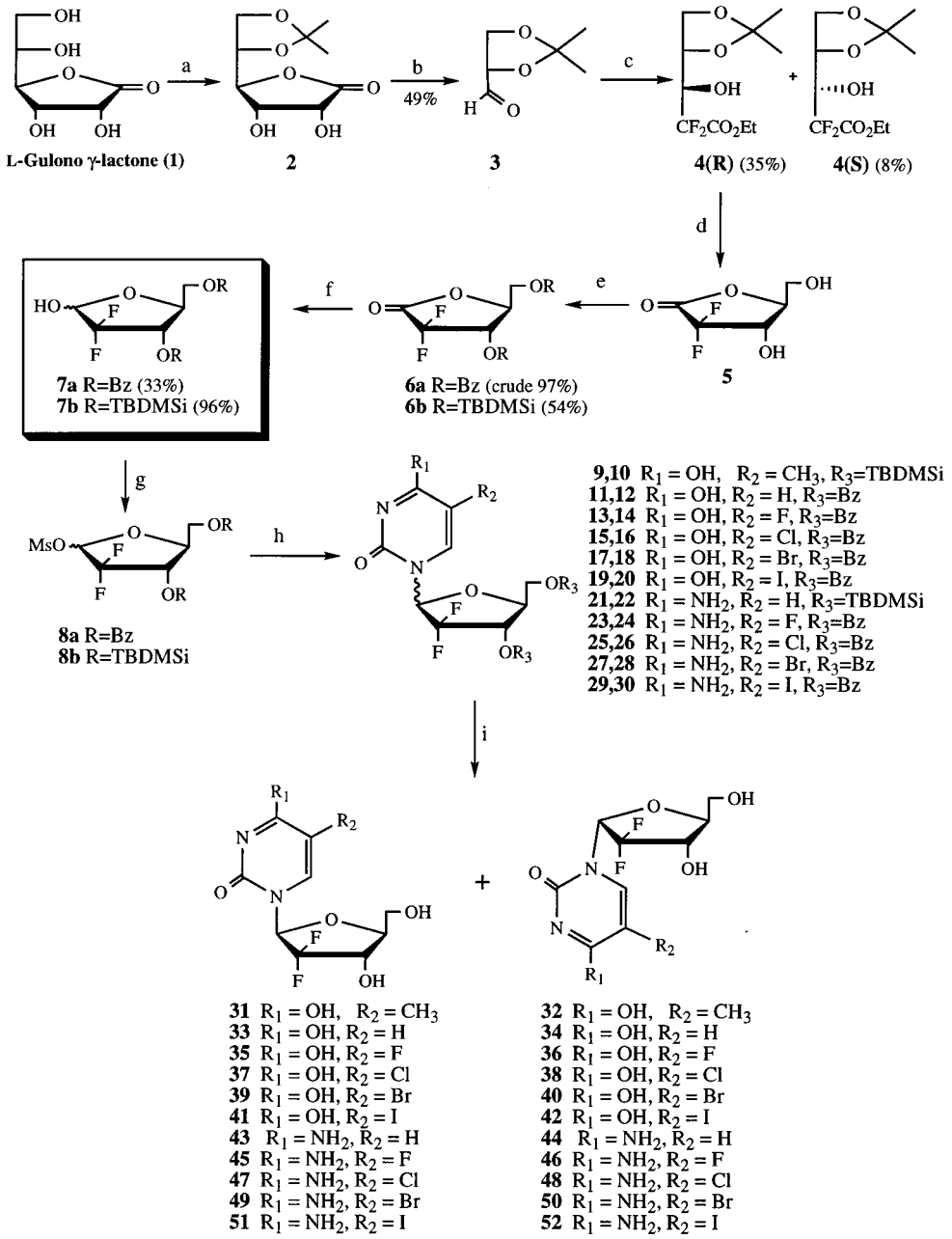


Figure 2. ORTEP drawing of 5-iodocytosine derivative **51**.

Scheme 1[a]



[a] (a) 2-Methoxypropene, *p*-TsOH, DMF, room temperature, 24 h; (b) $NaIO_4$, H_2O, pH 5-6, room temperature, 2 h; (c) $BrCF_2CO_2Et$, Zn, ether THF, 60 °C; (d) (i) 5% HCl, EtOH, 4 h, room temperature (ii) benzene, Dean−Stark, 95 °C, 25 h; or Dowex-50 (H^+), methanol, water, room temperature, 4 days; (e) BzCl, 2,6-lutidine, CH_2Cl_2, room temperature for **6a** (and) TBDMSiCl, imidazole, DMF, 40 °C, 16 h for **6b**; (f) Li(*t*-BuO)$_3$AlH, THF, −78 °C for **7a** and DIBAL-H, toluene, −85 °C, 2 h for **7b**; (g) MsCl, Et_3N, CH_2Cl_2, room temperature, 2 h; (h) silylated base, TMSOTf, DCE, 95−100 °C (or) NaI, silylated base, CH_3CN, reflux; (i) ammonia or methylamine, methanol, room temperature (or) *n*-Bu_4NF, THF, room temperature 2 h.

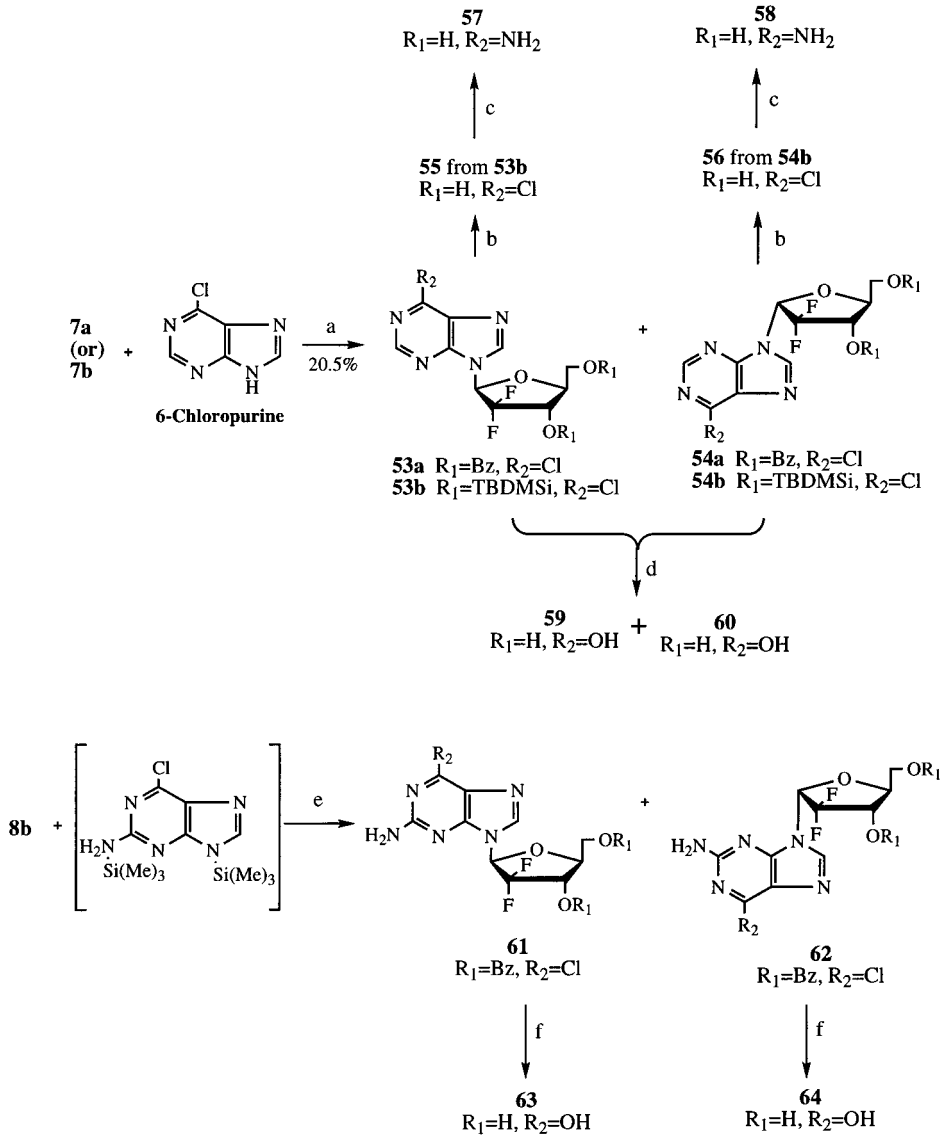
characteristic since a water molecule was often detected in the elemental analysis data as well.

Results and Discussion

All of the synthesized nucleosides, **31**−**52**, **57**−**60**, **63**, and **64** were evaluated for antiviral activity against human immunodeficiency virus type-1 (HIV-1), hepatitis B virus (HBV), herpes simplex virus type 1 and type 2 (HSV-1and HSV-2) (Table 1). The adenine analog **57** showed moderate activity against HIV-1 in PBM cells (3.4 μM) and no other compound showed any significant activity or toxicity up to 100 μM concentration against HIV-1, HBV, HSV-1 and -2.

To understand the structural characteristics of the difluoro L-nucleosides, the X-ray structures of compound **51** (this is the only one available for X-ray study in this class of compounds),[29] (−)-FTC,[30] and L-FMAU[16] were compared using fit procedure in SYBYL.[31] The X-ray structure of L-FMAU contains two molecules with similar conformational features ($P_1 = -76.1°$, $\nu_{1,max} = 46.62°$, $\chi_1 = 150.5°$, $\gamma_1 = -50.5°$ and $P_2 = -76.73°$, $\nu_{2,max} = 42.26°$, $\chi_2 = 154.0°$, $\gamma_2 = -46.1°$). Hence, only one molecule (with $P_1 = -76.1$) was considered in the studies. Figure 3 shows the overlap of compound **51** with (−)-FTC (part A) and with L-FMAU (part B), respectively. Compound **51** shows 3′-endo/2′-exo conformation ($P = 190.24°$, $\nu_{max} = 36.89°$, $\chi = 156.5°$, $\gamma = -42.7°$). However, (−)-FTC and L-FMAU possess a 3′-exo conformation ($P = 38.5°$, $\nu_{max} = 37.95°$, $\chi = 179.7°$, $\gamma = -171.4°$) and O4′-endo conformation, respectively.

Scheme 2[a]



[a] (a) DEAD, Ph_3P, THF, 8 h, room temperature; (b) *n*-Bu_4NF, THF, 2 h, room temperature; (c) NH_3, MeOH, steel bomb, 100 °C, 20 h; (d) 2-mercaptoethanol, NaOMe, MeOH, 70−80 °C, 24 h; (e) TMSOTf, DCE, 80−90 °C, 24 h; (f) 2-mercaptoethanol, NaOMe, MeOH 70−80 °C, 24 h.

Table 1. Anti-HIV, Anti-HBV, and Anti-HSV activities of 2′-deoxy-2′,2′-difluoro-L-nucleosides

compd	HIV-1 EC_{50} (μM)	HBV (2.2.15) (μM)	HSV (1 and 2) (μM)	toxicity (calorimetric assay) (IC_{50}, μM)		
				vero	CEM	PBM
AZT	0.004	>10	>100	29.0	13.0	>100
35	>100	>10	>100	>100	>100	>100
36	>100	>10	>100	>100	>100	>100
51	>100	>10	>100	>100	>100	>100
52	>100	>10	>100	>100	>100	>100
57	3.4	>20	>50	>100	>100	>100
58	>100	>20	>100	>100	>100	>100

The overlap of **51** with (−)-FTC and L-FMAU also shows these differences in the carbohydrate puckering (Figure 3).

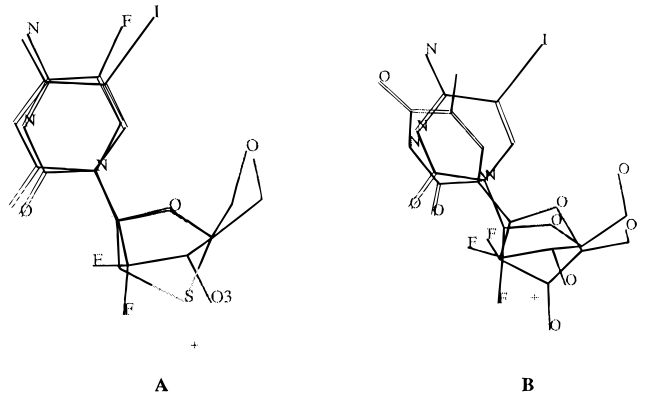


Figure 3. Overlap of the X-ray structures of compound **51** with (−)-FTC (A) and with L-FMAU (B).

One fluorine substitution at the 2′-position in arabino configuration in both D- and L-nucleosides produced active antiviral compounds.[16,32] Substitution with fluorine at 3′-position in erythro configuration in D-nucleosides also showed activity. However, the combination of these two effects or the opposite orientations of the fluorine atoms at the 2′,3′-positions in D-nucleosides did not result in active compounds. These observations related the activity of the nucleosides to the differences in the conformation of the sugar moiety. Previous studies have suggested that among D-nucleosides the

Table 2. ^{1}H NMR Data

compd	solvent	H-1′	H-3′	H-4′	H-5′	other
35	DMSO-d_6	6.02 (t, J = 7.18)	4.22 (pt)	4.85 (pd)	4.67 (2m)	12.01 (brs, 1H, NH, D_2O exch), 8.21 (d, 1H, J = 7.02, H-6), 6.33 (d, 3′-OH, D_2O exch), 5.43 (brs, 5′-OH, D_2O exch)
36	DMSO-d_6	6.18 (t, J = 11.85)	4.37 (m, 2H)		4.57 (2m)	11.65 (brs, 1H, NH, D_2O exch), 7.95 (d, 1H, J = 6.86, H-6), 6.40 (brs, 3′-OH, D_2O exch), 5.08 (brs, 1H, 5′-OH, D_2O exch)
51	DMSO-d_6	6.06 (t, J = 7.36)	4.20 (brt)	3.81 (brd)	3.59−3.76 (2m)	8.21 (s, 1H, H-6), 8.07, 6.86 (2s, 2H, NH_2, D_2O exch), 6.25 (d, 3′-OH, D_2O exch), 5.41 (brs, 1H, 5′-OH, D_2O exch)
52	DMSO-d_6	6.24 (t, J = 8.07)	4.33 (m)	4.26 (brd)	3.49−3.63 (2m)	7.84 (s, 1H, H-6), 8.08, 6.87 (2s, 2H, NH_2, D_2O exch), 6.34 (d, 3′-OH, D_2O exch), 5.08 (t, 1H, 5′-OH, D_2O exch)
57	DMSO-d_6	6.30 (dd, J_1=5.0, J_2=10.7)	4.56 (m)	3.93 (m)	3.77 (m)	8.35 (s, 1 H, H-8), 8.16 (s, 1 H, H-2), 7.44 (s, 2 H, NH_2), 6.36 (d, 1 H, 3′-OH), 5.25 (t, 1 H, 5′-OH)
58	DMSO-d_6	6.45 (t, J = 8.2)	4.39−4.46 (m, 2 H)		3.64 (m)	8.29 (s, 1H, H-8), 8.17 (s, 1H, H-2), 7.44 (s, 2H, NH_2), 6.55 (d, 1H, 3′-OH), 5.11 (t, 1H, 5′-OH)

Table 3. ^{13}C NMR Data

compd	δ (ppm)
35	157.94 (d, J = 26.14), 154.03, 140.97 (d, J = 231.77), 124.97 (d, J = 35.64), 123.74 (t, J = 258.27), 84.17 (t, J = 32.59), 81.75, 68.75 (t, J = 22.42), 59.39
36	157.57 (d, J = 26.22), 149.64, 140.49 (d, J = 231.89), 125.34 (d, 34.95), 123.53 (t, J = 259.10), 84.51 (d, J = 6.91), 83.96 (dd, J_1 = 19.62, J_2 = 39.96), 69.67 (dd, J_1 = 17.99, J_2 = 25.93), 60.24
51	164.46, 154.49, 147.22, 123.63 (t, J = 257.94), 84.26 (t, J = 33.52), 81.13, 68.54 (t, J = 22.28), 58.95, 58.21
52	164.77, 154.88, 147.89, 123.93 (t, J = 259.06), 84.61−85.20 (overlap m), 70.52 (dd, J_1 = 18.42, J_2 = 26.19), 60.71, 58.14

substitutions in 3′-erythro or 2′-arabino configurations resulting in extreme C4′-endo/C3′-exo conformations showed activity against HIV-1.[33]

In the present study, there are two fluorine atoms present at the 2′-position and the sugar moiety possesses 3′-endo/2′-exo conformation. While 2′-difluoro substitution in D-nucleosides showed antitumor activity, in L-nucleosides neither cytotoxicity nor significant antiviral activity was observed except for the adenine analog **57**. This indicates that the activity profiles of D-nucleosides may not always be reflected in L-series of nucleosides. Although D- and L-nucleosides are mirror images, the absolute spatial arrangement of the atoms is different which probably is important for their phosphorylation and subsequent biological activity. The two fluorine atoms are in a *gauche* orientation to O3′, and due to high electronegativity of these atoms, they may impart some degree of rigidity to the carbohydrate moiety. While there may be many reasons for differences in the activities of these compounds including the efficiency of phopshorylation, it certainly shows that the difluoro substituent at the 2′-position of the nucleoside has an influence on the sugar puckering resulting in a different biological profile in L-nucleosides.

Experimental Section

General. Melting points were determined on a MelTemp-II melting point apparatus and are uncorrected. UV spectra were recorded on a Beckman DU-650 spectrophotometer. NMR data were recorded on a Bruker-400 AMX spectrometer and the chemical shifts are reported in ppm (δ). Coupling constants (J) were reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), m (multiplet), pd (pseudo doublet), pt (pseudo triplet), brs (broad singlet). Optical rotations were performed on a JASCO DIP-300 digital polarimeter. Mass spectra were either recorded on a Micromass Autospec high-resolution mass spectrometer or obtained from the Chemical and Biological Sciences Mass Spectrometry facility at the University of Georgia. Elemental analyses were performed by either Atlantic Microlab, Inc., Norcross, GA, or by Galbraith Laboratories, Knoxville, TN. Standard workup procedure followed in the reactions, where specified, was to wash the reaction mixture with equal volume of saturated sodium bicarbonate solution (×2) and brine (×2) and dry the organic layer (sodium sulfate or magnesium sulfate). All of the chemicals were purchased from either Aldrich Chemical Co., Sigma Chemicals, or Lancaster Synthesis. ^{1}H and ^{13}C NMR data for representative compounds are compiled in Tables 2 and 3, respectively.

5,6-*O*-Isopropylidine-L-gulono-γ-lactone (2). Compound **2** was synthesized according to published procedures.[26]

2,3-*O*-Isopropylidine-L-glyceraldehyde (3).[26] A suspension of compound **2** (98 g, 0.45 mol) in water (450 mL) was cooled to 5−10 °C in an ice bath, and sodium periodate (193.13 g, 0.90 mol) was added in portions over a period of 45 min while adjusting the pH to 5.5 (approximately) with 2 N NaOH solution. The reaction mixture was stirred for another 2 h at room temperature and was saturated with NaCl. The white precipitate was filtered, and the pH of the aqueous layer was neutralized with a 2 N NaOH solution. The aqueous layer was extracted with EtOAc (5 × 300 mL), and the combined organic layers were dried (sodium sulfate). The organic layer was concentrated at 20 °C. The resulting brownish yellow oil was distilled at 25 mmHg, and the vapors at 58−60 °C were collected to obtain pure compound **3** (28.87 g, 49%). Compound **3** was used immediately for the next reaction.

(4*S*,3*R*)-Ethyl-2,2-difluoro-3-hydroxy-3-(2,2-dimethyl-1,3-dioxolan-4-yl)propionate (4(*R*)). A mixture of freshly distilled compound **3** (28.9 g, 0.22 mol), ethyl 2-bromo-2,2-difluoroacetate (61.0 g, 0.44 mol) in ether (84 mL), and tetrahydrofuran (84 mL) was added dropwise to activated zinc (65.4 g, 0.44 mol) while stirring under argon in such a way that a gentle reflux was maintained. The mixture was added over a period of 20 min and stirred for an additional 30 min at 50 °C. The reaction mixture was cooled and poured into 1 N HCl/ice (250 mL/250 g) mixture. The mixture was stirred until the ice was melted, and the aqueous layer was extracted with ether (2 × 150 mL). Combined organic layers were subjected to a standard workup procedure, and the organic layer was concentrated to obtain a mixture of compounds **4 (R)** and **4 (S)** (30.73 g, 54%). The mixture was subjected to silica gel column chromatography (0.5% MeOH:$CHCl_3$) to

afford the major isomer **4(R)** (19.7 g, 35%), the minor isomer **4(S)** (4.5 g, 8%), and the mixture (6.6 g, 12%).

2-Deoxy-2,2-difluoro-L-*erythro*-pentono-γ-lactone (5). Method A. Compound **4(R)** (19.7 g, 77.0 mmol) was treated with Dowex-50 (H^+) resin (111.0 g) in MeOH:water (2:1, 270 mL) and stirred for 5 days. The resin was filtered, and the solvent was evaporated to dryness. The syrup was coevaporated with toluene (2 × 100 mL) to obtain crude compound **5** (13.2 g, 102%). This was used for the next reaction without any further purification.

Method B. Compound **4(R)** (11.2 g, 51.9 mmol) was treated with concentrated HCl (13.9 mL) in ethanol (86.1 mL) and stirred at room temperature for 4 h. The solvent was evaporated, and the resulting syrup was refluxed in benzene (300 mL) in Dean−Stark apparatus at 95 °C for 20 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to obtain compound **5** as a colorless syrup (8.47 g, 97%).

3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-L-*erythro*-pentono-γ-lactone (6a). A solution of compound **5** (11.1 g, 66.1 mmol) in dichloromethane (300 mL) was treated with 2,6-lutidine (16.2 mL, 138.8 mmol) under nitrogen at 5−10 °C and stirred for 10 min. Benzoyl chloride (16.1 mL, 138.8 mmol) was added slowly to the reaction mixture and stirred at room temperature for 36 h. The solvent was evaporated, and the crude residue was dissolved in hot EtOAc (50 mL). The insoluble solid was filtered, and the filtrate was cooled to room temperature. The precipitate was filtered, and the above process was repeated twice to obtain about 90% pure compound **6a** (24.0 g, 97%) which was used as such for the next reaction. A small portion of the compound was purified by flash silica gel column chromatography (15−30% EtOAc:Hx) to obtain the analytical sample: IR (KBr) 1819.10, 1728.44, 1713.01 (lactone, C═O), 711.83 (C−F); MS (ESI) 377.0 (MH^+). Anal. ($C_{19}H_{14}F_2O_6 \cdot 0.75H_2O$) C, H, F.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-L-*erythro*-pentono-γ-lactone (6b). Compound **5** (6.5 g, 38.7 mmol) was dissolved in DMF (100 mL) and treated with imidazole (12 g, 176 mmol) and *tert*-butylchlorodimethylsilane (15 g, 120 mmol) under N_2. The reaction mixture was stirred at 40 °C for 16 h, and the solvent was evaporated under reduced pressure. The crude was purified by silica gel column chromatography (5% EtOAc:Hx) to obtain compound **6b** (8.3 g, 54%) as a colorless oil. Anal. ($C_{17}H_{34}F_2O_4Si_2$) C, H.

3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-L-*erythro*-pentofuranose (7a). A solution of compound **6a** (22.4 g, 59.5 mL) in dry THF (450 mL) was cooled to −78 °C under argon, and lithium tri-*tert*-butoxyalumino hydride (1 M solution in THF, 68.4 mL, 68.4 mmol) was added over a period of 20 min. The reaction mixture was stirred at −50 °C for an additional 40 min and quenched by slow addition of MeOH (20 mL). The reaction mixture was warmed to room temperature, and 100 mL of EtOAc was added. The reaction mixture was subjected to standard workup procedure, and the organic layer was concentrated to obtain a colorless syrup. The crude was purified on a silica column (15% EtOAc:Hx) to obtain pure compound **7a** (7.39 g, 33%): MS (ESI) 379.0 (MH^+). Anal. ($C_{19}H_{16}F_2O_6 \cdot 0.15H_2O$) C, H.

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-L-*erythro*-pentofuranose (7b). A solution of compound **6b** (5.0 g, 12.5 mmol) in dry toluene (50 mL) was cooled to −85 °C and was treated with DIBAL-H (16.7 mL, 25 mmol, 1.5 M solution in cyclohexane). The reaction mixture was stirred for 2 h at −65 °C and quenched with MeOH. The mixture was allowed to warm up to room temperature and poured into a 1 N HCl (50 mL) solution. The mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic layers were subjected to standard workup procedure. The crude compound was purified on a silica gel column (15% EtOAc: Hx) to obtain compound **7b** (4.8 g, 96%). Anal. ($C_{17}H_{36}F_2O_4Si_2$) C, H.

3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-1-*O*-(methylsulfonyl)-L-*erythro*-pentofuranose (8a). A solution of compound **7a** (500 mg, 1.32 mmol) in dichloromethane (25 mL) was treated with triethylamine (0.92 mL, 6.6 mmol) and methanesulfonyl chloride (0.13 mL, 1.59 mmol) under argon and stirred for 2 h at room temperature. Dichloromethane (50 mL) was added to the reaction mixture and was subjected to standard workup procedure. The organic layer was concentrated, and the crude product was dried under high vacuum for at least 12 h and was used without any further purification in the condensation reactions. A small portion was purified by preparative TLC (25% EtOAc:Hx) to obtain α and β anomers of compound **8a**. Compound **8a** (α): MS (ESI) 361.0 (MH^+). Compound **8a** (β): MS (ESI) 361.0 (MH^+).

3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-1-*O*-(methylsulfonyl)-L-*erythro*-pentofuranose (8b). Compound **7b** (1.0 g, 2.5 mmol) was treated with triethylamine (0.34 g, 3.6 mmol) and methanesulfonyl chloride (0.27 g, 2.4 mmol) in dichloromethane (100 mL) at room temperature and stirred for 3 h. The solvent was evaporated, and the residue was dissolved in EtOAc (50 mL) and subjected to standard workup procedure. The organic layer was concentrated to obtain compound **8b** (1.0 g, 84%).

1-[3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl]thymine (9) and 1-[3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl]thymine (10). Thymine (0.8 g, 6.0 mmol) was refluxed in 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 30 mL) in the presence of ammonium sulfate for 3 h. Excess HMDS was evaporated under reduced pressure to obtain a colorless oil. Compound **8b** (1.0 g, 2.1 mmol) dissolved in acetonitrile (50 mL) and sodium iodide (0.6 g, 4.0 mmol) was added to the silylated thymine, and the mixture was refluxed for 24 h. The solvent was evaporated, and the residue was dissolved in EtOAc (200 mL) and subjected to standard workup procedure. The organic layer was concentrated, and the crude was purified by silica column chromatography (20% EtOAc:Hx) to obtain an anomeric mixture of compounds **9** and **10** (760 mg, 71%): UV (MeOH) λ_{max} 262.0 nm.

1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)uracil (11) and 1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-uracil (12). Uracil (296 mg, 2.64 mmol) was treated with excess HMDS (15 mL) in the presence of ammonium sulfate (10 mg) under argon and refluxed at 125 °C for 4 h. Excess solvent was evaporated under reduced pressure, and the resulting syrup was dissolved in dry dichloroethane (10 mL). A solution of crude compound **8a** (prepared as described above, obtained from 500 mg of compound **7a**) in dichloroethane (15 mL) was added, and the mixture was stirred for 10 min under argon. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.51 mL, 2.64 mmol) was added to the mixture slowly while stirring, and the reaction was refluxed at 90−100 °C under argon for 10 h. The reaction mixture was cooled to room temperature and subjected to standard workup procedure. The organic layer was concentrated, and the crude was purified by flash column chromatography (2% MeOH:$CHCl_3$) to obtain the anomeric mixture of compound **11** and compound **12** (416 mg, 67%). Fractional crystallization from EtOAc afforded the pure compound **11** (61 mg) and the mixture of compound **11** and **12** (355 mg). Compound **11**: UV (MeOH) λ_{max} 257.0, 231.5 nm.

1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-fluorouracil (13) and 1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-fluorouracil (14). Crude compound **8a** was prepared from compound **7a** (500 mg, 1.3 mmol) as described above. 5-Fluorouracil (343 mg, 2.64 mmol) was condensed with crude compound **8a** as described above (compounds **11** and **12**) to obtain the crude anomeric mixture of compounds **13** and **14** (526 mg, 81%). The anomers could not be separated and the crude was used as such for the next reaction: UV (MeOH) λ_{max} 264.0, 231.5, 204.5 nm.

9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-chlorouracil (15) and 9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-chlorouracil (16). Crude compound **8a** was prepared from compound **7a** (500 mg, 1.3 mmol) as described above. 5-Chlorouracil (386.8 mg, 2.6 mmol) was condensed with compound **8a** as described above to obtain a crude anomeric mixture of compounds **15** and **16** (684 mg). The anomeric

mixture could not be separated at this stage and was used as such for the next reaction: UV (MeOH) λ_{max} 273.0, 236.0, 228.0, 204.0 nm.

9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-bromouracil (17) and 9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-bromouracil (18). Crude compound **8a** was prepared from compound **7a** (500 mg, 1.3 mmol) as described above. 5-Bromouracil (504.2 mg, 2.6 mmol) was condensed with crude compound **8a** as described above to obtain a crude anomeric mixture (626 mg) of compounds **17** and **18**. The anomeric mixture could not be resolved and was used as such for the next reaction: UV (MeOH) λ_{max} 274.0, 229.5, 203.0 nm.

9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-iodouracil (19) and 9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-iodouracil (20). Crude compound **8a** was prepared from compound **7a** (500 mg, 1.3 mmol) as described above. 5-Iodouracil (628.2 mg, 2.6 mmol) was condensed with crude compound **8a** as described above to obtain a crude anomeric mixture (590 mg, 75%) of compounds **19** and **20**. The anomeric mixture could not be separated and was used as such for the next reaction: UV (MeOH) λ_{max} 275.5, 230.0, 204.5 nm.

1-[3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl]cytosine (21) and 1-(3,5-Bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl]cytosine (22). 4-Acetylcytosine (0.80 g, 5.0 mmol) was silylated with HMDS (30 mL) in the presence of catalytic $(NH_4)_2SO_4$ as described above. Compound **8b** (1.0 g, 2.1 mmol) dissolved in acetonitrile (40 mL) and sodium iodide (0.3 g, 2.0 mmol) were added to the silylated 4-acetylcytosine, and the mixture was refluxed for 16 h. The solvent was evaporated, and the residue was dissolved in EtOAc and subjected to standard workup procedure. The organic layer was concentrated, and the crude product was purified on a silica gel column to obtain the anomeric mixture of compounds **21** and **22** (602 mg, 54%) which was used as such for the next reaction.

1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-fluoro cytosine (23) and 1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-fluorocytosine (24). Crude compound **8a** was prepared from compound **7a** (500 mg) as described above. 5-Fluorocytosine (340.7 mg, 2.64 mmol) was condensed with crude compound **8a** as described above (for compounds **11** and **12**). The crude anomeric mixture was purified by flash column chromatography (3% MeOH:$CHCl_3$) to obtain compound **23** (91 mg, 14%), compound **24** (130 mg, 20%), and a mixture of compounds **23** and **24** (150 mg, 23%). Compound **23**: UV (MeOH) λ_{max} 274.0, 232.0, 204.0 nm; MS (ESI) 490.0 (MH^+). Compound **24**: UV (MeOH) λ_{max} 274.0, 231.0 nm; MS (ESI) 490.0 (MH^+).

9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-chlorocytosine (25) and 9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-chlorocytosine (26). Crude compound **8a** was prepared from compound **7a** (1.5 g, 4 mmol) by treatment with triethylamine (2.7 mL, 19.9 mmol) and mesyl chloride (0.4 mL, 4.8 mmol) in dichloromethane (40 mL) as described above. 5-Chlorocytosine (873 mg, 6 mmol) was condensed with the crude compound **8a** dissolved in dichloroethane (40 mL) in the presence of TMSOTf (1.2 mL, 6 mmol) as described above, and the crude anomeric mixture was separated by flash column chromatography (1% MeOH:$CHCl_3$) to obtain pure compound **25** (355 mg, 18%) and compound **26** (283 mg, 14%). Compound **25**: UV (MeOH) λ_{max} 275.0, 231.0, 208.0 nm. Compound **26**: UV (MeOH) λ_{max} 281.5, 233.0, 209.0 nm.

9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-bromocytosine (27) and 9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-bromocytosine (28). Crude compound **8a** was prepared from compound **7a** (500 mg, 1.3 mmol) as described above. 5-Bromocytosine (464 mg, 2.44 mmol) was condensed with the crude compound **8a** as described above, and the crude anomeric mixture was separated by flash column chromatography (2% MeOH:$CHCl_3$) to obtain pure compound **27** (119 mg, 16%) and compound **28** (196 mg, 27%). Compound **27**: UV (MeOH) λ_{max} 281.5, 275.0, 232.0 nm. Compound **28**: UV (MeOH) λ_{max} 282.0, 276.5, 230.5 nm.

1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-iodocytosine (29) and 1-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-iodocytosine (30). Crude compound **8a** was prepared from compound **7a** (500 mg) as described above. 5-Iodocytosine (625.7 mg, 2.64 mmol) was condensed with compound **8a** as described above, and the crude product was purified by preparative TLC (2% MeOH:$CHCl_3$) to obtain compound **29** (171 mg, 22%) and compound **30** (196 mg, 25%) as white powder. Compound **29**: UV (λ_{max}) MeOH 282.0, 274.0, 228.0 nm. Compound **30**: UV (MeOH) λ_{max} 282.0, 275.0, 233.0 nm.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-thymine (31) and 1-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)thymine (32). The anomeric mixture of compounds **9** and **10** (760 mg, 1.5 mmol) was treated with *n*-Bu_4NF (3 mL, 1 M solution in THF) in THF (10 mL) and stirred at room temperature for 1 h. The solvent was evaporated, and the crude was purified by a silica gel column to obtain the anomeric mixture. The mixture was separated by HPLC (Waters Prep-500 C-18 column, 3% acetonitrile: water) to obtain compound **31** (50 mg, 9%) and compound **32** (200 mg, 34%) which were coevaporated with EtOAc and obtained as white foams. Compound **31**: $[\alpha]^{25}_D$ −44.4° (*c* 0.14, MeOH); UV (H_2O) λ_{max} 266.5 (9870, pH 2.0), 266.0 (8860, pH 7.0), 266.5 nm (7670, pH 11.0). Anal. ($C_{10}H_{12}F_2N_2O_5 \cdot 0.2H_2O$) C, H, N. Compound **32**: $[\alpha]^{25}_D$ +32.4° (*c* 0.33, MeOH); UV (H_2O) λ_{max} 266.5 (10 210, pH 2.0), 266.0 (7870, pH 7.0), 266.5 nm (9870, pH 11.0). Anal. ($C_{10}H_{12}F_2N_2O_5$) C, H, N.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-uracil (33). Compound **11** (58 mg, 0.12 mmol) was treated with methylamine (40% solution in water, 0.1 mL, 1.2 mmol) in MeOH (10 mL) at room temperature and stirred for 15 h. The solvent was evaporated, and the crude was purified by flash column chromatography (1% triethylamine:10% MeOH: $CHCl_3$) to obtain compound **33** (31 mg, 98%) as a hygroscopic white powder: $[\alpha]^{26}_D$ −45.8° (*c* 0.23, MeOH); UV (MeOH) λ_{max} 257.0, 207.5 nm; (H_2O) 258.5 (11 150), 252.5 (10 705), 209.0 (10 103), 203.5 nm (10 851) (pH 2.0); 258.5 (10 535), 204.0 nm (9666) (pH 7.0); 258.5 (8152), 219.0 (9642), 207.5 nm (4502) (pH 11.0); MS (ESI): 265.0 (MH^+). Anal. ($C_9H_{10}F_2N_2O_5 \cdot 0.5 H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-uracil (34). The anomeric mixture **11** and **12** (355 mg, 0.75 mmol) was deprotected with methylamine (40% solution in water, 0.76 mL, 8.8 mmol) in MeOH (15 mL) as described above, and the anomeric mixture was purified by flash column chromatography (8% MeOH:$CHCl_3$). The anomers were separated by preparative HPLC (Waters reverse phase C-18 column; flow rate 50 mL/min; mobile phase 10% MeOH:water) to obtain compound **33** (18 mg, 9.1%) and compound **34** (51 mg, 25.7%). Compound **34**: mp 77−80 °C; $[\alpha]^{26}_D$ −22.8° (*c* 0.27, MeOH); UV (MeOH) λ_{max} 256.0, 206.0 nm; (H_2O) 258.0 (10 021), 205.5 nm (9374) (pH 2.0); 258.5 (9975), 206.5 nm (8845) (pH 7.0); 259.0 (7672), 223.5 (8172), 212.0 nm (4875) (pH 11.0); MS (ESI) 265.0 (MH^+). Anal. ($C_9H_{10}F_2N_2O_5 \cdot 0.6 H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-fluorouracil (35) and 1-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-fluorouracil (36). A crude mixture of **13** and **14** (520 mg, 1.06 mmol) was deprotected with saturated NH_3 in MeOH (30 mL) as described above, and the crude product was purified by flash column chromatography (8% MeOH:CH_2Cl_2) to obtain pure compound **35** (64 mg, 21%) and **36** (71 mg, 25%). Compound **35**: mp 85−88 °C; $[\alpha]^{27}_D$ −61.5° (*c* 0.24, MeOH); UV (MeOH) λ_{max} 264.5, 207.0 nm; (H_2O) 265.0 (8681), 206.5 nm (9067) (pH 2.0); 264.5 (8610), 206.5 nm (10 791) (pH 7.0); 266.5 (7202), 224.5 nm (8418) (pH 11.0); MS (FAB) 283.0 (MH^+). Anal. ($C_9H_9F_3N_2O_5 \cdot 0.5H_2O$) C, H, N. Compound **36**: mp 199−203 °C; $[\alpha]^{28}_D$ −18.8° (*c* 0.22, MeOH); UV (MeOH) λ_{max} 264.0, 206.0 nm; (H_2O) 265.5 (8471), 205.5 nm (8822) (pH 2.0); 265.5 (8361), 207.5 nm (10 041) (pH 7.0); 266.5 (6633), 225.5 nm (7564) (pH 11.0); MS (FAB) 283.0 (MH^+). Anal. ($C_9H_9F_3N_2O_5 \cdot 0.53 H_2O$) C, H, N.

9-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-chlorouracil (37) and 9-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-chlorouracil (38). Crude anomeric mixture of compounds **15** and **16** (600 mg, 1.18 mmol) was deprotected with saturated NH_3 in MeOH (25 mL) as described above, and the crude product was purified by flash column chromatography (5% MeOH:CH_2Cl_2) to obtain pure compound **37** (62 mg, 16%) and compound **38** (121 mg, 31%) as a white powder. Compound **37**: mp 98−99 °C; $[\alpha]^{28}_D$ −36.9° (*c* 0.21, MeOH); UV (MeOH) λ_{max} 272.5, 209.5 nm; (H_2O) 272.5 (8915), 211.0 nm (9122) (pH 2); 273.0 (7802), 211.5 nm (9467) (pH 7.0); 272.5 (6414), 223.0 nm (8355) (pH 11.0); MS (FAB) 299.0 (22%), 301.0 (8%). Anal. ($C_9H_9ClF_2N_2O_5 \cdot 0.5H_2O$) C, H, N. Compound **38**: mp 70−72 °C; $[\alpha]^{27}_D$ −27.9° (*c* 0.28, MeOH); UV (MeOH) λ_{max} 272.0, 210.0 nm; (H_2O) 273.5 (6618), 211.5 nm (6643) (pH 2.0); 273.5 (6847), 212.0 nm (7983) (pH 7.0); 273.0 (5205), 222.5 nm (7100) (pH 11.0); MS (FAB) 299.0 (100), 301.0 (37). Anal. ($C_9H_9ClF_2N_2O_5 \cdot 0.78\ H_2O$) C, H, N.

9-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-bromouracil (39) and 9-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-bromouracil (40). A crude anomeric mixture of compounds **17** and **18** (615 mg, 1.12 mmol) was deprotected with saturated NH_3 in MeOH (25 mL) as described above, and the crude product was purified by flash column chromatography (5% MeOH:CH_2Cl_2) to obtain pure compound **39** (96 mg, 25%) and compound **40** (50 mg, 13%) as a white powder. Compound **39**: mp 98−102 °C; $[\alpha]^{27}_D$ −18.3° (*c* 0.27, MeOH); UV (MeOH) λ_{max} 275.0, 209.5 nm; (H_2O) 275.5 (9042), 209.5 nm (9794) (pH 2.0); 275.0 (8530), 210.0 nm (10 745) (pH 7.0); 274.0 (6761), 222.0 (9330) (pH 11.0); MS (FAB) 343.0 (16), 345 (16). Anal. ($C_9H_9BrF_2N_2O_5 \cdot 0.25H_2O$) C, H, N. Compound **40**: mp 82−86 °C; $[\alpha]^{27}_D$ −42.7° (*c* 0.22, MeOH); UV (MeOH) λ_{max} 274.0, 210.5 nm; (H_2O) 276.0 (9255), 210.0 nm (9934) (pH 2.0); 275.5 (8677), 210.5 nm (10 534) (pH 7.0); 274.5 (6620), 220.0 nm (9593) (pH 11.0); MS (FAB) 343 (46), 345 (45). Anal. ($C_9H_9BrF_2N_2O_5 \cdot 0.5H_2O$) C, H, N.

9-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-iodouracil (41) and 9-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-iodouracil (42). A crude anomeric mixture of compounds **19** and **20** (575 mg, 0.96 mmol) was deprotected with saturated NH_3 in MeOH (20 mL) as described above, and the crude product was purified by flash column chromatography (5% MeOH:CH_2Cl_2) to obtain pure compound **41** (63 mg, 17%) and compound **42** (95 mg, 25%) as a white powder. Compound **42**: mp 184−188 °C; $[\alpha]^{27}_D$ −0.6° (*c* 0.24, MeOH); UV (MeOH) λ_{max} 260.0, 214.5 nm; 283.5 (7714), 215.0 nm (11 667) (pH 2.0); 283.0 (6941), 215.0 nm (11 445) (pH 7.0); 276.0 (5683), 221.0 nm (12 757) (pH 11.0); MS (FAB) 391.0 (MH^+). Anal. ($C_9H_9F_2IN_2O_5$) C, H, N. Compound **42**: mp 84−86 °C; $[\alpha]^{27}_D$ −46.6° (*c* 0.20, MeOH); UV (MeOH) λ_{max} 279.0, 214.5 nm; (H_2O) 284.0 (6965), 215.5 nm (10 268) (pH 2.0); 283.5 (6691), 216.0 (10 648), 204.5 nm (9092) (pH 7.0); 276.5 (5300), 220.0 (12 342), 205.0 nm (8015) (pH 11.0); MS (FAB) 391.0 (MH^+). Anal. ($C_9H_9F_2IN_2O_5 \cdot 0.1H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-cytosine (43) and 1-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)cytosine (44). Anomeric mixture of compounds **21** and **22** (602 mg, 1.13 mmol) was treated with sodium (30 mg) dissolved in MeOH (10 mL), and the mixture was stirred for 2 h. The mixture was neutralized with AcOH, and the solvent was removed under reduced pressure. The crude mixture was treated with *n*-Bu_4NF (3 mL, 1 M solution in THF) in THF (10 mL) and stirred at room temperature for 1 h. The solvent was evaporated, and the crude was purified by a silica gel column to obtain the anomeric mixture. The mixture was separated by HPLC (Waters Prep-500 C-18 column, water) to obtain compound **43** (60 mg, 20%) and compound **44** (170 mg, 57%). Compound **43**: $[\alpha]^{25}_D$ +11.0° (*c* 0.36, MeOH); UV (H_2O) λ_{max} 272.0 (8140, pH 2.0), 271.5 (7180, pH 7.0), 271.5 nm (9830, pH 11.0). Anal. ($C_9H_{11}F_2N_3O_4 \cdot 1.5H_2O$) C, H, N. Compound **44**: $[\alpha]^{25}_D$ −39.4° (*c* 0.22, MeOH); UV (H_2O) λ_{max} 271.5 (8840, pH 2.0), 271.0 (9180, pH 7.0), 271.5 nm (7830, pH 11.0). Anal. ($C_9H_{11}F_2N_3O_4 \cdot 2.5H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-fluorocytosine (45). Compound **23** (85 mg, 0.17 mmol) was deprotected with methylamine (40% solution in water, 0.15 mL, 1.74 mmol) in MeOH (10 mL) as described above, and the crude product was purified by flash column chromatography (10% MeOH:$CHCl_3$) to obtain compound **45** (47.5 mg, quant): mp 208−211.5 °C; $[\alpha]^{27}_D$ −78.3° (*c* 0.28, MeOH); UV (MeOH) λ_{max} 279.5, 243.5, 204.5 nm; (H_2O) 281.5 (9323), 211.0 (9735), 202.5 nm (9908) (pH 2.0); 277.5 (7509), 239.0 (8386), 209.5 (8855), 202.5 nm (9800) (pH 7.0); 278.0 (7821), 239.0 (8433), 209.0 nm (5761) (pH 11.0); MS (FAB): 282.0 (MH^+). Anal. ($C_9H_{10}N_3O_4F_3 \cdot 1.3H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-fluorocytosine (46). Compound **24** (122 mg, 0.25 mmol) was deprotected with methylamine (0.22 mL, 2.5 mmol) in MeOH (10 mL) as described above, and the crude mixture was purified by flash column chromatography (10% MeOH:$CHCl_3$) to obtain pure compound **46** (39 mg, 55%) as a white powder: mp 130−135 °C; $[\alpha]^{26}_D$ +8.7° (*c* 0.40, MeOH); UV (MeOH) λ_{max} 279.0, 243.0, 209.0, 282.0 (8874), 212.0 nm (9251) (pH 2.0); 276.5 (8103), 236.5 (8954), 208.0 nm (10 703) (pH 7.0); 277.5 nm (7652), 237.0 (8138), 205. nm (4520) (pH 11.0); MS (FAB): 282.0 (MH^+). Anal. ($C_9H_{10}F_3N_3O_4 \cdot 0.3H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-chlorocytosine (47). Compound **25** (423 mg, 0.83 mmol) was deprotected with saturated NH_3 in MeOH (40 mL) as described above and purified by flash column chromatography (8% MeOH: $CHCl_3$) to obtain compound **47** (211 mg, 85.4%) as a white powder: mp 158−163 °C; $[\alpha]^{27}_D$ −45.3° (*c* 0.23, MeOH); UV (H_2O) λ_{max} 288.5 (8313), 216.5 (11 289), 203.0 nm (12 895) (pH 2.0); 284.0 (6857), 217.0 (10 991), 205.5 nm (13 111) (pH 7.0); 283.5 (6987), 220.0 (9972), 212.5 (5902), 204.0 nm (6927) (pH 11.0); MS (FAB) 298.0 (53), 300.0 (19). Anal. ($C_9H_{10}ClF_2N_3O_4 \cdot 0.55H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-chlorocytosine (48). Compound **26** (346 mg, 0.68 mmol) was deprotected with saturated NH_3 in MeOH (35 mL) as described above and purified by flash column chromatography (8% MeOH: $CHCl_3$) to obtain compound **48** (173 mg, 85.2%) as a white powder: mp 189−190.5 °C; $[\alpha]^{27}_D$ −14.0° (*c* 0.24, MeOH); UV (H_2O) λ_{max} 289.5 (9269), 216.0 nm (12 327), 202.5 nm (13 859) (pH 2.0); 283.5 (7451), 217.5 (11 852), 213.0 (11 888), 206.0 nm (15 181) (pH 7.0); 284.0 (7715), 221.5 nm (10 763), 213.0 (7746), 204.5 nm (5216) (pH 11.0); MS (FAB): 298.0 (100), 300.0 (36). Anal. ($C_9H_{10}ClF_2N_3O_4 \cdot 0.5H_2O$) C, H, N.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-bromocytosine (49). Compound **27** (116 mg, 0.21 mmol) was deprotected with saturated NH_3 in MeOH (20 mL) as described above and purified by flash column chromatography (15% MeOH: dichloromethane) to obtain compound **49** (62 mg, 86%) as white powder: mp 172−174 °C; $[\alpha]^{27}_D$ −39.1° (*c* 0.22, MeOH); UV (MeOH) λ_{max} 287.0, 206.5 nm; 291.5 (8018), 203.5 nm (13 392) (pH 2.0); 285.5 (6554), 204.0 (17 595) (pH 7.0); 286.0 (6665), 224.0 (8614), 221.5 nm (8898) (pH 11.0); MS (FAB): 342.0 (26), 344.0 (25). Anal. ($C_9H_{10}BrF_2N_3O_4 \cdot H_2O$) C, H.

1-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-bromocytosine (50). Compound **28** (189 mg, 0.34 mmol) was deprotected with saturated NH_3 in MeOH (25 mL) as described above, and the crude product was triturated with 8% MeOH:$CHCl_3$. The white precipitate obtained was collected as compound **50** (88 mg, 75.7%): mp 221.5−224.0 °C; $[\alpha]^{27}_D$ −27.3 ° (*c* 0.24, MeOH); UV (MeOH) λ_{max} 287.0, 209.5 nm; (H_2O) 292.5 (8807), 204.5 nm (13 400) (pH 2.0); 286.0 (6880), 204.0 nm (16 895) (pH 7.0); 286.5 (6695), 224.5 (8719), 221.0 nm (9167) (pH 11.0); MS (FAB) 342.0 (59), 344.0 (58). Anal. ($C_9H_{10}BrF_2N_3O_4$) C, H, N.

1-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-5-iodocytosine (51). Compound **29** (152 mg, 0.25 mmol) was deprotected with methylamine (0.22 mL, 2.5 mmol) in MeOH (15 mL) as described above, and the crude mixture was purified by flash column chromatography (8% MeOH:$CHCl_3$) to obtain pure compound **51** (85 mg, 87%) as white powder: mp 222−223.0 °C; $[\alpha]^{27}_D$ −18.0° (c 0.27, MeOH); UV (MeOH) λ_{max} 293.5, 203.0 nm; (H_2O) 303.5 (7306), 221.0 nm (14 905) (pH 2.0); 292.0 (6609), 220.0 nm (16 195) (pH 7.0); 293.0 (6309), 225.5 nm (14 637) (pH 11.0); MS (FAB) 390.0 (MH^+). Anal. ($C_9H_{10}F_2IN_3O_4 \cdot 1.3H_2O$) C, H, N.

1-(2-Deoxy-2, 2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-5-iodocytosine (52). Compound **30** (179 mg, 0.30 mmol) was deprotected with methylamine (0.25 mL, 3 mmol) in MeOH (15 mL) as described above, and the crude product was purified by flash column chromatography (8% MeOH:$CHCl_3$) to obtain pure compound **52** (108 mg, 92%) as a white powder: mp 217−218 °C; $[\alpha]^{27}_D$ −42.1° (*c* 0.24, MeOH); UV (MeOH) λ_{max} 293.5, 217.5 nm; (H_2O) 304.0 (7655), 221.5 nm (15 141) (pH 2.0); 292.5 (6116), 211.0 nm (16 256) (pH 7.0); 292.5 (6864), 226.5 nm (15 351) (pH 11.0); MS (FAB) 390.0 (MH^+). Anal. ($C_9H_{10}F_2IN_3O_4 \cdot 0.3H_2O$) C, H, N.

9-(3,5-Di-*O*-benzoyl-2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-6-chloropurine (53a) and 9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-6-chloropurine (54a). A suspension of compound **7a** (1.0 g, 3.64 mmol), 6-chloropurine (1.07 g, 6.95 mmol), and triphenylphosphine (1.8 g, 6.95 mmol) in dry tetrahydrofuran (25 mL) was cooled to 0 °C in an ice bath under argon, and diethyl azodicarboxylate (1.09 mL, 6.95 mmol) was added slowly. The reaction mixture turned to brownish yellow solution and was stirred at room temperature for 5 h. The mixture was diluted with EtOAc (100 mL) and followed standard workup procedure. The organic layer was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (25% EtOAc:Hx) to obtain pure compound **53a** (55 mg, 3%), compound **54a** (287 mg, 15%), and a mixture of **53a** and **54a** (230 mg, 12%). The anomeric mixture was used as such for the next reaction without further separation. Compound **53a**: UV (MeOH) λ_{max} 263.0, 231.5, 207.5 nm; MS (ESI) 514.8 (MH^+). Compound **54a**: UV (MeOH) λ_{max} 263.5, 231.5, 210.0 nm; MS (ESI) 514.8 (MH^+).

9-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-hypoxanthine (59) and 9-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)hypoxanthine (60). The anomeric mixture of **53a** and **54a** (222 mg, 0.43 mmol) was treated with 2-mercaptoethanol (0.18 mL, 2.59 mmol) and sodium methoxide (147 mg, 2.59 mmol) in MeOH (15 mL) under argon and refluxed at 70−80 °C for 24 h. The reaction mixture was cooled to room temperature and neutralized with glacial acetic acid. The solvent was evaporated, and the crude was purified by flash column chromatography (8% MeOH:$CHCl_3$) to obtain the pure anomeric mixture of compounds **59** and **60** (89 mg). This was separated by preparative HPLC (reverse phase C-18 ODS column, flow rate 50 mL/min, 5% MeOH:water) to obtain pure compounds **60** (retention time 31.37 min, 19 mg, 15%) and **59** (retention time 43.62 min, 54 mg, 44%). Compound **59**: mp 151−155 °C; $[\alpha]^{27}_D$ −45.3° (*c* 0.24, MeOH); UV (MeOH) λ_{max} 244.0, 202.5 nm; (H_2O) 247.0 (10 440), 203.0 nm (13 129) (pH 2.0); 247.0 (10 795), 204.5 nm (11 857) (pH 7.0); 252.5 (12 212), 217.5 (2975), 212.0 (6505), nm 201.0 (4404) (pH 11.0); MS (FAB): 289.0 (MH^+). Anal. ($C_{10}H_{10}F_2N_4O_4 \cdot 0.5H_2O$) C, H, N. Compound **60**: mp 132−135 °C; $[\alpha]^{27}_D$ −51.2° (*c* 0.14, MeOH); UV (MeOH) λ_{max} 244.0, 206.0 nm; (H_2O) 247.0 (10 733), 201.5 nm (17 038) (pH 2.0); 247.5 (11 164), 203.5 nm (15 088) (pH 7.0); 252.0 nm (11 193, pH 11.0); MS (FAB): 289.0 (MH^+). Anal. ($C_9H_{10}F_2N_4O_4 \cdot 0.9H_2O$) C, H, N.

6-Chloro-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl]purine (53b) and 6-Chloro-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl]purine (54b). A mixture of compound **7b** (1.2 g, 3 mmol), 6-chloropurine (0.81 g, 5.0 mmol), DEAD (0.8 mL, 5.0 mmol), and triphenylphosphine (1.32 g, 5.0 mmol) in THF was stirred at room temperature for 24 h. The solvent was evaporated, and residue was dissolved in EtOAc (200 mL) and subjected to a standard workup procedure. The organic layer was concentrated, and the residue was purified by silica column chromatography (15% EtOAc:Hx) to obtain compound **53b** (776 mg, 47%) and compound **54b** (246 mg, 15%). Compound **53b**: UV (MeOH) λ_{max} 263.0 nm. Compound **54b**: UV (MeOH) λ_{max} 263.0 nm.

6-Chloro-9-(2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)purine (55). Compound **53b** (776 mg, 1.41 mmol) was treated with *n*-Bu_4NF (3.4 mL, 1 M in THF) in THF (40 mL), and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure, and the residue was purified on a silica column (5% MeOH:$CHCl_3$) and coevaporated with EtOAC to obtain compound **55** (400 mg, 93%) as a white foam: UV (MeOH) λ_{max} 263.0 nm.

6-Chloro-9-(2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)purine (56). Compound **54b** (246 mg, 0.45 mmol) was treated with *n*-Bu_4NF (1 mL, 1 M solution in THF) in THF (5 mL) at room temperature, and the mixture was stirred for 30 min. The solvent was evaporated under reduced pressure, and the crude product was purified on a silica column (5% MeOH:$CHCl_3$) to obtain compound **56** (130 mg, 95%) as a white solid: mp 170−171 °C; UV (MeOH) λ_{max} 262.5 nm.

9-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-adenine (57). A solution of compound **55** (394 mg, 1.37 mmol) in saturated NH_3 in MeOH (30 mL) in a steel bomb was stirred at 100 °C for 20 h. The bomb was cooled, the solvent was evaporated under reduced pressure, and the residue was purified on a silica gel column (10% MeOH:$CHCl_3$) to obtain compound **57** (186 mg, 73%) as a white solid: mp 243−244 °C; $[\alpha]^{25}_D$ +2.1° (*c* 0.38, MeOH); UV (H_2O) λ_{max} 258.5 (13 670, pH 2.0), 258.5 (14 460, pH 7.0), 258.0 nm (13 660, pH 11.0). Anal. ($C_{10}H_{11}F_2N_5O_5 \cdot 0.25H_2O$) C, H, N.

9-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-adenine (58). Compound **56** (110 mg, 0.36 mmol) was treated with saturated ammonia in MeOH (30 mL) in a steel bomb, and the mixture was stirred for 20 h. The reaction mixture was cooled, the solvent was evaporated under reduced pressure, and the crude residue was purified on a silica gel column (10% MeOH:$CHCl_3$) to obtain compound **58** (90 mg, 93%) as a white solid: mp 168−170 °C; $[\alpha]^{25}_D$ −60.2° (*c* 0.26, MeOH); UV (MeOH) λ_{max} 258.5 (14 760, pH 2.0), 258.0 (15 220, pH 7.0), 258.5 nm (13 270, pH 11.0). Anal. ($C_{10}H_{11}F_2N_5O_5 \cdot 0.25H_2O$) C, H, N.

9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-2-amino-6-chloropurine (61) and 9-(3,5-Di-*O*-benzoyl-2-deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-2-amino-6-chloropurine (62). Crude compound **8b** was prepared from compound **7b** (1 g, 2.6 mmol) by treatment with triethylamine (1.8 mL, 13.2 mmol) and mesyl chloride (0.25 mL, 3.2 mmol) in dichloromethane (30 mL) as described above. 2-Amino-6-chloropurine (895 mg, 5.28 mmol) was silylated with HMDS (15 mL) and $(NH_4)_2SO_4$ (20 mg) as described above. Silylated 2-amino-6-chloropurine was condensed with crude compound **8b** dissolved in dichloroethane (30 mL) in the presence of TMSOTf (1 mL, 5.3 mmol) as described above. The crude mixture was separated by flash column chromatography (0.5% MeOH:$CHCl_3$) to obtain pure compound **61** (210 mg, 15%) and compound **62** (150 mg, 11%). Compound **61**: UV (MeOH) λ_{max} 324.5, 274.5, 226.0 nm. Compound **62**: UV (MeOH) λ_{max} 324.0, 274.5, 230.0 nm.

9-(2-Deoxy-2,2-difluoro-β-L-*erythro*-pentofuranos-1-yl)-guanine (63). Compound **61** (203 mg, 0.37 mmol) was treated with 2-mercaptoethanol (0.13 mL, 1.87 mmol) and sodium methoxide (95%, 106 mg, 1.87 mmol) in MeOH (20 mL) and refluxed at 70−80 °C for 26 h. The reaction mixture was cooled to room temperature, and the pH was adjusted to 7.0 by using glacial acetic acid. The solvent was evaporated, and the crude product was purified by flash column chromatography (10% MeOH:$CHCl_3$) to obtain compound **63** (29 mg, 26%) as white powder: mp 222−228 °C; $[\alpha]^{27}_D$ −47.3° (*c* 0.12, MeOH); UV (MeOH) λ_{max} 287.5, 242.5, 208.5 nm; (H_2O) 272.5 (3792), 248.5 (3460) (pH 2.0); 285.5 (4588), 212.5 nm (13.034) (pH 7.0); 282.5 (2474), 222.0 nm (8066) (pH 11.0); MS (FAB) 304.0857 (MH^+) (calcd 304.0855). Anal. ($C_9H_{11}F_2N_5O_4 \cdot 0.2CHCl_3 \cdot 0.38MeOH$) C, H, N.

9-(2-Deoxy-2,2-difluoro-α-L-*erythro*-pentofuranos-1-yl)-guanine (64). Compound **62** (149 mg, 0.28 mmol) was treated with 2-mercaptoethanol (0.10 mL, 1.38 mmol) and sodium methoxide (95%, 78 mg, 1.38 mmol) in MeOH (10 mL) as described for compound **63**, and the crude product was purified by flash column chromatography (10% MeOH:$CHCl_3$) to obtain compound **64** (67 mg, 79%) as white powder: mp 290 °C (char); $[\alpha]^{27}_D$ −25.7° (*c* 0.13, MeOH); UV (MeOH) λ_{max} 288.0, 241.0, 207.5 nm; (H_2O) 265.5 (shoulder, 5766), 248.0 (6512), 201.0 nm (14 497) (pH 2.0); 286.5 (7006), 214.0 nm (20 773) (pH 7.0);

283.0 (5319), 222.0 (11 141), 208.0 nm (4398) (pH 11.0); MS (FAB) 304.0 (MH^+). Anal. ($C_9H_{11}F_2N_5O_4 \cdot 0.5\ H_2O$) C, H, N.

Acknowledgment. We thank Dr. Michael Bartlett for providing the mass spectral analysis data. We acknowledge the financial support of the NIH Grants AI 32351 and AI 33655 and the Department of Veterans Affairs. We thank Ms. Susan Schlueter-Wirtz, Angela McMillan, and Sarah Kupfer for excellent technical assistance.

Supporting Information Available: Tables of Anti-HIV, anti-HBV, and anti-HSV activities and ^1H and ^{13}C NMR data (8 pages). Ordering information is given on any current masthead page.

References

(1) Chu, C. K.; Baker, D. C., Eds. *Nucleosides and Nucleotides as Antitumor agents and Antiviral Agents*: Plenum Press: New York, 1993.
(2) De Clercq, E. Toward improved anti-HIV chemotherapy: Therapeutic strategies for intervention with HIV infections. *J. Med. Chem.* **1995**, *38*, 2491−2517.
(3) Martin, J. L.; Brown, C. E.; Mathews-Davis, N.; Reardon, J. E. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. *Antimicrob. Agents Chemother.* **1994**, *38*, 2743−2749.
(4) Parker, W. B.; Cheng, Y. C. Mitochondrial toxicity of antiviral nucleoside analogs. *J. NIH Res.* **1994**, *6*, 57−61.
(5) Shirasada, T.; Kavlick, M. F.; Veno, T.; Gao, W.-Y.; Kojima, E.; Alcaide, M. L.; Chokekijchai, S.; Roy, B. M.; Arnold, E.; Yarchoan, R.; Mitsuya, H. Emergence of human immunodeficiency virus type 1 variants with resistance to multiple dideoxy nucleosides in patients receiving therapy with dideoxy nucleosides. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2398−2402.
(6) Chatis, P. A.; Crumpacker, C. S. Resistance of herpes viruses to antiviral drugs. *Antimicrob. Agents Chemother.* **1992**, *36*, 1589−1595.
(7) Jeong, L. S.; Schinazi, R. F.; Beach, J. W.; Kim, H. O.; Nampalli, S.; Shanmuganathan, K.; Alves, A. J.; McMillan, A.; Chu, C. K.; Mathis, R. Asymmetric synthesis and biological evaluation of β-L-(2R, 5S)- and α-L-(2R, 5R)-1,3-oxathiolane-pyrimidine and -purine nucleosides as potential anti-HIV agents. *J. Med. Chem.* **1993**, *36*, 181−195.
(8) Kim, H. O.; Schinazi, R. F.; Shanmuganathan, K.; Jeong, L. S.; Beach, J. W.; Nampalli, K.; Cannon, D. L.; Chu, C. K. L-β-(2S, 4S)- and L-α-(2S, 4R)-Dioxolanyl nucleosides as potential anti-HIV agents: Asymmetric synthesis and structure-activity relationships. *J. Med. Chem.* **1993**, *36*, 519−528.
(9) Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L. S.; Beach, J. W.; Choi, W.-B.; Yeola, S.; Liotta, D. C. Activities of the four optical isomers of 2′,3′-dideoxy-3′-thiacytidine (BCH-189) against human immunodeficiency virus type 1 in human lymphocytes. *Antimicrob. Agents Chemother.* **1992**, *36*, 672−676.
(10) Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. Synthesis of enantiomerically pure (2′R,5′S)-(−)-1,2-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine as a potent antiviral agent against hepatitis B virus (HBV) and human immunodeficiency virus (HIV). *J. Org. Chem.* **1992**, *57*, 2217−2219.
(11) Frick, L. W.; Lambe, C. U.; St. John, L.; Taylor, L. C.; Nelson, D. J. Pharmacokinetics, oral bioavailability, and metabolism in mice and Cynomolgus monkeys of (2′R,5′S)-*cis*-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine, as agent active against human immunodeficiency virus and human hepatitis B virus. *Antimicrob. Agents Chemother.* **1994**, *38*, 2722−2729.
(12) Lin, T.-S.; Luo, M.-Z.; Liu, M.-C. Synthesis of several pyrimidine L-nucleoside analogs as potential antiviral agents. *Tetrahedron* **1995**, *51*, 1055−1068.
(13) Lin, T.-S.; Luo, M.-Z.; Zhu, J. L.; Liu, M.-C.; Zhu, Y. L.; Dutschman, G. E.; Cheng, Y.-C. Synthesis of a series of purine 2′,3′-dideoxy-L-nucleoside analogs as potential antiviral agents. *Nucleosides Nucleotides* **1995**, *14*, 1759−1793.
(14) Gosselin, G.; Schinazi, R. F.; Sommadossi, J.-P.; Mathé, C.; Bergogne, M.-C.; Aubertin, A.-M.; Kiru, A.; Imbach, J.-L. Anti-human immunodeficiency virus activities of the β-L-enantiomer of 2′,3′-dideoxy cytidine and its 5-fluoro derivative *in vitro*. *Antimicrob. Agents Chemother.* **1994**, *38*, 1292−1297.
(15) Lin, T. S.; Luo, M. Z.; Pai, S. B.; Dutschman, G. E.; Cheng, Y.-C. Synthesis and biological evaluation of 2′,3′-dideoxy-L-pyrimidine nucleosides as potential antiviral agents against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). *J. Med. Chem.* **1994**, *37*, 798−803.
(16) Ma, T.; Pai, S. B.; Zhu, Y. L.; Lin, J. S.; Shanmuganathan, K.; Du, J. F.; Wang, C. W.; Kim, H.; Newton, M. G.; Cheng, Y.-C.; Chu, C. K. Structure-activity relationships of 1-(2-deoxy-2−fluoro-β-L-arabinofuranosyl) pyrimidine nucleosides as anti-hepatitis B virus agents. *J. Med. Chem.* **1996**, *39*, 2835−2843.
(17) Chu, C. K.; Ma, T. W.; Shanmuganathan, K.; Wang, C. G.; Xiang, Y. J.; Pai, S. B.; Yao, G. Q.; Sommadossi, J.-P.; Cheng, Y.-C. Use of 2′-fluoro-5-methyl-β-L-arabinofuranosyluracil as a novel antiviral agent for hepatitis B virus and Epstein-Barr virus. *Antimicrob. Agents Chemother.* **1995**, *39*, 979−981.
(18) Pai, S. B.; Liu, S. H.; Zhu, Y. L.; Chu, C. K.; Cheng. Y. C. Inhibition of hepatitis-B virus by a novel L-nucleoside, 2′-fluoro-5-methyl-β-L-arabinofuranosyl uracil. *Antimicrob. Agents Chemother.* **1996**, *40*, 380−386.
(19) Tennant, B.; Jacob, J.; Graham, L. A.; Peek, S.; Korba, B.; Gerin, J. L.; Witcher, J. W.; Boudinot, F. D.; Du, J.; Chu, C. K. Pharmacokinetic and pharmacodynamic studies of 1-(2−fluoro-5-methyl-β-L-arabinofuranosyl)uracil (L-FAMU) in the Woodchuck Model of Hepatitis B virus (HBV) infection. *Antiviral Res.* **1997**, *34 (2)*, A52.
(20) Hertel, L. W.; Kroin, J. S. 2′-Deoxy-2′,2′-difluoro-(4-substituted pyrimidine) nucleosides having antiviral and anti-cancer activity and intermediates. Eur. Pat. Appl. EP 576,230 1993; *Chem. Abstr.* **1993**, *121*, 57886q.
(21) Grindey, G. B.; Grossman, C. S.; Hertel, L. W.; Kroin, J. S. 2′-Deoxy-2′,2′-difluoro-(2,6,8−substituted) purine nucleosides having antiviral and anticancer activity and intermediates. *Eur. Pat. Appl. EP 576,227* **1993**; *Chem. Abstr.* **1993**, *121*, 57887r.
(22) Plunkett, W.; Gandhi, V.; Chubb, C.; Nowak, B.; Heinemann, V.; Mineishi, S.; Sen, A.; Hertel, L. W.; Grindey, G. B. 2′,2′-Difluorodeoxycytidine metabolism and mechanism of action in human leukemia cells. *Nucleosides Nucleotides* **1989**, *8*, 775−785.
(23) Ruiz, V. W. T.; Haperen, V.; Veerman, G.; Vermorken, J. B.; Peters, G. J. 2′,2′-Difluorodeoxycytidine (gemcitabine) incorporation into RNA and DNA of tumor cell lines. *Biochem. Pharmacol.* **1993**, *46*, 762−766.
(24) Gandhi, V.; Mineishi, S.; Huang, P.; Chapman, A. J.; Young, Y.; Chen, F.; Nowak, B.; Chubb, S.; Hertel, L. W.; Plunkett, W. Cytotoxicity, metabolism and mechanism of action of 2′,2′-difluorodeoxy guanosine in Chinese Hamster Ovary cells. *Cancer Res.* **1995**, *55*, 1517−1524.
(25) Xiang, Y. J.; Kotra, L. P.; Chu, C. K. Synthesis and anti-HIV activities of 2′-deoxy-2′,2″- difluoro-β-L-ribofuranosyl-pyrimidine and -purine nucleosides. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 743−748.
(26) Hubschwerlen, C. A convenient synthesis of L-(*S*)-glyceraldehydeacetonide from L-ascorbic acid. *Synthesis* **1986**, 962.
(27) Hertel, L. W.; Kroin, J. S.; Missner, J. W.; Tustin, J. M. Synthesis of 2-deoxy-2,2-difluoro-D-ribose and 2-deoxy-2,2-difluoro-D-ribofuranosyl nucleosides. *J. Org. Chem.* **1988**, *52*, 2406−2409.
(28) Szarek, W. A.; Depew, C.; Jarrell, H. C.; Jones, J. K. N. *J. Chem. Soc., Chem. Commun.* **1975**, 648−649.
(29) Colorless prism crystal of orthorhombic system with the lattice parameters: $a = 5.220(1)$ Å, $b = 15.034(2)$ Å, $c = 17.266(3)$ Å, $V = 1354.9(4)$ (Å)^3; space group $P2_12_12_1$.
(30) van Roey, P.; Pangborn, W. A.; Schinazi, R. F.; Painter, G.; Liotta, D. C. (−)-*cis*-5-Fluoro-1-(2−(hydroxymethyl)-1,3-oxathiolan-5-yl)cytosine absolute configuration, antiviral agent against human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus. *Antiviral Chem. Chemother.* **1993**, *4*, 369.
(31) Molecules were overlapped using "Fit Atoms" module in SYBYL (Tripos Associates Inc., St. Louis, MO) and the modeling was performed on a Silicon Graphics Indy workstation. X-ray structure of (−)-FTC was obtained from Cambridge Structural Database and that of L-FAMU was performed in our laboratories. The X-ray structures were not relaxed through minimization before fitting and the "fit" was performed by overlaping N1, C1′, and C4′ atoms or the corresponding atoms of the each molecule.
(32) Marquez, V. E.; Lin, B. B.; Barchi, J. J., Jr.; Nicklaus, M. C. Conformational studies and anti-HIV activity of mono- and difluorodideoxy nucleosides. In *Nucleosides and nucleotides as antitumor and antiviral agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993; pp 265−283.
(33) van Roey, P.; Chu, C. K. Crystal structures and molecular conformations of anti-HIV nucleosides. In: *Nucleosides and nucleotides as antitumor and antiviral agents*; Chu, C. K., Baker, D. C., Eds.; Plenum Press: New York, 1993; pp 285−302.

JM970275Y