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Synthesis of 2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofuranosyl nucleosides

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Abstract

Various 2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofuranosyl nucleosides were synthesized via the key intermediate, 5-*O*-benzoyl-2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofuranose (**6**). 2,3-*O*-Isopropylidene-L-glyceraldehyde was coupled with ethyl bromodifluoroacetate under Reformatsky conditions to obtain the diastereomeric mixture of ethyl (4*S*)-3-hydroxy-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro propionate (**1**). Treatment of compound **1** with carbon disulfide, sodium hydride and methyl iodide followed by reduction afforded ethyl (4*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro propionate (**3**). Compound **3** was treated with 5% HCl in ethanol, followed by refluxing in benzene under Dean–Stark conditions, to afford the lactone **4**. The compound **4** was protected and reduced to afford the key intermediate **6**. For the synthesis of pyrimidine derivatives **8**–**21**, compound **6** was converted to the mesylate **7** and condensed with various silyl protected pyrimidine bases. The inosine and adenine derivatives **38**–**41** were obtained from compound **6** and 6-chloropurine using standard procedures. Compounds **22**–**35** and **38**–**41** were evaluated for their antiviral activity against HIV-1, HBV, HSV-1 and HSV-2, and for cellular toxicity. None of the synthesized compounds showed any significant activity or toxicity. Single-crystal X-ray structure of 1-(2,3-dideoxy-2,2-difluoro-β-L-*glycero*-pentofuranosyl)-5-iodocytosine (**34**) suggested a 2′-exo/3′-endo conformation for the carbohydrate moiety.

Keywords: 2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofuranosyl nucleosides; X-ray structure; Nucleoside conformation

1. Introduction

In 1996, Gemzar™ (2′-deoxy-2′,2′-difluorocytidine, gemcitabine) was approved for the treatment of patients with inoperable pancreatic cancer and non-

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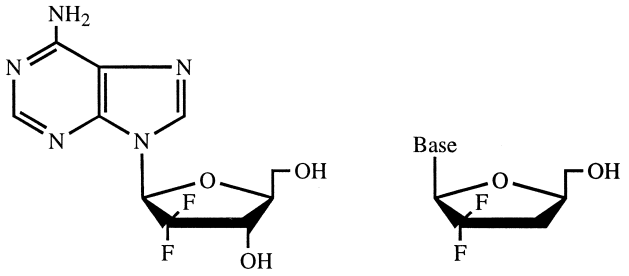
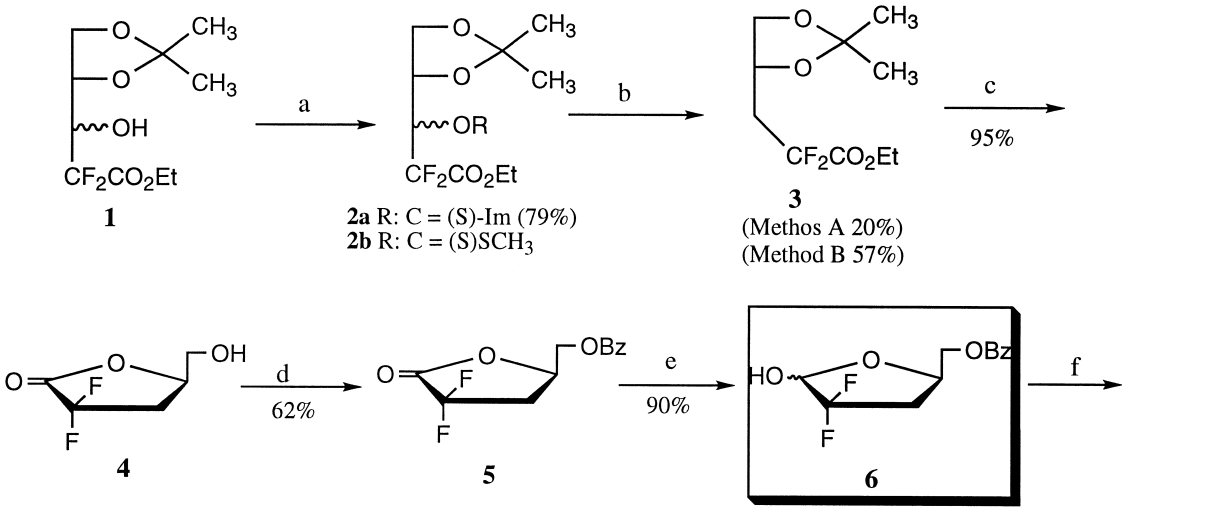
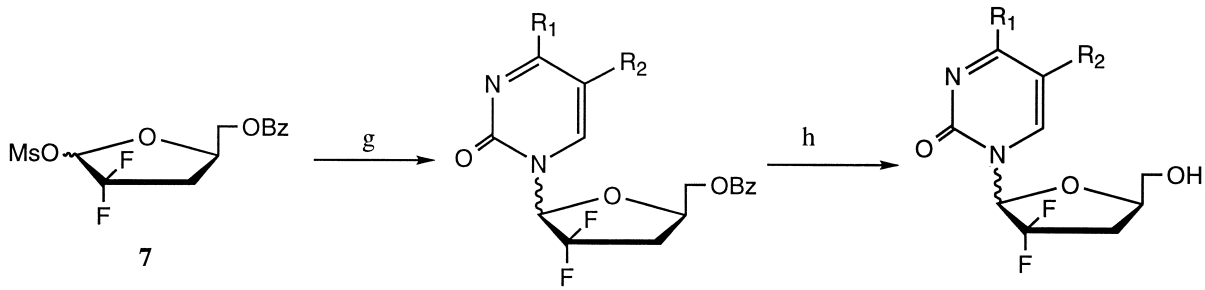


A B

Fig. 1. (A) 2′-Deoxy-2′,2′-difluoro-β-L-adenosine, (B) 2′,3′-dideoxy-2′,2′-difluoro-L-nucleosides.

small-cell lung carcinoma [1]. This compound possesses a difluoro substitution at the 2′-position of cytidine and has D-configuration [2]. Recently, we investigated the synthesis and anti-HIV activity of 2-deoxy-2,2-difluoro-L-ribofuranosyl nucleosides [3,4]. Among the synthesized compounds, the adenine analogue (Fig. 1A) showed moderate activity (EC_{50} 3.4 μM) against HIV-1 without any toxicity up to 100 μM in peripheral blood mononuclear (PBM), Vero and CEM cells. In view of the above interesting discoveries and as part of our continuous efforts to develop biologically active nucleosides, it





β	α	R_1	R_2
8	9	OH	CH_3
10	11	OH	H
12	13	OH	F
14	15	OH	I
16	17	NH_2	H
18	19	NH_2	F
20	21	NH_2	I

β	α	R_1	R_2
22	23	OH	CH_3
24	25	OH	H
26	27	OH	F
28	29	OH	I
30	31	NH_2	H
32	33	NH_2	F
34	35	NH_2	I

Scheme 1. Synthesis of various pyrimidine derivatives **22**–**35**. Reagents: (a) 1,1′-thiocarbonyldiimidazole, Me_2NCHO, 50 °C or carbon disulfide, NaH, iodomethane, Me_2NCHO, 0 °C; (b) tributyltin hydride (Bu_3SnH), AIBN, toluene, 90–100 °C; (c) (1) 5% HCl, EtOH, (2) benzene, 80 °C, Dean–Stark apparatus; (d) benzoyl chloride, 2,6-lutidine, CH_2Cl_2, rt; (e) lithiun tri(*tert*-butoxyaluminum hydride [Li(*tert*-BuO)$_3$AlH], tetrahydrofuran, −78 °C; (f) MsCl, Et_3N, CH_2Cl_2; (g) silylated base, sodium iodide, acetonitrile for compounds **8** and **9** or silylated base, Me_3SiOTf, DCE, 90–100 °C; (h) ammonia or methylamine, methanol, rt.

was of interest to synthesize 2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofuranosyl nucleosides (Fig. 1B) as potential antiviral agents. This class of compounds lacks the 2′- and 3′-OH groups. It was anticipated that the presence of 2′-difluoro substitution in the absence of 3′-OH would affect the conformation of 2′-deoxy-2′,2′-difluoro nucleosides [2] resulting in a potentially different biological profile. Herein, we wish to report the synthesis and biological activities of 2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofuranosylpyrimidine and purine nucleosides.

2. Synthesis

For the synthesis of the targetted nucleosides, 5-*O*-benzoyl-2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofuranose (**6**) was synthesized as the key intermediate (Scheme 1). Compound **6** was synthesized from L-gulono-γ-lactone via 2,3-dideoxy-2,2-difluoro-L-*glycero*-pentofurano-1,4-lactone (**4**). 2,3-*O*-Isopropylidene-L-glyceraldehyde was obtained from L-gulono γ-lactone in two steps [5] and was reacted with ethyl bromodifluoroacetate in the presence of zinc under Reformatsky conditions to obtain the diastereomeric mixture **1** in 54% yield. Compound **1** was treated with 1,1′-thiocarbonyldiimidazole in Me_2NCHO, followed by reduction with tributyltin hydride, to afford compound **3**. The yields of reduction of the thiocarbonylimidazolide **2a** to **3** were poor (20%) and were not suitable for large-scale preparations. Additionally, 1,1′-thiocarbonyldiimidazole is too expensive to carry out the reaction on a multigram scale. Thus, the treatment of compound **1** with carbon disulfide, sodium hydride and iodomethane to give compound **2b**, followed by the reduction with tributyltin hydride/AIBN, afforded compound **3** in fair yields (57%) [6]. Compound **3** was treated with 5% HCl in ethanol for 3 h, followed by refluxing in benzene at 95 °C in a Dean–Stark apparatus to afford compound **4** in a 95% yield. Cyclization of compound **3** as described above exclusively provided the furanose ring isomer **4**, whose structure was confirmed by a triplet signal for the 5′-OH in the ^1H NMR spectrum. Compound **4** was protected by treatment with benzoyl chloride and triethylamine in

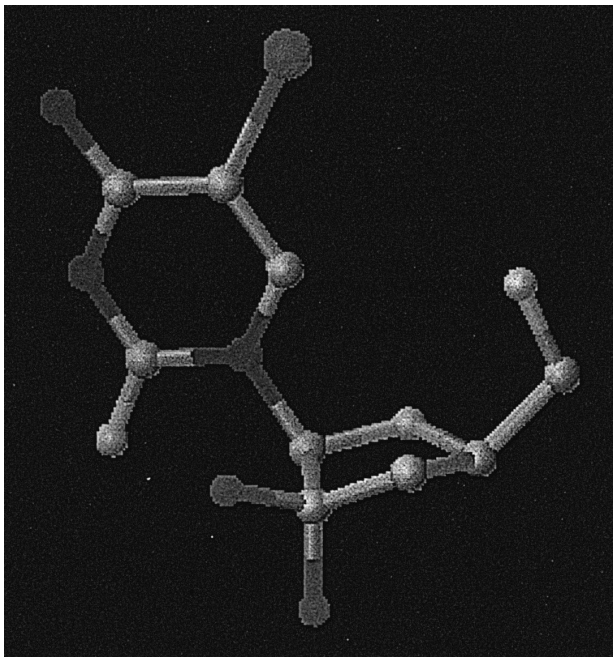
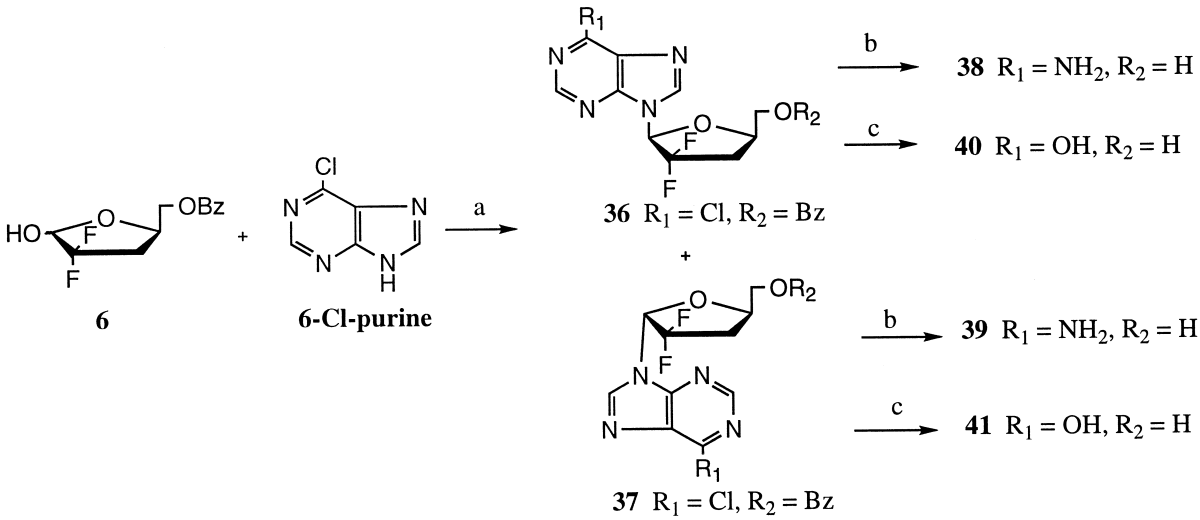


Fig. 2. X-ray structure of 5-iodocytosine analog **34**.



Scheme 2. Synthesis of adenine and hypoxanthine derivatives **38**–**41**. Reagents: (a) DEAD, Ph_3P, tetrahydrofuran, 8 h, argon; (b) ammonia, MeOH, steel bomb, 80–90 °C, 28 h; (c) 2-mercaptoethanol, NaOMe, MeOH, reflux.

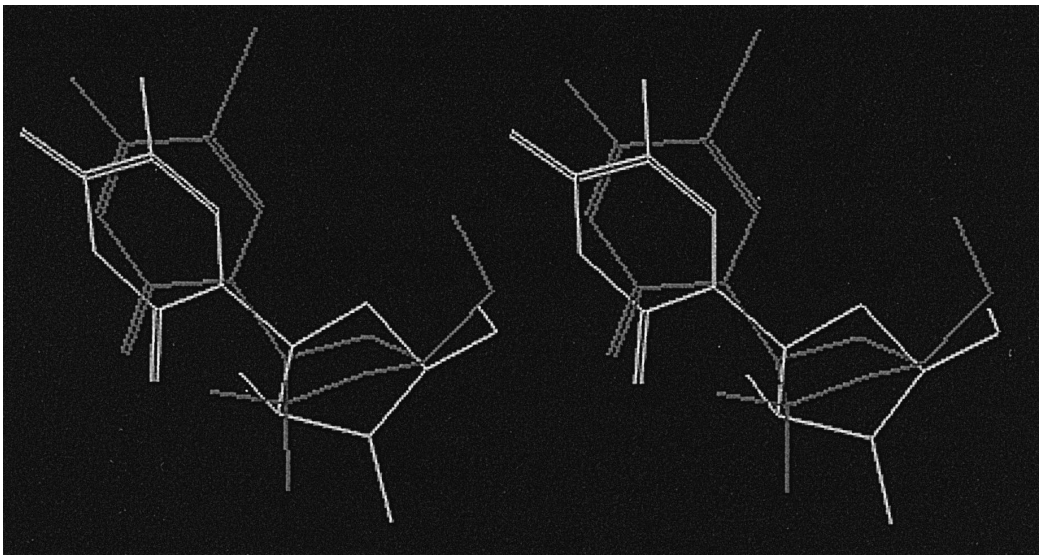


Fig. 3. Stereo view of overlap of the X-ray structures of **34** (green) with L-FMAU (red).

dichloromethane (62%) followed by reduction with lithium tri(*tert*-butoxy)aluminum hydride in tetrahydrofuran at −78 °C to give compound **6** (90%). For the preparation of thymine derivatives **8** and **9**, mesylate **7** was condensed with silylated thymine using sodium iodide as a catalyst in acetonitrile, resulting in poor yields (α:β/1:1, 15%) of the products. Hence, for the synthesis of uracil (**10**–**15**) and cytosine (**16**–**21**) derivatives, the mesylate **7** was condensed with various silyl-protected uracil and cytosine bases using Me_3SiOTf as a catalyst in dichloroethane at 90–100 °C [2]. In the condensation reactions, temperatures of 80–100 °C were critical for the condensation reaction, and lower temperatures did not result in good yields. Protected nucleosides were inseparable by silica gel column chromatography; hence, the anomeric mixture was used as such for the deprotection step. The free nucleosides **22**–**35** were obtained by treatment of the corresponding protected nucleosides with either methylamine or ammonia in MeOH at room temperature. The deprotected anomeric mixture was separated by silica gel column chromatography into the individual anomers. 6-Chloropurine analogs **36** and **37** were obtained by the condensation of compound **6** with 6-chloropurine under Mitsunobu conditions (Scheme 2) [7]. Compounds **36** and **37** were treated separately with ammonia in MeOH in a steel bomb at 80–90 °C, followed by chromatographic separation to obtain compounds **38** and **39**. Hypoxanthine analogs **40** and **41** were prepared by the treatment of compounds **36** and **37** separately with 2-mercaptoethanol and sodium methoxide in MeOH, followed by chromatographic separation [8]. The anomeric configuration of the final compounds were assigned based on the presence/absence of a cross-peak between H-1′, H-4′ in 2D NOESY experiments or the by comparison of the chemical shifts of the H-4′ signals of the α and β anomers in 1D experiments. The structure of compound **34** was also confirmed by single-crystal X-ray crystallography (Fig. 2) [1].

3. Conformational aspects

The X-ray structures of compound **34** and 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl) thymine (L-FMAU, Fig. 3) [9] were compared to understand the differences between these nucleoside conformations (Table 1) and the effect of difluoro substitution over the monofluoro substitution. L-FMAU is a thymine analog and exhibits potent anti-HBV activity [10]. Its structure contains a fluorine atom at the 2′-position in the arabino configuration. Compound **34** is a 5-iodocytosine analog and contains two fluorine atoms at the 2′-position. These molecules were compared by overlapping **34** and L-FMAU using SYBYL molecular modeling software [2]. Both structures possess the β-L configuration. The compound **34** is in 3′-*endo*

[1] Colorless prism crystal of orthorhombic system with the lattice parameters: *a*, 4.989(3) A°, *b*, 7.595(1) A°, *c*, 30.857(2) A°, *V*, 1169.2(7) (A°)3; space group $P2_12_12_1$.

[2] Molecules were overlapped using 'Fit Atoms' module in SYBYL (Tripos Associates, St. Louis, MO) on a Silicon Graphics Indy workstation.

Table 1
Conformational parameters for the compounds **34** and L-FMAU

Compound	Pseudorotation angle, P (deg)	Carbohydrate conformation	Puckering amplitude, υ_{max}	C-2–N-1–C-1′–O-4′ χ	C-3′–C-4′–C-5′–O-5′γ
34	194.4°	2′-exo/3′-endo	34.6	143.4°	−45.0°
34-(3′-OH)[a]	190.2°	2′-exo/3′-endo	36.9	156.5°	−42.7°
L-FMAU	−76.1°	O4′-endo	46.6	150.5°	−50.5°

[a] 2′-Deoxy-2′,2′-difluoro-5-iodo-L-cytidine [2].

conformation, whereas L-FMAU is in *O*-4′-*endo* conformation. The overlapped structures show the differences in the carbohydrate conformation as well as in the 4′-hydroxymethyl torsion angle (γ) (Fig. 3) [3]. The influence of these differences in the carbohydrate conformation of the 2′,3′-dideoxydifluoro nucleosides on the lack of biological activity is not clear at this time (vide infra). It should be noted that when the X-ray structure of 2′-deoxy-2′,2′-difluoro-5-iodo-L-cytidine [(**34**-(3′-OH), Table 1)] [2] was compared with that of compound **34**, similar conformational features were observed despite the lack of a 3′-hydroxyl group in compound **34** (figure not shown). This close similarity between the conformations may be due to the dominating effect of difluoro substituents on the carbohydrate conformation and indicates that the 3′-OH did not have much influence on the conformation of the '2′-deoxy-2′,2′-difluororibosyl' moiety.

4. Biological activity

Nucleoside derivatives **22**–**35** and **38**–**41** were evaluated for their antiviral activity against HIV-1, HBV, HSV-1 and HSV-2, and for cellular toxicity [11]. None of the synthesized compounds showed any significant antiviral activity and toxicity.

5. Experimental section

General methods.—Melting points were determined on a MelTemp-II melting point apparatus and are uncorrected. NMR data were recorded on a Bruker AMX 400 spectrometer, and the chemical shifts (δ) were reported in ppm. Coupling constants (J) were reported in hertz (Hz). The abbreviations used are: s (singlet), d (doublet), t (triplet), m (multiplet), pd (pseudo doublet), pt (pseudo triplet), bs (broad singlet). UV spectra were recorded on a Beckman DU-650 spectrophotometer. Optical rotations were recorded on a Jasco DIP-300 digital polarimeter. Mass spectra were either obtained from the Biological Sciences Mass Spectrometry facility at the University of Georgia or recorded on a Fison Autospec high-resolution mass spectrometer. Elemental analyses were performed by either Atlantic Microlab, 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 volumes of saturated $NaHCO_3$ solution and brine and dry the organic layer (Na_2SO_4). ^1H and ^{13}C NMR data are compiled in Tables 2 and 3, respectively.

Ethyl (4S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propionate (**1**).—Compound **1** was prepared from L-gulono-γ-lactone as previously described for the synthesis of 2-deoxy-2,2-difluoro-L-*glycero*-pentofuranosyl nucleosides [2,3].

Ethyl (4S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-(1-imdazolthiocarbonyloxy) propionate (**2a**). Compound **1** (10.3 g, 40.5 mmol) in dry Me_2NCHO (70 mL) was treated with 1,1′-thiocarbonyldiimidazole (14.4 g, 80.9 mmol) and stirred for 3 h at 50 °C. The solvent was evaporated, and the crude brown oil was purified in a flash column (5:95 EtOAc–$CHCl_3$) to obtain pure compound **2a** (11.6 g, 79.0%) as a yellow oil: Anal. Calcd for $C_{14}H_{18}F_2N_2O_5S$: C, 46.15; H, 4.98; N 7.68. Found: C, 46.32; H, 5.00; N, 7.50.

Ethyl (4S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-(methylthio-thiocarbonyloxy) propionate (**2b**). A solution of compound **1** (9.0 g, 35.4 mmol) and carbon disulfide (11.4 mL, 190.6 mmol) in Me_2NCHO (200 mL) was stirred at room temperature for 15 min under nitrogen gas. The solution was cooled in an ice bath, and sodium hydride (60% dispersion in mineral oil, 2.3 g, 57.2 mmol) was

[3] The X-ray structures of the nucleosides were overlaid using N-1, C-1′ and C-4′ atoms.

Table 2
^{1}H NMR data

#	Solvent	H-1	H-3	H-4	H-5	Others
2a	$CDCl_3$		6.23 (m, 1 H)	3.99–4.63 (m, 5 H, CH_2, CH_2CH_3, H-4)		8.37, 7.67, 7.07 (3 s, 3 H, imidazolyl), 1.38 (m, 9 H, 2 CH_3, CH_2CH_3)
2b	$CDCl_3$		6.53–6.61 (m, 1 H)	4.51 (m)	4.02–4.09, 4.11–4.14	2.61 (s, S CH_3), 1.33–1.38 (m, CH_2CH_3, 2 CH_3) (2 m)
3	$CDCl_3$		2.49–2.54, 2.24–2.32 (2 m)	4.29–4.34 (m, 3 H, CH_2CH_3, H-4)	4.12 (t, H-5a), 3.62 (t, H-5b)	1.33–1.39 (m, 9 H, 2 CH_3, CH_2CH_3
4	Me_2SO-d_6		2.85–2.98, 2.61–2.75 (2 m)	4.82 (m, 1 H, H-4)	3.71 (dd, H-5a), 3.52 (dd, H-5b)	5.28 (t, 5-OH, D_2O exch)
5	$CDCl_3$		2.88–2.96, 2.63–2.73 (2 m)	4.99–5.03 (m, H-4)	4.51 (dd, H-5a), 4.64 (dd, H-5b)	7.45–8.06 (m, 5 H, Bz)
6	$CDCl_3$	5.11–5.23 (m, H-1)	2.33–2.65 (2 m)	4.68–4.71 (m, H-4)	4.30–4.37, 4.42–4.50 (2 m, H-5)	δ 7.55–8.05 (m, 5 H, Bz), 7.28, 7.38 (2 d,1 H, OH, D_2O exch)
7	$CDCl_3$	5.99 (d, 1 H, H-1)	2.63–2.76, 2.45–2.54 (2 m)	4.90 (q, 1 H, H-4)	4.36–4.53 (m)	7.44–8.05 (m, 5 H, Bz), 3.16 (s, 1 H, CH_3)
#	Solvent	H-1′	H-3′	H-4′	H-5′	Others
8	$CDCl_3$	6.20 (t, *J* 8.2)	2.50–2.76 (m)	4.58–4.64 (m)	4.74 (t, 1 H), 4.5 (dd, 1 H)	7.07 (s, H-6), 8.53 (s, 1 H, NH), 7.47–8.08 (m, 5 H, Bz), 1.70 (s, 3 H, C
9	$CDCl_3$	6.27 (t, *J* 8.0)	2.50–2.88 (2 m)	4.90 (pt)	4.44–4.56 (m)	7.07 (s, H-6), 8.53 (s, 1 H, NH), 7.46–8.07 (m, 5 H, Bz), 1.95 (s, 3 H, C
10	$CDCl_3$	6.19 (dd, J_1 5.2, J_2 9.8)	2.43–2.73 (2 m)	4.53–4.72 (m, 3 H, H4′ and H-5′)		5.57 (d, H-5), 7.43 (d, H-6), 8.45 (brs, NH), 7.47–8.05 (m, Bz),
11	$CDCl_3$	6.29 (t, *J* 7.9)	2.60–2.84 (m)	4.89 (m)	4.44–4.57 (2 m)	5.78 (d, H-5), 7.27 (d, H-6), 8.55 (brs, NH), 7.46–8.07 (m, Bz)
16	Me_2SO-d_6	6.24 (d, *J* 6.8)	2.50–2.81 (2 m)	4.49–4.63 (m, H-4′, H-5′)		5.68 (d, H-5), 7.54–8.02 (m, 6 H, H-6, Bz), 7.38 (brs, NH_2)
17	Me_2SO-d_6	6.55 (brs)	2.63–2.93 (2 m)	4.96 (brt)	4.40–4.46 (m, 2 H)	5.76 (d, H-5), 7.48–8.01 (m, 6 H, H-6, Bz), 7.35 (d, 2 H, NH_2)
22	Me_2SO-d_6	6.12 (dd, J_1 2.5, J_2 12.1)	2.50–2.64 (m)	4.32–4.36 (m)	3.62–3.67, 3.83 (2 m)	7.85 (s, H-6), 11.60 (s, 1 H, NH, D_2O exch), 5.39 (t, 1 H, 5′-OH, D_2O e
23	Me_2SO-d_6	6.23 (dd, J_1 8.0, J_2 8.1)	2.59–2.80 (m)	4.68–4.72 (m)	3.50–3.64 (m)	7.52 (s, H-6), 11.57 (s, 1 H, NH, D_2O exch), 5.15 (t, 1 H, 5′-OH, D_2O e
24	Me_2SO-d_6	6.07 (dd, J_1 2.7, J_2 11.8)	2.41–2.61 (2 m)	4.29 (m)	3.54–3.77 (2 m, 2 H)	5.71 (d, H-5), 7.91 (s, H-6), 11.6 (brs, D_2O exch, NH), 5.30 (t, D_2O exc
25	Me_2SO-d_6	6.18 t, *J* 7.9)	2.50–2.68 (m)	4.60 (m)	3.44–3.59 (2 m, 2 H)	5.68 (d, H-5), 7.64 (d, H-6), 11.54 (s, D_2O exch, NH), 5.10 (t, D_2O exc
26	Me_2SO-d_6	6.04 (d, *J* 11.5)	2.51 (m)	4.31 (m)	3.59 (m) 3.79 (d)	8.36 (d, *J* 7.2), 1.08 (brs, D_2O exch, NH), 5.46 (t, D_2O exch 5′-OH)
27	Me_2SO-d_6	6.13 (t, *J* 7.4)	2.46–2.69 (m)	4.64 (m)	3.40–3.55 (2 m, 2 H)	7.98 (d, *J* 6.9, H-6), 11.87 (brs, D_2O exch, NH), 5.07 (t, D_2O exch, 5′-O
28	Me_2SO-d_6	6.03 (d, *J* 11.7)	2.52 (m)	4.33 (m)	3.57, 3.80 (2 m)	8.51 (s, H-6), 11.91 (s, D_2O exch, NH), 5.49 (t, D_2O exch, 5′-OH)
29	Me_2SO-d_6	6.15 (t, *J* 7.9)	2.62 (m)	4.68 (m)	3.46, 3.57 (2 m)	8.00 (s, H-6), 11.92 (s, D_2O exch, NH), 5.09 (t, D_2O exch, 5′-OH)
30	Me_2SO-d_6	6.15 (d, *J* 12.1)	2.36–2.53 (m, 2 H)	4.23 (m)	3.53–3.75 (2 m)	5.76 (d, H-5), 7.80 (d, H-6), 7.35 (d. D_2O exch, 2 H, NH_2), 5.22 (t, D_2
31	Me_2SO-d_6	6.25 (t, *J* 7.9)	2.47–2.65 (m, 2 H)	4.55 (m)	3.34–3.57 (2 m)	5.76 (d, H-5), 7.53 (d, H-6), 7.33 (d, D_2O exch, 2 H, NH_2), 5.08 (t, D_2
32	Me_2SO-d_6	6.07 (d, *J* 11.8)	2.47 (m)	4.26 (brd)	3.78, 3.58 (2 m)	8.18 (d, *J* 7.11, H-6), 7.99, 7.73 (2 brs, D_2O exch, NH_2), 5.38 (t, D_2O
33	Me_2SO-d_6	6.19 (t, *J* 7.1)	2.59 (m)	4.62 (m)	3.54, 3.42 (2 m)	7.86 (d, *J* 6.84, H-6), 7.98, 7.73 (2 brs, D_2O exch, NH_2), 5.08 (t, D_2O
34	Me_2SO-d_6	6.08 (t, *J* 12.0)	2.45 (m)	4.28 (m)	3.55, 3.77 (2 m)	8.36 (s, H-6), 8.03, 6.82 (2 brs, D_2O exch, NH_2), 5.42 (t, D_2O exch, 5′-
35	Me_2SO-d_6	6.20 (t, *J* 7.8)	2.52, 2.67 (2 m)	4.63 (m)	3.45, 3.56 (2 m)	7.87 (s, H-6), 8.05, 6.84 (2 brs, D_2O exch, NH_2), 5.08 (t, D_2O exch, 5′-
36	$CDCl_3$	6.32 (dd, J_1 4.7, J_2 10.3)	2.76–3.05 (2 m, 2 H)	4.63–4.77 (m, 3 H, H-4′, H-5′)		8.27 (s, H-2), 8.72 (s, H-8), 7.46–8.06 (m, 5 H, Bz)
38	Me_2SO-d_6	6.36 (dd, J_1 2.4, J_2 11.7)	2.71–2.2 (m, 2 H)	4.44 (m)	3.67–3.86 (2 m,2 H)	8.22 (s, H-2), 8.49 (s, H-8), 7.48 (brs, D_2O exch, NH_2), 5.35 (t, D_2Oex
39	Me_2SO-d_6	6.44 (pt, J_1 6.3, J_2 8.0)	2.64–3.02 (2 m)	4.83 (m)	3.52–3.63 (2 m)	8.18 (s, H-2), 8.34 (s, H-8), 7.41 (brs, D_2O exch, NH_2), 5.16 (brs D_2O
40	Me_2SO-d_6	6.34 (dd, J_1 1.9, J_2 11.5)	2.68–2.88 (m, 2 H)	4.45 (m)	3.68–3.85 (2 m, 2 H)	8.17 (s, H-2), 8.49, (s, H-8), 12.57 (brs, D_2O exch, NH), 5.35 (brs D_2O
41	Me_2SO-d_6	6.31 (pt, J_1 6.7, J_2 7.6)	2.53–2.84 (2 m, 2 H)	4.69 (m)	3.40–3.52 (2 m, 2 H)	8.00 (s, H-2), 8.19 (s, H-8), 12.40 (brs, D_2O exch, NH), 5.03 (brs, D_2O

Table 3
^{13}C NMR Data

#	
2a	117.72, 115.24, 109.77, 70.28 (dd, *J* 3.2 Hz), 69.67 (C-5), 63.31, 39.38 (t, *J* 22.8 Hz), 27.03, 25.93, 14.23
3	117.72, 115.24, 109.77, 70.28 (dd, J_1 3.25, J_2 6.17), 69.67, 63.31, 39.38 (t, *J* 22.88), 27.03, 25.93, 14.23)
4	171.24, 122.25 (t, *J* 251.25), 83.31 (d, *J* 3.06), 66.59, 37.32 (t, *J* 21.83)
16	166.08, 165.98, 155.11, 141.24, 141.17, 134.13, 129.78, 129.75, 129.61, 129.36, 127.47 (dd, J_1 250.26, J_2 258.97), 95.16, 85.68 (dd, J_1 17.35, J_2 20.80), 73.92, 73.86, 65.09, 46.21, 35.61 (t, *J* 23.69)
22	163.79, 150.60, 135.67, 127.78 (t, *J* 254.21), 109.96, 84.50, 77.70 (d, *J* 7.21), 60.64, 33.75 (d, *J* 22.68), 12.51
24	162.91, 150.37, 139.88, 127.49 (dd, J_1 249.49, J_2 259.41), 102.07, 84.60 (dd, J_1 22.95, J_2 44.32), 77.57 (d, *J* 7.10), 60.47, 33.56 (t, *J* 23.15)
25	163.36, 150.84, 141.28, 127.65 (t, *J* 254.79), 102.46, 85.28 (dd, J_1 21.03, J_2 62.91), 62.96, 34/81 (t, *J* 22.94)
26	157.33 (d, *J* 26.31), 149.40, 140.47 (d, *J* 231.15), 127.83 (dd, J_1 249.26, J_2 259.94), 124.44 (d, *J* 35.70), 85.10 (dd, J_1 21.51, J_2 44.38), 78.43 (d, *J* 7.33), 60.64, 33.36 (t, *J* 22.90)
30	166.16, 155.29, 141.14, 128.07 (dd, J_1 249.03, J_2 259.95), 94.94, 85.42 (dd, J_1 38.10, J_2 32.05), 77.31 (d, *J* 7.88), 61.08, 34.55 (*J* 22.90)
38	156.47, 153.29, 149.54, 138.99, 127.46 (dd, J_1 248.70, J_2 260.14), 118.86, 84.64 (dd, J_1 23.79, J_2 44.28), 78.27 (d, *J* 6.88), 61.57, 33.86 (t, *J* 22.67)
39	157.11, 154.06, 150.16, 140.39, 127.96 (t, *J* 255.01), 119.49, 85.46 (dd, J_1 22.62, J_2 42.20), 80.42, 63.53, 35.46 (t, *J* 22.82)
40	156.81, 148.37, 146.89, 138.42, 127.38 (dd, J_1 248.99, J_2 260.29), 124.14, 84.76 (dd, J_1 23.80, J_2 44.13), 78.60 (d, *J* 7.15), 61.36, 33.47 (d, *J* 22.54)
41	156.71, 148.35, 146.68, 139.20, 128.97, 126.99 (t, *J* 263.0), 85.12 (dd, J_1 22.80, J_2 41.86), 79.87, 62.64, 34.59 (t, *J* 22.93)

added slowly. The reaction mixture was stirred for 30 min at 0 °C and treated with iodomethane (6.5 g, 45.8 mmol). Stirring was continued for an additional 2 h. The solvent was evaporated to dryness, and the crude product was dissolved in EtOAc (300 mL) and subjected to the standard workup procedure. The organic layer was concentrated to obtain crude compound **2b** (12.8 g). A small portion was purified in a flash column (15:85 EtOAc–hexane) for spectrometric analysis.

Ethyl (4S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro propionate (**3**).—*Method* **2a**. A solution of compound **2a** (11.6 g, 31.9 mmol) in toluene (125 mL) was heated to 60 °C in an oil bath under argon under refluxing conditions. Tributyltin hydride (34.4 mL, 128 mmol) and AIBN (20 mg) were added, and the mixture was refluxed at 80 °C for 40 min. Then the reaction mixture was cooled to room temperature and the solvent was evaporated. The crude yellow oil was purified in a flash column (1:9 EtOAc–hexane) to obtain pure compound **3** (1.8 g, 20.0%) as a colorless oil: Anal. Calcd for $C_{10}H_{16}F_2O_4$: C, 50.41; H, 6.76. Found: C, 50.44; H, 6.70.

Method **2b**. Compound **2b** (12.8 g, 37.3 mmol) was dissolved in toluene (196 mL) and nitrogen gas was bubbled into the solution for 15 min. The solution was heated to 100 °C under nitrogen, and a solution of tributyltin hydride (17.2 g, 59.1 mmol) and AIBN (644.0 mg, 3.9 mmol) in toluene (196 mL) was added dropwise over a period of 10 min, with stirring. The reaction mixture was stirred for an additional 5 min and cooled to room temperature. The solvent was evaporated and the crude product was purified in a flash column (3–5:97–95 EtOAc–hexane) to obtain pure compound **3** (6.9 g, 57.0%).

(4S) - 2, 3 - Dideoxy - 2, 2 - difluoro - L - glycero - *pentofurano-1,4-lactone* (**4**).—Compound **3** (1.8 g, 7.5 mmol) was treated with HCl/EtOH (4 mL of 36% aqueous HCl dissolved in 16 mL of EtOH) and stirred at 40–50 °C for 3 h. The solvent was evaporated, and the residual water was removed by refluxing the syrup in benzene for 16 h at 95 °C using a Dean–Stark apparatus. Excess benzene was evaporated to obtain compound **4** (1.1 g, 95.0%) as a colorless syrup: IR (KBr): 1807.53 cm^{-1}; Anal. Calcd for $C_5H_6F_2O_3 \cdot 0.55H_2O$: C, 37.06; H, 4.41. Found: C, 37.07; H, 4.34.

5-O-*Benzoyl-2,3-dideoxy-2,2-difluoro*-L-glycero-*pentofurano-1,4-lactone* (**5**).—Compound **4** (1.1 g, 7.1 mmol) was dissolved in dry CH_2Cl_2 (20 mL), and 2,6-lutidine (0.9 g, 8.2 mmol), followed by benzoyl chloride (1.2 g, 8.2 mmol), were added slowly at 0–5 °C under argon. The reaction mixture was stirred for 14 h at room temperature, and the solvent was

evaporated. The crude product was coevaporated with toluene (2 × 25 mL), and the residue was purified quickly by a flash silica gel column chromatography (3:7 EtOAc–hexane) to obtain compound **5** (1.1 g, 62.0%) as syrup. Upon drying, the syrup slowly solidified: mp 39–42 °C. Anal. Calcd for $C_{12}H_{10}F_2O_4 \cdot 0.1H_2O$: C, 55.86; H, 3.98; F, 14.72. Found: C, 55.80; H, 4.27; F, 14.42.

5-O-*Benzoyl-2,3-dideoxy-2,2-difluoro*-L-glycero-*pentofuranose* (**6**).—A solution of compound **5** (1.1 g, 4.1 mmol) in 4:1 tetrahydrofuran–ether (15 mL) was cooled to −78 °C under argon and lithium tri-(*tert*-butoxy)aluminum hydride (1 M solution in tetrahydrofuran) (4.5 mL, 4.5 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C and was quenched by the slow addition of MeOH (1 mL). The reaction mixture was allowed to warm to room temperature, ether (50 mL) was added, and the mixture was subjected to the standard workup procedure. The organic layer was separated and concentrated to obtain chromatographically pure compound **6** (950 mg, 90%) as a colorless oil.

5-O-*Benzoyl-2,3-dideoxy-2,2-difluoro-1*-O-*methanesulfonyl*-L-glycero-*pentofuranose* (**7**).—Compound **6** (915.0 mg, 3.5 mmol) was dissolved in CH_2CL_2 (12 mL) under argon, and triethylamine (1.0 mL, 7.9 mmol) and methanesulfonyl chloride (0.3 mL, 3.8 mmol) were added slowly at room temperature. The reaction mixture was stirred for 8 h, diluted with 20 mL of CH_2CL_2, and subjected to standard workup procedure. The organic layer was concentrated to obtain crude compound **7** (1.1 g), which was directly used in the subsequent reactions. A small quantity was purified for spectroscopic identification.

1-(5-O-*Benzoyl-2,3-dideoxy-2,2-difluoro-β*-L-glycero-*pentofuranosyl)thymine* (**8**) *and 1-(5*-O-*benzoyl-2,3-dideoxy-2,2-difluoro-α*-L-glycero-*pentofuranosyl)thymine* (**9**).—Thymine (375 mg, 2.97 mmol) was suspended in acetonitrile (8 mL) and *N,O*-bis-trimethylsilylacetamide (1.1 mL, 4.5 mmol) was added under argon at room temperature and stirred for 1 h. After the suspension became clear, crude compound **7** (500 mg, 1.5 mmol) dissolved in acetonitrile (20 mL) was added, followed by NaI (50 mg), and the mixture was stirred under refluxing conditions at 60 °C for 48 h. The reaction mixture was cooled, EtOAc (75 mL) was added, and the standard workup procedure was carried out. The concentrated crude syrup was separated by prep TLC (3:1:96 dioxane–methanol–chloroform) to obtain pure compound **8** (41 mg, 8%) and compound **9** (41 mg, 8%) as a white powder: compound **8**: UV (MeOH) λ_{max} 262.0, 225.0 nm; MS (ESI) 367.0 (MH^+); compound **9**: UV (MeOH) λ_{max} 262.0, 227.5 nm; MS (ESI): 367.0 (MH^+).

1-(5-O-*Benzoyl-2,3-dideoxy-2,2-difluoro-β*-L-glycero-*pentofuranosyl)uracil* (**10**) and 1-(5-O-benzoyl-2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)uracil* (**11**).—Uracil (281.0 mg, 2.5 mmol) was reacted with 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 10 mL) and $(NH_4)_2SO_4$ (10 mg) under argon at 120–130 °C for 3 h. After the suspension turned clear, the reaction mixture was cooled to room temperature and excess solvent was evaporated. Crude compound **7** was dissolved in anhydrous dichloroethane (30 mL) and added to the silylated uracil. Trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf, 0.45 mL, 2.3 mmol) was added slowly, and the reaction mixture was stirred at 90–100 °C for 8 h. Chloroform (50 mL) was added to the reaction mixture and subjected to standard workup procedure. The organic layer was concentrated, and the crude product was purified by flash column chromatography (1:99 MeOH–$CHCl_3$) to obtain an anomeric mixture of nucleosides. The anomeric mixture was separated on a flash column (9:11 EtOAc–hexane) to obtain compound **10** (121 mg, 18%) and compound **11** (198 mg, 29%): compound **10**: UV (MeOH) λ_{max} 257.0, 230.0 nm; MS (ESI): 353.0 (MH^+); compound **11**: UV (MeOH) λ_{max} 256.5, 230.0 nm; MS (ESI): 353.0 (MH^+).

1-(5-O-*Benzoyl-2,3-dideoxy-2,2-difluoro-β*-L-glycero-*pentofuranosyl)-5-fluorouracil* (**12**) and 1-(5-O-benzoyl-2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-fluorouracil* (**13**).—The condensation of 5-fluorouracil (376.0 mg, 2.9 mmol) and compound **7** was carried out as described above in the presence of Me_3SiOTf. The crude product was purified by flash column chromatography (1:99 MeOH–$CHCl_3$) to obtain the anomeric mixture of **12** and **13** (389 mg, 55%). The anomeric mixture was used as such for the next reaction: UV (MeOH) λ_{max} 263.5, 230.0 nm; MS (ESI): 371.0 (MH^+).

1-(5-O-*Benzoyl-2,3-dideoxy-2,2-difluoro-β*-L-glycero-*pentofuranosyl)-5-iodouracil* (**14**) and 1-(5-O-benzoyl-2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-iodouracil* (**15**).—The condensation of 5-iodouracil (459.0 mg, 1.9 mmol) and compound **9** in the presence of Me_3SiOTf was carried out as described above for compounds **10** and **11**. The crude product was purified by flash column chromatography (3:97 MeOH–$CHCl_3$) to obtain the anomeric mixture of **14** and **15** (715 mg, 78%) as a white foam. The anomeric mixture was used as such

for the next reaction: UV (MeOH) λ_{max} 277.5, 226.5, 202.5 nm.

*1-(5-O-Benzoyl-2,3-dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)cytosine* (**16**) and 1-(5-O-benzoyl-2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)cytosine* (**17**).—Cytosine (321.6 mg, 2.9 mmol) was silylated and condensed with compound **7** in the presence of Me_3SiOTf (0.75 mL, 3.86 mmol) as described above. The crude product was purified in a flash column (1.5:4:94.5 Et_3N–MeOH–$CHCl_3$) to obtain compound **16** (99 mg, 28%) and compound **17** (94 mg, 27%): compound **16**: mp 166–167 °C; UV (MeOH) λ_{max} 267.5, 230.0, 201.5 nm; MS (ESI) 352.0 (MH^+); compound **17**: mp 75–79 °C; UV (MeOH) λ_{max} 269.5, 230.5, 201.5 nm; MS (ESI): 352.0 (MH^+).

*1-(5-O-Benzoyl-2,3-dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)-5-fluorocytosine* (**18**) and 1-(5-O-benzoyl-2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-fluorocytosine* (**19**).—5-Fluorocytosine (498.0 mg, 3.9 mmol) was silylated and condensed with the compound **7** in the presence of Me_3SiOTf (0.75 mL, 3.9 mmol) as described above. The crude product was purified in a flash silica column (4:96 EtOH–$CHCl_3$) to obtain the anomeric mixture of the compounds **18** and compound **19** (358 mg, 50%): UV (MeOH) λ_{max} 275.0, 230.5, 202.5 nm.

*1-(5-O-Benzoyl-2,3-dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)-5-iodocytosine* (**20**) and 1-(5-O-benzoyl-2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-iodocytosine* (**21**).—5-Iodocytosine (919 mg, 3.9 mmol) was silylated and condensed with compound **7** in the presence of Me_3SiOTf (0.75 mL, 3.9 mmol) as described above. The crude product was purified in a flash column (3:97 MeOH–$CHCl_3$) to obtain the anomeric mixture of the compounds **20** and compound **21** (444 mg, 48%): UV (MeOH) λ_{max} 282.0, 226.0, 205.0 nm.

*1-(2,3-Dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)thymine* (**22**).—Compound **8** (41 mg, 0.1 mmol) was treated with saturated ammonia in MeOH (10 mL), and the reaction mixture was stirred for 10 h at room temperature. Then the solvent was evaporated, and the crude product was purified by flash column chromatography (5:95 MeOH–$CHCl_3$) to obtain pure compound **22** (24 mg, 83%) as a white powder: mp 172–173 °C; $[\alpha]_D^{25}$ −14.6° (*c* 0.46, MeOH); UV (water) λ_{max} 264.0 (8742, 0.01 N HCl); 263.0 (7878), 210.5 (8208) (pH 7.0); 264.5 (5772), 228.5 nm (5723) (pH 11.0). Anal. Calcd for $C_{10}H_{12}F_2N_2O_4 \cdot 0.4H_2O$: C, 44.58; H, 4.75; N, 10.39. Found: C, 44.73; H, 4.65; N, 10.16. MS (ESI): 263.0 (MH^+).

*1-(2,3-Dideoxy-2,2-difluoro-α-*L*-glycero-pentofuranosyl)thymine* (**23**).—Compound **9** (41 mg, 0.11 mmol) was treated and purified in the same manner as described for the preparation of compound **22** to obtain compound **23** (23 mg, 80%) as a white powder: mp 145–147 °C; $[\alpha]_D^{25}$ +3.8° (*c* 0.3, MeOH); UV (MeOH) λ_{max} 263.0, 211.5; (water) 264.5 (9197, 0.01 N HCl); 264.5 (9597), 210.0 (9835) (pH 7.0); 264. nm (6653), 229.5 nm (6511) (pH 11.0). Anal. Calcd for $C_{10}H_{12}F_2N_2O_4 \cdot 0.2H_2O$: C, 45.18; H, 4.69; N, 10.53. Found: C, 45.43; H, 4.60; N, 10.15. MS (ESI): 263.0 (MH^+).

*1-(2,3-Dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)uracil* (**24**).—Compound **10** (87 mg, 0.25 mmol) was treated with saturated ammonia in MeOH (10 mL), and the reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated, the crude product was purified by flash column chromatography (5:95 MeOH–$CHCl_3$), and the product was freeze dried to obtain compound **24** (61 mg, 98%): mp 160.5–162.0 °C; $[\alpha]_D^{25}$ −21.4° (*c* 0.65, MeOH); UV (water) λ_{max} 259.5 nm (10,320), 206.5 nm (9873) (pH 2.0); 258.5 nm (9958), 208.5 nm (8671) (pH 7.0); 259.0 (7416), 231.5 (6408) (pH 11.0). Anal. Calcd for $C_9H_{10}F_2N_2O_4$: C, 43.55; H, 4.03; N, 11.29. Found: C, 43.46; H, 4.01; N, 11.21. MS (ESI): 249.0 (MH^+).

*1-(2,3-Dideoxy-2,2-difluoro-α-*L*-glycero-pentofuranosyl)uracil* (**25**).—Compound **11** (178 mg, 0.5 mmol) was treated with saturated ammonia in MeOH (15 mL), and the reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated, the crude product was purified by flash column chromatography (5:95 MeOH–$CHCl_3$), and the product was freeze dried to obtain compound **25** (51 mg, 41%): mp 70–73 °C; $[\alpha]_D^{25}$ −3.0° (*c* 0.49, MeOH); UV (water) λ_{max} 259.0 nm (10,267), 207.0 nm (9424) (pH 2.0); 259.0 nm (9927), 209.5 nm (8271) (pH 7.0); 259.5 nm (7660), 233.5 nm (6216) (pH 11.0). Anal. Calcd for $C_9H_{10}F_2N_2O_4 \cdot 0.35H_2O$: C, 42.26; H, 4.20; N, 11.01. Found: C, 42.10; H, 3.95; N, 11.35. MS (ESI): 249.0 (MH^+).

*1-(2,3-Dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)-5-fluorouracil* (**26**) and 1-(2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-fluorouracil* (**27**).—An anomeric mixture of compounds **12** and **13** (366 mg, 0.99 mmol) was treated with methylamine (40% aqueous solution, 0.43 mL, 4.95 mmol) in MeOH (15 mL) and stirred for 4 h. The solvent was evaporated, and the crude product

was purified on a flash silica column (5:95 MeOH–$CHCl_3$) to obtain pure compound **26** (100 mg, 38%) and compound **27** (47 mg, 18%): compound **26**: mp 117–118 °C; $[\alpha]_D^{25}$ −31.0° (*c* 0.53, MeOH); UV (water) λ_{max} 266.0 (9140), 207.0 (9804) (pH 2.0); 266.0 (7686), 210.0 (9590) (pH 7.0); 266.0 (8830), 233.5 nm (8856) (pH 11.0). Anal. Calcd for $C_9H_9F_3N_2O_4$: C, 40.60; H, 3.38; N, 10.53. Found: C, 40.48; H, 3.46; N, 10.47. MS (ESI): 267.0 (MH^+); compound **27**: mp 152–153 °C; $[\alpha]_D^{25}$ +7.9° (c 0.50, MeOH); UV (water) λ_{max} 266.0 (10,658), 207.0 (11,436) (pH 2.0); 266.0 (9138), 210.0 (11,296) (pH 7.0); 266.5 (8364), 233.0 nm (8443) (pH 11.0). Anal. Calcd for $C_9H_9F_3N_2O_4 \cdot 0.4H_2O$: C, 39.56; H, 3.59; N, 10.25. Found: C, 39.54; H, 3.33; N, 10.04. MS (ESI): 267.0 (MH^+).

1 - (2, 3 - Dideoxy - 2, 2 - difluoro - β - L - glycero - pentofuranosyl)-5-iodouracil (**28**) and 1-(2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-iodouracil* (**29**).—An anomeric mixture of compounds **14** and **15** (704 mg, 1.5 mmol) was treated with saturated ammonia in MeOH (30 mL) and stirred at room temperature for 20 h. The solvent was evaporated and the crude product was purified on a flash column (3:97 EtOH–$CHCl_3$) to obtain pure compound **28** (177 mg, 32%) and compound **29** (101 mg, 18%) as a white powder: compound **28**: mp 210–212 °C; $[\alpha]_D^{27}$ +2.1° (*c* 0.27, MeOH); UV (MeOH) λ_{max} 279.5, 216.0; (water) 284.0 (5544), 216.5 (8975) (pH 2.0); 282.5 (5214), 216.0 (9051) (pH 7.0); 277.0 (4240), 221.0 nm (10,847) (pH 11.0). Anal. Calcd for $C_9H_9F_2IN_2O_4$: C, 28.90; H, 2.41; N, 7.49. Found: C, 29.04; H, 2.46; N, 7.26. FABMS: 275.0 (MH^+); compound **29**: mp 177.5–180 °C; $[\alpha]_D^{27}$ −10.2° (*c* 0.21, MeOH); UV (MeOH) λ_{max} 279.5, 214.0; (water) 284.5 (6862), 215.5 (10,245) (pH 2.0); 283.5 (6646), 213.5 (11,532) (pH 7.0); 276.5 (5165), 220.0 nm (11,483) (pH 11.0). Anal. Calcd for $C_9H_9F_2IN_2O_4$: C, 28.90; H, 2.41; N, 7.49. Found: C, 28.93; H, 2.57; N, 6.94. FABMS 275.0 (MH^+).

1 - (2, 3 - Dideoxy - 2, 2 - difluoro - β - L - glycero - pentofuranosyl)cytosine (**30**).—Compound **16** (83.0 mg, 0.2 mmol) was treated with methylamine (40% aqueous solution, 0.2 mL, 2.4 mmol) in MeOH (10 mL) and stirred for 2 h. The solvent was evaporated, and the residue was purified by flash column chromatography (1:9 MeOH–$CHCl_3$) to obtain compound **30** (41 mg, 70%) as a white powder: mp 180–182 °C; $[\alpha]_D^{24}$ −46.9° (*c* 0.53, MeOH); UV (MeOH) λ_{max} 269.0, 211.5; (water) 277.0 nm (12,882), 211.5 (10,383) (pH 2.0); 269.0 (8850), 234.0 (7706), 202.5 (13,867) (pH 7.0); 269.0 (9232), 238.5 nm (8122) (pH 11.0). Anal. Calcd for $C_9H_{11}F_2N_3O_3$: C, 43.72; H, 4.45; N, 17.00. Found: C, 43.48; H, 4.54; N, 16.87. MS (ESI): 248.0 (MH^+).

1 - (2, 3 - Dideoxy - 2, 2 - difluoro - α - L - glycero - pentofuranosyl)cytosine (**31**).—Compound **17** (77.0 mg, 0.22 mmol) was treated with methylamine (40% aqueous solution, 0.36 mL, 4.4 mmol) in MeOH (20 mL) and stirred for 10 h. The solvent was evaporated, and the residue was purified by flash column chromatography (1:9 MeOH–$CHCl_3$) to obtain compound **31** (45 mg, 83%) as a white powder: mp 77–80 °C; $[\alpha]_D^{24}$ +21.5° (*c* 0.50, MeOH); UV (water) λ_{max} 277.5 (12,596), 211.5 (9967) (pH 2.0); 269.0 (8416), 232.0 (7555), 202.5 (13,494) (pH 7.0); 269.5 (8744), 237.5 nm (7592) (pH 11.0). Anal. Calcd for $C_9H_{11}F_2N_3O_3 \cdot 0.15H_2O$: C, 43.27; H, 4.52; N, 16.81. Found: C, 43.58; H, 4.89; N, 16.43. MS (ESI): 248.0 (MH^+).

1 - (2, 3 - Dideoxy - 2, 2 - difluoro - β - L - glycero - pentofuranosyl) - 5 - fluorocytosine (**32**) and 1-(2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-fluorocytosine* (**33**).—An anomeric mixture of compounds **18** and **19** (351 mg, 0.95 mmol) was treated with saturated ammonia in MeOH (20 mL) and stirred at room temperature for 12 h. The solvent was evaporated, and the crude product was purified in a flash column (5:95 MeOH–EtOAc) to obtain pure compound **32** (85 mg, 34%) as a sticky solid and compound **33** (85 mg, 34%) as a white powder: compound **32**: $[\alpha]_D^{27}$ −60.0° (*c* 0.22, MeOH); UV (MeOH) λ_{max} 280.0, 243.0, 203.0; (water) 282.0 (8316), 210.5 (8960) (pH 2.0); 278.0 (7318), 239 (7957), 207.0 (8784) (pH 7.0); 278.0 (7347), 239.0 nm (7993) (pH 11.0). Anal. Calcd for $C_9H_{10}F_3N_3O_3$: C, 40.77; H, 3.77; N, 15.84. Found: C, 40.47; H, 3.75; N, 15.58. FABMS: 266.0 (MH^+); compound **33**: mp 204–206 °C; $[\alpha]_D^{27}$ +37.7° (*c* 0.24, MeOH); UV (MeOH) λ_{max} 279.5, 243.0, 214.0; (water) 282.0 (9181), 211.5 (9697) (pH 2.0); 278.5 (7597), 238.5 (8192), 210.0 (9064) (pH 7.0); 279.0 (7821), 238.5 (8465), 217.5 nm (8636) (pH 11.0). Anal. Calcd for $C_9H_{10}N_3F_3O_3 \cdot H_2O$: C, 38.18; H, 4.24; N, 14.83. Found: C, 38.50; H, 4.18; N, 14.77. FABMS: 266.0 (MH^+).

1 - (2, 3 - Dideoxy - 2, 2 - difluoro - β - L - glycero - pentofuranosyl) - 5 - iodocytosine (**34**) and 1-(2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-5-iodocytosine* (**35**).—An anomeric mixture of compounds **20** and **21** (430 mg, 0.9 mmol) was treated with saturated ammonia in MeOH (20 mL) and stirred at room temperature for 24 h. The solvent was evaporated and the crude product was precipitated out from

MeOH to obtain the anomeric mixture of nucleosides as a white powder. The mixture was poorly soluble in either MeOH or water. The anomeric mixture was dissolved in hot MeOH and separated by prep TLC (2.5:97.5 MeOH–EtOAc) to obtain pure compound **34** (25 mg, 7%) as a white powder and compound **35** (31 mg, 9%) as a foam: compound **34**: mp 210–211.6 °C; $[\alpha]_D^{27}$ 14.9° (*c* 0.13, MeOH); UV (MeOH) λ_{max} 293.5, 218.5, 203.0; (water) 303.0 (6261), 221.0 (12,887) (pH 2.0); 292.0 (5080), 219.0 (13,886), 205.0 (15,544) (pH 7.0); 292.0 (5067), 222.0 nm (12,835) (pH 11.0). Anal. Calcd for $C_9H_{10}F_2IN_3O_3$: C, 28.98; H, 2.68; N, 11.26. Found: C, 29.00; H, 2.72; N, 10.83. FABMS: 375.0 (MH^+); compound **35**: $[\alpha]_D^{27}$ −2.0° (*c* 0.14, MeOH); UV (MeOH) λ_{max} 292.0, 203.0; (water) 303.5 (6831), 221.5 (13,725) (pH 2.0); 292.0 (5739), 219.5 (15,562), 203.5 (17,358) (pH 7.0); 292.0 (5414), 222.5 nm (13,516) (pH 11.0). Anal. Calcd for $C_9H_{10}F_2IN_3O_3 \cdot 0.2H_2O$: C, 28.70; H, 2.76; N, 11.15. Found: C, 28.97; H, 2.94; N, 10.76. FABMS: 375.0 (MH^+).

*9-(5-O-Benzoyl-2,3-dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)-6-chloropurine* (**36**) and 9-(5-O-benzoyl-2,3-dideoxy-2,2-difluoro-α-L-glycero-*pentofuranosyl)-6-chloropurine* (**37**).—A mixture of compound **6** (1 g, 3.9 mmol), 6-chloropurine (92 mg, 6 mmol) and triphenylphosphine (1.6 g, 6.0 mmol) in dry tetrahydrofuran (25 mL) was treated with diethyl azodicarboxylate (0.99 mL, 6 mmol) at room temperature under argon. The orange-colored solution was stirred at room temperature for 8 h, and EtOAc (25 mL) was added to the reaction mixture. The organic layer was subjected to standard workup procedure and concentrated. The crude product was purified by flash column chromatography (1.5:98.5 MeOH–$CHCl_3$) to obtain an anomeric mixture of nucleosides that was further subjected to flash column chromatography (5% Et_2O–CH_2Cl_2) to obtain compound **36** (164 mg, 11%) and compound **37** (322 mg, 21%): compound **36**: UV (MeOH) λ_{max} 263.5, 230.5, 204.5 nm; MS (ESI): 394.7 (MH^+); compound **37**: UV (MeOH) λ_{max} 263.5, 230.5, 203.5 nm; ESIMS: 394.7 (MH^+).

*9-(2,3-Dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)adenine* (**38**).—Compound **36** (80 mg, 0.2 mmol) was treated with saturated ammonia in MeOH and stirred at 80–90 °C in a steel bomb for 28 h. The solvent was evaporated, and the crude product was purified in a flash column (7:93 MeOH–$CHCl_3$) to obtain compound **38** (36 mg, 66%) as a white powder: mp 241–244 °C; $[\alpha]_D^{27}$ +8.0° (*c* 0.14, MeOH); UV (MeOH) λ_{max} 258.0, 209.0; (water) 256.0 (8241), 204.5 (13,560) (pH 2.0); 258.0 (8217), 208.5 (10,686) (pH 7.0); 258.5 nm (8584) (pH 11.0). Anal. Calcd for $C_{10}H_{11}F_2N_5O_2$: C, 44.28; H, 4.05; N, 25.83. Found: C, 44.31; H, 4.09; N, 25.69. ES-IMS: 272 (MH^+).

*9-(2,3-Dideoxy-2,2-difluoro-α-*L*-glycero-pentofuranosyl)adenine* (**39**).—Compound **37** (150 mg, 0.38 mmol) was treated with saturated ammonia in MeOH (20 mL) and stirred at 80–90 °C in a steel bomb for 26 h. The solvent was evaporated and the crude product was purified in a flash column (7:93 MeOH–$CHCl_3$) to obtain pure compound **39** (78 mg, 76%) as a white powder: mp 184–187 °C; $[\alpha]_D^{27}$ −35.0° (*c* 0.71, MeOH); UV (MeOH) λ_{max} 258.0, 210.0; (water) 256.5 (15,640), 204.5 (24,131) (pH 2.0); 258.5 (14,141), 207.5 (19,442) (pH 7.0); 258.5 nm (15,793) (pH 11.0). Anal. Calcd for $C_{10}H_{11}F_2N_5O_2 \cdot 0.72H_2O$: C, 42.25; H, 4.38; N, 25.49. Found: C, 42.20; H, 4.27; N, 25.24. ESIMS: 272 (MH^+).

*9-(2,3-Dideoxy-2,2-difluoro-β-*L*-glycero-pentofuranosyl)hypoxanthine* (**40**).—Compound **36** (81 mg, 0.2 mmol) was treated with 2-mercaptoethanol (0.06 mL, 0.8 mL) and NaOMe (95%, 43.2 mg, 0.8 mL) in MeOH (10 mL). The mixture was refluxed for 2 h under argon and cooled to room temperature. The reaction mixture was neutralized with glacial acetic acid and the solvent was evaporated. The residue was purified in a flash silica column (7:93 MeOH–$CHCl_3$) to obtain pure compound **40** (32 mg, 59%): mp 208–211 °C; $[\alpha]_D^{21}$ +10.0° (*c* 0.21, MeOH); UV (MeOH) λ_{max} 244.0, 203.5; (water) 247.0 (9261), 201.5 (14294) (pH 2.0); 247.5 (8870), 203.0 (11,561) (pH 7.0); 252.5 nm (10,223) (pH 11.0). Anal. Calcd for $C_{10}H_{10}F_2N_5O_2$: C, 44.14; H, 3.68; N, 20.58. Found: C, 44.13; H, 3.65; N, 20.46. ESIMS: 273.0 (MH^+).

*9-(2,3-Dideoxy-2,2-difluoro-α-*L*-glycero-pentofuranosyl)hypoxanthine* (**41**).—Compound **37** (147 mg, 0.37 mmol) was treated with 2-mercaptoethanol (0.1 mL, 1.48 mmol) and NaOMe (95%, 80 mg, 1.48 mmol) in MeOH (15 mL) and stirred at refluxing conditions for 2 days. The mixture was cooled and neutralized with glacial acetic acid. The solvent was evaporated, and the residue was purified by flash column chromatography (7:93 MeOH–$CHCl_3$) to obtain pure compound **41** (21 mg, 21%): mp 213–215 °C (dec.); $[\alpha]_D^{21}$ −35.5° (*c* 0.28, MeOH); UV (water) λ_{max} 247.5 (11,542), 202.5 (18,064) (pH 2.0); 247.5 (10,955), 204.5 (12,401) (pH 7.0); 252.5 nm (13,054) (pH 11.0). Anal. Calcd for $C_{10}H_{10}F_2N_5O_2 \cdot 0.55H_2O$: C, 42.59; H, 3.94; N,

19.85. Found: C, 42.91; H, 3.87; N, 19.45. ESIMS: 273 (MH^+).

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