Synthesis and Anti-HIV and Anti-HBV Activities of 2′-Fluoro-2′,3′-unsaturated L-Nucleosides

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The synthesis of L-nucleoside analogues containing 2′-vinylic fluoride was accomplished by direct condensation method, and their anti-HIV and anti-HBV activities were evaluated in vitro. The key intermediate **8**, the sugar moiety of our target compounds, was prepared from 1,2-*O*-isopropylidene-L-glyceraldehyde via (*R*)-2-fluorobutenolide intermediate **5** in five steps. Coupling of the acetate **8** with the appropriate heterocycles (silylated uracil, thymine, N^4-benzoylcytosine, N^4-benzoyl-5-fluorocytosine, 6-chloropurine, and 6-chloro-2-fluoropurine) in the presence of Lewis acid afforded a series of 2′-fluorinated L-nucleoside analogues (**15**−**18**, **23**−**26**, **36**−**45**). The newly synthesized compounds were evaluated for their antiviral activities against HIV-1 in human peripheral blood mononuclear (PBM) cells and HBV in 2.2.15 cells. Cytosine **23**, 5-fluorocytosine **25**, and adenine **36** derivatives exhibited moderate to potent anti-HIV (EC_{50} 0.51, 0.17, and 1.5 μM, respectively) and anti-HBV (EC_{50} 0.18, 0.225, and 1.7 μM, respectively) activities without significant cytotoxicity up to 100 μM in human PBM, Vero, CEM, and HepG2 cells.

Introduction

Intensive efforts in the search for safe and effective antiviral agents against human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have led to the discovery of 2′,3′-dideoxy nucleoside analogues, including 3′-azido-3′-dideoxythymidine (AZT),[1] 2′,3′-dideoxycytidine (ddC),[2] 2′,3′-dideoxyinosine (ddI),[3] 2′,3′-didehydro-3′-deoxythymidine (d4T),[4] (−)-(2*R*,5*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (3TC),[5] and (−)-(2*R*,5*S*)-5-fluoro-1-[2-(hydroxymethyl)oxathiolan-5-yl]cytosine (FTC).[6] Particularly, a class of nucleosides with the unnatural L-configurations has recently drawn considerable attention by medicinal chemists due to their unique potency, mechanism, and toxicity profile.[7] In connection with these efforts, Gosselin et al. and Lin et al. have reported the synthesis of L-2′,3′-didehydro-2′,3′-dideoxycytidine (β-L-d4C) and its 5-fluoro congener β-L-Fd4C, which showed potent anti-HIV and anti-HBV activity.[8] Recently, we have also described the synthesis and antiviral activity of β-L-2′,3′-dideoxy (β-L-d2N) and 2′,3′-didehydro-2′,3′-dideoxy (β-L-d4N) purine nucleosides, among which β-L-d4A exhibited the most potent antiviral activity against HIV and HBV.[9] However, it is well-established that d2 and d4 purine nucleosides are unstable in acidic media, resulting in glycosyl bond cleavage, thus limiting their usefulness as orally bioavailable drugs.[10] As an isosteric replacement for hydrogen, fluorine is attractive due to its similar size to hydrogen and provides acid stability to the dideoxy nucleosides when it is substituted at the 2′-position.[11] In addition, a number of nucleosides with a fluorinated sugar moiety have shown significant biological activities, including 3′-dideoxy-3′-fluorothymidine (FLT),[12] 2′-β-fluoro-2′,3′-dideoxyadenosine (F-ddA),[11] and β-L-2′-fluoro-5-methyl-1-(arabinofuranosyl)uracil (L-FMAU).[13,14] To date, three 2′-fluorinated 2′-ene-type nucleosides with D-configurations (β-D-2′-Fd4C, β-D-2′-Fd4U, and β-D-2′-Fd4T) have been reported, but they are less potent than AZT as antiviral agents.[15−17]

In view of the above findings, it was of interest to study the effects of 2′-vinylic fluoride of L-nucleosides in regard to antiviral activity. In a recent communication, we reported the preliminary results of adenine and hypoxanthine derivatives, in which β-L-2′-Fd4A showed moderately potent anti-HIV activity (EC_{50} 1.5 μM) in human peripheral blood mononuclear (PBM) cells.[18] Herein, we wish to report the full accounts of the synthesis and biological evaluation of the titled nucleosides.

Results and Discussion

Previously, the synthesis of 2′-ene-type nucleosides (d4N) was accomplished mainly by divergent methods, starting from readily available nucleoside analogues and involving lengthy modifications of individual nucleosides.[9,15,16,19] Moreover, this synthetic strategy for L-2′-Fd4N is compounded by additional difficulties as starting materials are not available from natural sources. The convergent approach for the preparation of nucleoside analogues is more versatile, since it can employ a variety of purine and pyrimidine nucleosides from the same intermediate, thus providing a facile and concise route for a variety of nucleosides. The most common methodology for condensation of a carbohydrate moiety with a heterocyclic base involves the use of a Lewis acid

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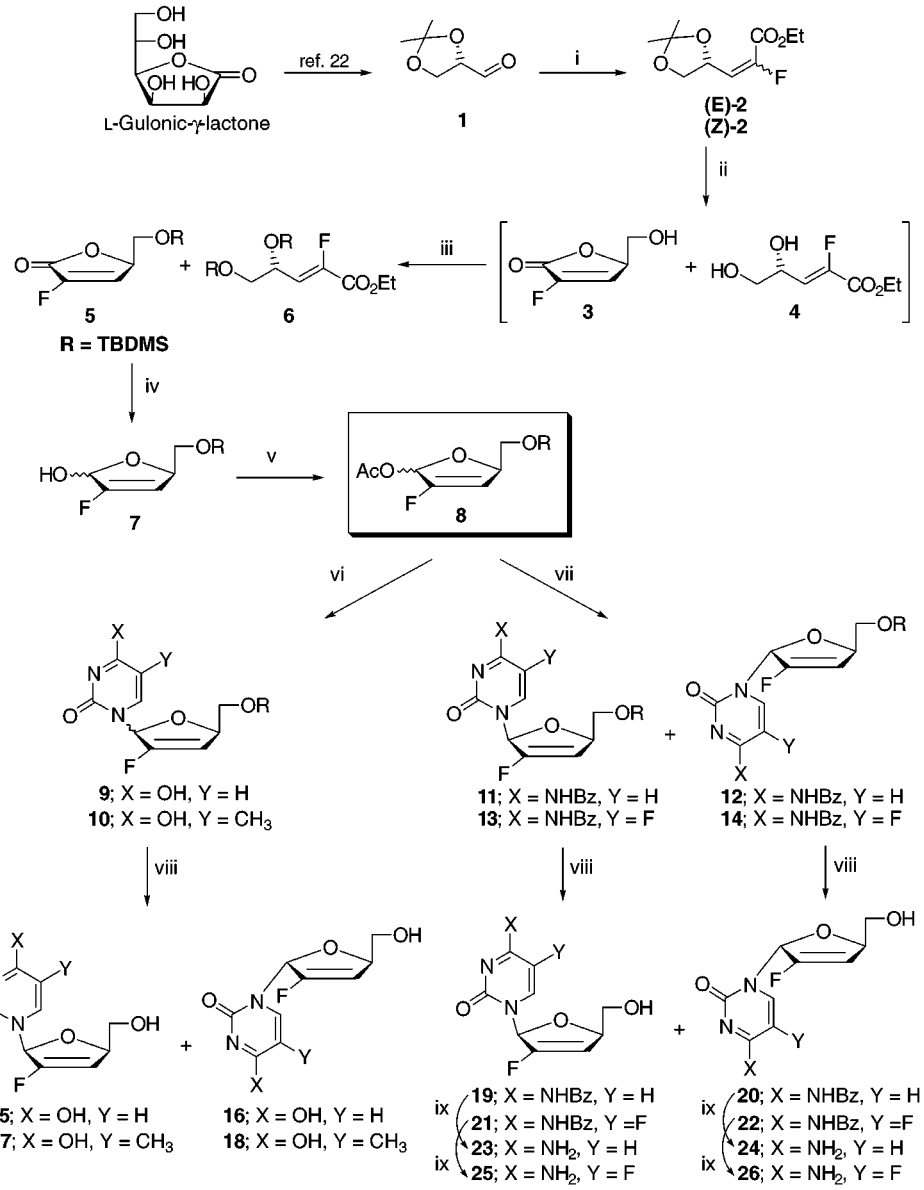
Scheme 1[a]

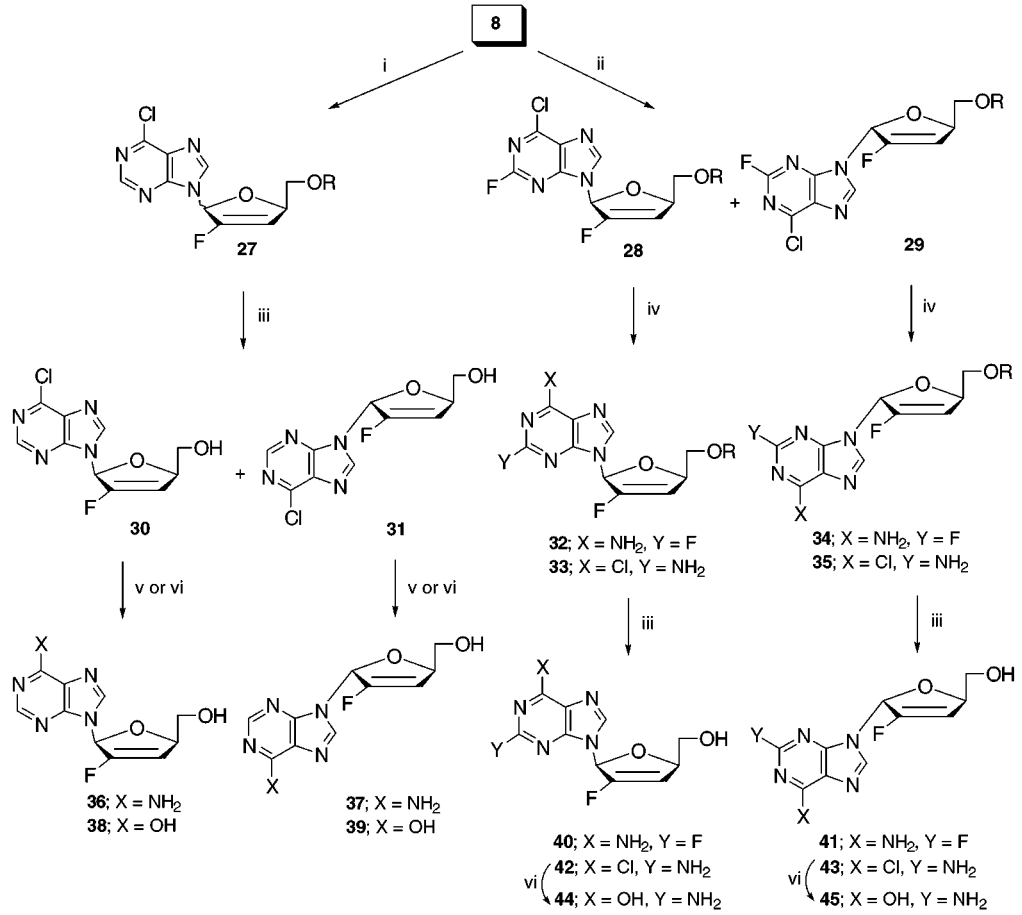


[a] Reagents: (i) $(EtO)_2P(O)CHFCO_2Et$, NaHMDS, THF, −78 °C; (ii) *c*-HCl, EtOH; (iii) TBDMSCl, imidazole, CH_2Cl_2; (iv) DIBAL-H, CH_2Cl_2, −78 °C; (v) Ac_2O, TEA, CH_2Cl_2; (vi) silylated uracil or thymine, TMSOTf, DCE; (vii) silylated N^4-Bz-cytosine or N^4-Bz-5-F-cytosine; TMSOTf, CH_3CN or DCE; (viii) TBAF, THF; (ix) satd NH_3/MeOH.

or an electrophile in conjunction with a 1-*O*-acyl/alkyl furano- or pyranoside which undergo an oxonium ion formation or a direct nucleophilic displacement.[20] However, due to lability of the 2,3-unsaturated sugar moiety under coupling conditions in the presence of Lewis acid, few examples are reported for the synthesis of 2′-ene-type nucleosides by direct condensation methods, except one case for pyrimidine derivatives via a thiophenyl intermediate.[21] We envisioned that a 2,3-unsaturated sugar moiety bearing a fluorine atom at the 2-position was amenable to direct coupling reaction conditions. Therefore, the required key intermediate **8** was constructed from L-glyceraldehyde acetonide (**1**) via (*R*)-2-fluorobutenolide (**5**) as a chiral template, leading to the target carbohydrate moiety, which was then successfully condensed with appropriate silylated heterocycles to reach the desired nucleosides (Scheme 1).

L-Glyceraldehyde acetonide (**1**) was obtained from L-gulonic-γ-lactone according to the literature, by isopropylidenation followed by oxidative cleavage using sodium periodate.[22] Aldehyde intermediate **1** was subjected to Horner−Emmons reaction in the presence of triethyl α-fluorophosphonoacetate and sodium bis(trimethylsilyl)amide in THF to give a mixture of (*E*)-**2**/(*Z*)-**2** (9:1 determined by ^{1}H NMR).[23,24] Due to difficulties in separation of (*E*)-**2**/(*Z*)-**2** isomers, the mixture was directly used in the cyclization reaction under acidic conditions to give the desired 2-fluorobutyrolactone **3** and diol **4**. The resulting mixture was further converted into corresponding silyl derivatives, which were readily separated to give **5** as a white solid (70.2% yield from aldehyde **1**). The silylated lactone **5** was then reduced by DIBAL-H in CH_2Cl_2 to provide lactol **7**, which was then treated with acetic anhydride to afford the key intermediate **8** in 62% yield from compound **5**. *N*-Glycosylation reactions of pyrimidine bases with sugar moiety **8** were conducted under the Vorbrüggen conditions using TMSOTf as a catalyst. 5′-Silyl-protected

Scheme 2[a]



[a] Reagents: (i) silylated 6-Cl-purine, TMSOTf, CH_2Cl_2; (ii) silylated 6-Cl-2-F-purine, TMSOTf, DCE; (iii) TBAF, CH_3CN; (iv) dry NH_3/DME; (v) satd NH_3/MeOH, 90 °C; (vi) $HSCH_2CH_2OH$, 1 M NaOMe, MeOH, reflux.

uracil and thymine nucleosides **9** and **10** were formed in 64−73% yield as inseparable α/*β* mixtures after condensation of **8** with silylated uracil or thymine. These anomeric mixtures **9** and **10** were treated with tetra-*n*-butylammonium fluoride in THF to afford free nucleosides **15**−**18**, which were readily separated by silica gel column chromatography (*β*:α = 1.5−1.58:1, 67−74%). Likewise, condensation of **8** with silyated N^4-benzoylcytosine in dry acetonitrile gave protected cytosine derivatives **11** and **12**, which were readily isolated by silica gel column chromatography (*β*:α = 1.48:1). Deprotections of individual anomers in the presence of tetra-*n*-butylammonium fluoride (69−75%), followed by ammonolysis using saturated methanolic ammonia at room temperature (76−95%), afforded the final cytosine derivatives **23** and **24**. The 5-fluorocytosine derivatives **25** and **26** (*β*:α = 1.39:1) were also obtained by similar procedures to that of cytosine derivatives.

The synthetic route for purine nucleosides **36**−**45** is described in Scheme 2. Condensation of the acetate **8** with silylated 6-chloropurine followed by removal of the 5′-silyl protection group provided 6-chloropurine nucleosides **30** and **31** (*β*:α = 1:1.29), which were utilized as intermediates for the preparation of L-2′-Fd4A and L-2′-Fd4I analogues. The *β*-6-chloropurine derivative **30** was transformed into its corresponding adenine derivative **36** in 75% yield by treatment with methanolic ammonia in a steel bomb at 90 °C for 24 h. The *β*-L-inosine analogue **38** was also obtained from **30** in 80% yield by refluxing with sodium methoxide and 2-mercaptoethanol in methanol. The corresponding α-anomers **37** and **39** were synthesized by procedures analogous to those used for the preparation of **36** and **38**. The key intermediate **8** was also utilized for the synthesis of guanine and related 2,6-disubstituted purine analogues (Scheme 2). Similarly, condensation of acetate **8** with silylated 2-fluoro-6-chloropurine in dry 1,2-dichloroethane (DCE) at room temperature gave *β*-anomer **28** (30%) and α-anomer **29** (22.1%) after silica gel column chromatography. A solution of **28** in ethylene glycol dimethyl ether (DME) was bubbled with dry ammonia at room temperature for 16 h to give 2-amino-6-chloropurine derivative **32** (28.9%) and 2-fluoro-6-aminopurine derivative **33** (39.4%), which were readily separated by silica gel column chromatography. Individual protected nucleosides **32** and **33** were treated with tetra-*n*-butylammonium fluoride to afford *β*-L-2′-fluoro-2′,3′-unsaturated 2-fluoroadenine **40** and -2-amino-6-chloropurine **42** in high yields. Compound **42** was then further transformed to guanine derivative **44** by refluxing in the presence of mercaptoethanol and sodium methoxide in 50.7% yield. The corresponding α-isomers **41**, **43**, and **45** were also prepared by similar procedures as their *β*-isomers. The stereochemical assignments of these compounds were determined on the basis of NOESY experiments on adenine derivatives **36** and **37**, in which cross-peaks exist between 1′-H and 4′-H and aromatic 8-H and 5′-H in *β*-isomer **36**, while no such cross-peak was observed in α-isomer **37**. Instead, a cross-peak between 8-H and 4′-H was observed in compound **37**. This stereochemis-

Table 1. Physical Data

no.	mp, °C (solv)[a]	$[\alpha]_D$, deg	formula	anal.
9	syrup	mixture	$C_{15}H_{23}FN_2O_4Si$	C, H, N
10	syrup	mixture	$C_{16}H_{25}FN_2O_4Si$	C, H, N
11	144−146 (A)	−20.47 (*c* 0.36, $CHCl_3$)	$C_{22}H_{28}FN_3O_4Si$	C, H, N
12	139−141 (A)	+157.68 (*c* 0.31, $CHCl_3$)	$C_{22}H_{28}FN_3O_4Si$	C, H, N
13	138−140 (A)	+7.38 (*c* 0.19, $CHCl_3$)	$C_{22}H_{27}F_2N_3O_4Si$	C, H, N
14	184−186 (A)	+97.90 (*c* 0.22, $CHCl_3$)	$C_{22}H_{27}F_2N_3O_4Si$	C, H, N
15	161−162 (B)	−13.412 (*c* 0.20, MeOH)	$C_9H_9FN_2O_4 \cdot 0.3H_2O$	C, H, N
16	136−137 (E)	+138.55 (*c* 0.14, MeOH)	$C_9H_9FN_2O_4 \cdot 0.2H_2O$	C, H, N
17	149−151 (C)	−30.44 (*c* 0.20, MeOH)	$C_{10}H_{11}FN_2O_4 \cdot 0.4H_2O$	C, H, N
18	116−118 (E)	+132.42 (*c* 0.25, MeOH)	$C_{10}H_{11}FN_2O_4 \cdot 0.3H_2O$	C, H, N
19	200−202 dec (B)	−54.89 (*c* 0.39, $CHCl_3$)	$C_{16}H_{14}FN_3O_4$	C, H, N
20	170−172 (B)	+136.38 (*c* 0.45, $CHCl_3$)	$C_{16}H_{14}FN_3O_4 \cdot 0.3H_2O$	C, H, N
21	173−174 (D)	−41.75 (*c* 0.22, MeOH)	$C_{16}H_{13}F_2N_3O_4$	C, H, N
22	183−185 (F)	+148.76 (*c* 0.19, MeOH)	$C_{16}H_{13}F_2N_3O_4$	C, H, N
23	173−174 (D)	−21.31 (*c* 0.25, MeOH)	$C_9H_{10}FN_3O_3 \cdot 0.4H_2O$	C, H, N
24	182−183 (B)	+159.15 (*c* 0.21, MeOH)	$C_9H_{10}FN_3O_3$	C, H, N
25	202−205 (D)	−26.76 (*c* 0.21, MeOH)	$C_9H_9F_2N_3O_3$	C, H, N
26	158−160 (B)	+145.89 (*c* 0.45, MeOH)	$C_9H_9F_2N_3O_3$	C, H, N
27	syrum	mixture	$C_{16}H_{22}FClN_4O_2Si$	C, H, N
28	foam	+9.80 (*c* 0.20, $CHCl_3$)	$C_{16}H_{21}F_2ClN_4O_2Si$	C, H, N
29	syrup	+139.67 (*c* 0.18, $CHCl_3$)	$C_{16}H_{21}F_2ClN_4O_2Si$	C, H, N
30	130−132 (B)	−43.04 (*c* 0.18, $CHCl_3$)	$C_{10}H_8FClN_4O_2 \cdot 0.1C_2H_6O$	C, H, N
31	foam	+157.63 (*c* 0.20, $CHCl_3$)	$C_{10}H_8FClN_4O_2$	C, H, N
32	180−182 (A)	+13.33 (*c* 0.54, $CHCl_3$)	$C_{16}H_{23}F_2N_5O_2Si \cdot 0.2C_3H_6O$	C, H, N
33	129−130 (A)	+90.22 (*c* 0.23, $CHCl_3$)	$C_{16}H_{23}FClN_5O_2Si$	C, H, N
34	184−186 (A)	+116.53 (*c* 0.13, $CHCl_3$)	$C_{16}H_{23}F_2N_5O_2Si \cdot 0.3C_3H_6O$	C, H, N
35	128−130 (A)	+89.87 (*c* 0.15, $CHCl_3$)	$C_{16}H_{23}FClN_5O_2Si$	C, H, N
36	188−190 (B)	−54.91 (*c* 0.17, MeOH)	$C_{10}H_{10}FN_5O_2 \cdot 0.2H_2O$	C, H, N
37	168−171 (B)	+160.62 (*c* 0.19, MeOH)	$C_{10}H_{10}FN_5O_2 \cdot 0.3CH_4O$	C, H, N
38	128−130 (E)	−50.21 (*c* 0.20, MeOH)	$C_{10}H_9FN_4O_3 \cdot 0.2H_2O$	C, H, N
39	>200 dec (B)	+157.30 (*c* 0.22, MeOH)	$C_{10}H_9FN_4O_3 \cdot 0.3H_2O$	C, H, N
40	185−188 dec (B)	−56.15 (*c* 0.16, MeOH)	$C_{10}H_9F_2N_5O_2 \cdot 0.6CH_4O$	C, H, N
41	180 dec (B)	+178.22 (*c* 0.10, MeOH)	$C_{10}H_9F_2N_5O_2 \cdot 0.4H_2O$	C, H, N
42	155−156 dec (B)	+10.64 (*c* 0.17, MeOH)	$C_{10}H_9ClFN_5O_2$	C, H, N
43	150−152 (B)	+142.49 (*c* 0.17, MeOH)	$C_{10}H_9ClFN_5O_2$	C, H, N
44	>200 dec (B)	+24.42 (*c* 0.11, DMF)	$C_{10}H_{10}FN_5O_3 \cdot 0.2H_2O$	C, H, N
45	>220 dec (B)	+58.68 (*c* 0.10, DMF)	$C_{10}H_{10}FN_5O_3 \cdot 0.7CH_2Cl_2$	C, H, N

[a] Solvents: A, EtOAc−hexanes; B, CH_2Cl_2−MeOH; C, THF−cyclohexane; D, hexanes−CH_2Cl_2−MeOH; E, lyophilized from water; F, EtOH.

try was also supported by lower field chemical shifts of 4′-H (α-form) compared to those of 4′-H (*β*-form) due to deshielding effects by heterocyclic bases. The detailed proton NMR data and physical properties of synthesized nucleosides are listed in Tables 1 and 2.

In preliminary studies, the effect of chemical stability of glycosyl bond by 2′-fluorine substitution was investigated, in which *β*-L-2′-Fd4FA (**40**) was found to have increased stability relative to the compound without a fluorine substitution at the 2′-position (*β*-L-d4FA). At physiological conditions (pH 7.4, 37 °C), the half-life of *β*-L-d4FA was approximately 30 h, while no degradation was observed for *β*-L-2′-Fd4FA (**40**) up to 6 days. The stability of *β*-L-2′-Fd4A (**36**) was also investigated at pH 2.0, 7.4, and 11, in which compound **36** was stable at pH 7.4 and 11, while at pH 2, the degradation began after 18 h with a half-life of approximately 3 days. Therefore, it is concluded that the 2′-fluorine incorporation significantly increased the chemical stability of glycosyl linkage of 2′,3′-didehydro-2′,3′-dideoxynucleosides without reduction of the antiviral activity.

Structure−Activity Relationships. The newly synthesized nucleosides were tested for their antiviral activities and cytotoxicities in vitro, and the results are summerized in Table 3. The anti-HIV-1 activities of the synthesized nucleosides were evaluated in human peripheral blood mononuclear (PBM) cells infected with HIV-1, and AZT was included as a positive control (Table 3). Among these nucleosides, *β*-L-2′-Fd4C (**23**) (EC_{50} 0.51 *μ*M) and *β*-L-2′-Fd4FC (**25**) (EC_{50} 0.17 *μ*M) were found to be the most potent compounds against HIV-1 with no significant cytotoxicity. However, uracil and thymine derivatives **15**−**18** showed no activity with EC_{50} values above 100 *μ*M. For purine analogues, *β*-L-2′-Fd4A (**36**) was the most potent nucleoside in the following decreasing order: *β*-L-2′-Fd4A (**36**) (1.5) > *β*-L-2′-Fd4FA (**40**) (2.2) > *β*-L-2′-Fd4I (**38**) (4.7) > α-L-2′-F-6-Cl-2-NH_2-purine (**43**) (14.5) > α-L-2′-Fd4A (**37**) (47.6) > α-L-2′-Fd4G (**45**) (76.9). It is interesting to note that **43** and **45** displayed some anti-HIV activities as α-isomers, while no activity was found in the corresponding *β*-isomers **42** and **44**, which may be related to the greater overall cell toxicity of these compounds compared to their *β*-isomers which produced lower multiplicity of the virus. We are confident about the assignment of the structures of these compounds since 6-chloro-2-fluoropurines **28** (*β*) and **29** (α) were also subsequently used for further modifications to 2-fluoroadenine derivatives, in which *β*-isomer **40** (2.2 *μ*M) was found to be significantly more potent than the corresponding α-isomer **41** (>100 *μ*M). Previously, several authors reported that *β*-D-2′-Fd4C showed anti-HIV activity with significant cytotoxicity.[15−17] In connection with these findings, it appears that *β*-L-2′-Fd4C (**23**) (0.51 *μ*M) displays enhanced potency against HIV-1 with more selectivity than that of its D-antipode (3−10 *μ*M). Furthermore, *β*-L-d4FC[8] is significantly more toxic than the corresponding 2′-fluoro derivative *β*-L-2′-Fd4FC (**25**),

Table 2. ^{1}H NMR Data

no.	H-1′	H-3′	H-4′	H-5′	other signals
9[a]	6.88 (m)	5.72 (m)	4.97 (m), 4.88 (m)	3.93−3.68 (m)	8.02 (s, NH), 7.94 (d, H-6, J = 8 Hz), 7.18 (d, H-5, J = 8 Hz), 0.92 (s, ^{t}Bu), 0.90 (s, ^{t}Bu), 0.10, 0.09, 0.085, 0.074 (4s, 4 × CH_3)
10[a]	6.96 (s), 6.87 (m)	5.73 (s), 5.66 (s)	4.98 (m), 4.84 (m)	3.83−3.67 (m)	8.15 (s, NH), 7.38 (s, H-6), 1.94 (s, 5-CH_3), 0.92 (s, ^{t}Bu), 0.90 (s, ^{t}Bu), 0.10, 0.09, 0.085, 0.074 (4s, 4 × CH_3)
11[a]	7.12 (s)	5.61 (s)	4.94 (s)	3.97−3.80 (m)	8.41 (d, H-6, J = 7.2 Hz), 7.93−7.50 (m, 6H, H-5, Ph-H), 0.94 (s, ^{t}Bu), 0.13, 0.12 (2s, 2 × CH_3)
12[a]	7.08 (ps t)	5.75 (s)	5.05 (ps, t, J = 4.4, 4.8 Hz)	3.82−3.71 (m)	7.91 (d, H-6, J = 6 Hz), 7.64−7.50 (m, 6H, H-5, Ph-H), 0.91 (s, ^{t}Bu), 0.09, 0.08, (2s, 2 × CH_3)
13[a]	6.94 (s)	6.62 (s)	4.92 (m)	3.92 (m)	8.32−7.44 (m, 6H, H-5, Ph-H), 0.94 (s, ^{t}Bu), 0.15, 0.14 (2s, 2 × CH_3)
14[a]	6.91 (ps t, J = 4.57, 4.75 Hz)	5.77 (s)	5.03 (m)	3.75 (m)	8.31−7.44 (m, 5H, Ph-H), 7.32 (d, J = 5.4 Hz, H-6), 0.91 (s, ^{t}Bu), 0.09, 0.08 (2s, 2 × CH_3)
15[b]	6.77 (s)	6.01 (s)	4.81 (s)	3.58 (s)	11.5 (s, -NH), 7.99 (d, H-6, J = 8 Hz), 5.71 (d, H-5, J = 8 Hz), 5.13 (t, J = 5.2 Hz, OH)
16[b]	6.77 (t, J = 4.4 Hz)	6.02 (d, J = 1.2 Hz)	5.02 (ps t, J = 4, 4.4 Hz)	3.56−3.45 (m)	11.5 (s, -NH), 7.56 (d, H-6, J = 8 Hz), 5.70 (d, H-5, J = 8 Hz), 4.94 (t, OH, J = 6 Hz)
17[b]	6.77 (s)	6.00 (s)	4.80 (s)	3.60 (s)	11,5 (s, -NH), 7.89 (s, H-6), 5.17 (t, J = 5.2 Hz, OH), 1.76 (s, 3H, CH_3-6)
18[b]	6.78 (ps t, J = 4, 4.4 Hz)	6.01 (s)	5.05 (t, J = 4 Hz)	3.68−3.45 (m)	11,5 (s, -NH), 7.37 (s, H-6), 4.94 (t, J = 6 Hz, OH), 1.81 (s, 3H, CH_3-6)
19[a]	7.01 (s)	5.71 (s)	4.99 (s)	3.88 (m)	8.21 (d, J = 8 Hz, H-6), 7.64−7.50 (m, H-5, Ph-H)
20[a]	7.16 (ps t, J = 3.6, 4.4 Hz)	5.74 (s)	5.13 (ps t, J = 3.2, 4.8 Hz)	3.73−3.69 (m)	7.92 (d, J = 7.2 Hz, H-6), 7.64−7.50 (m, H-5, Ph-H)
21[a]	6.93 (s)	5.71 (s)	4.95 (s)	3.99−3.80 (m)	8.30−7.44 (m, 6H, H-6, Ph-H)
22[a]	6.97 (ps t, J = 4.82, 4.43 Hz)	5.77 (s)	5.11 (ps t, J = 4.6, 4.7 Hz)	3.88−3.68 (m)	8.31−7.45 (m, 5H, Ph-H), 7.332 (d, J = 5.32, H-6)
23[b]	6.85 (s)	5.94 (d, J = 1.2 Hz)	4.76 (s)	3.56 (s)	7.86 (d, J = 7.2 Hz, H-6), 7.36, 7.32 (2s, NH_2), 5.77 (d, J = 7.2 Hz, H-5), 5.07 (t, J = 5.2 Hz, OH)
24[b]	6.86 (ps t, J = 4.4, 4.8 Hz)	5.94 (d, J = 1.6 Hz)	4.94 (m)	3.455−3.43 (m)	7.47 (d, J = 7.6 Hz, H-6), 7.35, 7.32 (2s, NH_2), 5.80 (d, J = 7.2 Hz, H-5)
25[b]	6.81 (s)	5.93 (m)	4.81 (m)	3.61 (m)	7.98, 7.73 (2s, 2H, NH_2), 5.4 (t, J = 5.1 Hz, OH)
26[b]	6.81 (s)	5.93 (d, J = 0.88 Hz)	5.05 (ps t, J = 3.9, 4.0 Hz)	3.54−3.43 (m)	7.99 (s, 1′H, NH), 7.76−7.73 (m, 2H, 6-H, NH)
27[a]	7.01 (s), 6.93 (t, J = 4.4 Hz)	5.85 (s), 5.78 (s)	5.18 (ps t, J = 4, 4.4 Hz), 5.02 (s)	3.85 (m)	8.79, 8.78 (2s, H-8), 8.60, 8.21 (2s, H-2), 0.92, 0.91 (2s, ^{t}Bu), 0.111, 0.105, 0.097, 0.095 (4s, 4 × CH_3)
28[a]	6.88 (s)	5.77 (s)	5.02 (s)	3.88 (m)	8.60 (s, H-8), 0.91 (s, ^{t}Bu), 0.112, 0.105 (2s, 2 × CH_3)
29[a]	6.81 (m)	5.84 (s)	5.19 (m)	3.81 (m)	8.17 (s, H-8), 0.92 (s, ^{t}Bu), 0.103, 0.089 (2s, 2 × CH_3)
30[a]	6.88 (s)	5.85 (s)	5.12 (m)	3.88 (m)	8.78 (s, H-8), 8.50 (s, H-2)
31[a]	7.00 (m)	5.86 (s)	5.29 (m)	3.87 (m)	8.78 (s, H-8), 8.22 (s, H-2)
32[a]	6.81 (m)	5.73 (d, J = 1.6 Hz)	4.96 (d, J = 2.8 Hz)	3.90−3.80 (m)	8.19 (s, H-8), 0.91 (s, ^{t}Bu), 0.09, 0.084 (2s, 2 × CH_3)
33[a]	6.78 (m)	5.75 (s)	4.95 (m)	3.81 (m)	8.14 (s, H-8), 5.11 (s, NH_2), 0.89 (s, ^{t}Bu), 0.076 (s, CH_3)
34[a]	6.76 (m)	5.80 (s)	5.13 (ps t, J = 4.4, 4.8 Hz)	3.76−3.65 (m)	7.84 (s, H-8), 0.91 (s, ^{t}Bu), 0.093, 0.08 (2s, 2 × CH_3)
35[a]	6.73 (ps t, J = 4.4, 4.8 Hz)	5.80 (s)	5.09 (m)	3.84−3.73 (m)	7.84 (s, H-8), 5.12 (s, NH_2), 0.91 (s, ^{t}Bu), 0.096, 0.082 (s, CH_3)
36[b]	6.90 (s)	6.08 (s)	4.91 (s)	3.63 (s)	8.40 (s, H-8), 8.17 (s, H-2), 7.40 (s, NH_2), 5.22 (t, J = 5.6 Hz, OH)
37[b]	6.89 (t, J = 4 Hz)	6.06 (s)	5.14 (ps t, J = 3.6, 4 Hz)	3.63−3.52 (m)	8.31 (s, H-8), 8.17 (s, H-2), 7.36 (s, NH_2), 4.97 (t, J = 6 Hz, OH)
38[b]	6.94 (m)	6.15 (t, J = 1.6 Hz)	4.98 (s)	3.67 (s)	12.57 (br s, NH), 8.43 (s, H-8), 8.17 (s, H-2), 5.17 (s, OH)
39[b]	6.87 (ps t, J = 2.7,5.3 Hz)	6.06 (s)	5.13 (ps t, J = 3.6, 3.7 Hz)	3.61−3.51 (m)	8.26 (s, H-8), 8.09 (s, H-2)
40[b]	6.80 (s)	6.09 (ps t, J = 1.2, 1.6 Hz)	4.90 (s)	3.62 (m)	8.38 (s, H-8), 7.99, 7.92 (2br s, NH_2), 5.09 (t, J = 5.6 Hz, OH)
41[b]	6.82 (m)	6.07 (d, J = 1.2 Hz)	5.12 (m)	3.61−3.51 (m)	8.30 (s, H-8), 7.96 (2s, NH_2)
42[b]	6.76 (s)	6.09 (s)	4.91 (s)	3.60 (s)	8.38 (s, H-8), 7.07 (s, NH_2), 5.10 (s, OH)
43[b]	6.72 (t, J = 4 Hz)	6.06 (d, J = 1.2 Hz)	5.16 (ps t, J = 3.6, 4 Hz)	3.62−3.51 (m)	8.30 (s, H-8), 7.04 (s, NH_2), 4.98 (t, J = 6 Hz, OH)
44[b]	6.60 (s)	6.03 (d, J = 1.2 Hz)	4.86 (s)	3.59 (s)	10.74 (br s, NH), 7.96 (s, H-8), 6.57 (s, NH_2), 5.08 (t, J = 5.2 Hz, OH)
45[b]	6.62 (m)	6.01 (d, J = 1.6 Hz)	5.08 (m)	3.64−3.42 (m)	7.82 (s, H-8), 6.57 (s, NH_2), 4.95 (t, J = 5.6 Hz, OH)

[a] $CDCl_3$. [b] DMSO-d_6.

suggesting that 2′-fluorine substitution can decrease toxicity of certain L-d4N analogues.

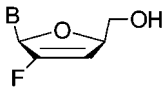
The synthesized nucleosides were also evaluated against HBV in vitro as shown in Table 3. β-L-2′-Fd4C (**23**) (0.18 μM), β-L-2′-Fd4FC (**25**) (0.225 μM), and β-L-2′-Fd4A (**36**) (1.7 μM) also exhibited significant anti-HBV activities in 2.2.15 cells without toxicity up to 100 μM. Therefore, we may conclude that the structural requirements for anti-HIV and anti-HBV activities are similar. However, it is not known at the present time whether the structural requirements are similar at the stage of kinases or polymerase level. Two nucleosides (**23** and **36**) showed no effect on mitochondrial DNA content of CEM cells upon long-term exposure. These compounds were also tested against HSV-1 in vitro and were inactive up to 50 μM.

In summary, we have developed an efficient synthetic methodology for a series of 2′-fluoro-2′,3′-unsaturated pyrimidine and purine L-nucleosides. Preliminary biological evaluation in vitro indicates that β-L-2′-Fd4C (**23**), β-L-2′-Fd4FC (**25**), and β-L-2′-Fd4FA (**36**) exhibited significant anti-HIV and anti-HBV activities with increased chemical stability.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker AMX400 400-MHz spec-

Table 3. Anti-HIV and Anti-HBV Activities of 2′-Fluoro-2′,3′-unsaturated L-Nucleosides



		EC_{50}, μM		toxicities (IC_{50}, μM)		
compd	B	HIV-1	HBV	PBM cells	Vero cells	CEM cells
15	uracil (β)	>100	>10	>100	>100	>100
16	uracil (α)	>100	>10	>100	>100	>100
17	thymine (β)	>100	>10	>100	>100	>100
18	thymine (α)	>100	>10	>100	>100	>100
23	cytosine (β)	0.51	0.18	>100	>100	>100
24	cytosine (α)	>100	>10	>100	>100	>100
25	5-F-cytosine (β)	0.17	0.225	>100	>100	>100
26	5-F-cytosine (α)	>100	>10	>100	>100	>100
36	adenine (β)	1.5	1.7	>100	>100	>100
37	adenine (α)	47.6	>10	>100	>100	>100
38	inosine (β)	4.7	>10	>100	>100	>100
39	inosine (α)	>100	>10	>100	>100	>100
40	2-F-adenine (β)	2.2	>10	25.8	~173	19.5
41	2-F-adenine (α)	>100	>10	>100	>100	>100
42	6-Cl-2-NH_2-purine (β)	>100	>10	>100	>100	>100
43	6-Cl-2-NH_2-purine (α)	14.5	>10	26.6	>100	28.2
44	guanine (β)	>100	>10	>100	>100	>100
45	guanine (α)	76.9	>10	>100	>100	>100
AZT		0.004	>10	>100	29.0	14.3

trometer with tetramethylsilane as the internal reference; chemical shifts (δ) are reported in parts per million (ppm), and the signals are described as s (singlet), d (doublet), t (triplet), q (quartet), br s (broad singlet), dm (doublet of multiplet), and m (multiplet). UV spectra were obtained on a Beckman DU 650 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Mass spectra were recorded on a Micromass AutoSpec high-resolution mass spectrometer (LSIMS). Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA. All reactions were monitored using thin-layer chromatography on Analtech, 200-mm silica gel GF plates. Dry 1,2-dichloroethane, dichloromethane, and acetonitrile were obtained by distillation from CaH_2 prior to use. Dry THF was obtained by distillation from Na and benzophenone when the solution became purple.

(*E*)/(*Z*)-Ethyl 3-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-fluoroacrylate (*E*-2 and *Z*-2). A solution of triethyl 2-fluorophosphonoacetate (39.2 g, 162 mmol) in THF (70 mL) was cooled to −78 °C, and sodium bis(trimethylsilyl)amide (1.0 M solution in THF, 162 mL, 162 mmol) was added dropwise. The mixture was kept for 30 min at −78 °C; then a solution of l-(*S*)-glyceraldehyde acetonide (**1**) (19.14 g, 147 mmol) in THF (70 mL) was added. After being stirred for 1 h at −78 °C, the reaction mixture was treated with aqueous NH_4Cl and extracted with ether. The ether phase was washed with saturated NaCl, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel to give mixture of ***E*-2** and ***Z*-2** (9:1 by ^{1}H NMR) as a yellowish oil (34.6 g, 97.9%): ^{1}H NMR ($CDCl_3$) δ 1.34, 1.36 (2t, J = 8 Hz, $-CH_2CH_3$), 1.40, 1.45 (2s, $-CH_3$), 3.69 (m, H_a-5), 4.28 (m, H_b-5, $-CH_2CH_3$), 5.02 (m, H-4), 5.40 (m, H-4), 6.02 (dd, J = 8, 20 Hz, H-3), 6.18 (dd, J = 8, 32 Hz, H-3).

(*R*)-(+)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-2-fluoro-2-buten-4-olide (5). A solution of ***E*/*Z*-2** (19.62 g, 89.89 mmol) in 110 mL of anhydrous EtOH was treated with 30 mL of concentrated HCl and stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was coevaporated with toluene (3 × 300 mL) to give lactone **3** and uncyclized ester **4**. The resulting yellowish syrup was used as such for the next reaction without further purification.

tert-Butyldimethylsilyl chloride (27.1 g, 180 mmol) and imidazole (12.3 g, 180 mmol) were added to a solution of **3** and **4** in CH_2Cl_2 (250 mL), and the mixture was reacted for 4 h at room temperature. The resulting mixture was treated with ice and diluted with CH_2Cl_2. The organic layer were combined, dried over $MgSO_4$, and concentrated to dryness. Purification on silica gel (4% EtOAc/hexanes) furnished 28.0 g (70.2% from compound **1**) of crystalline solid **5**: mp 48−50 °C; $[\alpha]^{28}_D$ +105 0.3 (*c* 1.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.07, 0.08 (2s, 2 × CH_3), 0.88 (s, *t*-Bu), 3.88 (m, 2H, H-5), 5.01 (m, 1H, H-4), 6.73 (ps t, 1H, J = 4 Hz). Anal. Calcd for $C_{10}H_{19}FO_3Si$: C, 53.63; H, 7.77. Found: C, 53.70; H, 7.75.

1-Acetyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-2-fluoro-2-buten-4-olide (8). Lactone **5** (20.58 g, 83.54 mmol) was dissolved in 200 mL of CH_2Cl_2 under nitrogen atmosphere; then the mixture was cooled to −78 °C and treated with a 1.0 M solution of DIBAL-H in CH_2Cl_2 (125 mL). The resulting mixture was reacted for 2 h at −78 °C. The cold mixture was treated with dilute nitric acid, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave an anomeric mixture of **7** as a pale-yellow oil (16.6 g, crude yield 80%), which was used as such for the next step.

Acetic anhydride (8.2 mL, 87.12 mmol) was added to a solution of **7** (5.41 g, 21.78 mmol) and triethylamine (12.1 mL, 87.12 mmol) in CH_2Cl_2 (45 mL) at 0 °C, and the resulting mixture was kept for 2 h at room temperature. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (6.5% EtOAc/hexanes) to give acetate **8** (6.1 g, 77.5% from **7**) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ 0.06, 0.10 (2s, 2 × CH_3), 0.88, 0.90, 0.92 (3s, *t*-Bu, 2 × CH_3), 3.61, 3.77 (m, 2H, H-5), 4.77, 4.96 (m, 1H, H-4), 5.63 (br s 1H, 3-H), 6.67−6.70 (m, 1H, H-1).

General Procedure for Condensation of Acetate 8 with Pyrimidine Bases. A mixture of uracil (420 mg, 3.75 mmol), hexamethyldisilazane (15 mL), and ammonium sulfate (20 mg) was refluxed for 3 h under nitrogen. The clear solution obtained was concentrated to dryness in vacuo. TMSOTf (0.7 mL, 3.14 mL) was added to the solution of sugar **8** (728 mg, 2.50 mmol) and silylated base in dry DCE (20 mL) at 0 °C. The reaction mixture was stirred for 2 h under nitrogen, poured into cooled saturated $NaHCO_3$ solution (30 mL), and stirred for 15 min. The resulting mixture was washed, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (3% MeOH/$CHCl_3$) to afford **9** (960 mg, 73%) as an inseparable anomeric mixture, which was used in the next step without separation.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-2-fluoro-L-*glycero*-pent-2-eno-furanosyl]uracil (9): UV ($CHCl_3$) λ_{max} 257.5 nm. Anal. ($C_{15}H_{23}FN_2O_4Si$) C, H, N.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-2-fluoro-L-*glycero*-pent-2-eno-furanosyl]thymine (10). Silylated thymine, which was prepared from thymine (242 mg, 1.92 mmol) and HMDS (20 mL), was treated with **8** (500 mg, 1.72 mmol) and TMSOTf (0.5 mL, 2.25 mmol) in dry DCE at room

temperature for 2 h under nitrogen. After workup similar to that of **9**, purification by silica gel column chromatography (3% MeOH/$CHCl_3$) gave an inseparable anomeric mixture of **10** (392 mg, 64%): UV ($CHCl_3$) λ_{max} 262.0 nm. Anal. ($C_{16}H_{25}FN_2O_4Si$) C, H, N.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl]-*N*^{4}-benzoylcytosine (11) and Its α-Isomer (12). Silylated *N*^{4}-benzoylcytosine [prepared from 790 mg (3.67 mmol) of *N*^{4}-benzoylcytosine and 20 mL of HMDS], **8** (470 mg, 1.62 mmol), and TMSOTf (0.5 mL, 2.25 mmol) in dry acetonitrile (20 mL) were reacted for 2 h at room temperature under nitrogen. After workup similar to that of **9**, isolation by silica gel column chromatography (30% EtOAc/hexanes) afforded *β*-anomer **11** (0.34 g, 47.1%) and α-anomer **12** (0.23 g, 31.8%) as white solids. **11**: UV ($CHCl_3$) λ_{max} 260.5 nm. Anal. ($C_{22}H_{28}FN_3O_4Si$) C, H, N. **12**: UV ($CHCl_3$) λ_{max} 260.5 nm. Anal. ($C_{22}H_{28}FN_3O_4Si$) C, H, N.

5-Fluoro-1-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl]-*N*^{4}-benzoylcytosine (13) and Its α-Isomer (14). Silylated *N*^{4}-benzoyl-5-fluorocytosine [prepared from 637.6 mg (2.73 mmol) of *N*^{4}-benzoyl-5-fluorocytosine and 20 mL of HMDS], **8** (528.5 mg, 1.82 mmol), and TMSOTf (0.5 mL, 2.73 mmol) in dry DCE (20 mL) were reacted for 1 h at room temperature under nitrogen. After workup similar to that of **9**, isolation by silica gel column chromatography (25% EtOAc/hexanes) afforded *β*-anomer **13** (0.38 g, 44.5%) and α-anomer **14** (0.27 g, 32%) as white solids. **13**: UV ($CHCl_3$) λ_{max} 326.0 nm. Anal. ($C_{22}H_{27}F_2N_3O_4Si$) C, H, N. **14**: UV ($CHCl_3$) λ_{max} 325.5 nm. Anal. ($C_{22}H_{27}F_2N_3O_4Si$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl)uracil (15) and Its α-Isomer (16). Tetra-*n*-butylammonium fluoride (0.6 mL, 0.6 mmol) was added to anomeric mixture **9** (177 mg, 0.52 mmol) in THF (15 mL), and the reaction mixture was stirred at room temperature for 15 min. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (2% MeOH/CH_2Cl_2) to give *β*-anomer **15** (52.8 mg, 44.5%) as a white solid and α-anomer **16** (35.1 mg, 29.6%) as a white solid. **15**: UV (H_2O) λ_{max} 257.0 nm (ε 16 500) (pH 7), 258.0 nm (ε 18 200) (pH 2), 257.0 nm (ε 8 200) (pH 11); HRMS (LSIMS, *m*/*z*) 229.0626 (calcd 229.0624). Anal. ($C_9H_9FN_2O_4 \cdot 0.3H_2O$) C, H, N. **16**: UV ($H_2O$) λ_{max} 257.5 nm (ε 16 700) (pH 7), 258.0 nm (ε 18 900) (pH 2), 257.0 nm (ε 8 300) (pH 11); HRMS (LSIMS, *m*/*z*) 229.0632 (calcd 229.0624). Anal. ($C_9H_9FN_2O_4 \cdot 0.2H_2O$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl)thymine (17) and Its α-Isomer (18). Tetra-*n*-butylammonium fluoride (0.8 mL, 0.8 mmol) was added to a mixture of **10** (240 mg, 0.67 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature at room temperature for 30 min. The solvent was removed, and the resulting residue was purified by silica gel column chromatography (40% THF/cyclohexane) to give *β*-anomer **17** (66.5 mg, 41%) as a white solid and α-anomer **18** (52.8 mg, 26%) as a white solid. **17**: UV (H_2O) λ_{max} 262.0 nm (ε 5 600) (pH 7), 262.5 nm (ε 10 000) (pH 2), 263.5 nm (ε 7 500) (pH 11); HRMS (LSIMS, *m*/*z*) 243.0781 (calcd 243.0781). Anal. ($C_{10}H_{11}FN_2O_4 \cdot 0.4H_2O$) C, H, N. **18**: UV ($H_2O$) λ_{max} 262.5 nm (ε 6 700) (pH 7), 263.5 nm (ε 10 800) (pH 2), 264.5 nm (ε 7 400) (pH 11); HRMS (LSIMS, *m*/*z*) 243.0760 (calcd 243.0781). Anal. ($C_9H_9FN_2O_4 \cdot 0.3H_2O$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl)-*N*^{4}-benzoylcytosine (19). Tetra-*n*-butylammonium fluoride (1 M in THF) (1 mL, 1 mmol) was added to a solution of the *β*-anomer **11** (280 mg, 0.63 mmol) in THF (10 mL) at 0 °C, and the resulting reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, which was purified by silica gel column chromatography using 2.5% MeOH−CH_2Cl_2 as an eluent to give **19** (218 mg, 75%) as a white solid: UV (MeOH) λ_{max} 260.5 nm. Anal. ($C_{16}H_{14}FN_3O_4$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)-*N*^{4}-benzoylcytosine (20). Compound **20** was prepared from **12** on a 0.63-mmol scale by the method described for compound **19**. Flash chromatography (silica gel, 2.5% MeOH/CH_2Cl_2) gave 145.8 mg (69%) of the titled product as a white solid: UV (MeOH) λ_{max} 260.5 nm. Anal. ($C_{16}H_{14}FN_3O_4 \cdot 0.3H_2O$) C, H, N.

5-Fluoro-1-(2,3-dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl)-*N*^{4}-benzoylcytosine (21). Compound **21** was prepared from **13** on a 0.77-mmol scale by the method described for compound **19**. Flash chromatography (silica gel, 2% MeOH/$CHCl_3$) and subsequent recrystallization (hexanes−MeOH−CH_2Cl_2) gave 201.7 mg (75%) of the titled product as a white solid: UV (MeOH) λ_{max} 325.5 nm. Anal. ($C_{16}H_{13}F_2N_3O_4$) C, H, N.

5-Fluoro-1-(2,3-dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)-*N*^{4}-benzoylcytosine (22). Compound **22** was prepared from **14** on a 0.56-mmol scale by the method described for compound **19**. Flash chromatography (silica gel, 2% MeOH/CH_2Cl_2) and subsequent recrystallization (hot EtOH) gave 167.7 mg (86%) of the titled product as a white solid: UV (MeOH) λ_{max} 326.0 nm. Anal. ($C_{16}H_{13}F_2N_3O_4$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl)cytosine (23). A solution of the *β*-anomer **19** (67.60 mg, 0.20 mmol) in MeOH (5 mL) was treated with saturated methanolic ammonia (10 mL), and the reaction mixture was stirred at room temperature until the disappearance of starting material was observed (10 h). The mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC using 12% MeOH−CH_2Cl_2 as an eluent. The material obtained from the plate gave **23** (43 mg, 93.1%) as a white solid on trituation with hexanes−MeOH−CH_2Cl_2: UV (H_2O) λ_{max} 266.5 nm (ε 7 400) (pH 7), 276.0 nm (ε 12 900) (pH 2), 267.0 nm (ε 9 400) (pH 11); HRMS (LSIMS, *m*/*z*) 228.0782 (calcd 228.0784). Anal. ($C_9H_{10}FN_3O_3 \cdot 0.4H_2O$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)cytosine (24). A solution of the α-anomer **20** (65.9 mg, 0.20 mmol) in MeOH (5 mL) was treated with saturated methanolic ammonia (10 mL), and the reaction mixture was allowed to stir at room temperature until the disappearance of starting material was observed (16 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (12% MeOH/CH_2Cl_2) to give **24** (42.5 mg, 94.5%) as a white solid: UV (H_2O) λ_{max} 267.0 nm (ε 7 300) (pH 7), 275.5 nm (ε 14 400) (pH 2), 267.5 nm (ε 9 500) (pH 11); HRMS (LSIMS, *m*/*z*) 228.0775 (calcd 243.0784). Anal. ($C_9H_{10}FN_3O_3$) C, H, N.

5-Fluoro-1-(2,3-dideoxy-2-fluoro-*β*-L-*glycero*-pent-2-enofuranosyl)cytosine (25). Compound **21** (86.7 mg, 0.25 mmol) was treated with saturated methanolic ammonia solution (15 mL), and the reaction mixture was allowed to stir at room temperature until the disappearance of starting material was observed (14 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) to give **25** (46.6 mg, 76%) as a solid, which was recrystallized from hexanes−MeOH−CH_2Cl_2: UV (H_2O) λ_{max} 277.0 nm (ε 13 200) (pH 7), 282.0 nm (ε 15 800) (pH 2), 277.0 nm (ε 13 600) (pH 11); HRMS (LSIMS, *m*/*z*) 246.0672 (calcd 246.0690). Anal. ($C_9H_9F_2N_3O_3$) C, H, N.

5-Fluoro-1-(2,3-dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)cytosine (26). Compound **22** (84 mg, 0.24 mmol) was treated with saturated methanolic ammonia (15 mL), and the reaction mixture was allowed to stir at room temperature until the disappearance of starting material was observed (14 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (12% MeOH/CH_2Cl_2) to give **26** (45.3 mg, 77%) as a white solid: UV (H_2O) λ_{max} 277.0 nm (ε 8 100) (pH 7), 282.0 nm (ε 10 400) (pH 2), 276.0 nm (ε 7 100) (pH 11); HRMS (LSIMS, *m*/*z*) 246.0694 (calcd 246.0690). Anal. ($C_9H_{19}F_2N_3O_3$) C, H, N.

General Procedure for Condensation of Acetate 8 with Purine Bases. A mixture of 6-chloropurine (1.20 g, 7.75 mmol), hexamethyldisilazane (25 mL), and ammonium sulfate

(catalytic amount) was refluxed for 4 h under nitrogen. The clear solution obtained was concentrated in vacuo, and the residue was dissolved in dry CH_2Cl_2 (10 mL) and reacted with a solution of **8** (1.50 g, 5.17 mmol) in DCE (40 mL) and trimethylsilyl triflate (1.5 mL, 7.75 mmol) at room temperature. After stirring for 1 h at room temperature under nitrogen, the reaction solution was then poured into an ice-cold saturated $NaHCO_3$ solution (20 mL) and stirred for 15 min. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the residue was separated by silica gel column chromatography (17% EtOAc/hexanes) to give anomeric mixture **27** (1.25 g, 62.9%) as a syrup.

6-Chloro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-L-*glycero*-pent-2-enofuranosyl]purine (27): UV (MeOH) λ_{max} 265.0 nm. Anal. ($C_{16}H_{22}ClFN_4O_2$ Si) C, H, N.

6-Chloro-2-fluoro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl]purine (28) and Its α-Isomer (29). A mixture of silylated 2-fluoro-6-chloropurine [prepared from 1.170 g (6.78 mmol) of 2-fluoro-6-chloropurine and dry DCE (40 mL)] was stirred for 2 h at room temperature. After workup similar to that of **27**, purification by silica gel column chromatography (12% EtOAc/hexanes) gave β-anomer **28** (685 mg, 30.0%) as a white foam and α-anomer **29** as an yellowish syrup. **28:** UV (MeOH) λ_{max} 268.5 nm. Anal. ($C_{16}H_{21}F_2$ Cl N_4O_2Si) C, H, N. **29:** UV (MeOH) λ_{max} 269.0 nm. Anal. ($C_{16}H_{21}F_2ClN_4O_2$Si) C, H, N.

6-Chloro-9-(2,3-dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl)purine (30) and Its α-Isomer (31). A solution of **27** (1.2 g, 3.12 mmol) in dry CH_3CN (20 mL) was treated with tetra-*n*-butylammonium fluoride (1 M solution in THF) (3.2 mL, 3.2 mmol) and stirred for 1 h at room temperature. After evaporation of solvent, the residue was purified by column chromatography (3% MeOH/CH_2Cl_2) to obtain β- anomer **30** (296 mg, 35%) as a white solid and α-anomer **31** (380 mg, 45%) as a foam. **30:** UV (MeOH) λ_{max} 265.0 nm. Anal. ($C_{16}H_8FCl$ N_4O_2·0.1EtOH) C, H, N. **31:** UV (MeOH) λ_{max} 265.0 nm. Anal. ($C_{16}H_8FClN_4O_2$) C, H, N.

6-Amino-2-fluoro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl]-purine (32) and 6-Chloro-2-amino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl]purine (33). Dry ammonia was bubbled into a stirred solution of **28** (420 mg, 1.04 mmol) in dry DME (35 mL) at room temperature overnight. The salts were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified by preparative TLC (25% EtOAc/hexanes) to give two compounds, **32** (114 mg, 28.9%) as a white solid and **33** (164 mg, 39.4%) as a white solid. **32:** UV (MeOH) λ_{max} 268.5 nm. Anal. ($C_{16}H_{23}F_2N_5O_2Si$·0.2 acetone) C, H, N. **33:** UV (MeOH) λ_{max} 307.5 nm. Anal. ($C_{16}H_{23}FN_5O_2$-ClSi) C, H, N, Cl.

6-Amino-2-fluoro-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl]-purine (34) and 6-Chloro-2-amino-9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl]purine (35). Dry ammonia was bubbled into a stirred solution of **29** (420 mg, 1.04 mmol) in dry DME (35 mL) at room temperature overnight. The salts were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified by preparative TLC (25% EtOAc/hexanes) to give two compounds, **34** (150 mg, 36.5%) as a white solid and **35** (69.3 mg, 17.3%) as a white solid. **34:** UV (MeOH) λ_{max} 269.0 nm. Anal. ($C_{16}H_{23}F_2N_5O_2Si$·0.3 acetone) C, H, N. **35:** UV (MeOH) λ_{max} 309.5 nm. Anal. ($C_{16}H_{23}FClN_5O_2$ Si) C, H, N.

9-(2,3-Dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl)adenine (36). A solution of **30** (100 mg, 0.37 mmol) and saturated metahnolic ammonia (50 mL) was heated at 90 °C in a steel bomb for 24 h. After cooling to room temperature, the solvent was removed in vacuo and the residual syrup was purified by column chromatography using 6% MeOH−CH_2Cl_2 as an eluent to give **36** (70 mg, 75%) as a white solid**:** UV (H_2O) λ_{max} 258.5 nm (ϵ 18 800) (pH 7), 258.0 nm (ϵ 18 800) (pH 2), 258.5 nm (ϵ 19 100) (pH 11). Anal. ($C_{10}H_{10}FN_5O_2$·0.2H_2O) C, H, N.

9-(2,3-Dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)adenine (37). A solution of **31** (99 mg, 0.37 mmol) and saturated NH_3/MeOH (50 mL) was heated at 90 °C in a steel bomb for 27 h. After cooling to room temperature, the solvent was removed in vacuo and the residual syrup was purified by column chromatography using 6% MeOH−CH_2Cl_2 as an eluent to give **37** (72 mg, 78%) as a white solid**:** UV (H_2O) λ_{max} 259.0 nm (ϵ 21 500) (pH 7), 258.0 nm (ϵ 21 100) (pH 2), 259.0 nm (ϵ 22 600) (pH 11). Anal. ($C_{10}H_{10}FN_5O_2$·0.3MeOH) C, H, N.

9-(2,3-Dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl)hypoxanthine (38). A mixture of **30** (100 mg, 0.37 mmol), NaOMe (1 M solution in MeOH) (1.46 mL, 1.46 mmol), and $HSCH_2CH_2OH$ (0.1 mL, 1.46 mmol) in MeOH (20 mL) was refluxed for 4 h under nitrogen. The reaction mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness in vacuo. The residue was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) to afford **38** (74 mg, 80%) as a white solid**:** UV (H_2O) λ_{max} 247.0 nm (ϵ 13 000) (pH 7), 247.5 nm (ϵ 12 400) (pH 2), 253 nm (ϵ 13 100) (pH 11). Anal. ($C_{10}H_9FN_4O_3$·0.2H_2O) C, H, N.

9-(2,3-Dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)hypoxanthine (39). A mixture of **31** (134 mg, 0.50 mmol), NaOMe (1 M solution in MeOH) (1.98 mL, 1.98 mmol), and $HSCH_2CH_2OH$ (0.14 mL, 1.98 mmol) in MeOH (20 mL) was refluxed for 4 h under nitrogen. The reaction mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness in vacuo. The residue was purified by silica gel column chromatography (9% MeOH/CH_2Cl_2) to afford **39** (93 mg, 70.5%) as a white solid**:** UV (H_2O) λ_{max} 247.5 nm (ϵ 13 700) (pH 7), 247.5 nm (ϵ 12 700) (pH 2), 252.5 nm (ϵ 13 100) (pH 11). Anal. ($C_{10}H_9FN_4O_3$·0.3H_2O) C, H, N.

2-Fluoro-6-amino-9-(2,3-dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl)purine (40). A solution of **32** (101 mg, 0.26 mmol) in dry acetonitrile (15 mL) was treated with tetra-*n*-butylammonium fluoride (1 M solution in THF) (0.35 mL, 0.35 mmol) and stirred for 30 min at room temperature. After evaporation of solvent, the dryness was purified by column chromatography (9% MeOH/CH_2Cl_2) to obtain **40** (64.7 mg, 92.3%) as a white crystalline solid: UV (H_2O) λ_{max} 260.0 nm (ϵ 12 600) (pH 7), 260.0 nm (ϵ 14 100) (pH 2), 260.0 nm (ϵ 11 000) (pH 11); HRMS (LSIMS, *m*/*z*) 270.0801 (calcd 270.0803). Anal. ($C_{10}H_9F_2N_5O_2$·0.6MeOH) C, H, N.

2-Fluoro-6-amino-9-(2,3-dideoxy-2-fluoro-α-L-*gylcero*-pent-2-enofuranosyl)purine (41). The titled compound was prepared from **34** on a 0.19-mmol scale by the procedure described for **40**. After evaporation of solvent, the residue was purified by column chromatography (9% MeOH/CH_2Cl_2) to obtain product **41** (46.2 mg, 90.3%) as a white crystalline solid: UV (H_2O) λ_{max} 260.5 nm (ϵ 13 400) (pH 7), 260.0 nm (ϵ 11 900) (pH 2), 260.5 nm (ϵ 10 400) (pH 11); HRMS (LSIMS, *m*/*z*) 270.0774 (calcd 270.0803). Anal. ($C_{10}H_9F_2N_5O_2$·0.4H_2O) C, H, N.

2-Amino-6-chloro-9-(2,3-dideoxy-2-fluoro-β-L-*glycero*-pent-2-enofuranosyl)purine (42). The titled compound was prepared from **33** on a 0.40-mmol scale by the procedure described for **40**. After evaporation of solvent, the dryness was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to obtain product **42** (109 mg, 95.5%) as a white crystalline solid: HRMS (LSIMS, *m*/*z*) 286.0514 (calcd 286.0507). Anal. ($C_{10}H_9FClN_5O_2$) C, H, N.

2-Amino-6-chloro-9-(2,3-dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)purine (43). The titled compound was prepared from **35** on a 0.36-mmol scale by the procedure described for **40**. Silica gel column chromatography (9% MeOH/CH_2Cl_2) gave product **43** (99.9 mg, 96.4%) as a white solid: HRMS (LSIMS, *m*/*z*) 286.0510 (calcd 286.0507). Anal. ($C_{10}H_9$-$ClFN_5O_2$) C, H, N.

9-(2,3-Dideoxy-2-fluoro-β-L-*gycero*-pent-2-enofuranosyl)-guanine (44). A mixture of **42** (63.6 mg, 0.22 mmol), 2-mercaptoethanol (0.06 mL, 0.89 mmol), and 1 N NaOMe (0.89 mL, 0.89 mmol) in MeOH (10 mL) was refluxed for 5 h under

nitrogen. The mixture was cooled, neutralized with glacial AcOH, and evaporated to dryness in vacuo. Purification on silica gel (12% MeOH/CH_2Cl_2) afforded **44** (30.1 mg, 50.7%) as a white solid: UV (H_2O) λ_{max} 251.0 nm (ϵ 13 200) (pH 7), 252.5 nm (ϵ 12 400) (pH 2), 256.5 nm (ϵ 7 900) (pH 11); HRMS (LSIMS, *m*/*z*) 268.0862 (calcd 268.0846). Anal. ($C_{10}H_{10}FN_5O_3 \cdot 0.2H_2O$) C, H, N.

9-(2,3-Dideoxy-2-fluoro-α-L-*glycero*-pent-2-enofuranosyl)guanine (45). The titled compound was prepared from **43** on a 0.21-mmol scale by the procedure described for **44**. Purification on silica gel (12.5% MeOH/CH_2Cl_2) afforded product **45** (28.0 mg, 50.5%) as a white solid: UV (H_2O) λ_{max} 251.5 nm (ϵ 13 200) (pH 7), 252.0 nm (ϵ 12 600) (pH 2), 257.0 nm (ϵ 9 800) (pH 11); HRMS (LSIMS, *m*/*z*) 268.0821 (calcd 268.0846). Anal. ($C_{10}H_{10}FN_5O_3 \cdot 0.7CH_2Cl_2$) C, H, N.

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