Syntheses and Biological Evaluations of 3'-Deoxy-3'-C-Branched-Chain-Substituted Nucleosides

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Various 3'-deoxy-3'-C-(hydroxymethyl)-, 3'-deoxy-3'-C-(fluoromethyl)-, 3'-deoxy-3'-C-(azidomethyl)-, and 3'-deoxy-3'-C-(aminomethyl)-substituted nucleosides (total 12 compounds) have been synthesized and evaluated against L1210, P388, S-180, and CCRF-CEM cells and HSV-1, HSV-2, and HIV-1 in culture. Only 3'-deoxy-3'-C-(hydroxymethyl)thymidine (**36**) was found to show significant anticancer activity against L1210, P388, S-180, and CCRF-CEM cells with ED_{50} values of 50, 5, 10, and 1 μM, respectively. None of these compounds demonstrated significant antiviral activity against HSV-1, HSV-2, or HIV-1. These compounds were also evaluated against thymidine kinases derived from HSV-I (strain KOS), HSV-2 (strain 333), and mammalian (K562) cells. The thymidine kinase (HSV-1 strain KOS) was inhibited significantly by both 3'-deoxy-3'-C-(hydroxymethyl)- and 3'-deoxy-3'-C-(fluoromethyl)thymidine.

Branched-chain sugar nucleosides, such as 9-[3-deoxy-3-C-(2-hydroxyethyl)-β-D-ribofuranosyl]adenine and related compounds, were first synthesized by Rosenthal et al.[1,2] Later, Acton et al.[3] reported the synthesis of 3'-C-(hydroxymethyl)-2',3'-dideoxythioguanosine and its α-isomer. Both the α- and β-nucleosides were equally inhibitory to the growth of WI-L2 human lymphoblastoid cells. Recently, Pudlo and Townsend[4] described a novel approach toward the synthesis of 3'-deoxy- and 2',3'-dideoxy-3'-hydroxymethyl ribofuranosides. Subsequently, Bamford et al.[5,6] reported the syntheses and antiviral evaluation of a series of 3'-deoxy-3'-C-(fluoromethyl)-, 3'-deoxy-3'-C-(difluoromethyl)-, and 3'-deoxy-3'-C-(hydroxymethyl)-*arabino*-pentofuranosyl nucleosides and other related compounds. Sterzycki et al.[7] described the synthesis and antiviral evaluation of various 3'-branched nucleoside analogues; and Svansson et al.[8] reported the synthesis of 2',3'-dideoxy-3'-C-(hydroxymethyl) nucleosides as potential inhibitors of HIV. Tseng et al.[9] also described the synthesis of 3'-C-(hydroxymethyl)-2',3'-dideoxyadenosine, which possessed an activity profile similar to oxetanocin A against HIV in ATH 8 cells.

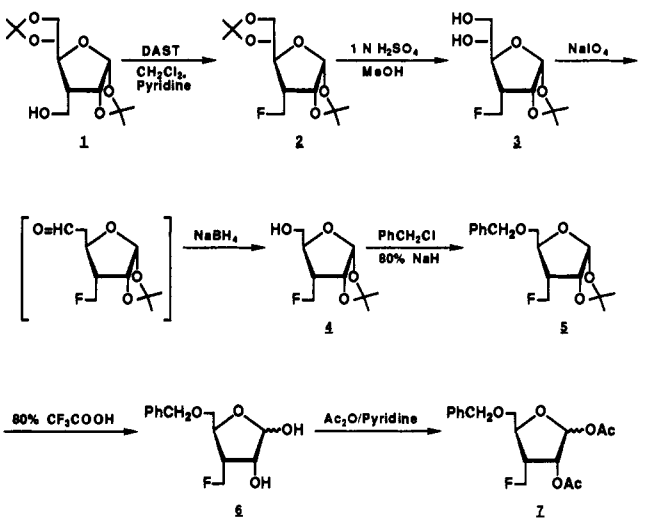
This report describes the syntheses and biological evaluation of the 3'-deoxy-3'-C-(azidomethyl) and 3'-deoxy-3'-C-(fluoromethyl) homologues of 3'-azido-3'-deoxythymidine (AZT) and 3'-fluoro-3'-deoxythymidine (3'-FddT), which are among the most potent anti-human immunodeficiency virus type 1 (HIV-1) agents,[10-12] and other related compounds.

Chemistry

Various 3'-deoxy-3'-C-branched-chain-substituted nucleoside analogues have been synthesized by coupling the silylated base with the appropriate 3-deoxy-3-branched-chain-substituted sugar derivatives. The syntheses of the key intermediates, 3-deoxy-3-(fluoromethyl)-, 3-deoxy-3-(azidomethyl)-, and 3-deoxy-3-(hydroxymethyl)ribofuranosyl acetates and their related nucleoside analogues are described as follows.

The 3-deoxy-3-fluoromethyl sugar derivative **7** was synthesized as depicted in Scheme I. The 3-deoxy-3-hydroxymethyl derivative **1** was reacted with (diethylamido)sulfur trifluoride (DAST)[13] to yield 3-deoxy-3-

Scheme I



(fluoromethyl)-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**2**). ^1H NMR spectrum of compound **2** showed that the resonances of 3-CH_2-F methylene protons were at δ 4.61–4.74 ($J_{H_A,F}$ = 47 Hz) and δ 4.75–4.87 ($J_{H_B,F}$ = 47 Hz). Selective hydrolysis of compound **2** with H_2SO_4/MeOH[14] afforded 3-deoxy-3-(fluoromethyl)-1,2-O-isopropylidene-α-D-allofuranose (**3**), which was used directly for the next reaction without further purification. Periodate oxidation of compound **3** produced the aldehyde which was immediately reduced with sodium borohydride[2,3] to give 3-deoxy-3-(fluoromethyl)-1,2-O-isopropylidene-α-D-ribofuranose (**4**). Benzylation[3] of compound **4** gave the 5-O-benzyl derivative **5** which was then hydrolyzed with 80% trifluoroacetic acid, followed by acetylation with acetic anhydride in pyridine to afford the acetate **7**.

The 3-deoxy-3-azidomethyl sugar derivative **16** was synthesized as shown in Scheme II. Treatment of 1,2-O-isopropylidene-α-D-xylofuranose (**8**) with *tert*-butyldimethylsilyl chloride in pyridine[15] produced the 5-O-(*tert*-butyldimethylsilyl) derivative **9**. Oxidation[16] of compound **9** with chromium trioxide/pyridine/acetic anhydride complex (1:2:1, molar ratio) in methylene chloride yielded the 3-keto derivative **10**, which was then converted to the 3-methylene analogue **11** by a Wittig reaction[17,18] with

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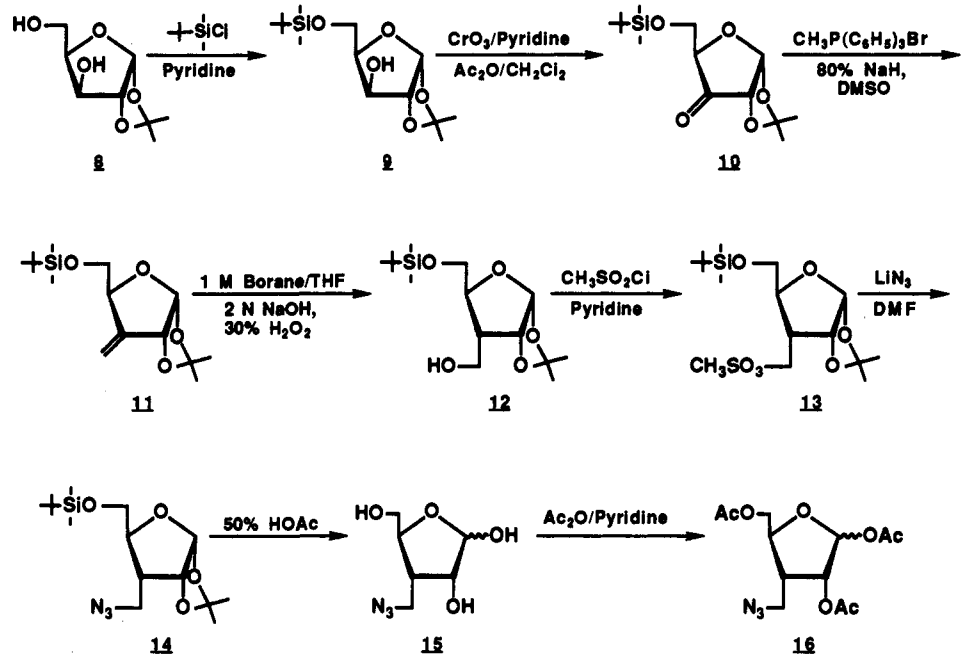
Scheme II



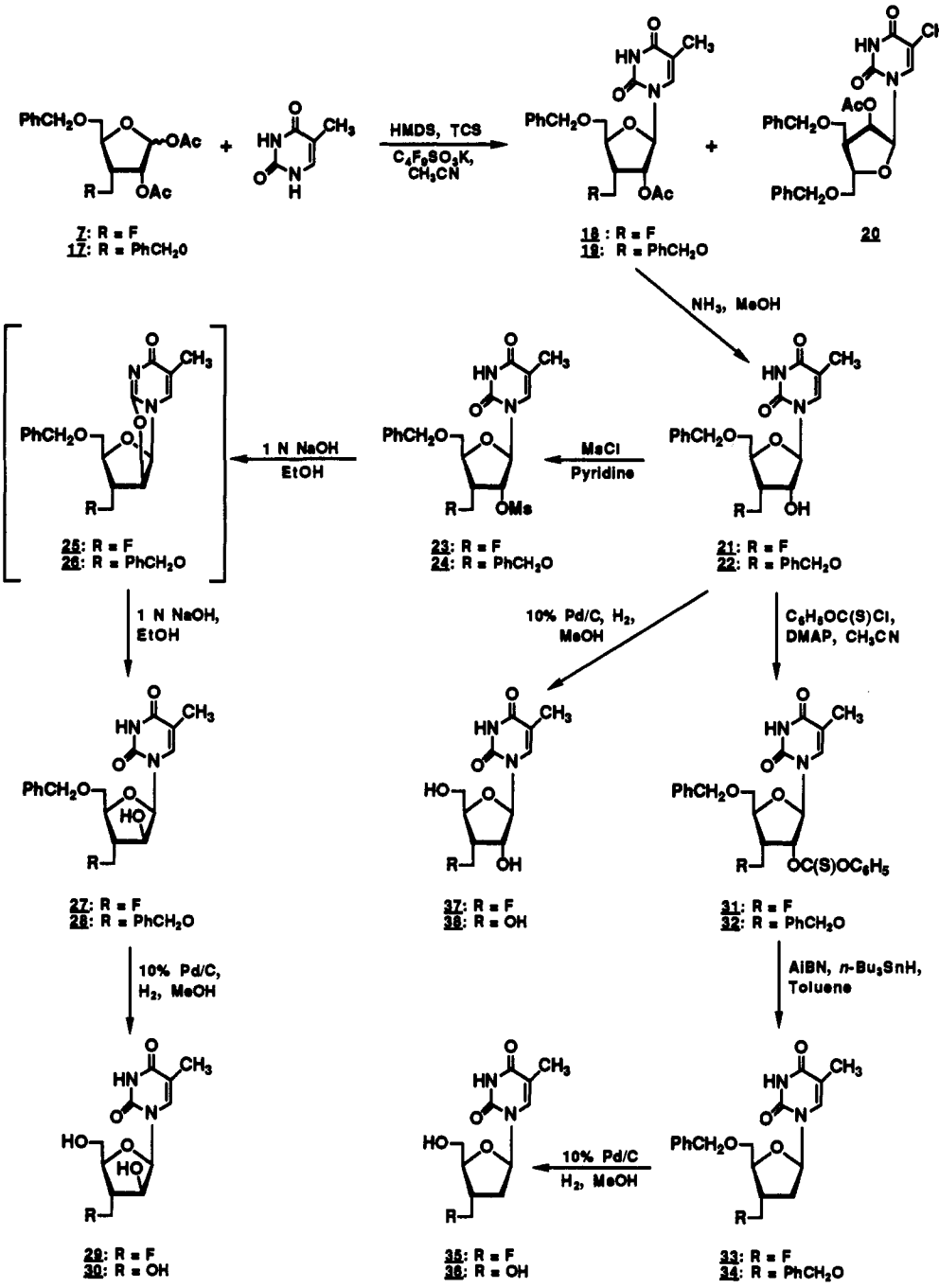
methylenetriphenylphosphorane in anhydrous DMSO under nitrogen. Hydroboration–oxidation[3] of compound **11** afforded the 3-deoxy-3-hydroxymethyl derivative **12**. Treatment of compound **12** with methanesulfonyl chloride in pyridine gave the methanesulfonate **13**, which was reacted with lithium azide in DMF[19] to yield the azido analogue **14**. Deblocking[20] compound **14** with 50% acetic acid at 100 °C for 1 h produced compound **15**. Acetylation of compound **15** with acetic anhydride/pyridine gave a mixture of α and β anomers of 1,2,5-tri-*O*-acetyl-3-(azidomethyl)-3-deoxy-D-ribofuranose (**16**).

The 3-deoxy-3-hydroxymethyl sugar derivative, 1,2-*O*-diacetyl-5-*O*-benzyl-3-[(benzyloxy)methyl]-3-deoxy-D-ribofuranose (**17**), was synthesized by hydrolysis of 5-*O*-benzyl-3-[(benzyloxy)methyl]-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose[3,21] with 80% trifluoroacetic acid, followed by acetylation with acetic anhydride in pyridine.[1]

The syntheses of the 3′-deoxy-3′-*C*-fluoromethyl and 3′-deoxy-3′-*C*-hydroxymethyl homologues of 1-β-D-arabinofuranosylthymine (*ara*-*T*), 1-β-D-ribofuranosylthymine, and 3′-deoxy-3′-fluorothymidine (3′-FddT) are depicted in Scheme III. Coupling of the 3-deoxy-3-fluoromethyl and 3-deoxy-3-hydroxymethyl sugar derivatives, compounds **7** and **17**, and thymine in the presence of hexamethyldisilazane (HMDS), trimethylchlorosilane (TCS), and potassium nonafluoro-1-butanesulfonate ($C_4F_9SO_3K$) by the methodology of Vorbrüggen and Bennua[22] yielded the respective nucleosides, compound **18** (84% yield), and compound **19** (87% yield) and its α-isomer **20** (6% yield). In the first case, no α-isomer of **18** was isolated. The ^{1}H NMR spectrum showed that the anomeric 1′-H resonance in compound **18** appeared at δ 5.98 as a doublet ($J_{1',2'}$ = 3.5 Hz). The 1′-H resonance in compound **19** appeared at δ 6.02 as a doublet ($J_{1',2'}$ = 3.2 Hz) and the 1′-H resonance in compound **20** appeared at δ 6.80 also as a doublet but with a much larger coupling constant ($J_{1',2'}$ = 9.4 Hz). Treatment of compounds **18** and **19** with methanolic ammonia gave the 2′-deblocked nucleosides **21** and **22**. Mesylation[22] of compounds **21** and **22** afforded the corresponding sulfonates **23** and **24**, which were refluxed with 1 N NaOH/EtOH for 2 h[23] to yield compounds **27** and **28** via the 2,2′-anhydro intermediates **25** and **26**, respectively. Catalytic hydrogenation of compounds **27** and **28** with 10% Pd/C produced the corresponding 3′-deoxy-3′-*C*-(fluoromethyl) and 3′-deoxy-3′-*C*-(hydroxymethyl) arabinonucleosides **29** and **30**. Treatment[24] of compounds **21** and **22** with phenyl chlorothionocarbonate and 4-(dimethylamino)pyridine in acetonitrile under nitrogen at room temperature gave the 2′-*O*-phenoxythiocarbonyl derivatives **31** and **32**. Reduction[24] of compounds **31** and **32** with tri-*n*-butyltin hydride and 2,2′-azobis(2-methylpropionitrile) (AIBN) in toluene at reflux temperature produced the 2′-deoxynucleosides **33** and **34**, which were then debenzylated by catalytic hydrogenation with 10% Pd/C to afford the corresponding 2′,3′-dideoxy-3′-*C*-(fluoromethyl) and 2′,3′-dideoxy-3′-*C*-(hydroxymethyl) nucleoside analogues **35** and **36**. Catalytic hydrogenation (10% Pd/C) of compounds **21** and **22** yielded the 3′-deoxy-3′-*C*-(fluoromethyl) and 3′-deoxy-3′-*C*-(hydroxymethyl) ribonucleoside derivatives **37** and **38**, respectively.

The syntheses of the 3′-deoxy-3′-*C*-(azidomethyl) and 3′-deoxy-3′-*C*-(aminomethyl) nucleoside homologues of 1-β-arabinofuranosylthymine (*ara*-T), 1-β-D-ribofuranosylthymine, and 3′-deoxy-3′-azidothymidine (AZT) are described in Scheme IV. Condensation[22] of the 3-deoxy-3-azidomethyl sugar derivative **16** and thymine in the presence of hexamethyldisilazane (HMDS), trimethylchlorosilane (TCS) and potassium nonafluoro-1-butanesulfonate ($C_4F_9SO_3K$) afforded 1-[2,5-*O*-diacetyl-3-*C*-(azidomethyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (**39**, 41% yield) and its α-isomer (**40**, 27% yield). The 1′-H resonance of compounds **39** and **40** were a doublet at δ 5.66 ($J_{1',2'}$ = 2.7 Hz) and δ 5.89 ($J_{1',2'}$ = 9.6 Hz), respectively. Deacetylation of compound **39** with methanolic ammonia gave the 3′-deoxy-3′-*C*-(azidomethyl) riboside **41**. Treatment[15,25] of compound **41** with *tert*-butyldimethylsilyl chloride/silver nitrate/pyridine yielded the 5′-*O*-*tert*-butyldimethylsilyl-protected nucleoside **44**, which was then converted to the 2′-arabino analogue **47** via **45** and **46**, and the 2′-deoxy ana-

Scheme III



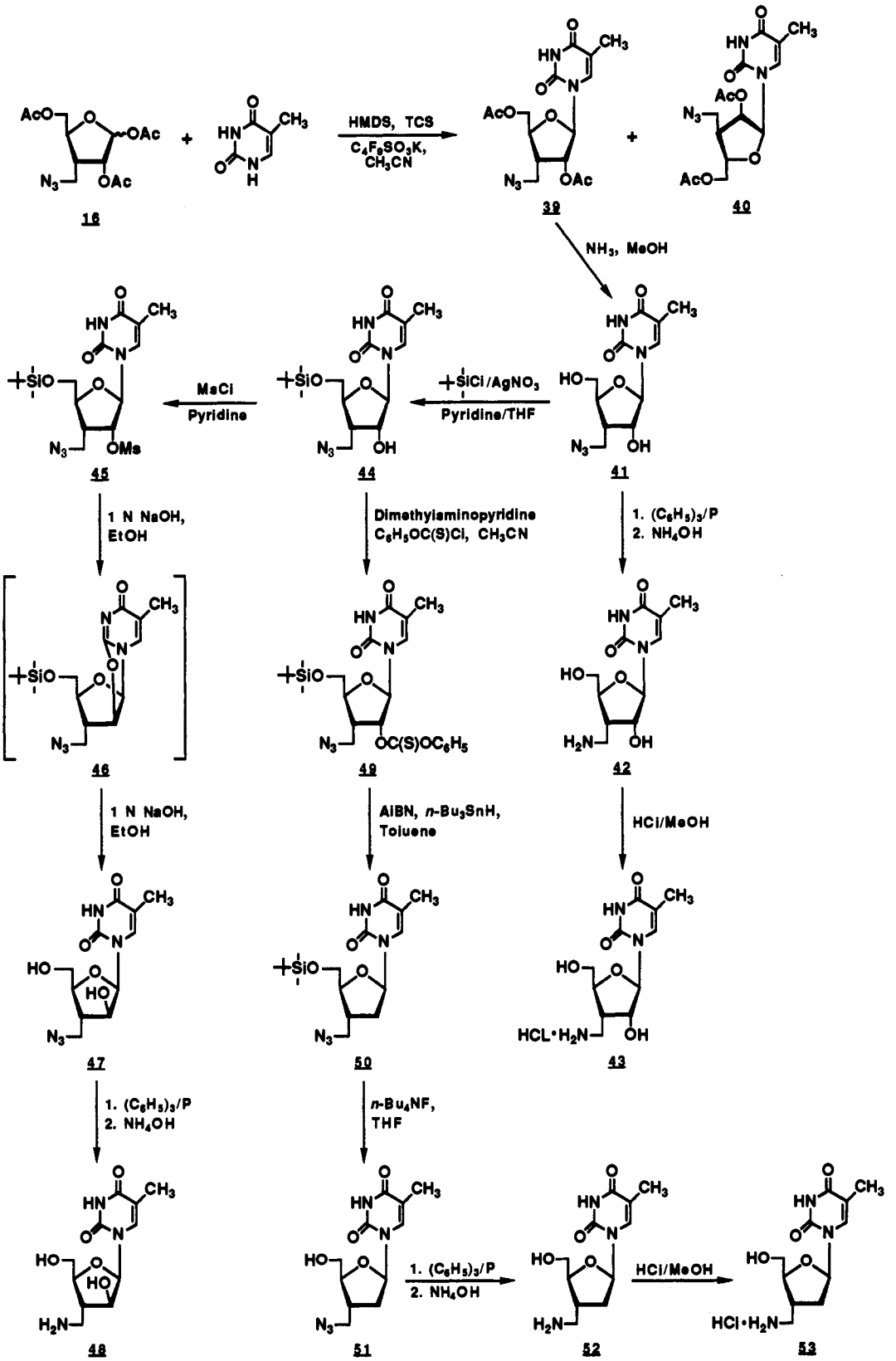
logue **50** via **49**, respectively, by the similar methodology as previously described. Reaction[15] of compound **50** with tetra-*n*-butylammonium fluoride (*n*-Bu_4NF)/THF afforded the 5'-deprotected nucleoside **51**. Treatment[26,27] of compounds **41**, **47**, and **51** with triphenylphosphine in pyridine at room temperature, followed by hydrolysis with concentrated ammonium hydroxide produced the 3'-deoxy-3'-*C*-(aminomethyl) nucleoside analogues **42**, **48**, and **52**, respectively. Compounds **42** and **52** were converted to their corresponding hydrochloride salts and compounds **43** and **53** were isolated as solid products.

Biological Evaluation

The synthesized compounds were evaluated in culture for their anticancer activity by growth inhibition studies using three murine cell lines; leukemia L1210, leukemia P388, Sarcoma 180, as well as human CCRF-CEM lymphoblastic leukemia cells. Only the 3'-deoxy-3'-*C*-(hydroxymethyl)thymidine (**36**) showed significant activity against L1210, P388, S-180, and CCRF-CEM cells with the respective ED_{50} values of 50, 5, 10, and 1 μM. The other compounds were not active against these cell lines at concentrations up to 100 μM. The results are summarized in Table I.

Among these 3'-deoxy-3'-branched chain nucleoside analogues, 1-[2,3-dideoxy-3-*C*-(fluoromethyl)-β-D-*erythro*-pentofuranosyl]thymine (**35**) and 1-[2,3-dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]thymine (**36**), were found to demonstrate significant inhibitory effects against thymidine kinase (TK) derived from herpes simplex type 1 (KOS strain) infected HeLa (Bu-25-TK^-) cells,[28,29] yielding the corresponding 85.2% and 59.1% inhibition at 500 μM concentration. Whereas, at the same

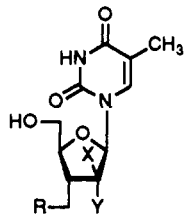
Scheme IV



concentration, 1-β-D-arabinofuranosylthymine (*ara*-T) and 3′-deoxy-3′-fluorothymidine (3′-FddT), which are known potent inhibitors of thymidine kinase,[30] produced 55.1% and 62.4% inhibition of the enzyme, respectively. The findings are summarized in Table II.

None of the compounds showed antiviral activity against HSV-1 and HSV-2 in culture at a concentration of 100 μM. In addition, the 3′-deoxy-3′-*C*-(fluoromethyl) derivatives **29**, **35**, and **37** and the 3′-deoxy-3′-*C*-(azidomethyl) derivatives **41**, **47**, and **51** were also evaluated against HIV-1 (HTLV-III B) in MT-2 cells and were not active at a concentration up to 100 μM. In comparison to 3′-deoxy-3′-fluorothymidine (3′-FddT) and 3′-azido-3′-deoxythymidine (AZT), the insertion of a methylene group between the 3′-carbon and the fluoro or the azido moiety in compounds **35** and **51**, respectively, resulted in the total

Table I. Comparison of the ED_{50} Values of Various 3'-Deoxy-3'-C-Branched-Chain-Substituted Nucleoside Analogues on the Replication of L1210, P388, S-180, and CCRF-CEM Cells in Vitro



				ED_{50},[a] μM, against cell lines			
compd	X	Y	R	L1210	P388	S-180	CCRF-CEM
29	OH	H	F	>100	>100	>100	>100
30	OH	H	OH	>100	>100	>100	>100
35	H	H	F	>100	>100	>100	>100
36	H	H	OH	50	5	10	1
37	H	OH	F	>100	>100	>100	>100
38	H	OH	OH	>100	>100	>100	>100
41	H	OH	N_3	>100	>100	>100	>100
43	H	OH	NH_2	>100	>100	>100	>100
47	OH	H	N_3	10	>100	>100	>100
48	OH	H	NH_2	>100	>100	>100	>100
51	H	H	N_3	>100	>100	>100	>100
53	H	H	NH_2	>100	>100	>100	>100

[a] The ED_{50} values were estimated from dose–response curves compiled from at least two independent experiments and represent the drug concentration (μM) required to inhibit replication of the respective L1210, P388, S-180, and CCRF-CEM cell lines by 50% after 72-h incubation.

Table II. Effects of 3'-Deoxy-3'-Branched-Chain Nucleoside Analogues on the Activity of Thymidine Kinases Isolated from Herpes Simplex Type 1 (KOS Strain) and Herpes Simplex Type 2 (333 Strain) Infected HeLa (Bu-25-TK$^-$) Cells, Respectively; and K562 Mammalian Cells

		activity, % inhibition,[a] on thymidine kinase[b]		
compd	conc, μM	HSV-1 (KOS)	HSV-2 (333)	mammalian (K562)
29	500	13.8	10.9	7.1
30	500	11.7	6.9	0.7
35	500	85.2	4.0	5.4
36	500	59.1	0	3.0
37	500	7.0	4.9	2.5
38	500	2.6	0	3.0
ara-T	500	55.1	22.0	5.0
3'-FddT	500	62.4	0	60.3

[a] The enzymatic activity is 100% in the absence of the tested analogues. [b] Standard mix contains ~90 μM thymidine and 1.1, 0.9, or 1.5 units of KOS, 333, or K562 enzyme, respectively. The volume of the reation mixture was 0.1 mL.

loss of anti-HIV activity. Compounds **35** and **51** are probably not the substrates for the relevant kinase.

Experimental Section

Melting points were determined with a Thomas–Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) NMR spectrometer or a Bruker WM-500 (500 MHz) spectrometer (for the final products **29**, **30**, **35**, **36**, **37**, **38**, **41**, **43**, **47**, **48**, **51**, and **53**) with Me_4Si as the internal reference. Chemical ionization (CI-MS) mass spectra were determined with a Kratos MS80 RFA high-resolution instrument. IR spectra were obtained with a Perkin-Elmer 1420 spectrophotometer. The UV spectra were recorded on a Beckman-25 spectrophotometer. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value.

3-Deoxy-3-(fluoromethyl)-1,2:5,6-di-*O*-isopropylidene-α-allofuranose (2). (Diethylamido)sulfur trifluoride (DAST, 10.3 g, 64.2 mmol) was dissolved in methylene chloride (150 mL) and pyridine (11 mL) at 0 °C under nitrogen. Compound **1** (11.0 g, 40.1 mmol) was added slowly, and the solution was warmed to room temperature. After 4 h, the solvent was removed under vacuum to dryness to give a syrup, which was purified by silica gel column chromatography (eluting with hexane/EtOAc, 10:1, v/v) to yield 4.2 g (40%) of product as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.34, 1.35, 1.38, and 1.53 (4 s, 12 H, 4 × CH_3), 2.36–2.42 (m, 1 H, 3-H), 3.72–3.76 (m, 1 H, 4-H), 3.92 (dd, 1 H, 6-H_A), 4.10 (dd, 1 H, 6-H_B), 4.00–4.04 (m, 1 H, 5-H), 4.61–4.74 (m, 1 H, 3-CH_AF, $J_{H_A,F}$ = 47 Hz), 4.75–4.87 (m, 1 H, 3-CH_BF, $J_{H_B,F}$ = 47 Hz), 4.78 (t, 1 H, 2-H), 5.82 (d, 1 H, 1-H). Anal. ($C_{13}H_{21}FO_5$) C, H, F.

3-Deoxy-3-(fluoromethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (4). To a solution of compound **2** (4.9 g, 17.7 mmol) in MeOH (150 mL) was added 2 N sulfuric acid (27 mL). After the mixture was stirred at room temperature for 8 h, the reaction mixture was neutralized with solid sodium hydrogen carbonate and extracted with chloroform (3 × 60 mL). The combined chloroform extracts were dried over $MgSO_4$, filtered, and evaporated under diminished pressure to afford a syrup (**3**).

To a solution of syrup **3** in ethanol (150 mL) was added a saturated solution of $NaHCO_3$ (7 mL) followed by sodium metaperiodate solution (4.54 g, 21.2 mmol, in 150 mL of water). After the reaction mixture stirred at room temperature for 4 h, the excess sodium metaperiodate was destroyed by the addition of methylene glycol (7 mL). The resulting aldehyde was immediately reduced with sodium borohydride (1.64 g, 42.4 mmol), and the solution was stirred at room temperature for 18 h. Acetone (4 mL) was added, and the mixture was stirred for an additional 0.5 h. After the solid material was removed by filtration, the filtrate was evaporated to dryness and the residue was chromatographed on a silica gel column (hexane/EtOAc, 10:1, v/v) to afford 3.2 g (87%) of product as a syrup: ^{1}H NMR ($CDCl_3$) δ 1.33, 1.50 (2 s, 6 H, 2 × CH_3), 2.10 (br, 1 H, 5-OH, D_2O exchangeable), 2.25–2.70 (m, 1 H, 3-H), 3.45–4.25 (m, 3 H, 4-H, 5-H), 4.30–4.60 (m, 1 H, CH_AF, $J_{H_A,F}$ = 45 Hz), 4.80–5.15 (m, 1 H, CH_BF, $J_{H_B,F}$ = 45 Hz), 4.70 (t, 1 H, 2-H), 5.70 (d, 1 H, 1-H). Anal. ($C_9H_{15}FO_4$) C, H, F.

5-*O*-Benzyl-3-deoxy-3-(fluoromethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (5). A suspension of 80% sodium hydride/mineral oil dispersion (0.76 g, 25.2 mmol) in DMF (100 mL) was stirred at 0–5 °C under N_2 and treated with a solution of compound **4** (3.47 g, 16.8 mmol) in DMF (10 mL), added in small portions over a period of 10 min. After 30 min at 0–5 °C, benzyl chloride (5.3 g, 42.0 mmol) was added and the solution was stirred overnight at room temperature. The mixture was treated with water (35 mL) in portions, with cooling. After 20 min of stirring, the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated (<65 °C) to give a syrup, which was used in the next step without further purification. The crude product (450 mg) was purified by column chromatography on silica gel with CH_2Cl_2/CH_3COCH_3 (30:1, v/v) to yield 370 mg (66%) of product as a syrup: ^{1}H NMR ($CDCl_3$) δ 1.30 and 1.50 (2 s, 6 H, 2 × CH_3), 2.23–2.67 (m, 1 H, 3-H), 3.36–3.77 (m, 2 H, 5-H), 3.90–4.15 (m, 1 H, 4-H), 4.23–4.50 (m, 1 H, CH_AF, $J_{H_A,F}$ = 45 Hz), 4.72–5.00 (m, 1 H, CH_BF, $J_{H_B,F}$ = 45 Hz), 4.50 (s, 2 H, CH_2Ph), 4.63 (t, 1 H, 2-H), 5.76 (d, 1 H, 1-H), 7.25 (s, 5 H, ArH). Anal. ($C_{16}H_{21}FO_4$) C, H, F.

1,2-*O*-Diacetyl-5-*O*-benzyl-3-deoxy-3-(fluoromethyl)-D-ribofuranose (7). Compound **5** (4.52 g, 16.8 mmol) was allowed to react with an 80% solution of trifluoroacetic acid (30 mL) in an ice bath for 2 h, followed by neutralization with solid $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. Upon drying over anhydrous $MgSO_4$, the combined methylene chloride extract was evaporated in vacuo to give a syrup (compound **6**). Compound **6** was then dissolved in acetic anhydride (13.4 mL) and pyridine (13.4 mL) with stirring for 2 h at room temperature. The solvent was removed under vacuum to dryness, and the residue was purified by chromatography on a silica gel column (hexane/EtOAc, 10:1, v/v) to yield 2.9 g (51%) of product as a syrup: ^{1}H NMR ($CDCl_3$) δ 1.90, 2.03, and 2.06 (3 s, 6 H, 2 × $COCH_3$), 2.53–3.10 (m, 1 H, 3-H), 3.33–3.68 (m, 2 H, 5-H), 4.00–4.38, and 4.70–4.82 (m, 3 H, 4-H, CH_2F, $J_{F,H}$ = 45 Hz), 4.52 (s, 2 H, CH_2Ph),

5.10–5.40 (m, 1 H, 2-H), 6.00 (s, 0.5 H, 1-H_β), 6.35 (d, 0.5 H, 1-H_α), 7.25 (s, 5 H, ArH). Anal. ($C_{17}H_{21}FO_6$) C, H, F.

3-Deoxy-3-methylene-5-*O*-[(*tert*-butyldimethyl)silyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (11). To a stirred suspension of CrO_3 (6.8 g, 67.3 mmol), pyridine (11.4 mL), and acetic anhydride (7 mL) in CH_2Cl_2 (60 mL) was added compound **9** (5.0 g, 16.4 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 4 h. The dark brown solution was poured into EtOAc (500 mL), and the resulting mixture was filtered through a 2-cm layer of silica gel in a sinter-glass filter. The precipitated solid and silica gel were washed with EtOAc (200 mL), and the combined filtrates were evaporated in vacuo (<30 °C) to dryness. The residue was coevaporated with toluene (50 mL), followed by chloroform (2 × 25 mL), to yield the ketone **10** as a syrup, which was used immediately for the next reaction without further purification.

A suspension of NaH (1.74 g, 57.9 mmol, 80% dispersion in mineral oil) in Me_2SO (75 mL) was heated at 65 °C under nitrogen until all the sodium hydride had dissolved. The solution was cooled to room temperature, and methyltriphenylphosphonium bromide (22.8 g, 63.7 mmol) was added with stirring. After 1.5 h, compound **10** in Me_2SO (25 mL) was added and the mixture was stirred for 2.5 h in an ice-bath. The mixture was poured into ice-water (600 mL) and extracted with petroleum ether (4 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a syrup, which was then chromatographed on a silica gel column (hexane/EtOAc, 15/1, v/v) to afford 3.5 g (73%) of product as a foam: ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, $SiCMe_3$), 1.40 and 1.50 (2 s, 6 H, CMe_2), 3.70 (d, 2 H, 5-H), 4.58–4.85 (m, 2 H, 4-H and 2-H), 5.24 (d, 2 H, methylene), 5.83 (d, 1 H, 1-H). Anal. ($C_{15}H_{29}O_4Si$) C, H.

3-Deoxy-3-(hydroxymethyl)-5-*O*-[(*tert*-butyldimethyl)silyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (12). An anhydrous tetrahydrofuran (THF) solution of 1 M borane/THF complex (66.6 mL, 66.6 mmol) was stirred at 0–5 °C under a nitrogen atmosphere and was treated dropwise with compound **11** (8.51 g, 28.3 mmol) in THF (60 mL). The solution was stirred at room temperature for 3 h. After cooling, the mixture was subsequently treated with THF/H_2O (44.3 mL, 1:1, v/v), 2 N NaOH (53.2 mL), and 30% H_2O_2 (44.3 mL). The turbid mixture was stirred at room temperature for 2 h. Ether (300 mL) was added to the reaction mixture, which was then washed twice with ice–water (50 mL) and saturated NaCl solution (50 mL). After drying over anhydrous $MgSO_4$, the solvents were evaporated and the residue was purified by chromatography on a silica gel column (CH_2Cl_2/EtOAc, 20:1, v/v) to give 6.7 g (75%) of product as a foam: ^1H NMR ($CDCl_3$) δ 0.14 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, $SiCMe_3$), 1.35 and 1.58 (2 s, 6 H, CMe_2), 2.00–2.30 (m, 1 H, 3-H), 3.10 (t, 1 H, OH, D_2O exchangeable), 3.64–4.20 (m, 5 H, 3-CH_2, 5-H and 4-H), 4.75 (t, 1 H, 2-H), 5.80 (d, 1 H, 1-H). Anal. ($C_{15}H_{30}O_5Si$) C, H.

3-(Azidomethyl)-3-deoxy-5-*O*-[(*tert*-butyldimethyl)silyl]-1,2-*O*-isopropylidene-α-D-ribofuranose (14). Methanesulfonyl chloride (4.02 g, 35.1 mmol) was added to a solution of compound **12** (4.3 g, 13.5 mmol) in pyridine (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 h, and then the solvent was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL), washed with $NaHCO_3$ solution and H_2O, and dried over anhydrous $MgSO_4$. The solvent was removed under diminished pressure to give a syrup (**13**) which was used in the following reaction without further purification.

A solution of compound **13** and lithium azide (6.6 g, 135 mmol) in DMF (250 mL) was heated with stirring at 95 °C for 1.5 h. The reaction mixture was evaporated to dryness in vacuo and the residue was dissolved in CH_2Cl_2 (150 mL). The organic layer was washed with water (3 × 30 mL), dried over anhydrous $MgSO_4$, and evaporated to give a syrup, which was purified by silica gel column (CH_2Cl_2/EtOAc, 50:1, v/v) to yield 4.1 g (88%) of product as a syrup: IR (KBr) ν_{max} 2100 cm^{-1} (azido); ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, $SiCMe_3$), 1.35 and 1.52 (2 s, 6 H, CMe_2), 2.15–2.50 (m, 1 H, 3-H), 3.23–3.55 (m, 2 H, 3-CH_2), 3.57–4.00 (m, 3 H, 5-H and 4-H), 4.67 (t, 1 H, 2-H), 5.80 (d, 1 H, 1-H). Anal. ($C_{15}H_{29}N_3O_4Si$) C, H, N.

1,2,5-Tri-*O*-acetyl-3-(azidomethyl)-3-deoxy-D-ribofuranose (16). A solution of **14** (5.0 g, 14.6 mmol) in 50% HOAc (100 mL) was heated at 100 °C for 1 h. The reaction mixture was allowed to cool, water was added (100 mL), and the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The water layer was evaporated under vacuum to get a syrup (compound **15**), to which was added pyridine (10 mL) and acetic anhydrite (10 mL). The solution was stirred at room temperature for 2 h. The solvent was removed under vacuum, and the resulting residue was purified by silica gel column (CH_2Cl_2/EtOAc, 25:1 v/v) to yield 4.1 g (90%) of syrup: IR (KBr) ν_{max} 2120 cm^{-1} (azido); ^1H NMR ($CDCl_3$) δ 2.10, 2.13, and 2.16 (3 s, 9 H, $COCH_3$), 2.37–2.70 (m, 1 H, 3-H), 3.32–3.60 (m, 2 H, 3-CH_2), 4.00–4.33 (m, 3 H, 4-H and 5-H), 5.20 (d, 1 H, 2-H), 6.30 (m, 1 H, 1-H). Anal. ($C_{12}H_{17}N_3O_7$) C, H, N.

1,2-*O*-Diacetyl-5-*O*-benzyl-3-[(benzyloxy)methyl]-3-deoxy-D-ribofuranose (17). This compound was synthesized from 5-*O*-benzyl-3-[(benzyloxy)methyl]-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose[3,21] by the same methodology as described for the synthesis of **7**: yield 1.2 g (58%); ^1H NMR ($CDCl_3$) δ 1.95, 2.00, and 2.05 (3 s, 6 H, 2 × $COCH_3$), 2.67–2.95 (m, 1 H, 3-H), 3.40–3.80 (m, 4 H, 5-H and 3-CH_2), 4.10–4.40 (m, 1 H, 4-H), 4.50 and 4.60 (2 s, 4 H, 2 × CH_2Ph), 5.32 (d, 1 H, 2-H), 6.03 (s, 0.5 H, 1-H_β), 6.32 (d, 0.5 H, 1-H_α), 7.35 (s, 10 H, ArH). Anal. ($C_{24}H_{28}O_7$) C, H.

This compound was obtained as a 1:1 mixture of α and β anomers. The assignment of the anomeric configuration was based on its NMR spectrum. The resonance for C-1 proton of β-anomer appeared as a singlet at δ 6.03, whereas the α-anomer appeared as a doublet at δ 6.32. The ratio of the α and β anomers was determined by the ratio of the integration of the respective C-1 proton in the mixture.

1-[2-*O*-Acetyl-5-*O*-benzyl-3-deoxy-3-*C*-(fluoromethyl)-β-D-*erythro*-pentofuranosyl]thymine (18). To a suspension of thymine (1.28 g, 10.1 mmol), compound **7** (2.86 g, 8.45 mmol) and $C_4F_9SO_3K$ (6.86 g, 20.3 mmol) in acetonitrile (100 mL) was added HMDS (1.4 mL), and TCS (3.8 mL). After 24 h of refluxing, the reaction mixture was filtered. The filtrate was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL). The solution was extracted with saturated $NaHCO_3$ solution (3 × 25 mL). After reextracting the aqueous phase with CH_2Cl_2 (2 × 10 mL). The combined organic phase was washed with aqueous saturated NaCl solution (3 × 25 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated, and the residue was purified by column chromatography with CH_2Cl_2/CH_3OH (20:1, v/v) to yield 2.9 g (84%) of product as a foam: UV (MeOH) λ_{max} 265 nm (ε 10 450), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 264 nm (ε 10 820), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 268 nm (ε 9 960), λ_{min} 236 nm; ^1H NMR ($CHCl_3$) δ 1.61 (s, 3 H, 5-CH_3), 2.13 (s, 3 H, $COCH_3$), 2.94–3.02 (m, 1 H, 3′-H), 3.63–3.66 and 3.95–3.97 (2 dd, 2 H, 5′-H), 4.35–4.38 (m, 1 H, 4′-H), 4.47–4.67 (m, 4 H, CH_2Ph and CH_2F, $J_{H,F}$ = 50 Hz), 5.47–5.49 (m, 1 H, 2′-H), 5.98 (d, 1 H, 1′-H, $J_{1',2'}$ = 3.5 Hz), 7.31–7.39 (m, 5 H, ArH), 7.60 (s, 1 H, 6-H), 8.44 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{20}H_{23}FN_2O_6$) C, H, F, N.

1-[2-*O*-Acetyl-5-*O*-benzyl-3-*C*-[(benzyloxy)methyl]-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (19) and Its α-Anomer (20). These compounds were synthesized from **17** (5.5 g, 12.8 mmol) by the same methodology as described for the synthesis of **18**. Compound **19**, the β-anomer (5.5 g, 87%): UV (MeOH) λ_{max} 263 nm (ε 9 190), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 266 nm (ε 7 610), λ_{min} 235 nm; UV (0.01 N NaOH) λ_{max} 268 nm (ε 7 700), λ_{min} 238 nm; ^1H NMR δ 1.56 (s, 3 H, 5-CH_3), 2.03 (s, 3 H, $COCH_3$), 2.87–2.92 (m, 1 H, 3′-H), 3.48–3.96 (m, 4 H, 3′-CH_2 and 5′-H), 4.28–4.30 (m, 1 H, 4′-H), 4.49–4.60 (m, 4 H, 2 × CH_2-Ph), 5.44–5.46 (dd, 1 H, 2′-H, $J_{1',2'}$ = 3.2 Hz), 6.02 (d, 1 H, 1′-H, $J_{1',2'}$ = 3.2 Hz), 7.28–7.36 (m, 10 H, ArH), 7.66 (d, 1 H, 6-H), 8.38 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{27}H_{30}N_2O_7$) C, H, N.

Compound **20**, the α-anomer (0.4 g, 6%): UV (MeOH) λ_{max} 265 nm (ε 8 090), λ_{min} 237 nm; UV (0.01 N HCl) λ_{max} 264 nm (ε 8 540), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 265 nm (ε 8 450), λ_{min} 238 nm; ^1H NMR δ 1.50 (s, 3 H, 5-CH_3), 1.87 (d, 3 H, $COCH_3$), 2.62–2.65 (m, 1 H, 3′-H), 3.61–4.02 (m, 4 H, 3′-CH_2 and 5′-H), 4.28–4.49 (m, 1 H, 4′-H), 4.51–4.61 (m, 4 H, 2 × –CH_2Ph), 5.79 (dd, 1 H, 2′-H), 6.80 (d, 1 H, 1′-H, $J_{1',2'}$ = 9.4 Hz), 7.27–7.37 (m, 10 H, ArH), 7.93 (d, 1 H, 6-H), 9.65 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{27}H_{30}N_2O_7$) C, H, N.

1-[5-*O*-Benzyl-3-*C*-(fluoromethyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (21). Compound **18** (2.6 g, 6.5 mmol)

was dissolved in methanolic ammonia solution (75 mL), and the solution was stirred at room temperature for 24 h. After evaporation of the methanolic ammonia, the residue was crystallized from ethanol to give 2.0 g (85%) of product as a white crystals: mp 158–159 °C; UV (MeOH) λ_{max} 267 nm (ϵ 7 800), λ_{min} 235 nm; UV (0.01 N HCl) λ_{max} 265 nm (ϵ 8 980), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 266 nm (ϵ 8 780), λ_{min} 234 nm; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3 H, 5-CH_3), 2.77–2.78 (m, 1 H, 3'-H), 3.68 (dd, 1 H, 5'-H_A), 4.10 (dd, 1 H, 5'-H_B), 4.42–4.93 [m, 6 H, 2'-H, 4'-H, -CH_2F, ($J_{H,F}$ = 47.6 Hz) and CH_2Ph], 5.26 (s, 1 H, 2'-OH, D_2O exchangeable), 5.78 (s, 1 H, 1'-H), 7.30–7.36 (m, 5 H, ArH), 8.01 (d, 1 H, 6-H), 10.4 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{16}H_{21}FN_2O_5$) C, H, F, N.

1-[5-*O*-Benzyl-3-*C*-[(benzyloxy)methyl]-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (22). This compound was synthesized from **19** (5.32 g, 10.6 mmol) by the same methodology as described for the synthesis of **21**: yield 4.75 g (95%) of white crystals; mp 148–150 °C; UV (MeOH) λ_{max} 267 nm (ϵ 11 720), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 268 nm (ϵ 6 370), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 270 nm (ϵ 6 820), λ_{min} 240 nm; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3 H, 5-CH_3), 2.62–2.67 (m, 1 H, 3'-H), 3.61–4.03 (m, 4 H, 3'-CH_2 and 5'-H), 4.35–4.37 (m, 2 H, 4'-H and 2'-H), 4.48–4.61 (m, 4 H, 2 × CH_2Ph), 4.95 (s, 1 H, 2'-OH, D_2O exchangeable), 5.77 (s, 1 H, 1'-H), 7.26–7.34 (m, 10 H, ArH), 7.96 (d, 1 H, 6-H), 10.08 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{25}H_{28}N_2O_6$) C, H, N.

1-[5-*O*-Benzyl-3-deoxy-3-*C*-(fluoromethyl)-2-*O*-(methylsulfonyl)-β-D-*erythro*-pentofuranosyl]thymine (23). Compound **21** (0.40 g, 1.1 mmol) was dissolved in pyridine (20 mL) at room temperature. The solution was cooled in an ice bath and methanesulfonyl chloride (0.22 mL, 0.33 g, 2.85 mmol) was added. The resulting solution was allowed to stir at 0 °C for 5 h. To the solution was added MeOH (1 mL) and then stirred for 0.5 h. The reaction solution was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with $NaHCO_3$ solution and water and then dried over anhydrous $MgSO_4$. The solvent was removed under diminished pressure to give a syrup, which was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 20:1, v/v), to afford 0.41 g (84%) of product as a foam: UV (MeOH) λ_{max} 260 nm (ϵ 8 460), λ_{min} 230 nm; UV (0.01 N HCl) λ_{max} 260 nm (ϵ 8 080), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 258 nm (ϵ 7 310), λ_{min} 235 nm; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 3 H, 5-CH_3), 2.60–3.30 (m, 1 H, 3'-H), 3.25 (s, 3 H, SO_2CH_3), 3.60 and 4.33 (2 dd, 2 H, 5'-H), 4.14–5.10 (m, 5 H, 4'-H, CH_2Ph and CH_2F), 5.18 (d, 1 H, 2'-H), 5.80 (s, 1 H, 1'-H), 7.28 (s, 5 H, ArH), 7.71 (d, 1 H, 6-H), 10.22 (s, 1 H, 3-NH, D_2O exchangeable).

1-[5-*O*-Benzyl-3-deoxy-3-*C*-(fluoromethyl)-β-D-*threo*-pentofuranosyl]thymine (27). Compound **23** (0.35 g, 0.79 mmol) in ethanol (90%, 30 mL) and 1 N NaOH (1.8 mL) was refluxed for 15 min. Additional 1 N NaOH (3.3 mL) was added, and the solution was refluxed for 2 more hours. The pH of solution was then adjusted to 7 with HOAc, and to the reaction solution water (60 mL) was added. The precipitate was collected by filtration and washed with water. The crude product was crystallized from ethanol to give 0.26 g (92%) of product as white crystals: mp 179–180 °C; UV (MeOH) λ_{max} 268 nm (ϵ 8 420), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 264 nm (ϵ 10 560), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 269 nm (ϵ 8 850), λ_{min} 237 nm; ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3 H, 5-CH_3), 2.37–2.48 (m, 1 H, 3'-H), 3.65 and 3.77 (2 dd, 2 H, 5'-H), 3.92–3.95 (m, 1 H, 4'-H), 4.23–4.26 (m, 1 H, 2'-H), 4.53 (d, 2 H, CH_2Ph), 4.45 and 4.54 (2 dd, 2 H, CH_2F, $J_{H,F}$ = 47.3 Hz), 5.41 (d, 1 H, 2'-OH, D_2O exchangeable), 5.95 (d, 1 H, 1'-H, $J_{1',2'}$ = 5.7 Hz), 7.26 (d, 5 H, ArH), 7.45 (d, 1 H, 6-H), 10.9 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{18}H_{21}FN_2O_5$) C, H, F, N.

1-[5-*O*-Benzyl-3-*C*-[(benzyloxy)methyl]-3-deoxy-β-D-*threo*-pentofuranosyl]thymine (28). Compound **22** (1.73 g, 4.07 mmol) was dissolved in pyridine (25 mL) at room temperature. The solution was cooled in an ice bath and methanesulfonyl chloride (0.82 mL, 1.21 g, 10.6 mmol) was added. The resulting solution was allowed to stir at 0 °C for 4 h, after which was added MeOH (5 mL). The reaction solution was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), and the organic layer was washed with $NaHCO_3$ solution and water and then dried over anhydrous $MgSO_4$. The solvent was removed under diminished pressure to give a syrup (**24**), which was used in the next step reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3 H, 5-CH_3), 2.80–3.10 (m, 1 H, 3'-H), 3.33 (s, 3 H, SO_2CH_3), 3.60–4.40 (m, 5 H, 3'-CH_2, 5'-H, and 4'-H), 4.43–4.67 (m, 4 H, 2 × CH_2Ph), 5.25 (d, 1 H, 2'-H), 5.93 (s, 1 H, 1'-H), 7.33 (s, 10 H, ArH), 7.85 (s, 1 H, 6-H), 9.33 (br, 1 H, 3-NH, D_2O exchangeable).

Compound **24** in ethanol (90%, 87 mL) and 1 N NaOH (5.2 mL) was refluxed for 15 min. Additional 1 N NaOH (10 mL) was added, and the solution was refluxed for 2 h. The pH of solution was then brought to 7 with HOAc, and to the reaction solution was added water (100 mL). The precipitate was collected by filtration and washed with water. The crude product was crystallized from ethanol to afford 1.6 g (90%) of white crystals: mp 145–146 °C; UV (MeOH) λ_{max} 268 nm (ϵ 8 900), λ_{min} 235 nm; UV (0.01 N HCl) λ_{max} 266 nm (ϵ 8 900), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 269 nm (ϵ 8 240), λ_{min} 238 nm; ^{1}H NMR δ 1.62 (s, 3 H, 5-CH_3), 2.53–2.57 (m, 1 H, 3'-H), 3.55–3.63 (m, 3 H, 3'-CH_2 and 5'-H_A), 3.91–3.93 (m, 2 H, 5'-H_B and 2'-OH, D_2O exchangeable), 4.13–4.15 (m, 1 H, 4'-H), 4.31–4.35 (m, 1 H, 2'-H), 4.49–4.64 (m, 4 H, 2 × CH_2Ph), 6.04 (d, 1 H, 1'-H, $J_{1',2'}$ = 4.7 Hz), 7.25–7.37 (m, 10 H, ArH), 7.67 (d, 1 H, 6-H), 8.93 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{25}H_{28}N_2O_6$) C, H, N.

1-[3-*C*-(Fluoromethyl)-3-deoxy-β-D-*threo*-pentofuranosyl]thymine (29).[5] Compound **27** (0.25 g, 0.64 mmol) in methanol (40 mL) was hydrogenated over 10% palladium (120 mg) on charcoal at 50 psi hydrogen pressure at room temperature for 4 h. The catalyst was removed by filtration, and the solvent was evaporated in vacuo. The residue was crystallized from ethanol to give 0.11 g (57%) of white crystals: mp 205–206 °C; UV (MeOH) λ_{max} 264 nm (ϵ 8 990), λ_{min} 231 nm; UV (0.01 N HCl) λ_{max} 268 nm (ϵ 9 850), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 266 nm (ϵ 9 500), λ_{min} 235 nm; ^{1}H NMR (DMSO-d_6) δ 1.75 (s, 3 H, 5-CH_3), 2.31–2.44 (m, 1 H, 3'-H), 3.57–3.62 (m, 1 H, 5'-H_A), 3.69–3.72 (m, 1 H, 5'-H_B), 3.76–3.79 (m, 1 H, 4'-H), 4.22 (dd, 1 H, 2'-H), 4.57 (dd, 2 H, CH_2F, $J_{H,F}$ = 47.3 Hz), 5.13 (t, 1 H, 5'-OH, D_2O exchangeable), 5.57 (d, 1 H, 2'-OH, D_2O exchangeable), 5.57 (d, 1 H, 2'-OH, D_2O exchangeable), 5.92 (d, 1 H, 1'-H, $J_{1',2'}$ = 5.7 Hz), 7.70 (d, 1 H, 6-H), 11.2 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 275 (M^+ + 1), 126 (thymine), 149 ($C_6H_{10}FO_3$, sugar residue). Anal. ($C_{11}H_{15}FN_2O_5$) C, H, F, N.

1-[3-Deoxy-3-*C*-(hydroxymethyl)-β-D-*threo*-pentofuranosyl]thymine (30).[6] This compound was synthesized from **28** (1.0 g, 2.2 mmol) by the same methodology as described for the synthesis of **29**: yield 0.34 g (56%) as white crystals; mp 176–177 °C; UV (MeOH) λ_{max} 266 nm (ϵ 6 630), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 266 nm (ϵ 6 650), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 265 nm (ϵ 7 020), λ_{min} 234 nm; ^{1}H NMR (DMSO-d_6) δ 1.75 (s, 3 H, 5-CH_3), 2.05–2.09 (m, 1 H, 3'-H), 3.31–3.69 (m, 4 H, 3'-CH_2 and 5'-H), 3.75–3.77 (m, 1 H, 4'-H), 4.16 (d, 1 H, 2'-H), 4.80 (t, 1 H, 5'-OH, D_2O exchangeable), 5.07 (s, 1 H, 3'-OH, D_2O exchangeable), 5.35 (d, 1 H, 2'-OH, D_2O exchangeable), 5.88 (dd, 1 H, 1'-H, $J_{1',2'}$ = 5.4 Hz), 7.70 (s, 1 H, 6-H) 11.2 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 273 (M^+ + 1), 126 (thymine), 147 ($C_6H_{11}O_4$ sugar residue). Anal. ($C_{11}H_{16}N_2O_6$) C, H, N.

1-[5-*O*-Benzyl-3-*C*-(fluoromethyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine (33). To a solution of compound **21** (1.40 g, 3.84 mmol) and (dimethylamino)pyridine (0.94 g, 7.68 mmol) in CH_3CN (80 mL) was added gradually phenyl chlorothionocarbonate (0.90 g, 5.19 mmol) in an ice bath. The mixture was stirred at 0 °C for 4 h and then at room temperature for 12 h. The solvent was removed in vacuo, and the residue was dissolved in EtOAc (100 mL). The solution was washed with water (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give a syrup (**31**). The syrup was dissolved in toluene (80 mL) to which was added 2,2'-azobis(2-methylpropionitrile) (AIBN, 1.62 g, 9.88 mmol) and tri-*n*-butyltin hydride (2.2 g, 7.6 mmol) at 50–60 °C under N_2. The reaction mixture was stirred at 95–100 °C for 5 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 2:1, v/v) to produce a syrup, which was then crystallized from MeOH to afford 1.1 g (85%) of white crystals: mp 110–111 °C; UV (MeOH) λ_{max} 264 nm (ϵ 6 850), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 268 nm (ϵ 9 430), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 265 nm (ϵ 9 910), λ_{min} 234 nm; 1H NMR ($CDCl_3$) δ 1.60 (s, 3 H, 5-CH_3), 2.10–2.30 (m, 2 H, 2'-H), 2.50–3.00 (m, 1 H, 3'-H), 3.50–4.10 (m, 3 H, 5'-H and 4'-H), 4.17

and 4.66 (dd, 2 H, CH_2F, $J_{H,F}$ = 46.5 Hz), 4.50 (s, 2 H, CH_2Ph), 6.02 (t, 1 H, 1'-H), 7.25 (s, 5 H, ArH), 7.56 (s, 1 H, 6-H), 8.95 (br, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{16}H_{21}FN_2O_4$) C, H, F, N.

1-[5-*O*-Benzyl-3-*C*-[(benzyloxy)methyl]-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine (34). This compound was synthesized from **22** (2.2 g, 4.86 mmol) by the same methodology as described for synthesis of compound **33**: yield 0.99 g (47%) as white crystals; mp 109–110 °C; UV (MeOH) λ_{max} 276 nm (ε 7 880), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 266 nm (ε 8 390), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 264 nm (ε 7 720), λ_{min} 234 nm; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3 H, 5-CH_3), 2.00–2.30 (m, 2 H, 2'-H), 2.45–2.85 (m, 1 H, 3'-H), 3.40–4.20 (m, 5 H, 3'-CH_2, 5'-H, and 4'-H), 4.53 (d, 4 H, 2 × CH_2Ph), 6.10 (t, 1 H, 1'-H), 7.30 (s, 10 H, ArH), 7.70 (s, 1 H, 6-H), 8.70 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{25}H_{28}N_2O_5$) C, H, N.

Compounds **35–38** were synthesized by the same methodology as described for the synthesis of compound **29**.

1-[2,3-Dideoxy-3-*C*-(fluoromethyl)-β-D-*erythro*-pentofuranosyl]thymine (35):[7b] yield 0.26 g (64%); mp 106–107 °C; UV (MeOH) λ_{max} 263 nm (ε 8 430), λ_{min} 230 nm; UV (0.01 N HCl) λ_{max} 269 nm (ε 9 900), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 266 nm (ε 9 310), λ_{min} 234 nm; ^1H NMR (DMSO-d_6) δ 1.77 (s, 3 H, 5-CH_3), 2.10–2.17 (m, 2 H, 2'-H), 2.60–2.65 (m, 1 H, 3'-H), 3.53–3.71 (m, 2 H, 5'-H), 3.80–3.83 (m, 1 H, 4'-H), 4.54 (dd, 2 H, 3'-CH_2-F, $J_{H,F}$ = 47 Hz), 5.08 (t, 1 H, 5'-OH, D_2O exchangeable), 6.00 (dd, 1 H, 1'-H), 7.80 (d, 1 H, 6-H), 11.2 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 259 (M^+ + 1), 126 (thymine), 133 ($C_6H_{10}FO_2$, sugar residue). Anal. ($C_{11}H_{15}FN_2O_4$) C, H, F, N.

1-[2,3-Dideoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]thymine (36):[4-8] yield 0.26 g (50%) as white crystals; mp 130–131 °C; UV (MeOH) λ_{max} 269 nm (ε 9 420), λ_{min} 235 nm, UV (0.01 N HCl) λ_{max} 269 nm (ε 9 640), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 269 nm (ε 9 970), λ_{min} 238 nm; ^1H NMR (Me_2SO-d_6) δ 1.75 (s, 3 H, 5-CH_3), 1.96–2.14 (m, 2 H, 2'-H, $J_{1',2'}$ = 4.6 Hz), 2.32–2.37 (m, 1 H, 3'-H), 3.41–3.43 (m, 2 H, 3'-CH_2), 3.52–3.70 (m, 2 H, 5'-H), 3.74–3.77 (m, 1 H, 4'-H), 4.76 and 5.03 (2 t, 2 H, 2 × OH, D_2O exchangeable), 5.96 (dd, 1 H, 1'-H, $J_{1',2'}$ = 4.6 Hz), 7.83 (d, 1 H, 6-H), 11.2 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 257 (M^+ + 1), 126 (thymine), 131 ($C_6H_{11}O_3$, sugar residue). Anal. ($C_{11}H_{16}N_2O_5$) C, H, N.

1-[3-*C*-(Fluoromethyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (37): yield 0.1 g (68%); mp 91–92 °C; UV (MeOH) λ_{max} 269 nm (ε 9 230), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 268 nm (ε 8 650), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 265 nm (ε 7 440), λ_{min} 234 nm; ^1H NMR ($CDCl_3$) δ 1.74 (s, 3 H, 5-CH_3), 2.57–2.48 (m, 1 H, 3'-H), 3.52–3.56 (m, 1 H, 5'-H_A), 3.74–3.78 (m, 1 H, 5'-H_B), 4.02 (t, 1 H, 4'-H), 4.22–4.25 (m, 1 H, 2'-H), 4.48 and 5.58 (2 dd, 1 H, CH_AF = 47.0 Hz), 4.61 and 4.70 (2 dd, 1 H, CH_BF, $J_{H_B,F}$ = 47.0 Hz), 5.18 (t, 1 H, 5'-OH, D_2O exchangeable), 5.66 (d, 1 H, 1'-H, $J_{1',2'}$ = 2.3 Hz), 5.80 (d, 1 H, 2'-OH, D_2O, exchangeable), 7.90 (s, 1 H, 6-H), 11.3 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 275 (M^+ + 1), 126 (thymine), 149 ($C_6H_{11}FO_3$, sugar residue). Anal. ($C_{11}H_{15}FN_2O_5$) C, H, F, N.

1-[3-Deoxy-3-*C*-(hydroxymethyl)-β-D-*erythro*-pentofuranosyl]thymine (38): yield 0.21 g (71%); mp 185.0–186.5 °C; UV (MeOH) λ_{max} 268 nm (ε 8 820), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 268 nm (ε 9 170), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 268 nm (ε 8 060), λ_{min} 236 nm; ^1H NMR (DMSO-d_6) δ 1.75 (s, 3 H, 5-CH_3), 2.19–2.24 (m, 1 H, 3'-H), 3.44–3.79 (m, 4 H, 3'-CH_2 and 5'-H), 3.93–3.96 (m, 1 H, 4'-H), 4.15 (dd, 1 H, 2'-H), 4.50 and 5.16 (2 t, 2 H, 5'- and 3'-OH, D_2O exchangeable) 5.55 (d, 1 H, 2'-OH, D_2O exchangeable), 5.65 (d, 1 H, 1'-H, $J_{1',2'}$ = 2 Hz), 7.99 (d, 1 H, 6-H), 11.3 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 273 (M^+ + 1), 126 (thymine), 147 ($C_6H_{11}O_4$ sugar residue). Anal. ($C_{11}H_{16}N_2O_6$) C, H, N.

1-[2,5-*O*-Diacetyl-3-*C*-(azidomethyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (39) and Its α-Anomer (40). These compounds were synthesized from **16** (6.4 g, 20.3 mmol) by the same methodology as described for synthesis of **18**. Compound **39**, the β-anomer (3.1 g, 41%), was obtained as a foam: UV (CH_3OH) λ_{max} 266 nm (ε 9 390), λ_{min} 235 nm; UV (0.01 N HCl) λ_{max} 260 nm (ε 11 400), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 267 nm (ε 10 200), λ_{min} 237 nm; IR (KBr) ν_{max} 2140 cm^{-1} (azido); ^1H NMR ($CDCl_3$) δ 1.94 (s, 3 H, 5-CH_3), 2.14 and 2.17 (2 s, 6 H, $COCH_3$), 2.72–2.78 (m, 1 H, 3'-H), 3.43 and 3.62 (2 dd, 2 H, 3'-CH_2), 4.22–4.25 (m, 1 H, 4'-H), 4.32 and 4.44 (2 dd, 2 H, 5'-H), 5.48 (dd, 1 H, 2'-H), 5.66 (d, 1 H, 1'-H, $J_{1',2'}$ = 2.7 Hz), 7.15 (d, 1 H, 6-H), 8.56 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{16}H_{19}N_5O_7$) C, H, N.

Compound **40**, the α-anomer (2.1 g, 27%), was isolated as crystals: mp 145–147 °C; UV (CH_3OH) λ_{max} 263 nm (ε 7 050), λ_{min} 233 nm; UV (0.01 N HCl) λ_{max} 260 nm (ε 8 860), λ_{min} 230 nm; UV (0.01 N NaOH) λ_{max} 265 nm (ε 7 770), λ_{min} 237 nm; IR (KBr) ν_{max} 2120 cm^{-1} (azido); ^1H NMR ($CDCl_3$) δ 1.94 (s, 3 H, 5-CH_3), 2.08 and 2.15 (2 s, 6 H, $COCH_3$), 2.82–2.86 (m, 1 H, 3'-H), 2.67–3.75 (m, 2 H, 3'-CH_2), 3.80–3.83 (dd, 1 H, 2'-H), 4.02–4.08 (m, 1 H, 4'-H), 5.15–5.20 (m, 2 H, 5'-H), 5.89 (d, 1 H, 1'-H, $J_{1',2}$ = 9.6 Hz), 7.11 (d, 1 H, 6-H), 8.41 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{15}H_{19}N_5O_7$) C, H, N.

1-[3-*C*-(Azidomethyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (41). This compound was synthesized from **39** (3.38 g, 8.86 mmol) by the same methodology as described for the synthesis of **21**: yield 2.5 g (96%) as white crystals; mp 127–129 °C; UV (MeOH) λ_{max} 268 nm (ε 9 250), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 265 nm (ε 10 130), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 268 nm (ε 9 580), λ_{min} 236 nm; IR (KBr) ν_{max} 2140 cm^{-1} (azido); ^1H NMR (Me_2SO-d_6) δ 1.75 (s, 3 H, 5-CH_3), 2.33–2.39 (m, 1 H, 3'-H), 3.34–3.37 (m, 1 H, 4'-H), 3.54–3.60 (m, 2 H, 5'-H), 3.74–3.78 (m, 1 H, 2'-H), 3.88–4.20 (m, 2 H, 3'-CH_2), 5.16 (t, 1 H, 5'-OH, D_2O exchangeable), 5.65 (d, 1 H, 1'-H, $J_{1',2'}$ = 2.0 Hz), 5.86 (d, 1 H, 2'-OH, D_2O exchangeable), 7.92 (d, 1 H, 6-H), 11.2 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 298 (M^+ + 1), 126 (thymine). Anal. ($C_{11}H_{15}N_5O_5$) C, H, N.

1-[3-*C*-(Aminomethyl)-3-deoxy-β-D-*erythro*-pentofuranosyl]thymine (42) and Its Hydrochloride Salt (43). Compound **41** (750 mg, 2.5 mmol) and triphenylphosphine (1.05 g, 4.01 mmol) were dissolved in pyridine (30 mL) and stirred at room temperature. After 1 h, concentrated ammonium hydroxide (25 mL) was added and the solution was allowed to stir for an additional 2 h. Pyridine was removed at reduced pressure, water (50 mL) was added, and the unreacted triphenylphosphine and triphenylphosphine oxide was removed by filtration. The filtrate was extracted with benzene and then water and concentrated to dryness to give a syrup (**42**): ^1H NMR (DMSO-d_6) δ 1.77 (s, 3 H, 5-CH_3), 1.90–3.00 (m, 3 H, 3'-H and 3'-CH_2), 3.30–3.75 (m, 2 H, 5'-H), 3.75–3.96 (m, 1 H, 4'-H), 4.00–4.20 (m, 1 H, 2'-H) 4.70 (br, 4 H, NH_2, 2'-OH, and 5'-OH, D_2O exchangeable), 5.55 (s, 1 H, 1'-H), 7.82 (s, 1 H, 6-H).

Compound **42** was converted to its hydrochloride salt by treatment with acetyl chloride (0.40 g, 5 mmol) in MeOH (10 mL), followed by evaporation in vacuo to dryness and crystallization from ethanol, to afford 0.23 g (30%) of product as white crystals: mp 216–217 °C dec; UV (MeOH) λ_{max} 267 nm (ε 9 030), λ_{min} 233 nm; UV (0.01 N HCl) λ_{max} 269 nm (ε 9 170), λ_{min} 236 nm; UV (0.01 N NaOH), λ_{max} 268 nm (ε 9 600), λ_{min} 235 nm; ^1H NMR (DMSO-d_6) δ 1.74 (s, 3 H, 5-CH_3), 2.41–2.45 (m, 1 H, 3'-H), 2.82–2.85 and 2.98–3.03 (2 m, 2 H, 3'-CH_2), 3.60 and 3.76 (2 dd, 2 H, 5'-H), 3.89–3.92 (m, 1 H, 4'-H), 4.26–4.27 (m, 1 H, 2'-H), 5.65 (d, 1 H, 1'-H, $J_{1',2'}$ = 1.6 Hz), 7.91 (d, 1 H, 6-H); MS *m/z* 272 (M^+ + 1), 126 (thymine), 146 ($C_6H_{12}NO_3$, sugar, residue). Anal. ($C_{11}H_{18}ClN_3O_5$) C, H, N.

1-[3-*C*-(Azidomethyl)-3-deoxy-5-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl)thymine (44). To a mixture of compound **41** (2.2 g, 7.4 mmol) and pyridine (3.6 mL, 44.4 mmol) in THF (120 mL) was added silver nitrate (1.87 g, 11.0 mmol) and *tert*-butyldimethylsilyl chloride (1.56 g, 10.4 mmol). The mixture was stirred at room temperature for 20 h, after which the reaction solution was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), and the organic layer was washed twice with aqueous sodium bicarbonate solution (5%, 2 × 20 mL), dried over anhydrous $MgSO_4$, and evaporated to dryness to produce a residue, which was then purified by silica gel column chromatography (CH_2Cl_2/MeOH, 25:1, v/v) to yield 2.8 g (92%) of foam: UV (MeOH) λ_{max} 269 nm (ε 9 910), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 265 nm (ε 7 010), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 267 nm (ε 4 570), λ_{min} 236 nm; IR (KBr) ν_{max} 2100 cm^{-1} (azido); ^1H NMR (Me_2SO-d_6) δ 0.07 (2 s, 6 H, $SiMe_2$), 0.88 (s, 9 H, $SiCMe_3$), 1.77 (s, 3 H, 5-CH_3), 2.34–2.40 (m, 1 H, 3'-H), 3.34–3.37 (m, 1 H, 4'-H), 3.63 and 3.73 (2 dd, 2 H, 3'-CH_2), 3.89–3.94 (m, 2 H, 5'-H), 4.23–4.26 (m, 1 H, 2'-H), 5.68 (d, 1 H, 1'-H, $J_{1',2'}$ = 2.78 Hz), 5.84

(d, 1 H, 2'-OH, D_2O exchangeable), 7.45 (d, 1 H, 6-H), 11.3 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{17}H_{29}N_5O_5Si$) C, H, N.

1-[3-*C*-(Azidomethyl)-5-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-2-*O*-methylsulfonyl-β-D-*erythro*-pentofuranosyl]thymine (45). This compound was synthesized from **44** (1.2 g, 2.9 mmol) by the same methodology as described for the synthesis of **23**: yield 0.92 g (64%) as a foam; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, $SiCMe_3$), 1.90 (s, 3 H, 5-CH_3), 2.50–2.82 (m, 1 H, 3'-H), 3.30 (s, 3 H, SO_2CH_3), 3.40–4.20 (m, 5 H, 4'-H, 3'-CH_2, and 5'-H), 5.20 (d, 1 H, 2'-H), 5.70 (s, 1 H, 1'-H), 7.50 (s, 1 H, 6-H) 9.90 (s, 1 H, 3-NH, D_2O exchangeable).

1-[3-*C*-(Azidomethyl)-3-deoxy-β-D-*threo*-pentofuranosyl]thymine (47). This compound was synthesized from **45** (0.72 g, 1.47 mmol) by the same methodology as described for the synthesis of **27**: yield 0.30 g (68%) as white crystals; mp 127–129 °C; UV (MeOH) λ_{max} 268 nm (ε 9 540), λ_{min} 235 nm; UV (0.01 N HCl) λ_{max} 265 nm (ε 9 980), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 266 nm (ε 10 500), λ_{min} 234 nm; IR (KBr) ν_{max} 2120 cm^{-1} (azido); ^1H NMR (Me_2SO-d_6) δ 1.75 (s, 3 H, 5-CH_3), 2.21–2.24 (m, 1 H, 3'-H), 3.51–3.71 (m, 5 H, 3'-CH_2, 5'-H, and 4'-H), 4.14–4.17 (m, 1 H, 2'-H), 5.09 (d, 1 H, 5'-OH, D_2O exchangeable), 5.53 (d, 1 H, 2'-OH, D_2O exchangeable), 5.92 (d, 1 H, 1'-H, $J_{1',2'}$ = 5.8 Hz), 7.67 (d, 1 H, 6-H), 11.2 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 298 (M^+ + 1), 126 (thymine). Anal. ($C_{11}H_{15}N_5O_5$) C, H, N.

1-[3-*C*-(Aminomethyl)-3-deoxy-β-D-*threo*-pentofuranosyl]thymine (48). This compound was synthesized from **47** (0.40 g, 1.33 mmol) by the same methodology as described for the synthesis of **42**: yield 0.16 g (44%) as white crystals; mp 178–180 °C; UV (MeOH) λ_{max} 266 nm (ε 7 930), λ_{min} 233 nm; UV (0.01 N HCl) λ_{max} 270 nm (ε 9 430), λ_{min} 237 nm; UV (0.01 N NaOH) λ_{max} 266 nm (ε 9 090), λ_{min} 233 nm; ^1H NMR (DMSO-d_6) δ 1.75 (s, 3 H, 5-CH_3), 1.93–1.97 (m, 1 H, 3'-H), 2.56 and 2.79 (2 dd, 2 H, 3'-CH_2), 3.58–3.67 (m, 3 H, 4'-H and 5'-H), 4.13 (t, 1 H, 2'-H), 5.90 (d, 1 H, 1'-H, $J_{1',2'}$ = 5.8 Hz), 7.61 (s, 1 H, 6-H), 3.32 and 5.70 (2 br, 4 H, 3'-NH_2, 2'-OH, and 5'-OH, D_2O exchangeable); MS *m/z* 272 (M^+ + 1), 126 (thymine), 146 ($C_6H_{12}NO_3$ sugar residue). Anal. ($C_{11}H_{17}N_3O_5$) C, H, N.

1-[3-*C*-(Azidomethyl)-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine (50). This compound was synthesized from **44** (1.25 g, 3.04 mmol) by the same methodology as described for synthesis of compound **33**: yield 0.51 g (43%); mp 109–111 °C; UV (MeOH) λ_{max} 264 nm (ε 11 120), λ_{min} 231 nm; UV (0.01 N HCl) λ_{max} 266 nm (ε 11 190), λ_{min} 233 nm; UV (0.01 N NaOH) λ_{max} 270 nm (ε 8 880), λ_{min} 238 nm; IR (KBr) ν_{max} 2140 cm^{-1} (azido); ^1H NMR ($CDCl_3$) δ 0.13 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, $SiCMe_3$), 1.90 (s, 3 H, 5-CH_3), 2.05–2.23 (m, 2 H, 2'-H), 2.33–2.70 (m, 1 H, 3'-H), 3.41 (d, 2 H, 5'-H), 3.60–4.06 (m, 3 H, 3'-CH_2 and 4'-H), 6.10 (t, 1 H, 1'-H), 7.46 (s, 1 H, 6-H), 9.23 (s, 1 H, 3-NH, D_2O exchangeable). Anal. ($C_{17}H_{29}N_5O_4Si$) C, H, N.

1-[3-*C*-(Azidomethyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine (51).[7b] Compound **50** (0.66 g, 1.76 mmol) in THF (25 mL) was stirred with *n*-Bu_4NF (8.5 mL, 8.5 mmol, 1.0 M in THF) at room temperature for 1 h. The solution was then evaporated in vacuo to give a syrup, which was purified by silica gel column chromatography (EtOAc/MeOH, 25:1, v/v) to yield 0.38 g (81%) of product as a syrup: UV (MeOH) λ_{max} 266 nm (ε 9 230), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 268 nm (ε 9 390), λ_{min} 235 nm; UV (0.01 N NaOH) λ_{max} 269 nm (ε 9 280), λ_{min} 238 nm; IR (KBr) ν_{max} 2100 cm^{-1} (azido); ^1H NMR (DMSO-d_6) δ 1.76 (s, 3 H, 5-CH_3), 2.10–2.13 (m, 2 H, 2'-H), 2.48–2.52 (m, 1 H, 3'-H), 3.50 (d, 2 H, 5'-H), 3.54–3.57 (m, 1 H, 4'-H), 3.67–3.72 (m, 2 H, 3'-CH_2), 5.10 (t, 1 H, 5'-OH, D_2O exchangeable), 5.99 (t, 1 H, 1'-H), 7.80 (d, 1 H, 6-H), 11.2 (s, 1 H, 3-NH, D_2O exchangeable); MS *m/z* 282 (M^+ + 1), 126 (thymine), 166 ($C_6H_{10}N_3O_2$, sugar residue). Anal. ($C_{11}H_{15}N_5O_4$) C, H, N.

1-[3-*C*-(Aminomethyl)-2,3-dideoxy-β-D-*erythro*-pentofuranosyl]thymine (52) and Its Hydrochloride Salt (53). Compounds **52** and **53** were synthesized from **51** (0.30 g, 1.07 mmol) by the same methodology as described for the syntheses of **42** and **43**.

Compound **52** (0.26 g, 95%) was obtained as a syrup: ^1H NMR (DMSO-d_6) δ 1.78 (s, 3 H, 5-CH_3), 1.85–2.35 (m, 3 H, 2'-H and 3'-H), 2.40–2.65 (m, 2 H, 3'-CH_2), 3.48–3.78 (m, 3 H, 5'-H and 4'-H), 4.33 (br, 3 H, NH_2 and 5'-OH, D_2O exchangeable), 5.90 (t, 1 H, 1'-H), 7.72 (s, 1 H, 6-H).

Compound **53** was isolated as white crystals: yield 0.25 g (81%); mp 199–201 °C; UV (MeOH) λ_{max} 269 nm (ε 6 950), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 267 nm (ε 8 190), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 267 nm (ε 7 630), λ_{min} 235 nm; ^1H NMR (DMSO-d_6) δ 1.76 (s, 3 H, 5-CH_3), 2.19–2.26 (m, 2 H, 2'-H), 2.56–2.79 (m, 1 H, 3'-H), 2.82–2.94 (m, 1 H, 4'-H), 3.63–3.80 (m, 4 H, 3'-CH_2 and 5'-H), 5.29 (br, 1 H, 5'-OH, D_2O exchangeable), 5.97–6.02 (m, 1 H, 1'-H), 7.87 (dd, 1 H, 6-H), 8.12 (br, 2 H, NH_2), 11.3 (s, 1 H, 3-NH); MS *m/z* 256 (M^+ + 1), 126 (thymine), 130 ($C_6H_{12}NO_2$, sugar residue). Anal. ($C_{11}H_{18}ClN_3O_4$) C, H, N.

Anticancer Assays. The synthesized compounds were evaluated in culture for their anticancer activity by growth inhibition studies using murine L1210 leukemia, P388, Sarcoma 180, and human CCRF-CEM lymphoblastic leukemia cells as described as follows: Murine L1210, P388, and S-180 cells were maintained as suspension cultures in Fisher's medium and CCRF-CEM cells were maintained as a suspension culture in Roswell Park Memorial Institute 1640 medium, both media supplemented with 10% horse serum and all cells maintained at 37 °C in a humidified atmosphere of 5% CO_2/95% air. Under these conditions, the generation time for L1210, P388, S-180, and CCRF-CEM cells is approximately 12, 12, 18, and 20 h, respectively. Each compound was added at various concentrations to L1210, P388, S-180, and CCRF-CEM cells (2×10^4 cells/mL) in their exponential phase of growth. The cell number of the drug-free cultures (control), as well as that of the cultures containing with the compounds, were determined after 24, 48, and 72 h of growth.

Antiviral Assays. In a modification of a procedure by Larder et al.,[31] the compounds were tested in drug susceptibility assays using MT-2 cells. Triplicate wells in a 96-well tissue culture plate containing 1×10^4 cells infected with HIV-1 (HTLV-III) virus at a multiplicity of infection of 0.5 $TCID_{50}$/cell were treated with serial dilutions of drugs. After 7 days, MTT dye was added and the antiviral effect was determined by comparing the A_{570} of infected cells with the A_{570} of uninfected cells without drugs.[32]

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