mL) was added and the solvent was removed. The residue was taken up in 80% acetic acid (9 mL), and the solution was stirred at 80 °C for 20 min. Water (3 mL) was added and the solution was extracted with hexane (2 × 10 mL). The aqueous layer was retained and the solvent was removed. The residue was partitioned between saturated aqueous $NaHCO_3$ and chloroform, and the organic layer was dried ($MgSO_4$) and the solvent removed. The residue was purified by column chromatography on silica gel, eluting with chloroform–methanol (14:1) to afford **22**, which was obtained as a white crystalline solid after trituration with methanol (235 mg, 76%): mp 116–118 °C; UV (MeOH) λ_{max} 223 (ϵ 36700) and 309 (6680) nm; IR (KBr) ν_{max} 3320, 1710, 1610, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.83 (1 H, m, $CHCH_2CH_2$), 1.93 (2 H, q, J 7.1 Hz, $CHCH_2CH_2$), 3.52 (2 H, t, J 5.3 Hz, D_2O exchange gives d, CH_2OH), 4.19 (2 H, t, J 7.0 Hz, CH_2N), 4.2–4.3 (2 H, ABX, J_{AB} 11.0 Hz, $J_{AX} = J_{BX}$ 5.6 Hz, CH_2OCO), 4.69 (1 H, t, J 5.2 Hz, D_2O exchangeable, OH), 6.43 (2 H, s, D_2O exchangeable, 2-NH_2), 7.5–7.9 (5 H, m, C_6H_5), 8.10 (1 H, s, 8-H), and 8.55 (1 H, s, 6-H). Anal. ($C_{17}H_{19}N_5O_3$) C, H, N.

(*R*,*S*)-2-Amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine Phosphate (23). To an ice-cooled solution of phosphorus oxychloride (0.10 mL, 1.1 mmol) in pyridine (2 mL) was added dropwise over 15 min a solution of **19** (0.78 g, 1.0 mmol) in pyridine (2 mL). The solution was stirred for a further 30 min at room temperature and was then added dropwise to a solution of $NaHCO_3$ (0.5 g, 6.0 mmol) in water (7 mL). The solvent was removed, the residue was taken up in 80% acetic acid (10 mL), and the solution was stirred at 70 °C for 25 min. The solvent was removed, and the residue was taken up in water and brought to pH 6 by addition of ammonia. The solution was extracted twice with chloroform, and the solvent was removed. The residue was purified by preparative high-pressure liquid chromatography on a C_{18} reverse-phase μBondapak column eluting with 3% methanol in ammonium acetate buffer (pH 4.5; 50 mM) to afford **23** as a hygroscopic white powder (85 mg, 25%): UV (H_2O) λ_{max} 220 (ϵ 26100), 241 (3860), and 303 (6350) nm; IR (KBr) ν_{max} 3410, 1660, 1620, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.57 (1 H, m, $CHCH_2CH_2$), 1.77 (2 H, m, $CHCH_2CH_2$), 3.37 (2 H, d, J 4.4 Hz, CH_2OH), 3.77 (2 H, t, J 5.6 Hz, CH_2OP), 4.12 (2 H, t, J 7.4 Hz, CH_2N), 6.48 (2 H, s, D_2O exchangeable, 2-NH_2), 8.08 (1 H, s, 8-H), and 8.54 (1 H, s, 6-H). Anal. ($C_{10}H_{16}N_5O_5P$·0.5NH_3·H_2O) H, N; C: calcd, 34.94; found, 35.53.

2-Amino-9-[4-hydroxy-3-(hydroxymethyl)but-1-yl]purine Cyclic Phosphate (24). To an ice-cooled solution of phosphorus oxychloride (93 μL, 1.0 mmol) in pyridine (2 mL) was added dropwise over 45 min a solution of **20** (0.46 g, 0.9 mmol) in pyridine (4 mL). The solution was stirred for a further 20 min at room temperature and was then added dropwise to a solution of $NaHCO_3$ (0.34 g, 4.0 mmol) in water (6 mL). The solvent was removed, the residue was taken up in 80% acetic acid (9 mL), and the solution was stirred at 70 °C for 25 min. The solvent was removed, and the residue was taken up in water and brought to pH 6 by addition of ammonia. The solution was extracted twice with chloroform, and the solvent was removed. The residue was purified by preparative high-pressure liquid chromatography on a C_{18} reverse-phase μBondapak column, eluting with 4% methanol in ammonium acetate buffer (pH 4.5, 50 mM) to afford **24** as a white powder (225 mg, 75%): UV (H_2O) λ_{max} 220 (ϵ 25600), 242 (3900), and 303 (6270) nm; IR (KBr) ν_{max} 2900–3200 (br), 1705, 1615, and 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.63 (1 H, m, $CHCH_2CH_2$), 1.74 (2 H, q, J 7.0 Hz, $CHCH_2CH_2$), 3.80 (2 H, q, J 9.2 Hz, 2 × H_{ax}), 3.98 (2 H, ddd, J 14.3, 10.9, and 3.5 Hz, 2 × H_{eq}), 4.08 (2 H, t, J 7.1 Hz, CH_2N), 6.51 (2 H, s, D_2O exchangeable, 2-NH_2), 8.10 (1 H, s, 8-H), and 8.56 (1 H, s, 6-H). Anal. ($C_{10}H_{14}N_5O_4P$·0.3NH_3·1.5H_2O) C, H, N.

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3′-Fluoro-2′,3′-dideoxy-5-chlorouridine: Most Selective Anti-HIV-1 Agent among a Series of New 2′- and 3′-Fluorinated 2′,3′-Dideoxynucleoside Analogues

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A series of 2′- and 3′-fluorinated 2′,3′-dideoxynucleosides and 3′-azido-2′,3′-dideoxynucleosides were synthesized and evaluated for their inhibitory activity against human immunodeficiency virus-1 (HIV-1) replication in MT-4 cells. Neither conversion of 3′-fluoro- or 3′-azido-2′,3′-dideoxyadenosine to the corresponding inosine derivatives nor 8-bromination of 2′,3′-dideoxyadenosine resulted in increased anti-HIV-1 activity. Nor did introduction of a 2′-fluorine in the erythro or threo configuration lead to improved anti-HIV-1 activity of the parent 2′,3′-dideoxynucleosides. 1-(2-Fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)cytosine and 1-(2-fluoro-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine were only marginally active. However, 3′-fluoro-2′,3′-dideoxyuridine (FddUrd) proved to be potent and a relatively nontoxic inhibitor of HIV-1. 5-Halogenated derivatives of FddUrd were prepared in attempts to further increase its anti-HIV potency and selectivity. Of these 5-halogenated derivatives, 3′-fluoro-2′,3′-dideoxy-5-chlorouridine emerged as the most selective inhibitor of HIV-1 replication. Its selectivity index was comparable to that of azidothymidine when evaluated under the same conditions.

The discovery of the human immunodeficiency virus (HIV) as the causative agent of AIDS[1,2] and the identification of HIV as a retrovirus have prompted the search for agents that would be able to block the HIV replication process. Our efforts have mainly focused on the design and synthesis of reverse transcriptase inhibitors.[3-6] 2′,3′-Dideoxynucleoside analogues (for a recent review see

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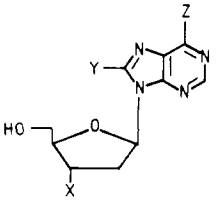
0022-2623/89/1832-1743$01.50/0

ref 7) have attracted considerable attention as anti-HIV compounds, and several congeners of this class are currently subject of clinical trials. 2′,3′-Dideoxyadenosine (ddAdo) (**3**) is markedly active against HIV,[8,9] but in vivo



	X	Y	Z
1	F	H	NH_2
2	N_3	H	NH_2
3	H	H	NH_2
4	F	H	OH
5	N_3	H	OH
6	N_3	Br	NH_2
7	H	Br	NH_2

it is deaminated rapidly to 2′,3′-dideoxyinosine which in vitro appears to be slightly less toxic than ddAdo.[10] Therefore, the inosine analogues **4** and **5**, which could be considered as the counterparts of 3′-azido-2′,3′-dideoxyadenosine[4] (**2**) and of 3′-fluoro-2′,3′-dideoxyadenosine[4] (**1**) were synthesized with the aim to reduce the toxicity of **2** and to increase the activity of **1**.

Since the introduction of a bulky bromine in the 8-position of purines enables nucleoside analogues to assume the syn conformation[11] and since 8-bromoadenosines are highly resistant to adenosine deaminase,[12] we decided to synthesize compounds **6** and **7**.

The most potent anti-HIV compound that has been reported thus far is 3′-fluoro-2′,3′-dideoxythymidine[13] (FddThd), and another promising congener, which is now entering clinical trials, is 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine[8] (D4T). Both features, the 3′-fluoro substituent and the 2′,3′-double bond, were combined, thus affording compound **10**.

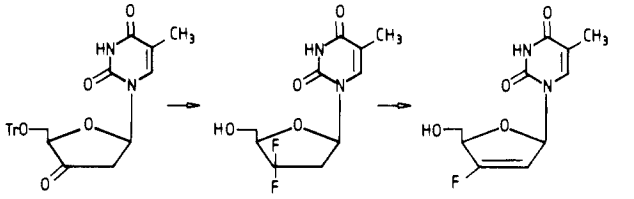
Since the discovery of 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)-5-iodouracil (FIAC) and its congeners as potent and selective anti-herpesvirus agents,[14,15] nucleoside chemists have kept an interest in the synthesis of 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)pyrimidine analogues. These compounds were deoxygenated at the 3′-position, which resulted in the preparation of **12a** and **14b**; **15a** was synthesized from **12a** by a new methodology[16] for conversion of thymidine to 5-methylcytidine analogues.

In addition to FddThd, 3′-fluoro-2′,3′-dideoxyuridine (FddUrd) is also a potent and selective anti-HIV compound.[13] In view of the low affinity of FddUrd for thymidine kinase, the enzyme required for the activation of the thymidine analogues, the 5-halogeno-substituted derivatives of FddUrd, **17a–c** and **24**, were synthesized. This rationale was based on our previous knowledge that introduction of an halogen atom at the C-5 position of 2′-deoxyuridine markedly increased the substrate affinity of these compounds for cytosol dThd kinase.[17]

The 3′-fluoro-2′,3′-dideoxypyrimidine series was extended to the analogues **17d**, **19**, and **21**. Finally, compound **26**, a 2′-regioisomer of FddThd, was also synthesized.

Chemistry

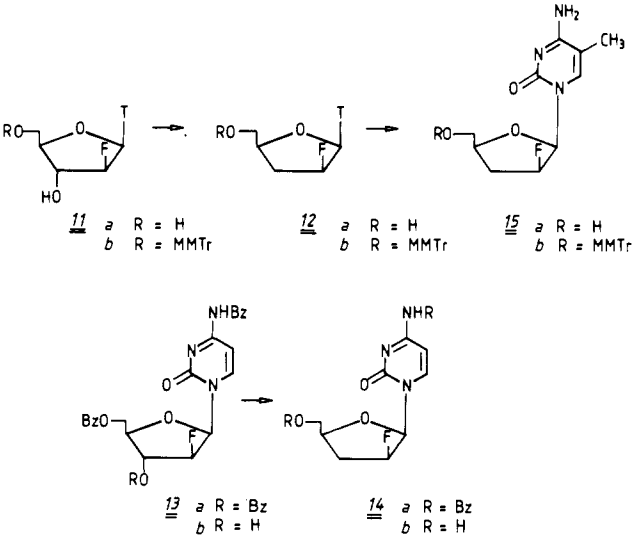
3′-Fluoro-2′,3′-dideoxyinosine (**4**) was synthesized in 70% yield from its adenosine counterpart[4] (**1**) by the action of adenosine deaminase. Bromination of C-8 of 3′-azido-2′,3′-dideoxyadenosine[3] (**2**) and 2′,3′-dideoxyadenosine[18] (**3**) with bromine in H_2O–MeOH at pH 4.3 (ref 19) afforded the 8-bromoadenosine analogues **6** and **7** in 92% and 83% yield, respectively. Reaction of the tritylated 3′-ketothymidine **8** with (diethylamido)sulfur trifluoride (DAST)



8 **9** **10**

in CH_2Cl_2 at reflux temperature overnight gave, after detritylation and purification, 3′,3′-difluoro-2′,3′-dideoxythymidine (**9**), as has been reported by Bergstrom.[20] Treatment of **9** with 3 equiv of sodium methanolate in anhydrous dimethylformamide for 30 min at room temperature yielded 62% of the 1-(3-fluoro-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (**10**) as a foam.

The 5′-position of 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)thymine[21] (**11a**) was protected by reaction with



11 a R = H, b R = MMTr **12** a R = H, b R = MMTr **15** a R = H, b R = MMTr

13 a R = Bz, b R = H **14** a R = Bz, b R = H

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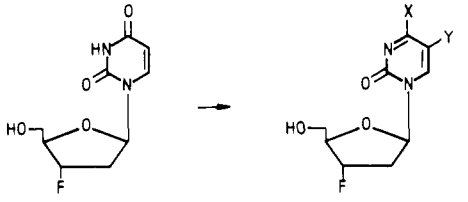
monomethoxytrityl chloride to yield **11b**. Deoxygenation at the 3'-position was obtained by a classical reaction sequence:[22] acylation with phenyl chlorothionocarbonate, followed by treatment of the resulting oil with 1.6 equiv of tri-*n*-butyltin hydride in toluene at 75 °C and finally detritylation with 80% acetic acid at 60 °C for 1 h. 1-(2-Fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (**12a**) was obtained from **11b** in 57% crystalline yield. The cytidine analogue **14b** was prepared starting from perbenzoylated 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)cytosine[23] (**13a**), which was selectively 3'-deacylated with ammonia in dioxane, affording **13b** in 30% yield. Acylation with phenyl chlorothionocarbonate followed by radicalar reduction with tri-*n*-butyltin hydride afforded 70% of **14a**, which was treated with ammonia in methanol to give 1-(2-fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)cytosine (**14b**) in 94% yield. Crystallization occurred after conversion of the compound to its hydrochloride salt.

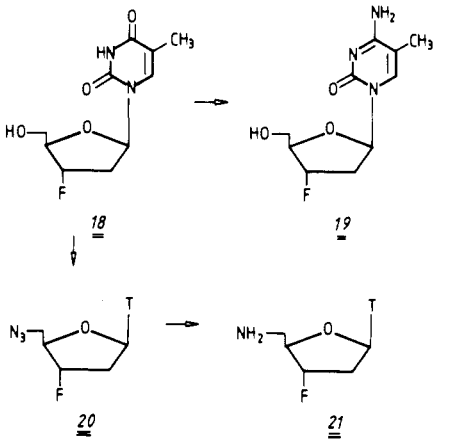
Conversion of the thymidine to the 5-methylcytidine analogue was achieved by using the trifluoromethanesulfonyl moiety as a leaving group.[16] Therefore, the 5'-position of **12a** was first protected with a monomethoxytrityl group to yield **12b** (70%), which was dissolved in dichloroethane–pyridine (5:1) and cooled to 0 °C. Then 3 equiv of trifluoromethanesulfonic anhydride was added dropwise. After 4 h at room temperature, the mixture was poured into a saturated solution of ammonia in MeOH, yielding 69% **15b**. This was followed by detritylation with 80% acetic acid to afford **15a** in 74% yield.

Reaction of 3'-fluoro-2',3'-dideoxyuridine (FddUrd, **16a**)[24] with *N*-bromosuccinimide (NBS) in glacial acetic acid[25] for 30 min at reflux temperature gave a mixture of



16	X	Y
17a	OH	Cl
17b	OH	Br
17c	OH	I
17d	OCH_3	H

3'-fluoro-2',3'-dideoxy-5-bromouridine (FddBrUrd, **17b**) and its 5'-acylated analogue. The former was isolated in 45% yield. Therefore, bromination of the 5-position with bromine in pyridine[26] is recommended. After 3 h at room temperature, crystalline **17b** was obtained in 89% yield. Chlorination of the 5-position was performed with *N*-chlorosuccinimide (NCS).[25] Therefore, the 5'-hydroxyl group was first protected by acetylation with acetic anhydride in pyridine. The chlorination was first tried in acetic acid. Reaction for 30 min at 110 °C and subsequent deacylation gave only 20% yield of 3'-fluoro-2',3'-dideoxy-5-chlorouridine (FddClUrd, **17a**). On the other hand, reaction of 5'-acylated **16** with NCS in anhydrous pyridine at 100 °C for 30 min gave a single reaction product on TLC ($CHCl_3$–MeOh 9:1) and deacylation yielded 59% of crystalline **17a** (starting from **16**). Iodination of **16** with 1.5 equiv of iodine monochloride in methanol[27] for 3 h at reflux temperature gave 66% of 3'-fluoro-2',3'-dideoxy-5-iodouridine (**17c**). The O^4-methylated analogue was prepared by the method of Matsuda et al.[28] Tritylated FddUrd[24] (**16b**) was treated with $POCl_3$/*N*-methylimidazole in acetonitrile, followed by addition of methanol and triethylamine. On detritylation with 80% acetic acid considerable loss of the O^4-methyl group was noted, yielding 25% of 1-(3-fluoro-2,3-dideoxy-β-D-ribofuranosyl)-4-methoxy-pyrimidin-2(1*H*)-one (**17d**). To convert FddThd to its 5-methylcytidine analogue **19**, the same strategy was followed as for the



synthesis of **15a**. Treatment of 5'-protected FddThd with trifluoromethanesulfonic anhydride gave an unstable intermediate, which was converted to 3'-fluoro-2',3'-dideoxy-5-methylcytidine (**19**) by reaction with ammonia in methanol.

Synthesis of 3'-fluoro-5'-amino-2',3',5'-trideoxythymidine (**21**) was straightforward. Mesylation of FddThd, followed by nucleophilic displacement with sodium azide, gave the 5'-azido analogue **20**, which was easily reduced with triphenylphosphine and ammonia[29] to yield **21**. The latter was isolated as its hydrochloride salt.

2'-Deoxy-5-fluorouridine **22** was used as starting material for the synthesis of **24**. After protection of the 5'-hydroxyl function with a monomethoxytrityl group, the configuration in the 3'-position was inverted as described.[30] Treatment of **23** with 2 equiv of DAST in a mixture of dichloromethane–THF (9:1)[31] and detritylation afforded 3'-fluoro-2',3'-dideoxy-5-fluorouridine (**24**), which proved difficult to purify. Acetylation of the 5'-position, chromatographic purification, and finally deacylation gave **24** in 35% yield (from **23**). Reaction of 5'-*O*-(monomethoxytrityl)-1-(2,3-anhydro-β-D-lyxofuranosyl)thymine with

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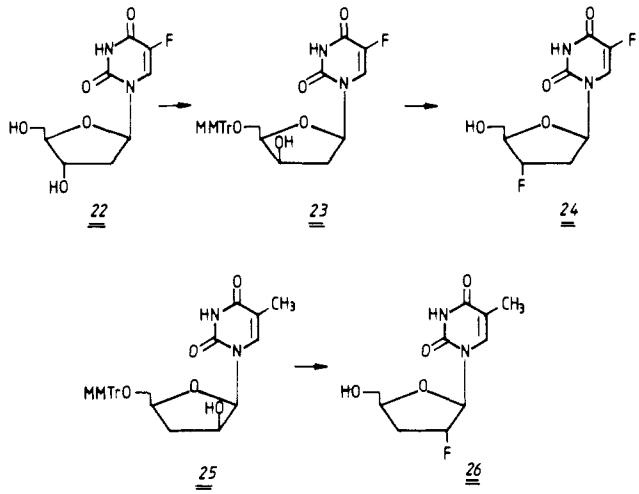
(31) This solvent mixture was reported as being the best combination for the synthesis of fluorinated nucleosides with DAST. Cf. Sterzycki, R.; Mansuri, M.; Brankovan, V.; Buroker, R.; Ghazzouli, I.; Hitchock, M.; Sommadossi, J.-P.; Martin, J. C. *Nucleosides Nucleotides*, in press. However, we didn't notice much difference when using only dichloromethane as a solvent. We feel, however, that the quality of DAST can influence the yield to a great extent.



lithium triethylborohydride gave the 1-(3-deoxy-β-D-*threo*-pentofuranosyl)thymine analogue **25** as reported by Webb et al.[32] Reaction of **25** with 2 equiv of DAST in dichloroethane and detritylation afforded 1-(2-fluoro-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine (**26**) in 57% yield. 3'-Azido-2',3'-dideoxyinosine (**5**) was synthesized according to ref 33.

Antiviral Activity

The anti-HIV-1 activity and cytotoxicity of the 2',3'-dideoxynucleoside analogues are shown in Table I. No improvement in selectivity index (SI) was noted when compounds **1** and **2** were converted to their inosine counterparts **4** and **5**. In fact, the latter compounds were less active than the corresponding adenosine analogues. Bromination at the 8-position (**7**) annihilated the antiretrovirus activity of ddAdo (**3**).[8] Similarly, compound **6** was totally inactive as an anti-HIV-1 agent. Thus, introduction of a bulky substituent in the 8-position of the purine ring appears incompatible with anti-HIV-1 activity. Although D4T[8,34] and FddThd[13] are both excellent antiretrovirus agents, combination of their structural features, as in **10**, afforded only moderate activity (ED_{50} = 11 μM).

The pyrimidine 2',3'-dideoxynucleoside analogues with a 2'-fluorine in the "up" configuration do not hold great promise as anti-HIV agents: the thymidine (**12a**) and 5-methylcytidine (**15a**) analogues were totally devoid of activity, whereas the cytidine derivative (**14b**) proved only moderately active (ED_{50} = 9.8 μM). Halogenation at the 5-position of FddUrd[24] yielded products **17a–c** and **24**; **17a–c** had about 10-fold lower potency than FddUrd, whereas **24** was virtually inactive. Likewise the O^4-methyl analogue of FddUrd (**17d**) was only marginally active.

The most important feature was the very low cytotoxicity of FddClUrd (**17a**), which gave this product a selectivity index of 1408. Thus, FddClUrd was about as selective in its anti-HIV activity as AZT (SI = 1600, when run in parallel), but as FddClUrd is less toxic than AZT, it may be considered as a potential candidate for AIDS therapy.[35] FddClUrd needs to be further explored for pharmacological behavior,[36,37] metabolic fate, and toxicity in different cell systems (including bone marrow cell colony formation).

Table I. Comparative Potency and Selectivity of 2',3'-Dideoxynucleoside Analogues as Inhibitors of HIV-1 Replication in MT-4 Cells

compd	ED_{50}[a], μM	CD_{50}[b], μM	SI[c]
4	484	500	1
5	>8	15	<2
6	>500	409	<1
7	484	500	1
10	11	240	22
12a	>500	>500	
14b	9.8	117	12
15a	>500	>500	
17a	0.38	535	1408
17b	0.41	24	59
17c	0.16	2.17	13.6
17d	46	348	7.6
19	1.7	7.7	4.5
21	>500	>500	
24	>20	40	<2
26	53	>500	>9.4
FddAdo[4]	50	557	11.1
AzddAdo[4]	5	10	2
ddAdo[8]	6.4	890	139
FddUrd[13]	0.04	16	400
FddThd[13]	0.001	0.197	197
AZT	0.003	4.8	1600

[a] Effective dose of compound, achieving 50% protection of MT-4 cells against the cytopathic effect of HIV. [b] Cytotoxic dose of compound, required to reduce the viability of normal uninfected MT-4 cells by 50%. [c] Selectivity index or ratio of CD_{50} to ED_{50}.

An effort to reduce the cytotoxicity of FddThd, without affecting its activity, by converting the compound to its 5-methylcytidine derivative **19** was not successful: the SI of **19** was even lower than that of FddThd. Substitution of the 5'-hydroxyl group of FddThd by an amino group led to a totally inactive product (**21**). The inactivity of **21** may be due to its lack of phosphorylation by cellular kinases. The 2'-regioisomer of FddThd (**26**) showed only minimal anti-HIV-1 activity.

Experimental Section

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 257 spectrophotometer on samples in potassium bromide disks at 1.5%. Ultraviolet spectra were recorded with a Beckman UV 5230 spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as integral standard (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal). Electron-impact mass spectra (70 eV) were recorded on a AEI-MS12 mass spectrometer: B = base and S = sugar. Elemental analyses were carried out by Dr. Rozdzinksi at the Institut für Organische Chemie in Stuttgart. Precoated Merck silica gel F254 plates were used for TLC. Column chromatography was performed on Merck silica gel (0.063–0.200 mm). Anhydrous *N,N*-dimethylformamide was obtained by distillation with benzene followed by distillation in vacuo. Pyridine was dried by distillation after it had been refluxed on potassium hydroxide for 24 h. Dichloromethane and dichloroethane were dried with calcium chloride and distilled on phosphorus pentoxide. Tetrahydrofuran was refluxed for 10 h on lithium aluminum hydride and distilled.

3'-Fluoro-2',3'-dideoxyinosine (4). A mixture of 100 mg (0.39 mmol) of 3'-fluoro-2',3'-dideoxyadenosine[4] (**1**) and 0.5 mL of a suspension of adenosine deaminase in 100 mL of 0.05 M phosphate buffer, pH 7.5, was incubated for 30 min at 30 °C. The reaction mixture was concentrated, the residue was diluted with 10 mL of H_2O, and the crystalline precipitate was collected and re-

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crystallized from H_2O, yielding 70 mg (0.27 mmol, 70%) of the title compound 4: mp 147 °C (softens); MS *m/e* 254 (M^+), 136 (B + H, 100), 119 (S); UV (MeOH) λ_{max} 250 nm (ϵ 12 500); ^1H NMR (DMSO-d_6) δ 2.65 (m, H-2', H-2''), 3.62 (m, H-5', H-5''), 4.26 (dt, $J_{4',F}$ = 26 Hz, H-4'), 5.45 (dm, $J_{3',F}$ = 54.5 Hz, H-3'), 6.37 (dd, J = 6.2 and 8.5 Hz, H-1'), 8.09 (s, H-8), 8.30 (s, H-2) ppm. Anal. ($C_{10}H_{11}FN_4O_3 \cdot H_2O$) C, H, N.

8-Bromo-3'-azido-2',3'-dideoxyadenosine (6). A solution of 170 mg (0.61 mmol) of 3'-azido-2',3'-dideoxyadenosine[3] (**2**) in 5 mL of methanol was diluted with 3 mL of a 1 M acetate buffer, pH 4.3, and 0.06 mL (1.2 mmol) of bromine was added. The reaction mixture was stirred for 3 h at room temperature, evaporated, and purified by column chromatography ($CHCl_3$–MeOH 98:2). The title compound was crystallized from MeOH, yielding 200 mg (0.56 mmol, 92%) of **6**: mp 159–160 °C; MS *m/e* 354 (M^+), 282 (M – CHO – N_3), 213 (B + H, 100), 142 (S); IR (KBr) 2100 cm^{-1} (N_3); UV (MeOH) λ_{max} 265 nm (ϵ 16 200); ^1H NMR ($CDCl_3$) δ 2.23–2.49 (ddd, H-2'), 2.99–3.36 (ddd, H-2''), 3.73 (dd, H-5'), 4.04 (dd, H-5''), 4.23 (q, H-4'), 4.65 (m, H-3'), 6.25 (br s, NH_2), 6.35 (dd, J = 5.5 and 9.2 Hz, H-1'), 8.25 (s, H-2) ppm. Anal. ($C_{10}H_{11}BrN_8O_2$) C, H, N.

8-Bromo-2',3'-dideoxyadenosine (7). A solution of 120 mg (0.5 mmol) of 2',3'-dideoxyadenosine[18] (**3**) and 0.05 mL (1 mmol) of bromine in methanol (5 mL)–1 M acetate buffer, pH 4.3 (3 mL), was kept for 8 h at room temperature. The reaction mixture was evaporated and purified by column chromatography ($CHCl_3$–MeOH 98:2) to yield 130 mg (0.41 mmol, 83%) of the title compound **7**, which was crystallized from MeOH: mp 164 °C (softens); MS *m/e* 313 (M^+), 213 (B + H, 100), 101 (S); UV (MeOH) λ_{max} 265 nm (ϵ 17 100); ^1H NMR ($CDCl_3$) δ 2.14–2.95 (m, H-2', H-2'', H-3', H-3''), 3.59 (dd, H-5'), 4.04 (dd, H-5''), 4.37 (m, H-4'), 5.72 (br s, NH_2), 6.20 (m, H-1' and 5'-OH), 8.28 (s, H-2) ppm. Anal. ($C_{10}H_{12}BrN_5O_2$) C, H, N.

1-(3-Fluoro-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (10). A mixture of 103 mg (0.4 mmol) of 3',3'-difluoro-2',3'-dideoxythymidine[20] (**9**) and 65 mg (1.2 mmol) of sodium methanolate in 5 mL of anhydrous dimethylformamide was kept for 30 min at room temperature. The reaction mixture was poured into 50 mL of methanol, neutralized with Dowex 50 WX8 (H^+), filtered, and evaporated. The residual oil was purified by preparative TLC ($C_2H_4Cl_2$–MeOH 92:8) yielding 58 mg (0.25 mmol, 62%) of **10** as a foam: MS *m/e* 242 (M^+), 126 (B + H), 117 (S); UV (MeOH) λ_{max} 265 nm (ϵ 9600); ^1H NMR ($CDCl_3$) δ 1.84 (s, CH_3), 3.88 (m, H-5', H-5''), 4.70 (m, H-4'), 5.27 (m, H-2'), 7.01 (m, H-1'), 7.71 (s, H-6) ppm; ^1H NMR (DMSO-d_6) δ 1.75 (d, CH_3), 3.63 (m, H-5', H-5''), 4.73 (m, H-4'), 5.31 (m, 5'-OH), 5.60 (m, H-2'), 6.81 (m, H-1'), 7.88 (d, H-6) ppm; ^{13}C NMR ($CDCl_3$) δ 12.0 (CH_3), 60.4 (C-5'), 79.7 (C-4', J = 24.4 Hz), 85.5 (C-1', J = 15.9 Hz), 99.6 (C-2', J = 11.0 Hz), 110.7 (C-5), 136.7 (C-6), 150.6 (C-2), 161.5 (C-3', J = 286.9 Hz), 164.0 (C-4) ppm. Anal. ($C_{10}H_{11}N_2O_4F \cdot 0.3C_2H_4Cl_2$) C, H, N.

1-(2-Fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine (12a). To a mixture of 2.58 g (5 mmol) of 1-[5-*O*-(monomethoxytrityl)-2-fluoro-2-deoxy-β-D-arabinofuranosyl]thymine[21] (**11b**) and 1.35 g (11 mmol) of (dimethylamino)pyridine in 100 mL of acetonitrile was added 1.1 mL (6 mmol) of phenyl chlorothionocarbonate. The reaction mixture was stirred for 16 h at room temperature and evaporated. The residue was dissolved in 150 mL of EtOAc and washed with H_2O (100 mL), 0.1 N HCl (100 mL), 5% $NaHCO_3$ (100 mL), and H_2O (100 mL), dried, and evaporated. The residual oil was dissolved in 100 mL of toluene and a spatula point of 2,2'-azobis(2-methylpropionitrile) and 2.2 mL (8 mmol) of tri-*n*-butyltin hydride was added. The reaction was heated for 2 h at 75 °C and evaporated. TLC analysis revealed mainly one compound ($CHCl_3$–MeOH 95:5, R_f 0.64), which was purified by column chromatography ($CHCl_3$–MeOH 97:3) and detritylated with 80% acetic acid (100 mL) at 60 °C for 1 h. Evaporation, coevaporation with toluene and chromatographic purification ($CHCl_3$–MeOH 95:5) gave 700 mg (2.87 mmol, 57%) of the title compound **12a** as crystalline material: mp 163–164 °C (MeOH–Et_2O); UV (MeOH) λ_{max} 265 nm (ϵ 10 400); MS *m/e* 244 (M^+), 126 (B + H, 100), 119 (S); ^1H NMR (pyridine-d_5) δ 1.84 (s, CH_3) 2.50 (m, H-3', H-3''), 4.05 (m, H-5', H-5''), 4.40 (m, H-4'), 5.83 (m, $^1/_2$ of H-2', the other part is hidden by HOD at 5.20 ppm), 6.47 (dd, J = 3.5 Hz, $J_{1',F}$ = 20.9 Hz, H-1'), 7.93 (s, H-6) ppm; ^{13}C NMR (pyridine-d_5) δ 11.5 ($CHCl_3$), 32.2 (d, J = 20.7 Hz, C-3'), 62.5 (C-5'), 77.6 (C-4'), 84.9 (d, J = 17.1 Hz, C-1'), 91.0 (d, J = 188.0 Hz, C-2'), 108.6 (C-5), 136.6 (d, J = 2.4 Hz, C-6), 150.6 (C-2), 164.2 (C-4) ppm. Anal. ($C_{10}H_{13}FN_2O_4$) C, H, N.

1-(2-Fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)cytosine (14b). (a). A solution of 1.67 g (3.3 mmol) of N^4-benzoyl-1-(3,5-*O*-dibenzoyl-2-fluoro-2-deoxy-β-D-arabinofuranosyl)cytosine[23] (**13a**) in 100 mL of dioxane containing 20 mL of concentrated ammonia (32%) was kept for 2 days at 4 °C. TLC analysis of the reaction mixture ($CHCl_3$–MeOH 90:10) revealed three new compounds. After evaporation, the residual oil was purified by column chromatography [(1) $CHCl_3$, (2) $CHCl_3$–MeOH 98:2, (3) $CHCl_3$–MeOH 95:5], yielding 450 mg (1 mmol, 30%) of N^4-benzoyl-1-(5-*O*-benzoyl-2-fluoro-2-deoxy-β-D-arabinofuranosyl)-cytosine (**13b**). UV (MeOH) λ_{max} 261 nm (ϵ 22 100); ^1H NMR ($CDCl_3$) δ 4.37–4.70 (m, 4 H, H-3', H-4', H-5', H-5''), 5.39 (dm, 1 H, $J_{2',F}$ = 50.3 Hz, H-2'), 6.43 (dd, 1 H, $J_{1',F}$ = 20.2 Hz, H-1'), 7.20–8.12 (m, 12 H, H-5, H-6, 2 x benzoyl) ppm.

(b). The same modus operandi was used as for the synthesis of the thymine analogue. The reaction of **13b** with phenyl chlorothionocarbonate was finished after 45 min [yield: 60% after column chromatography ($CHCl_3$–MeOH 98:2)]. The radicalar reduction with tri-*n*-butyltin hydride was done by heating at 75 °C overnight followed by a chromatographic purification ($CHCl_3$–MeOH 99:1) (yield 70%). Final debenzoylation with methanol, saturated with ammonia, overnight at room temperature and chromatographic purification ($CHCl_3$–MeOH 8:2) yielded 80 mg (0.35 mmol, 94%) of 1-(2-fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)cytosine (**14b**). The compound was identified after conversion into its hydrochloride salt. Therefore, the compound was dissolved in methanol, 1 equiv of HCl dissolved in methanol was added and the salt was precipitated by addition of Et_2O: mp >230 °C dec; UV (H_2O) λ_{max} 277 nm (ϵ 11 300); MS *m/e* 229 (M^+), 112 (B + H_2, 100), 111 (B + H); ^1H NMR (pyridine-d_5) δ 2.43 (m, H-3', H-3''), 4.02 (m, H-5', H-5''), 4.45 (m, H-4'), H-2' is hidden by HOD, 6.14 (d, J = 7 Hz, H-5), 6.47 (dd, J = 3.3 Hz, $J_{1',F}$ = 18 Hz, H-1'), 8.11 (d, J = 7 Hz, H-6) ppm; ^{13}C NMR (pyridine-d_5) δ 33.2 (d, J = 19.5 Hz, C-3'), 63.5 (C-5'), 78.5 (C-4'), 86.8 (d, J = 15.9 Hz, C-1'), 91.3 (d, J = 187 Hz, C-2'), 93.8 (C-5), 142.4 (d, J = 2.4 Hz, C-6) 154.6 (C-2), 165.4 (C-4) ppm. Anal. ($C_9H_{12}FN_3O_3 \cdot HCl$) C, H, N.

1-(2-Fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)-5-methylcytidine (15a). Monomethoxytritylation of 490 mg (2 mmol) of **12a** with 1.3 equiv of 4-anisylchlorodiphenylmethane in pyridine at room temperature overnight gave 725 mg (1.4 mmol, 70%) of **12b**. This was dissolved in 18 mL of 1,2-dichloroethane–pyridine (5:1) and cooled on an ice bath. A freshly prepared 10% stock solution of trifluoromethanesulfonic anhydride in dichloroethane (8 mL, 4.5 mmol) was added dropwise and the reaction mixture was left at room temperature for 4 h when TLC ($CHCl_3$–MeOH 95:5) indicated complete conversion to a product with zero mobility. The mixture was poured into 100 mL of MeOH saturated with NH_3 and left at room temperature overnight. Evaporation and chromatographic purification ($CHCl_3$–MeOH 96:4) yielded 500 mg (0.97 mmol, 69%) of an orange foam, **15b**: UV (MeOH) λ_{max} 276 nm. Detritylation with 80% acetic acid at 60 °C for 40 min, followed by evaporation, coevaporation with toluene, and purification on 30 g of silica gel, yielded 180 mg (0.74 mmol, 76%) of a pale yellow oil. The title compound **15a** was crystallized as its hydrochloride salt from MeOH–acetone: mp (HCl) 220–221 °C; UV (H_2O, pH 7) λ_{max} 278 (ϵ = 9400), (MeOH) λ_{max} 289 (ϵ = 11 650); MS *m/e* 234 (M^+), 125 (B + H, 100); ^1H NMR (DMSO-d_6) δ 1.90 (s, CH_3), 2.67–3.45 (m, H-3'), 3.58 (d, J = 5 Hz, H-5'), 4.08 (m, H-4'), 4.58 (br, 5'-OH), 5.26 (m, $J_{2',F}$ = 55.6 Hz, H-2'), 5.96 (dd, $J_{1',F}$ = 18 Hz, H-1'), 7.42 (br s, NH_2), 7.62 (s, H-6) ppm; ^{13}C NMR (DMSO-d_6) δ 13.2 (CH_3), 32.7 (C-3', J = 19.6 Hz), 62.8 (C-5'), 77.6 (C-4'), 85.7 (C-1', J = 15.9 Hz), 91.1 (C-2', J = 186.8 Hz), 100.8 (C-5), 139.4 (C-6, J = 2.5 Hz), 154.3 (C-2), 164.9 (C-4) ppm. Anal. ($C_{10}H_{14}FN_3O_3 \cdot HCl$) C, H, N.

3'-Fluoro-2',3'-dideoxy-5-chlorouridine (17a). Acylation of 380 mg (1.65 mmol) of 3'-fluorodideoxyuridine[24] (**16**) was performed with acetic anhydride in pyridine for 2 h at room temperature. The reaction mixture was evaporated and coevaporated twice with toluene to remove excess anhydride and acetic acid. The residue was taken up in 20 mL of anhydrous pyridine, 1.5 equiv of chlorosuccinimide (332 mg, 2.5 mmol) was added and

the mixture was heated for 30 min at 100 °C (coloring dark brown). Evaporation yielded an oil which was treated overnight at room temperature with a saturated solution of ammonia in methanol. Evaporation and purification on 40 g of silica gel ($CHCl_3$–MeOH 97:3) yielded 257 mg (0.97 mmol, 59%) of **17a**: mp (acetone–hexane) 181 °C dec; UV (MeOH) λ_{max} 276.5 nm (ϵ 8650); MS *m/e* 264 (M^+), 147 (B + H_2), 146 (B + H), 119 (S, 100), 99 (S – HF); ^{1}H NMR (DMSO-d_6) δ 2.01–2.63 (m, H-2′, H-2″), 3.65 (m, H-5′, H-5″), 4.21 (dt, H-4′, J = 3.5 Hz, $J_{4',F}$ = 27.3 Hz), 5.30 (t, 5′-OH, exchangeable D_2O), 5.31 (dd, H-3′, J = 4 Hz, $J_{3',F}$ = 54.4 Hz), 6.18 (t, H-1′, J = 7.2 Hz), 8.24 (s, H-6), 11.80 (br s, N-H, exchangeable D_2O) ppm; ^{13}C NMR (DMSO-d_6) δ 37.7 (C-2′, J = 20.8 Hz), 60.8 (C-5′, J = 9.8 Hz), 84.8 (C-1′), 85.3 (C-4′, 23.2 Hz), 94.7 (C-3′, J = 174.6 Hz), 107.6 (C-5), 137.5 (C-6), 149.5 (C-2), 158.9 (C-4) ppm. Anal. ($C_9H_{10}N_2O_4FCl$) C, H, N.

3′-Fluoro-2′,3′-dideoxy-5-bromouridine (17b). Method A. To a solution of 230 mg (1 mmol) of **16** in 15 mL of glacial acetic acid was added 270 mg (1.5 mmol) of *N*-bromosuccinimide and the mixture was refluxed for 30 min. Evaporation and coevaporation with toluene gave an oil which was purified on 30 g of silica, yielding 138 mg (0.45 mmol, 45%) of **17b**.

Method B. To a solution of 850 mg (3.7 mmol) of 3′-fluorodideoxyuridine[24] (**16**) in 25 mL of anhydrous pyridine was added a solution of 0.3 mL (5 mmol) of bromine in 3 mL carbon tetrachloride. The reaction was stirred for 2 h at room temperature when TLC indicated complete conversion. Evaporation and chromatographic purification afforded 1.015 g (3.29 mmol, 89%) of **17b**: mp (MeOH–EtOAc) 154–155 °C dec; UV (MeOH) λ_{max} 278 nm (ϵ 8650); MS *m/e* 308 (M^+), 191 (B + H_2), 190 (B + H), 119 (S, 100), 99 (S – HF); ^{1}H NMR (DMSO-d_6) δ 2.27–2.60 (m, H-2′, H-2″), 3.64 (m, H-5′, H-5″), 4.20 (dt, H-4′, $J_{4',F}$ = 26.3 Hz), 5.30 (t, 5′-OH), 5.31 (dm, H-3′, $J_{3',F}$ = 53.6 Hz), 6.17 (dt, H-1′), 8.32 (s, H-6), 11.81 (br s, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 37.9 (C-2′, J = 19.5 Hz), 60.8 (C-5′, J = 12.2 Hz), 84.8 (C-1′), 85.3 (C-4′, J = 23.2 Hz), 91.3 (C-5), 94.8 (C-3′, J = 174.6 Hz), 140.1 (C-6), 149.9 (C-2), 159.1 (C-4) ppm. Anal. ($C_9H_{10}N_2O_4FBr$) C, H, N.

3′-Fluoro-2′,3′-dideoxy-5-iodouridine (17c). To a solution of 233 mg (1 mmol) of 3′-fluoro-2′,3′-dideoxyuridine[24] (**16**) in 20 mL of methanol was added 10 mL (1.5 equiv) of a stock solution of iodine monochloride in methanol and the mixture was heated at reflux temperature for 3 h. Evaporation and coevaporation with methanol and water (3×) gave an oil which was purified on 20 g of silica ($CHCl_3$–MeOH 97:3), yielding 236 mg (0.66 mmol, 66%) of the title compound, which was crystallized from MeOH–EtOAc: mp 159–160 °C dec; UV (MeOH) λ_{max} 284 nm (br max) (ϵ 7200); MS *m/e* 356 (M^+), 238 (B + H, 100), 119 (S), 99 (S – HF); ^{1}H NMR (DMSO-d_6) δ 2.06–2.63 (m, H-2′, H-2″), 3.65 (m, H-5′, H-5″), 4.19 (dt, H-4′, $J_{4',F}$ = 27.3 Hz), 5.27 (t, 5′-OH), 5.29 (dm, H-3′, $J_{3',F}$ = 53.9 Hz), 6.16 (dt, H-1′), 8.34 (s, H-6), 11.69 (br s, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 37.8 (C-2′, J = 20.8 Hz), 60.8 (C-5′, J = 9.8 Hz), 69.9 (C-5), 84.6 (C-1′), 85.2 (C-4′, J = 23.2 Hz), 94.8 (C-3′, J = 173.3 Hz), 144.8 (C-6), 150.1 (C-2), 160.4 (C-4) ppm. Anal. ($C_9H_{10}N_2O_4FI$) C, H, N.

1-(3-Fluoro-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-4-methoxypyrimidin-2(1*H*)-one (17d). To a mixture of 0.84 mL (9 mmol) of phosphoryl chloride and 2.4 mL (30 mmol) of 1-methylimidazole in 60 mL of acetonitrile at 0 °C was added 1.5 g (2.97 mmol) of 5′-monomethoxytritylated FddUrd. After 4 h at room temperature, 6 mL of anhydrous MeOH and 4 mL of anhydrous triethylamine were added and the mixture was stirred for 20 h at room temperature. Evaporation yielded on oil, which was dissolved in $CHCl_3$ and washed twice with a saturated solution of $NaHCO_3$. Evaporation gave a foam, which was treated with 100 mL of 80% acetic acid at 60 °C for 40 min. After evaporation, the residue was purified twice on silica gel, yielding 180 mg (0.73 mmol, 25%) of **17d**, which crystallized from acetone–hexane: mp 137–138 °C; UV (MeOH) λ_{max} 277 (ϵ 5800); MS *m/e* 244 (M^+), 127 (B + 2H, 100), 126 (B + H), 119 (S); ^{1}H NMR ($CDCl_3$) δ 1.87–2.93 (m, H-2′, H-2″), 3.72 (s, OCH_3), 3.88 (d, H-5′, H-5″), 4.37 (dm, H-4′, $J_{4',F}$ = 26.8 Hz), 5.32 (dm, H-3′, $J_{3',F}$ = 54.0 Hz), 5.30 (br s, 5′-OH), 5.89 (d, H-5, J = 7.5 Hz), 6.36 (dd, H-1′, J = 5.7 Hz, $J_{1',F}$ = 9 Hz), 8.20 (d, H-6, J = 7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 39.3 (C-2′, J = 20.7 Hz), 54.1 (OCH_3), 61.3 (C-5′, J = 11 Hz), 86.1 (C-4′, J = 23.2 Hz), 87.4 (C-1′), 94.8 (C-3′, J = 177 Hz), 95.7 (C-5), 143.4 (C-6), 155.8 (C-2), 171.5 (C-4) ppm. Anal. ($C_{10}H_{13}FN_2O_4$) C, H, N.

A substantial amount (205 mg, 0.9 mmol, 30%) of the starting material (FddUrd) was recovered from the reaction mixture.

3′-Fluoro-2′,3′-dideoxy-5-methylcytidine (19). The same strategy was followed as for the synthesis of (**15a**). Starting from 650 mg (1.26 mmol) of 5′-monomethoxytritylated FddThd, 430 mg (0.83 mmol, 66%) of the tritylated 5-methylcytidine analogue was isolated. Heating the reddish-brown foam with 50 mL of 80% acetic acid at 60 °C for 45 min gave **19**, which was purified twice on silica gel and crystallized from methanol–diethyl ether as its hydrochloride salt: yield 112 mg (0.4 mmol, 31% overall); mp (HCl) 173–174 °C dec; UV (H_2O, pH 7) λ_{max} 278 (ϵ 8200); MS *m/e* 243 (M^+), 126 (B + 2H), 125 (B + H, 100); ^{1}H NMR (DMSO-d_6) δ 1.88 (s, CH_3) 2.20–2.50 (m, H-2′), 2.95–3.25 (m, H-2″), 3.62 (d, J = 4 Hz, H-5′, H-5″), 4.15 (dt, J = 4 Hz, $J_{4',F}$ = 27.7 Hz, H-4′), 4.20 (br s, 5′-OH), 5.29 (dd, J = 4 Hz, $J_{3',F}$ = 54.5 Hz, H-3′), 6.25 (dd, J = 5.7 Hz and 9.2 Hz, H-1′), 7.25 (br s, NH_2), 7.69 (s, H-6) ppm; ^{13}C NMR (DMSO-d_6) δ 13.0 (CH_3, J = 4.9 Hz), 37.7 (C-2′, J = 19.5 Hz), 60.9 (C-5′, J = 11.0 Hz), 84.9 (C-4′, J = 23.2 Hz), 85.1 (C-1′), 95.3 (C-3′, J = 174.6 Hz), 101.8 (C-5), 138.5 (C-6), 154.3 (C-2), 164.7 (C-4) ppm. Anal. ($C_{10}H_{14}FN_3O_3$·HCl) C, H, N.

3′-Fluoro-5′-amino-2′,3′,5′-trideoxythymidine (21). (a). After coevaporating twice with dry pyridine, 560 mg (2.29 mmol) of FddThd[3] (**18**) was dissolved in 20 mL of anhydrous pyridine and cooled on an ice bath. Methanesulfonyl chloride (0.5 mL, 6.5 mmol) was added and TLC ($CHCl_3$–MeOH 9:1) indicated complete reaction after 2 h at 0 °C. After evaporation, the oil was dissolved in EtOAc and washed with a saturated solution of $NaHCO_3$ (2×) and with brine. The organic phase was dried, evaporated, and dissolved in 40 mL of DMF to which 650 mg (10 mmol) of NaN_3 was added. The reaction mixture was heated for 90 min at 80 °C and evaporated in vacuo. The residue was dissolved in EtOAc and washed with a $NaHCO_3$ solution (2×) and with brine. Purification on silica gel ($CHCl_3$–MeOH 98:2) yielded 530 mg (1.97 mmol, 86%) of 3′-fluoro-5′-azido-2′,3′,5′-trideoxythymidine (**20**) as a light yellow oil: UV (MeOH) λ_{max} 267 nm; IR (KBr) 2100 cm^{-1} (N_3); MS *m/e* 269 (M^+), 144 (S), 127 (B + 2H), 126 (B + H, 100); ^{1}H NMR ($CDCl_3$) δ 1.93 (s, CH_3), 1.97–2.95 (m, H-2′, H-2″), 3.68 (d, J = 4 Hz, H-5′, H-5″), 4.31 (dm, $J_{4',F}$ = 27.2 Hz, H-4′), 5.26 (dm, $J_{3',F}$ = 54.1 Hz, H-3′), 6.31 (dd, J = 5.7 and 8.8 Hz, H-1′), 7.31 (s, H-6), 9.92 (br s, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 37.5 (C-2′, J = 20.7 Hz), 52.0 (C-5′, J = 8.5 Hz), 82.4 (C-4′, J = 26.8 Hz), 85.2 (C-1′), 93.3 (C-3′, J = 180.7 Hz), 111.5 (C-5), 135.0 (C-6), 150.3 (C-2), 163.6 (C-4) ppm.

(b). The oil (510 mg, 1.9 mmol) obtained from the previous preparation was dissolved in 25 mL of anhydrous pyridine to which 1.05 g (4 mmol) of triphenylphosphine and 10 mL of concentrated ammonia was added. After 3 h at room temperature, TLC ($CHCl_3$–MeOH 8:2) indicated the reaction to be complete and the mixture was evaporated. The residue was dissolved in water and washed twice with diethyl ether. The water phase was evaporated and the title compound **21** was crystallized as its hydrochloride salt: yield 318 mg (1.13 mmol, 60%); mp (HCl) 231–232 °C dec; UV (H_2O, pH 7) λ_{max} 266 nm (ϵ 9900); MS *m/e* 243 (M^+), 126 (B + H), 118 (S); ^{1}H NMR (DMSO-d_6) δ 1.79 (s, CH_3), 2.40 (dm, $J_{2',F}$ = 28 Hz, H-2′, H-2″, partially hidden by DMSO), 2.77 (d, J = 5.7 Hz, H-5′, H-5″), 4.02 (dt, J = 5.3 Hz, $J_{4',F}$ = 27.7 Hz, H-4′), 4.56 (br s, NH_2), 5.30 (dm, $J_{3',F}$ = 54.0 Hz, H-3′), 6.16 (t, J = 7 Hz, H-1′), 7.55 (s, H-6), 11.05 (br s, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 12.3 (CH_3), 36.5 (C-2′, J = 20.8 Hz), 43.0 (C-5′, J = 9.8 Hz), 84.2 (C-1′), 85.6 (C-4′, J = 22.0 Hz), 94.8 (C-3′, J = 173.3 Hz), 110.2 (C-5), 136.4 (C-6), 150.7 (C-2), 164.0 (C-4) ppm. Anal. ($C_{10}H_{14}N_3O_3F$·HCl) C, H, N.

1-[2-Deoxy-5-(monomethoxytrityl)-β-D-*threo*-pentofuranosyl]-5-fluorouridine (23). The inversion of the configuration in the 3′-position was performed in a one-pot procedure, as it is described in the original publication by J. J. Fox.[30] After coevaporating twice with anhydrous pyridine, 986 mg (4 mmol) of 2′-deoxy-5-fluorouridine (**22**) was reacted with 1.55 g (5 mmol) of monomethoxytrityl chloride in 20 mL of anhydrous pyridine for 4 h at room temperature. The mixture was cooled on an ice bath and 0.8 mL (10 mmol) of methanesulfonyl chloride was added. After 3 h at 0 °C the mixture was concentrated, diluted with 100 mL of $CHCl_3$, and washed twice with a saturated solution of $NaHCO_3$. The water phases were extracted once more with 100 mL of $CHCl_3$. Drying of the organic phase (Na_2SO_4) and evaporation yielded an oil, which was dissolved in 100 mL of 96%

EtOH to which 2 mL of a 10 N NaOH solution was added. After 2 h at 80 °C (oil bath) TLC indicated complete conversion of the 3′-configuration. The solution was cooled, neutralized, and evaporated and the residue was dissolved in 100 mL of $CHCl_3$ which was washed twice again with a $NaHCO_3$ solution. After drying of the organic phase and subsequent evaporation, the residue was purified on 40 g of silica gel ($CHCl_3$–MeOH 98:2) yielding 1.69 (3.25 mmol, 81%) of the title compound **23**: UV (MeOH) λ_{max} 230 and 266 nm; ^1H NMR ($CDCl_3$) δ 1.96–2.21 (m, H-2′), 2.35–2.72 (m, H-2″), 3.56 (m, H-5′, H-5″), 3.78 (s, OCH_3), 3.98 (m, H-4′), 4.41 (m, H-3′), 6.18 (d, J = 7.5 Hz, H-1′), 6.84 (d), 7.18–7.51 (m) (trityl), 7.98 (d, 6.6 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 40.6 (C-2′), 55.1 (OCH_3), 61.5 (C-5′), 70.6 (C-3′), 83.0 (C-4′), 85.3 (C-1′), 87.3 (Ph_3C), 125.5 (C-6, J = 35.4 Hz), 140.0 (C-5, J = 229.2 Hz), 149.0 (C-2), 157.0 (C-4, J = 26.9 Hz) ppm.

3′-Fluoro-2′,3′-dideoxy-5-fluorouridine (24). The foam **23** obtained from the previous preparation (1.64 g, 3.16 mmol) was dissolved in 50 mL of dichloromethane–THF (9:1).[31] After cooling on an ice bath, 850 μL (6 mmol) of DAST was added and the reaction was left at room temperature for 2 h. The mixture was poured into 100 mL of a saturated $NaHCO_3$ solution and extracted twice with 100 mL of $CHCl_3$. The organic phase was washed once more with $NaHCO_3$, dried, and evaporated. The residue was treated with 75 mL of 80% acetic acid for 30 min at 60 °C. Evaporation and coevaporation with toluene yielded an oil which proved difficult to purify. Therefore the residue was acylated with 40 mL of pyridine–acetic anhydride (3:1) for 1 h at room temperature. The mixture was evaporated and purified by column chromatography ($CHCl_3$–MeOH 99:1) yielding 442 mg (1.52 mmol, 48%) of acylated **24**. Treatment with 50 mL of methanol saturated with ammonia for 5 h at ambient temperature and chromatographic purification yielded 280 mg (1.12 mmol, 35%) of the title compound **24**, which was crystallized from acetone–hexane: mp 171–172 °C; UV (MeOH) λ_{max} 268 nm (ϵ 8500); MS m/e 248 (M^+), 131 (B + 2H), 130 (B + H), 119 (S, 100); ^1H NMR (DMSO-d_6) δ 1.85–2.63 (m, H-2′, H-2″), 3.64 (d, J = 3.5 Hz, H-5′, H-5″), 4.19 (dt, $J_{4',F}$ = 26.8 Hz, H-4′), 5.30 (dm, $J_{3',F}$ = 52.7 Hz, H-3′), 6.19 (dt, J = 7 Hz, H-1′), 8.17 (d, J = 7.2 Hz, H-6), 11.98 (br s, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 37.8 (C-2′, J = 20.7 Hz), 61.1 (C-5′, J = 12.3 Hz), 85.0 (C-1′), 85.5 (C-4′, J =24.4 Hz), 95.2 (C-3′, J = 173.3 Hz), 124.8 (C-6, J = 34.2 Hz), 140.5 (C-5, J = 232 Hz), 149.3 (C-2), 157.3 (C-4, J = 26.8 Hz) ppm. Anal. ($C_9H_{10}F_2N_2O_4$) C, H, N.

1-(2-Fluoro-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)thymine (26). A solution of 515 mg (1 mmol) of 1-[3-deoxy-5-*O*-(monomethoxytrityl)-β-D-*threo*-pentofuranosyl]thymine[14] (**25**) in 20 mL of dichloroethane was cooled on an ice bath. Under stirring, 0.3 mL (2.1 mmol) of DAST was added and the reaction was left at room temperature for 2 h, when TLC ($CHCl_3$–MeOH 95:5) indicated complete reaction. The mixture was poured into 50 mL of a saturated $NaHCO_3$ solution and stirred for 10 min. The product was extracted with 50 mL of $CHCl_3$ (2×) and the organic phase was washed once more with $NaHCO_3$. After evaporation, the residue was treated with 50 mL of 80% acetic acid for 45 min at 60 °C. Evaporation followed by coevaporation with toluene and chromatographic purification yielded 140 mg (0.57 mmol, 57%) of **26**, which crystallized from acetone–hexane: mp 186–187 °C; UV (MeOH) λ_{max} 266 nm (ϵ 9450); MS m/e 244 (M^+), 126 (B + H, 100), 119 (S); ^1H NMR (DMSO-d_6) δ 1.75 (s, CH_3), 1.85–2.55 (m, H-3′, H-3″), 3.43–3.97 (m, H-5′, H-5″), 4.30 (m, H-4′), 5.21 (t, J = 5.0 Hz, 5′-OH), 5.29 (dm, $J_{2',F}$ = 51.9 Hz, H-2′), 5.88 (d, $J_{1',F}$ = 17.5 Hz, H-1′), 7.83 (s, H-6), 11.31 (s, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 12.4 (CH_3), 31.6 (C-3′, J = 19.5 Hz), 60.8 (C-5′), 81.4 (C-4′), 89.8 (C-1′, J = 36.6 Hz), 97.2 (C-2′, J = 178.2 Hz), 109.1 (C-5), 136.2 (C-6), 150.4 (C-2), 164.1 (C-4) ppm. Anal. ($C_{10}H_{13}FN_2O_4$) C, H, N.

Antiviral Test Procedures. The HTLV-III_B strain of HIV was used throughout all experiments. The virus was prepared from the culture supernatant of a persistently HTLV-III_B-infected HUT-78 cell line. The antiviral assays[38] were based on the protection of HIV-infected MT-4 cells against virus-induced cytopathogenicity. They were run in parallel with the cytotoxicity assays aimed at establishing the toxicity of the compounds for uninfected MT-4 cells.

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N-Azamonobactams. 2. Synthesis of Some *N*-Iminoacetic Acid and *N*-Glycyl Analogues

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The synthesis of the title compounds has been accomplished. The *N*-iminoacetic acid analogues (**12a** and **12b**) containing the aminothiazole type side chain exhibited good in vitro antibacterial activity against Gram-negative organisms. The corresponding *N*-glycyl derivative (**17**) was not active.

Recently, we described the synthesis of some *N*-azamonobactam derivatives.[1] This work coupled with the published accounts of *N*-oxo derivatives (**1a**)[2] and *N*-thio (**2a**)[3] compounds prompted the synthesis of the corresponding *N*-aza analogues (**1c** and **1d**) described herein.

Chemistry

The starting materials for the synthesis of these compounds were the previously described *N*-amino derivatives

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