First Synthesis of a Dideoxydifluoro Nucleoside with a β-D-*lyxo* Configuration. An Unprecedented Effect of the *cis*-Fluorines on the Reactivity of the Aglycon

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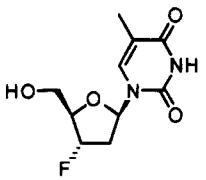
Received February 6, 1995

Introduction

The effect of a single fluorine atom at various positions of the glycon moiety in dideoxynucleosides that function as reverse transcriptase inhibitors has been investigated extensively.[1,2] These investigations have led to the discovery of compounds with potential use in the treatment of AIDS, such as 1-(2,3-dideoxy-3-fluoro-β-D-*erythro*-pentofuranosyl)thymine (**1**)[3–6] and 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**2**).[7–9] These two compounds are currently at various stages of clinical development as anti-HIV agents.



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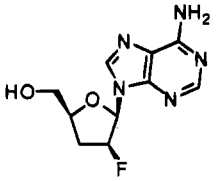

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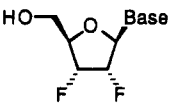
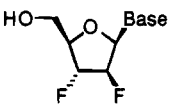
The structure–activity relationship for these and other monofluoro dideoxynucleosides shows that for different aglycon moieties, a fluorine atom at positions 3′-"down" or 2′- "up" correlates well with anti-HIV activity.[2] On the other hand, fluorine atoms at the same positions, but with inverted stereochemistry, consistently produced inactive compounds.[2] The preferred pseudoaxial disposition of the C–F bond in these molecules has been identified as the major driving force responsible for inducing a specific form of ring puckering in the sugar moiety of these compounds. Hence, for the active analogues **1** and **2**, a fluorine-induced 2′-*endo*/3′-*exo* conformation, characteristic of the southern hemisphere of the pseudorotational cycle,[10] has been associated with good anti-HIV activity.[2] This tendency of the C–F bond to adopt a pseudoaxial orientation in the furanose ring is a direct consequence of the so called *gauche* effect which results from the attractive interaction forces between the very electronegative fluorine atom and the furanose oxygen.[2,11,12] Such an attractive interaction peaks when the C–F bond is pseudoaxially disposed.[2]

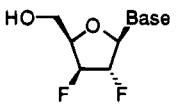
A similar correlation for vicinal substituted dideoxydifluoro nucleosides is expected to be more complicated due to competing *gauche* interactions between the fluorine atoms themselves and the individual fluorines with the furan oxygen. However, to this date, the complete set of all possible dideoxydifluoro nucleosides has not been available to study this phenomenon. Dideoxydifluoro nucleosides with β-D-*ribo*- (**I**),[13–16] β-D-*ara*- (**II**),[13,17] and β-D-*xylo*- (**III**)[2,18] configurations are known, but the β-D-*lyxo*- (**IV**) configuration is not.[13,19] In the present investigation, we would like to describe, for the first time, the synthesis of a pyrimidine dideoxydifluoro nucleoside with the elusive β-D-*lyxo*-configuration.[20] An unexpected result observed with this *all-cis* substituted lyxofuranoside was the unusual fluorine-induced enhanced reactivity of the pyrimidine ring which is strikingly different from that seen with comparable pyrimidine nucleosides.



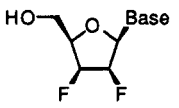
β-D-ribo (I)



β-D-ara (II)



β-D-xylo (III)



β-D-lyxo (IV)

Results and Discussion

The requisite monofluoro uracil nucleoside **5** was prepared as described by Martin et al.[17] through the

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(19) Previous attempts to prepare dideoxydifluoro nucleosides with the D-*lyxo* configuration are reported in ref 18 and in Jeong, L. S.; Lim, B. B.; Marquez, V. E. *Carbohydr. Res.* **1994**, *262*, 103.
(20) A comprehensive ^{1}H NMR analysis of the glycones' coupling constants at various temperatures with examples from each of the difluorinated templates (**I**–**IV**) will be performed using the PSEUROT program (De Leeuw, F. A. A. M.; Altona, C. *J. Comput. Chem.* **1983**, *4*, 428) to investigate the conformational preferences of each template.

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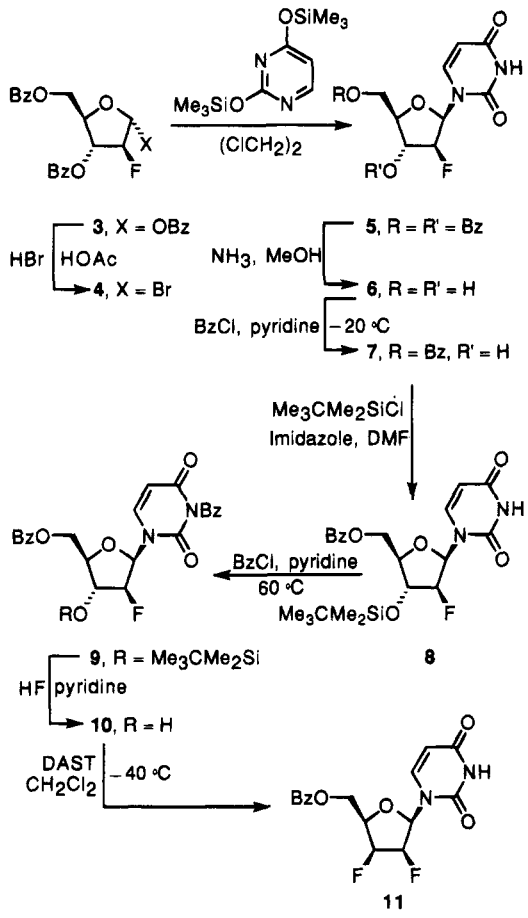
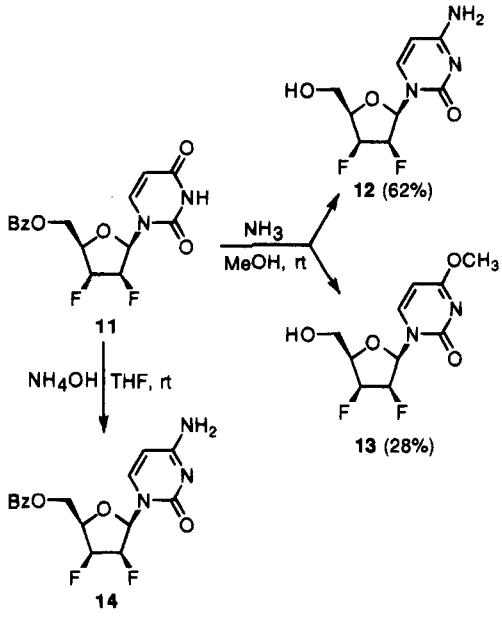
Scheme 1



coupling of 2-deoxy-2-fluoro-3,5-di-*O*-benzoyl-α-D-arabinofuranosyl bromide (**4**) with persilylated uracil (Scheme 1). The preparation of the important fluorosugar precursor **4** was described earlier by Tann et al.[21] Following the treatment of **5** with methanolic ammonia, the fully deprotected 2′-deoxyuridine **6**[17] was obtained. Since the use of different protective groups was important to achieve our goal, the 5′-hydroxyl group in **6** was selectively rebenzoylated with benzoyl chloride in pyridine at low temperature to give intermediate **7** (95%) exclusively. Subsequently, the 3′-hydroxyl group was protected as the *tert*-butyldimethylsilyl ether to give compound **8**. In order to prevent the extremely facile formation of anhydronucleosides, which is typically observed when (diethylamido)sulfur trifluoride (DAST) is used with pyrimidine nucleosides with "down" hydroxyl groups,[18,22,23] the NH of the uracil ring was protected as the N^3-benzoyl derivative **9**. After the selective removal of the silyl ether protection with HF·pyridine compound **10** was obtained. Treatment of **10** with DAST at −40 °C produced the desired, highly congested *all-cis* substituted lyxofuranoside **11** in 26% yield. This reaction proceeded with the simultaneous removal of the N^3-benzoyl group.

Seeking to prepare first the fully deprotected uridine analogue by removing the 5′-*O*-benzoyl group, compound **11** was treated, as usual, with methanolic ammonia at room temperature (Scheme 2). To our surprise, a mixture of two products consisting of 1-(2,3-dideoxy-2,3-difluoro-β-D-lyxofuranosyl)cytosine **12** (62%) and 1-(2,3-dideoxy-2,3-difluoro-β-D-lyxofuranosyl)-O^4-methyluracil **13** (28%) was obtained. This is highly unusual since conversion of a uracil-nucleoside into the corresponding cytosine-nucleoside always requires activation of the uracil moiety prior to displacement with ammonia. Activation of the uracil ring is generally achieved chemically in various ways: (1) via the formation of a 4-chloropyrimidin-2(1*H*)-one nucleoside intermediate which then reacts readily with ammonia,[24] (2) by prior conversion of the uracil moiety into a 4-thiouracil moiety; however, the ensuing reaction with ammonia requires heating to 100 °C in a sealed tube,[25] (3) via the corresponding 4-(methylthio)-derivatives which are more reactive than the 4-thio-derivatives;[26] and more recently, (4) via the formation of either 4-(1,2,4-triazol-1-yl)- or 4-(3-nitro-1,2,4-triazol-1-yl)pyrimidin-2(1*H*)-one nucleoside intermediates which react smoothly with ammonia at room temperature.[27] With related nucleosides containing one or two fluorine substituents in the sugar moiety, activation of the uracil ring was also necessary.[13,14,17,18] To date, a direct transformation of a uracil nucleoside into the corresponding cytosine nucleoside with ammonia at room temperature has never been reported. To illustrate further the enhanced reactivity of this system, compound **11** was treated with aqueous ammonium hydroxide in THF at room temperature. Under these extremely mild conditions, the uracil ring reacted preferentially with conversion to cytosine, but leaving the 5′-benzoate ester intact to give **14**. Such a mild transformation of a uracil moiety into cytosine is, to our knowledge, unprecedented.

Scheme 2



An equivalent enzymatic transformation of a uracil nucleoside into the corresponding cytosine nucleoside, such as in the biosynthesis of CTP from UTP with ammonia and ATP, also proceeds with activation requiring the cleavage of ATP to ADP and inorganic phosphate.[28] On the other hand, if the equilibrium of the hydrolytic reaction of cytidine to uridine and ammonia

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is considered, it is unlikely, according to Wolfenden,[28] that the reverse reaction will take place at all since the ammonia concentrations required would be extremely high. Indeed, cytidine formation in 2 M ammonium hydroxide (pH 9.2) at 25 °C proceeded with only a 0.015% yield from 10 mM uridine.[29] In light of the above, the observed quantitative conversion of **11** to **14** would argue that the presence of two fluorine atoms on the same side of the uracil ring, which is characteristic of the new difluoro-*lyxo*-furanoside template, augments the reactivity of the uracil ring to an unprecedented level. It is well known that hydroxypyrimidines exist mainly in the form of the oxo tautomers and that the proportion of hydroxy tautomer is insignificant.[30] However, in order to displace effectively the 4-hydroxy group of **11** with ammonia, it would be required for the oxo–enol equilibrium to shift significantly to the enol form. Since the UV spectra of the neutral species of 2- and 4-pyrimidinones are very similar to those of their *N*-methyl derivatives (oxo tautomers)[30] and different from those of their methyl ethers (analogous to the enol tautomers),[30] we compared the UV spectra of the of **11** and **13** in methanol against the spectra of two monofluorinated analogues (**15** and **16**) having, respectively, a fluorine atom "up" at positions 2′ or 3′.[31] Compounds **15** and **16** are also 5′-*O*-benzoylated intermediates as compound **11**. As seen in Figure 1, the spectra of compounds **15** and **16** with a single fluorine subsitution above the sugar ring are nearly identical to each other irrespective of the position of the fluorine: the λ_{max} for the 3′-fluoro-compound (**15**) appears at 260.0 nm, and that for the 2′-fluoro-compound (**16**) appears at 258.6 nm. These λ_{max} values reflect a small hypsochromic shift relative to uridine (λ_{max} = 261.6 nm, not shown) measured under the same conditions. On the other hand, the UV spectrum of **11** has only an inflection point at 250 nm, and the 250–300 nm region is closer in appearance to the spectrum of the methyl ether **13** (λ_{max} = 256.6 nm). It is possible, therefore, that a significant increase in the presence of the enol tautomer in **11**, which appears to be induced solely by the proximity of two fluorine atoms above the plane of the glycon, may account for the unusual reactivity of this compound.[32]

The biological activity of 1-(2,3-dideoxy-2,3-difluoro-β-D-lyxofuranosyl)cytosine (**12**) was examined. In Molt-4 cells incubated for 48 h at 37 °C in the presence of various concentrations of **12**, ranging from 0.01 to 100 μM, inhibition of cell growth was only 10% at the highest concentration. Also, no anti-HIV activity was observed for this compound over the same dose range in ATH-8 cells infected with the virus. Finally, the compound was assayed as a possible inhibitor of cytidine deaminase, but inhibition of this enzyme by **12** was minimal even at 100 μM concentration.

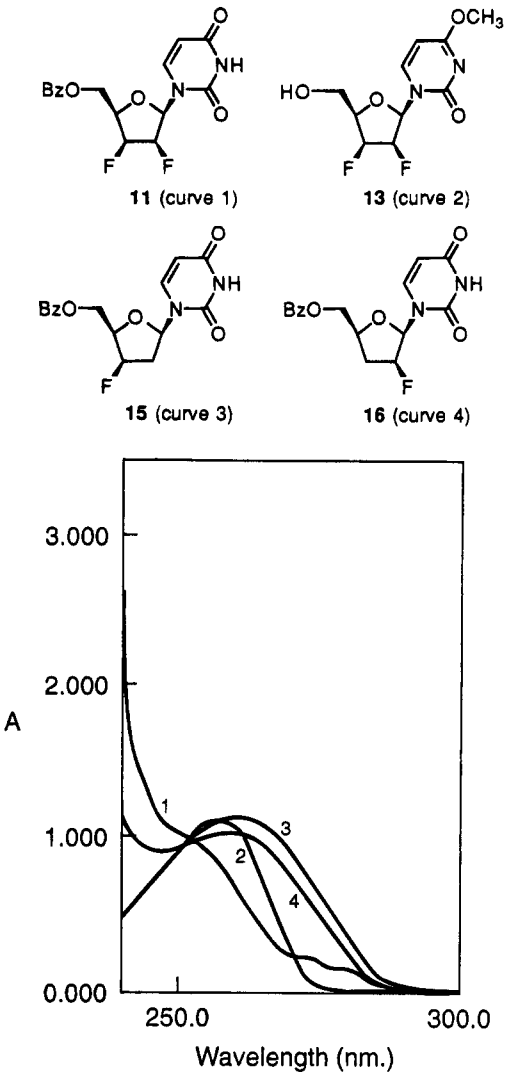

Figure 1. UV spectra of compounds **11**, **13**, **15**, and **16** in MeOH.

Experimental Section

General Methods. Silica gel column chromatography was performed on Silica Gel 60 (E. Merck, 230–400 mesh) and analytical TLC was performed on Analtech Uniplates silica gel GF with the solvents indicated. Detection of compounds by TLC was accomplished either by UV light or by 10% methanol–sulfuric acid spray, followed by heating on a hot plate. UV spectra, specific rotations, and $^1H/^{13}C$ NMR spectra were recorded in standard laboratory instruments. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained by using samples dissolved in a glycerol matrix, and ionization was effected by a beam of xenon atoms derived by neutralizing xenon ions accelerated through 8.6 kV. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or by Galbraith Laboratories, Inc., Knoxville, TN. All solvents of inclusion as indicated in the elemental analyses were observed by ^1H NMR spectroscopy.

1-(3,5-*O*-Dibenzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (5). This compound was prepared in 89% yield

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(31) Compounds **15** and **16** were synthesized as part of a study to determine the influence of a single fluorine on the conformation of monofluoro uracil nucleosides by ^1H NMR. Part of these results appear in reference 2 and a more comprehensive report will be published elsewhere.

(32) One reviewer suggested that this unusual reactivity of **11** could result from an alteration of the anomeric effect by the fluorine substituents. It is possible that as O4′ experiences the electron-withdrawing effect of the fluorines, it tunes the hyperconjugative n(O4′) → σ*(N) participation (anomeric effect), and that this change could have an effect on the shift of the oxo–enol tautomerism in favor of the enol tautomer. We reasoned that since electron-withdrawing effects are operative through σ-bonds, the influence on the anomeric effect ought to be independent of stereochemistry, and hence, an equally anomalous reactivity should be observed for all difluorinated uracil nucleosides. Such was not the case. Indeed, in references 2, 13, 14, and 17, difluoro uracil nucleosides with *ribo*-, *ara*-, or *xylo*-configurations had to be "activated" prior to conversion to the corresponding cytidine analogues. We favor a through-space interaction between either fluorine and the π-system of the pyrimidine ring as the cause of the shift in the oxo–enol tautomerism. One can speculate that when there is only one fluorine atom above the plane of the sugar ring (2′ or 3′), such a fluorine–pyrimidine interaction could be diminished, or avoided, by changes in the puckering of the sugar ring. On the other hand, when two fluorines are present, this interaction is inescapable.

following a procedure similar to that described by Martin et al.;[17] mp 186–187 °C [lit. mp 185–187 °C].[17]

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (6). This compound was prepared in 82% yield following a similar procedure to that described by Martin et al.[17]

1-(5-*O*-Benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-uracil (7). A stirred solution of **6** (3.30 g, 6.66 mmol) in dry CH_2Cl_2 (50 mL) containing dry pyridine (5 mL) was cooled to −20 °C and treated with benzoyl chloride (1.7 mL, 7.33 mmol) for 1 h. After the addition of a mixture of MeOH and ice, all volatiles were removed under reduced pressure. The residue was dissolved in EtOAc (150 mL), washed consecutively with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and reduced to dryness. The residue was purified by silica gel column chromatography using $CHCl_3$:MeOH (20:1) as eluant to give the title compound **7** (4.2 g, 93%) as a white solid; mp 111–114 °C; ^{1}H NMR ($CDCl_3$) δ 3.31 (br s, 1 H), 4.12 (distorted quartet, 1 H), 4.35 (dm, $J_{F,H}$ = 19.3 Hz, 1 H), 4.57 (m, 2 H), 5.09 (dm, $J_{F,H}$ = 53.3 Hz, 1 H), 5.57 (d, J = 8.1 Hz, 1 H), 6.18 (dd, $J_{F,H}$ = 17.7 Hz, $J_{H,H}$ = 4.0 Hz, 1 H), 7.23–8.11 (m, 6 H), 11.50 (br s, 1 H). Anal. Calcd for $C_{16}H_{15}N_2O_6F$: C, 54.86; H, 4.31; N, 8.00. Found: C, 55.02; H, 4.37; N, 7.84.

1-(5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (8). A stirred solution of **7** (4.2 g, 6.66 mmol) in dry DMF (50 mL) was treated with a mixture of imidazole (4.22 g, 33.34 mmol) and *tert*-butyldimethylsilyl chloride (4.28 mL, 18.67 mmol) for 40 h at room temperature. The solvent was removed under reduced pressure, and the residue was diluted with EtOAc (150 mL), washed with brine, dried ($MgSO_4$), and evaporated. The semisolid obtained was purified by silica gel column chromatography using hexanes:EtOAc (1:1) as eluant to give **8** (3.46 g, 62%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 6 H), 0.91 (s, 9 H), 4.25 (q, J = 8.1 and 4.8 Hz, 1 H), 4.41 (dm, $J_{F,H}$ = 18.3 Hz, 1 H), 4.54 (d, J = 4.9 Hz, 2 H), 4.95 (dq, $J_{F,H}$ = 51.7 Hz, $J_{H,H}$ = 1.5 Hz, 1 H), 5.65 (dd, J = 8.2, 2.2 Hz, 1 H), 6.23 (dd, $J_{F,H}$ = 20.4 Hz, $J_{H,H}$ = 3.0 Hz, 1 H), 7.40–7.65 (m, 4 H), 8.00 (m, 2 H), 8.39 (br s, 1 H). Anal. Calcd for $C_{22}H_{29}FN_2O_6Si$: C, 56.88; H, 6.29; N, 6.03. Found: C, 56.93; H, 6.33; N, 6.01.

1-(5-*O*-Benzoyl-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*N*^{3}-benzoyluracil (9). A stirred solution of **8** (3.4 g, 7.49 mmol) in dry pyridine (60 mL) was treated with benzoyl chloride (1.74 mL, 14.98 mmol) at room temperature. Immediately after, the temperature was raised to 70 °C and stirring continued for 35 h. After cooling to room temperature, a mixture of MeOH and ice was added, and the solvents were removed under reduced pressure. The residue obtained was diluted with EtOAc (150 mL), washed with a saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated. The semisolid residue was purified by silica gel column chromatography using hexanes:EtOAc (2:1) as eluant to give **9** (3.40 g, 82%) as a white foam: ^{1}H NMR ($CDCl_3$) δ 0.31 (s, 6 H), 0.81 (s, 9 H), 4.28 (m, 1 H), 4.42 (dm, $J_{F,H}$ = 15.7 Hz, 1 H), 4.58 (d, J = 5.0 Hz, 2 H), 4.95 (dq, $J_{F,H}$ = 51.6 Hz, $J_{H,H}$ = 1.4 Hz, 1 H), 5.79 (d, J = 8.3 Hz, 1 H), 6.25 (dd, $J_{F,H}$ = 20.5 Hz, $J_{H,H}$ = 2.9 Hz, 1 H), 7.40–7.65 (m, 4 H), 7.80–8.10 (m, 2 H). This compound was used in the following step without further purification.

1-(5-*O*-Benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-*N*^{3}-benzoyluracil (10). A stirred solution of **9** (2.0 g, 3.59 mmol) in dry THF (50 mL) was treated with HF·pyridine (6.0 mL) and maintained at room temperature for 48 h. A mixture of ice and $CHCl_3$ was added, and the organic layer was later separated, washed consecutively with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography using hexanes:EtOAc (1:1) as eluant to give **10** (1.45 g, 85%) as a white solid: mp 176–178 °C; ^{1}H NMR ($CDCl_3$) δ 3.48 (d, J = 4.4 Hz, 1 H), 4.33 (m, 1 H), 4.49 (dm, $J_{F,H}$ = 13.8 Hz, 1 H), 4.62 (m, 2 H), 5.05 (dq, $J_{F,H}$ = 51.4 Hz, $J_{H,H}$ = 1.4 Hz, 1 H), 5.57 (d, J = 8.3 Hz), 6.25 (dd, $J_{F,H}$ = 19.9 Hz, $J_{H,H}$ = 3.1 Hz, 1 H), 7.44–8.07 (multiplets, 11 H). Anal. Calcd for $C_{23}H_{19}FN_2O_7 \cdot 0.2H_2O$: C, 60.33; H, 4.27; N, 6.27. Found: C, 60.21; H, 4.20; N, 6.05.

1-(5-*O*-Benzoyl-2,3-dideoxy-2,3-difluoro-β-D-lyxofuranosyl)uracil (11). A stirred solution of **10** (0.5 g, 1.10 mmol) in CH_2Cl_2 (20 mL) was cooled to −40 °C and treated dropwise with (diethylamido)sulfur trifluoride (DAST, 1.50 mL, 11.35 mmol) and maintained at that temperature for 0.5 h. The temperature was then allowed to reach ambient conditions and stirring continued for 15 h more. A mixture of $CHCl_3$ and a saturated solution of $NaHCO_3$ was added, and the mixture was stirred for 30 min. The organic layer was separated, washed succesively with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography using hexanes:EtOAc (1:1) as eluant to give **11** (0.100 g, 29%) as a crystalline solid; mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 4.54 (dd, J = 12.2, 7.5 Hz, 1 H), 4.72 (dd, J = 12.2, 4.2 Hz, 1 H), 5.01 (m, 1 H), 5.33 (dt, $J_{F,H}$ = 51.3 Hz, $J_{H,H}$ = 4.1 Hz, 1 H), 5.80 (dm, $J_{F,H}$ = 19.5 Hz, 1 H), 5.97 (dd, $J_{F,H}$ = 59.8 Hz, $J_{H,H}$ = 5.8 Hz, 1 H), 6.64 (dd, J = 5.5, 2.6 Hz, 1 H), 7.35–7.60 (m, 3 H), 8.00 (m, 2 H), 8.49 (dd, J = 5.5, 2.2 Hz, 1 H), 9.40 (br s, 1 H). Anal. Calcd for $C_{16}H_{14}F_2N_2O_5$: C, 54.55; H, 4.00; N, 7.95. Found: C, 54.32; H, 3.73; N, 7.93.

1-(2,3-Dideoxy-2,3-difluoro-β-D-lyxofuranosyl)cytosine (12) and 1-(2,3-Dideoxy-2,3-difluoro-β-D-lyxofuranosyl)-*O*^{4}-methyluracil (13). A solution of **11** (0.10 g, 0.28 mmol) in concentrated methanolic ammonia (15 mL) was initially stirred at room temperature for 5 h. TLC analysis (silica gel, $CHCl_3$:MeOH, 10:1) showed two products: a major product with R_f = 0.51, and a minor product with R_f = 0.29. The solvent was evaporated, and the residue was treated again under the same conditions for 72 h. After such a time, the ratio of products changed in favor of the lower R_f compound. Purification by silica gel column chromatography using $CHCl_3$:MeOH (10:1) gave **12** (0.038 g, R_f = 0.29, 62%) and **13** (0.018 g, R_f = 0.51, 28%) as white solids.

Compound **12**: mp 132–134 °C; $[\alpha]^{25}_D$ +10.7° (*c* 0.14, MeOH); UV (MeOH) λ_{max} 270 nm; ^{1}H NMR (Me_2SO-d_6) δ 3.51 (m, 2 H), 4.51 (m, 1 H), 4.85 (t, J = 5.5 Hz, 1 H), 5.41 (dt, $J_{F,H}$ = 56.2 Hz, $J_{H,H}$ = 5.2 Hz, 1 H), 5.60 (dm, $J_{F,H}$ = 18.7 Hz, 1 H), 6.09 (dd, $J_{F,H}$ = 61.2 Hz, $J_{H,H}$ = 6.6 Hz, 1 H), 6.13 (d, J = 5.8 Hz, 1 H), 7.00 (br s, 2 H), 7.88 (d, J = 5.8 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 60.26, 71.50 ($J_{F,C}$ = 13.6 Hz), 81.41, 92.10 ($J_{F,C}$ = 188.3, 37.9 Hz), 100.20, 111.20 ($J_{F,C}$ = 218.4, 33.2 Hz), 156.21, 163.83, 165.50; FAB MS *m*/*z* (relative intensity) 248 (MH^+, 100). Anal. Calcd for $C_9H_{11}F_2N_3O_3$: C, 43.73; H, 4.48; N, 17.00. Found: C, 43.90; H, 4.52; N, 17.05.

Compound **13**: mp 104–105 °C; $[\alpha]^{25}_D$ −5.88° (*c* 0.17, MeOH); UV (MeOH) λ_{max} 256 nm; ^{1}H NMR (CD_3OD) δ 3.57 (m, 2 H), 3.91 (s, 3 H), 4.57 (m, 1 H), 5.47 (dt, $J_{F,H}$ = 56.2 Hz, $J_{H,H}$ = 5.2 Hz, 1 H), 5.72 (dm, $J_{F,H}$ = 18.7 Hz, 1 H), 6.14 (dd, $J_{F,H}$ = 61.2 Hz, $J_{H,H}$ = 6.6 Hz, 1 H), 6.63 (d, J = 5.8 Hz, 1 H), 8.31 (d, J = 5.8 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 54.00, 59.84, 72.60 ($J_{F,C}$ = 13. 6 Hz), 81.39, 92.50 ($J_{F,C}$ = 190, 38.1 Hz), 102.70, 111.10 ($J_{F,C}$ = 218.9, 34.0 Hz), 159.04, 163.74, 171.17; FAB MS *m*/*z* (relative intensity) 263 (MH^+, 100).

1-(5-*O*-Benzoyl-2,3-dideoxy-2,3-difluoro-β-D-lyxofuranosyl)cytosine (14). A solution of **11** (0.015 g, 0.043 mmol) in THF (5 mL) was treated with concd NH_4OH (5 drops) and stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative TLC [silica gel, hexanes:EtOAc (1:1)] to give **14** (0.014 g, 99%) as a white solid: mp 182–183 °C; UV (MeOH) λ_{max} 270 nm; NMR ($CDCl_3$) δ 4.35 (dd, J = 11.9, 7.3 Hz, 1 H), 4.48 (dd, J = 12.0, 4.0 Hz, 1 H), 4.97 (m, 1 H), 5.47 (dt, $J_{F,H}$ = 51.2 Hz, $J_{H,H}$ = 4.3 Hz, 1 H), 5.70 (dm, $J_{F,H}$ = 22.3 Hz, 1 H), 6.14 (d, J = 5.7 Hz, 1 H), 6.18 (dd, $J_{F,H}$ = 59.6 Hz, $J_{H,H}$ = 5.9 Hz, 1 H), 7.15 (br s, 2 H),7.48–7.95 (m, 6 H); FAB MS *m*/*z* (relative intensity) 351 (MH^+, 100). Anal. Calcd for $C_{16}H_{15}F_2N_3O_4$: C, 54.70; H, 4.30; N, 11.96. Found: C, 54.98; H, 4.59; N, 11.47.

Acknowledgment. The authors wish to thank Dr. Hiroaki Mitsuya, Clinical Oncology Program, DCT, National Cancer Institute, NIH for the anti-HIV testing. Similarly, we wish to express our thanks to Dr. David A. Cooney and Dr. Zhang Hao of this laboratory, and to Mr. Michael Weinberg, 1994 Summer Fellow, for the cytotoxicity and cytidine deaminase data.

JO950234E