in AcOEt (75 mL) and stirred with 700 mg of neutral charcoal for 1 h. The mixture was filtered over Celite, and the filtrate was evaporated to give a colorless solid. Crystallization from 50% AcOEt–hexane (10 mL) gave 1.25 g (64%) of **10**: mp 171–172 °C; IR (KBr) 1728, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02–2.30 (11 H, m, 5 × CH_2 + CH), 2.65 (2 H, s, 2 × CH); ^{13}C NMR ($CDCl_3$) δ 27.02 (CH), 37.36 (CH_2), 38.14 (CH_2), 39.69 (CH_2), 39.9 (C-1), 45.43 (CH), 181.43 (CO_2H), 217.3 (C=O); MS m/z 195 $(M + H)^+$. Anal. ($C_{11}H_{14}O_3$) C, H.

The corresponding methyl ester, prepared with CH_2N_2 in CH_2Cl_2, had mp 53–54 °C (from hexane); IR ($CHCl_3$) 1722 (ester C=O), 1688 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00–2.20 (11 H, m, 5 × CH_2 + CH), 2.57 (2 H, s, 2 × CH), 3.65 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ 27.14 (CH), 37.7 (CH_2), 38.2 (CH_2), 40.1 (CH_2), 40.2 (C-1), 45.6 (CH), 51.9 (CH_3), 176.0 (C=O ester), 216.3 (C=O, ketone); MS m/z 208 (100, M^+). Anal. ($C_{12}H_{16}O_3$) C, H.

1-Carboxy-4-adamantanol (12). A solution of 1-carboxy-4-adamantanone (**10**) (970 mg, 5 mmol) in 10 mL of EtOH was treated with $NaBH_4$ (900 mg). The mixture was stirred at 50 °C for 30 min and at room temperature for 3.5 h and was worked up as for the preparation of **11**. Crystallization from AcOEt–hexane gave 420 mg (43%) of **12**: mp 151–155 °C; IR (KBr) 3460 (OH), 1708 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) revealed CH-4 at δ 3.84 and 3.92 in a ratio of 2:3; ^{13}C NMR ($CDCl_3$) δ 26.8 (CH), 29.7 (CH_2), 31.9 (CH_2), 33.8 (CH_2), 34.1 (CH), 35.2 (CH_2), 37.7 (CH_2), 38.6 (CH_2), 72.9 and 73.4 (C-4), 182.8 and 182.9 (CO_2H); MS m/z 196 (M^+). Anal. ($C_{11}H_{16}O_3$) C, H.

1-Acetyl-4-adamantanol (15). Hydroxy acid **12** (576 mg, 2.9 mmol) in 12 mL anhydrous THF was allowed to react with 20 mL of 1.6 M (ethereal) MeLi under the conditions specified for the preparation of **13** to give 380 mg of crude **15**. Chromatography over 35 g of silica (70–23 mesh) with 60% AcOEt in hexane as eluant gave 220 mg of **15** as colorless crystals: mp 66–74 °C; IR ($CHCl_3$) 3610 (OH), 1692 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.2 (14 H, m, 5 × CH_2 + 3 × CH + OH), 2.10 (3 H, s, CH_3CO), 3.90 (1 H, br s, CH-4); ^{13}C NMR ($CDCl_3$) δ 24.4 (CH_3), 27.2 (CH), 30.0 (CH_2), 31.8 (CH_2), 34.0 (CH), 34.4 (CH), 35.3 (CH_2), 37.3 (CH_2), 38.3 (CH_2), 72.7 and 73.3 (C-4), 214 (C=O); MS m/z 194 (M^+), 151. Anal. ($C_{12}H_{18}O_2$) C, H.

1-Acetyl-4-adamantanol Oxime (18). Oxime **18** was prepared from ketone **15** (97 mg, 0.5 mmol) and hydroxylamine hydrochloride (100 mg) according to the procedure given for **16**. Crystallization from AcOEt gave 63 mg (60%) of **18**: mp 208–215 °C; IR 3450–3100 (OH), 1658 (weak, C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–2.1 (13 H, m, 5 × CH_2 + 3 × CH), 1.84 (3 H, s, CH_3), 3.88 (1 H, br s, CH-4), 7.61 (OH); ^{13}C NMR ($CDCl_3$–d-Me_2SO) δ 8.9 (CH_3), 27.5 (CH), 30.23 (CH_2), 33.8 (CH_2), 34.2 (CH), 34.3 (CH), 35.6 (CH_2), 38.1 (C-1), 38.5 (CH_2), 39.6 (CH_2), 73.4 (CH-4), 160.3 (C=NOH); MS m/z 209 (M^+). Anal. ($C_{12}H_{19}NO_2$) C, H, N.

1-(1-Aminoethyl)-4-adamantanol Hydrochloride (5). A solution of oxime **18** (31.3 mg, 0.15 mmol) in anhydrous THF (4 mL) was treated with $LiAlH_4$ (65 mg). The mixture was boiled under reflux for 16 h, cooled to room temperature, and treated cautiously with 5 mL of water followed by 1 mL of 1 N NaOH and 15 mL of water. The mixture was extracted with CH_2Cl_2 (2 × 25 mL), and the extract was washed with saturated brine (25 mL), dried ($MgSO_4$), and evaporated to give 24 mg of **5** as a gum: NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 7 Hz, CH_3), 1.3–2.2 (15 H, m), 2.45 (1 H, q, J = 6 Hz, $CHNH_2$), 3.85 (1 H, br s, CH-4); MS m/z 195 (M^+). A solution of **5** in Et_2O was treated with HCl gas in 1 mL of Et_2O to give a precipitate of the corresponding hydrochloride, mp 245–255 °C. Anal. ($C_{12}H_{22}ClNO$) C, H, N.

Antiviral Assay. The compounds were assayed for antiviral activity in Madin Darby Canine Kidney (MDCK) cells by using a viral cytopathogenicity inhibition assay as described previously.[4] To confluent monolayers of cells in 96-well microtiter plates was added compound at the desired concentration in serial 2-fold dilutions across the plate. Virus suspension containing 100 $TCID_{50}$ was added to the monolayers, and plates were incubated at 35 °C for 48 h. Cells were fixed, stained, and evaluated microscopically for cytopathic effect (cpe). The results are expressed as the dose of compound required to inhibit virus cpe by 50% when infected, control cultures just reached 100% cpe. The susceptibility of influenza A virus isolates to inhibition by test compounds was confirmed by ELISA in a test modified from that described previously.[4,13] The validation of the test using the appropriate controls has been described previously.[4,13] MDCK cells were grown in microtiter plates and infected with virus in the presence or absence of test compound. Plates were incubated at 37 °C for 18–24 h. Cells were fixed with 0.05% glutaraldehyde in PBS at room temperature for 15 min, washed, and incubated for 1 h at 37 °C with 50 μL of a 10^{-3} dilution of ferret antiserum to influenza A H3N2 (Mississippi/85-like) virus in PBS containing 0.5% bovine serum albumin (BSA). The plates were washed and incubated for 1 h at 37 °C with 50 μL of a 10^{-3} dilution of protein A-horseradish peroxidase conjugate (Bio-Rad Laboratories, Richmond, CA) in PBS and incubated at room temperature for 2–5 min with 50 μL o-phenylenediamine (Abbott Laboratories, North Chicago, IL) and buffer containing 0.02% H_2O_2; the reaction was stopped by the addition of 100 μL of 1 M H_2SO_4, and ODs at 450 nm were determined.

Acknowledgment. We very much appreciate the technical assistance provided by C. Enny and J. Leone in the preparation of some of the intermediates.

Synthesis of 1-Methyl-5-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)uracil and 1-Methyl-5-(3-azido-2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)uracil. The C-Nucleoside Isostere of 3′-Azido-3′-deoxythymidine and Its 2′-"Up"-Fluoro Analogue[1]

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1-Methyl-5-(3-azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)uracil (C-AZT), a C-nucleoside isostere of the potent anti-AIDS nucleoside 3′-azido-3′-deoxythymidine (AZT), was synthesized. 1-Methyl-2′-deoxy-5′-*O*-tritylpseudouridine (**2a**) was oxidized with CrO_3/pyridine/Ac_2O complex to 1-methyl-5-(5-*O*-trityl-β-D-*glycero*-pentofuranos-3-ulosyl)uracil (**12a**), which was selectively reduced to 1-methyl-5-(5-*O*-trityl-β-D-*threo*-pentofuranosyl)uracil (**13a**). Mesylation of **13a** to **14a** followed by nucleophilic displacement of the mesyloxy group with azide afforded 3′-azido-2′,3′-dideoxy-5′-*O*-trityl-1-methylpseudoridine (**15a**), which was detritylated to C-AZT. In a similar manner, 1-methyl-5-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (C-FMAU, a potent antiherpetic nucleoside) was converted into the 3′-azido analogue (3′-azido-C-FMAU). Both C-AZT and 3′-azido-C-FMAU, however, did not exhibit any significant inhibitory activity against HIV in H9 cells.

The primary pathogen that causes the acquired immunodeficiency syndrome (AIDS) and AIDS related complex (ARC) has been identified as a retrovirus, human T-lymphotropic virus type III (HTLV-III), also called lympha-

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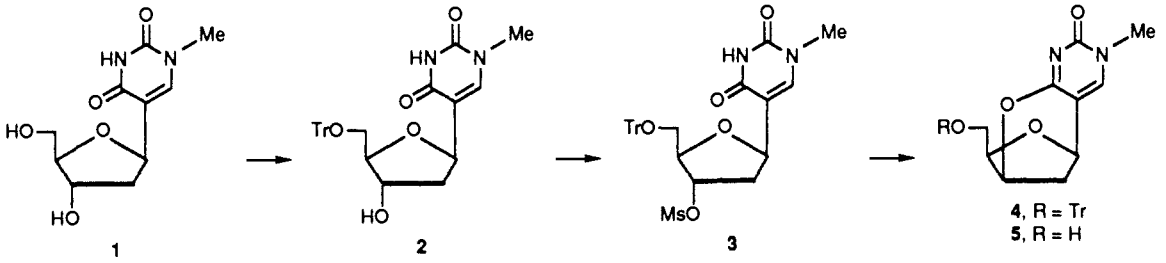
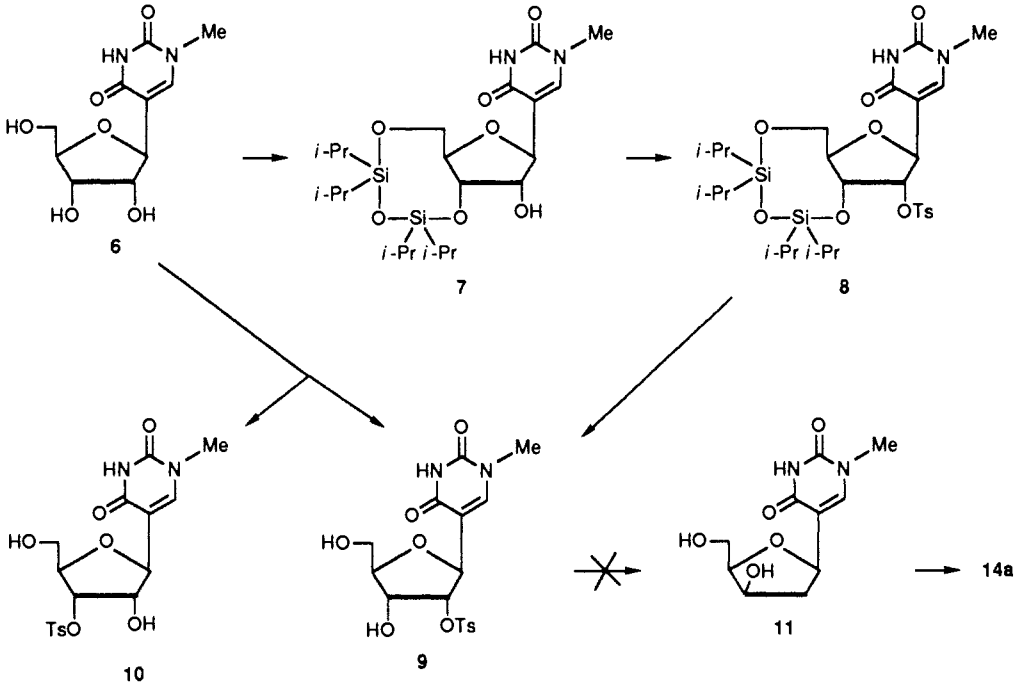
Scheme I



Scheme II



denopathy-associated virus (LAV) or human immunodeficiency virus (HIV).[2-10] At present, suramin, 3′-azido-3′-deoxythymidine (AZT) and ribavirin undergo clinical trials.[11] More recently, 2′,3′-dideoxycytidine has been found to be an even more potent inhibitor of the reverse transcriptase of HTLV-III than AZT.[12,13] Of these drugs, AZT is being used for treatment of AIDS patients. This drug does prolong the lives of AIDS or ARC patients,[14] although very little is known about the mechanism of this drug action. All of these drugs, however, exert toxic side effects.[11]

In this report we describe the synthesis of 1-methyl-5-(2,3-dideoxy-3-azido-β-D-*erythro*-pentofuranosyl)uracil (C-AZT, Scheme III), a C-nucleoside isostere of AZT, as a potential anti-AIDS agent. Since such C-nucleoside and its metabolites are not substrates of phosphorylases, C-AZT may have a longer half-life in plasma. We also synthesized 1-methyl-5-(3-azido-2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)uracil, a C-AZT analogue that contains

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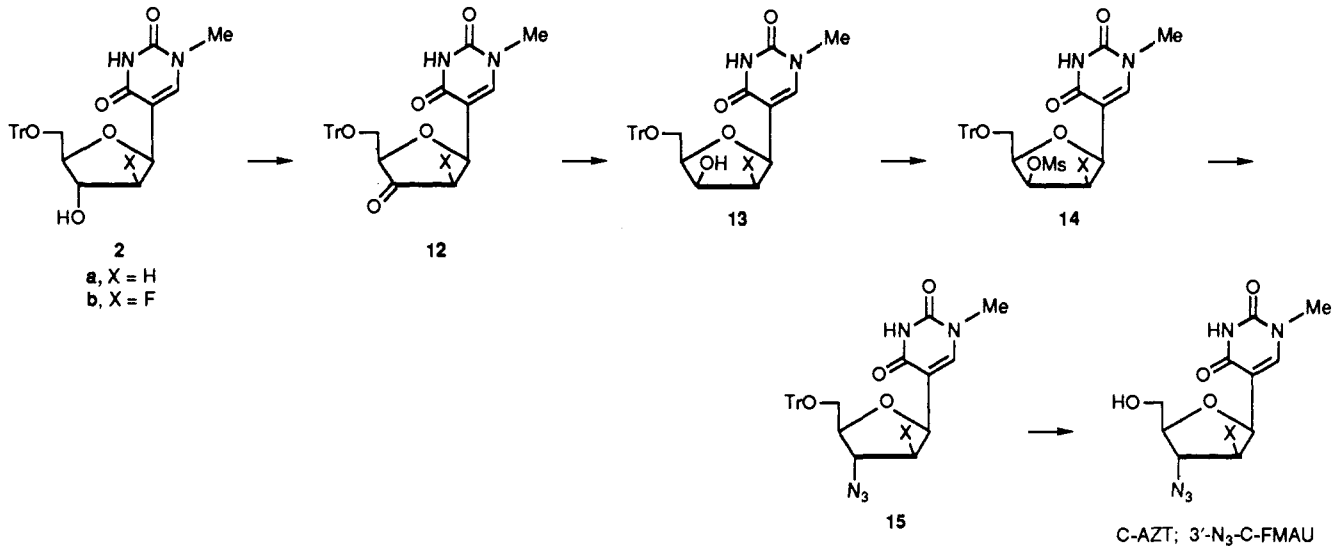
(2) Poiesz, B. J.; Ruscetti, F. W.; Gazdar, A. F.; Bunn, P. A.; Minna, J. D.; Gallo, R. C. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 7415.
(3) Essex, M.; McLane, M. F.; Lee, T. H.; Falk, L.; Howe, C. W. S.; Mullins, J. I. *Science* **1983**, *220*, 859.
(4) Gelmann, E. P.; Popovic, M.; Blayney, D.; Masur, H.; Sidhu, G.; Stahl, R. E.; Gallo, R. C. *Science* **1983**, *220*, 865.
(5) Barre-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Charmaret, S.; Gruest, J.; Danget, C.; Axler-Blin, C.; Vesinet-Brun, F.; Rouzioux, C.; Rosenbaum, W.; Montagnier, L. *Science* **1983**, *220*, 868.
(6) Broder, S.; Gallo, R. C. *N. Engl. J. Med.* **1984**, *311*, 1292.
(7) Popovic, M.; Sarngadharan, M. G.; Read, E.; Gallo, R. C. *Science* **1984**, *224*, 497.
(8) Gallo, R. C.; Salahuddin, S. Z.; Popovic, M.; Shearer, G. M.; Kaplan, M.; Haynes, B. F.; Palkes, T. J.; Redfield, R.; Oleske, J.; Safai, B.; White, G.; Foster, P.; Markham, F. D. *Science* **1984**, *224*, 500.
(9) Kaltzman, D.; Champange, E.; Chamaret, S.; Gruest, J.; Guetard, D.; Hercend, T.; Gluckman, J.-C.; Montagnier, L. *Nature* **1984**, *312*, 767.
(10) Levy, J. A.; Hoffman, A. D.; Kramer, S. M.; Landis, J. A.; Shimabukuro, J. M. *Science* **1984**, *225*, 840.
(11) Yarchoan, R.; Klecker, R. W.; Weinhold, K. J.; Markham, P. D.; Lyerly, H. K.; Durack, D. T.; Gelmann, E.; Nusinoff-Lehrman, S.; Blum, R. M.; Barry, D. W.; Shearer, G. M.; Fischl, M. A.; Mitsuya, H.; Gallo, R. C.; Collins, J. M.; Bolognesi, D. P.; Myers, C. E.; Broder, S. *Lancet* **1986**, 1.
(12) Mitsuya, H.; Weinhold, K. J.; Furman, F. A.; St. Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, r. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *82*, 7096.
(13) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.
(14) Fischl, M. A.; Richman, D. D.; Grieco, M. H.; Gottlieb, M. S.; Volberding, P. A.; Laskin, O. L.; Leedom, J. M.; Groopman, J. E.; Mildvan, D.; Schooley, R. T.; Jackson, G. G.; Durack, D. T.; King D. AZT Collaborative Working Group, *N. Engl. J. Med.* **1987**, *317*, 185.

Scheme III



a fluorine substituent at C2′ in the "up"-arabino configuration on the basis of our finding that such fluorine introduction greatly enhanced the potency of antiviral nucleosides.[15-20]

The most logical approach to the synthesis of C-AZT would be to apply the procedure employed for the preparation of AZT from thymidine[21-23] to 2′-deoxy-1-methylpseudouridine (1)[24,25] (Scheme I). Selective tritylation of 1 would afford 5′-tritylate **2**, which after mesylation to **3** would be converted into the 4,3′-anhydronucleoside **4**. Nucleophilic opening of the anhydronucleoside linkage of **4** with azide ion would afford the protected C-AZT. This procedure went smoothly up to the formation of anhydronucleoside **4**, which was obtained in high yield. However, the anhydro linkage of this compound was found to be too stable to undergo nucleophilic opening. Compound **4** and its 5′-unprotected C-nucleoside **5** were recovered unchanged after treatment with azide ion even in HMPA at 100 °C for several hours. The extraordinary stability of the 4,3′-anhydro linkage in C-nucleoside did not surprise us, since the anhydro linkage of 4,2′-anhydropseudoisocytidine[26] and 4,2′-anhydropseudouridine[27] had been found to be much more stable than the corresponding anhydro bond of 2,2′-anhydrocytidine and 2,2′-anhydrouridine.

The next approach we undertook was to tosylate 1-methylpseudouridine[28] (**6a**) selectively at C-2′ to **9** (Scheme II). One-step conversion of the 2′-tosylate into the 2′-deoxy-*threo*-C-nucleoside **11** might be achieved by treatment with lithium triethylborohydride (LTBH) according to Hansske and Robins,[29] who reported that 2′-*O*-tosyladenosine was converted into 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine in good yield by this procedure. After tritylation and sulfonylation of **11** to **14a** (Scheme III), the 3′-sulfonate group of **14a** should be readily displaced with azide to give **15a**, which would be detritylated to C-AZT.

We found that treatment of **6** with dibutyltin oxide followed by reaction with TsCl afforded **9** (Scheme II) as the major product (49%) together with the 3′-tosylate **10** (34%), which were separated on a silica gel column. We also prepared **9** by tosylation of 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-ylene)-1-methylpseudouridine (**7**)[24] to **8** followed by desilylation. The former procedure was found to be more practical. All our attempts to convert **9** into **11**, by the Hansske–Robins procedure, however, failed. Apparently, the uracil ring was reduced under these conditions, and formation of an intractable mixture of non-UV-absorbing products occurred. We therefore searched for an alternate procedure for the synthesis of **11**. We found that 2′-deoxy-1-methyl-5′-*O*-tritylpseudouridine (**2a**)[25] (Scheme III) could be oxidized smoothly by a mixture of CrO_3, pyridine, and Ac_2O (1:2:1) to the 3′-ulosyl C-nucleoside **12a**. Reduction of **12a** with $NaBH_4$ afforded the desired 2′-deoxy-D-*threo* derivative **13a** (tritylated **11**) in high yield. The ^1H NMR spectrum of the crude reaction mixture showed the presence of a very small amount (<5%) of another isomer **2a**, which was also isolated during chromatographic purification of **13a**. Mesylation of **13a** afforded **14a**, which was isolated by column chromtography and obtained in crystalline form. Treatment of **14a** with LiN_3 in HMPA gave the 3′-azide **15a**. Upon detritylation of **15a**, C-AZT was obtained in high yield.

(15) *Watanabe*, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1979**, *22*, 21.
(16) Fox, J. J.; Lopez, C.; Watanabe, K. A. *Medicinal Chemistry Advances*; de las Heras, F. G., Vega, S., Eds.; Pergamon Press: New York, 1981; p 27.
(17) Su, T-L.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 151.
(18) Fox, J. J.; Lopez, C.; Watanabe, K. A. *Antiviral Chemotherapy: Design of Inhibitors*; Gauri, K. K., Ed.; Academic Press: New York, 1981; p 219.
(19) Watanabe, K. A.; Su, T-L.; Klein, R. S.; Chu, C. K.; Matsuda, A.; Chun, M. W.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1983**, *28*, 152.
(20) Watanabe, K. A.; Su, T-L.; Reichman, U.; Greenberg, N.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1984**, *27*, 91.
(21) Horwitz, J. P.; Chua, J.; Noel, M. *J. Org. Chem.* **1964**, *29*, 2076.
(22) Lin, T-S.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 109.
(23) Matsuda, A.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1980**, *45*, 3274.
(24) Pankiewicz, K. W.; Matsuda, A.; Watanabe, K. A. *J. Org. Chem.* **1982**, *47*, 485.
(25) Matsuda, A.; Chu, C. K.; Reichman, U.; Pankiewicz, K. W.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 3603.
(26) Chu, C. K.; Reichman, U.; Watanabe, K. A.; Fox, J. J. *J. Med. Chem.* **1978**, *21*, 96.
(27) Pankiewicz, K. W.; Watanabe, K. A. *Nucleosides Nucleotides* **1985**, *4*, 613.
(28) Reichman, U.; Hirota, K.; Chu, C. K.; Watanabe, K. A.; Fox, J. J. *J. Antibiot. (Tokyo)* **1977**, *30*, 129.
(29) Hansske, F.; Robins, M. J. *Tetrahedron Lett.* **1983**, *24*, 1589.

We have recently synthesized 1-methyl-5-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (C-FMAU),[30] a C-nucleoside isostere of the potent antiviral agent FMAU. We found that 5′-*O*-tritylated C-FMAU (**2b**) was also readily oxidized to the 3′-ulosyl derivative **12b**, which was selectively reduced to the 2′-deoxy-*threo*-pentosyl C-nucleoside **23b** and mesylated to **14b**. Nucleophilic displacement of the mesyloxy group in **14b** by azide ion to form **15b** required, as expected by the presence of the neighboring fluoro substituent, much more stringent conditions than those for the conversion of **14a** into **15a**. Detritylation of **15b** in a usual manner in 80% acetic acid afforded 3′-azido-C-FMAU.

Unfortunately, both C-AZT and 3′-N_3-C-FMAU showed no activity at 1, 10, or 100 μM concentration against HTLV-III in H-9 cells in an assay procedure to be described elsewhere.[31]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on a silica gel G60 (70–230 mesh, ASTM, Merck). Thin-layer chromatography was performed on Analtech Uniplates with short-wavelength UV light for visualization. Elementary analyses were performed by M.H.W. Laboratories, Phoenix, AZ, or Spang Analytical Laboratory, Eagle Harbor, MI. ^{1}H NMR spectra were recorded on a JEOL FX90Q spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ), and signals are described as a (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), dd (double doublet), dm (double multiplet). Values given for coupling constants are first order.

1-Methyl-2′-deoxy-5′-*O*-tritylpseudouridine (2a). A solution of 1-methyl-2′-deoxypseudouridine[24,25] (920 mg, 3.8 mmol) and TrCl (1.27 g, 4.5 mmol) in dry pyridine (20 mL) was stirred for 24 h at room temperature. An additional TrCl (380 mg) was added, and the mixture was stirred for 2 more days. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ (100 mL) and H_2O (20 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and concentrated, and the residue was chromatographed on a silica gel column with 2% EtOH in CHCl, as the eluent to give **2a** (1.65 g, 89.6%) as a foam. The ^{1}H NMR spectrum of this product was identical with that of an authentic sample.[25]

In a similar manner, **1-methyl-5-(2-deoxy-2-fluoro-5-*O*-trityl-β-D-arabinofuranosyl)uracil (2b)** (165 mg, 78%) was prepared as a foam from C-FMAU[30] (120 mg, 0.46 mmol): ^{1}H NMR (Me_2SO-d_9) δ 3.20–3.30 (5 H, m, NMe and H-5′,5″), 3.88–3.96 (1 H, m, H-4′), 4.07 (1 H, dm, H-3′, $J_{3',F}$ = 20.0 Hz), 4.83 (1 H, dd, H-1′, $J_{1',2'}$ = 3.0, $J_{1',F}$ = 28.0 Hz), 4.89 (1 H, dd, H-2′, $J_{1',2'}$ = 3.0, $J_{2',F}$ = 51.3, $J_{2',3'}$ = 0 Hz), 5.74 (1 H, d, 3′-OH), 7.29–7.38 (16 H, m, Tr and H-6), 11.45 (1 H, s, 3-NH); ^{19}F NMR (Me_2SO-d_6) δ −73.6 (in reference to $CFCl_3$) (octet, $J_{2',F}$ = 51.3, $J_{1',F}$ = 28.0, $J_{3',F}$ = 20.0 Hz); MS *m/e* 503 (MH^+, 50), 243 (Tr, 100). Anal. ($C_{29}H_{27}FN_2O_5$) C, H, N, F.

1-Methyl-2′-deoxy-3′-*O*-mesyl-5′-*O*-tritylpseudouridine (3). A mixture of **2a** (484 mg, 1 mmol) and MsCl (230 μL, 3 mmol) in pyridine (5 mL) was stirred at room temperature for 12 h. The mixture was concentrated in vacuo, and the residue was chromatographed on a silica gel column using $CHCl_3$–EtOH (19:1 v/v) as the eluent. The UV-absorbing fractions were collected and concentrated in vacuo, and the residue which contained traces of impurities was rechromatographed ($CHCl_3$–Me_2CO) to afford pure **3** (339 mg, 66%) as a foam: ^{1}HNMR (Me_2SO-d_6) δ 2.11–2.32 (2 H, m, H-2′,2″), 3.15 (3 H, s, Ms), 3.20 (3 H, s, NMe), 3.37–3.54 (2 H, m, H-5′,5″), 4.06–4.17 (1 H, m, H-4′), 4.80 (1 H, dd, H-1′, $J_{1',2'}$ = $J_{1',2''}$ = 5.5 Hz), 5.18 (1 H, m, H-3′), 7.10–7.42 (15 H, m, Tr), 7.54 (1 H, s, H-6), 13.36 (1 H, s, NH). Anal. ($C_{20}H_{30}N_2O_6S \cdot {}^2/_5CHCl_3$) C, H. N. This particular amount of $CHCl_3$ was detected in the ^{1}H NMR spectrum of the particular analytical sample.

3′,4-Anhydro-5-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)-1-methyluracil (4). A solution of **3** (100 mg, 0.18 mmol) and DBU (50 μL) in DMF (2 mL) was stirred at room temperature for 2 days and then partitioned between EtOAc (50 mL) and H_2O (20 mL). The organic layer was separated, washed (H_2O, 2 × 10 mL), dried (Na_2SO_4), and concentrated, and the residue was chromatographed ($CHCl_3$–EtOH, 33:1 v/v) to give **4** (80 mg, 94%) as a foam: ^{1}H NMR (Me_2SO-d_6) δ 2.23 (2 H, m, H′,2″), 3.02 (2 H, d, H-5′, 5″), 3.29 (3 H, s, NMe), 4.24 (1 H, dt, H-4′, $J_{3',4'}$ = 2.5, $J_{4',5'}$ = $J_{4',5''}$ = 6.3 Hz), 4.94 (1 H, d, H-3′, $J_{3',4'}$ = 2.5, $J_{2',3'}$ = $J_{2'',3'}$ = 0 Hz), 5.22 (1 H, m, H-1′), 8.00 (1 H, s, H-6). Anal. ($C_{29}H_{26}N_2O_4$) C, H, N.

3′,4-Anhydro-5-(2-deoxy-β-D-*threo*-pentofuranosyl)-1-methyluracil (5). Compound **4** (58 mg, 0.14 mmol) was dissolved in 80% AcOH, and the solution was stirred overnight at room temperature. The reaction mixture was concentrated, and the residue was crystallized from EtOH to give **5** (20 mg, 62%): mp 160–162 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.22–2.27 (2 H, m, H-2′,2″), 3.30 (3 H, s, NMe), 3.39 (2 H, d, H-5′,5″), 4.06 (1 H, dt, $J_{3',4'}$ = 2.7, $J_{2',3'}$ = $J_{2'',3'}$ = 6.6 Hz), 4.87 (1 H, t, 5′-OH), 5.14 (1 H, m, H-1′), 7.92 (1 H, s, H-6). Anal. ($C_{10}H_{12}N_2O_4$) C, H, N.

3′,5′-*O*-(1,1,3,3-Tetraisopropyldisiloxan-1,3-ylene)-2′-*O*-tosyl-1-methylpseudouridine (8). A mixture of **7**[27] (500 mg, 1 mmol) and TsCl (285 mg, 1.5 mmol) in pyridine (10 mL) was stirred at room temperature for 2 days. A second charge of TsCl (190 mg, 1 mmol) was added to the mixture, and stirring was continued 1 more day. The mixture was diluted with EtOH and concentrated in vacuo. Traces of pyridine were removed azeotropically with EtOH and PhMe. The residue was dissolved in $CHCl_3$, washed (H_2O), dried (Na_2SO_4), and chromatographed on a silica gel column using $CHCl_3$–EtOAc (3:2 v/v) as the eluent to give **8** (752 mg, 87%) as a foam: ^{1}H NMR (Me_2SO-d_6) δ 0.95–1.01 (28 H, m, *i*-Pr), 2.38 (3 H, s, *Me*Ph), 3.19 (3 H, s, NMe), 3.75 (2 H, m, H-5′,5″), 4.12–4.20 (3 H, m, H-1′,3′,4′), 4.39 (1 H, m, H-2′), 7.35–7.85 (5 H, m, Me*Ph* and H-6), 11.36 (1 H, s, NH). Anal. ($C_{29}H_{46}N_2O_9SSi_2$) C, H. N.

1-Methyl-2′-*O*-tosylpseudouridine (9). Method A. A mixture of **8** (6.5 mg, 1 mmol) in 1 M solution of Et_3NHF in THF (3 mL) was stirred overnight at room temperature. The excess Et_3NHF was destroyed by addition of aqueous $NaHCO_3$, and the mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ (30 mL) and H_2O (15 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on a silica gel column ($CHCl_3$–EtOH, 19:1 v/v first, followed by 10:1) to give **9** (255 mg, 62%) as a foam: ^{1}H NMR (Me_2SO-d_6) δ 2.57 (3 H, s, *Me*Ph), 3.16 (3 H, s, NMe), 3.43–3.51 (2 H, m, H-5,5″), 3.72–3.84 (1 H, m, H-4′), 4.02–4.18 (1 H, m, H-3′, collapsed to a dd upon addition of D_2O, $J_{3',4'}$ = 3.6, $J_{2',3'}$ = 5.2 Hz), 4.45 (1 H, d, H-1′, $J_{1',2'}$ = 7.4 Hz), 4.76–4.96 (2 H, m, H-2′ and 5′-OH, became dd after D_2O exchange), 5.62 (1 H, d, 2′-OH), 7.35 (2 H, d, Ph), 7.53 (1 H, s, H-6), 7.66 (2 H, d, Ph), 11.9 (1 H, s, NH). Anal. ($C_{17}H_{20}N_2O_8S$) C, H, N, S.

Method B. A mixture of **6**[28] (1.29 g, 5 mmol) and *n*-Bu_2SnO (1.25 g, 5 mmol) in MeOH (125 mL) was heated under reflux for 30 min. The clear solution obtained was concentrated in vacuo to dryness, and the residue was dissolved in DMF (40 mL). TsCl (0.96 mg, 5 mmol) was added to the solution, and the mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo, and the residue chromtographed on a silica gel column using $CHCl_3$–EtOH (19:1 v/v) as the eluent. **1-Methyl-3′-*O*-tosylpseudouridine (10)** (700 mg, 34%) was eluted first followed by the 2′-tolsylate **9** (1.02 g, 49.2%). The ^{1}H NMR spectrum of the latter was identical with that of authentic **9**. **10**: ^{1}H NMR (Me_2SO-d_6) δ 2.41 (3 H, s, *Me*Ph), 3.23–3.48 (5 H, m, NMe and H-5′,5″), 3.86–3.90 (1 H, m, H-4′), 4.11–4.31 (1 H, m, H-2′), 4.43 (1 H, d, H-1′, $J_{1',2'}$ = 7.4 Hz), 4.71–4.93 (2 H, m, H-3′ and 5′-OH), 5.50 (1 H, d, 2′-OH), 7.46 (2 H, d, Ph), 7.60–7.88 (3 H, m, Ph and H-6), 11.39 (1 H, s, NH). Anal. ($C_{17}H_{20}N_2O_8S$) C, H, N. S.

1-Methyl-5-(2-deoxy-5-*O*-trityl-β-D-*glycero*-pentofuranos-3-uloysl)uracil (12a). Compound **2a** (680 mg, 1.4 mmol) was added to a solution of premixed complex of CrO_3–pyridine–Ac_2O (420 mg:0.7 mL:0.42 mL, molar ratio 1:2:1) in CH_2Cl_2 (10 mL), and the mixture was stirred for 1 h at room

(30) Pankiewicz, K. W.; Nawrot, B.; Gadler, H.; Price, R. W.; Watanabe, K. A. *J. Med. Chem.* **1987**, *30*, 2314.

(31) Detailed biological studies of these compounds will be published elsewhere together with those of many other nucleosides.

temperature. The resulting brown solution was poured into EtOAc (50 mL), and the precipitates were removed by filtration through a silica gel pad and washed with EtOAc (100 mL). The combined filtrate and washings were concentrated in vacuo. Traces of pyridine and Ac_2O were removed by several azeotropic distillation with PhMe and $CHCl_3$ to give **12a** (555 mg, 82%) as a foam: ^1H NMR (Me_2SO-d_6) δ 2.66–2.83 (2 H, m, H-2′,2″), 3.15–3.17 (5 H, m, NMe and H-5′,5″), 4.18–4.21 (1 H, m, H-4′), 5.10 (1 H, t, H-1′, $J_{1',2'} = J_{1',2''} = 8.0$ Hz), 7.32–7.55 (15 H, m Tr), 7.72 (1 H, s, H-6), 11.42 (1 H, s, NH); MS m/e 483 (MH^+, 20), 243 (Tr, 100). Anal. ($C_{29}H_{26}N_2O_5 \cdot {}^1/_2CHCl_3$) C, H, N. The particular amount of $CHCl_3$ was detected in ^1H NMR spectrum of this particular analytical sample.

1-Methyl-5-(2-deoxy-5-*O*-trityl-β-D-*threo*-pentofuranosyl)uracil (13a). A mixture of **12a** (540 mg, 1.12 mmol) and $NaBH_4$ (170 mg, 4.5 mmol) in EtOH (25 mL) was stirred at 0 °C for 2 h. The reaction was quenched by addition of MeOH (10 mL), and the solvent was removed in vacuo. The residue was partitioned between EtOAc (25 mL) and brine containing 2% of AcOH (10 mL). The organic layer was separated, washed with brine containing 2% AcOH (2 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo to give crude **13a** (415 mg), which was contaminated with a small amount of **2a**.

One hundred milligrams of crude **13a** was purified by silica gel chromatography (2% EtOH in $CHCl_3$ and then 3% and 5% EtOH in $CHCl_3$). Compound **13a** (75 mg) was eluted first from the column followed by **2a** (5 mg). The former was isolated as a foam. **13a**: ^1H NMR (Me_2SO-d_6) δ 1.34–1.76 (1 H, m, H-2′), 2.30–2.71 (1 H, m, H-2″), 2.91–3.28 (5 H, m, NMe and H-5′,5″), 3.88–4.12 (2 H, m, H-3′,4′), 4.75 (1 H, dd, H-1′, $J_{1',2'} = 5.2$, $J_{1',2''} = 8.5$ Hz), 7.26–7.45 (16 H, m, Tr and H-6), 11.36 (1 H, s, NH); MS m/e 485 (MH^+, 10), 243 (Tr, 100). Anal. ($C_{29}H_{28}N_2O_5$) C, H, N. The ^1H NMR spectrum of the latter was identical with that of authentic **2a**.

1-Methyl-5-(2-deoxy-2-fluoro-5-*O*-trityl-β-D-lyxofuranosyl)uracil (13b). Compound **2b** (160 mg, 0.32 mmol) was oxidized, in a similar manner as described for the preparation of **12a** from **2a**, to give 98 mg of crude **12b**, which was treated with $NaBH_4$ and the crude product was purified on a silica gel column using 5% EtOH in $CHCl_3$ and 10% EtOH in $CHCl_3$. Compound **8b** (83 mg, 52%) was the only isolable product: ^1H NMR (Me_2SO-d_6) δ 3.04–0.42 (5 H, m, NMe and H-5′,5″), 4.23–4.45 (1.5 H, m, H-4′, half of H-3′), 4.51–4.65 (1.5 H, m, half each of H-1′,2′,3′), 4.97 (0.5 H, d, $^1/_2$ H-1′, $J_{1',2'} = 2.8$ Hz), 5.19–5.32 (1.5 H, m, $^1/_2$ H-2′ and 3′-OH, collapsed to a pseudo t on addition of D_2O, $J_{1',2'} = J_{1',3'} = 2.8$ Hz), 7.28–7.44 (16 H, m, Tr and H-6), 11.43 (1 H, s, NH); ^{19}F NMR (Me_2SO-d_6) δ (in reference to $CFCl_3$) −87.55 (sextet, $J_{1',F} = 23.0$, $J_{2',F} = 56.04$, $J_{3',F} = 22.0$ Hz); MS m/e 503 (NH^+, 40), 243 (Tr, 100). This product was used directly in the next step.

1-Methyl-5-(2-deoxy-3-*O*-mesyl-5-*O*-trityl-β-D-*threo*-pentofuranosyl)uracil (14a). A mixture of crude **13a** (415 mg, 0.86 mmol) and MsCl (344 mg, 2.6 mmol) in pyridine (5 mL) was stirred at 0 °C for 2 h and then at room temperature for 2 h. The reaction was quenched by addition of EtOH (1 mL), and the solvent was removed in vacuo. The residue was chromatographed on a silica gel column (1% EtOH in $CHCl_3$) to give **14a** (420 mg, 86%), which was crystallized from EtOH: mp 118–119 °C; ^1H NMR (Me_2SO-d_6) δ 1.60–2.75 (2 H, m, H-2′,2″), 2.98 (3 H, s, Ms), 3.19 (5 H, m, NMe and H-5′,5″), 4.17–4.26 (1 H, m, H-4′), 4.77 (1 H, pseudo t, H-1′, $J_{1',2'} = J_{1',2''} = 7.3$ Hz), 5.27 (1 H, m, H-3′), 7.18–7.39 (16 H, m, Tr and H-6), 11.57 (1 H, s, NH); MS m/e 563 (MH^+, 10), 243 (Tr, 100). Anal. ($C_{30}H_{30}N_2O_7 \cdot {}^1/_4CHCl_3$) C, H, N. This particular analytical sample contained $^1/_4CHCl_3$ according to ^1H NMR spectral analysis.

In a similar manner, treatment of **13b** (80 mg, 0.16 mmol) with MsCl (57 mg, 0.5 mmol) in pyridine afforded **14b** (80 mg, 86%) as a foam: ^1H NMR (Me_2SO-d_6) δ 3.12 (3 H, s, Ms), 3.12–3.22 (2 H, m, H-5′,5″), 3.22 (3 H, s, NMe), 4.20–4.46 (1 H, m, H-4′), 4.70 (0.5 H, d, $^1/_2$ H-1′, $J_{1',2'} = 2.6$ Hz), 4.91–4.99 (1 H, m, half of each of H-1′ and H-2′), 5.33–5.59 (1.5 H, m, H-3′ and $^1/_2$ H-2′), 7.20 (1 H, d, H-6, $J_{1',6} = 0.8$ Hz), 7.29–7.38 (15 H, m, Tr), 11.5 (1 H, s, NH); ^{19}F NMR (Me_2SO-d_6) δ −86 (in reference to $CFCl_3$) (octet, $J_{1',F} = 17$, $J_{2',F} = 51$, $J_{3',F} = 25$ Hz); MS m/e 581 (MH^+, 7), 243 (Tr, 100). This compound was directly used in the next step.

3′-Azido-2′,3′-dideoxy-5′-*O*-trityl-1-methylpseudouridine (15a). A mixture of **14a** (420 mg, 0.75 mmol) and LiN_3 (110 mg, 2.25 mmol) in HMPA (3 mL) was stirred overnight at room temperature. The mixture was partitioned between EtOAc (100 mL) and H_2O (50 mL), and the organic layer was separated, washed (H_2O, 3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on a silica gel column using $CHCl_3$ as the eluent to give **15a** (260 mg, 68%) as a foam: ^1H NMR (Me_2SO-d_6) δ 2.06–2.23 (2 H, m, H-2′,2″), 3.11–3.20 (5 H, m, NMe, H-5′,5″), 3.82–3.87 (1 H, m, H-4′), 4.21–4.26 (1 H, m, H-3′), 4.76 (1 H, pseudo t, H-1′, $J_{1',2'} < J_{1',2''} = 7.0$ Hz), 7.26–7.50 (16 H, m, Tr and H-6), 11.35 (1 H, s, NH); MS m/e 510 (MH^+, 15), 243 (Tr, 100). Anal. ($C_{29}H_{27}N_5O_4 \cdot {}^2/_5CHCl_3$) C, H. N. The presence of $2/_5CHCl_3$ was determined by ^1H NMR.

1-Methyl-5-(3-azido-2,3-dideoxy-2-fluoro-5-*O*-trityl-β-D-arabinofuranosyl)uracil (15b). Treatment of **14b** (80 mg, 0.14 mmol) with LiN_3 (20 mg, 0.4 mmol) in HMPA (1 mL) for 7 h at 100 °C afforded, after workup as described above, **15b** (51 mg, 69%) as a foam: ^1H NMR (Me_2SO-d_6) δ 3.22 (5 H, apparent s, NMe, H5′,5″), 3.86–4.02 (1 H, m, H-4′), 4.33 (1 H, dd, H-3′, $J_{2',3'} = 4.5$ $J_{3',F} = 21.9$ Hz), 4.76 (1 H, dd, H-1′, $J_{1',2'} = 2.0$, $J_{1',F} = 26.8$ Hz), 5.12 (1 H, dd, H-2′, $J_{1',2'} = 2.0$, $J_{2',F} = 48.8$ Hz), 7.28–7.45 (16 H, m, Tr and H-6), 11.48 (1 H, s, NH); ^{19}F NMR (Me_2SO-d_6) δ −70.7 (in reference to $CFCl_3$) (octet, $J_{1',F} = 26.8$, $J_{2',F} = 48.8$, $J_{3',F} = 21.9$ Hz); MS m/e 528 (MH^+, 40), 243 (Tr, 100). This compound was used directly in the next step.

3′-Azido-2′,3′-dideoxy-1-methylpseudouridine (C-AZT). Compound **15a** (230 mg, 0.45 mmol) was dissolved in 80% HOAc (10 mL), and the solution was stirred overnight at room temperature. Water (10 mL) was added, and the precipitates were removed by filtration. The filtrate was concentrated in vacuo, and traces of AcOH were azeotropically removed with PhMe to give C-AZT (110 mg, 91%) as a homogeneous glass: ^1H NMR (Me_2SO-d_6) δ 2.01–2.17 (2 H, m, H-2′,2″), 3.24 (3 H, s, NMe), 3.46–3.49 (2 H, m, H-5′,5″), 3.71–3.85 (1 H, m, H-4′), 4.16–4.27 (1 H, m, H-3′), 4.73 (1 H, apparent t, H-1′, $J_{1',2'} < J_{1',2''} = 7.0$ Hz), 7.64 (1 H, s, H-6), 11.3 (1 H, br s, NH); ^{13}C NMR (Me_2SO-d_6) δ 163.1 (s, C-2), 151.1 (s, C-4), 143.1 (d, C-6, $J_{C6,H6} = 181.9$ Hz), 112.3 (s, C-5), 84.2 (d, C-1′, $J_{C1',H1'} = 147.7$ Hz), 73.6 (d, C-3′, $J_{C3',H3'} = 147.7$ Hz), 62.6 (d, C-4′, $J_{C4',H4'} = 151.4$ Hz), 61.8 (t, C-5′, $J_{C5',H5'} = J_{C5',H5''} = 142.0$ Hz), 37.2 (t, C-2′, $J_{C2',H2'} = J_{C2',H2''} = 135.5$ Hz), 35.5 (q, NMe, $J_{C,H} = 144.0$ Hz); IR (KBr) 2100 cm^{-1} (N_3); MS m/e 268 (MH^+). Anal. ($C_{10}H_{13}N_5O_4$) C, H, N.

In a similar manner, **15b** (50 mg, 0.09 mmol) was de-O-tritylated with 80% AcOH. The crude product was purified by silica gel chromatography using 2% EtOH in $CHCl_3$ followed by 5% EtOH in $CHCl_3$ to give **1-methyl-5-(3-azido-2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)uracil (3′-N_3-C-FMAU)** (25 mg, 92%) as a glass: ^1H NMR (Me_2SO-d_6) δ 3.28 (3 H, s, NMe), 3.55–3.62 (2 H, m, H-5′,5″), 3.74–3.89 (1 H, m, H-4′), 4.35 (1 H, ddd, H-3′, $J_{2',3'} = 1.4$, $J_{3',4'} = 4.5$, $J_{3',F} = 21.5$ Hz), 4.78 (1 H, ddd, H-1′, $J_{1',2'} = 3.5$, $J_{1',6} = 1.1$, $J_{1',F} = 27.0$ Hz), 5.05 (1 H, t, 5′-OH), 5.12 (1 H, ddd, H-2′, $J_{1',2'} = 3.5$, $J_{2',3'} = 1.4$, $J_{2',F} = 51.0$ Hz), 7.58 (1 H, d, H-6, $J_{1',6} = 1.1$ Hz), 11.47 (1 H, s, NH); ^{19}F NMR (Me_2SO-d_6) δ −70.06 (in reference to $CFCl_3$) (octet, $J_{1',F} = 27.0$, $J_{2',F} = 51.0$, $J_{3',F} = 21.5$ Hz); MS m/e 286 (MH^+, 10). Anal. ($C_{10}H_{12}FN_5O_4$) C, H, N.

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