= 7.7 Hz, NH) (The presence of EtOAc, noted in the elemental analysis, was confirmed by NMR); mass spectrum (FAB) m/z 511 ([M + H$^+$], 20), 364 (M - NHCH(CO_2H)$CH_2CH_2CO_2H$, 100). Anal. ($C_{18}H_{26}N_2O_{11}S_2$·1.1TFA·0.45EtOAc) C, H, N, S, F. This compound reacted positively (blue color) with the Epstein spray reagent.

Compound **8** (0.09 g, 82%), 4-[(2-chloroethyl)[2-(mesyloxy)-ethyl]amino]benzoyl-L-glutamic acid, was similarly obtained from **5**: NMR (Me_2SO-d_6) δ 1.99 (m, 2 H, $CH_2CH_2CO_2H$), 2.33 (t, 2 H, J = 7.3 Hz, $CH_2CH_2CO_2H$), 3.16 (s, 3 H, CH_3SO_3), 3.77 (s, 4 H, $ClCH_2CH_2$), 3.83 (t, 2 H, J = 5.7 Hz, $CH_3SO_3CH_2CH_2$), 4.33 (m, 3 H, $CH_3SO_3CH_2CH_2$ and CH), 6.82 (AB q, 2 H, J = 9.0 Hz, arom H-3,5), 7.77 (AB q, 2 H, arom H-2,6), 8.29 (d, 1 H, J = 7.7 Hz, NH); mass spectrum (FAB) m/z 451 ([M + H$^+$], 5), 401 (M - $ClCH_2$, 4), 341 (M - $CH_3SO_3CH_2$, 7). Anal. ($C_{17}H_{23}N_2O_8ClS$·0.25 TFA) C, H, N, Cl, F, S. This compound reacted positively (blue color) with the Epstein spray reagent.

Compound **9** (0.33 g, 94%), 4-[bis(2-chloroethyl)amino]-benzoyl-L-glutamic acid, was likewise obtained from **6**: NMR (Me_2SO-d_6) δ 2.00 (m, 2 H, $CH_2CH_2CO_2H$), 2.34 (t, 2 H, J = 7.4 Hz, $CH_2CH_2CO_2H$), 3.78 (t, 8 H, J = 5.2 Hz, 2 $ClCH_2CH_2$), 4.34 (m, 1 H, CH), 6.80 (AB q, 2 H, J = 9.0 Hz, arom H-3,5), 7.77 (AB q, 2 H, arom H-2,6), 8.29 (d, 1 H, J = 7.8 Hz, NH); mass spectrum m/z 372 (M - H_2O, 12), 244 (M - NHCH(CO_2H)$CH_2CH_2CO_2H$, 45). Anal. ($C_{16}H_{20}N_2O_5Cl_2$·0.4 TFA) C, H, N, Cl, F. This compound reacted positively (blue color) with the Epstein spray reagent.

Biological Methods. Each prodrug compound (**7**-**9**) and the parent drug, compound **12**, was incubated at a range of concentrations (0.5-800 μM) with the two cell lines (5×10^4 mL^{-1}, cells grown in DMEM). Prodrug or parent drug was made up just prior to use, adjusted to pH 7.4, and added in the same concentration three times at 24-h intervals. Each concentration was performed in duplicate. CPG2 (6 units mL^{-1} final concentration) was added to test wells in equivalent cultures with each dose of prodrug to achieve active drug in situ. Cell viability was determined by hemocytometry 24 h after the last treatment and the results were compared to those of untreated controls.

Acknowledgment. This work was supported by the Cancer Research Campaign, at the Institute of Cancer Research and the Cancer Research Campaign Laboratories, Department of Medical Oncology, Charing Cross Hospital. We thank Dr. D. E. V. Wilman for the gift of compound **12**, T. J. Thornton for discussions, and M. H. Baker for performing the mass spectra. We gratefully acknowledge a gift of CPG2 from Drs. R. G. Melton and R. F. Sherwood at Porton Down.

Registry No. 1, 88050-23-1; **2**, 76282-66-1; **3**, 123724-54-9; **4**, 123724-55-0; **5**, 123724-56-1; **6**, 123724-57-2; **7**, 123724-58-3; **8**, 122665-73-0; **9**, 3086-06-4; **10**, 93985-39-8; 11, 122665-70-7; **12**, 1141-37-3; CPG2, 9074-87-7; di-*tert*-butyl L-glutamate hydrochloride, 32677-01-3; 4-nitrobenzoyl chloride, 122-04-3.

The Preparation of 2′-Deoxy-2′-fluoro-1′,2′-seconucleosides as Potential Antiviral Agents[1]

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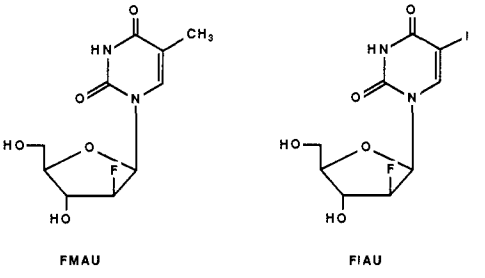
Received April 13, 1989

The preparation of (*R*,*R*)-1,3-dibenzyl-4-fluorobutane-1,2,3-triol (**6**) from D-isoascorbic acid and subsequent chloromethylation of this chiron made possible the synthesis of a series of 2′-deoxy-2′-fluoro-1′,2′-seconucleosides. Among them were the uridine (**10**), thymidine, (11), 5-iodouridine (**14**), ribavirin (**17**), and guanosine (**19**) analogues. They were evaluated for antiviral activity primarily against RNA viruses and found to be inactive. In addition to the aforementioned acyclonucleosides, the 3′,5′-cyclic phosphates of the uridine (**22**) and thymidine (**23**) analogues were prepared from their respective 4-nitrophenyl 3′,5′-cyclic phosphate triesters. The triesters were also examined for antiviral activity, but like their nucleoside counterparts exhibited only marginal activity.

The synthesis of sugar-fluorinated nucleoside analogues continues to attract attention as potential antiviral agents.[2-5] To date, those which have demonstrated significant activity possess a 2′-*ara*-fluoro substituent,[6-8] e.g., 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-methyluracil (FMAU) and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (FIAU). Prompted by these reports, we initiated a program aimed at the synthesis of chiral 2′-deoxy-2′-fluoro-1′,2′-seconucleosides and -nucleotides, acyclonucleic acid components which incorporate similar structural features of FMAU, FIAU, and their analogues.[9]



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(9) The structural formulas of the 2′-deoxy-2′-fluoro-1′,2′-seconucleosides/nucleotides depicted in this paper are drawn in the "arabinose-like" conformation to point out their similarity with certain 2′-fluoroarabinosylpyrimidine nucleosides, e.g., FIAU and FMAU, that have demonstrated significant antiviral activity. In the text the naming and numbering of these analogues follow nucleoside nomenclature, however; in the Experimental Section the acyclic side chains of the 1′,2′-seconucleosides/nucleotides are named and numbered in accordance with butanetriol nomenclature.

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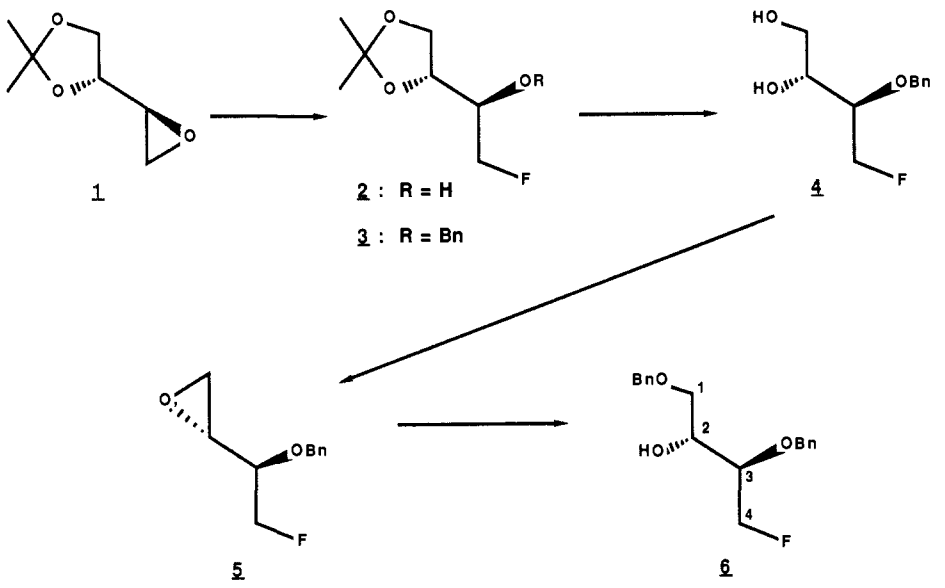
Scheme I

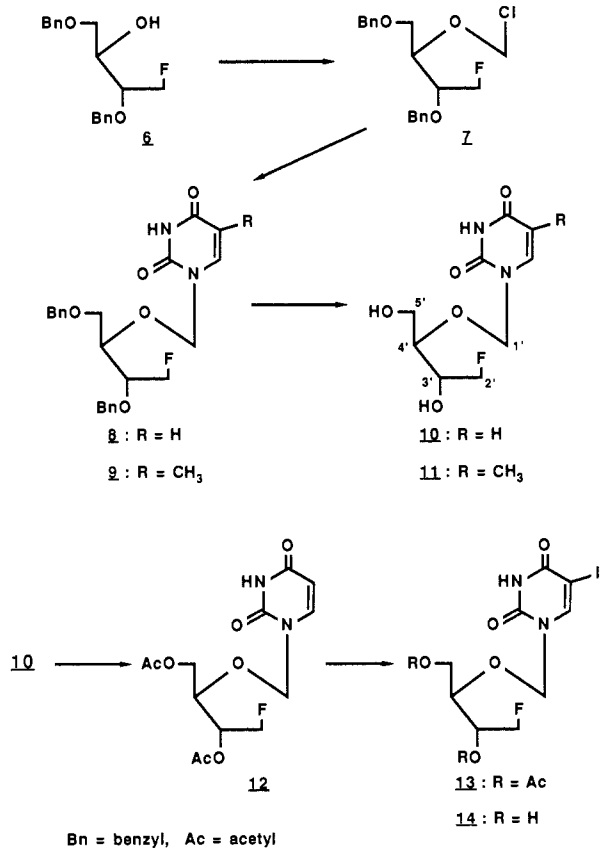


Chemistry and Discussion

We recently developed an efficient route for the preparation of chiral butanetriols and -tetrols from L-ascorbic and D-isoascorbic acid.[10] An intermediate in one pathway (2*R*,3*S*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (**1**), which is derived from D-isoascorbic acid, was selected as starting material for this project. Treatment of **1** with anhydrous tetrabutylammonium fluoride (TBAF) in dry benzene at reflux provided fluoro alcohol **2** (Scheme I) in good yield.[11] Benzylation of **2** using benzyl bromide in the presence of sodium hydride led to **3**, which on deacetonation afforded **4**. This monoprotected fluoro triol (**4**) was then converted to epoxide **5** via the Mitsunobu reaction.[12] Regiospecific ring opening of **5** with sodium benzylate furnished the desired, selectively protected fluoro triol **6**.

The targeted, pyrimidine acyclonucleosides **10**, **11**, and **14** were prepared as depicted in Scheme II. The chiron (*R*,*R*)-1,3-di-*O*-benzyl-4-fluorobutane-1,2,3-triol (**6**) was chloromethylated with paraformaldehyde and hydrogen chloride gas in dichloromethane at 0 °C to give **7**. Depending on the run, the percent purity[13] of **7** fluctuated between 80 and 90%. Once generated, chloromethyl ether **7** in dry dichloromethane was coupled with the desired persilylated heterocycle in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI) to furnish the blocked 1′,2′-seconucleosides. Thus, reaction with persilylated uracil and thymine gave **8** and **9**, respectively. Debenzylation of their respective, acyclic side chains using Pearlman's catalyst[13] provided **10** and **11** (the 1′,2′-seco analogue of FMAU) in excellent yields. 2′-Deoxy-2′-fluoro-1′,2′-secouridine (**10**) served as starting material for the preparation of FIAU analogue **14**. Acetylation of **10** using acetic anhydride–pyridine at room temperature led to **12** in high yield. Next, **12** was reacted with iodine monochloride (ICl) in dichloromethane[14] at reflux to give

Scheme II



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(11) Opening of the epoxide was investigated with a variety of conditions and solvents at reflux, i.e., using potassium fluoride and 18-crown-6 in acetonitrile (Mengel, R.; Guschlbauer, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 525), the same reagents in benzene (Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2250), potassium fluoride and tetrabutylammonium chloride in benzene (Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514), and potassium hydrogen fluoride in 1,2-ethanediol (Barford, A. D.; Foster, A. B.; Westwood, J. H.; Hall, L. D.; Johnson, R. N. *Carbohydr. Res.* **1971**, *19*, 49) as well as *tert*-butyl alcohol (Sarel-Imber, M.; Bergmann, E. D. *Carbohydr. Res.* **1973**, *27*, 73). All of these methods failed to yield **2**. The opening of **1** with TBAF gives on average a 65% yield of **2**.

(12) Mitsunobu, O. *Synthesis* **1981**, 1.

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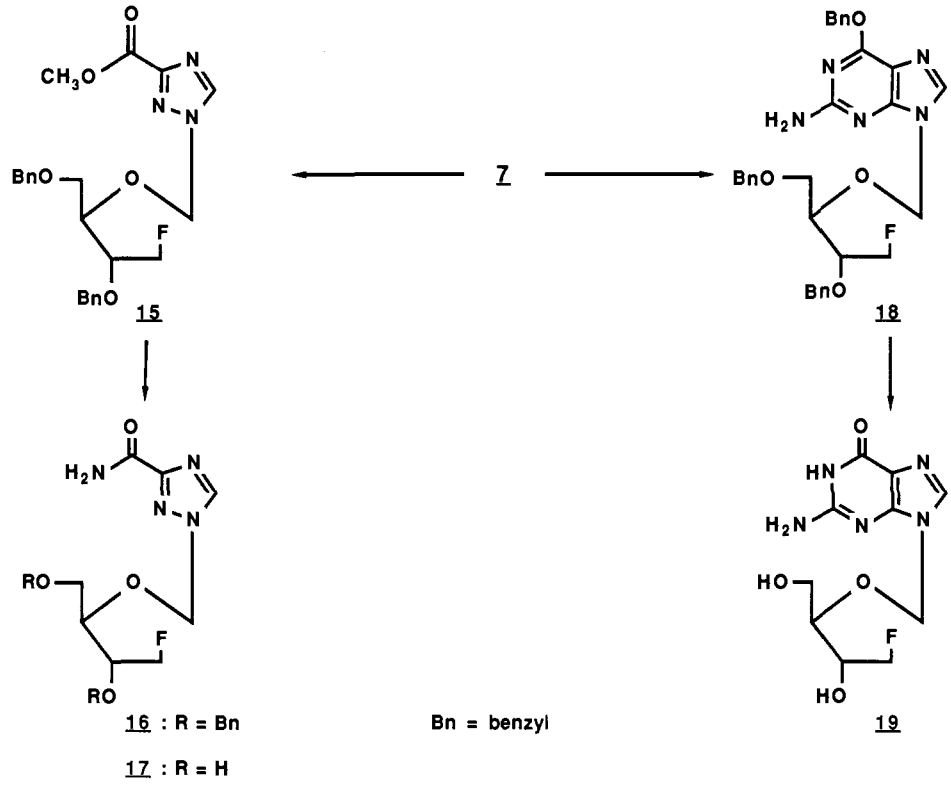
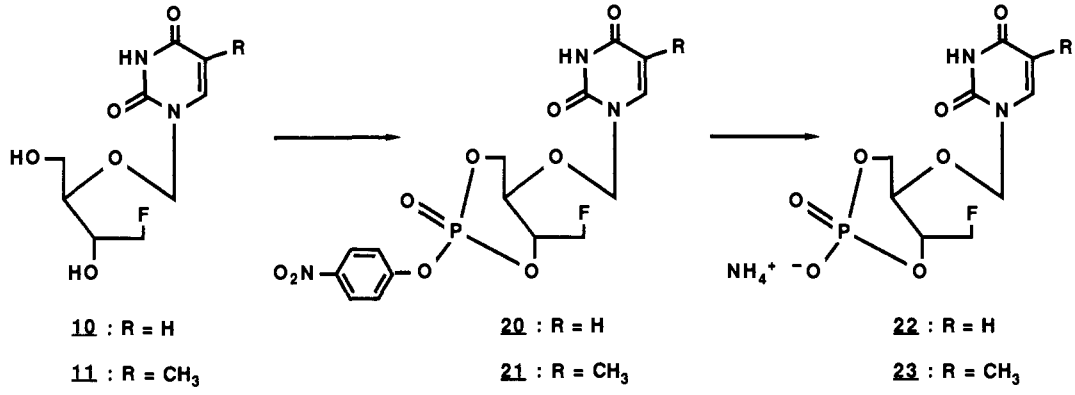
Scheme III



Scheme IV



13 in 88% yield. Treatment of 13 with potassium carbonate in aqueous methanol[15] afforded the desired 14.

With the ready availability of chiron 6, we turned our attention to synthesis of other chiral 2'-deoxy-2'-fluoro-1',2'-seconucleosides which might exhibit potent antiviral activity. Ribavirin analogue 17 (Scheme III) was prepared in a similar manner as that described for the pyrimidine analogues. Silylated methyl 1,2,4-triazole-3-carboxylate was condensed with chloromethyl ether 7 to provide blocked ester 15. The ester group on 15 was easily converted to the carboxamide function by methanolic ammonia at room temperature. Deblocking of amide 16 was carried out by transfer hydrogenation over Pearlman's catalyst.

The preparation of guanosine analogue 19 (Scheme III) followed synthetic methodology recently reported by Kjellberg and co-workers.[16] They found that a solution of 2-amino-6-(benzyloxy)-9*H*-purine[17] in dry DMF and in the presence of lithium hydride reacted regioselectively with 4-bromobutyl acetate to give the N(9)-alkylated derivative in a 6:1 (N9/N7) ratio. With the same experimental conditions, with the exception that 7 replaced 4-bromobutyl acetate, the N(9)- and N(7)-alkylated 2-amino-6-(benzyloxy)-9*H*-purines were obtained in a 15:1 (N(9)/N(7)) ratio. The enhanced regioselectivity may reflect the inherent differences in the properties of the two alkylating agents. Removal of the three benzyl protecting groups on N(9) isomer 18 was accomplished in one step by transfer hydrogenation to furnish 2'-deoxy-2'-fluoro-1',2'-secoguanosine (19).

The site of alkylation for the targeted pyrimidine analogues 10 and 11 was determined by UV spectroscopy. In the case of the 2'-deoxy-2'-fluoro-1',2'-seconucleosides of

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(17) For an improved synthesis of 2-amino-6-(benzyloxy)-9*H*-purine, see: MacCoss, M.; Chen, A.; Tolman, R. L. *Tetrahedron Lett.* **1985**, *26*, 1815 and references cited therein.

ribavirin and guanosine, ^{1}H NMR spectroscopy was employed.[13,18]

The effectiveness of acyclic nucleosides as antiviral agents is highly dependent on whether they are substrates for phosphorylating enzymes.[19] In an effort to penetrate the cell membrane and then, once in the cell, bypass the aforementioned activation requirement, we synthesized the 4-nitrophenyl 3′,5′-cyclic phosphate triesters[20] of **10** and **11** (Scheme IV). This was accomplished in one step by treating either 2′-deoxy-2′-fluoro-1′,2′-secouridine (**10**) or -thymidine (**11**) with 4-nitrophenyl phosphorodichloridate in dry acetonitrile and in the presence of pyridine. Triesters **20** and **21** were formed in good yields (ca. 70%). Coversion to their respective 3′,5′-cyclic phosphates (**22** and **23**) was achieved by dissolving the triesters in *p*-dioxane and treating the individual solutions with concentrated ammonium hydroxide. It is worth mentioning that DHPG,[19] certain 5-halocytidines,[21] and ribavirin[22] when derivatized as their 3′,5′-cyclic phosphates still exhibited good antiviral activity.

Biological Evaluation

Compounds **10**, **11**, **14**, **17**, and **19** were screened for activity against Vesicular Stomatitus (VSV) virus, Rift Valley Fever (RVF) virus, Adenovirus Type 2 (AD2), Vaccinia (VV) virus, Punta Toro (PT) virus, Japanese Encephalitis (JBE) virus, Sicilian Sandfly Fever (SSF) virus, and Yellow Fever (YF) virus. In addition, compounds **10**, **11**, and **19** were tested against Human Immunodeficiency virus (HIV), and compound **11** was tested against Pichinde (PIC) virus. The in vitro test results of these compounds were negative. Triesters **20** and **21** were assessed for activity against VSV, AD2, and VV and like their nucleoside counterparts were inactive. Nucleotides **22** and **23** are still undergoing evaluation.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian EM-390 spectrometer. Chemical shifts are in parts per million with respect to TMS. Optical rotations were obtained with a Perkin-Elmer Model 141 digital readout polarimeter. Ultraviolet absorption spectra were recorded with a Beckman DU-7 spectrophotometer. Silica gel (60–200 mesh) suitable for chromatographic use was purchased from Fisher Scientific Co. Thin-layer chromatography was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and shortwave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. All solvent proportions are by volume unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

(*R*,*R*)-4-Fluoro-1,2-*O*-isopropylidene-1,2,3-butanetriol (2). Tetrabutylammonium fluoride trihydrate (TBAF·3H_2O; 53.0 g, 0.168 mol) was added to dry benzene (105 mL) in a 250-mL round-bottomed flask which was fitted with a Dean–Stark apparatus and condensor. The solution was heated at reflux for 3.5 h and the water of hydration was removed as an azeotropic mixture. Epoxide **1**[10] (23.02 g, 0.16 mmol) was added to the above dried solution, stirred, and heated at reflux for 20 h. Next, the benzene was removed under diminished pressure and the resulting layered liquid was poured into a separatory funnel. The viscous, heavier layer was separated (the lighter, upper layer was shown by ^{1}H NMR spectroscopy to be tri-*n*-butylamine), placed on a silica gel column, and gradient eluted with a ethyl acetate–hexane solvent system (5:95 → 20:80). Chromatography furnished 19.0 g (72.5%) of **2** as a colorless liquid: $[\alpha]^{25}_D$ = +6.53° (*c* = 1.655, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H, CH_3), 1.4 (s, 3 H, CH_3), 3.23 (d, *J* = 2 Hz, 1 H, O*H*; D_2O exchangeable), 3.4–4.42 (m, 4 H), 4.52 (dm, *J* = 48 Hz, 2 H, CH_2F). Anal. ($C_7H_{13}FO_3$) C, H, F.

(*R*,*R*)-3-*O*-Benzyl-4-fluoro-1,2-*O*-isopropylidene-1,2,3-butanetriol (3). Fluoro alcohol **2** (22.02 g, 0.134 mol) in dry DMF (20 mL) was added dropwise to a cold (0 °C), mechanically stirred suspension of NaH (4.9 g, 0.204 mol; previously washed three times with dry benzene) in DMF (25 mL). After the mixture was stirred for 30 min, a solution of benzyl bromide (25.9 g, 0.151 mol) in dry DMF (20 mL) was added over 30 min, and the resulting mixture was stirred for 1.5 h. Next, water (5.0 mL) was carefully added to the reaction flask, the mixture was stirred, and then the mixture was poured into water (500 mL). The product was extracted with ethyl ether (4 × 150 mL). The ether extracts were combined, washed with water (4 × 100 mL), and dried over anhydrous $MgSO_4$. Removal of the ether under diminished pressure gave **3** (30.7 g, 90%). An analytical sample was obtained by silical gel chromatography using hexane–ethyl acetate (95:5): $[\alpha]^{25}_D$ = +42.7° (*c* = 1.495, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 3.28–5.0 (m, 6 H), 4.63 (AB q, 2 H, $OCH_2C_6H_5$), 7.28 (s, 5 H, C_6H_5). Anal. ($C_{14}H_{19}FO_3$) C, H, F.

(*R*,*R*)-3-*O*-Benzyl-4-fluoro-1,2,3-butanetriol (4). Amberlite IR-120 resin (70.0 g), water (85 mL), and concentrated hydrochloric acid (10 mL) were added to a stirred solution of **3** (85.1 g, 0.335 mol) in ethanol (853 mL). The reaction mixture was stirred for 16 h at room temperature and then filtered, and the filtrate was concentrated under diminished pressure to furnish an oily material. This material was extracted into ethyl ether (4 × 100 mL) and dried over anhydrous $MgSO_4$. The dried organic layer was filtered and the excess solvent was removed under diminished pressure to provide pure **4** in quantitative yield. Analytically pure **4** was obtained by chromatography on silica gel using ethtyl acetate as eluent: $[\alpha]^{25}_D$ = +19.5° (*c* = 1.08, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.88–4.00 (m, 6 H; 2 H are D_2O exchangeable), 4.59 (dm, *J* = 46.5 Hz, 2 H, CH_2F), 4.57 (AB q, *J* = 12 Hz, 2 H, $OCH_2C_6H_5$), 7.28 (s, 5 H, C_6H_5). Anal. ($C_{11}H_{15}FO_3$) C, H, F.

(*R*,*R*)-3-(Benzyloxy)-1,2-epoxy-4-fluorobutane (5). Diisopropyl diazodicarboxylate (DIAD, 16.31 g, 0.082 mol) was added dropwise to a stirred solution of **4** (15.01 g, 0.071 mol) and triphenylphosphine (TPP, 21.17 g, 0.081) in dry benzene (100 mL). After the addition was complete, the reaction mixture was allowed to cool to room temperature. The benzene was removed from the reaction mixture under diminished pressure and the resulting oily residue was distilled at 95–102 °C (0.2 mmHg) to give 10.68 g (77.7%) of pure **5**: $[\alpha]^{25}_D$ = −1.96° (*c* = 1.89, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.62–2.93 (m, 2 H), 2.97–3.17 (m, 1 H), 3.50 (dq, *J* = 18.75 and 4.5 Hz, 1 H), 4.50 (dd, *J* = 4.5 and 48 Hz, 2 H, CH_2F), 4.63 (s, 2 H, $OCH_2C_6H_5$), 7.3 (s, 5 H, $OCH_2C_6H_5$). Anal. ($C_{11}H_{13}FO_2$) C, H, F.

(*R*,*R*)-1,3-Di-*O*-benzyl-4-fluoro-1,2,3-butanetriol (6). A solution of sodium hydroxide (4.55 g, 0.114 mol) in water (4.6 mL) was added to a stirred solution of benzyl alcohol (40.5 mL), **5** (11.08 g, 0.057 mol), and *tert*-butyl alcohol (149 mL) at room temperature. The reaction mixture was stirred vigorously for 3 h at 90 °C. The reaction mixture was then diluted with water (50 mL) and extracted with ethyl ether (3 × 50 mL). The ether extracts were combined, washed with a saturated sodium chloride solution (2 × 30 mL) and dried over anhydrous $MgSO_4$. The ether and traces of benzyl alcohol were removed under diminished pressure to furnish pure **6** (14.16 g, 82.4%): $[\alpha]^{25}_D$ = +20.5° (*c* = 1.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.65 (d, *J* = 6 Hz, 1 H, OH; exchangeable with D_2O), 3.4–4.03 (m, 4 H), 4.08–5.08 (m, 6 H), 7.27 (s, 10 H, $OCH_2C_6H_5$). Anal. ($C_{18}H_{21}FO_3$) C, H, F.

(*R*,*R*)-2-(Chloromethoxy)-1,3-bis(benzyloxy)-4-fluorobutane (7). The chloromethyl ether was prepared according to literature procedures.[13,23] In a typical experiment, a solution of **6** (2.5 g, 8.2 mmol) in dry dichloromethane (CH_2Cl_2, 20 mL) was

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(23) Vemishetti, P.; Abushanab, E.; Leiby, R. W.; Panzica, R. P. *Nucleosides Nucleotides* **1989**, *8*, 201.

treated with paraformaldehyde (0.37 g) and dry hydrogen chloride gas at ice-bath temperature. After workup, 7 [2.9 g, 88.2% pure (^{1}H NMR[13,23])] was obtained as an oil.

1-[[1,3(*R*)-Bis(benzyloxy)-4-fluoro-2(*R*)-butoxy]methyl]uracil (8). Uracil (2.66 g, 24 mmol) and a catalytic amount of ammonium sulfate were added to hexamethyldisilazane (HMDS, 70 mL) and the mixture was stirred and heated at reflux overnight with the exclusion of moisture. The excess HMDS was removed under reduced pressure and the residue was dried in vacuo. A solution of 7 (5.89 g, 88.2% pure, 15 mmol) in dry CH_2Cl_2 (100 mL) and 50 mg of tetrabutylammonium iodide (TBAI) were added to the persilylated uracil and this mixture was stirred and heated at reflux for 4.5 h. After cooling, the reaction mixture was diluted with water (10 mL) and methanol (60 mL), stirred for 10 min, and then evaporated to dryness. The residue was dissolved in 50 mL of CH_2Cl_2 and the organic layer was washed in turn with a saturated sodium chloride solution (40 mL) and water (40 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the remaining residue was chromatographed on a silica gel column. Elution with hexane–ethyl acetate (1:1) furnished 8 (6.2 g, 99%): $[\alpha]^{25}_D = -10.5°$ (c = 1.43 EtOH); ^{1}H NMR ($CDCl_3$) δ 3.4–4.2 (m, 4 H), 4.52 (dm, J = 48 Hz, 2 H, CH_2F), 4.45 (s, 2 H, OCH_2Ph), 4.53 (AB q, J = 10 Hz, 2 H, OCH_2C$_6$H$_5$), 5.17 (AB q, J = 12 Hz, 2 H, OCH_2N), 5.56 (d, J = 7.5 Hz, 1 H, C(5)H), 7.14 (d, J = 7.5 Hz, 1 H, C(6)H), 7.25 (s, 10 H, C$_6$H$_5$), 9.18 (br s, 1 H, NH; D_2O exchangeable). Anal. ($C_{23}H_{25}FN_2O_5$) C, H, F, N.

1-[[1,3(*R*)-Bis(benzyloxy)-4-fluoro-2(*R*)-butoxy]methyl]thymine (9). Persilylated thymine [obtained from 1.2 g (9.6 mmol) of thymine] was coupled as described for 8 with 7 (2.9 g, 88.2% pure, 8.2 mmol) in dry CH_2Cl_2 (25 mL) and in the presence of TBAI (20 mg). The reaction mixture was stirred and heated at reflux for 24 h. Workup and chromatography afforded pure 9 (3.2 g, 76%): $[\alpha]^{25}_D = -11.9°$ (c = 1.08, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3 H, CH_3), 3.4–4.17 (m, 4 H), 4.47 (s, 2 H, OCH_2Ph), 4.55 (dm, J = 48 Hz, 2 H, CH_2F), 4.57 (AB q, J = 9 Hz, 2 H, OCH_2C$_6$H$_5$), 5.18 (AB q, 2 H, OCH_2N), 7.05 (s, 1 H, C(6)H), 7.32 (s, 10 H, C$_6H_5$), 10.1 (s, 1 H, NH; D_2O exchangeable). Anal. ($C_{24}H_{27}FN_2O_5$) C, H, F, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]uracil (10). Compound 8 (4.36 g, 10 mmol) was dissolved in absolute ethanol (54 mL) and to this solution was added 20% $Pd(OH)_2$/C (1.51 g) and cyclohexene (15 mL). The reaction mixture was stirred and heated at reflux for 15 h. The reaction mixture was then filtered through Celite and the filter cake was washed with warm ethanol. The filtrate and wash were combined and concentrated under diminished pressure to furnish 10 (quantitative) as a gum: $[\alpha]^{25}_D = -19.65°$ (c = 1.735, DMF); UV λ_{max} (pH 1) 258.5 nm (ϵ 10 853), λ_{max} (EtOH) 258 nm (10 734), λ_{max} (pH 11) 258 nm (8294); ^{1}H NMR (DMSO-d_6) δ 3.0–4.88 (m, 8 H; 2 H are exchangeable), 5.15 (AB q, J = 9.75 Hz, 2 H), 5.54 (dd, J = 7.5 and 1.5 Hz, 1 H, C(5)H; it becomes a doublet, J = 7.5 Hz, on addition of D_2O), 7.64 (d, J = 7.5 Hz, 1 H, C(6)H), 11.17 (s, 1 H, NH; D_2O exchangeable). Anal. ($C_9H_{13}FN_2O_5$) C, H, F, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]thymine (11). Catalytic transfer hydrogenation of 9 (3.17 g, 7.18 mmol) in 40 mL of absolute ethanol was carried out as described for 10 in the presence of 20% $Pd(OH)_2$/C (1.05 g) and cyclohexene (17 mL) to give 1.72 g (91.4%) of pure 11 as a gum: $[\alpha]^{25}_D = -0.8°$ (c = 1.5, EtOH); UV λ_{max} (pH 1) 265 nm (ϵ 8550), λ_{max} (EtOH) 263 nm (8295), λ_{max} (pH 11) 263 nm (7048); ^{1}H NMR (DMSO-d_6), δ 1.77 (s, 3 H, CH_3), 3.0–4.87 (m, 8 H; 2 H are exchangeable), 5.12 (AB q, J = 9.75 Hz, 2 H, OCH_2N), 7.5 (s, 1 H, C(6)H), 11.17 (s, 1 H, NH; D_2O exchangeable). Anal. ($C_{10}H_{15}FN_2O_5$) C, H, F, N.

1-[(1,3(*R*)-Diacetoxy-4-fluoro-2(*R*)-butoxy)methyl]uracil (12). Freshly distilled acetic anhydride (10 mL) was added to 1.52 g (4.03 mmol) of compound 10 in 10 mL of dry pyridine. After stirring for 1 day at room temperature, the excess reagents were removed under diminished pressure, the resulting residue was stirred with 10 mL of 0.1 N HCl for 5 min, and the mixture was taken to dryness in vacuo. The syrupy material was dissolved in a minimum amount of ethyl acetate and placed on a silica gel column, and the column was eluted with the same solvent to provide 12 (1.05 g, 78.1%) as a viscous oil: $[\alpha]^{25}_D = -24.7°$ (c = 1.215, EtOH); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H, OCOCH_3), 2.08 (s, 3 H, OCOCH_3), 3.93–4.53 (m, 3 H), 4.54 (dm, J = 46.5 Hz, 2 H, CH_2F), 4.67–5.07 (m, 1 H), 5.27 (AB q, J = 10.5 Hz, 2 H, OCH_2N), 5.78 (d, J = 7.5 Hz, 1 H, C(5)H), 7.29 (d, J = 7.5 Hz, 1 H, C(6)H), 9.63 (br s, 1 H, NH; exchangeable with D_2O). Anal. ($C_{13}H_{17}FN_2O_7$) H, F, N.

1-[(1,3(*R*)-Diacetoxy-4-fluoro-2(*R*)-butoxy)methyl]-5-iodouracil (13). Iodine monochloride (370 mg, 2.23 mmol) was added to a solution of 12 (490 mg, 1.48 mmol) in 10 mL of dry CH_2Cl_2 and stirred at reflux for 3 h. After cooling to room temperature, the solution was washed with a minimum amount (ca. 5 mL) of 2% $NaHSO_3$ solution, water, and finally with a saturated sodium chloride solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated under diminished pressure to give 280 mg (87.5%) of 13, as a gum: $[\alpha]^{25}_D = -3.49°$ (c = 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.0 (s, 3 H, OCOCH_3), 2.07 (s, 3 H, OCOCH_3), 3.88–4.48 (m, 3 H), 4.5 (dm, J = 48 Hz, CH_2F), 4.57–5.37 (m, 1 H), 5. 2 (s, 2 H, OCH_2N), 7.7 (s, 1 H, C(6)H), 9.6 (br s, 1 H, NH; exchangeable with D_2O). Anal. ($C_{13}H_{16}FN_2O_7I$) C, H, F, I, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]-5-iodouracil (14). To a solution of 13 (1.33 g, 2.91 mmol) in methanol (15 mL) and water (3 mL) was added potassium carbonate (0.4 g, 2.87 mmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was then neutralized with Dowex-50 (H^+) resin (ca. 2.8 g). The resin was removed by filtration and washed with methanol (2 × 10 mL). The filtrate and wash were evaporated in vacuo to a light pink gum. The gum was dissolved in methanol (10 mL), treated with activated charcoal, and filtered through a Celite pad, and the filtrate was taken to dryness. The resulting solid was crystallized from methanol to provide 14 (1.02 g, 94%): mp 64–67 °C; $[\alpha]^{25}_D = -27.2°$ (c = 1.76, EtOH); ^{1}H NMR (DMSO-d_6) δ 3.15–4.93 (m, 8 H; 2 H are D_2O exchangeable), 5.15 (AB q, 2 H, OCH_2N), 8.17 (s, 1 H, C(6)H), 11.6 (s, 1 H, NH; exchangeable with D_2O). Anal. ($C_9H_{12}FIN_2O_5$) C, H, F, I, N.

Methyl 1-[[1,3(*R*)-Bis(benzyloxy)-4-fluoro-2(*R*)-butoxy]methyl]-1,2,4-triazole-3-carboxylate (15). The silylated triazole ester [obtained from 1.67 g (13 mmol) of methyl 1,2,4-triazole-3-carboxylate] was treated as described earlier for 8 with 2(R)-(chloromethoxy)-1,3(S)-bis(benzyloxy)-4-fluorobutane (7; 5.78 g, 80% pure, 13 mmol) previously dissolved in dry acetonitrile (80 mL) which contained 23 mg of TBAI. The mixture was heated at reflux for 4.5 h and then for 3 days at room temperature. The acetonitrile was removed in vacuo and the residue was dissolved in 50 mL of CH_2Cl_2. This solution was washed with water, 10% aqueous sodium thiosulfate, water, and a saturated sodium chloride solution. The organic layer was dried over anhydrous $MgSO_4$ and then concentrated under diminished pressure to furnish 7.8 g of a viscous oil. This material was column chromatographed over silica gel using hexane–ethyl acetate (65:35) to provide 0.87 g (11%) of methyl 1-[[1,3(S)-bis(benzyloxy)-4-fluoro-2(R)-butoxy]methyl]-1,2,4-triazole-5-carboxylate and 3.7 g (46.8%) of the title compound 15.

Physical constants of the triazole-5-carboxylate: $[\alpha]^{25}_D = -13.7°$ (c = 2.17, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.33–4.27 (m, 4 H), 3.96 (s, 3 H, CO_2CH_3), 4.43 (s, 2 H, OCH_2C$_6$H$_5$), 4.44 (dm, J = 46.5 Hz, 2 H, CH_2F), 4.5 (AB q, 2 H, OCH_2C$_6$H$_5$), 5.98 (s, 2 H, OCH_2N), 7.22 (s, 5 H, C$_6H_5$), 7.28 (s, 5 H, C$_6H_5$), 7.92 (s, 1 H, C(3)H). Anal. ($C_{23}H_{26}FN_3O_5$) C, H, N, F.

Physical constants of the title compound 15: $[\alpha]^{25}_D = -18.6°$ (c = 1.395, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.37–4.08 (m, 4 H), 3.92 (s, 3 H, CO_2CH_3), 4.4 (s, 2 H, OCH_2C$_6$H$_5$), 4.43 (dm, J = 46.5 Hz, 2 H, CH_2F), 4.51 (AB q, 2 H, OCH_2C$_6$H$_5$), 5.63 (s, 2 H, OCH_2N), 7.25 (s, 10, C$_6H_5$), 8.25 (s, 1 H, C(5)H). Anal. ($C_{23}H_{26}FN_3O_5$) C, H, N, F.

1-[[1,3(*R*)-Bis(benzyloxy)-4-fluoro-2(*R*)-butoxy]methyl]-1,2,4-triazole-3-carboxamide (16). Cold, saturated methanolic ammonia (saturated at −10 °C) was added to 15 (3.19 g, 7.21 mmol) and kept in a sealed flask for 68 h at room temperature. At the end of this period, the excess ammonia was vented off and the solvent was removed under diminished pressure. The crystalline solid was collected by filtration, washed with cold methanol (10 mL), and air-dried to provide a quantitative yield of 16: mp 135–137 °C; $[\alpha]^{25}_D = -24.3°$ (c = 1.495, DMF); ^{1}H NMR (DMSO-d_6) δ 3.4–5.0 (m, 6 H), 4.42 (s, 2 H, OCH$_2$C$_6$H$_5$), 4.45 (AB q, 2 H, OCH_2C$_6$H$_5$), 5.68 (s, 2 H, OCH_2N), 7.27 (s, 10 H, C$_6H_5$), 7.67 (d, 2 H, CONH_2), 8.75 (s, 1 H, C(5)H).

Anal. ($C_{22}H_{25}FN_4O_4$) C, H, F, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2-butoxy)methyl]-1,2,4-triazole-3-carboxamide (17). A mixture of 16 (1.52 g, 3.54 mmol), 20% $Pd(OH)_2/C$ (0.4 g), cyclohexene (7 mL), and absolute ethanol (35 mL) was stirred and heated at reflux for 15 h. The hot mixture was filtered through a Celite pad, the pad washed with hot ethanol (2 × 10 mL), and the filtrate and wash were concentrated under diminished pressure. The resulting gum was dissolved in a small amount of ethyl acetate and applied to a silica gel column. Elution of the column with ethyl acetate provided 1,2,4-triazole-3-carboxamide. Further elution with ethyl acetate–methanol afforded 17. The title compound was dissolved in water (10 mL) and lyophylized to give 17 (0.39 g, 44.4%) as a glass: $[\alpha]^{25}_D = -31.5°$ (c = 1.79 EtOH); ^{1}H NMR (DMSO-d_6) δ 3.0–5.5 (m, 8 H; 2 H D_2O exchangeable), 5.17 (AB q, 2 H, OCH_2N), 7.91 (br d, 2 H, $CONH_2$; D_2O exchangeable), 8.82 (s, 1 H, C(5)H). Anal. ($C_8H_{13}FN_4O_4 \cdot 0.75H_2O$)[24] C, H, N.

2-Amino-6-(benzyloxy)-9-[[1,3(*R*)-bis(benzyloxy)-4-fluoro-2(*R*)-butoxy]methyl]purine (18). Lithium hydride (320 mg, 40.0 mmol) was added, in one portion, to a stirred solution of 2-amino-6-(benzyloxy)-9*H*-purine (6.0 g, 25 mmol) in dry DMF (130 mL). After the suspension stirred for 2 h at room temperature, chloromethyl ether 7 (10.8 g, 81.5% pure, 25 mmol), which was dissolved in DMF (35 mL), was added in one portion. The reaction mixture was stirred at 80 °C for 3 h, cooled to room temperature, and quenched with water (5 mL). The mixture was concentrated to ca. 50 mL in vacuo and then 200 mL of water was added. This mixture was extracted with ethyl acetate (4 × 50 mL) and the separated organic layer was washed with water (4 × 50 mL) and dried over anhydrous $MgSO_4$. The dried organic layer was concentrated under diminished pressure to provide a crude residue which was chromatographed over silica gel with hexane–ethyl acetate (1:1) as eluent. Chromatography afforded 4.78 g (34.3%) of pure 18 and 0.32 g (2.3%) of the N(7) isomer. The title compound 18 exhibited the following physical data: $[\alpha]^{25}_D = -13.7°$ (c = 1.16, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.3–4.08 (m, 4 H), 4.40 (s, 2 H, $CH_2C_6H_5$), 4.44 (dm, J = 46.5 Hz, 2 H, CH_2F), 4.51 (AB q, 2 H, $OCH_2C_6H_5$), 5.0 (br s, 2 H, NH_2, D_2O exchangeable), 5.5 (s, 4 H, OCH_2N and C(6)$OCH_2C_6H_5$), 7.33–7.53 (m, 15 H, C_6H_5), 7.58 (s, 1 H, C(8)H). Anal. ($C_{31}H_{32}FN_5O_4$) C, H, F, N.

9-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]-guanine (19). Catalytic transfer hydrogenation of 18 (1.9 g, 3.41 mmol) in absolute ethanol (100 mL) was carried out, as described for 17, in the presence of 20% $Pd(OH)_2/C$ (1.78 g) and cyclohexene (48 mL). The reaction mixture was stirred and heated at reflux and monitored by TLC. After 20 h, the reaction was not complete and additional amounts (one-half the above stated quantities) of $Pd(OH)_2/C$ and cyclohexene were added and the reaction continued. This process was repeated again after 30 h and the reaction was heated and stirred an additional 12 h. After workup, 19 (0.66 g, 66.4%) was obtained as a solid. An analytical sample was prepared by recrystallization from 95% ethanol: mp 320 °C dec; $[\alpha]^{25}_D = -49.0°$ (c = 1.075, DMF); ^{1}H NMR (DMSO-d_6) δ 3.0–5.32 (m, 8 H, 2 H are exchangeable), 5.43 (s, 2 H, OCH_2N), 6.58 (br s, 2 H, NH_2; exchangeable with D_2O), 7.78 (s, 1 H, C(8)*H*), 10.0–11.23 (br s, 1 H, N*H*; D_2O exchangeable). Anal. ($C_{10}H_{14}FN_5O_4 \cdot H_2O$) C, H, F, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]uracil 1′,3′-(Cyclic *p*-nitrophenyl phosphate) (20). To a stirred solution of 10 (1.2 g, 4.84 mmol) in dry acetonitrile (20 mL) was added dry pyridine (5 mL) and *p*-nitrophenyl phosphorodichloridate (1.86 g, 7.26 mmol). This mixture was stirred at room temperature for 24 h with the exclusion of moisture. The excess solvents were removed in vacuo, the resulting residue was dissolved in CH_2Cl_2 (100 mL), and the organic layer was washed successively with water (30 mL), a saturated sodium chloride solution (20 mL), and water (30 mL). After drying over anhydrous $MgSO_4$, the organic layer was evaporated under diminished pressure and the residue was dissolved in a minimal amount of ethyl acetate and applied to a silica gel column. Elution of the column with ethyl acetate provided 20 (1.45 g, 69.5%) as a crystalline solid: mp 147–152 °C dec; ^{1}H NMR (DMSO-d_6) δ 4.12-5.4 (m, 8 H), 5.68 (d, J = 7 Hz, 1 H), 7.4–7.84 (m, 3 H), 8.3 (d, J = 9 Hz, 2 H), 11.4 (br s, 1 H, N*H*). Anal. ($C_{15}H_{15}FN_3O_9P$) C, H, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]thymine 1′,3′-(Cyclic *p*-nitrophenyl phosphate) (21). Similar experimental conditions as those described for 20 were used to prepare 21. Thus, 11 (0.814 g, 3.1 mmol), dry pyridine (3 mL), and *p*-nitrophenyl phosphorodichloridate (1.2 g, 4.65 mmol) in dry acetonitrile (25 mL) afforded, after workup, 21 (0.910 g, 66%) as a white crystalline solid: mp 179–181 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3 H, CH_3), 4.06–5.3 (m, 8 H), 7.1 (s, 1 H), 7.33 (d, J = 9 Hz, 2 H), 8.16 (d, J = 9 Hz, 2 H), 9.56 (br s, 1 H). Anal. ($C_{16}H_{17}FN_3O_9P$) C, H, F, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]uracil 1′,3′-(Cyclic phosphate) Ammonium Salt (22). Triester 20 (1.18 g, 2.7 mmol) was dissolved in *p*-dioxane (50 mL) and to this solution was added concentrated ammonium hydroxide (6.4 mL, 5.5 mmol). After stirring overnight at room temperature, the excess solvents were removed in vacuo, and the resulting residue was purified by silica gel column chromatography. The column was eluted with ethyl acetate–methanol (7:3) to give 22 (0.72 g, 80%) as a white solid: mp 180–186 °C dec; ^{1}H NMR (D_2O) δ 3.6–5.4 (m), 5.82 (d, J = 8 Hz, 1 H), 7.68 (d, J = 8 Hz, 1 H). Anal. ($C_9H_{15}FN_3O_7P$) C, H, N.

1-[(1,3(*R*)-Dihydroxy-4-fluoro-2(*R*)-butoxy)methyl]thymine 1′,3′-(Cyclic phosphate) Ammonium Salt (23). Similar experimental conditions as those described for 22 were used to prepare 23. A solution of triester 21 (0.665 g, 1.5 mmol) in *p*-dioxane (30 mL) was treated with concentrated ammonium hydroxide (2.6 mL, 3 mmol) and after workup furnished 23 (0.25 g, 49%) as a white solid: mp 150–155 °C dec; ^{1}H NMR (D_2O) δ 1.84 (s, 3 H, CH_3), 3.9–5.36 (m), 7.48 (s, 1 H, C(6)H)). Anal. ($C_{10}H_{17}FN_3O_7P$) C, H, N.

In Vitro Antiviral Assays.[25-28] **(a) Inhibition of Cytopathic Effect (CPE).** Virus was absorbed for 1 h in 96-well monolayer cultures of Vero cells (Pt, JBE, SFS, YF), H.Ep.2 cultures (AD2), or LLC-MK2 cells (PT), after which tissue culture medium containing various drug concentrations was added. At the day of maximum CPE in virus control wells, medium was removed and monolayers were stained with crystal violet for microscopic CPE determination.

(b) Inhibition of Virus Plaque Formation. RVF plaque reduction was determined by adding a semisolid agarose overlay containing various drug concentrations to Vero monolayers after adsorption with 40–100 plaque-forming units (pfu) of RVF virus. After 96 h, the overlay was removed and plaques were visualized by crystal violet staining of the monolayers.

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Registry No. 1, 74134-78-4; 2, 123903-52-6; 3, 123903-53-7; 4, 123903-54-8; 5, 123903-55-9; 6, 123903-56-0; 7, 123903-57-1; 8, 123903-58-2; 9, 123903-59-3; 10, 123903-60-6; 11, 123903-61-7; 12, 123903-62-8; 13, 123903-63-9; 14, 123903-64-0; 15, 123903-65-1; 15 (5-isomer), 123903-73-1; 16, 123903-66-2; 17, 123903-67-3; 18, 123903-68-4; 18 (N^7-isomer), 123903-74-2; 19, 123933-27-7; 20, 123903-69-5; 21, 123903-70-8; 22, 123903-71-9; 23, 123903-72-0; uracil, 66-22-8; thymine, 65-71-4; methyl 1,2,4-triazole-3-carboxylate, 4928-88-5; 2-amino-6-(benzyloxy)-9*H*-purine, 19916-73-5; *p*-nitrophenyl phosphorochloridate, 777-52-6.

(24) Water of hydration was observed by ^{1}H NMR spectroscopy.

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