Phosphonate Analogs of Carbocyclic Nucleotides

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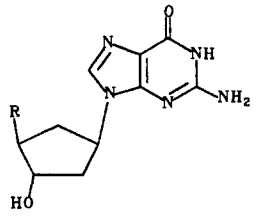
Received November 8, 1993•

Cyclopentadiene was converted in six steps to the key intermediate (±)-(1α,2β,4α)-4-amino-2-(benzyloxy)cyclopentanol (**10**), which in turn was converted to the carbocyclic nucleoside analogs **14** and **19** by standard procedures developed in these laboratories. Compounds **14** and **19** were then further converted to the target phosphonates **1b** and **2b** by modification of literature procedures. The phosphonate **1b** was 40-fold more cytotoxic to HEp-2 cells than its parent, CDG, presumably after conversion to the diphosphoryl phosphonate.

Introduction

The low level or lack of cytotoxicity of certain carbocyclic nucleosides, such as carbocyclic 2′-deoxyguanosine (CDG, **1a**)[1] and carbocyclic 6-(methylthio)purine 2′-deoxyribonucleoside (**2a**),[2] to human cancer cells in culture is due to their failure to be phosphorylated to a significant extent in these cells. CDG is, however, a potent antiviral agent[1] and has been shown to be phosphorylated in cells infected with Herpes Simplex 1.[3] A virally encoded kinase is responsible for the initial phosphorylation to the monophosphate, which is further phosphorylated by cellular kinases to the triphosphate. The triphosphate is then incorporated into both viral and cellular DNA.[4]



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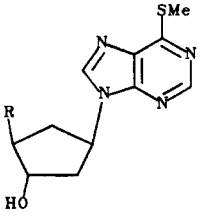
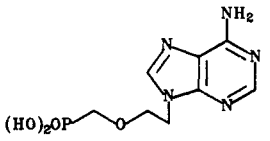
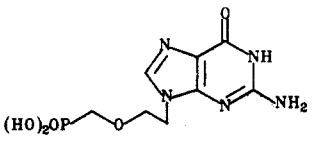


2

a: R = $HOCH_2$
b: R = $(HO)_2OPCH_2O$



PMEA



PMEG

The antiviral activity of 9-[2-(phosphonomethoxy)ethyl]-adenine (PMEA) and the corresponding guanine (PMEG)[5] suggested a similar approach to the design of cytotoxic analogs of CDG and other nontoxic carbocyclic nucleosides, since such PME derivatives of adenine and guanine are phosphorylated *in vivo* and the resulting diphosphoryl phosphonates are inhibitors of HIV reverse transcriptase.[6] This approach has been applied to other carbocyclic nucleosides with anti-HIV activity to enhance their selectivity[7,8] but not to the design of cytotoxic agents with potential anticancer activity.

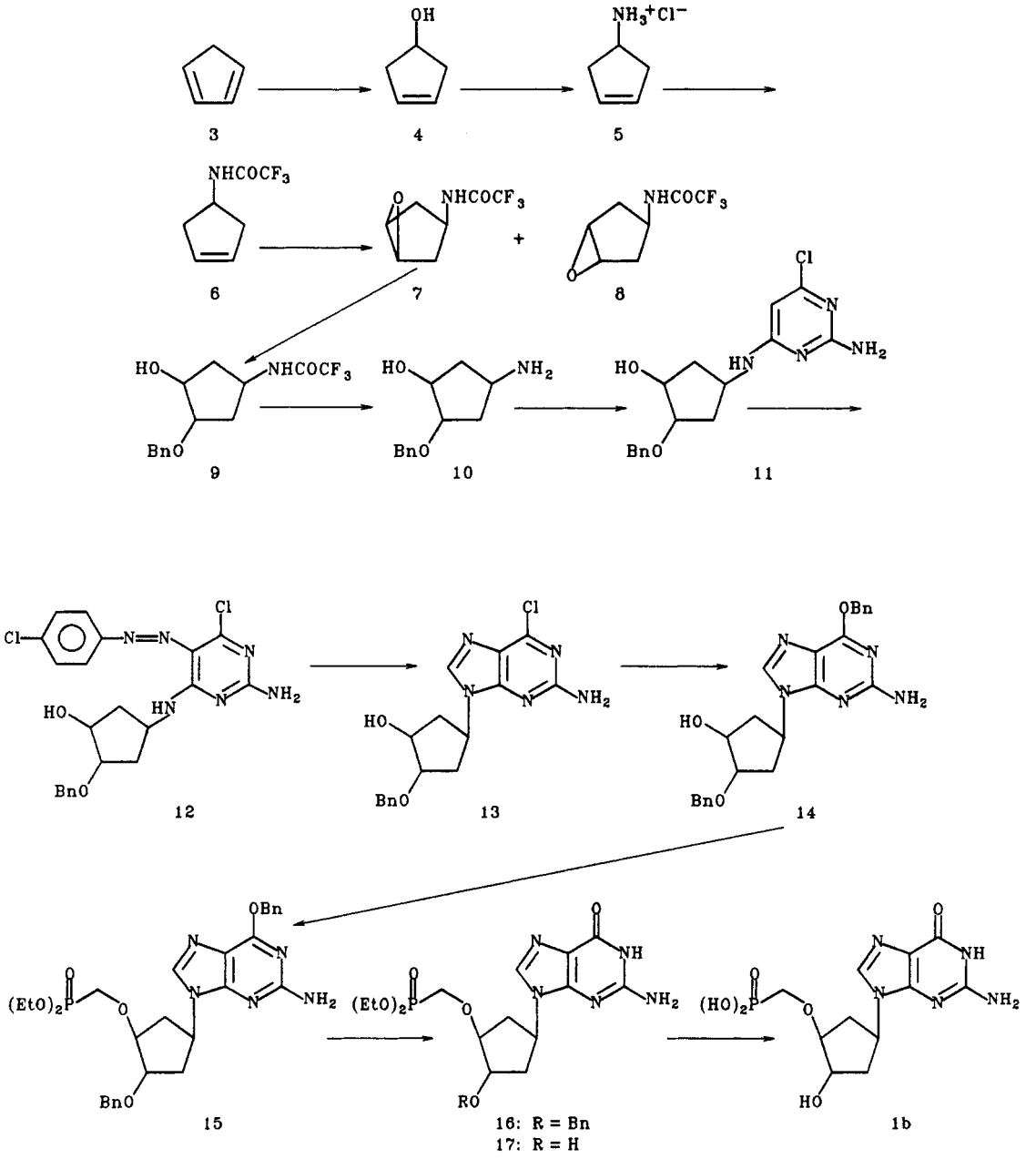
Chemistry

The route selected for the synthesis of **1b** is shown in Scheme 1. The key intermediate **10** was prepared from redistilled cyclopentadiene which was hydroborated and oxidized to give a 29% yield of the alcohol **4**.[9] A Mitsunobu coupling of **4** with hydrazoic acid gave a 40% yield of the amine **5** as the hydrochloride. Treatment of **5** with trifluoroacetic anhydride and triethylamine gave the trifluoroacetamide **6** in 93% yield. Epoxidation of **4** with *m*-chloroperbenzoic acid gave a 92% yield of the *cis*-epoxide (**7**).[10] A low yield (2%) of the *trans*-epoxide (**8**) was isolated from a previous run. The diastereomers **7** and **8** were distinguished by comparing the amide NH and the epoxide protons of their ^{1}H-NMR spectra in the manner described for the benzamides corresponding to **7** and **8**.[11] The NH region for **7** (δ = 8.74 ppm) is shielded by the *cis*-epoxide relative to the NH in **8** (δ = 9.35 ppm), whereas the epoxide protons of **8** (δ = 3.54 ppm) are shielded by the cis nitrogen compared to the epoxide protons in **7** (δ = 3.57 ppm). Further evidence for the structure of **7** was obtained from its derivative **13**, which is discussed below. Boron trifluoride acidification of the epoxide **7** allowed trans opening of the ring with the benzyl alcohol to give a 74% yield of the racemic mixture **9**. Basic hydrolysis of **9** gave a 98% yield of the amino alcohol **10**, which was heated with 2-amino-4,6-dichloropyrimidine and *N,N*-diisopropylethylamine in butanol to give an 87% yield of pyrimidine intermediate **11**.[12] Reaction of **11** with 4-chlorobenzenediazonium chloride gave a 91% yield of the azo intermediate **12**, which was reduced and cyclized to give a 50% yield of the 2-amino-6-chloropurine **13**. The unambiguous assignment of the ^{1}H-NMR spectrum of **13** was possible because 1-OH was coupled to H-1 ($J_{1,1\text{-OH}}$ = 4.0 Hz). The large chemical shift difference ($\Delta\delta$ = 0.63 ppm) between the geminal hydrogens on C-5 indicated that the purine and 1-OH were in a 1,3-cis relationship. Furthermore, the very small chemical shift difference ($\Delta\delta$ = 0.0 ppm) between the geminal C-3 hydrogens indicated that the 2-*O*-benzyl group and the purine are in a 1,3-trans relationship.[13] NOE experiments allowed us to confirm the configuration of the carbocyclic ring in **13** (Scheme 1). The irradiation of H-1 gave a 1.4% and a 3.4% enhancement of H-4 and H-5β, respectively. The irradiation of H-4 gave a 0.9% and a 3.8% enhancement of H-1 and H-5β, respectively. The irradiation of H-8 caused NOE's of 2.6% and 2.4% to H-4 and H-5α, respectively. These data confirm that H-1, H-5β, and H-4 are on the same side of the ring. Therefore, the 1-OH and the base are in a 1,3-cis relationship. Treatment of **13** with sodium benzyl oxide gave the 2-amino-6-(benzyloxy)-purine **14** in 80% yield. The phosphono group was introduced by treatment of the sodium salt of **14** with

† Deceased.
• Abstract published in *Advance ACS Abstracts*, February 15, 1994.

0022-2623/94/1837-0739$04.50/0

Scheme 1

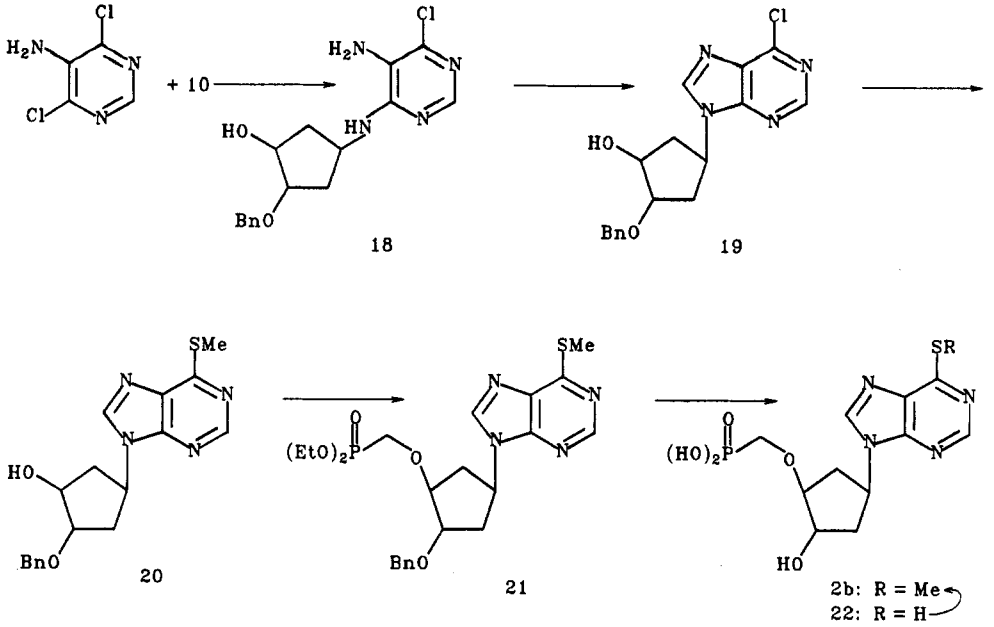


diethyl *p*-((tolylsulfonyl)oxy)methanephosphonate[14,15] to give a 51% yield of the carbocyclic phosphonate **15**. Partial debenzylation of **15** could be clearly achieved by hydrogenation for 3 h in the presence of 5% Pd on carbon to give a 72% yield of **16**. Complete debenzylation of **15** could be accomplished by hydrogenation for 20 h in the presence of 10% Pd on carbon to give an 87% yield of **17**. Treatment of **17** with trimethylsilyl bromide gave an 87% yield of the unblocked phosphonate **1b**.

The versatile benzyloxy amino alcohol **10** was also used for the synthesis of the (methylthio)purine phosphonate **2b** as shown in Scheme 2. Reaction of **10** with 5-amino-4,6-dichloropurine and *N,N*-diisopropylethylamine in butanol gave a 79% yield of **18**.[16] Ring closure was carried out with triethyl orthoformate and concentrated hydrochloric acid[17] to give an 84% yield of **19**. The chlorine of **19** was then displaced by treatment with sodium methyl mercaptide to give an 85% yield of **20**. Treatment of the sodium salt of **20** with diethyl *p*-((tolylsulfonyl)oxy)-methanephosphonate gave a 57% yield of the phosphonate ester **21**. Cleavage of the ester groups of **21** with trimethylsilyl iodide gave a 2:1 mixture of the desired phosphonate **2b** and the demethylated byproduct **22**. Treatment of the mixture with methyl iodide converted the thiol **22** to the methylthio target **2b**, which was isolated in 52% yield using ion-exchange chromatography.

Cell Culture Cytotoxicity.[18] The phosphonate **1b** was 40-fold more cytotoxic to human epidermoid carcinoma cells no. 2 (HEp-2) in culture than CDG with an IC_{50} of 2.4 μM vs 95 μM for CDG. It is metabolized in HEp-2 cells, but the metabolite has not been characterized. Guanylate kinase from pig brain[19] converted **1b** to a single product, which had a retention time on an anion-exchange column[20] consistent with that of a diphosphate of a phosphonate analog.[21] Alkaline phosphatase converted this product back to **1b**, as judged by its retention time on HPLC. The phosphonate **2b** was not cytotoxic to HEp-2 cells, probably because it is not efficiently phosphorylated, since 6-(methylthio)purine ribonucleoside, although cytotoxic, is very slowly converted to the triphosphate.[22] Neither compound was cytotoxic to murine leukemia L1210 cells.

Scheme 2



Experimental Section

All evaporations were carried out *in vacuo* with a rotary evaporator or by short-path distillation into a dry ice/acetone-cooled receiver under high vacuum. Analytical samples were normally dried *in vacuo* over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated aqueous $(NH_4)_2SO_4$. All analytical samples were homogeneous by TLC. Melting points were determined with a Mel-Temp apparatus unless otherwise specified. Purifications by gravity column and by flash chromatography were carried out on Merck silica gel 60 (230–400 mesh) using the slurry method of column packing. The UV absorption spectra were determined in 0.1 N HCl (pH 1), pH 7 buffer, and 0.1 N NaOH (pH 13) with a Cary 17 spectrophotometer and a Perkin-Elmer ultraviolet–visible near-infrared spectrophotometer Model Lambda 9: the maxima are reported in nanometers ($\epsilon \times 10^{-3}$ M^{-1} cm^{-1}). The NMR spectra were determined with a Nicolet/GE NT 300NB spectrometer operating at 300.35 MHz for ^{1}H-NMR spectra with tetramethylsilane as an internal reference. Chemical shifts (δ, ppm) quoted in the case of multiplets are measured from the approximate center. The mass spectra were obtained with a Varian-MAT 311A mass spectrometer in the fast-atom-bombardment mode (glycerol matrix). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

For the NOE measurements, the Me_2SO-d_6 solution was degassed. The spectral conditions were as follows: number of data points 32K; relaxation delay 20 s; an irradiation time of 2 s with irradiation power yield of >95%. To minimize the effects of magnetic perturbations, eight fid's were acquired with the decoupler set at a desired frequency, and eight fid's were acquired with the decoupler off-resonance. The process was repeated until 1000 fid's had been accumulated for each experiment. Subsequent subtraction of the two spectra afforded the net enhancement.

(±)-(1α,3β,4α)-2-Amino-1,9-dihydro-9-(3-hydroxy-4-(phosphonomethoxy)cyclopentyl)-6*H*-purin-6-one (1b). A stirred solution of **17** (409 mg, 0.997 mmol) in anhydrous DMF (15 mL) under N_2 was treated with trimethylsilyl bromide (1.32 mL, 9.97 mmol) and stirred for 19 h. The reaction mixture was placed under water aspirator vacuum for a few minutes to remove EtBr and then concentrated under high vacuum to remove DMF. A solution of the residue in 1 N NH_4OH (15 mL) was refrigerated overnight and then evaporated to a solid *in vacuo*. A flash column of silica gel (80 g) was washed with 1.2 L of *n*-BuOH–AcOH–H_2O (10:2:3) to remove acid-soluble components. A solution of the product residue in the above-mentioned solvent (50 mL) was applied to the column and eluted with the same solvent. The product fraction was evaporated to give a white solid: yield 315 mg (87%); mp >300 °C dec (partially decomposed from 280 °C); MS pos. *m/z* 346 $(M + H)^+$; neg. *m/z* 344 $(M - H)^-$; UV λ_{max} nm ($\epsilon \times 10^{-3}$) pH 1, 254 (12.0), 278 sh (7.1); pH 7, 254 (13.0); pH 13, 268 (11.4); ^{1}H NMR (Me_2SO-d_6) δ 10.52 (br s, 1, NH), 7.79 (s, 1, H-8), 6.43 (s, 2, NH_2), 4.86 (m, 1, H-1′), 4.20 (m, 1, H-3′), 3.80 (m, 1, H-4′), 3.60 (d, 2, PCH_2, $^2J_{PCH}$ = 9.4 Hz), 2.51 (m, 1, H-5′β), 2.14 (m, 1, H-2′β), 2.04 (m, 1, H-2′α), 1.88 (m, 1, H-5′α). Anal. ($C_{11}H_{16}N_5O_6P \cdot 0.9H_2O$) C, H, N.

(±)-(1α,2β,4β)-2-(Phosphonomethoxy)-4-[6-(methylthio)-9*H*-purin-9-yl]cyclopentanol (2b). A stirred solution of **21** (106 mg, 0.209 mmol) in anhydrous DMF (5 mL) under argon was treated in portions with trimethylsilyl iodide (298 μL, 2.09 mmol) and stirred with protection from light for 5 days. Additional trimethylsilyl iodide (150 μL, 1.05 mmol) was added; the reaction mixture was stirred an additional 2 days and evaporated to dryness under high vacuum. The residue of viscous yellow oil was flash chromatographed (25 g silica gel, 3:1 MeCN–1 N NH_4OH) to give 69 mg of a 1:2 mixture of **2b** and the demethylated byproduct **22** as determined by ^{1}H NMR and HPLC. This suspension in anhydrous DMF (5.5 mL) under N_2 was treated with MeI (9.1 μL, 0.15 mmol), stirred for 18 h in the dark, and then evaporated to dryness under high vacuum. A solution of the residue in 1 N NH_4OH (5 mL) was filtered and evaporated *in vacuo* to a semisolid. A solution of the residue in H_2O (2 mL) was applied to an ion-exchange column of Bio-Rad AG 1-X8 resin (200–400 mesh, formate form). The product was eluted with formic acid, gradually increasing the concentration from 0.1 to 7 N acid. The product fraction was evaporated to a gum which was dissolved H_2O (20 mL), frozen, and lyophilized to give the product as a fluffy white solid: yield 42 mg (52%); MS pos. *m/z* 361 $(M + H)^+$; neg. 359 $(M - H)^-$; ^{1}H NMR (Me_2SO-d_6) δ 8.70 (s, 1, H-2), 8.55 (s, 1, H-8), 5.16 (m, 1, H-4), 4.26 (m, 1, H-1), 3.95 (m, 1, H-2), 3.60 (d, 2, PCH_2, $^2J_{PCH}$ = 9.6 Hz), 2.66 (s, 3, SCH_3), 2.60 (m, 2, H-3α), 2.24 and 2.16 (m, m, 2, H-5α, H-5β), 2.03 (m, 1, H-3α). Anal. ($C_{12}H_{17}N_4O_5PS \cdot 0.2NH_3 \cdot 1.2H_2O$) C, H, N.

3-Cyclopenten-1-ylamine Hydrochloride (5). A 29% yield of 3-cyclopenten-1-ol was obtained by hydroboration of freshly distilled cyclopentadiene followed by H_2O_2 oxidation in base.[9] To a solution of the cyclopentenol (21.3 g, 254 mmol) in anhydrous THF (128 mL) under argon was added a 1.56 M solution of HN_3 in benzene (195 mL, 304 mmol) followed by a solution of diisopropyl azodicarboxylate (55 mL, 280 mmol) in THF (125 mL). To this solution was added dropwise a solution of triphenylphosphine (146 g, 556 mmol) in THF (760 mL) at a rate

that allowed the exothermic reaction to remain at 27–28 °C. Ice and later water baths were necessary to maintain this temperature. The solution was stirred for 1 h at 28–30 °C and then for 3 h at 50 °C. Water (25.3 mL) was added and the solution stirred at 50 °C for 3 h. The THF and benzene were removed *in vacuo* (water aspirator), and the residual liquid was partitioned between 1 N HCl (1 L) and CH_2Cl_2 (1 L). The aqueous layer was further washed with CH_2Cl_2 (3 × 1 L) and evaporated to a syrup (water aspirator, bath ~40 °C) and the residue evaporated several times with EtOH. The crystalline residue was recrystallized from EtOH (75 mL) with Et_2O (253 mL) to give pure 3-cyclopenten-1-ylamine hydrochloride: yield 12.2 g (40%); mp 211–213 °C dec (lit.[23] mp 219–221 °C); MS *m/z* 84 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.18 (s, 3, NH_3^+), 5.71 (m, 2, CH=CH), 3.78 (m, 1, CHN), 2.67 (q, 2, *H*CH), 2.36 (dd, 2, HC*H*).

***N*-(3-Cyclopenten-1-yl)trifluoroacetamide (6).** A stirred suspension of **5** (12.0 g, 100 mmol) in anhydrous pyridine (144 mL) and Et_3N (16.0 mL, 115 mmol) was cooled under argon in an ice bath and treated dropwise at ca. 25 °C with a solution of trifluoroacetic anhydride (15.5 mL, 110 mmol) in anhydrous CH_2Cl_2 (96 mL). The mixture was stirred an additional 4 h at 25 °C, treated dropwise with H_2O (2.87 mL), stirred for 5 min, and mixed in a separatory funnel with CH_2Cl_2 (1 L) and 1 N HCl (1 L). The CH_2Cl_2 layer was separated, washed with additional 1 N HCl (3 × 1 L), dried over $MgSO_4$, and evaporated carefully under water aspirator vacuum to a crystalline residue. To avoid loss of product, the residue was further dried under water aspirator vacuum for three 15-min periods (until constant weight) to give pure **6**: yield 16.6 g (93%); mp 62 °C; MS *m/z* 180 $(M + H)^+$, neg. *m/z* 178 $(M - H)^-$; ^1H NMR (Me_2SO-d_6) δ 9.53 (br s, 1, NH), 5.71 (m, 2, CH=CH), 4.38 (br s, 1, CHN), 2.65, 2.29 (m s, 4, CH_2's). Anal. ($C_7H_8F_3NO$) C, H, N.

(1α,3α,5α)-*N*-(6-Oxabicyclo[3.1.0]hex-3-yl)trifluoroacetamide (7). A stirred solution of **6** (16.0 g, 89.3 mmol) in CH_2Cl_2 (900 mL) under N_2 in an ice bath was treated in portions with 50–60% *m*-chloroperbenzoic acid (30.9 g, 89.5 mmol, based on 50% purity). The solution was stirred for an additional 20 min at 0 °C and then for 90 min at 25 °C. Cyclopentene (2 mL) was added to decompose excess MCPBA, and stirring was continued for 15 min. The reaction mixture was dried over $MgSO_4$, filtered, and evaporated to a thick slurry which was filtered, and the precipitate of *m*-chlorobenzoic acid (MCBA) was rinsed with CH_2Cl_2. The filtrate and wash were further concentrated *in vacuo*, removing more MCBA when appropriate. The evaporated filtrate in CH_2Cl_2 was cooled in an ice bath and treated with Et_3N (1.25 mL, 9 mmol) to form a salt of the remaining MCBA. This mixture in 2:1 CH_2Cl_2–C_6H_{12} was applied to a flash column of 250 g of silica gel and eluted with the same solvent. The product fraction was evaporated under water aspirator vacuum to give the crystalline epoxide **7**: yield 16.0 g (92%); mp 48–50 °C; MS *m/z* 196 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.74 (br s, 1, NH), 4.13 (m, 1, CHN), 3.58 (s, 2, OCH), 2.72–1.96 (m, 4, CH_2's). Anal. ($C_7H_8F_3NO_2$·0.2H_2O) C, H, N. In an earlier synthesis, a slower traveling isomer (**8**) was isolated in very low yield (2%) and identified as the *trans*-epoxide isomer by ^1H NMR: (Me_2SO-d_6) δ 9.35 (br d, 1, NH), 3.83 (m, 1, CHN), 3.54 (s, 2, OCH), 2.28 (dd, 2, CH_aH$_b$, J = 7.8 Hz, J = 14 Hz), 1.67 (dd, 2, CH$_a$H$_b$, J = 8.9 Hz).

(±)-(1α,3β,4α)-*N*-(3-(Benzyloxy)-4-hydroxycyclopentyl)trifluoroacetamide (9). A stirred solution of **7** (15.5 g, 79.4 mmol) in 4A molecular sieve dried benzyl alcohol (155 mL) was cooled under N_2 in an ice bath and treated dropwise with BF_3·Et_2O (7.81 mL, 63.5 mmol) over a period of 5 min. The solution was stirred at 25 °C for 2.5 h and evaporated to a thick syrup under high vacuum at 50–55 °C. A short-path lyophilizer-type distillation apparatus was necessary to remove the benzyl alcohol. The residual syrup in $CHCl_3$ was applied to a flash column of 500 g of silica gel and the column eluted with $CHCl_3$ until all of the benzyl alcohol came off. The solvent was then changed to 98:2 $CHCl_3$–MeOH. A crude fraction (2 g) was discarded and a pure fraction evaporated to give a crystalline solid: yield 17.7 g (74%); mp 65–66 °C; MS *m/z* 304 $(M + H)^+$, 288 $(M - OH)^+$, 196 $(M - OBn)^+$; ^1H NMR (Me_2SO-d_6) δ 9.37 (br s, 1, NH), 7.33 (m, 5, C_6H_5), 5.06 (br d, 1, OH), 4.50 (AB quartet, 2, $PhCH_2$), 4.19 (m, 1, H-1), 4.00 (m, 1, H-4), 3.77 (m, 1, H-3), 2.28 (m, 1, H-5β), 2.02–1.87 (m, 2, H-2α, H-2β), 1.55 (m, 1, H-5α). Anal. ($C_{14}H_{16}F_3NO_3$) C, H, N.

(±)-(1α,2β,4α)-4-Amino-2-(benzyloxy)cyclopentanol (10). A solution of 1 N NaOH (122 mL, 122 mmol) was poured slowly into a solution of **9** (17.5 g, 57.8 mmol) in MeOH (400 mL) and the resulting solution heated slowly to 50 °C over 30 min and then heated at 50 °C for 3 h. The reaction mixture was concentrated *in vacuo* (water aspirator) to ca. 75 mL and then extracted with $CHCl_3$ (4 × 100 mL). The extract was dried over $MgSO_4$, filtered through Celite, and evaporated to a syrup *in vacuo*. The syrup crystallized to give 11.7 g of **10** (98%): mp 62–64 °C; MS *m/z* 208 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 7.30 (m, 5, C_6H_5), 4.47 (AB quartet, 2, $PhCH_2$), 3.92 (m, 1, H-1), 3.77 (m, 1, H-2), 3.28 (m, 1, H-4), 2.05 (m, 1, H-5β), 1.79 (m, 1, H-3β), 1.64 (m, 1, H-3α), 1.24 (m, 1, H-5α). Anal. ($C_{12}H_{17}NO_2$·0.1H_2O) C, H, N.

(±)-(1α,2β,4α)-4-[(2-Amino-6-chloropyrimidin-4-yl)amino]-2-(benzyloxy)cyclopentanol (11). A solution of **10** (5.00 g, 24.2 mmol), 2-amino-4,6-dichloropyrimidine (4.36 g, 26.6 mmol), and *N*,*N*-diisopropylethylamine (9.24 mL, 53.1 mmol) in 1-butanol (170 mL) was stirred at reflux temperature under N_2 for 2 days. The reaction mixture was concentrated to a syrup on a rotary evaporator and the syrup co-evaporated with toluene. A solution of the residue in 96:4 $CHCl_3$–MeOH was applied to a flash column of 500 g of silica gel and eluted with the same solvent. The product fraction was collected and evaporated to give a crystalline solid: yield 7.06 g (87%); mp 111–112 °C; MS *m/z* 335 $(M + H)^+$, 243 $(M - Bn)^+$; ^1H NMR (Me_2SO-d_6) δ 7.33 (m, 5, C_6H_5), 7.14 (br s, 1, NH), 6.37 (s, 2, NH_2), 5.71 (s, 1, H-5), 4.99 (d, 1, 1-OH, $J_{1,1\text{-OH}}$ = 4.0 Hz), 4.50 (AB quartet, 2, CH_2Ph), 4.37 (br m, 1, H-4), 4.00 (m, 1, H-1), 3.76 (m, 1, H-2), 2.32 (m, 1, H-5β), 2.03 (m, 1, H-3α), 1.75 (m, 1, H-3β), 1.35 (m, 1, H-5α). Anal. ($C_{16}H_{19}ClN_4O_2$) C, H, N.

(±)-(1α,2β,4α)-4-[[2-Amino-6-chloro-5-[(4-chlorophenyl)azo]pyrimidin-4-yl]amino]-2-(benzyloxy)cyclopentanol (12). A cold solution of 4-chlorobenzenediazonium chloride was prepared by adding a solution of $NaNO_2$ (2.22 g of 97%, 31.3 mmol) in H_2O (17 mL) to a solution of 4-chloroaniline (3.77 g, 29.5 mmol) in H_2O (50 mL) and 12 N HCl (17 mL) at 0 °C (ice bath). This solution of diazonium salt was stirred an additional 5 min and added rapidly to a stirred solution of **11** (6.61 g, 19.7 mmol) and NaOAc·3H_2O (43.1 g) in acetic acid (100 mL) and H_2O (100 mL) at 25 °C. After being stirred for 20 h, the reaction mixture was cooled in an ice bath and the yellow precipitate of product was collected, washed with cold H_2O, and dried *in vacuo* (P_2O_5): yield 9.33 g (91%); mp 174–177 °C; MS *m/z* 473 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 12.0 (br s, H^+ of acetic acid), 10.63 (d, 1, NH), 7.74 (d, 2, 2H of phenylazo), 7.56 (d, 3H of phenylazo), 7.49 (br s, NH_2), 7.33 (m, 5, C_6H_5), 5.27 (br s, 1, 4-OH), 4.79 (m, 1, H-4), 4.51 (AB quartet, 2, $PhCH_2$), 4.17 (m, 1, H-1), 3.91 (m, 1, H-2), 2.28 (m, 1, H-5β), 2.13 (m, 1, H-3α), 1.98 (m, H-3β), 1.58 (m, 1, H-5α), 1.91 (s, CH_3 of acetic acid). Anal. ($C_{22}H_{22}Cl_2N_6O_2$·0.75HOAc) C, H, N.

(±)-(1α,2β,4α)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-2-(benzyloxy)cyclopentanol (13). A mixture of **12** (8.90 g, 17.2 mmol), EtOH (325 mL), H_2O (325 mL), acetic acid (7.23 mL), and powdered Zn (12.3 g) was stirred at reflux temperature under N_2 in an oil bath at 90–95 °C for 5 h and cooled to 25 °C. The solution was filtered under N_2 and the unreacted Zn rinsed with EtOH. The filtrate and wash were adjusted to pH 7 under N_2 using 50% NaOH and concentrated on a rotary evaporator under water aspirator pressure at 25 °C to remove the EtOH and much of the H_2O. The remaining aqueous mixture was mixed with $CHCl_3$ (200 mL) and enough $MgSO_4$ to take up the H_2O. The mixture was filtered and the $MgSO_4$ rinsed with $CHCl_3$ (200 mL). The $CHCl_3$ filtrate and wash were applied directly to a flash column of 500 g of silica gel prepared in, and eluted with, 96:4 $CHCl_3$–MeOH. The product fraction (R_f 0.3 in 95:5 $CHCl_3$–MeOH) was evaporated to give (±)-(1α,2β,4α)-4-[(2,5-diamino-6-chloropyrimidin-4-yl)amino]-2-(benzyloxy)cyclopentanol as a foam: ^1H NMR (Me_2SO-d_6) δ 7.32 (m, 5, C_6H_5), 6.40 (d, 1, NH, J = 8 Hz), 5.59 (s, 2, 2-NH_2), 5.01 (d, 1, 1-OH, $J_{1,1\text{-OH}}$ = 4.2 Hz), 4.51 (AB quartet, 2, OCH_2), 4.41 (m, 1, H-4), 4.01 (m, 1, H-1), 3.90 (s, 2, 5-NH_2), 3.78 (m, 1, H-2), 2.35 (m, 1, H-5β), 2.05 (m, 1, H-3β), 1.84 (m, 1, H-3α), 1.41 (m, 1, H-5α).

A solution of this amine in diethoxymethyl acetate (13 mL) was stirred in a stoppered flask in an oil bath at 80 °C for 24 h. After 24 h, the solution was evaporated to dryness under high vacuum, and the residue in THF (400 mL) was treated slowly with 0.5 N HCl (198 mL) and stirred at 25 °C for 40 min. The solution was evaporated to dryness under high vacuum, and the residue in MeOH (400 mL) was neutralized with IRA-400 (OH) resin, filtered and evaporated to a foam. A solution of the foam in 97.5:2.5 $CHCl_3$–MeOH was applied to a flash column of 500 g of silica gel and eluted with the same solvent. The product fraction was evaporated under high vacuum to give **13**, a foam: yield 3.18 g (50%); MS *m/z* 360 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.23 (s, 1, H-8), 7.33 (m, 5, C_6H_5), 6.90 (s, 2, NH_2), 5.32 (d, 1, 1-OH, $J_{1,1\text{-OH}}$ = 4.0 Hz), 4.91 (m, 1, H-4), 4.56 (AB quartet, 2, OCH_2), 4.18 (m, 1, H-1), 3.97 (m, 1, H-2), 2.53 (m, 1, H-5β), 2.30 (m, 2, H-3β, H-3α), 1.90 (m, 1, H-5α). Anal. ($C_{17}H_{18}ClN_5O_2$·0.1MeOH·0.06$CHCl_3$) C, H, N.

(±)-(1α,2β,4α)-4-(2-Amino-6-(benzyloxy)-9*H*-purin-9-yl)-2-(benzyloxy)cyclopentanol (14). A mixture of anhydrous benzyl alcohol (15 mL) and 60% NaH/mineral oil (364 mg, 9.10 mmol) was stirred under N_2 until H_2 evolution was complete. To this solution was added under N_2 a solution of **13** (3.06 g, 8.27 mmol) in benzyl alcohol. The resulting mixture was stirred for 20 h and was evaporated to a syrup under high vacuum. The syrup was triturated and washed with Et_2O to remove benzyl alcohol and dried. A solution of the residue in a minimum of 98:2 $CHCl_3$–MeOH was applied to a flash column of 125 g of silica gel and eluted with the same solvent. The product fraction (R_f 0.4 in 96:4 $CHCl_3$–MeOH) was evaporated under high vacuum, and the residue was triturated with Et_2O and dried: yield 2.85 g (80%); mp 145–146 °C; MS *m/z* 432 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 7.96 (s, 1, H-8), 7.50–7.25 (m, 10, C_6H_5), 6.43 (s, 2, NH_2), 5.48 (s, 2, 6-OCH_2), 5.35 (d, 1, 1-OH, $J_{1,1\text{-OH}}$ = 4.2 Hz), 4.89 (m, 1, H-4), 4.53 (AB quartet, 2, CH_2O), 4.16 (m, 1, H-1), 3.94 (m, 1, H-2), 2.51 (m, 1, H-5β), 2.25 (m, 2, H-3β, H-3α), 1.86 (m, 1, H-5α). Anal. ($C_{24}H_{25}N_5O_3$) C, H, N.

(±)-(1α,3β,4α)-6-(Benzyloxy)-9-(3-(benzyloxy)-4-((diethylphosphono)methoxy)cyclopentyl)-9*H*-purin-2-amine (15). A suspension of **14** (1.50 g, 3.47 mmol) and 60% NaH mineral oil emulsion (267 mg, 6.66 mmol) in anhydrous THF (42 mL) under argon was stirred for 5 min, treated with (diethylphosphono)methyl *p*-toluenesulfonate (2.67 g, 8.29 mmol), and stirred in a stoppered flask for 18 h. The reaction mixture was treated with EtOH (200 μL), stirred for 20 min, treated with acetic acid (156 μL, 2.72 mmol), and filtered, and the precipitate was rinsed with THF (3 × 10 mL). The filtrate and wash were evaporated to a syrup, and a solution of the syrup in $CHCl_3$ was applied to a flash column of 125 g of silica gel. The column was developed with 98.5:1.5 $CHCl_3$–MeOH and the product fraction (R_f 0.4 in 96:4 $CHCl_3$–MeOH) collected and evaporated to a syrup which crystallized: yield 747 mg; mp 109–110 °C. Additional product 269 mg, mp 109–110 °C, was obtained by rechromatographing the less pure fractions from the column above: total yield 1.02 g (51%); MS *m/z* 582 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 7.95 (s, 1, H-8), 7.52–7.24 (m, 10, C_6H_5), 6.45 (s, 2, NH_2), 5.49 (s, 2, 6-O$CH_2C_6H_5$), 4.90 (m, 1, H-1′), 4.57 (s, 2, $C_6H_5CH_2$), 4.08 (m, 6, CH_3CH_2, H-3′, H-4′), 3.91 (d, 2, PCH_2, $^2J_{PCH}$ = 9.1 Hz), 2.58 (m, 1, H-5′β), 2.28 (m, 2, H-2′β, H-2′α), 2.04 (m, 1, H-5′α), 1.24 (t, 6, CH_3). Anal. ($C_{24}H_{25}N_5O_3$) C, H, N.

(±)-(1α,3β,4α)-2-Amino-9-(3-(benzyloxy)-4-((diethylphosphono)methoxy)cyclopentyl)-1,9-dihydro-6*H*-purin-6-one (16). A solution of **15** (66 mg, 0.113 mmol) in EtOH (10 mL) containing 5% Pd on carbon (66 mg) was hydrogenated at 25 °C and atmospheric pressure for 3 h 6 min to give an apparent uptake of 5.6 mL of H_2. The reaction solution was filtered and the catalyst washed with EtOH. The filtrate and wash combined were evaporated to give 41 mg of pure title compound, as a partial hydrate: mp 177–180 °C (72%); MS *m/z* 492 $(M + H)^+$, 514 $(M + Na)^+$; UV λ_{max} nm ($\epsilon \times 10^{-3}$) pH 1, 255 (12.6), 278 (8.4); pH 7, 254 (13.8); pH 13, 268 (11.8); ^1H NMR (Me_2SO-d_6) δ 10.62 (s br, 1, NH), 7.76 (s, 1, H-8), 7.37 (m, 5, C_6H_5), 6.46 (s, 2, NH_2), 4.80 (m, 1, H-1′), 4.55 (AB quartet, 2, $C_6H_5CH_2$), 4.00–4.12 (m, 6, CH_2 of Et, H-3′, H-4′), 3.90 (m, 2, PCH_2, J_{gem} = 14.0, $^2J_{PCH}$ = 9.2 Hz), 2.56 (m, 1, H-5′β), 2.23 (m, 1, H-2′β, H-2′α), 1.98 (m, 1, H-5′α), 1.24 (t, 6, CH_3). Anal. ($C_{22}H_{30}N_5O_6P$·0.6H_2O) C, H, N.

(±)-(1α,3β,4α)-2-Amino-9-(4-(diethylphosphono)methoxy)-3-hydroxycyclopentyl)-1,9-dihydro-6*H*-purin-6-one (17). A solution of **15** (900 mg, 1.55 mmol) in EtOH (100 mL) and H_2O (75 mL) containing 1.8 g of 10% Pd/activated C + 50% H_2O (Degussa activated, Aldrich) was hydrogenated at room temperature and atmospheric pressure for 20 h. The reduction mixture was filtered and the catalyst washed with 30 mL of 1:1 EtOH–H_2O followed by 80 mL of boiling 1:1 EtOH–H_2O. The filtrate and wash were evaporated to a white solid: yield 553 mg (87%); mp 180–183 °C (melt resolidifies and becomes foam at ~195 °C); MS *m/z* 402 $(M + H)^+$, 424 $(M + Na)^+$; ^1H NMR (Me_2SO-d_6) δ 10.74 (s br, 1, NH), 7.72 (s, 1, H-8), 6.51 (s, 2, NH_2), 5.10 (s, 1, 3′-OH), 4.86 (m, 1, H-1′), 4.20 (s, 1, H-3′), 4.07 (m, 4, CH_3CH_2), 3.90 (m, 2, PCH_2, J_{gem} = 14.4, $^2J_{PCH}$ = 9.2 Hz), 3.82 (m, 1, H-4′), 2.50 (m, 1, H-2′β), 2.08 (m, 1, H-5′α, H-5′β), 1.88 (m, 1, H-2′α), 1.25 (t, 6, CH_3). Anal. ($C_{15}H_{24}N_5O_6P$·0.5H_2O) C, H, N.

(±)-(1α,2β,4α)-4-[(5-Amino-6-chloropyrimidin-4-yl)amino]-2-(benzyloxy)cyclopentanol (18). A solution of **10** (2.55 g, 12.3 mmol), *N*,*N*-diisopropylethylamine (4.57 mL, 26.2 mmol), and 5-amino-4,6-dichloropyrimidine (2.15 g, 13.1 mmol) in 1-butanol (130 mL) was heated at reflux temperature under N_2 for 22 h and evaporated under vacuum to a syrup. This syrup was reevaporated from toluene (2 × 50 mL) and the residue purified by flash chromatography (500 g of silica gel, with a linear gradient of $CHCl_3$–MeOH (100:0 to 96:4)). The product fraction was evaporated under high vacuum to give a yellow-amber foam: yield 3.23 g (79%); MS *m/z* 425 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 7.72 (s, 1, H-2), 7.32 (m, 5, C_6H_5), 6.75 (d, 1, NH, $J_{4,NH}$ = 6.4 Hz), 5.07 (s, 2, NH_2), 5.03 (d, 1, 1-OH, $J_{1,1\text{-OH}}$ = 4.0 Hz), 4.51 (AB quartet, 2, $PhCH_2$), 4.43 (m, 1, H-4), 4.04 (m, 1, H-1), 3.80 (m, 1, H-2), 2.39 (m, 1, H-5β), 2.10 (m, H-3β), 1.84 (m, 1, H-3α), 1.45 (m, 1, H-5α). Anal. ($C_{16}H_{19}ClN_4O_2$·0.2$CHCl_3$) C, H, N.

(±)-(1α,2β,4α)-2-(Benzyloxy)-4-(6-chloro-9*H*-purin-9-yl)-cyclopentanol (19). A solution of **18** (3.19 g, 9.53 mmol) in triethyl orthoformate (39 mL) was treated dropwise with concentrated HCl (0.95 mL, 11 mmol) to give a heavy gummy precipitate which quickly dissolved. The solution was stirred for 2.5 h at 25 °C and for 15 min at 50 °C. The reaction mixture was evaporated under high vacuum to an oil which was dissolved in EtOH (30 mL), diluted with H_2O (20 mL), and acidified to pH 1–2 with 1 N HCl. After 2 h at 25 °C, the solution was evaporated to dryness and the residue purified by flash chromatography (150 g of silica gel, 99:1 $CHCl_3$–MeOH and then 98:2 $CHCl_3$–MeOH) to give the product **19** as a white solid: yield 3.16 g (84%); MS *m/z* 345 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.79 (s, 2, H-2, H-8), 7.34 (m, 5, C_6H_5), 5.36 (d, 1, 1-OH, $J_{1,1\text{-OH}}$ = 4.2 Hz), 5.17 (m, 1, H-4), 4.57 (AB quartet, 2, $PhCH_2$), 4.21 (m, 1, H-1), 4.01 (m, 1, H-2), 2.60 (m, 1, H-5β), 2.48–2.34 (m, 2, H-3β, H-3α), 2.05 (m, 1, H-5α). Anal. ($C_{17}H_{17}ClN_4O_2$·0.4$CHCl_3$) C, H, N.

(±)-(1α,2β,4α)-2-(Benzyloxy)-4-(6-(methylthio)-9*H*-purin-9-yl)cyclopentanol (20). A solution of solvated **19** (2.55 g, 6.50 mmol) in anhydrous THF (45 mL) under N_2 was treated with sodium thiomethoxide (2.09 g, 29.7 mmol) and stirred for 2 h. The reaction mixture was concentrated to ~5 mL *in vacuo*, diluted with $CHCl_3$ (60 mL), and filtered through Celite. The filtrate was washed with H_2O (50 mL), dried ($MgSO_4$), and evaporated to an oil which was purified by flash chromatography (85 g of silica gel, 99:1 $CHCl_3$–MeOH) to afford a colorless oil. The oil upon heating at 60 °C for 5 h *in vacuo* gave a crystalline solid: yield 1.97 g (85%) mp 112–115 °C; MS *m/z* 357 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.73 (s, 1, H-2), 8.55 (s, 1, H-8), 7.33 (m, 5, C_6H_5), 5.38 (d, 1, 1-OH, $J_{1,1\text{-OH}}$ = 4.0 Hz), 5.12 (m, 1, H-4), 4.57 (AB quartet, 2, $PhCH_2$), 4.20 (m, 1, H-1), 4.00 (m, 1, H-2), 2.66 (s, 3, SMe), 2.58 (m, 1, H-5β), 2.37 (m, 2, H-3β, H-3α), 2.02 (m, 1, H-5α). Anal. ($C_{18}H_{20}N_4O_2S$·0.2H_2O) C, H, N.

(±)-(1α,3β,4α)-9-(3-Benzyloxy)-4-((diethylphosphono)-methoxy)cyclopentyl)-6-(methylthio)-9*H*-purine (21). A solution of **20** (1.78 g, 4.99 μmol) in anhydrous THF (60 mL) under argon was treated with a 60% dispersion of NaH in mineral oil (382 mg, 9.55 mmol), stirred for 2 min, treated with diethyl ((*p*-tolylsulfonyl)oxy)methanephosphonate (3.84 g, 11.9 mmol), stirred for 18 h, treated dropwise with glacial HOAc (0.92 mL), and stirred for 5 min. The reaction mixture was filtered and the white precipitate washed with THF (3 × 10 mL). The filtrate and wash were evaporated to a syrup. A solution of the residue in 99:1 $CHCl_3$–MeOH was applied to a flash column of 250 g of

silica gel. The column was eluted with the same solvent, and the product-containing fraction, evaporated to an amber oil, was dissolved in toluene (20 mL). The solution evaporated under high vacuum to give the product as an amber oil: yield 1.44 g (57%); MS m/z 507 $(M + H)^+$; ^1H NMR (Me_2SO-d_6) δ 8.72 (s, 1, H-2), 8.51 (s, 1, H-8), 7.34 (m, 5, C_6H_5), 5.13 (m, 1, H-1′), 4.58 (s, 2, $PhCH_2$), 4.17, 4.15–4.20 (m, 2, H-3′, H-4′), 4.05 (m, 4, CH_3CH_2), 3.91 (d, 2, PCH_2, $^2J_{PCH}$ = 9.3 Hz), 2.66 (s and m, 4, SCH_3 and H-5′β), 2.40 (m, 2, H-2′α, H-2′β), 2.18 (m, 1, H-5′α), 1.23 (t, 6, CH_3CH_2).

Acknowledgment. This investigation was supported by the National Cancer Institute, NIH, DHHS, Grant P01 CA34200. We thank the Molecular Spectroscopy Section of Southern Research Institute for analytical and spectral data and Ms. Paula Allan, Ms. Doris Adamson, and Mrs. Lucy Rose for the biologic data.

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