was crystallized from benzene (30 mL). The solid obtained (1.41 g, 38%) was recrystallized from acetonitrile (25 mL) to give the desired product **89** (0.98 g, 27%). ^{13}C NMR (CD_3OD, 67.5 MHz): δ 31.6, 35.3, 39.1, 42.1, 125.4, 127.1, 127.7, 131.0, 133.0, 151.4, 172.0, 172.6. Anal. ($C_{14}H_{19}NO_3S$) C, H, N, S.

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Synthesis of New (±)-3,5-Dihydroxypentyl Nucleoside Analogues from 1-Amino-5-(benzyloxy)pentan-3-ol and Their Antiviral Evaluation

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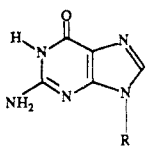
The synthesis and antiviral evaluation of a series of (±)-3,5-dihydroxypentyl nucleoside analogues related to acyclic nucleoside antiviral agents are reported. All purine and pyrimidine nucleoside analogues described in this paper have been obtained from 1-amino-5-(benzyloxy)pentan-3-ol. A synthesis of this amine is reported from 1-(benzyloxy)but-3-ene after epoxidation and regiospecific diethylaluminum chloride catalyzed opening of the epoxide by trimethylsilyl cyanide. The compounds were tested in vitro in infected MRC5 and CEM cells. None of the compounds exhibited antiviral activity against HSV-1, HCMV, and HIV-1 with the exception of the guanine derivative **7**, which inhibited the cytopathic effect of HSV-1 by 50% at 12.5 μg/mL.

The discovery of the potent and selective anti-HSV (herpes simplex virus) activity of acyclovir[1] (ACV) has stimulated extensive research in the synthesis of new acyclic nucleoside analogues in which the cyclic carbohydrate moiety has been replaced by acyclic chains mimicking the sugar portion of naturally occurring nucleosides.

Analogues **2–6** exhibit potent antiherpes virus activity in cell cultures[4,5,7-11] and some of them (DHPG, DHBG, BRL 39123) were found to be superior to ACV in infectious animal models.[2,3,7,12] ACV, DHPG, BRL 39123, and 2 HM-HBG are also inhibitory of varicella zoster virus (VZV).[5,8,10]



1 : R = $CH_2OCH_2CH_2OH$ (ACV)

2 : R = CH_2OCHCH_2OH (CH_2OH) (DHPG)

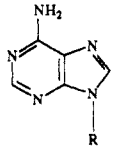
3 : R = $CH_2CH_2CHCH_2OH$ (OH) (R-DHBG)

4 : R = $CH_2CH_2CH_2CH_2OH$ (HBG)

5 : R = $CH_2CH_2CHCH_2OH$ (CH_2OH) (BRL 39123)

6 : R = $CH_2CHCH_2CH_2OH$ (CH_2OH) ((+/-)2HMHBG)

7 : R = $CH_2CH_2CHCH_2CH_2OH$ (OH)



8 : R = CH_2CHCH_2OH (OH) ((S)-DHPA)

9 : R = $CH{=}C{=}CHCH_2OH$ ((+/-)adenallene)

10 : R = $CH_2CHOCH_2PO_3H_2$ (CH_2OH) (S-HPMPA)

11 : R = $CH_2CH_2OCH_2PO_3H_2$ (PMEA)

12 : R = $CH_2CH_2CHCH_2CH_2OH$ (OH)

These acyclic nucleosides share the common property[10] of being preferentially phosphorylated by the virus-coded thymidine kinase.[18] A second level of selectivity is achieved through the inhibitory activity of their triphosphate form against the virus-coded DNA polymerase while cellular polymerases are much less affected.

However, activity of acyclic nucleosides is not restricted

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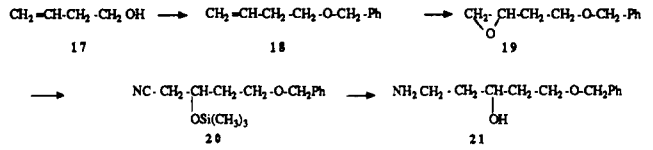
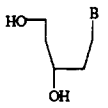
Scheme I



to HSV and VZV. For example DHPG is a powerful inhibitor of the human cytomegalovirus (HCMV),[5] and at the present time, this compound bears great interest for the treatment of severe cytomegalovirus infections in immunocompromised patients.

Furthermore, acyclic adenosine derivatives (compounds 8–11) possess interesting features. DHPA has broad activity against DNA and RNA viruses,[13] S-HPMPA is active on both adenovirus and HSV,[14,15] while PMEA and adenallene display antiretrovirus activity.[16,17] HCMV and HIV do not possess virus-coded nucleoside kinases, but clearly, sufficient selectivity can be obtained by acting at the level of the virus-coded polymerase.[6] In the case of HIV (human immunodeficiency virus) this target (reverse transcriptase) proved to be extremely important in the synthesis of a number of 2′,3′-dideoxynucleosides with antiviral activity, including AZT.[20]

We were interested in studying the antiviral properties against HSV, HCMV, and HIV of nucleosides bearing a pentane-3,5-diol chain, in particular the thymidine (**14**),



13 : B = uracil
14 : B = thymine
15 : B = cytosine
16 : B = 7-deazaguanine

the cytidine (**15**), and the 7-deazaguanosine (**16**) analogues. To make our study more complete, we also synthesized the guanosine (**7**), the adenosine (**12**) and the uridine (**13**) analogues. Compound **7** has been previously examined against HSV-1,[18] but its synthesis was not reported to the best of our knowledge, while **12** and **13** were tested only against vaccinia and vesicular stomatitis viruses.[19]

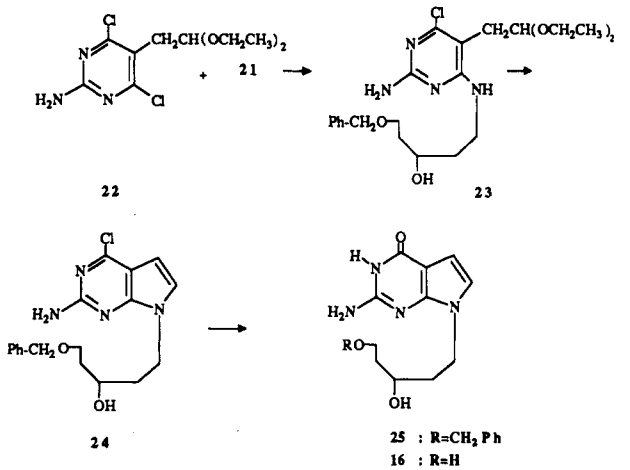
In order to synthesize these compounds, we needed a general method of preparation of all possible nucleoside analogues bearing a pentane-3,5-diol chain including base-modified derivatives. In this respect, the direct alkylation of the sodium salt of the base by the monotosylate of pentane-1,3,5-triol, used previously,[21] could not be applied. Therefore, we turned to a different strategy which started with 1-amino-5-(benzyloxy)pentan-3-ol. We report in the present paper the synthesis of the nitrile precursor of this amine as well as the synthesis and antiviral evaluation of the six compounds mentioned above, namely **7** and **12–16**.

Chemistry

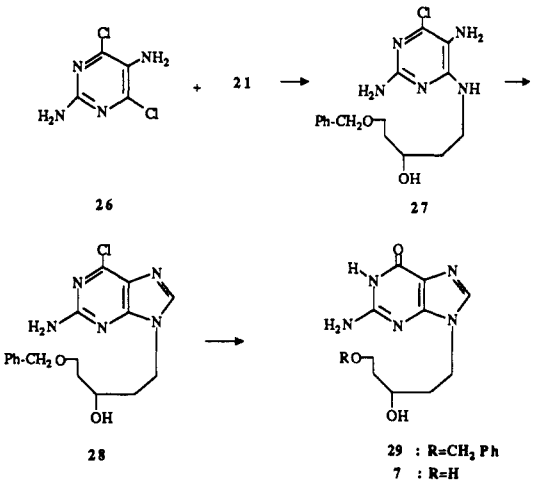
Benzylation of but-3-en-1-ol (**17**) was carried out in toluene with benzyl chloride in order to facilitate the purification of the different intermediates **19–21** (Scheme I).

Alkene **18** was epoxidized with *m*-chloroperbenzoic acid in dichloromethane in high yield (81%). Conversion of epoxide **19** to the hydroxycyanide derivative was achieved with trimethylsilyl cyanide in the presence of diethylaluminum chloride, which is known to catalyze the selective attack of cyanide ion on the less substituted carbon.[22]

Scheme II



Scheme III



The regiospecificity of this reaction is very high since cyanide **20** was obtained in almost quantitative yield. The complete reduction of nitrile **20** was carried out with lithium aluminum hydride in diethyl ether and led to **21** in 58% yield. Amine **21** was condensed with 2-amino-4,6-dichloro-5-(2,2-diethoxyethyl)pyrimidine[23] (**22**) in butan-1-ol at 100 °C for 3 days and produced pyrimidine **23**. Acetal **23** cyclized to pyrrolo[2,3-*d*]pyrimidine **24** on treatment with dilute aqueous HCl (0.2 N) in ethanol at room temperature. Conversion of **24** into 7-deaza guanine derivative **25** was accomplished by acidic hydrolysis at 100 °C. The removal of the benzyl group from **25** to give compound **16** was performed with boron trichloride at −78 °C (Scheme II). The synthesis of guanine nucleoside analogue **7** is outlined in Scheme III and started with 2,5-diamino-4,6-dichloropyrimidine[24,25] (**26**) which was condensed with amine **21** in the usual way. Condensation product **27** was used quickly to avoid degradation which could be observed by TLC after 24 h and its cyclization was achieved in *N*,*N*-dimethylacetamide with triethyl orthoformate in the presence of catalytic amounts of hydrochloric acid. Conversion of **28** into the guanine derivative **29** was carried out by acidic hydrolysis at 100 °C while the debenzylation was obtained with boron tri-

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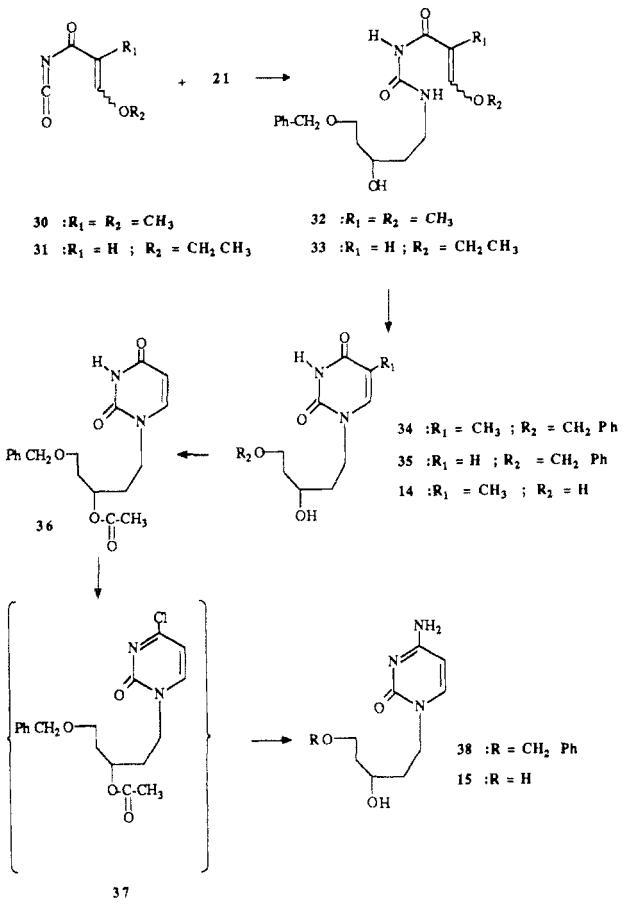
Scheme IV



chloride in the same conditions as for **25**.

The synthesis of the thymidine and cytidine nucleoside analogues **14** and **15** was performed as outlined in Scheme IV, essentially according to Shaw and Warrener[26] and to Shealy et al.[27]

Isocyanate **30** was reacted with **21** in dry benzene at room temperature to afford **32** which was purified by column chromatography in 71% yield. Cyclization of **32** in 2 N sulfuric acid under reflux afforded a 83% yield of the desired thymine derivative **34**. Debenzylation of **34** was carried out in high yield (92%) by catalytic hydrogenation over palladium on charcoal under hydrogen pressure (6 bar) and gave **14**.

Cytidine analogue **15** was synthesized from derivative **37**, which was obtained from **35**, as shown in Scheme IV, after acetylation of the secondary alcohol by acetic anhydride followed by a chlorination by DMF–$SOCl_2$ in chloroform. Chlorine aminolysis of **37** was carried out with ammonia at 100 °C and deprotection with palladium on charcoal furnished the cytidine analogue **15**. The adenine derivative **12** and the uracil derivative **13** have been described previously[21] and have been obtained from amine **21**. Uridine analogue **13** was obtained from **35** according to the general method reported here (Scheme IV). Adenosine analogue **12** was obtained by the classical three-step sequence including substitution of 5-amino-4,6-dichloropyrimidine by **21**, cyclization with triethyl orthoformate, and chlorine aminolysis in ammonia. A further debenzylation step gave **12** presenting the same physical properties as those already described.[21]

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Results and Discussion

Toxicity in exponentially growing, uninfected CEM cells was noticed only with compound **13**, which decreased cell viability by 60% at 25 μg/mL. For compound **12**, the concentration devoid of cytotoxicity in MRC5 cells was 25 μg/mL. None of the compounds were found inhibitory against HIV-1 and HCMV. When tested against HSV-1, only compound **7** did show activity:50% inhibition of the CPE was induced at 12.5 μg/mL and complete suppression at 50 μg/mL, while no toxicity occurred at the highest concentration tested (100 μg/mL).

Replacement of the acyclic chains of guanines **1–6** by the pentane-3,5-diol chain (in **7**) considerably reduced anti-HSV activity and did not give rise to anti-HCMV properties. No activity was noticed when the guanine (in **7**) was replaced by deazaguanine (in **16**).

Previous data indicated that the use of other bases (adenine, pyrimidines) has little effect in generating antiviral activity,[19] particularly in the series of DHPG analogues.[28] On the other hand, it was hoped that the pentane-3,5-diol chain could bring about antiviral properties when coupled to pyrimidine and to adenine bases since some acyclic derivatives of adenine do exert antiviral properties (8–11).

However, this was not the case. Furthermore, none of the compounds displayed anti-HIV activity, indicating that replacement of the carbohydrate moiety of the different naturally occurring nucleosides by a pentane-3,5-diol chain does not give rise to antiviral activity against HSV-1, HCMV, and HIV-1, as observed with other acyclic nucleoside **1–6** and **8–11**, with the exception of anti-HSV-1 activity observed with guanine derivative **7**.

Experimental Section

Chemistry. ^1H NMR spectra were recorded on a Varian XL100 spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. Coupling constants (*J*) are reported in hertz. Elemental analyses were performed by Service Central de Microanalyse, ICSN, CNRS, 91190 Gif Sur Yvette, France. Medium-pressure liquid chromatography (10 bar) was carried out in glass columns packed with silica gel (230–400 mesh, Merck). Mass spectra were obtained with a Ribermag spectrometer (ICMO, Université de Paris XI, 91405 Orsay).

Antiviral Assays. Compounds **7** and **12–16** were evaluated for their protective activity against the cytopathic effect (CPE) induced by the human HIV-1 (LAV strain), type HSV-1 (HF strain), and HCMV, (Davis strain) in cell cultures. A 25-μL sample of each compound dilution (1:2, beginning at 1 mg/mL) in phosphate-buffered saline (PBS) or 25 μL of PBS alone were distributed in triplicate wells of a 96-well tissue-culture plates. For HIV studies, 125 μL of a CEM cell suspension (6000 cells/mL in RPMI 1640, 10% FCS, penicillin, and streptomycine sulfate at, respectively, 100 units and 100 μg/mL) was added. After a 1-h incubation, 100 μL/well of a HIV-1 suspension (100–200 TC ID_{50}) was added; mock infected cultures were carried out in parallel to determine cytotoxicity. After culturing for 7 days, cell viability was determined by colorimetric staining as described previously.[29] The extent of the CPE was 60–70% in untreated cultures. For HSV-1 and CMV studies, 200 μL of cells (10 000 and 5000, respectively) in BME, 10% FCS, and antibiotics as above was added. Four hours later, cells were infected with 2.5 μL of a virus suspension (20–50 TC ID_{50}); CPE was both scored at the microscope and by staining the residual cell monolayer with 0.1% crystal violet. Its degree was 90–100% at 4 and 6 days postinfection, with HSV-1 and HCMV, respectively.

1-(Benzyloxy)but-3-ene (18). A solution of but-3-en-1-ol (100 g, 1.38 mol) and sodium (31.9 g, 1.38 mol) in toluene (400 mL) was heated at reflux for 12 h. Benzyl chloride (175.8 g, 1.39 mol) was added and the mixture was heated at reflux for 12 h. The

(29) Schwartz, O.; Henin, Y.; Marechal, V.; Montagnier, C. *AIDS Res. Human Retrovirus* **1988**, *4*, 441.

solution was cooled and washed twice with 1 N aqueous hydrochloric acid (100 mL). The organic phase was dried ($MgSO_4$) and the toluene was evaporated. The resulting oily residue was distilled to afford **18** in 79% yield: bp 108–110 °C (19 mm); ^1H NMR ($CDCl_3$) δ 2.33 (m, 2 H, CH_2-2), 3.52 (t, 2 H, CH_2O), 4.50 (s, 2 H, CH_2Ar), 5.11 (m, 2 H, CH_2=), 5.83 (m, 1 H, CH=), 7.36 (s, 5 H, Ar*H*). Anal. ($C_{11}H_{14}O$) C, H.

1-(Benzyloxy)-3,4-epoxybutane (19). A solution of dry *m*-chloroperbenzoic acid (70 g, 0.405 mol) in dichloromethane (1 L) was added dropwise at 0 °C to a solution of **18** (50 g, 0.308 mol) in dichloromethane (250 mL). The mixture was stirred overnight at room temperature and was diluted with dichloromethane (1 L). Solid calcium hydroxide (30 g) and water (1 L) were added, and stirring was continued for 30 min. The organic phase was washed several times with 200-mL portions of water, dried ($MgSO_4$), and evaporated to dryness. The oily residue was chromatographed on a silica gel column prepared with *n*-hexane. Compound **19** was eluted with 2% of ethyl acetate in *n*-hexane as a colorless oil: yield 87%; ^1H NMR ($CDCl_3$) δ 1.86 (m, 2 H, CH_2CH_2O), 2.66 (m, 2 H, CH_2-epoxide), 3.08 (m, 1 H, CH-epoxide), 3.66 (t, 2 H, CH_2O), 4.56 (s, 2 H, CH_2Ar), 7.38 (s, 5 H, Ar*H*). Anal. ($C_{11}H_{14}O_2$) C, H.

(±)-5-(Benzyloxy)-3-(trimethylsiloxy)pentanenitrile (20). A solution of epoxide **19** (9 g, 50.5 mmol) in *n*-hexane (10 mL) was added dropwise to a mixture of trimethylsilyl cyanide (5 g, 50.39 mmol) and diethylaluminum chloride (1.5 mL of a 1 M solution in hexane) under an inert atmosphere (argon). (The flask must be equipped with a reflux condenser.) The mixture was then stirred at room temperature overnight and a 3 N sodium hydroxide aqueous solution (20 mL) was added. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness to an oil which was distilled: 95% yield; bp 130 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 0.17 (s, 9 H, $Si(CH_3)_3$), 1.86 (m, 2 H, OCH_2CH_2), 2.50 (m, 2 H, $NCCH_2$), 3.56 (t, 2 H, OCH_2), 4.18 (m, 1 H, CHOSi), 4.50 (s, 2 H, CH_2Ar), 7.34 (s, 5 H, Ar*H*). Anal. ($C_{15}H_{23}NO_2Si$) C, H, N.

(±)-1-Amino-5-(benzyloxy)pentan-3-ol (21). A solution of **20** (11 g, 39.7 mmol) in diethyl ether (75 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (3.25 g, 84 mmol) in dry diethyl ether (150 mL). The mixture was stirred for 2 h at room temperature and 2 mL of water was added slowly. A 10% solution of $NaHCO_3$ was then slowly added. The organic phase was dried ($MgSO_4$) and evaporated to dryness to afford a 58% yield of a colorless oil which was sufficiently pure for the next steps. An analytical sample of **21** was obtained by column chromatography on aluminum oxide eluting with dichloromethane–ethanol (28% aqueous)–ammonium hydroxide 80:20:1: ^1H NMR ($CDCl_3$) δ 1.68 (m, 4 H, 2 × CH_2), 2.95 (m, 2 H, CH_2O), 3.66 (t, 2 H, CH_2NH_2), 3.98 (m, 1 H, CHOH), 4.52 (s, 2 H, CH_2Ar), 7.33 (s, 5 H, Ar*H*). MS (by desorption–chemical ionization in NH_3) *m/z* 210 (MH^+). Anal. ($C_{12}H_{19}NO_2$) C, H, N.

(±)-1-[[2-Amino-4-chloro-5-(2,2-diethoxyethyl)pyrimidin-6-yl]amino]-5-(benzyloxy)pentan-3-ol (23). A solution of 1-amino-5-(benzyloxy)pentan-3-ol (4.67 g, 22.3 mmol), 2-amino-4,6-dichloro-5-(2,2-diethoxyethyl)pyrimidine[23] (6.55 g, 23.39 mmol), and triethylamine (20 mL) in *n*-butan-1-ol (250 mL) was heated at 100 °C under nitrogen for 3 days. The mixture was evaporated to dryness and the residue was coevaporated several times with toluene. The residue was then partitioned between dichloromethane (300 mL) and water (30 mL). The organic phase was washed with water (30 mL) three times, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography (eluting with dichloromethane–ethanol, 98:2) to afford 8.35 g of an oil which crystallized on standing. An analytical sample was obtained by recrystallization in a mixture of toluene–hexane 9:1: mp 82 °C; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H, CH_3), 1.20 (t, 3 H, CH_3), 1.74 (m, 4 H, 2 × CH_2), 2.79 (d, 2 H, CH_2-pyrim), 3.20–3.80 (m, 9 H, CHOH, 2 × CH_2-ethyl, CH_2NH, CH_2O), 4.36 (br d, 1 H, OH), 4.49 (t, 1 H, CH-ketal), 4.50 (s, 2 H, CH_2Ar), 4.78 (s, 2 H, NH_2), 6.20 (t, 1 H, NH), 7.31 (s, 5 H, Ar*H*). Anal. ($C_{22}H_{33}N_4O_4Cl$) C, H, N, Cl.

(±)-1-(2-Amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-(benzyloxy)pentan-3-ol (24). A solution of (±)-1-[[2-amino-4-chloro-5-(2,2-diethoxyethyl)pyrimidin-6-yl]amino]-5-(benzyloxy)pentan-3-ol (2 g, 4.41 mmol) in hydrochloric acid (0.25 N, 100 mL) containing 75% of ethanol was stirred at room temperature for 3 days. The mixture was treated with ammonium hydroxide in excess before it was evaporated to dryness. The residue was dissolved in dichloromethane (200 mL) and washed with water (3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The title compound was then purified by silica gel column chromatography eluting with petroleum ether–ethyl acetate (3:1). The pure fractions were combined and evaporated to an oil which crystallized on standing (1.19 g, 75%). This material was used in the next step without further purification. An analytical sample was obtained by recrystallization from *n*-hexane–ethyl acetate: mp 110 °C; ^1H NMR ($CDCl_3$) δ 1.64–2.05 (m, 4 H, 2 × CH_2), 3.62 (m, 4 H, CH_2N, CH_2O), 4.07–4.37 (m, 2 H, CHOH), 4.48 (s, 2 H, CH_2Ar), 4.97 (s, 2 H, NH_2), 6.40 (d, 1 H, H5, J_{5-6} = 3.5), 6.64 (d, 1 H, H6), 7.30 (s, 5 H, Ar*H*). Anal. ($C_{18}H_{21}N_4O_2Cl$) C, H, N, Cl.

(±)-2-Amino-7-[5-(benzyloxy)-3-hydroxypent-1-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (25). A solution of (±)-1-(2-amino-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-(benzyloxy)pentan-3-ol (1 g, 2.77 mmol) in hydrochloric acid (1 N, 100 mL) containing 50% of ethanol was boiled under reflux for 18 h with stirring. The ethanol was evaporated in vacuo and the aqueous solution was treated with an excess of ammonium hydroxide before evaporation to dryness. The residue was partitioned between ethyl acetate (200 mL) and water. The aqueous phase was saturated with sodium chloride and extracted with ethyl acetate (2 × 100 mL). The organic phases were combined, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized in ethyl acetate–ethanol (0.76 g, 80.4%): mp 183 °C; ^1H NMR (Me_2SO-d_6) δ 1.65 (m, 4 H, 2 × CH_2), 3.50 (m, 3 H, CH_2O, CHOH), 3.98 (t, 2 H, CH_2N), 4.41 (s, 2 H, CH_2Ar), 4.64 (d, 1 H, OH, J = 5.5), 6.17 (s, 2 H, NH_2), 6.20 (d, 1 H, H5), 6.69 (d, 1 H, H6, J = 3.5), 7.29 (s, 5 H, Ar*H*), 10.22 (s, 1 H, NH). Anal. ($C_{18}H_{22}N_4O_3$) C, H, N.

(±)-2-Amino-7-(3,5-dihydroxypent-1-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (16). A solution of (±)-2-amino-3,4-dihydro-7-[5-(benzyloxy)-3-hydroxypent-1-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (0.23 g, 0.67 mmol) in dichloromethane (20 mL) was treated at −78 °C under argon with a solution (1 M) of boron trichloride in dichloromethane (6 mL). After 3 h with stirring at −78 °C, 6 mL of the boron trichloride solution was added, and stirring continued for 2 h. Methanol (25 mL) was added and the solution was stirred for 50 min before evaporation to dryness. The residue was recrystallized twice from boiling ethanol to give 84 mg (50%) of pure product: mp 170–172 °C; ^1H NMR (Me_2SO-d_6) δ 1.42–1.92 (m, 4 H, 2 × CH_2), 3.52 (m, 3 H, CH_2O, CHOH), 4.03 (t, 2 H, CH_2N), 6.28 (d, 1 H, H5, J = 2.5), 6.76 (d, 1 H, H6, J = 2.5), 10.52 (s, 1 H, NH). Anal. ($C_{11}H_{16}N_4O_3$) C, H, N.

(±)-2,5-Diamino-6-chloro-4-[[5-(benzyloxy)-3-hydroxypent-1-yl]amino]pyrimidine (27). A solution of **26** (829.3 mg, 5.7 mmol), **21** (982.3 mg, 4.7 mmol), and triethylamine (10 mL) in *n*-butan-1-ol (100 mL) was heated at 100 °C for 48 h under nitrogen. The solution was cooled and evaporated to dryness. The oily residue was dissolved in dichloromethane (100 mL) and washed with water (20 mL) twice. The organic phase was dried ($MgSO_4$) and the residue of evaporation was purified by column chromatography eluting with dichloromethane–ethanol 95:5. Title compound **27** was obtained as an oil (1.2 g, 72%) which was sufficiently pure for the next step: ^1H NMR ($CDCl_3$) δ 1.86–1.93 (m, 4 H, H2′, H4′), 3.50–3.83 (m, 7 H, H1′, H3′, H5′, NH_2), 4.51 (s, 2 H, CH_2O), 4.66 (s, 2 H, NH_2), 5.96 (t, 1 H, NH), 6.32 (s br, 1 H, OH), 7.32 (s, 5 H, Ar*H*).

(±)-2-Amino-6-chloro-9-[5-(benzyloxy)-3-hydroxypent-1-yl]-9*H*-purine (28). A solution of **27** (600 mg, 1.7 mmol) in distilled dimethylacetamide (20 mL) was cooled to 0 °C. Freshly distilled triethyl orthoformate (20 mL) and concentrated hydrochloric acid (0.5 mL) were added, and stirring was continued overnight at room temperature. The mixture was evaporated to dryness (oil pump) and the syrup was stirred in aqueous acetic acid (50%, 20 mL) for 4 h at room temperature. The solution was concentrated in vacuo to an oil which was redissolved in a solution of ammonia in methanol (10%) and stirred for 4 h at room temperature. After evaporation to dryness, the residue was chromatographed on silica gel eluting with dichloromethane–ethanol 98:2. The pure compound (**28**) crystallized from ethanol: mp 138 °C; yield 83%; ^1H NMR (Me_2SO-d_6) δ 1.70–1.76 (m, 2 H, H4′), 1.87–1.94 (m, 2 H, H2′), 3.54 (m, 3 H, H5′, H3′), 4.17 (t,

2 H, H1′, J = 7.2), 4.44 (s, 2 H, CH_2Ar), 4.72 (d, 1 H, OH, J = 5.6), 6.89 (s br, 2 H, NH_2), 7.32 (s, 5 H, ArH), 8.12 (s, 1 H, H8). Anal. ($C_{17}H_{20}N_5O_2Cl$) C, H, N.

(±)-9-[5-(Benzyloxy)-3-hydroxypent-1-yl]guanine (29). A solution of **28** (150 mg, 0.14 mmol) in 1 N hydrochloric acid (25 mL) was refluxed for 6 h with stirring. The mixture was cooled, concentrated in vacuo, and coevaporated several times with ethanol. The residue was dissolved in water (2 mL) and neutralized with 6 N sodium hydroxide. The title compound (**29**) crystallized in water: mp 86–88 °C; yield 35%. A significant amount (25%) of debenzylated compound (**7**) was formed in this experiment and remained in water: ^{1}H NMR (Me_2SO-d_6) δ 1.62–1.88 (m, 4 H, H2′, H4′), 3.54 (m, 3 H, H5′, H3′), 4.05 (t, 2 H, H1′), 4.44 (s, 2 H, CH_2Ar), 4.72 (d, 1 H, OH, J = 5.4), 6.43 (s, 2 H, NH_2), 7.32 (s, 5 H, ArH), 7.67 (s, 1 H, H8), 10.52 (s, 1 H, NH). Anal. ($C_{17}H_{21}N_5O_3 \cdot {}^3/_4H_2O$) C, H, N.

(±)-9-(3,5-Dihydroxypent-1-yl)guanine (7). A solution of boron trichloride (1 M) in dichloromethane was added (3.5 mL, 3.5 mmol) to a solution of **29** (100 mg, 0.39 mmol) in dichloromethane (10 mL) at −78 °C with exclusion of moisture. The mixture was stirred for 6 h at −78 °C and a solution of dichloromethane–ethanol 1:1 (10 mL) was added dropwise while the mixture was allowed to warm to room temperature. The mixture was evaporated to dryness, redissolved in a few milliliters of ethanol, and neutralized with 1 N sodium hydroxide. The residue of evaporation was adsorbed on silica gel and chromatographed eluting with dichloromethane–ethanol 8:2. The product (**7**) was obtained as a hygroscopic solid after evaporation and gave an amorphous hydrate in ethanol–water: mp 234–235 °C; yield 91%; MS (chemical ionization, NH_3) m/z 255 (MH^+, 100); ^{1}H NMR (Me_2SO-d_6) δ 1.50–1.86 (m, 4 H, 2 × CH_2), 3.49–3.54 (m, 3 H, CH_2OH, CHOH), 4.04 (t, 2 H, CH_2N), 4.35 (t, 1 H, CH_2OH), 4.70 (d, 1 H, OH 3′), 6.57 (s, 2 H, NH_2), 7.68 (s, 1 H, H8), 10.61 (s, 1 H, NH). Anal. ($C_{10}H_{15}N_5O_3 \cdot 3.25\ H_2O$) C, H.

(±)-*N*-[[[5-(Benzyloxy)-3-hydroxypent-1-yl]amino]carbonyl]-3-methoxy-2-methyl-2-propenamide (32). Acyl isocyanate **30**, (0.67 g, 4.7 mmol) prepared in anhydrous benzene from 3-methoxy-2-methylacryloyl chloride and silver cyanate as described,[27] was added dropwise under dry nitrogen into a solution of **21** (1 g, 4.7 mmol) in anhydrous benzene (15 mL) at 0 °C. The mixture was then stirred at room temperature for 4 h under nitrogen and evaporated to dryness. The oily residue was chromatographed on a silica gel column eluting which dichloromethane–ethanol 98:2 to afford **32** as an oil which was sufficiently pure for the next step: yield 71%; ^{1}H NMR ($CDCl_3$) δ 1.47–1.79 (m, 4 H, 2 × CH_2), 1.79 (d, 3 H, CH_3), 3.25–3.75 (m, 5 H, CH_2OH, CHOH, CH_2N), 3.87 (s, 3 H, OCH_3), 4.54 (s, 2 H, CH_2Ar), 4.73 (q, 1 H, H3), 7.37 (s, 5 H, ArH), 7.78 (s, 1 H, NH), 8.81 (t, 1 H, NH).

(±)-1-[5-(Benzyloxy)-3-hydroxypent-1-yl]-5-methylpyrimidine-2,4-dione (34). A solution of **32** (500 mg, 1.43 mmol) in 2 N sulfuric acid (25 mL) was heated under reflux for 3 h. The mixture was cooled, neutralized with $NaHCO_3$ at 0 °C, and extracted with dichloromethane (3 × 50 mL). The organic phases were dried ($MgSO_4$), evaporated to dryness, and chromatographed on a silica gel column eluting with dichloromethane to give a colorless oil (375 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 1.73–1.83 (m, 4 H, 2 × CH_2), 1.92 (d, 3 H, CH_3), 2.75 (br, 1 H, OH), 3.53–3.95 (m, 5 H, CH_2O, CH_2N, CHOH), 4.53 (s, 2 H, CH_2Ar), 7.08 (q, 1 H, H6), 7.32 (s, 5 H, ArH), 8.58 (s, 1 H, NH). Anal. ($C_{17}H_{22}N_2O_4$) C, H, N.

(±)-1-(3,5-Dihydroxypent-1-yl)-5-methylpyrimidine-2,4-dione (14). A solution of **34** (150 mg, 0.47 mmol) in ethanol (250 mL) and palladium on charcoal (10%) (40 mg) were stirred at 80 °C overnight under pressurized hydrogen (6 bar). The mixture was cooled, filtered on Celite, and chromatographed on a silica gel column eluting with dichloromethane–ethanol 95:5, affording **14** a colorless oil: yield 92%; ^{1}H NMR (Me_2SO-d_6) δ 1.50–1.74 (m, 4 H, 2 × CH_2), 1.78 (d, 3 H, CH_3), 3.43–3.83 (m, 5 H, CH_2OH, CH_2N, CHOH), 4.33 (t, 1 H, CH$_2$OH, J = 4.8), 4.52 (d, 1 H, CHOH, J = 5.4), 7.50 (q, 1 H, H6), 11.16 (s, 1 H, NH). Anal. ($C_{10}H_{16}N_2O_4$) C, H, N.

(±)-*N*-[[[5-(Benzyloxy)-3-hydroxypent-1-yl]amino]carbonyl]-3-ethoxy-2-propenamide (33). Acyl isocyanate **31** (0.79 g, 5.6 mmol) in anhydrous benzene (15 mL) was added dropwise at 0 °C under dry nitrogen into a solution of **21** (1.41 g, 5.6 mmol) in dry benzene (20 mL). The mixture was then stirred at room temperature for 4 h under nitrogen and evaporated to dryness. The residue was chromatographed eluting with dichloromethane to give a colorless syrup which could not be crystallized: yield 73%; ^{1}H NMR ($CDCl_3$) δ 1.25–1.42 (dt, 3 H, CH_3), 1.59–1.81 (m, 4 H, 2 × CH_2), 3.13–4.00 (m, 8 H, CH_2N, CH_2O, CHOH, CHOH, CH_2-ethyl), 4.52 (s, 2 H, CH_2Ar), 5.10–5.33 (2 d, 1 H, H3), 6.22 (br t, 1 H, NH), 7.32 (s, 5 H, ArH), 7.46–7.71 (2 d, 1 H, H2), 8.86 (s, 1 H, NH).

(±)-1-[5-(Benzyloxy)-3-hydroxypent-1-yl]pyrimidine-2,4-dione (35). A solution of **33** (150 mg, 0.4 mmol) in 2 N sulfuric acid (15 mL) was heated under reflux for 3 h. The mixture was cooled, neutralized ($NaHCO_3$) at 0 °C, extracted with dichloromethane, and dried ($MgSO_4$) before evaporation to dryness. Purification by column chromatography eluting with dichloromethane–ethanol 98:2 afforded 110 mg (85%) of syrupy material: ^{1}H NMR ($CDCl_3$) δ 1.64–1.94 (m, 4 H, 2 × CH_2), 3.39 (d, 1 H, OH), 3.52–3.96 (m, 5 H, CH_2N, CH_2O, CHOH), 4.52 (s, 2 H, CH_2Ar), 5.67 (d, 1 H, H6, J = 8), 7.32 (s, 5 H, ArH), 7.33 (d, 1 H, H5), 8.62 (s, 1 H, NH). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

(±)-4-Amino-1-[5-(benzyloxy)-3-hydroxypent-1-yl]pyrimidin-2(1*H*)-one (38). A solution of **35** (200 mg, 0.65 mmol), triethylamine (0.2 mL), acetic anhydride (0.12 mL), and 4-(dimethylamino)pyridine (2 mg) in acetonitrile (25 mL) was stirred at room temperature for 3 h. Methanol (5 mL) was added and stirring was continued for 5 min. The mixture was evaporated and dissolved in chloroform and the organic phase was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue (**36**) was dissolved in dry chloroform (30 mL) with thionyl chloride (distilled over linseed oil)[30] (1 g, 8.18 mmol) and dry dimethylformamide (0.25 mL) and refluxed overnight. The mixture was evaporated to dryness and transferred in methanol (200 mL) into an autoclave containing liquid ammonia (130 mL). The autoclave was then heated at 100 °C for 24 h. After evaporation of ammonia and methanol, the residue was chromatographed on silica gel eluting with dichloromethane–ethanol 9:1. The title compound (**38**) crystallized in acetone: yield 21%; mp 159–160 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.68 (m, 4 H, 2 × CH_2), 3.54 (t, 2 H, CH_2O), 3.74 (m, 3 H, CH_2N, CHOH), 4.46 (s, 2 H, CH_2Ar), 4.65 (d, 1 H, CHOH, J = 5.5), 5.67 (d, 1 H, H6, J = 7.2), 6.96 (s, 2 H, NH_2), 7.34 (s, 5 H, ArH), 7.55 (d, 1 H, H5). Anal. ($C_{16}H_{21}N_3O_3$) C, H, N.

(±)-4-Amino-1-(3,5-dihydroxypent-1-yl)pyrimidin-2(1*H*)-one (15). A solution of boron trichloride in dichloromethane (1 M, 5 mL) and **38** (100 mg, 0.33 mmol) was stirred at −78 °C under argon for 6 h. A solution of methanol and dichloromethane 1:1 was then added cautiously and the mixture was stirred for 30 min to room temperature before evaporation to dryness. The residue in ethanol (10 mL) was neutralized with 1 N sodium hydroxide, evaporated to dryness, and chromatographed on silica gel eluting with dichloromethane–ethanol 9:1 to afford a colorless oil: yield 82%; ^{1}H NMR (Me_2SO-d_6) δ 1.27–1.43 (m, 4 H, 2 × CH_2), 3.18–3.55 (m, 3 H, CH_2OH, CHOH), 3.74 (t, 2 H, CH_2N), 4.04 (t, 1 H, CH$_2$OH), 4.66 (d, 1 H, CHOH, J = 5.5), 5.71 (d, 1 H, H6, J = 7), 7.0 (s, 2 H, NH_2), 7.60 (d, 1 H, H5). Anal. ($C_9H_{15}N_3O_3$) C, H, N.

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