Synthesis and Biological Evaluation of 4-Purinylpyrrolidine Nucleosides

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The synthesis of several novel carbocyclic purine nucleosides that incorporate a nitrogen in place of carbon 3 of the cyclopentyl moiety are described. These analogues are all derived from the key stereochemically defined intermediate *N*-(*tert*-butoxycarbonyl)-*O*-[(4-methoxyphenyl)diphenylmethyl]-*trans*-4-hydroxy-D-prolinol (**19**), which was accessible in 61.1% overall yield for a five-step sequence starting from *cis*-4-hydroxy-D-proline. The heterocyclic bases, 6-chloropurine and 2-amino-6-chloropurine, are efficiently introduced onto the pyrrolidine ring via a Mitsunobu-type coupling procedure with triphenylphosphine and diethyl azodicarboxylate. Standard transformations and removal of protecting groups gave the *cis*-adenine (**26**), hypoxanthine (**27**), 2,6-diaminopurine (**28**), and guanine (**29**) D-prolinol derivatives. In addition, a related sequence from *trans*-4-hydroxy-L-proline provided the enantiomeric L-prolinol guanine derivative (**36**). Lastly, the 6-(dimethylamino)purine analogue, **37**, was coupled to *N*-(benzyloxycarbonyl)-*p*-methoxy-L-phenylalanine to provide, after deprotection, the novel puromycin-like analogue **39**. The analogues **26–29**, **36**, and **39** were all evaluated for antitumor and, except for **39**, for antiviral activity. These compounds failed to appreciably inhibit the growth of P388 mouse leukemia cells in vitro at concentrations up to 100 μg/mL. In addition, they did not exhibit noticeable activity against the human immunodeficiency virus or herpes simplex virus type 1 at concentrations as high as 100 μM. The adenine analogue, **26**, did, however, prove to be a substrate for adenosine deaminase. It possessed an affinity for the enzyme only 50% less than that of adenosine with a K_i = 85 μM.

Nucleosides, as well as analogues and derivatives thereof, have been widely explored as potential antitumor and antiviral chemotherapeutic agents.[1-4] Among the best screening leads for antiviral action in general are analogues of the naturally occurring purine and pyrimidine nucleosides. Primarily as a result of the utility and efficacy of certain 2',3'-dideoxy nucleosides,[5] most notably 3'-azido-2',3'-dideoxythymidine (AZT),[6] 2',3'-dideoxycytidine (DDC),[7] and 2',3'-dideoxyinosine (DDI)[8] in combatting the human immunodeficiency virus (HIV), the etiological agent of acquired immunodeficiency syndrome (AIDS),[9] tremendous interest has been focused on this area. Unfortunately, most of the above materials possess some undesirable pharmacological properties.[7b,10-13] Therefore, numerous synthetic efforts have been undertaken that were directed at modifying these structures to provide compounds that retain inhibitory activity without detrimental side effects.[14] A range of structural modifications, both on the heterocyclic base and on the sugar moiety, have been investigated. The new active derivatives which have been discovered from modification of these known agents, 3'-fluoro, 3'-azido, and 2',3'-didehydro-2',3'-dideoxy nucleosides, are all very similar to the known leads and, for the most part, offer no substantial advantage over the compounds already being studied. Further, the general lack of functionality of these structures, although primarily responsible for their biological potency, restricts the number and type of analogues that can be made in an effort to circumvent the problems associated with them.

For this reason, compounds that would substantially mimic the 2',3'-dideoxy nucleoside structure, but which, in addition, provided a site for further modification to allow for the synthesis of a wide variety of derivatives with potentially different activities was considered desirable. The need for new, more adaptable agents is underscored by the recent isolation of AZT resistant strains of HIV[15]

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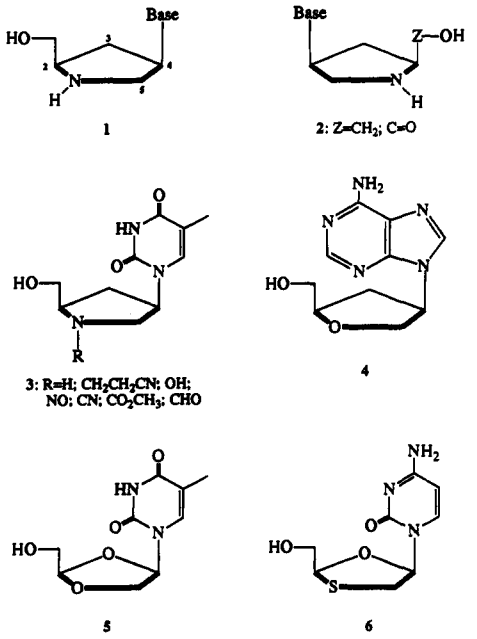

Figure 1.

and of a second human immunodeficiency virus (HIV-2) that is implicated in AIDS.[16] Of further significance is the report that 2',3'-dideoxy nucleosides are less inhibitory toward HIV-2.[17] Carbocyclic nucleosides, wherein the furanose oxygen is replaced by a methylene group, are analogues which have been found to possess interesting and useful biological activity.[18,19] Both naturally occurring and synthetic examples have been found to have antitumor and antiviral properties. These structures prove to be more resistant to the action of certain enzymes, such as phosphorylases, that can deactivate the corresponding nucleoside. The carbocyclic analogue of 2',3'-dideoxy-2',3'-didehydroguanosine (carbovir) has recently been reported to have substantial anti-HIV activity.[20]

However, in a situation similar to that encountered with the natural nucleosides, further modification of this structure is precluded by the lack of appropriate functionality on the cyclopentyl ring. A carbocyclic nucleoside analogue in which the 3-position of the cyclopentyl ring is occupied by a nitrogen in place of the carbon (Figure 1, 1) was envisioned to offer an intriguing solution to this problem. Conformational studies on the pyrrolidine ring in proline and 4-hydroxyproline have indicated substantial similarity to the furan and cyclopentyl structures.[21] The small perturbation could very possibly be significant as far as antiviral activity is concerned. The furan–cyclopentyl difference likewise is not very great, yet many carbocyclic nucleosides have a unique activity that is not mirrored in their natural counterparts.

Surprisingly, a search of the literature found that these pyrrolidine nucleosides were the subject of previous synthetic efforts.[22] However, the routes chosen did not proceed efficiently, and only minimal biological potency was reported. More importantly, these earlier studies started their syntheses from *trans*-4-hydroxy-L-proline. This resulted in formation of products (2) enantiomeric to those required for direct analogy to the natural D-ribonucleosides. This is particularly significant. The crystal structures of the naturally occurring carbocyclic nucleosides aristeromycin[23] and neplanocin A[24] and of the active (+)-isomer of carbocyclic thymidine[25] indicate that they all possess an absolute configuration that mimics that of the natural nucleoside isosteres. Further, for the carbocyclic analogues of adenosine,[26] ara-A[27] puromycin,[28] and thymidine,[25c] for which the optical isomers have been resolved, it has been demonstrated that the biological activity resides in that structure that possesses a configuration analogous to that of D-ribose. A similar result has been described for the individual isomers of a fluorine-substituted carbocyclic guanine derivative[29] and for the carbocyclic analogues of 5-iodo-2'-deoxyuridine and (*E*)-5-(2-bromovinyl)-2'-deoxyuridine.[30] It is not surprising,

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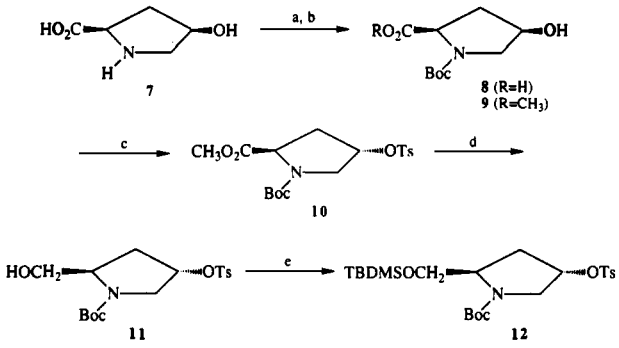
Scheme I[a]

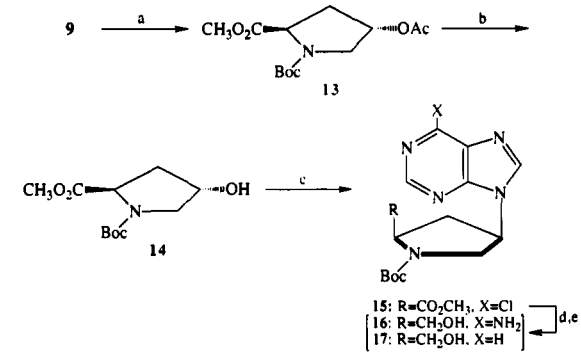


[a] (a) (t-$BuO_2C)_2O$, 10% aqueous NaOH, THF-H_2O (82.5%); (b) CH_2N_2, ether-dioxane, 5 °C (92.4%); (c) CH_3OTs, Ph_3P, DEAD, THF, 0 °C → room temperature; (d) $LiBH_4$, THF, 0 °C → room temperature (57.7%, 2 steps); (e) TBDMSCl, imidazole, DMF (84.4%).

therefore, that the biological activity of the previously reported compounds was insignificant. It must be noted, however, that in the latter cases,[30] both enantiomers of the carbocyclic analogues were found to possess antiviral activity. Here too, however, the material that mimicked the D-ribose configuration had a potency 10–400 times that of its optical antipode. A reinvestigation into the synthesis of these novel structures in the interest of obtaining compounds with antiviral and/or antitumor activity seemed warranted.

Indeed, since initiation of these studies, such a conclusion has been reached by others. Orgel and Ng have recently reported the synthesis of the thymine analogue containing a pyrrolidine ring in place of the ribose, as well as several N-substituted derivatives thereof (**3**).[31] The only biological activity rested in the hydroxylamine derivative (**3**, R = OH) with an IC_{50} = 0.08–14.02 μM being obtained for a panel of human tumor cell lines. In addition, a derivative of carbocyclic 2′,3′-dideoxyadenosine, in which an oxygen atom replaces the 3′-carbon (**4**), has been found to possess anti-HIV activity in the same range as 2′,3′-dideoxyadenosine itself (ED_{50} = 5–15 μM).[32] Pyrimidine analogues in which the 3′-carbon has been substituted by a heteroatom, but that retain the furanose oxygen, have also been reported. The dioxolane–thymidine derivative **5** provided a 50% level of protection against viral-induced cytopathogenic effects at a concentration of 20 μM, while exhibiting reduced toxicity as compared to AZT toward normal cells.[33] The corresponding 1,3-oxothiolane material **6** also provided substantial antiretroviral activity (ED_{50} = 0.3–0.4 μM) with diminished toxicity.[34,35]

Scheme II[a]



[a] (a) CH_3CO_2H, Ph_3P, DEAD, THF, 0 °C → room temperature (93.9%); (b) $NaOCH_3$, CH_3OH (93.9%); (c) 6-chloropurine, Ph_3P, DEAD, THF, room temperature, ON (77.6%); (d) $LiBHEt_3$, THF, 0 °C; (e) NH_3, 80 °C (bomb) [**16** (15.0%), **17** (9.5%)].

Chemistry

The synthetic approach to the desired targets was based upon a convergent strategy whereby the purine moiety could be attached in one step to the pyrrolidine nucleus. Classically, carbocyclic nucleosides are constructed by building the heterocyclic moiety from a correctly stereochemically defined amine.[18] It was anticipated that a leaving group in the 4-position of the ring could be successfully alkylated with the salt of a purine base. Although this approach had met with a varied degree of success previously,[22b] the ability of subsequent investigators to build carbocyclic isomers via this methodology provided confidence for its potential.[36–40] A suitably protected *trans*-D-prolinol intermediate was required. Unfortunately, the only commercially available compound with the correct absolute stereochemistry is the cis isomer of 4-hydroxy-D-proline. The corresponding trans isomer is accessible via a multistep sequence from the less expensive *trans*-4-hydroxy-L-proline.[41] It was decided to start from the former and incorporate steps to invert the stereochemistry at the 4-position into our protocol (Scheme I).

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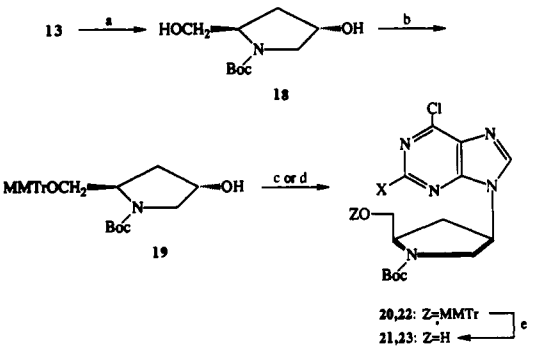
The amino acid derivative 9 was made by standard methodology as reported for *trans*-4-hydroxy-L-proline involving first protection of the amine as the *N*-*tert*-butoxycarbonyl[42] derivative 8 followed by formation of the methyl ester with diazomethane. Use of a triphenylphosphine–diethyl azodicarboxylate Mitsunobu inversion procedure[43] using methyl *p*-toluenesulfonate as the nucleophilic partner gave the trans-tosylated intermediate 10 directly from the alcohol.[44] It has been demonstrated in a number of instances that application of this methodology proceeds with inversion in this type of system.[45] Although this material was difficult to separate from the diethylhydrazine dicarboxylate side byproduct formed during this process, purification could be achieved after reduction of the methyl ester to the primary alcohol 11 with lithium borohydride.[46] Protection of the hydroxyl as its *tert*-butyldimethylsilyl ether[47] yielded 12, the desired substrate for the nucleophilic attachment of the purine base. However, attempts to displace the tosylate with either the sodium or potassium salt of 6-chloropurine resulted in either recovery or, at higher temperatures, decomposition of the starting material.

Before initiating the exploration of other leaving groups, the success of the triphenylphosphine–diethyl azodicarboxylate reaction prompted the study of this methodology for direct introduction of the heterocycle. Previously, Szarek had adapted this procedure for the synthesis of nucleosides of aldoses and ketoses by direct replacement of the anomeric hydroxyl.[48] He also constructed some unusual thiazole nucleosides via this type of reaction.[49] More recently, Marquez has employed this method for the completion of the synthesis of some neplanocin derivatives, although no experimental details were given.[50,51] Since this work was undertaken, the Mitsunobu process has been shown to have utility in the synthesis of natural nucleoside derivatives as well.[52] In addition, this methodology has been used for the formation of alkyl[53] and N^9-alkoxy[54,55] nucleoside analogues. In order for this protocol to be useful in this case, the trans 4-hydroxy compound 14 was required (Scheme II).

Scheme III[a]



[a] (a) $LiBH_4$, THF, 0 °C → room temperature (97.4%); (b) MMTrCl, Et_3N, DMAP, CH_2Cl_2–THF, room temperature (87.7%); (c) 6-chloropurine, Ph_3P–DEAD, THF, room temperature, ON; (d) 2-amino-6-chloropurine, Ph_3P–DEAD, THF, room temperature, ON; (e) 80% HOAc, room temperature, ON [21 (X = H, 68.8%, 2 steps), 23 (X = NH_2, 70.2%, 2 steps)].

Inverting esterification of 9 with the DEAD–Ph_3P couple in the presence of acetic acid, followed by hydrolysis of the acetate 13 gave the alcohol 14 in 88.2% yield. This alcohol was then successfully and efficiently coupled to 6-chloropurine under Mitsunobu conditions to produce 15. Unfortunately, reduction of the ester to the alcohol with a variety of reagents, diisobutylaluminum hydride, lithium borohydride, and calcium borohydride, was complicated by concomitant reduction of the 6-chloro substituent on the heteroaromatic moiety together with other unidentified auxiliary reactions. In the best case, from the reaction of 15 with lithium triethylborohydride, followed by treatment of the mixture of products obtained with liquid ammonia under pressure, the desired 6-aminopurine 16 was accessed, but in only 15.0% yield, along with a smaller amount of the 9-purinyl derivative 17 (9.5%).

In order to circumvent this difficulty, modification of the reaction sequence so that execution of the reduction preceded coupling of the purine was introduced without actually adding to the overall number of individual synthetic steps (Scheme III). Hence, reaction of 13 with lithium borohydride gave the *N*-Boc-D-prolinol derivative 18 in excellent yield. Selective protection of the primary alcohol as its *p*-methoxytriphenylmethyl (monomethoxytrityl = MMTr) ether[56] produced 19, what would prove to be the key intermediate for the successful completion of the desired syntheses. Overall, the sequence of 7 → 19 proceeded in 61.1% yield.

Coupling of 19 to 6-chloropurine also proceeded efficiently, but chromatographic separation from the hydrazine byproduct could only be partially achieved. In order to more accurately ascertain the yield in this process, treatment of impure 20 with 80% acetic acid liberated the primary hydroxyl and allowed for easy purification. This two-step sequence led to the production of 21 in 68.8% yield. In a similar manner, reaction of 2-amino-6-chloropurine with 19 in the presence of DEAD–Ph_3P provided a route to the guanine and 2,6-diaminopurine analogues. In this instance, purification of the coupled nucleoside 22 was complicated by the persistence of the triphenylphosphine oxide byproduct. Determination of an accurate yield was therefore again made after cleavage of the monomethoxytrityl ether. This process proceeded to give 23 in 70.2% yield.

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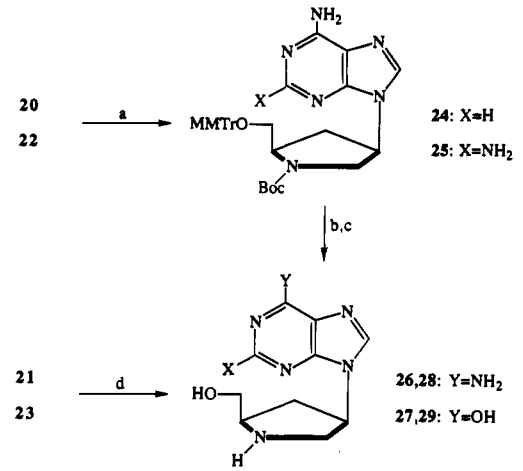
Scheme IV[a]

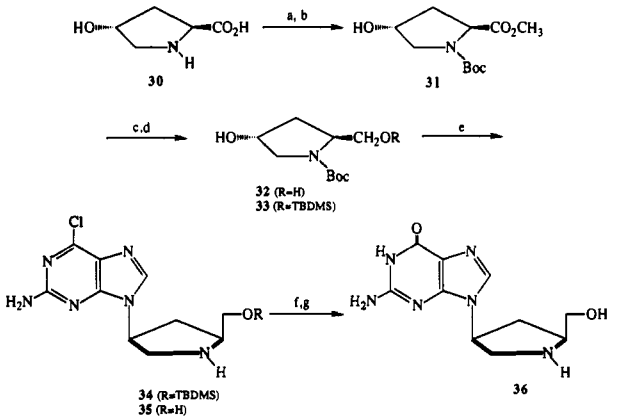


[a](a) NH_3, MeOH, 80–85 °C (bomb) [**24** (91.4%), **25** (97.3%)]; (b) CF_3CO_2H, room temperature, 1 h; (c) Dowex SBR (OH^-) [**26**, X = H (84.3%); **28**, X = NH_2 (58.8%)]; (d) 1–2 NHCl, Δ, 4 h [**27**, X = H (85.7%); **29**, X = NH_2 (48.4%)].

A noteworthy feature of this coupling process was the regioselectivity it exhibited. Many of the direct procedures for introduction of the heterocycle, particularly with 2,6-disubstituted purines, give mixtures of N^7- and N^9-substituted products.[36-40] Here, however, the N^9-substituted purines were essentially the sole products obtained. This is supported by the ^1H NMR and UV spectra of the coupled products and the targets derived from them. Some evidence suggests that the procedure may not be completely regiospecific, however. It has been reported that for other 2,6-disubstituted purine nucleoside analogues, the N^7 regioisomer can be identified based upon characteristic downfield shifts for H8 and upfield shifts for a 2-NH_2 moiety.[57-59] These shifts are more definitively diagnostic for N^7 substitution than the more classical use of UV spectra. In the case of **28**, the crude ^1H NMR spectrum showed small resonances upfield from the major ones for the purine proton and downfield from the amino resonance were observed. These resonances disappeared upon recrystallization. It was not determined whether this was due to N^7 material that was an exception to the above general trends or merely some other impurity. Further, the fact that both **26** and **28** proved to be substrates for adenosine deaminase (vide infra) suggests that they were indeed the desired N^9 isomer.

For the most part, completion of the syntheses of the target structures proceeded straightforwardly (Scheme IV). For the adenine analogue, the still fully protected intermediate **20** obtained on partial purification from the coupling was used. Displacement with ammonia to provide **24**, followed by treatment with neat trifluoroacetic acid provided, after ion exchange resin neutralization, the 6-aminopurine derivative **26**. Alternatively, acidic hydrolysis of the partially deprotected intermediate **21** provided the hypoxanthine **27** after ion exchange chromatography. Curiously, it proved difficult to obtain the same material in analytically pure form from the fully protected precursor **20**. Likewise for the products from the other sequence, displacement with ammonia on the fully protected 2-amino-6-chloropurine **22** to provide **25**, followed by removal of both protecting moieties with trifluoroacetic acid and neutralization gave the 2,6-diaminopurine derivative **28**. Acidic hydrolysis of **22** failed, as with the hypoxanthine analogue, to give the guanine derivative in analytically pure form. However, successful access to **29** was obtained from **23**.

Scheme V[a]



[a](a) (t-$BuO_2C)_2O$, 10% aqueous NaOH, THF–H_2O (93.2%); (b) CH_2N_2, ether–dioxane, 5 °C (92.0%); (c) $LiBH_4$, THF, 0 °C → room temperature (99.0%); (d) TBDMSCl, DMAP–Et_3N, CH_2Cl_2, 0 °C → room temperature (62.6%); (e) 2-amino-6-chloropurine, Ph_3P, DEAD, THF, room temperature, ON; (f) $Bu_4N^+F^-$, THF, room temperature (44.4%, 2 steps); (h) 1–2 N HCl, Δ, 3.5–4 h (24.6%).

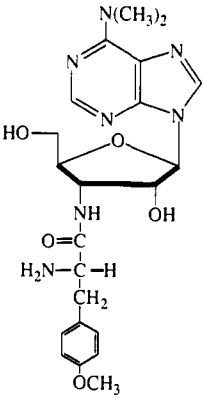


Figure 2. Puromycin.

In order to have at least one of the enantiomeric materials for comparison purposes, the corresponding L-prolinol guanine derivative was synthesized starting from *trans*-4-hydroxy-L-proline (**30**). The sequence used was identical to that shown for its optical antipode except for the protecting methodology employed for the primary hydroxyl and, of course, the elimination of the unneeded inversion step (Scheme V). The amino acid was protected as its *N*-Boc methyfl ester (**31**) using the standard methodology already described. Reduction of the ester followed by selective protection of the primary hydroxyl of **32** as the *tert*-butyldimethylsilyl ether[47] provided **33**. Coupling with 2-amino-6-chloropurine using the Mitsunobu conditions proceeded well to yield the protected nucleoside derivative **34**. Cleavage of the silyl ether with tetrabutylammonium fluoride followed by acidic hydrolysis of the 6-chloro moiety provided **36**, the desired enantiomer of **29**.

One other analogue was of interest. In the previous investigations with these nucleoside systems,[22a] a novel analogue of puromycin, a potent antibiotic isolated in 1952 from *Streptomyces alboniger* (Figure 2),[60] had been made

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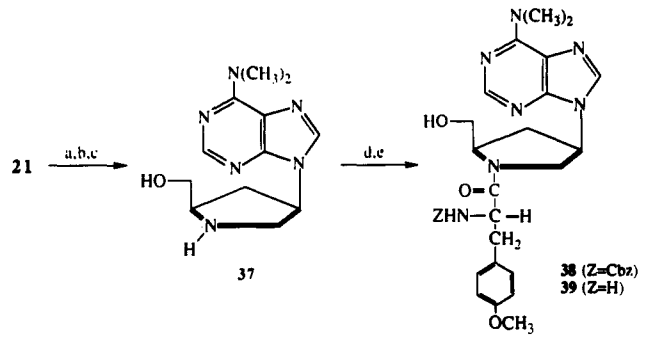
Scheme VI[a]



[a] (a) 40% aqueous $(CH_3)_2NH$, Δ; (b) CF_3CO_2H, room temperature, 1 h; (c) Dowex SBR (OH^-) (84.9%, 3 steps); (d) Cbz-*p*-OMe-L-Phe, DCC, *N*-hydroxysuccinimide; (e) H_2/Pd–C, CH_3CO_2H (69.5%, 2 steps).

by attaching the requisite amino acid component of the antibiotic to the pyrrolidine ring nitrogen. A number of carbocyclic nucleoside analogues of this material have been synthesized and have been reported to exhibit antimicrobial activity comparable to the natural isostere without its concomitant nephrotoxicity.[28,61,62] Intrigued by the possibility that the correct enantiomer of this compound might also possess interesting biological properties, its construction was undertaken beginning from the available 6-chloropurine intermediate **21** (Scheme VI). Displacement of the halide with refluxing aqueous dimethylamine followed by standard deprotection and neutralization gave the 6-(dimethylamino)purine derivative **37**. Coupling of this to *N*-(benzyloxycarbonyl)-*p*-methoxy-L-phenylalanine with dicyclohexylcarbodiimide (DCC) in the presence of *N*-hydroxysuccinimide[22a,28,61a] proceeded efficiently to give **38**. Removal of the amino protecting group by catalytic hydrogenation in acetic acid provided the puromycin-like analogue **39**.

Biological Results

The purine derivatives **26–29**, **36**, and **39** were investigated for their ability to inhibit the growth of P388 mouse leukemia cells in vitro.[63] At concentrations from 3.1 to 100 μM, only slight inhibition at the higher levels was observed. One important note was the complete lack of any observed effect of the guanine derivative (**36**) when compared with its D-prolinol counterpart (**29**). The disappointing lack of activity of the puromycin-styled nucleoside **39** could be due to the absence of the 2-hydroxyl group. Although not definitive in this case, the requirement for this structural feature in puromycin has very recently been demonstrated.[64] However, it was known previously that this moiety was necessary for the acceptor activity of aminoacyl adnosines, which are thought to bind to the ribosome in a manner analogous to that of puromycin.[61,65]

The purines **26–29** and **36** were also screened for antiviral activity against both HIV and herpes simplex virus type 1 (HSV-1). However, in each case, the materials failed to prohibit the appearance of viral cytopathogenic effects at concentrations from 0.1 to 100 μM. This was disappointingly consistent with the report that no antiviral activity was obtained for the series of thymine analogues as well.[31]

In an effort to probe the reasons for the lack of biological effects, the potential of one of these compounds, the adenine analogue **26**, to act as an inhibitor or substrate for a typical enzyme involved in nucleoside metabolism was investigated. It was found to be a weak inhibitor of adenosine deaminase, with a K_i = 85 μM. Interestingly, this material possessed affinity for the enzyme only 50% of that observed for the natural substrate, adenosine. In addition, although a detailed kinetic analysis was not done, qualitative experiments indicated that **28** was also a substrate for adenosine deaminase, although a much poorer one than **26**. Therefore, it is possible that the cause of the absence of activity is not merely due to an inability of the target enzymes to recognize this type of analogue. However, it must be concluded that the charge on the pyrrolidine nitrogen, which would be protonated at physiological pH, must be having some effect, due to the substantial difference in activity against HIV observed between **26** and the corresponding O-substituted adenine analogue (**4**).[32] Studies have indicated a requirement that for a nucleoside to have anti-HIV activity, it must occupy a particular conformational space.[66] Although a detailed analysis has not been done for these molecules, this cannot be discounted as a further reason for the observed difference.

Experimental Section[67]

General. All reactions involving air-sensitive reagents were carried out under a nitrogen atmosphere in oven-dried glassware. Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^1H nuclear magnetic resonance spectra were obtained either on a Nicolet NT-300 operating at 300.0745 MHz or on an IBM AF-300 operating at 300.135 MHz in the solvent listed and are given as parts per million (δ) relative to internal tetramethylsilane (TMS) or for those molecules containing CH_3Si, to that peak, as reference. Resonances are reported as [apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, others as described), coupling constant (*J*) if appropriate, relative integral, assignment if known]. For the pyrrolidine ring, the numbering system shown for compound **1** in Figure 1 has been used. Fourier transform infrared spectra were taken with a Nicolet 5-DXC instrument and are reported as wavenumbers (cm^{-1}). Major bands are given and designated as broad (br), very strong (vs), or strong (s) where appropriate to signify their intensity. Ultraviolet spectra were obtained on a Beckman DU-70 spectrometer. Reported wavelengths, in nanometers, are maxima or are designated as a shoulder (sh) or a slight shoulder (slsh). The relative heights of the bands are given parenthetically. Electron impact (EI) mass spectra were obtained with an AEI Scientific Apparatus Limited MS-30 mass spectrometer. Chemical ionization (CI) mass spectral data was obtained on a Finnigan 4000 mass spectrometer using the reagent gas indicated for the individual compounds. Fast-atom bombardment (FAB) mass spectral data was recorded with a VG7070E-HF mass spectrometer using the indicated matrix. For CI and FAB spectra, both positive and negative detection modes were employed, thus key ions are reported with a plus (+) or minus (−) to distinguish between the two. The peaks listed are those from the molecular ion, designated M^+, and fragments that can be assigned as either plus or minus

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(67) All new compounds (**8–39**) gave spectral data and/or elemental analyses consistent with the assigned structures.

relative to the molecular ion or the complete purine or pyrimidine portion of the molecule, designated P, as well as other prominent or significant peaks. The intensities of the fragments are given parenthetically relative to the base peak, listed as 100. Thin-layer chromatography (TLC) was done using 0.25-mm layers of Merck silica gel 60F-254 on glass-backed plates. Plates were visualized by viewing under ultraviolet light, by exposure to iodine vapor, or by spraying with a 5% solution of phosphomolybdic acid in absolute ethanol followed by heating. Column chromatography was performed on Merck silica gel 60 (230–400 mesh). The solvent systems used for chromatography were as follows. Solvent A: ethyl acetate–hexanes (relative volumes as specified). Solvent B: 100% ethyl acetate. Solvent C: MeOH–$CHCl_3$ (relative volumes as specified). Solvent D: concentrated NH_4OH–*n*-PrOH (relative volumes as specified). Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. 6-Chloropurine, 2-amino-6-chloropurine, *cis*-4-hydroxy-D-proline, *trans*-4-hydroxy-L-proline, and all anhydrous solvents were obtained from Aldrich Chemical Co., Milwaukee, WI. Adenosine and adenosine deaminase (adenosine aminohydrolase, EC 3.5.4.4) type VI from calf intestinal mucosa were purchased from Sigma Chemical Co.

***N*-(*tert*-Butoxycarbonyl)-*cis*-4-hydroxy-D-proline (8).** The procedure of Jouille[42] for *trans*-4-hydroxy-L-proline was employed. In 125 mL of THF–H_2O (2:1) was suspended 10.0 g (76.3 mmol) *cis*-4-hydroxy-D-proline (7), and then 42 mL of a 10% aqueous solution of NaOH was added. To the resultant biphasic mixture was added 22.6 g (103.6 mmol) of di-*tert*-butyl dicarbonate in 125 mL of THF–H_2O (2:1). The reaction was allowed to stir overnight at ambient temperature, and then the THF was removed by evaporation in vacuo. The residual aqueous solution was adjusted to pH 2 by the addition of approximately 150 mL of 10% aqueous $KHSO_4$. The acidic solution was extracted several times with ethyl acetate. The combined organic extracts were washed with H_2O and saturated aqueous NaCl and then dried over anhydrous Na_2SO_4. Removal of the dessicant and evaporation of the solvent in vacuo gave 18.6 g of a white solid, which was recrystallized from ethyl acetate to give 12.8 g of 8. An additional 1.69 g (total yield 82.5%) was recovered from the filtrate in two crops: mp 142.5–143.5 °C (dec with effervescence); $[\alpha]^{22}_D$ (*c* 0.67, MeOH) = +47.7°; ^{1}H NMR (DMSO-d_6) δ 4.19 and 4.08 (each m, each 1, C_2H and C_4H), 3.45–3.52 and 3.06–3.13 (each m, each 1, $C_3H_aH_b$), 3.33 (br s, 1, O*H*, D_2O exchangeable), 2.24–2.38 (m, 1, C_3H_b), 1.77–1.85 (m, 1, C_3H_a), 1.39 and 1.34 [each s, total 9 (1:2 ratio), $(CH_3)_3CO$ rotamers[42]]; IR (KBr) 3445, 3300–2500 (br) with maxima at 2981, 2926 and 2881, 1739 (s), 1707, 1671 (s), 1410 (s), 1347, 1257, 1178, 1166, 1131, 1091, 904, 771; CIMS (90 °C, NH_3) *m/z* 249 [(M + 18)$^+$, 3.8], 232 [(M + H)$^+$, 13.8], 193 [(M + 18 – t-Bu + H)$^+$, 100], 176 [(M + 2 H – t-Bu)$^+$, 14.2], 132 [(M + 2 H – Boc)$^+$, 29.2], 86 [(M – Boc – CO_2)$^+$], 230 [(M – H)$^-$, 100], 130 [(M – Boc)$^-$, 17.7]; FABMS (thioglycerol) *m/z* 232 [(M + H)$^+$, 20.8], 176 [(M + 2 H – t-Bu)$^+$, 100], 132 [(M + 2 H – Boc)$^+$, 90.6], 130 [(M – Boc)$^+$, 99.2], 230 [(M – H)$^-$, 100], 130 [(M – Boc)$^-$, 19.2]. Anal. ($C_{10}H_{17}NO_5$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*cis*-4-hydroxy-D-proline Methyl Ester (9).** In a mixture of 125 mL of anhydrous dioxane and 125 mL of ether was slowly dissolved 8.11 g (35.1 mmol) of 8. The solution was cooled to 5 °C and then treated dropwise with a freshly prepared solution of diazomethane in ether until a yellow color persisted in the reaction flask. The solution was stirred 0.25 h at 5 °C and then treated with a small amount of glacial acetic acid to scavenge the excess diazomethane. Anhydrous magnesium sulfate was added to the clear solution, which was allowed to stir overnight at room temperature. Removal of the dessicant and evaporation of the solvent in vacuo gave 9.03 g of a light yellow solid, which was recrystallized from ethyl acetate–hexanes (1:4) to give 7.44 g of 9. Additional material, 0.51 g (total yield 92.4%), was obtained from the filtrate: mp 82.5–83.0 °C; TLC R_f = 0.16 [solvent A (1:1)]; $[\alpha]^{22}_D$ (*c* 0.52, MeOH) = +26.6°; ^{1}H NMR (DMSO-d_6) δ 4.98 and 4.94 [each br d, both J = 2.2 Hz, total 1 (2:1 ratio), O*H* rotamers, D_2O exchangeable], 4.20 (m, 2, C_2H and C_4H), 3.63 and 3.60 [each s, total 3 (2:1 ratio), OCH_3 rotamers], 3.45–3.51 (m, 1, C_3H_a), 3.08–3.15 (m, 1, C_3H_b), 2.30–2.39 (m, 1, C_3H_a), 1.78–1.86 (dt, J = 4.8, 12.8 Hz, 1, C_3H_b), 1.40 and 1.33 [each s, total 9 (1:2 ratio), $(CH_3)_3CO$ rotamers]; ^{1}H NMR ($CDCl_3$) δ 4.28–4.39 (m, 2, C_2H and C_4H), 3.80 and 3.78 [each s, total 3 (45:55 ratio), OCH_3 rotamers], 3.46–3.73 (m, 1, C_3H_2N), 3.24 (d, J = 10.1 Hz, O*H*), 2.26–2.40 (m, 1, C_3H_a), 2.05–2.12 (dt, J = 4.8, 12.8 Hz, 1, C_3H_b), 1.47 and 1.42 [each s, total 9 (4:5 ratio), $(CH_3)_3CO$ rotamers]; IR (KBr) 3466 (s), 2985, 2957, 2929, 1729 (s), 1681 (s), 1425 (s), 1283, 1263, 1178, 1163, 1123, 1090, 969, 771, 596 (br); EIMS (110 °C, 30 eV) *m/z* 245 (M$^+$, 1.2), 227 (M – H_2O, 1.7), 186 (M – CO_2CH_3, 25.7), 144 (M – Boc, 39.9), 130 (M + H – t-Bu – CO_2CH_3, 79.6), 86 (100), 57 (C_4H_9, 99.5). Anal. ($C_{11}H_{19}NO_5$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*trans*-4-(*p*-toluenesulfonyloxy)-D-proline Methyl Ester (10).** To 0.350 g (1.43 mmol) of **9** and 0.46 g (1.75 mmol) of Ph_3P in 15 mL of anhydrous THF at 0 °C was added a solution of 0.31 g (1.78 mmol) of diethyl azodicarboxylate (DEAD) in 5 mL of anhydrous THF. The yellow mixture was stirred for 5 min, and then 0.33 g (1.71 mmol) of methyl *p*-toluenesulfonate in 6 mL of anhydrous THF was added dropwise. The solution was maintained for 10 min at 0 °C and then stirred for 5 h at ambient temperature. Removal of the solvent in vacuo followed by chromatography of the residue on silica gel with solvent C (1:500) gave 0.603 g of a semisolid material that contained **10** contaminated with significant quantities of diethylhydrazine dicarboxylate [R_f = 0.20, solvent C (1:75)]. It was used in the next reaction without further purification. In a separate trial, repeated chromatography provided a purer sample of **10** for spectral characterization: TLC R_f = 0.53 [solvent A (1:1)], R_f = 0.48 [solvent C (1:75)]; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2, C*H* phenyl), 7.35 (d, J = 8.1 Hz, 2, C*H* phenyl), 5.04 (br m, 1, C_4H), 4.35 (m, 1, C_2H), 3.72 (s, 3, OCH_3), 3.61 (br m, 2, C_3H_2), 2.38–2.54 (m, partially obscured by next resonance, C_3H_a), 2.46 [s, 4 (includes preceding resonance, CH_3Ph], 2.09–2.20 (m, 1, C_3H_b), 1.42 and 1.39 [each s, total 9 (2:3 ratio), $(CH_3)_3CO$ rotamers]; IR (KBr) 3092, 2979, 2955, 2934, 1750 (s), 1705 (s), 1595, 1402 (s), 1367 (s), 1207, 1189, 1178, 1160, 902, 756, 555.

The corresponding cis isomer was synthesized from **9** by treatment with *p*-toluenesulfonyl chloride and pyridine: ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.9 Hz, 2, C*H* phenyl), 7.34 (d, J = 7.9 Hz, 2, C*H* phenyl), 5.05 (br m, 1, C_4H), 4.43 and 4.33 (each m, each 0.5, C_2H), 3.59–3.74 [m, 5 (includes resonance at δ 3.72), C_3H_2], 3.72 (s, OCH_3), 2.22–2.52 [m, 5 (includes resonance at δ 2.45), $C_3H_aH_b$), 2.45 (s, CH_3Ph), 1.44 and 1.40 [each s, total 9 (4:5 ratio), $(CH_3)_3CO$ rotamers]. From consideration of the regions associated with the C_2H resonance, it appeared that no detectable amount of the cis isomer was present in the purified sample of **10**.

***N*-(*tert*-Butoxycarbonyl)-*trans*-4-(*p*-toluenesulfonyloxy)-D-prolinol[68] (11).** The impure **10** obtained above was dissolved in 20 mL of anhydrous 1,2-dimethoxyethane and cooled to 0 °C. To this was added 0.137 g (6.39 mmol) of solid $LiBH_4$; a homogeneous solution resulted. The mixture was allowed to warm gradually to ambient temperature and then stirred for 17.5 h. The excess borohydride was carefully destroyed by the successive addition of H_2O and acetic acid. After separation of the organic phase, the aqueous layer was extracted with two portions of ethyl acetate–ether (3:1), and the combined organic layers were dried over anhydrous Na_2SO_4. The dessicant was removed by filtration, and the filtrate was evaporated in vacuo. Chromatography of the residue on silica using solvent A (1:1) provided 0.305 g (57.7%, 2 steps) of **11** as an oil: TLC R_f = 0.27 [solvent A (1:1)]; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2, C*H* phenyl), 7.36 (d, J = 8.2 Hz, 2, C*H* phenyl), 5.00 (br m, 1, C_4H), 4.37 (br s, 1, O*H*), 4.04 (br m, 1, C_2H), 3.73 and 3.69 (each br m, total 2, CH_2OH), 3.42–3.54 (m, 2, C_3H_2), 2.46 (s, 3, CH_3Ph), 2.17 (br m, 1, C_3H_a), 1.73 (br m, 1, C_3H_b), 1.44 [s, 9, $(CH_3)_3CO$]; IR (KBr) 3431 (br), 2981, 2931, 2882, 1736, 1694 (s), 1595, 1407 (s), 1367 (s), 1177 (s), 964.

***N*-(*tert*-Butoxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-*trans*-4-(*p*-toluenesulfonyloxy)-D-prolinol (12).** In 5 mL of anhydrous DMF, 0.170 g (1.13 mmol) of *tert*-butyldimethylsilyl chloride, 0.144 g (2.11 mmol) of imidazole, and 0.291 g (0.78 mmol) of **11** were combined and then stirred for 41 h at room temperature. The solvent was removed in vacuo (1 Torr) to leave a yellow oil. Chromatography of the oil on silica with solvent A (1:5) gave 0.322 g (84.4%) of **12**: TLC R_f = 0.83 [solvent A (1:1)]; ^{1}H NMR

(68) Alternatively, these compounds could be named as derivatives of 2-pyrrolidinemethanol, i.e. **26** would be (2*R*,4*R*)-4-(6-amino-9*H*-purin-9-yl)-2-pyrrolidinemethanol.

($CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2, CH phenyl), 7.34 (d, J = 8.0 Hz, 2, CH phenyl), 5.07 (br m, 1, C_4H), 3.90–4.03 (m, 2), 3.73–3.80 (m, 0.5), 3.34–3.63 (m, 2.5), 2.45 (s, 3, CH_3Ph), 2.04–2.30 (m, 2, $C_3H_aH_b$), 1.43 [br s, 9, $(CH_3)_3$CO], 0.84 [s, 9, $(CH_3)_3$CSi], 0.00 [br s, 6, $(CH_3)_2$Si]; IR (KBr) 2952, 2931, 2861, 1699 (s), 1598, 1401 (s), 1368 (s), 1178 (s), 837 (s), 554.

***N*-(*tert*-Butoxycarbonyl)-*trans*-4-acetoxy-D-proline Methyl Ester (13).** To 8.41 g (34.3 mmol) of **9** in 100 mL of anhydrous THF was added 15.74 g (60.0 mmol) of Ph_3P followed by 3.30 mL (57.6 mmol) of glacial acetic acid. The mixture was cooled to 0 °C, and a solution of 11.56 g (66.4 mmol) of DEAD in 35 mL of anhydrous THF was added dropwise over 0.25 h. The resulting yellow-orange reaction mixture was allowed to warm gradually to room temperature and then stirred overnight. After 23 h the reaction was not complete, so 4.25 g (16.2 mmol) of Ph_3P, 0.6 mL (10.5 mmol) of HOAc, and 3.0 g (17.2 mmol) of DEAD additional were introduced. After 19 h more, TLC indicated no starting material remained. The solvent was removed in vacuo to leave a syrup from which a 75-mL portion of ether was evaporated. Treatment of the residue with ether then caused a copious amount of white solid (diethylhydrazine dicarboxylate and triphenylphosphine oxide) to form. The mixture was refrigerated for 1.5 h, and then the solid removed by filtration. Evaporation of the filtrate and chromatography of the resulting yellow syrup on silica with solvent A (1:5) gave 9.25 g (93.9%) of **13** as a syrup: TLC R_f = 0.53 [solvent A (1:1)]; $[\alpha]^{22}_D$ (c 0.58, abs EtOH) = +47.2°; ^{1}H NMR ($CDCl_3$) δ 5.28 (br m, 1, C_4HOAc), 4.38 [m (approximate dt), 1, C_2H], 3.50–3.83 [m, 5 (includes resonance at δ 3.74), C_3H_2], 3.74 (s, OCH_3), 2.29–2.45 (m, 1, C_3H_a), 2.11–2.27 (m, 1, C_3H_b), 2.06 (s, 3, CH_3C=O), 1.46 and 1.42 [each s, total 9 (3:4 ratio), $(CH_3)_3$CO rotamers]; IR (neat) 2979, 2957, 2936, 1743 (s), 1701 (s), 1398 (s), 1370, 1237 (s), 1209 (s), 1159 (s), 1124, 1068, 1019, 897, 771; FABMS (thioglycerol) m/z 288 [(M + H)$^+$, 11.5], 232 [(M + 2 H - t-Bu)$^+$, 58.9], 188 [(M + 2 H - Boc)$^+$, 100], 186 [(M - Boc)$^+$, 17.7], 126 [(M - Boc - CO_2CH_3)$^+$, 51.5)]. Anal. ($C_{13}H_{21}NO_6$) C, H, N. The corresponding cis isomer was synthesized from **9** by treatment with acetic anhydride and pyridine: ^{1}H NMR ($CDCl_3$) δ 5.22 (m, 1, C_4H), 4.50 (dd, J = 1.9, 9.0 Hz, 0.5) and 4.38 (dd, J = 2.2, 9.0 Hz, 0.5) [C_2H], 3.48–3.79 [m, 5 (includes resonance at δ 3.74), C_3H_2], 3.74 (s, OCH_3), 2.36–2.55 (m, 1, C_3H_a), 2.30 and 2.25 (each br m, total 1, C_3H_b), 2.00 (s, 3, CH_3C=O), 1.47 and 1.43 [each s, total 9 (1:1 ratio), $(CH_3)_3$CO rotamers]. From consideration of the regions associated with the C_2H resonance, no detectable amount of the cis isomer was present in **13**.

***N*-(*tert*-Butoxycarbonyl)-*trans*-4-hydroxy-D-proline Methyl Ester (14).** A mixture of 3.46 g (12.1 mmol) of **13** and 1.02 g (18.9 mmol) of NaOMe in 75 mL of MeOH was stirred at room temperature for 1 h at which time TLC indicated the hydrolysis was complete. The solvent was removed in vacuo, and the residue was chromatographed on silica gel with solvent A (1:1) to leave 2.78 g (93.9%) of **14** as a lightly yellow syrup: TLC R_f = 0.18 [Solvent A (1:1)]; $[\alpha]^{22}_D$ (c 0.10, abs EtOH) = +116.0°; ^{1}H NMR ($CDCl_3$) δ 4.50 (br m, 1, C_4H), 4.40 [m (approximate q), 1, C_2H], 3.70–3.82 [m, 4 (includes resonance at δ 3.73), C_3H_a], 3.73 (s, OCH_3), 3.66 and 3.62 [each d, each J = 4.3 Hz, total 1 (1:2 ratio), OH rotamers], 3.40–3.60 (m, 1, C_3H_b), 2.21–2.35 (m, 1, C_3H_a), 2.04–2.12 (m, 1, C_3H_b), 1.46 and 1.41 [each s, total 9 (2:5 ratio), $(CH_3)_3$CO]; IR (neat) 3445 (br), 2979, 2953, 1750 (s), 1701 (s), 1678 (s), 1405 (s), 1368 (s), 1204 (s), 1159 (s), 1129, 1088, 982, 896, 774; EIMS (50 °C, 30 eV) m/z 245 (M$^+$, 0.9), 186 (M - CO_2CH_3, 17.5), 144 (M - Boc, 32.0), 130 (M + H - t-Bu - CO_2CH_3, 67.0), 86 (100), 68 (66.0), 57 (C_4H_9, 79.1); FABMS (thioglycerol) m/z 491 [(2 M + H)$^+$, 0.8], 246 [(M + H)$^+$, 18.0], 190 [(M + 2 H - t-Bu)$^+$, 74.3], 146 [(M + 2 H - Boc)$^+$, 100], 144 [(M - Boc)$^+$, 52.9]. Anal. ($C_{11}H_{19}NO_5$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*cis*-4-(6-chloro-9*H*-purin-9-yl)-D-proline Methyl Ester (15).** Triphenylphosphine, 0.28 g (1.07 mmol), was dissolved in 20 mL of anhydrous THF and then 0.15 g (0.97 mmol) of 6-chloropurine was suspended in the resultant solution. To this was added 0.19 g (1.09 mmol) of diethylazodicarboxylate (DEAD) in 5 mL of anhydrous THF. The orange mixture was stirred for 0.16 h at which time all the solid had dissolved and then was treated with 0.20 g (0.80 mmol) of **14** in 10 mL of anhydrous THF. The solution was stirred overnight at ambient temperature, and then the solvent was removed in vacuo. Chromatography of the syrupy residue on silica using solvent A (65:35) as eluent provided 0.24 g (77.6%) of **15** as a yellowish glass: mp 55–58 °C (shrivels 45 °C); TLC R_f = 0.42 (solvent B); ^{1}H NMR ($CDCl_3$) δ 8.74 (s, 1, CH purine), 8.31 (s, 1, CH purine), 5.25 (br m, 1, C_4H), 4.50 (br m, 1), 4.20 [m (approximate t), 1], 3.98–4.13 (dual m, 1) 3.73 (br s, OCH_3), 2.99 (m, 1, $C_3H_aH_bC$), 2.56 (m, 1, C_3H_b), 1.47 [br s, 9, $(CH_3)_3$CO]; ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1, CH purine), 8.75 (s, 1, CH purine), 5.23 (m, 1, C_4H), 4.42 (t, J = 8.1 Hz, 1, C_2H), 4.09 [dd, J = 7.3, 10.5 Hz, C_3H_a], 3.84 [dd, J = 8.5, 10.5 Hz, C_3H_b], 3.67 and 3.65 [each s, total 3 (2:1 ratio), OCH_3 rotamers], 2.91 (m, 1, C_3H_a), 2.66 (m, 1, C_3H_b), 1.42 and 1.37 [each s, total 9 (1:2 ratio), $(CH_3)_3$CO rotamers]; IR (KBr) 3111, 3073, 2982, 2957, 2935, 1751, 1704 (s), 1593, 1561, 1400 (s), 1200, 1157 (s), 1118, 957, 636; EIMS (180 °C, 30 eV) m/z 384 (M + 3, 0.5), 382 (M + 1, 0.8), 280 (M - Boc, 2.1), 222 (M + H - Boc - CO_2CH_3, 12.0), 155 (P + 2 H, 41.0), 127 (M - Boc - P, 66.0), 68 (81.1), 57 (C_4H_9, 100). Anal. ($C_{16}H_{20}N_5O_4Cl$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*trans*-4-hydroxy-D-prolinol (18).** A solution of 7.38 g (25.7 mmol) of **13** in 55 mL of anhydrous THF was treated with 30.0 mL of a 2.0 M solution of $LiBH_4$ in THF at 0 °C. The mixture was allowed to gradually warm to room temperature while stirring overnight. The excess hydride was carefully destroyed by the successive addition of water and acetic acid. Evaporation of the solvent left an oil plus a white granular solid. Chromatography of the residue on silica using solvent B as eluent provided 5.44 g of **18** (97.4%) as a thick syrup, which solidified upon standing: mp 59–62 °C; TLC R_f = 0.17 (solvent B); $[\alpha]^{22}_D$ (c 0.50, abs EtOH) = +53.6° [lit.[69] for enantiomer -58.9° (c 1.009, EtOH)]; ^{1}H NMR ($CDCl_3$) δ 5.00 (br s, 1, OH, D_2O exchangeable), 4.38 (br m, 1, C_4H), 4.13 (br t, J = 7.3 Hz, 1, OH, D_2O exchangeable), 3.40–3.80 (m, 5, C_3H_2 + C_2H + CH_2OH), 2.00–2.13 (m, 2, C_3H_2), 1.47 [s, 9, OC$(CH_3)_3$]; IR (KBr) 3409 (br), 2977, 2934, 2885, 1671 (s), 1415 (s), 1368, 1165, 1127, 1051, 772; EIMS (135 °C, 30 eV) m/z 218 (M + 1, 0.25), 217 (M$^+$, 0.61), 186 (M - CH_2OH, 9.1), 144 (M - Ot-Bu, 8.4), 86 (62.1), 57 (C_4H_9, 100). Anal. ($C_{10}H_{19}NO_4$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*O*-[(4-methoxyphenyl)diphenylmethyl]-*trans*-4-hydroxy-D-prolinol (19).** To a solution of 5.01 g (23.1 mmol) of **18** in 60 mL of anhydrous CH_2Cl_2 and 25 mL of anhydrous THF was sequentially added 7.4 mL (53.1 mmol) of Et_3N, 0.28 g (2.29 mmol) of 4-(dimethylamino)pyridine (DMAP), and 9.58 g (31.0 mmol) of *p*-anisylchlorodiphenylmethane. The yellow solution was stirred at ambient temperature for 43 h. TLC indicated no starting material remained at that time. The reaction mixture was poured into 75 mL of ice-cold H_2O, and, after separation of layers, the aqueous solution was washed with CH_2Cl_2. The combined organic washes were in turn treated with saturated aqueous NaCl and H_2O and then dried over anhydrous $MgSO_4$. The syrup obtained from evaporation of the dried solution was chromatographed on silica with elution by solvent A (gradient, 3:7 → 1:1) to provide 9.91 g of **19** (87.7%) as a light yellow foam. Repetition of the experiment in THF alone starting from 7.40 g of **18** yielded 83.9% of **19**: mp 87–90 °C; TLC R_f = 0.29 [solvent A (1:1)]; $[\alpha]^{22}_D$ (c 0.54, abs EtOH) = +38.3°; ^{1}H NMR ($CDCl_3$) δ 7.17–7.41 (m, 12, CH phenyl), 6.81 (d, J = 9.5 Hz, 2, CH phenyl), 4.53 (br s, 1, OH), 4.11 (m, 1, C_4H), 3.78 (s, 3, OCH_3), 3.54 (br m, 3), 3.17 (br m, 1.5), 2.96 (br m, 0.5), 1.87–2.26 (m, 2, C_3H_2), 1.48 and 1.32 [each br s, total 9 (1:2 ratio), $(CH_3)_3$CO rotamers]; IR (KBr) 3425 (br), 3059, 2975, 2933, 1695 (s), 1671 (s), 1608, 1510 (s), 1407 (s), 1252 (s), 1179 (s), 1165 (s), 1034, 832, 766, 708, 700, 589; CIMS (225 °C, CH_4) m/z 490 [(M + H)$^+$, 0.1], 489 (M$^+$, 0.3), 488 [(M - H)$^+$, 0.6], 274 (22.6), 273 [(MMTr)$^+$, 100]. Anal. ($C_{30}H_{35}NO_5$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*O*-[(4-methoxyphenyl)diphenylmethyl]-*cis*-4-(6-chloro-9*H*-purin-9-yl)-D-prolinol (20).** Triphenylphosphine, 4.25 g (16.2 mmol), was dissolved in 75 mL of anhydrous THF, and then 1.78 g (11.5 mmol) of 6-chloropurine was suspended in the solution. DEAD, 3.74 g, (21.5 mmol), in 25 mL of anhydrous THF was added, and the majority of the solid dissolved giving a yellow solution. To this was added 4.51 g (9.22 mmol) of **19** in 35 mL of anhydrous THF, and the reaction mixture was allowed to stir at ambient temperature for 19 h. The dark

(69) Ojima, I.; Kogure, T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728.

brown solution was evaporated to dryness in vacuo and the residue chromatographed on silica with solvent A (gradient, 1:3 → 2:3). This gave 8.85 g of a pink foam. Although the bulk material could not be completely purified away from the diethylhydrazine dicarboxylate byproduct (R_f = 0.65, solvent B), selective cutting of chromatography fractions provided an analytical sample of **20** (0.373 g, 6.5%) as a white foam: mp 98–102 °C dec; TLC R_f = 0.61 (solvent B); $[\alpha]^{22}_D$ (*c* 0.49, abs EtOH) = +7.3°; ^{1}H NMR (DMSO-d_6) δ 8.72 (s, 1, C*H* purine), 8.70 (s, 1, C*H* purine), 7.16–7.42 (m, 12, C*H* phenyl), 6.86 (d, *J* = 9.0 Hz, 2, C*H* phenyl), 5.13 [m (approximate quintet), 1, C_4H], 4.03–4.22 [m (includes an apparent dd at δ 4.18), 2, C_2H + CH_aH_bOMMTr], 3.70–3.90 [m, 4 (includes resonance at δ 3.74), CH_aH_bOMMTr], 3.74 (s, OCH_3), 3.34 [m (partially obscured by H_2O), C_3H_a], 2.98 (br m, 1, C_3H_b), 2.75 (br m, 2, C_3H_2), 1.40 and 1.26 [each br s, total 9 (1:2 ratio), $(CH_3)_3CO$ rotamers]; IR (KBr) 3058, 2973, 2931, 1698 (s), 1590, 1559, 1509, 1401 (s), 1253 (s), 1162 (s), 1112, 1034, 938, 933, 833, 767, 702; CIMS (250 °C, CH_4) *m/z* 626 [(M + H)$^+$, 9.2], 624 [(M – H)$^+$, 16.9], 274 [(MMTr + H)$^+$, 30.8], 273 [(MMTr)$^+$, 100], 197 [(MMTr + H – C_6H_5)$^+$, 20.1], 167 [(MMTr + H – $CH_3OC_6H_4$)$^+$, 12.0], 57 (57.6), 626 [(M + H)$^-$, 7.4], 624 [(M – H)$^-$, 16.9], 352 [(M – MMTr)$^-$, 100], 152 (61.5), 118 (55.9). Anal. ($C_{35}H_{36}ClN_5O_4$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*cis*-4-(6-chloro-9*H*-purin-9-yl)-D-prolinol (21).** The impure **20**, 8.48 g (maximum 8.63 mmol), obtained above was treated with 200 mL of 80% acetic acid and stirred at ambient temperature overnight. The solvent was removed in vacuo, and a portion of absolute ethanol was evaporated from the syrupy residue. Chromatography on silica with solvent C (1:49) gave 2.10 g (68.8%, two steps) of **21**: mp 64–68 °C; TLC R_f = 0.19 (solvent B); $[\alpha]^{22}_D$ (*c* 0.85, abs EtOH) = +12.3°; ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1, C*H* purine), 8.77 (s, 1, C*H* purine), 5.10 [m (approximate quintet), 1, C_4H], 4.83 (t, *J* = 5.6 Hz, 1, O*H*, D_2O exchangeable), 4.17 [m (br t with D_2O exchange), 1], 3.91 (m, 1), 3.50–3.70 (m, 3), 2.68 (m, 1, C_3H_a), 2.51 (m, substantially obscured by DMSO-d_5, C_3H_b), 1.43 [s, 9, $OC(CH_3)_3$]; IR (KBr) 3409 (br), 2981, 2931, 2882, 1694 (s), 1593 (s), 1561, 1402 (s), 1367, 1338, 1163 (s), 1115, 959, 944, 637; UV λ_{max} 265 (1.8), 213 (1.6) nm in 0.1 N HCl–MeOH, 263 (1.9), 214 (1.6) nm in MeOH, 307 (0.1), 265 (0.6), 250 (sh, 0.5), 225 (sh, 0.5), 207 (1.3) nm in 0.1 N NaOH–MeOH; CIMS (170 °C, NH_3) *m/z* 356 [(M + H + 2)$^+$, ^{37}Cl isotope, 38.7], 354 [(M + H)$^+$, 100], 389 [(M + HCl)$^-$ and/or (M – H + Cl)$^-$, ^{37}Cl isotope, 2.2], 387 [(M – H + Cl)$^-$, 3.3], 354 [(M – H)$^-$, ^{37}Cl isotope, 45.2], 352 [(M – H)$^-$, 100], 154 [(P – H)$^-$, ^{37}Cl isotope, 1.2], 152 [(P – H)$^-$, 3.0]; CIMS (200 °C, CH_4) *m/z* 356 [(M + H + 2)$^+$, ^{37}Cl isotope, 32.4], 354 [(M + H)$^+$, 100], 57 (C_4H_9, 58.0), 388 [(M + Cl)$^-$, 11.4], 355 [(M + 2)$^-$, ^{37}Cl isotope, 36.0], 353 (M$^-$, 100); FABMS (thioglycerol) *m/z* 354 [(M + H)$^+$, 100], 155 (P$^+$, 73), 388 [(M + Cl)$^-$, 33], 153 [(P – 2 H)$^-$, 100]. Anal. ($C_{15}H_{20}ClN_5O_3$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*O*-[(4-methoxyphenyl)diphenylmethyl]-*cis*-4-(6-amino-9*H*-purin-9-yl)-D-prolinol (24).** Into a stainless steel bomb containing 1.91 g (3.05 mmol) of **20** in 10 mL of methanol was added excess anhydrous liquid ammonia. The bomb was sealed and then heated at 80–81 °C for 39.5 h. After cooling and evaporation of the ammonia, the residue was treated with methanol and the precipitated NH_4Cl removed by filtration. The syrup obtained from evaporation of the filtrate was chromatographed on silica with elution of the nonpolar impurities with solvent B followed by elution of the product with solvent C (1:19) gave 1.69 g (91.4%) of **24** as a white foam: mp 160–163 °C; TLC R_f = 0.29 [solvent C (1:19)]; $[\alpha]^{22}_D$ (*c* 0.49, MeOH) = +16.1°; ^{1}H MMR (DMSO-d_6) δ 8.14 (s, 1, C*H* purine), 8.11 (s, 1, C*H* purine), 7.18–7.42 [m, 14, C*H* phenyl and NH_2 (apparent s at δ 7.23, D_2O exchangeable)], 6.87 (d, *J* = 8.9 Hz, 2, C*H* phenyl), 4.95 [m (approximate quintet), 1, C_4H], 4.11 (dd, *J* = 7.7, 10.8 Hz, overlaps with next resonance), 4.05 [br m, 2 (includes preceding resonance)], 3.65–3.86 [br m, 4 (includes resonance at δ 3.73)], 3.73 (s, OCH_3), 3.28 (br m, overlapped by H_2O), 3.06 (br m, ~1), 2.72 (br m, 2, C_3H_2), 1.40 and 1.23 [each v br s, total 9 (1:2 ratio), $OC(CH_3)_3$ rotamers]; IR (KBr) 3500–2800 (br) with maxima at 3323, 3172, 2975 and 2933, 1698 (s), 1639 (s), 1598, 1510, 1411 (s), 1251 (s), 1162 (s), 1114, 1033, 701; CIMS (270 °C, CH_4) *m/z* 608 [(M + 2 H)$^+$, 1.4], 607 [(M + H)$^+$, 3.1], 507 [(M + 2 H – Boc)$^+$, 15.4], 274 [(MMTr + H)$^+$, 26.4], 273 [(MMTr)$^+$, 100], 197 [(MMTr + H – C_6H_5)$^+$, 9.1], 167 [(MMTr + H – $CH_3OC_6H_4$)$^+$, 4.5], 136 [(P + 2 H)$^+$, 29.7], 605 [(M – H)$^-$, 0.6], 505 [(M – Boc)$^-$, 1.2], 333 [(M – MMTr)$^-$, 2.3], 259 (41.6), 233 (54.7), 134 (P$^-$, 100). Anal. ($C_{35}H_{38}N_6O_4$) C, H, N.

***cis*-4-(6-Amino-9*H*-purin-9-yl)-D-prolinol (26).** Trifluoroacetic acid, 30 mL, was added to 0.850 g (1.40 mmol) of **24**, and the bright orange-red solution was stirred at room temperature for 1 h. The mixture was evaporated in vacuo, and the syrupy residue was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted with two additional quantities of $CHCl_3$; the colored material concentrated in the organic washings. The aqueous solution was evaporated to approximately 40 mL and applied to a 50-mL column of Dowex SBR (OH^-) resin. The column was washed with distilled H_2O until no further UV active material was observed in the eluent (~900 mL). Evaporation of that eluent gave 0.276 g (84.3%) of a chromatographically homogeneous white solid, which was recrystallized from ethanol–ethyl acetate (1:2) to produce 0.191 g of **26** as a lightly pink powder: mp 171–173 °C dec; TLC R_f = 0.37 [solvent D (1:4)]; $[\alpha]^{22}_D$ (*c* 0.56, H_2O) = +21.3°; ^{1}H NMR (DMSO-d_6) δ 8.26 (s, 1, C*H* purine), 8.12 (s, 1, C*H* purine), 7.15 (br s, 2, NH_2, D_2O exchangeable), 4.96 [m (approximate quintet), 1, C_4H], 4.65 (br s, 1, O*H*, D_2O exchangeable), 3.46 (m, 2, CH_2OH), 3.12–3.25 (m, 2, C_3H_a + C_2H), 3.05–3.10 (m, 1, C_3H_b), 2.87 (br s, 1, N*H*, D_2O exchangeable), 2.41 (m, 1, C_3H_a), 1.78 (m, 1, C_3H_b); IR (KBr) 3500–3000 (br) with maxima at 3423, 3332, and 3198, 2868, 1645 (s), 1604 (s), 1595 (s), 1575, 1482, 1416, 1330, 1311, 1257, 1070, 1059, 982, 798, 647; UV λ_{max} 258 (0.5), 206 (0.6) nm in 0.1 N HCl, 260 (0.4), 209 (0.5) nm in H_2O, 262 (0.3), 216 (1.6) nm in 0.1 N NaOH; EIMS (225 °C, 20 eV) *m/z* 235 (M + H, self CI, 2.4), 162 (12.0), 136 (P + 2 H, 100), 135 (P + H, 4.8), 99 (25.0), 68 (62.6). Anal. ($C_{10}H_{14}N_6O$) C, H, N.

(3*R*,5*R*)-1,9-Dihydro-9-[5-(hydroxymethyl)-3-pyrrolidinyl]-6*H*-purin-6-one (27). A suspension of 0.372 g (0.59 mmol) of **20** in 35 mL of 2 N HCl was heated to reflux for 17 h. The solid dissolved to give a yellow-brown shortly after initiation of the heating. Upon cooling, a yellow solid precipitated out. The aqueous solution was washed with four portions of $CHCl_3$, which dissolved the solid; a slight yellow color remained in the aqueous layer. The pH was adjusted to 8 by the dropwise addition of 12 N NaOH; the solution took on a pink tint. In a separate trial, 0.248 g (0.70 mmol) of **21** was treated with 30 mL of 1 N HCl and heated to reflux for 5 h. The solvent was removed in vacuo, and the residue was dissolved in ~2 mL of H_2O. The pH was adjusted to 8 by the dropwise addition of 12 N NaOH, and then this was combined with the solution obtained from **20** described above. The volume of the combined aqueous solution was descreased to approximately 25 mL, and then it was applied to a 20-mL column of Dowex 50X4-50 (H^+) resin. The column was washed with distilled H_2O until the eluent showed pH 5 (~150 mL). This was followed by elution with 2 N NH_4OH until no further UV active material was seen in the eluent (~200 mL). Evaporation of the basic eluent gave 0.261 g (1.11 mmol, 85.7%) of a generally white, chromatographically homogeneous, solid. This was recrystallized from ethanol–ethyl acetate to yield 0.115 g of **27** as a pinkish, fluffy powder: mp 205–210 °C dec; TLC R_f = 0.18 [solvent D (1:4)]; $[\alpha]^{22}_D$ (*c* 0.27, H_2O) = +15.1°; ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1, C*H* purine), 8.02 (s, 1, C*H* purine), 4.95 [m (approximate quintet with fine structure), 1, C_4H], 4.66 (br s, 1, O*H*, D_2O exchangeable), 3.46 (m, 2, CH_2OH), 3.15–3.24 (m, 2, C_3H_a + C_2H), 3.03–3.09 (m, 1, C_3H_b), 2.47 (m, 1, C_3H_a), 1.77 (m, 1, C_3H_b); IR (KBr) 3600–3000 (br) with maxima at 3431 (s), 3262, 3128 and 3051, 3000–2400 (br) with maxima at 2931 and 2868, 1735 (s), 1696 (s), 1586, 1547, 1415, 1340, 1221, 1132, 788; UV λ_{max} 249 (1.5), 203 (2.2) nm in 0.1 N HCl, 250 (1.4), 201 (2.4) nm in H_2O, 255 (2.8), 216 (1.7) nm in 0.1 N NaOH; EIMS (300 °C, 30 eV) *m/z* 236 (M + H, self CI, 1.4), 204 (M – CH_2OH, 2.6), 137 (P + 2 H, 65.4), 136 (P + H, 21.5), 99 (31.8), 68 (100); CIMS (270 °C, CH_4) *m/z* 237 [(M + 2 H)$^+$, 15.4], 236 [(M + H)$^+$, 100], 137 [(P + 2 H)$^+$, 59.5], 248 [(M + CH_3)$^-$, 1.3], 235 (M$^-$, 1.0), 233 [(M – 2 H)$^-$, 11.1], 134 [(P – H)$^-$, 46.9], 45 (100). Anal. ($C_{10}H_{13}N_5O_2 \cdot 0.25H_2O$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*O*-[(4-methoxyphenyl)diphenylmethyl]-*cis*-4-(2-amino-6-chloro-9*H*-purin-9-yl)-D-prolinol (22).** Triphenylphosphine, 3.06 g (11.7 mmol), was dissolved in 100 mL of anhydrous THF and then 1.27 g (7.49 mmol) of 2-amino-6-chloropurine was suspended in the solution. DEAD, 2.45 g (14.1 mmol), in 20 mL of anhydrous THF was then

added. Some of the solid dissolved and an orange-red color persisted in the solution. This mixture was allowed to stir for 10 min, 3.11 g (6.36 mmol) of **19** in 35 mL of anhydrous THF was added, and the reaction was allowed to stir at ambient temperature for 5.67 h. At this time, 0.70 g (2.67 mmol) of Ph_3P and 0.70 g (4.02 mmol) of DEAD additional were introduced into the mixture. This resulted in a homogeneous orange-brown solution. The reaction was allowed to proceed for 16 h more, the solvent was removed in vacuo, and the residue was chromatographed on silica with solvent A (gradient, 1:3 → 1:1) to yield 1.70 g (41.7%) of chromatographically pure **22** together with 3.0 g of an impure sample of **22** as a yellow foam. Although the bulk material could not be completely purified from the triphenylphosphine oxide byproduct (R_f = 0.24, solvent B), selective cutting of chromatography fractions in a separate trial provided an analytical sample of **22** as a white foam: mp 132–133 °C dec; TLC R_f = 0.55 (solvent B); $[\alpha]^{22}_D$ (*c* 1.7, abs EtOH) = +1.5°; ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1, C*H* purine), 7.16–7.39 and 6.83–6.90 [m (simplifies slightly upon D_2O exchange), 16, C*H* phenyl + NH_2], 4.83 [m (approximate quintet), 1, C_4H], 3.97–4.17 (m, 3), 3.73 (s, 3, OCH_3), 3.62 (m, 1), 2.98 (m, 1), 2.73 (m, 1), 1.12–1.52 [br with shoulder, 9, OC(CH_3)$_3$ rotamers]; IR (KBr) 3500–3300 (br) with maxima at 3480, 3395 and 3332, 3206, 2973, 2931, 1698 (s), 1611 (s), 1561 (s), 1509, 1464, 1406 (s), 1251, 1163, 1114, 1033, 909, 701. Anal. ($C_{35}H_{37}ClN_6O_4$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*cis*-4-(2-amino-6-chloro-9*H*-purin-9-yl)-D-prolinol (23).** The impure **22** obtained above, 3.00 g (maximum 3.71 mmol), was dissolved in 200 mL of 80% acetic acid and allowed to stir at ambient temperature for 19 h. The solvent was removed in vacuo, and the yellow syrupy residue was dried under vacuum (1 Torr). Chromatography on silica with solvent C (gradient, 1:49 → 1:19) gave 0.962 g (70.2%, 2 steps) of **23** as a lightly yellow foam: mp 113–115 °C partial dec; TLC R_f = 0.05 [solvent A (3:1)]; $[\alpha]^{22}_D$ (*c* 0.54, abs EtOH) = +25.2°; ^{1}H NMR (DMSO-d_6) δ 8.20 (s, 1, C*H* purine), 6.91 (br s, 2, NH_2, D_2O exchangeable), 4.83 [m (seen after D_2O exchange), 1, C_4H], 4.82 (t, *J* = 5.6 Hz, 1, CH_2OH, D_2O exchangeable), 4.09 (m, 1), 3.87 (m, 1), 3.66 [m (simplifies with D_2O exchange), 1], 3.42–3.53 [m (simplifies with D_2O exchange), 2], 2.59 (m, 1, C_3H_a), 2.41 (m, 1, C_3H_b), 1.43 [s, 9, OC(CH_3)$_3$]; IR (KBr) 3500–3000 (br) with maxima at 3332 and 3213, 2973, 2931, 2882, 1685, 1615 (s), 1562 (s), 1514, 1466, 1407 (s), 1368, 1162, 1117, 911, 785; UV λ_{max} 307 (0.6), 248 (0.5), 222 (1.6), 207 (sh, 1.1) nm in 0.1 N HCl–MeOH, 307 (0.9), 248 (0.7), 224 (1.7), 209 (sh, 1.4) nm in MeOH, 307 (0.7), 266 (0.8), 251 (0.9), 222 (1.7), 212 (sh, 1.5) nm in 0.1 N NaOH–MeOH; CIMS (230 °C, CH_4) *m/z* 371 [(M + H + 2)$^+$, ^{37}Cl isotope, 18.0], 369 [(M + H)$^+$, 52.2], 341 [(M − OH)$^+$, 13.9], 313 [(M + 2 H − t-Bu)$^+$, 32.3], 269 [(M + 2 H − Boc)$^+$, 27.0], 172 [(P + 2 H + 2)$^+$, ^{37}Cl isotope, 16.7], 170 [(P + 2 H)$^+$, 52.9], 57 [$(C_4H_9)^+$, 100], 370 [(M + 2)$^-$, ^{37}Cl isotope, 34.0], 368 (M$^-$, 100); FABMS (thioglycerol) *m/z* 369 [(M + H)$^+$], 170 [(P + 2 H)$^+$], 403 [(M + Cl)$^-$]. Anal. ($C_{15}H_{21}ClN_6O_3$) C, H, N.

(3*R*,5*R*)-2-Amino-1,9-dihydro-9-[5-(hydroxymethyl)-3-pyrrolidinyl]-6*H*-purin-6-one (29). A solution of 0.4281 g (1.16 mmol) of **23** in 60 mL of 2 N HCl was heated to reflux for 14 h. The yellow solution was evaporated to dryness, and then the residue was partitioned between H_2O and $CHCl_3$. The aqueous layer was washed with two additional portions of $CHCl_3$ and then evaporated to a volume of 5–10 mL. The pH was then adjusted to 8 by the dropwise addition of 12 N NaOH. A large amount of solid forms over the course of the next 0.25 h. The solution was reheated to dissolve the solid and gravity filtered to remove some impurities, and the total volume of the filtrate was adjusted to 5 mL. Cooling gave 0.141 g (48.4%) of a peach-colored powder, **29**: mp 316–318 °C dec; TLC R_f = 0.24 [solvent D (1:4)]; $[\alpha]^{22}_D$ (*c* 0.38, H_2O) = +18.9°; ^{1}H NMR (DMSO-d_6) δ 7.82 (s, 1, C*H* purine), 6.49 (br s, 2, NH_2, D_2O exchangeable), 4.83 [m (approximate quintet), 1, C_4H], 2.90–3.70 (v br, 1, CH_2OH and N*H*, D_2O exchangeable), 3.51 (d, *J* = 5.4 Hz, ~2, CH_2OH), 3.21–3.31 (m, ~2, C_3H_a + C_2H), 3.09–3.16 (m, ~1, C_3H_b), 2.41 (m, 1, C_3H_a), 1.74 (m, 1, C_3H_b); IR (KBr) 3600–2600 (br) with maxima at 3318, 3198, 2889, 2847 and 2727, 1727, 1691, 1632 (s), 1606, 1571, 1538, 1486, 1412, 1389, 1178, 1065, 1031, 778, 651; UV λ_{max} 276 (sh, 1.0), 254 (1.5), 203 (2.2) nm in 0.1 N HCl, 272 (sh, 0.6), 252 (0.9), 207 (0.9) nm in H_2O, 268 (1.2), 257 (sh, 1.1), 217 (1.8) nm in 0.1 N NaOH; FABMS (thioglycerol) *m/z* 251 [(M + H)$^+$], 249 [(M − H)$^-$]. Anal. ($C_{10}H_{14}N_6O_2 \cdot 1.75H_2O$) C, H, N.

(3*R*,5*R*)-2-Amino-1,9-dihydro-9-[5-(hydroxymethyl)-3-pyrrolidinyl]-6*H*-purin-6-one Dihydrochloride (29·2HCl). To 0.176 g of **29** was added 35 mL of 3 N HCl, and the solution was stirred at ambient temperature for 1.5 h. The solvent was removed in vacuo to leave a slightly brown solid, which was recrystallized from EtOH–H_2O to give 0.140 g of the hydrochloride salt as a white powder: mp 335–338 °C dec with effervescence; $[\alpha]^{22}_D$ (*c* 0.54, H_2O) = +25.0°; ^{1}H NMR (DMSO-d_6) δ 11.62 (s, 1, *H*NC=O, D_2O exchangeable), 10.20 (br s, 1, D_2O exchangeable), 9.00 (br s, overlaps with next resonance, D_2O exchangeable), 8.95 [s, 2 (with preceding resonance), C*H* purine], 7.43 (br s, 2, NH_2, D_2O exchangeable), 5.25 [br m (overlaps with resonance at δ 5.17), 1, C_4H], 5.17 (br s, H_2O + O*H*, D_2O exchangeable), 3.46 (m, 2, CH_2OH), 3.76 and 3.70 [each br s (m at δ 3.60–3.90 upon D_2O exchange), 5, CH_2OH + C_3H_2 + C_2H], 2.65 (m, 1, C_3H_a), 2.12 (m, 1, C_3H_b); IR (KBr) 3600–2300 (v br) with maxima at 3339, 3135, 2777 and 2692, 1720 (s), 1644 (s), 1607, 1597, 1526, 1358, 1159, 1075, 1043, 846, 766, 674; UV λ_{max} 276 (sh, 1.0), 254 (1.5), 203 (2.2) nm in 0.1 N HCl, 274 (sh, 1.1), 251 (1.6), 204 (sh, 2.2) nm in H_2O, 268 (2.0), 257 (sh, 1.9), 218 (2.7) nm in 0.1 N NaOH; FABMS (thioglycerol) *m/z* 359 [(M + H + HCl)$^+$], 251 [(M + H − 2HCl)$^+$], 321 [(M − H)$^-$], 285 [(M − H − HCl)$^-$], 249 [M − H − 2 HCl)$^-$]. Anal. ($C_{10}H_{14}N_6O_2 \cdot 2HCl \cdot H_2O$) C, H, N.

***N*-(*tert*-Butoxycarbonyl)-*O*-[(4-methoxyphenyl)diphenylmethyl]-*cis*-4-(2,6-diamino-9*H*-purin-9-yl)-D-prolinol (22).** Into a stainless steel bomb was introduced **22**, 1.70 g (2.65 mmol), in 5 mL of methanol, which was then treated with excess liquid anhydrous ammonia. The bomb was sealed and heated to 85–87 °C for 60 h. The yellow residue that remained after cooling and evaporation of the NH_3 was chromatographed on silica with solvent C (gradient, 1:49 → 1:19) as eluent to provide 1.61 g (97.3%) of **25** as a light yellow foam: mp 134–138 °C partial dec; TLC R_f = 0.10 [solvent C (1:19)]; $[\alpha]^{22}_D$ (*c* 0.54, abs EtOH) = +15.1°; ^{1}H NMR (DMSO-d_6) δ 8.31 (s, 1, C*H* purine), 7.19–7.73 and 6.85–6.90 (m, total 14, C*H* phenyl), 6.69 (br s, 2, NH_2, D_2O exchangeable), 5.66 (br s, 2, NH_2, D_2O exchangeable), 4.76 [m (approximate quintet), 1, C_4H], 4.04 (m, 2), 3.73 (s, 3, OCH_3), 3.55 (m, 1), 3.30 (m, obscured by H_2O, seen with D_2O exchange), 3.06 (m, 1), 2.40–2.75 (m, overlapped by DMSO-d_5, C_3H_2), 1.05–1.55 [br with a shoulder at δ 1.37 and major peak at δ 1.23,9, OC(CH_3)$_3$ rotamers]; IR (KBr) 3500–2800 (br) with maxima at 3473, 3388, 3332, 3184, 2973 and 2931, 1698, 1601 (s), 1509, 1473, 1448, 1408 (s), 1251, 1163, 1114, 1079, 1033, 701; FABMS (thioglycerol) *m/z* 622 [(M + H)$^+$], 273 [(MMTr)$^+$], 151 [(P + 2 H)$^+$], 656 [(M + Cl)$^-$], 620 [(M − H)$^-$]. Anal. ($C_{35}H_{39}N_7O_4$) C, H, N.

***cis*-4-(2,6-Diamino-9*H*-purin-9-yl)-D-prolinol (28).** Trifluoroacetic acid, 35 mL, was added to 1.39 g (2.24 mmol) of **25** to give a bright orange-red solution, which was stirred at room temperature for 1.25 h. Evaporation of the excess acid in vacuo left a red-brown syrup, which was partitioned between H_2O and $CHCl_3$ and transferred to a separatory funnel. The aqueous layer was washed with three additional portions of $CHCl_3$, and then the volume was decreased to approximately 60 mL. The pH was adjusted to 9 by the addition of Dowex SBR(OH^-) resin. The resin was removed and washed well with H_2O; the filtrate and washings were evaporated in vacuo and absolute EtOH evaporated from the residue to give 0.328 g (58.8%) of a chromatographically homogeneous white solid. This was recrystallized from ethanol–ethyl acetate to yield 0.194 g of **28** as a white powder: mp 192–195 °C; TLC R_f = 0.27 [solvent D (1:4)]; $[\alpha]^{22}_D$ (*c* 0.50, abs EtOH) = +23.6°; ^{1}H NMR (DMSO-d_6) δ 7.83 (s, 1, C*H* purine), 6.60 (br s, 2, NH_2, D_2O exchangeable), 5.70 (br s, 2, NH_2, D_2O exchangeable), 4.76 [m (approximate quintet), 1, C_4H], 4.62 (br s, 1, CH_2OH, D_2O exchangeable), 3.44 (m, 2, CH_2OH), 3.08–3.19 (m, 2, C_5H_a), 2.95–3.01 (m, 1, C_3H_b), 2.83 (br s, 1, N*H*, D_2O exchangeable), 2.33 (m, 1, C_3H_a), 1.69 (m, 1, C_3H_b); IR (KBr) 3600–2800 (br) with maxima at 3487, 3306, 3122, 2986, 2938 and 2849, 1676, 1623 (s), 1591 (s), 1479, 1471, 1465, 1455, 1444, 1406, 1347, 1287, 1276, 1239, 1058, 792, 701, 645; UV λ_{max} 291 (0.7), 252 (0.7), 213 (1.2) nm in 0.1 N HCl, 280 (1.5), 255 (1.2), 215 (3.5) nm in H_2O, 280 (0.9), 256 (0.8), 220 (1.7), 209 (slsh, 1.5) nm in 0.1 N NaOH; EIMS (260 °C, 30 eV) *m/z* 250 (M + H, self CI, 0.4), 249 (M$^+$, 0.7), 151 (P + 2 H, 100), 150 (P + H, 10.8), 134 (P + 2 H − NH_3, 10.3), 68 (34.1); CIMS (210 °C, NH_3) *m/z* 251 [(M + 2 H)$^+$, 13.3], 250 [(M + H)$^+$, 97.1], 232 [(M − OH)$^+$, 20.5], 218 [(M

– $CH_2OH)^+$, 3.3], 151 [$(P + 2\ H)^+$, 100], 248 [$(M - H)^-$, 54.1], 230 [$(M - H - H_2O)^-$, 2.5], 149 (P^-, 100). Anal. ($C_{10}H_{15}N_7O$) C, H, N.

Before crystallization, the ^1H NMR showed small (~5%) resonances at δ 7.81, 6.68, and 5.77. These were not present in the recrystallized material.

(3*S*,5*S*)-2-Amino-1,9-dihydro-9-[5-(hydroxymethyl)-3-pyrrolidinyl]-6*H*-purin-6-one (36). A solution of 0.276 g (0.75 mmol) of **35** in 20 mL of 1 N HCl was heated to reflux for 3.5 h. Separately, 0.22 g (0.60 mmol) of **35** was dissolved in 25 mL of 2 N HCl and heated to reflux for 4 h. A small amount of solid came out of the first reaction mixture upon cooling. Each of the aqueous solutions was extracted with chloroform, and then the volumes were adjusted to about 5 mL by evaporation in vacuo. The pH's were adjusted to 7–9 by the dropwise addition of 12 N NaOH. No precipitate could be induced to form from either of the neutralized solutions, so each was evaporated in vacuo to a generally white solid. These solids were combined, dissolved in hot water, and treated with a small amount of decolorizing charcoal, and the filtrate obtained after removal of the charcoal was evaporated to approximately 3 mL. A pink solid, 0.0716 g (0.29 mmol, 21.3%), formed upon refrigeration and was identified as **36**: mp 311–313 °C dec; TLC R_f = 0.32 [solvent D (1:3)]; $[\alpha]^{22}_D$ (*c* 0.25, H_2O) = –18.8°; ^1H NMR (DMSO-d_6) δ 7.81 (s, 1, C*H* purine), 6.46 (br s, 2, NH_2, D_2O exchangeable), 4.82 [m (approximate quintet), 1, C_4H], 2.85–3.65 (very br, 1, CH_2OH and N*H*, D_2O exchangeable), 3.51 (d, *J* = 5.4 Hz, ~2, CH_2OH), 3.21–3.32 (m, ~2, $C_3H_a + C_2H$), 3.09–3.14 (m, ~1, C_3H_b), 2.41 (m, 1, C_3H_a), 1.73 (m, 1, C_3H_b); IR (KBr) 3600–3000 (br) with maxima at 3402, 3325 (s), and 3191, 2889, 2734, 1727, 1692 (s), 1632 (s), 1607, 1538, 1484, 1411, 1388, 1180, 1064, 778, 674, 581; UV λ_{max} 276 (sh, 1.5), 254 (2.1), 204 (2.8) nm in 0.1 N HCl, 272 (sh, 1.0), 251 (1.3), 207 (1.2) nm in H_2O, 268 (1.1), 256 (sh, 1.0), 217 (1.7) nm in 0.1 N NaOH; FABMS (thioglycerol) *m/z* 251 [$(M + H)^+$], 249 [$(M - H)^-$], high-resolution FABMS calcd 251.1256, found 251.1250. Anal. ($C_{10}H_{14}N_6O_2 \cdot 1.75H_2O$) C, H, N.

***cis*-4-(6-(Dimethylamino)-9*H*-purin-9-yl)-D-prolinol (37).** A solution of 0.894 g (2.53 mmol) of **21** in 50 mL of 40% aqueous dimethylamine was heated to reflux for 4 h. The solvent was removed in vacuo, and absolute EtOH was evaporated from the residue. The crude protected 6-(dimethylamino)purine [R_f = 0.18, solvent B (developed twice)] was then treated with 45 mL of trifluoroacetic acid, and the resulting brown solution was stirred at room temperature for 1 h. Evaporation of the acid left a syrup, which was dissolved in 75 mL of H_2O, and the pH was adjusted to 10 by the addition of Dowex SBR(OH^-) resin. Removal and washing of the resin followed by evaporation of the filtrate and washings gave 0.562 g (84.9%) of **37** as a chromatographically homogeneous light brown glass. This was recrystallized from EtOH–EtOAc to give 0.182 g of **37** as tan crystals: mp 123–125 °C; TLC R_f = 0.49 [solvent D (1:4)]; $[\alpha]^{22}_D$ (*c* 0.27, H_2O) = +18.5°; ^1H NMR (DMSO-d_6) δ 8.27 (s, 1, C*H* purine), 8.19 (s, 1, C*H* purine), 4.99 [m (approximate quintet), 1, C_4H], 4.67 (br s, 1, CH_2OH, D_2O exchangeable), 3.45 [br s with fine structure, m with D_2O exchange, 8, $N(CH_3)_2 + CH_2OH$], 3.00–3.23 (m, 3, $C_3H_2 + C_2H$), 2.41 (m, 1, C_3H_a), 1.76 (m, C_3H_b); IR (KBr) 3600–2400 (br) with maxima at 3423, 3262, 3107, 2933, 2917 and 2879, 1601 (vs), 1567, 1559, 1427, 1402, 1339, 1299, 1238, 1038, 791, 652; UV λ_{max} 268 (1.4), 210 (1.3), 201 (sh, 1.1) nm in 0.1 N HCl, 276 (1.7), 214 (1.5) nm in H_2O, 276 (3.1), 218 (2.3) nm in 0.1 N NaOH; EIMS (180 °C, 30 eV) *m/z* 263 (M + H, self CI, 0.4), 244 (M – H_2O, 0.2), 190 (6.1), 165 (9.6), 164 (P + 2 H, 100), 148 (5.6), 134 (8.8), 120 (3.3), 99 (3.1), 68 (30.7). Anal. ($C_{12}H_{16}N_6O$) C, H, N.

***N*-(*N*-(Benzyloxycarbonyl)-*O*-methyl-L-tyrosinyl)-*cis*-4-(6-(dimethylamino)-9*H*-purin-9-yl)-D-prolinol (38).** The procedure of Vince and Daluge[28,61a] for the carbocyclic analogue of puromycin was followed. *N*-(Benzyloxycarbonyl)-*p*-methoxy-L-phenylalanine,[70] 0.415 g (1.26 mmol), **37**, 0.297 g (1.13 mmol), and *N*-hydroxysuccinimide, 0.174 g (1.51 mmol), were dissolved in 25 mL of anhydrous DMF and cooled to 0 °C. To this was added 0.261 g (1.26 mmol) dicyclohexylcarbodiimide, and the solution was stirred at 0 °C for 0.5 h and then at room temperature for 25 h. The solid that precipitated out over this time was filtered off, and the filtrate was evaporated in vacuo (1.5 Torr) to leave a brown semisolid residue. This was treated with 15 mL of EtOAc, and a white solid formed. The solid was refrigerated, and then this solid was removed and washed well with EtOAc. The combined EtOAc portions were washed successively with H_2O, 50% saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and H_2O, then dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 0.594 g (~91%) of slightly impure **38** as a yellowish foam: TLC R_f = 0.89 [solvent C (1:6, developed twice)]; ^1H NMR (DMSO-d_6) δ 13.63 (br s, 1, N*H*), 8.23 (s, 1, C*H* purine), 8.16 (s, 1, C*H* purine), 7.10–7.40 and 6.77–6.87 (m, total 9, C*H* phenyl), 4.67–5.05, 4.67–4.55 and 4.35–4.52 (m, total 6), 3.25–4.10 [m (overlapped by H_2O), contains δ 3.72 (s, OCH_3) and δ 3.46 [br s, $N(CH_3)_2$], 2.65–3.00 (m, 2), 2.30–2.57 (m, partially obscured by DMSO-d_5); IR (KBr) 3448 (br), 3316 (br), 3088, 3031, 2931, 1715, 1693, 1637, 1598 (vs), 1513, 1452, 1425, 1301, 1247, 1039, 822, 792, 698, 648.

***N*-(*O*-Methyl-L-tyrosinyl)-*cis*-4-(6-(dimethylamino)-9*H*-purin-9-yl)-D-prolinol (39).** A solution of 0.138 g (0.240 mmol) of impure **38** in 8 mL of glacial acetic acid was combined with 88.7 mg of 10% palladium on carbon and then shaken under 1 atm of H_2 on a Parr apparatus for 1 h. The mixture was filtered through a Celite pad to remove the catalyst, and the catalyst was washed with additional acetic acid. Evaporation of the filtrate and washings in vacuo left a yellow syrup. This was dissolved in MeOH and applied to a 17-mL column of Dowex SBR(OH^-) resin, which was eluted with methanol until no further UV active material was observed in the eluent (~150 mL). Removal of solvent left **39** as a chromatographically homogeneous foam, 0.0730 g (69.5%, 2 steps): mp 75–98 °C; TLC R_f = 0.25 [solvent C (1:6, developed twice)]; ^1H NMR (DMSO-d_6) δ 8.23 (s, 1, C*H* purine), 8.14 (s, 1, C*H* purine), 7.16 and 6.85 (each d, *J* = 8.5 Hz, each 2, C*H* phenyl), 4.88 (br s, 1, O*H*, D_2O exchangeable), 4.49 (m, 1, C_4H), 4.05 [m, 1, C(=O)C*H*NH_2], 3.60–3.90 [m, contains δ 3.73 (s, OCH_3), 5], 3.45 [br s, 6, $N(CH_3)_2$], 2.30–2.80 (m, overlaps DMSO-d_5); IR (KBr) 3600–2700 (br) with maxima at 3374, 3297 (sh), 3106, 3034, 2935 and 2836, 1637, 1597 (s), 1563, 1513, 1482, 1462 (sh), 1447, 1424, 1377, 1337, 1301, 1247, 1179. 1036, 820, 792, 648. Anal. ($C_{22}H_{29}N_7O_3 \cdot H_2O$) C, H; N: calcd 21.43, found 19.78.

Kinetic Assay for the Action of Adenosine Deaminase on 26. The measurements of the rates of the enzymatic reactions were performed at 25 °C in 0.05 M phosphate buffer at pH 7.4. The substrate, or substrate and inhibitor mixture, was dissolved in buffer (1 mL), and the reaction was initiated by the addition of 10 μL enzyme (20 milliunits). Initial reaction rates were measured by decrease in absorption at 265 nm using a Beckman Model 25 recording spectrometer. The kinetic parameters were determined from double reciprocal plots using a Wilkinson analysis.[71]

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Registry No. **7**, 2584-71-6; **8**, 135042-12-5; **9**, 114676-69-6; *cis*-**10**, 135042-09-0; *trans*-**10**, 135042-13-6; **11**, 135042-14-7; **12**, 135042-15-8; *cis*-**13**, 135042-10-3; *trans*-**13**, 135042-16-9; **14**, 135042-17-0; **15**, 135042-18-1; **16**, 135042-19-2; **17**, 135042-20-5; **18**, 77450-03-4; **19**, 135042-21-6; **20**, 135042-22-7; **21**, 135042-23-8; **22**, 135042-24-9; **23**, 135042-25-0; **24**, 135042-26-1; **25**, 135042-27-2; **26**, 135042-28-3; **27**, 135042-29-4; **28**, 135042-30-7; **29**, 135042-31-8; **29**·2HCl, 135042-11-4; **30**, 51-35-4; **31**, 74844-91-0; **32**, 61478-26-0; **33**, 125653-58-9; **34**, 135042-32-9; **35**, 135042-33-0; **36**, 57653-47-1; **37**, 135042-34-1; **38**, 135042-35-2; **39**, 135042-36-3; Cbz-*P*-OMe-L-Phe, 17554-34-6; 2-amino-6-chloropurine, 10310-21-1; 6-chloropurine, 87-42-3; *p*-anisylchlorodiphenylmethane, 14470-28-1.

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