Synthesis of Novel Carbocyclic Adenosine Analogues as Inhibitors of Adenosine Kinase

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Several new 4′-amino substituted carbocyclic adenosine analogues (**6**, **7**, **31**) were prepared as potential inhibitors of the enzyme adenosine kinase. Three different heterocyclic base moieties (adenine, 8-azaadenine, and pyrazolo[3,4-*d*]pyrimidine) were incorporated into carbocyclic nucleoside analogues through the use of two different synthetic strategies. In both strategies, bicyclic isoxazolidine **9** (prepared through a hetero Diels−Alder reaction with cyclopentadiene) was used as the starting material. In one route, the N−O bond was reductively cleaved, and the hydroxyl group (after inversion and ring functionalization) was used as a leaving group to incorporate the heterocyclic base moiety as the key bond-forming step. A second, more efficient and higher yielding synthetic route was developed as a general solution to the synthesis of the target 4′-amino substituted carbocyclic adenosine analogues. In this methodology, the allylic C−O bond in the bicyclic isoxazolidine **9** was cleaved with double stereoinversion under palladium(0) catalysis as the key bond-forming step to stereospecifically incorporate the heterocyclic base moiety into the cyclopentane ring. The regioselectivity of key bond-forming steps was established principally by NMR methods, especially through ^{13}C NMR shifts and by NOE effects seen in the analogues, as well as by HMBC/HMQC experiments.

Introduction

Carbocyclic nucleosides[1−3] in which the ribofuranose ring oxygen is replaced with a methylene moiety are resistant to acid-catalyzed (e.g., stomach acid) and enzyme-catalyzed (e.g., nucleosidase) hydrolysis. Additionally, the replacement of the ribofuranose ring by a 2′,3′-dihydroxycyclopentane moiety ensures stability toward hydrolysis of 4′-truncated compounds, in which the 4′-methylene moiety seen in ribonucleoside analogues is removed. Truncation of the 4′-methylene carbon may beneficially affect the pharmacological properties of the resultant analogues, possibly increasing binding to target macromolecules and decreasing interactions with other biological macromolecules, thereby leading to increased activity and fewer side effects.

Several carbocyclic nucleosides, such as the antibiotics aristeromycin[1] (**1**) and neplanocin A[2] (**2**) (an inhibitor of *S*-adenosyl-L-homocysteine hydrolase), are natural products. Several carbocyclic nucleosides with interesting pharmacological profiles have been described,[3] including noraristeromycin (**3a**), described by Patil et al., and (**3b**−**d**), described by Wolfe et al. (Figure 1).

To date there have been a number of synthetic approaches to carbocyclic nucleoside and adenosine analogues[3,4] (Scheme 1). Three types of approaches to the key cyclopentane−base bond construction have been described: (i) hydroxyl displacement through use of the Mitsunobu reaction or a nucleophilic displacement of an appropriately substituted hydroxycyclopentane by a purine analogue with net inversion of the hydroxyl stere-

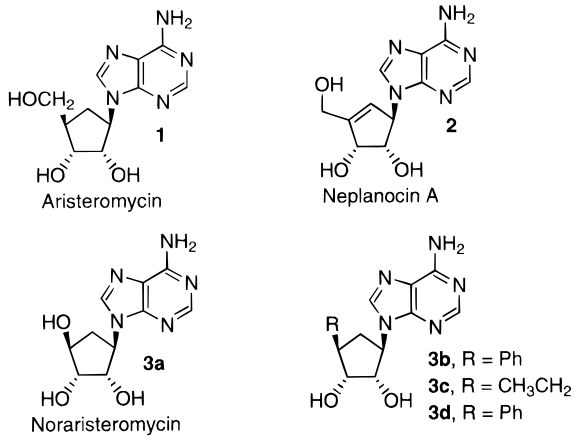

Figure 1.

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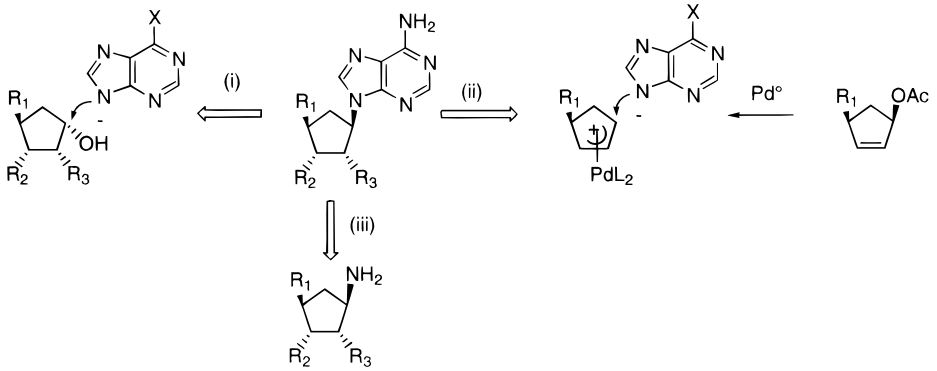
Scheme 1

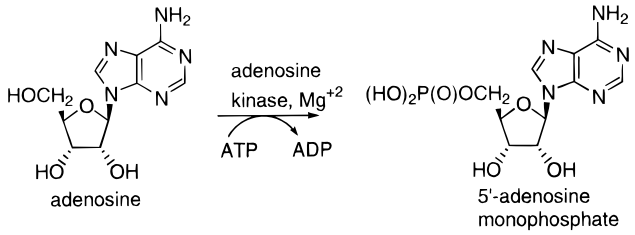


ochemistry,[5] (ii) use of a Pd^0-catalyzed double displacement of an allylic cyclopentenyl acetate or phosphate with net retention of configuration,[6] and (iii) elaboration of an aminocyclopentane into a product wherein the cyclopentane−amine bond was previously synthesized[7] by method (i) or (ii), followed by subsequent construction of the heterocyclic base moiety.

The value of adenosinergic approaches to a variety of therapeutic disease states has been described.[8] Toward this end, one of our goals has been the preparation of compounds that inhibit the enzyme adenosine kinase (AK).[9,10] It has been proposed that such compounds might represent a novel therapeutic approach to the treatment of neurodegenerative disorders such as epilepsy, stroke, and head injury, as well as cardiac ischemia.[11]

Adenosine and adenosine agonists have been demonstrated to exert beneficial effects, including antiinflammatory and neuroprotective actions in a variety of tissues. These effects are mediated by specific adenosine receptors, stimulation of which can decrease excitatory amino acid release, increase membrane polarization, reduce Ca^{2+} influx, and inhibit neutrophil degranulation and superoxide production. However, the utility of adenosine agonists as therapeutic agents is compromised by cardiovascular and renal side effects. Because 5′-phosphorylation of adenosine by AK is the major pathway of brain adenosine metabolism (Scheme 2), it is proposed that inhibition of AK would prolong the elevation of adenosine released from compromised tissues and protect tissues, with fewer of the undesired systemic effects seen with adenosine agonists.

Scheme 2



There have been several reports of natural and synthetic nucleoside analogues capable of inhibiting AK.[12] It has been found that replacement of the 5′-hydroxyl group of adenosine (**4**) with a 5′-amino group (compound **5**) leads to a 30-fold increase in potency (Figure 2). We sought to incorporate the potency-enhancing amino group found in 5′-aminoadenosine into 4′-truncated carbocyclic nucleoside analogues **6**−**8** with the goals of increasing potency and selectivity. The resulting analogues (**6**−**8**, Figure 2) should also be immune to the acid- or enzyme-catalyzed glycoside hydrolysis possible in the natural ribonucleoside analogues.

Results and Discussion

Compound **6** was prepared by either of two routes, with both routes utilizing the bicyclic isoxazolidine **9** as a common starting material (Scheme 3). The hetero Diels−Alder reaction of cyclopentadiene and the nitrosocarbam-

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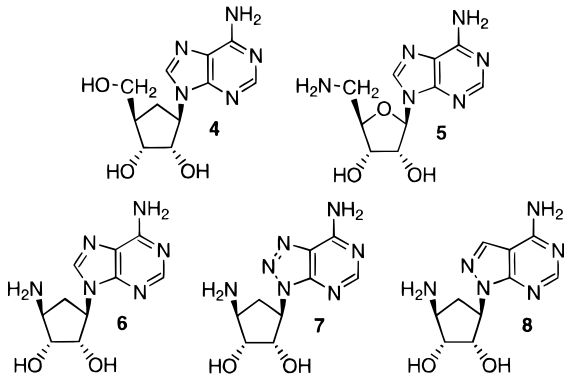

Figure 2.

ate,[13] prepared by in situ oxidation of *t*Boc hydroxycarbamate with $(^nBu)_4N^+IO_4^-$ proceeded to afford **9** in quantitative yield. Racemic **9** was used for the preparation of the target analogues described in this work. However, optically enriched analogues have been described,[14] and their use would allow the present targets to be prepared in enantiomerically pure form. The stereospecific cis-hydroxylation of **9** was effected using OsO_4 to give **10**. In our hands, the cis-hydroxylation was completely stereoselective, producing the exo-cis-diol as determined by NMR techniques. This is presumably a result of the steric influence of the large BocNO moiety directing the osmium tetroxide to attack on the opposite side of the cyclopentene ring. This effect has been observed by other groups[15] when OsO_4 was used to cis-hydroxylate protected bicyclic isoxazolidines of related structure. Protection of the diol **10** was accomplished by stirring with a catalytic amount of PTSA in acetone/2,2-dimethoxypropane as solvent to give **11** in 83% yield. The nitrogen−oxygen bond in **11** was found to be conveniently cleaved by dissolving metal reduction with sodium in liquid ammonia in 46% yield.

We next sought to use a Mitsunobu reaction to introduce the key heterocycle−cyclopentane bond in an intermediate leading the target compound **6**. This type of approach has been used by other researchers in other carbocyclic systems.[5d,e] For this purpose, if the target **6** was to be prepared with the correct stereochemistry, it would be necessary to invert the hydroxyl stereochemistry in **12**. This was accomplished by oxidation of **12** to the ketone **13** under Swern conditions (90%) or alternately by PCC oxidation (75%), followed by stereoselective reduction with L-selectride. The reduction was seen to be completely stereoselective, possibly as a result of the controlling influence of the isopropylidene moiety, so that the hydride is delivered solely from the less hindered *β*-face of the heterobicyclo[3.3.0] ketone to give the α-alcohol **14**. We also found that inversion of the hydroxyl group of **12** could be accomplished by using 4-nitrobenzoic acid[16] in a Mitsunobu reaction, which when followed by basic hydrolysis of the resulting ester gave **14**. This sequence was also found to be a viable alternative for hydroxyl inversion, albeit with lower overall isolated yield.

The Mitsunobu reaction of **14** with 6-chloropurine gave the desired **15**, in low (8%) overall yield, which was considerably less efficient than related Mitsunobu reactions involving heterocycles with cyclopentanols.[5d,e] The reaction produced a large number of byproducts, as observed by TLC, with none prominent. Chromatographic separation of **15** from these byproducts was incomplete, so the product was carried forward without complete purification. The chloropurine **15** was converted to **16** by ammonia at 85 °C in aqueous dioxane in 51% purified yield. The isopropylidene and *tert*-butoxycarbonyl protecting groups in **16** could both be removed in the same reaction vessel by treatment of **16** with 6 M aqueous HCl to give the target 4′-amino truncated carbocycle **6**.

In seeking a more efficient route for the preparation of **6**, we sought to avoid the Mitsunobu reaction for the key heterocycle−cyclopentane bond formation wherein **14** was converted to **15** in unsatisfactory yield and purity. To this end we were pleasantly surprised to find that when the heterobicycle **9** was treated with the lithium salt of 6-chloropurine in the presence of Pd^0 as a catalyst, **18** was produced in 40% yield in one step (Scheme 4). The reaction almost certainly occurs through the intermediacy of a *π*-allyl palladium complex like **17**, produced by backside attack of the allylic ether bond in **9** by zerovalent palladium species. This *π*-allyl palladium species is in turn subject to another backside attack on the carbon−palladium bond by the heterocyclic anion of the 6-chloropurine, with expulsion of PdL_2. The overall reaction therefore proceeds with net retention.[6] The relative stereochemistry was confirmed by 2D-NMR NOE experiments on subsequent intermediates (**20** and **20a**), where it was confirmed that the heterocycle and NBoc groups possessed a syn configuration, with exclusive alkylation at N(9) (vida infra). Additional proof of the syn relative stereochemistry of **18** was obtained from the single-crystal X-ray structure of the OTBS derivative of **18** (recrystallized from hexane). The surprising propensity of the allylic ether moiety to undergo Pd^0-catalyzed backside attack is probably facilitated by the acidity of the hydroxamic acid[17,18] (pK_a of 10), thus rendering this moiety a good leaving group. Thus it is seen that the reaction actually falls within a pK_a range observed for leaving groups in Pd^0-induced allylic substitution reactions.

In the reaction of **9** to yield **18**, use of only 1 equiv of 6-chloropurine anion afforded an isolated yield of only 22% of **18** and 14% of **19**. The latter oligomeric product probably arises because the hydroxamic acid anion of **18** is an excellent nucleophile and competes with the 6-chloropurine anion to react with the intermediate *π*-allyl Pd cationic species. This hypothesis is supported by the observation that use of 2 equiv of 6-chloropurine anion in the reaction eliminates formation of **19** and increases the yield of **18** to 40%.

The olefin **18** could be cis-hydroxylated to **20** with catalytic OsO_4 and trimethylamine *N*-oxide in 14% yield, but a higher yielding sequence involved prior conversion of **18** to its TBS ether with TBSCl/imidazole (94%),

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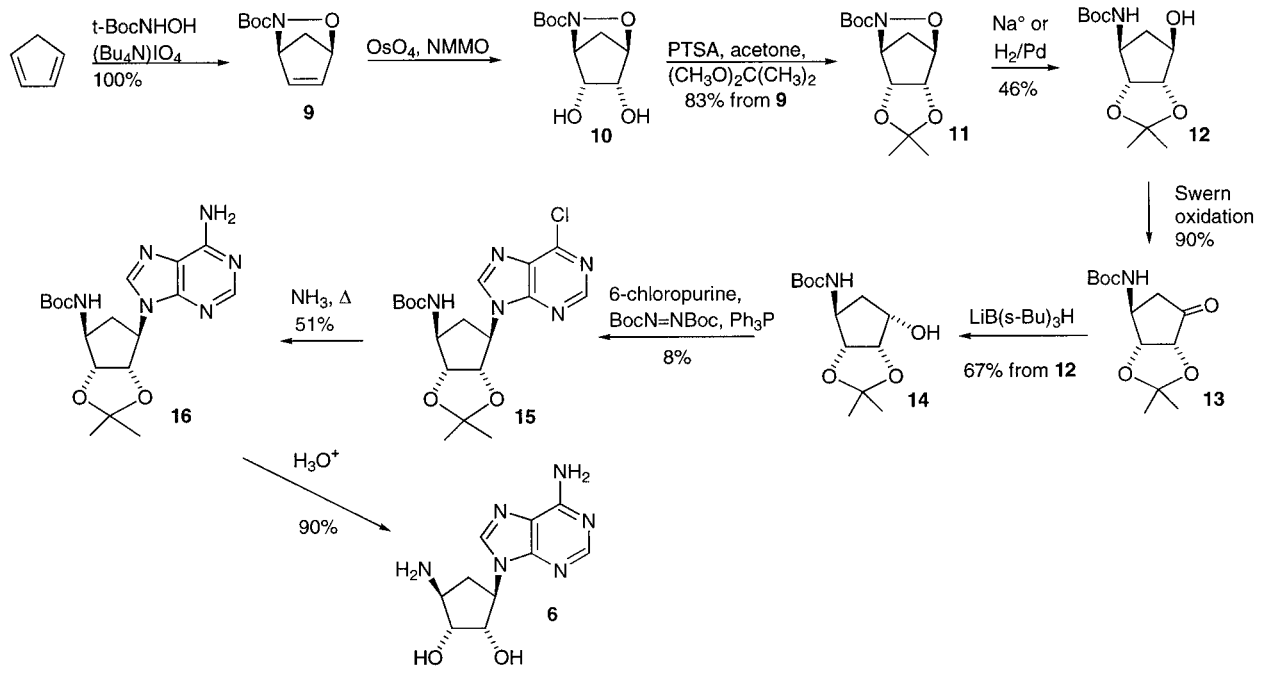
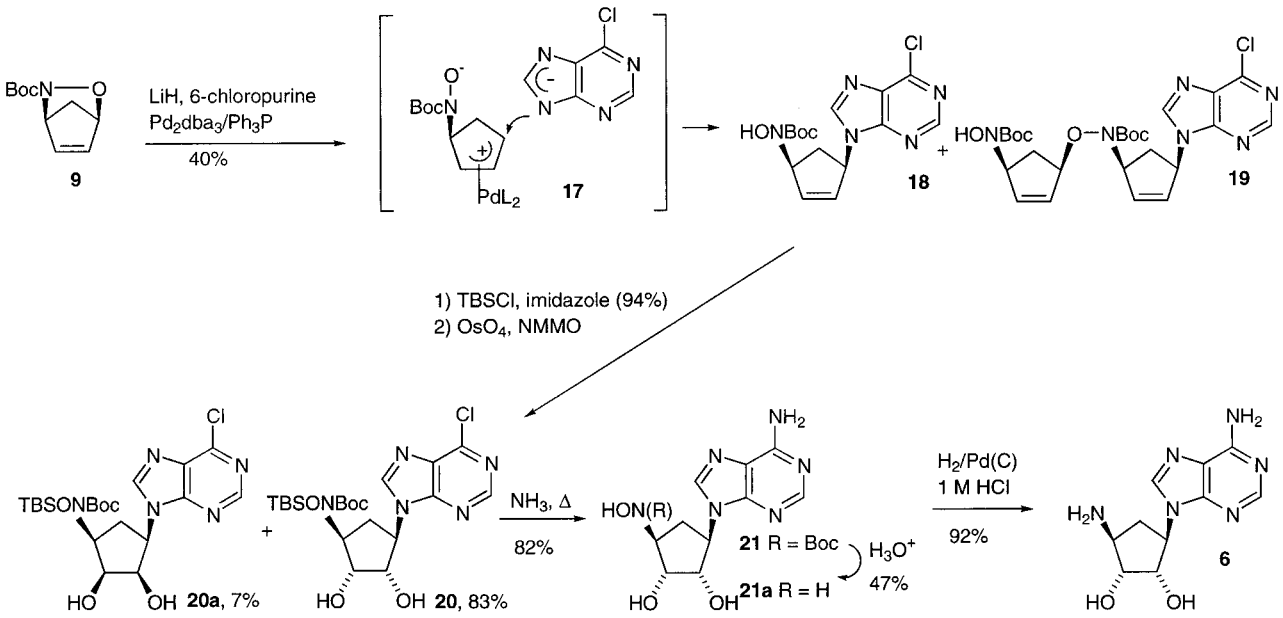
Scheme 3. Synthetic Routes to Truncated Substituted Carbocyclic Nucleosides



Scheme 4. Synthetic Routes to Truncated 4′-NH_2 Substituted Carbocyclic Nucleosides



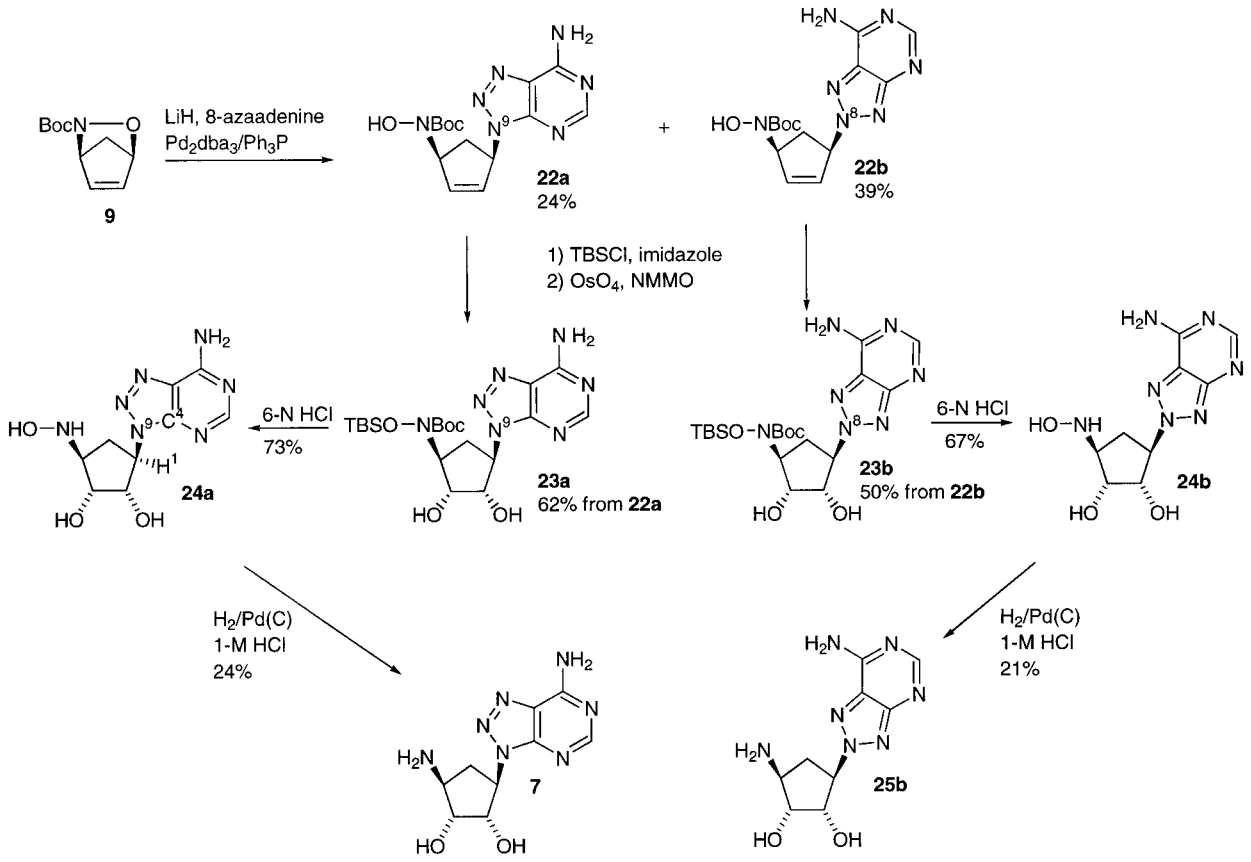
followed by treatment with catalytic OsO_4 and trimethylamine *N*-oxide to give **20** in 83% yield. In this case, the diastereomeric all-cis diol **20a** was produced in 7% yield and was readily separated from **20** by flash chromatography. The relative stereochemistry of all four cyclopentane substituents in both **20** and **20a** was confirmed by 2D-NMR (NOE and COSY) experiments.

When **20** was heated with saturated ammonia in methanol at 95 °C, the chlorine atom was replaced by an amino group, and the TBS group was adventitiously removed to provide **21** in 82% yield, along with 11% of TBS-protected **21**. Compound **21** was subjected to hydrogenolysis under 1 atm of hydrogen in 1 M HCl to give **6** in 92% yield, which was found to be identical (NMR, HPLC) to the product **6** prepared in Scheme 2. It was also found that treatment of **21** with 6 M aqueous HCl gave the hydroxylamine **21a** in 50% yield and that **21a** could be subsequently hydrogenated to **6** in 94% yield. Overall, it was found that the five-step synthetic route shown in Scheme 3 was the more efficient route, providing **6** in an overall yield of 13%, whereas the overall yield of **6** from the eight-step route shown in Scheme 2 was only 0.7%.

It was next sought to apply the palladium coupling methodology used for the synthesis of **6** in Scheme 3 to the synthesis of truncated carbocyclic nucleoside analogues such as **7** and **8** containing 8-azaadenine and pyrazolo[3,4-*d*]pyrimidine as heterocyclic base moieties.

When **9** was subjected to the Pd^0 catalyzed reaction with the lithium salt of 8-azaadenine, a mixture of N(9)- and N(8)-alkylated products **22a** and **22b**, which were formed in 24% and 39% yield, respectively (Scheme 5). 2D-NMR ROESY experiments indicated an NOE between H(1′) and H(4′) of the cyclopentane moiety, thereby

Scheme 5



confirming that in **22a** and **22b** the substituents possessed the syn-[1,4] stereochemistry. Alkylation of 8-azaadenine and analogues has previously been reported to produce mixtures of N(9) and N(8) alkylation products, with little or no N(7) alkylation.[19] Attempts to cis-hydroxylate **22a** and **22b** with OsO_4 were unsuccessful; it was found that many polar products were produced. However, when **22a** and **22b** were converted into their respective TBS ethers prior to oxidative cis-hydroxylation, the cis-hydroxylation reaction with OsO_4 proceeded in good yield after purification for both **23a** (62% from **22a**) and **23b** (50% from **22b)**. 2D-NMR ROESY and COSY experiments on **23a** and **23b** confirmed the expected α-cis stereochemistry of the two hydroxyl groups. Treatment of these compounds with 6 N HCl removed the Boc groups to give **24a** (73% from **23a**) and **24b** (67% from **23b**) as the dihydrochloride salts.

The assignment of the site of N-alkylation of azaadenines was achieved by careful consideration of evidence from the NMR (^{1}H, ^{13}C, COSY, HMBC,[20] and HMQC[21]) spectra. Holy et al.[19] have assigned ^{13}C resonances of the N(7), N(8), and N(9) azaadenines in reference compounds produced by alkylation of 8-azaadenine and related bases. The diagnostic ^{13}C NMR C(4) resonance in compounds **22a** (148.5 ppm) and **24a** (148.71 ppm) corresponded to the C(4) resonance seen in N(9)-alkylated reference compounds (149.4 ppm). The C(4) resonance of **22b** (156.6 ppm) and **24b** (151.01 ppm) matched that seen in reference N(8)-alkylated compounds (158.01 ppm). N(7) alkylation was also ruled out, as the diagnostic C(5) resonance of the reference N(7)-alkylated compounds (109.8 ppm) was far upfield of the C(5) resonances of the intermediates shown in Scheme 5 (**22a**: 123.9 ppm; **22b**: 125.3 ppm; **24a**: 124.06 ppm; **24b**: 124.91 ppm).

In the case of **24a**, the HMBC NMR spectra showed a correlation between H(1′) and C(4), confirming alkylation at N(9), whereas **24b** showed no H(1′) correlation to the heterocyclic ring, consistent with a cyclopentane−heterocycle connection at N(8). Hydrogenolysis of **24a** produced the target analogue **7** in 24% purified yield, and **24b** gave a 21% yield of **7**.

For the synthesis of the target pyrazolo[3,4-*d*]pyrimidine carbocycle analogue **8**, the extreme insolubility of **26** even in DMSO precluded an efficient palladium-catalyzed reaction of **26** with **9** (Scheme 6). This prompted us to prepare the heterocyclic base dimethylformamidine pyrazolo[3,4-*d*]pyrimidine[22] **27**, which was expected to be more soluble in DMSO. This was prepared simply by stirring **26** in DMFDMA (dimethylformamide dimethyl acetal) in DMF for 2 d followed by filtration to give **27** quantitatively. The palladium-catalyzed reaction of **27** with **9** gave **28** as the major product in 29% isolated yield. Treatment of **28** with OsO_4/NMMO gave cis-hydroxylation, accompanied by several byproducts. A more efficient route was to first remove the dimethylformamidine protecting group of **28** with methanolic ammonia (98%) and then to protect the hydroxyl group of the carbamate

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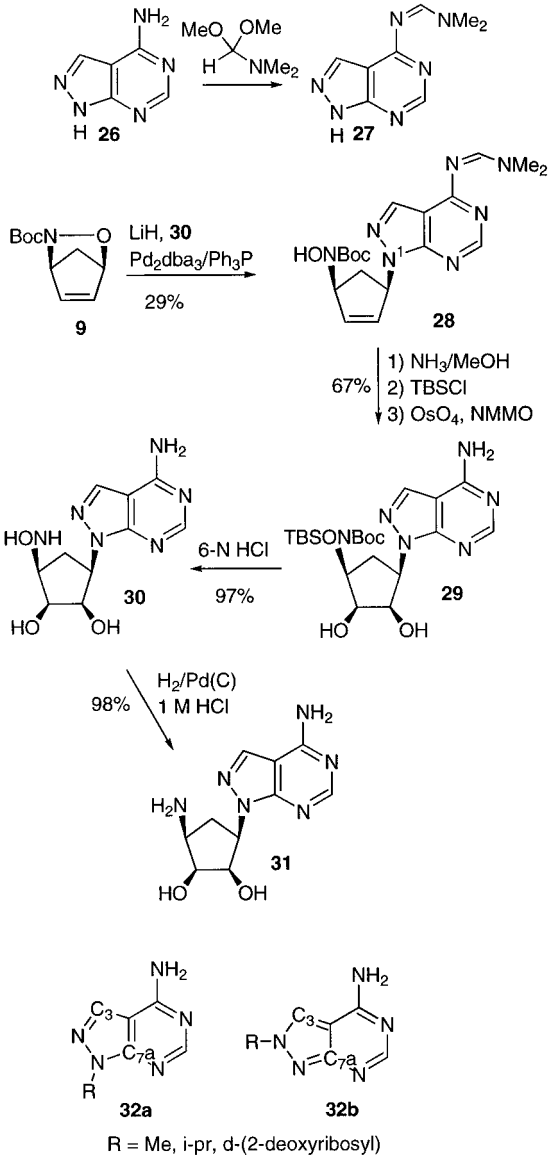
Scheme 6



as a TBS ether, which was followed by reaction with OsO_4/NMMO to provide **29** in 67% overall yield. We were surprised to find that the major cis-hydroxylation product from **28** was the β,β diol (the relative stereochemistry of the substituents was determined by NMR experiments on compound **31**). This stereochemical preference for the β,β-cis-hydroxylation may be the result of some sort of osmium-coordination ability of the pyrazole N(2) to direct the osmylation to the β face, as has been noted by Trost,[23] or alternately a stereoelectronic mechanism, as has been proposed in cyclopentenes by Poli.[24]

Deprotection of **29** was effected in 6 N HCl to give **30** in 97% yield. Hydrogenolysis of **30** gave **31** in 98% yield. It has been reported[25] that for pyrazolopyrimidine compounds with structures very similar to **28**−**31** ^{13}C NMR shift data are diagnostic for the site of heterocycle attachment (Scheme 6). N(1)-alkylated pyrazolopyrimidines (**32a**) display C(7a) at about 153 ppm and C(3) at about 132 ppm. In contrast, N(2) alkylated pyrazolopyrimidines (**32b**) display C(7a) at about 160 ppm and C(3) at about 125 ppm. We found that in the ^{13}C NMR spectrum of compound **31** C(7a) was found at 153.6 ppm and C(3) was found at 133 ppm, supporting an N(1)-alkylated structure. Additional confirmation of alkylation at N(1) and all-cis stereochemistry was obtained through HMBC and NOE experiments on **31**.

Conclusions

Several new truncated 4′-amino substituted carbocyclic adenosine analogues (**6**, **7**, **31**) were prepared as putative inhibitors of the enzyme adenosine kinase. Three different heterocyclic base moieties (adenine, 8-azaadenine, and pyrazolo[3,4-*d*]pyrimidine) were incorporated into cyclopentanyl nucleoside analogues using either of two different synthetic strategies, including a Mitsunobu reaction or a palladium-mediated coupling as the key step. The most efficient synthetic methodology utilized a Pd^0-catalyzed reaction of the bicyclic isoxazolidine **9** with a heterocyclic base analogue to sterospecifically incorporate the heterocyclic base moiety to the cyclopentane ring. Of the compounds described, **6** and **7** were by far the most potent and inhibit adenosine kinase with values for IC_{50} of less than 200 nM. The biological activity of the carbocyclic nucleoside analogues will be described in greater detail elsewhere.

Experimental Section

General Methods. All solvents were of anhydrous reagent grade from Aldrich Chemical Co. The ^1H NMR spectra were obtained at 300 MHz on a Nicolet/GE QE300 spectrometer, and the same instrument was used to obtain the ^{13}C spectra at 75 MHz. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS or TSP as internal standard. Mass spectra were obtained on a Kratos MS-50 instrument. High-resolution mass spectra were recorded by Midwest Analytical Services. Elemental analyses were performed by Abbott Laboratories Pharmaceutical Products Division Structural Chemistry Department or by Robertson Microlit Laboratories, Inc., Madison, N. J. Flash chromatography was carried out using silica gel 60 (E. Merck, 230−400 mesh), and thin-layer chromatography was performed on 250 μM silica-coated glass plates from EM Science. Analytical HPLC was run using a C18 reversed-phase Dynamax column, eluting at 0.2 mL/min with a generally 0−15% MeOH gradient in 50 mM ammonium acetate. Preparative HPLC was run with a C18 reversed-phase Dynamax column, eluting at 0.5−1.5 mL/min with buffers as described below. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. Unless otherwise noted, all chemicals and reagents were obtained commercially and used without purification.

3-*tert*-Butoxycarbonyl-2-oxa-3-azabicyclo[2.2.1]heptene[18] (9). To a solution of 5.7 g (86 mmol) of freshly prepared cyclopentadiene and 25 g (58 mmol) of $(^nBu)_4N^+IO_4^-$ in 200 mL of CH_2Cl_2 at 25 °C was added 7.7 g (58 mmol) of BocNHOH over 5 min. After 1 h, the reaction mixture was washed with 10% sodium thiosulfate (2 × 70 mL) and then with saturated $NaHCO_3$ (100 mL). The organic phase was dried over Na_2SO_4

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(26) **Note added in proof:** two reports have recently been published of different syntheses of optically active **6** (Hedge, V. R., Seley, K. L., Schneller, S. W. *J. Org. Chem.* **1998**, *63*, 7092) and optically acitve **21a** (Mulvihill, M. J.; Miller, M. J. *Tetrahedron* **1998**, *54*, 6605) by synthetic methods differing from that described here.

and concentrated in vacuo to a black solid. This was dissolved in 50 mL of refluxing 4% MeOH/EtOAc. On cooling, a mass of tan crystals separated which was removed by filtration and discarded. The filtrate was concentrated in vacuo and purified by flash column chromatography, eluting with 30% EtOAc/hexane to give 8.4 g (74%) of the product **9** as a yellow syrup: R_f 0.60 in 50% EtOAc/hexane; ^{1}H NMR ($CDCl_3$) δ 6.4 (m, 2H), 5.20 (m, 1H), 4.98 (m, 1H), 1.98 (dt, J = 8.7, 2.1 Hz, 1H), 1.72 (d, J = 8.7 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 158.46, 134.04, 132.85, 83.43, 81.90, 64.92, 48.04, 28.09; MS (DCI/NH_3) 198 $[M + H]^+$. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.04. Found: C, 61.15; H, 7.67; N, 7.04.

[5α,6α]-3-*tert*-Butoxycarbonyl-5,6-dihydroxy-2-oxa-3-azabicyclo[2.2.1]heptane (10). To a solution of 8.2 g (41.6 mmol) of **9** and 6.44 g (58.0 mmol) of trimethylamine-*N*-oxide in 85 mL of ^{t}BuOH was added 2 g of 1% OsO_4 on polyvinylpyridine. The mixture was heated at reflux for 8 h, cooled, and filtered to remove solids. The filtrate was concentrated in vacuo and then purified by flash chromatography, eluting with 80% EtOAc/hexane, to provide 8.5 g (89%) of the product **10** as a mass of white waxy crystals: R_f (EtOAc) 0.67; mp 50−51 °C; ^{1}H NMR ($CDCl_3$) δ 4.35 (m, 1H), 4.24 (m, 1H), 3.90 (m, 1H), 3.88 (m, 1H), 2.17 (d, J = 10.5 Hz, 1H), 1.68 (m, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 158.72, 83.68, 81.37, 72.20, 71.52, 63.47, 32.30, 28.40; HRMS calcd for $[M + H]^+$ $C_{10}H_{18}NO_5$ 232.1185, found 232.1178. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.60; H, 7.30; N, 5.85.

[5α,6α]-3-*tert*-Butoxycarbonyl-5,6-isopropylidinedioxy-2-oxa-3-azabicyclo[2.2.1]heptane (11). To a solution of 8.43 g (36.5 mmol) of **10** in 45 mL of 2,2-dimethoxypropane and 45 mL of acetone was added 46 mg of PTSA. After 5 h, the reaction was stopped by addition of 5 g of $NaHCO_3$. After 30 min of vigorous stirring, solids were removed by filtration, and the filtrate was concentrated in vacuo to a clear syrup. The syrup was partitioned between 100 mL of water and 200 mL of 25% EtOAc/hexane. The organic phase was dried (MgSO4) and concentrated in vacuo to a white solid which was recrystallized from hexane to give 8.24 g (83%) of **11** as a white solid: R_f (20% EtOAc/hexane) 0.46; mp 93−95 °C; ^{1}H NMR ($CDCl_3$) δ 4.60 (m, 1H), 4.50 (m, 1H), 4.33 (m, 2H), 2.17 (d, J = 10.5 Hz, 1H), 1.69 (m, 1H), 1.49 (s, 9H), 1.45 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.86, 111.29, 82.61, 78.28, 59.70, 31.08, 28.09, 25.58, 24.29; HRMS calcd for $[M + H]^+$ $C_{13}H_{22}NO_5$ 272.1498, found 272.1516. Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.56; H, 7.88; N, 5.14.

(±)-(1*β*,2α,3α,4*β*)-2,3-(Dimethylmethylenedioxy)-4-*tert*-butoxycarbonylamino-cyclopentanol (12). A 2.73 g (119 mmol) portion of freshly cut sodium metal was added to 250 mL of ammonia containing 100 mL of THF at reflux temperature (−33 °C). After the sodium dissolved, the reaction mixture was cooled to −50 °C, and a solution of 4.59 g (17 mmol) of **11** in 70 mL of THF was added over 15 min. After 15 min at −50 °C, TLC indicated that the reaction was complete, and 9 g of dry NH_4Cl was cautiously added to quench excess dissolved sodium. Ammonia was removed under a stream of nitrogen, and the residue was partitioned between 150 mL of water and 260 mL of 30% EtOAc/hexane. The organic phase was then washed with 100 mL of saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to a white solid. This was purified by flash chromatography, eluting with 50% EtOAc/hexane, to give the product as a white solid. This was further purified by recrystallization from EtOAc/hexane to give 3.63 g (46%) of pure **12** as a white solid: R_f (50% EtOAc/hexane) 0.62; mp 140−141 °C; ^{1}H NMR ($CDCl_3$) δ 4.57 (dd, J = 4.0, 0.6 Hz, 1H), 4.48 (dd,J = 4.0, 1.5 Hz, 1H), 4.26 (m, 1H), 4.09 (d, J = 6.0 Hz, 1H), 2.27 (m, 1H), 1.67 (d, J = 13.5 Hz, 1H), 1.45 (s, 9H), 1.40 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.17, 110.13, 86.22, 79.50, 77.47, 56.85, 35.50, 28.41, 26.22, 23.87; HRMS calcd for $[M + H]^+$ $C_{13}H_{24}NO_5$ 274.1654, found 274.1655. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.01; H, 8.11; N, 5.08.

(±)-(2α,3α,4*β*)-2,3-(Dimethylmethylenedioxy)-4-*tert*-butoxycarbonylamino-cyclopentanone (13). To a solution of 2.31 g (18.2 mmol) of oxalyl chloride in 41 mL of CH_2Cl_2 at −60 °C was added 2.84 g (36.4 mmol) of DMSO in 8 mL of CH_2Cl_2 over 2 min. After 2 min, a solution of 2.50 g (9.1 mmol) of **12** in 9 mL of CH_2Cl_2 was added over 5 min. After 15 min of stirring at −60 °C, 5.28 g (41 mmol) of diisopropylethylamine was added over 5 min. The cooling bath was removed, and the reaction mixture was allowed to warm to 20 °C over 25 min; diluted with 200 mL of EtOAc; washed with 1 M aqueous NaH_2PO_4 (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and saturated NaCl (50 mL); and dried over Na_2SO_4. After purification by flash chromatography, eluting with 2:1 hexane/EtOAc, 2.22 g (90%) of the ketone **13** was obtained as a white solid which was used immediately in the next step: R_f (50% EtOAc/hexane) 0.70; mp 103−104 °C; HRMS calcd for $[M + H]^+$ $C_{13}H_{22}NO_5$ 272.1498, found 272.1491. Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.24; H, 7.77; N, 5.15. Found: C, 57.55; H, 7.80; N, 5.16.

(±)-(1α,2α,3α,4*β*)-2,3-(Dimethylmethylenedioxy)-4-*tert*-butoxycarbonylamino-cyclopentanol (14). To a solution of 8.86 mmol of $LiB(^sBu)_3H$ in 13 mL of THF at −78 °C was added 800 mg (2.95 mmol) of **13** in 6 mL of THF over 2 min. After 3 h at −78 °C, the reaction mixture was allowed to warm to −20 °C, and 5 mL of water was added. The reaction mixture was poured into 200 mL of EtOAc and washed with a mixture of 50 mL of water, 50 mL of saturated NaCl, and 50 mL of 1 N NaOH. The organic phase was washed with 50 mL of saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo to a clear syrup. Purification by flash chromatography, eluting with 50% EtOAc/hexane, gave 680 mg (84%) of **14** as a foam, which slowly crystallized to a white solid: R_f (50% EtOAc/hexane) 0.32; mp 104−106 °C; ^{1}H NMR (CD_3OD) δ 4.86 (d, J = 5.4 Hz, 1H), 4.48 (t, J = 5.4 Hz, 1H), 4.12 (m, 1H), 3.67 (d, J = 5.4 Hz, 1H), 1.97 (m, 1H), 1.78 (m, 1H), 1.45 (s, 3H), 1.43 (s, 9H), 1.30 (s, 3H); ^{13}C NMR (CD_3OD) δ 155.50, 112.25, 85.93, 80.25, 72.70, 54.63, 36.34, 28.74, 26.28, 24.36; HRMS calcd for $[M + H]^+$ $C_{13}H_{24}NO_5$ 274.1654, found 274.1651. Anal. Calcd for $C_{13}H_{23}NO_5$ (0.5 H_2O): C, 55.30; H, 8.57; N, 4.96. Found: C, 55.19; H, 8.30; N, 4.57.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(6-Chloro-purin-9-yl)-2′,3′-(dimethylmethylenedioxy)-4′-*tert*-butoxycarbonylamino-cyclopentane (15). To a mixture of 344 mg (2.22 mmol) of 6-chloropurine, 581 mg (2.22 mmol) of Ph_3P, and 511 mg (2.22 mmol) of di-*tert*-butyl azodicarboxylate was added a solution of 404 mg (1.48 mmol) of **14** in 7 mL of THF. After 3 h at 25 °C, TLC indicated that no reaction had occurred. The reaction mixture was heated at reflux for 20 h, at which time TLC indicated incomplete consumption of **14**. Additional Ph_3P, 6-chloropurine, and di-*tert*-butyl azodicarboxylate (1 mmol of each) was added, with 2 mL of THF. The reaction was heated at reflux an additional 24 h, then worked up by pouring into 150 mL of 50% EtOAc/CH_2Cl_2. This was washed with 50 mL of saturated $NaHCO_3$ and saturated NaCl. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography, eluting with 50−100% EtOAc/hexane to give 46 mg (8%) of the impure product as a clear glass: R_f (50% EtOAc/hexane) 0.25; ^{1}H NMR ($CDCl_3$) δ 8.74 (s, 1H), 8.19 (s, 1H), 5.72 (broad s, 1H), 5.09 (dd, J = 6.6, 4.5 Hz, 1H), 4.82 (dt, J = 12.3, 4.5 Hz, 1H), 4.72 (dd, J = 6.6, 2.7 Hz, 1H), 4.20 (m, 1H), 2.92 (dt, J = 13.8, 7.9 Hz, 1H), 2.48 (dt, J = 13.8, 6.6 Hz, 1H), 1.58 (s, 3H), 1.43 (s, 9H), 1.31 (s, 3H); HRMS calcd for $[M + H]^+$ $C_{18}H_{25}NO_4Cl$ 410.1613, found 410.1595.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(6-Amino-purin-9-yl)-2′,3′-(dimethylmethylenedioxy)-4′-*tert*-butoxycarbonylamino-cyclopentane (16). A solution of 48 mg (0.12 mmol) of **15** in 5 mL of dioxane and 5 mL of saturated aqueous NH_4OH was heated at 85 °C in a sealed tube for 6 h. The reaction mixture was concentrated to dryness in vacuo and purified by flash chromatography, eluting with 10% MeOH/EtOAc, to give 22 mg (51%) of **16** as a clear glass: R_f (20% MeOH/EtOAc) 0.63; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 8.23 (s, 1H), 8.09 (s, 1H), 5.09 (dd, J = 6.6, 4.5 Hz, 1H), 4.85 (dt, J = 12.3, 4.5 Hz, 1H), 4.71 (dd, J = 6.6, 2.7 Hz, 1H), 4.15 (m, 1H), 2.80 (m, 1H), 2.45 (dt, J = 13.8, 4.5 Hz, 1H), 1.58 (s, 3H), 1.46 (s, 9H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 155.56, 155.30, 151.65, 148.38, 139.99,

119.00, 112.75, 84.32, 82.79, 60.86, 54.38, 35.85, 27.33, 26.17, 23.89; HRMS calcd for $[M + H]^+$ $C_{18}H_{27}N_6O_4$ 391.2094, found 391.2079.

(±)-(1′*β*,2′α,3′α,4′*β*)-4′-(6-Amino-purin-9-yl)-2′,3′-(dimethylmethylenedioxy)-4′amino-cyclopentane (6). A solution of 21.8 mg (0.056 mmol) of **16** in 8 mL of 6 N HCl was stirred for 5 h. The reaction was concentrated to dryness by lyophilization, to give 19.3 mg of **6** as a clear glass: R_f (3:1:1 CH_3CN/water/acetic acid) 0.31; ^{1}H NMR (D_2O) δ 8.23 (s, 1H), 8.21 (s, 1H), 5.00 (m, 1H), 4.68 (t, J = 5.7 Hz, 1H), 4.22 (t, J = 5.1 Hz, 1H), 3.79 (m, 1H), 2.94 (m, 1H), 2.19 (m, 1H); ^{13}C NMR (D_2O) δ 152.79, 151.43, 147.00, 121.89, 76.34, 75.34, 62.65, 56.94, 32.87; HRMS calcd for $[M + H]^+$ $C_{10}H_{15}N_6O_4$ 251.1256, found 251.1274. Anal. Calcd for $C_{10}H_{14}N_6O_2$ (3.0 HCl, 1.3 H_2O): C, 31.36; H, 5.16; N, 21.94. Found: C, 31.29; H, 4.78; N, 21.62.

Alternatively, **6** was prepared by stirring a mixture of 900 mg (2.46 mmol) of **21**, 73 mg of $PdCl_2$, and 80 mg of 10% Pd on carbon in 25 mL of 1 N HCl under 1 atm of hydrogen for 2 d. The catalyst was removed by filtration and washed with water. The filtrate was lyophilized twice to give 866 mg (92%) of **6**, with ^{1}H NMR/TLC/HPLC behavior identical to that of **6** prepared as above.

Alternatively, **6** was prepared by stirring mixture of 58 mg (0.22 mmol) of **21a** and 100 mg of 10% Pd on carbon in 1.8 mL of water under 1 atm of hydrogen for 3 d, at which time HPLC showed the reaction to be complete with a single product formed. Comparison of the retention times and co-injection experiments of products formed by acid treatment of **16** and the hydrogenation products of **21** and **21a** showed that an identical product (**6**) was produced in each case in pure form (C18 reversed-phase YMC ODC column, eluted with 0−5% MeOH/0.1% CF_3CO_2H.

(±)-(1′*β*,4′*β*)-Δ$_{2′,3′}$-4′-(Hydroxy-*tert*-butoxycarbonylamino)-1′-(6-chloro-purin-9-yl)-cyclopentene (18). To a flask containing 5.91 g (30.0 mmol) of **9**, 9.3 g (60 mmol) of 6-chloropurine, 1.0 g (0.9 mmol) of $(Ph_3P)_4Pd$, and 24 mg (3 mmol) of LiH was added 30 mL of DMSO in one portion. After 3 h of stirring at 22 °C, the reaction mixture was poured into 300 mL of EtOAc and washed three times with 100 mL of aqueous (50 mM) pH 7 phosphate buffer. The organic phase was dried over Na_2SO_4 and then concentrated in vacuo to a brown foam which was purified by flash chromatography, eluting with 3:1 EtOAc/hexane to give 4.2 g (40%) of **18** as a white solid: R_f (75% EtOAc/hexane) 0.42; mp 158−161 °C; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.39 (s, 1H), 6.26 (dt, J = 5.1, 1.5 Hz, 1H), 6.07 (dt, J = 5.1, 1.5 Hz, 1H), 5.75 (m, 1H), 5.33 (m, 1H), 3.05 (dt, J = 14.4, 8.7 Hz, 1H), 2.09 (dt, J = 14.4, 3.6 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.76, 156.50, 151.20, 151.76, 150.68, 144.76, 137.00, 131.08, 82.38, 63.47, 58.07, 34.61, 27.80; HRMS calcd for $[M + H]^+$ $C_{15}H_{19}N_5O_3Cl$ 352.1176, found 352.1186. Anal. Calcd for $C_{15}H_{18}N5O_3Cl$ (0.15 EtOAc): C, 51.33; H, 5.30; N, 19.19. Found: C, 51.70; H, 5.02; N, 19.56.

In a reaction run with 313 mg (2.0 mmol) of 6-chloropurine, 16 mg (2.0 mmol) of LiH, 233 mg (0.2 mmol) of $Pd(Ph_3P)_4$, and 398 mg (2.0 mmol) of **9** in 7 mL of 2:1 DME/DMSO, workup and purification as described above provided in addition to **18** (22%) the dimeric product **19** in 17% yield as a clear foam: R_f (75% EtOAc/hexane) 0.51; MS (CI) at 495 for $[M + H]^+$ $C_{13}H_{24}NO_5$.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(6-Chloro-purin-9-yl)-2′,3′-(dihydroxy)-4′-(*N*-*tert*-butyldimethylsilyloxy-*tert*-butoxycarbonyl)amino-cyclopentane (20). To a solution of 863 mg (2.45 mmol) of **18** in 5 mL of DMF were added 407 mg (2.70 mmol) of TBSCl and 200 mg (2.94 mmol) of imidazole. After 24 h, more TBSCl (81 mg) and imidazole (40 mg) were added. After an additional 12 h, the reaction mixture was poured into 150 mL of EtOAc and washed with 4 × 50 mL of water, dried over $MgSO_4$, concentrated in vacuo, and recrystallized from hexane to give 1.07 g (94%) of the protected olefin ((±)-(1′*β*,4′*β*)-Δ$_{2′,3′}$-1-(6-chloro-purin-9-yl)-4-(*N*-*tert*-butyldimethylsilyloxy-*tert*-butoxycarbonylamino)-cyclopentene a white waxy solid: mp 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 8.36 (s, 1H), 6.25 (dt, J = 5.4, 1.8 Hz, 1H), 5.96 (dt, J = 5.4, 1.8 Hz, 1H), 5.78 (m, 1H), 5.13 (m, 1H), 3.05 (dt, J = 13.1, 6.0 Hz, 1H), 2.08 (dt, J = 13.1, 6.0 Hz, 1H), 1.49 (s, 9H), 0.96 (s, 9H), 0.19 (s, 6H).

To a solution of 4.60 g (9.87 mmol) of the protected olefin in 209 mL of ^{t}BuOH were added 4 mL of a 2.5% solution of OsO_4 in ^{t}BuOH and 2.89 g (24.7 mmol) of NMMO. The reaction mixture was stirred at room temperature for 16 h, at which time 25 mL of EtOAc, 125 mL of CH_2Cl_2, 20 mL of saturated aqueous $NaHCO_3$, and 20 mL of 8% aqueous Na_2SO_3 were added sequentially with vigorous stirring. After 30 min, the mixture was poured into 125 mL of CH_2Cl_2 and washed with 2 × 100 mL of water. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to a white powder. The solid was recrystallized from EtOAc to give 2.56 g (56%) of **20**. The mother liquor was concentrated in vacuo and purified by flash chromatography, eluting with 50% EtOAc/CH_2Cl_2, to give 1.23 g (27%) of **20** and 0.33 g (7%) of the epimeric diol **20a**. **20**: a white solid, R_f (50% EtOAc/hexane) 0.26; mp 195−196 °C; ^{1}H NMR (CD_3OD) δ 8.75 (s, 1H), 8.55 (s, 1H), 4.78 (m, 1H), 4.63 (m, 1H), 4.20 (m, 1H), 4.17 (m, 1H), 2.75 (m, 1H), 2.42 (m, 1H), 1.50 (s, 9H), 1.01 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (CD_3OD) δ 160.30, 153.15, 152.51, 151.25, 148.03, 83.59, 74.53, 72.41, 68.61, 62.08, 28.61, 28.48, 26.62, 19.04, -4.19, -4.26; HRMS calcd for $[M + H]^+$ $C_{21}H_{35}N_5O_5ClSi$ 500.2096, found 500.2106. Anal. Calcd for $C_{21}H_{34}N_5O_5ClSi$: C, 50.44 H, 6.85; N, 14.00 Found: C, 50.30; H, 6.94 N, 13.92. The relative stereochemistry of all four cyclopentane substituents in **20** was confirmed by 2D-NMR (NOE and COSY) experiments, where strong NOE effects were observed between the proton pairs H(2′)−H(3′), H(1′)−H(5′α), H(4′)−H(5′α), and H(2′)−H(5′*β*), and there was an absence of observable NOE between H(1′)−H(2′), and H(3′)−H(4′).

20a: a clear glass; R_f (50% EtOAc/hexane) 0.36; ^{1}H NMR (CD_3SOCD_3 with a trace of D_2O) δ 8.76 (s, 1H), 8.60 (s, 1H), 5.15 (d, J = 3.3 Hz, 1H), 5.00 (m, 1H), 4.50 (d, J = 4.5 Hz, 1H), 4.30 (m, 1H), 4.27 (m, 1H), 4.13 (m, 1H), 2.74 (dd, J = 7.5, 13.5 Hz, 1H), 2.01 (m, 1H), 1.43 (s, 9H), 0.92 (s, 9H), 0.90 (s, 3H), 0.85 (s, 3H).^{13}C NMR (CD_3OD) δ 161.35, 153.61, 152.78, 151.04, 147.82, 83.21, 73.01, 71.59, 63.05, 55.34, 31.96, 28.55, 26.56, 18.93, −4.00, −4.19; HRMS calcd for $[M + H]^+$ $C_{21}H_{35}N_5O_5ClSi$ 500.2096, found 500.2091. Anal. Calcd for $C_{21}H_{34}N_5O_5ClSi$ (0.2 H_2O): C, 50.08 H, 6.88; N, 13.90. Found: C, 50.40; H, 6.71; N, 13.53. The all-cis stereochemistry of **20a** was supported by the 2D NOE and COSY NMR experiments wherein NOEs were observed between the proton pairs H(1′)−H(5′), H(4′)−H(5′α), H(1′)−H(4′), H(1′)−H(2′), H(2′)−H(3′), and both hydroxyl protons and the purine H(8). The H(5′α) and H(5′*β*) were differentiated by an NOE between H(5′*β*) and the purine H(8).

((±)-(1′*β*,2′α,3′α,4′*β*)-1′-(6-Amino-purin-9-yl)-2′,3′-(dihydroxy)-4′-(*N*-hydroxy-*N*-*tert*-butoxycarbonyl)amino-cyclopentane (21). A 2.95 g portion (5.90 mmol) of **20** was added to 50 mL of MeOH saturated with ammonia and heated at 100 °C for 16 h. After concentration in vacuo, the crude mixture was purified by flash chromatography, eluting with 3:1 EtOAc/MeOH to give 1.76 g (82%) of **21**, along with 0.32 g (11%) of TBS-protected **21**. **21**: a white amorphous powder; R_f (75% EtOAc/MeOH) 0.50; mp 140−142 °C; ^{1}H NMR (CD_3OD) δ 8.22 (s, 1H), 8.20 (s, 1H), 4.80 (m, 1H), 4.52 (m, 2H), 4.28 (m, 1H), 2.60 (m, 1H), 2.33 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (CD_3OD) δ 153.51, 152.05, 141.34, 82.71, 76.00, 73.88, 64.17, 60.46, 30.03, 28.58; LRMS *m*/*z* at 367 for $[M + H]^+$. Anal. Calcd for $C_{15}H_{22}N_6O_5$ (1.0 H_2O, 1.0 HCl): C, 42.81 H, 5.99; N, 19.97. Found: C, 42.65; H, 5.87; N, 19.96.

((±)-(1′*β*,2′α,3′α,4′*β*)-1′-(6-Amino-purin-9-yl)-2′,3′-(dihydroxy)-4′-(*N*-hydroxy)amino-cyclopentane (21a). A 255 mg portion (0.53 mmol) of **21** was added to 10 mL of 6 N HCl and stirred for 4 h. Solvent was removed in vacuo, and the glassy residue was lyophilized twice from 15 mL of water. Half of the sample was purified by reversed-phase preparative HPLC on a Dynamax C18 column, eluting with 0.5 mL/min 7% MeOH/0.1% CF_3CO_2H to give 121 mg (47%) of pure product as a clear glass after removal of solvent in vacuo: R_f (3:1:1 $CH_3CN/CH_3CO_2H/H_2O$) 0.46; ^{1}H NMR (D_2O) δ 8.37 (s, 1H), 8.32 (s, 1H), 4.93 (m, 1H), 4.67 (m, 1H), 4.35 (m, 1H), 3.69 (m,

1H), 2.78 (m, 1H), 2.16 (m, 1H); ^{13}C NMR (D_2O) δ 152.69, 151.76, 147.08, 146.55, 121.65, 76.99, 72.16, 66.45, 61.97, 29.25; HRMS calcd for $[M + H]^+$ $C_{10}H_{15}N_6O_3$ 267.1206, found 267.1207. Anal. Calcd for $C_{10}H_{14}N_6O_3$ (1.0 CF_3CO_2H, 3.0 HCl): C 29.43 H, 3.71; N, 17.16. Found: C, 29.29; H, 3.71; N, 17.48.

(±)-(1′*β*, 4′*β*)-Δ$_{2′,3′}$-4′-(Hydroxy-*tert*-butoxycarbonylamino)-1′-(8-azaadenin-9-yl)-cyclopentene (22a) and (±)-(1′*β*, 4′*β*)-Δ$_{2′,3′}$-4′-(hydroxy-*tert*-butoxycarbonylamino)-1′-(8-azaadenin-8-yl)-cyclopentene (22b). To a flask containing 1.15 g (5.84 mmol) of **9**, 1.59 g (11.7 mmol) of 8-azaadenine, 0.34 g (0.29 mmol) of $(Ph_3P)_4Pd$, and 5 mg (0.58 mmol) of LiH was added 10 mL of DMSO in one portion. After 4 h of stirring at 22 °C, the reaction mixture was poured into 300 mL of EtOAc and washed three times with 100 mL of water. The organic phase was dried over Na_2SO_4 and then concentrated in vacuo to a brown foam which was purified by flash chromatography, eluting with 19:1 EtOAc/MeOH to give 0.47 g (24%) of **22a** as a white foam. NMR HMQC, HMBC, and NOESY experiments were used to assign the proton and carbon resonances:^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H, OH), 8.39 (bs, 1H, NH), 8.29 (s, 1H, H^2), 8.03 (bs, 1H, NH), 6.17 (dt, J = 5.1, 1.5 Hz, 1H, H(2′) olefin), 6.03 (dt, J = 5.1, 1.5 Hz, 1H, H(3′) olefin), 5.78 (m, 1H, H(1′)), 5.24 (m, 1H, H(4′)), 2.81 (dt, J = 14.4, 8.7 Hz, 1H, H(5′α)), 2.34 (dt, J = 14.4, 8.7 Hz, 1H, H(5′*β*)), 1.43 (s, 9H, Boc); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.5, 156.1, 155.7, 148.5, 135.0, 131.1, 123.9, 79.8, 62.8, 60.5, 33.6, 28.0; LRMS m/z at 334 for $[M + H]^+$.

22b was a white foam (0.75 g, 39%), and NMR HMQC, HMBC, and NOESY experiments were used to assign the proton and carbon resonances:^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H, OH), 8.28 (s, 1H, H(2)), 8.18 (bs, 1H, NH), 7.99 (bs, 1H, NH), 6.20 (dt, J = 5.1, 1.5 Hz, 1H, H(2′) olefin), 6.06 (dt, J = 5.1, 1.5 Hz, 1H, H(2′) olefin), 5.87 (m, 1H, H(1′)), 5.22 (m, 1H, H(4′)), 2.87 (dt, J = 14.4, 8.7 Hz, 1H, H(5′α)), 2.34 (dt, J = 14.4, 8.7 Hz, 1H, H(5′*β*)), 1.43 (s, 9H, Boc); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.6, 156.6, 156.55, 155.7, 135.7, 130.7, 125.73, 79.9, 69.7, 62.7, 33.9, 28.0; LRMS m/z at 334 for $[M + H]^+$.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(8-Azaadenin-9-yl)-2′,3′-(dihydroxy)-4-′(*N*-*tert*-butyldimethylsilyloxy-*tert*-butoxycarbonyl)-amino-cyclopentane (23a). A mixture of 392 mg (1.18 mmol) of **22a**, 120 mg (1.77 mmol) of sublimed imidazole, and 196 mg (1.30 mmol) of TBSCl in 5 mL of DMF was stirred for 4 h at 30 °C, poured into 80 mL of EtOAc, and washed with 50 mL of water containing 5 mL of saturated $NaHCO_3$. Drying over Na_2SO_4, followed by concentration in vacuo, gave 545 mg of the TBS-protected olefin as a waxy white solid: LRMS m/z at 448 for $[M + H]^+$. Preparation of diol **23a**: to a mixture of 211 mg (0.47 mmol) of the TBS-protected olefin and 275 mg (2.35 mmol) of NMMO in 2.5 mL of CH_3CN and 1.5 mL of water was added 1 mL of a 2.5% solution of OsO_4 in ^{t}BuOH. After 16 h of stirring, the reaction mixture was concentrated in vacuo to remove organic solvents, poured into 80 mL of EtOAc, and washed with water (2 × 50 mL). Drying over Na_2SO_4, followed by concentration in vacuo, gave 209 mg of a waxy solid. This was purified by flash chromatography, eluting with 95% CH_2Cl_2/EtOAc to give 136 mg of diol **23a** (62% from **22a**) as a white solid: LRMS m/z at 482 for $[M + H]^+$.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(8-Azaadenin-8-yl)-2′,3′-(dihydroxy)-4′-(*N*-*tert*-butyldimethylsilyloxy-*tert*-butoxycarbonyl)-amino-cyclopentane (23b). A mixture of 351 mg (1.05 mmol) of **22b**, 147 mg (2.16 mmol) of sublimed imidazole, and 205 mg (1.36 mmol) of TBSCl in 3 mL of DMF was stirred for 4 h, poured into 80 mL of EtOAc, and washed with 50 mL of water containing 5 mL of saturated $NaHCO_3$. Drying over Na_2SO_4, followed by concentration in vacuo, gave 423 mg of the TBS ether as a waxy white solid: LRMS m/z at 448 for $[M + H]^+$. Preparation of diol **23b**: to a mixture of 222 mg (0.50 mmol) of TBS-protected olefin and 293 mg (2.5 mmol) of NMMO in 4.5 mL of CH_3CN and 1.5 mL of water was added 1 mL of a 2.5% solution of OsO_4 in ^{t}BuOH. After 16 h of stirring, the reaction mixture was concentrated in vacuo to remove organic solvents, poured into 80 mL of EtOAc, and washed with water (2 × 50 mL). Drying over Na_2SO_4, followed by concentration in vacuo, gave 222 mg of a waxy solid. This was purified by flash chromatography, eluting with 95% CH_2Cl_2/EtOAc to give 132 mg of diol **23b** (50% from **22b**) as a white solid: LRMS m/z at 482 for $[M + H]^+$.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(8-Azaadenin-8-yl)-2′,3′-(dihydroxy)-4′-(*N*-hydroxy)amino-cyclopentane (24b). A 40 mg portion (0.08 mmol) of **23b** was stirred in 5 mL of 6 N HCl for 1 h, concentrated by lyophilization, washed with EtOAc, and dried in vacuo to give 24 mg of **24b** (67%) as white powder. Analytical HPLC (C18 reversed-phase Dynamax column, eluting with 0.2 mL/min 10% MeOH/50 mM ammonium acetate) traces showed the sample to be >97% pure. The NOE, ROESY, COSY and HMBC NMR spectra supported the proposed structure: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.9 (bs, 1H), 11.15 (bs, 1H), 9.9 (bs, 1H), 9.4 (bs, 1H), 8.49 (s, 1H), 5.15 (m, 1H), 4.48 (dd, J = 7.5, 5.0 Hz, 1H), 4.25 (dd, J = 5.0, 3.0 Hz, 1H) 3.6 (m, 1H), 2.76 (m, 1H), 2.42 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.41, 154.37, 151.01, 124.91, 75.48, 69.86, 63.44, 60.19, 27.76; LRMS m/z at 268 for $[M + H]^+$. Anal. Calcd for $C_9H_{13}N_7O_3$ (2.1 HCl, 0.1 EtOAc): C 32.02; H, 4.54; N, 27.80. Found: C, 32.03; H, 4.42; N, 27.80.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(8-Azaadenin-9-yl)-2′,3′-(dihydroxy)-4′-(N-hydroxy)amino-cyclopentane (24a). A 121 mg portion (0.25 mmol) of **23a** was stirred in 5 mL of 6 N HCl for 1 h, concentrated by lyophilization, washed with EtOAc, dried in vacuo, and recrystallized from DMF/MeOH/EtOAc/hexane to give 84.5 mg of the product as a white powder (92%). Analytical HPLC showed the sample to be >98% pure: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.9 (bs, 1H), 11.1 (bs, 1H), 9.25 (bs, 1H), 8.85 (bs, 1H), 8.42 (s, 1H), 5.10 (m, 1H), 4.69 (dd, J = 9.5, 7 Hz, 1H), 4.26 (dd, J = 5.0, 3.0 Hz, 1H) 3.6 (m, 1H), 2.62 (m, 1H), 2.40 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.17, 153.71, 148.71, 124.06 74.21, 69.29, 63.32, 60.24, 27.15; LRMS m/z at 268 for $[M + H]^+$. Anal. Calcd for $C_9H_{13}N_7O_3$ (2.0 HCl, 0.9 H_2O, 0.1 EtOAc): C 30.92; H, 4.86; N, 26.85. Found: C, 30.73; H, 4.96; N, 27.98.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(8-Azaadenin-9-yl)-2′,3′-(dihydroxy)-4′-amino-cyclopentane (7). A mixture of 60 mg of **24a** (0.2 mmol) and 30 mg of 10% Pd(C) in 3 mL of 1:1 DMF/water was stirred under 1 atm of hydrogen for 16 h, filtered, and treated with 20 mL of 1.5 M HCl. After 24 h, solvent was removed by lyophilization to give 281 mg of a yellow oil. A portion of the sample was further purified by preparative HPLC (C18 reversed-phase Dynamax column, eluting with 0.5 mL/min 5% MeOH/50 mM ammonium acetate buffer) to give 17 mg (24%) of the product as a white powder after lyophilization: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (bs, 1H), 8.25 (s, 1H), 8.02 (bs, 1H), 5.01 (dd, J = 16.5, 7.5 Hz, 1H), 4.67 (dd, J = 7.5, 4.5 Hz, 1H), 3.66 (t, J = 4.5 Hz, 1H) 3.18 (m, 1H), 2.55 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.3, 156.2, 124.2, 77.9, 74.6, 61.8, 55.4, 35.8; LRMS m/z at 252 for $[M + H]^+$; HRMS calcd for $[M + H]^+$ $C_9H_{14}N_7O_3$ 252.1209, found 252.1212. Anal. Calcd for $C_9H_{13}N_7O_3$ (1.2 HCl, 0.9 AcOH): C 37.16; H, 5.14; N, 28.09. Found: C, 37.34; H, 4.64; N, 28.28.

(±)-(1′*β*,2′α,3′α,4′*β*)-1′-(8-Azaadenin-8-yl)-2′,3′-(dihydroxy)-4′-amino-cyclopentane (25b). A mixture of 47 mg of **24b** (0.15 mmol) and 30 mg of 10% Pd(C) in 3 mL of 1:1 DMF/water was stirred under 1 atm of hydrogen for 16 h, filtered, and treated with 20 mL of 1.5 M HCl. After 24 h, solvent was removed by lyophilization to give 71 mg of a tan foam, **25b**. A portion of the sample was further purified by preparative HPLC (C18 reversed-phase Dynamax column, eluting with 0.5 mL/min5% MeOH/50 mM ammonium acetate buffer) to give 8 mg (21%) of the product as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.15 (bs, 1H), 7.96 (bs, 1H), 4.98 (dd, J = 16.5, 7.5 Hz, 1H), 4.48 (dd, J = 7.5, 6.0 Hz, 1H), 3.62 (t, J = 3.0 Hz, 1H) 3.20 (m, 1H), 2.62 (m, 1H), 1.82 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.7, 156.5, 156.4, 112.8, 76.2, 71.2, 61.8, 55.4, 38.2; LRMS m/z at 252 for $[M + H]^+$; HRMS calcd for $[M + H]^+$ $C_9H_{14}N_7O_3$ 252.1209, found 252.1203.

(±)-(1′*β*,4′*β*)-Δ$_{2′,3′}$-4′-(Hydroxy-*tert*-butoxycarbonylamino)-1′-(4-dimethylformamidinyl-pyrazolo[3,4-*d*]pyrimidin-1-yl)-cyclopentene (28). To a flask containing 1.05 g (5.33 mmol) of **9**, 2.05 g (10.7 mmol) of **27**, 0.31 g (0.27 mmol)

of $(Ph_3)_4Pd$, and 21 mg (2.7 mmol) of LiH was added 10 mL of DMSO in one portion. After 24 h of stirring at 22 °C, the reaction mixture was poured into 300 mL of EtOAc and washed three times with 100 mL of aqueous (50 mM) pH 7 phosphate buffer. The organic phase was dried over Na_2SO_4 and then concentrated in vacuo to a brown foam which was purified by flash chromatography, eluting with 4:1 EtOAc/ethanol to give 569 mg (29%) of olefin **28** as a white solid: R_f (7:3 EtOAc/ethanol) 0.41; ^{1}H NMR (DMSO-d_6) δ 9.00 (s, 1H), 8.94 (s, 2H), 8.45 (s, 1H), 8.10 (s, 1H), 5.95 (m, 2H), 5.80 (m, 1H), 5.18 (m, 1H), 3.23 (s, 3H), 3.16 (s, 1H), 2.62 (dt, J = 12, 4.5 Hz, 1H), 2.35 (dt, J = 12, 4.5 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 157.93, 155.67, 155.62, 152.73, 133.91, 132.48. 131.93, 100.10, 79.69, 62.52, 59.24, 33.26, 27.99; LRMS m/z at 332 for $[M + H]^+$.

(±)-(1′*β*,2′*β*,3′*β*,4′*β*)-1′-(4-Amino-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2′,3′-(dihydroxy)-4′-(*N*-*tert*-butyldimethylsilyloxy-*tert*-butoxycarbonyl)amino-cyclopentane (29). A 442 mg portion (1.14 mmol) of **28** was stirred in 50 mL of MeOH saturated with ammonia for 16 h and then concentrated in vacuo to a white solid: LRMS m/z at 332 for $[M + H]^+$. A solution of 373 mg (1.12 mmol) of this solid, 185 mg (1.23 mmol) of TBSCl, and 114 mg (1.68 mmol) of sublimed imidazole in 3 mL of DMF was stirred for 16 h, poured into EtOAc, and washed with water. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography, eluting with (4:1) EtOAc/ethanol to give 466 mg of a waxy white solid: LRMS m/z at 447 for $[M + H]^+$. A solution of 430 mg (0.96 mmol) of this solid, 338 mg (2.89 mmol) of NMMO, and 1 mL of a 2.5% solution of OsO_4 in ^{t}BuOH in a solution of 6 mL of CH_3CN and 2 mL of water was stirred for 24 h, concentrated in vacuo, and purified by flash chromatography, eluting with 7:3:3 EtOAc/ethanol/hexane, to give 308 mg (67%) of **29**: R_f (4:1 EtOAc/ethanol) 0.49; ^{1}H NMR (DMSO-d_6) δ 8.13 (s, 1H), 8.08 (s, 1H), 7.65 (bs, 2H), 4.97 (d, J = 5.9 Hz, 1H, OH), 4.90 (m, 1H), 4.76 (d, J = 5.6 Hz, 1H, OH), 4.25 (m, 1H), 4. 19 (m, 2H), 2.1−2.25 (m, 2H), 1.45 (m, 9H), 0.95 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 158.18, 157.94, 155.54, 153.18, 131.91, 100.13, 81.05, 73.77, 70.65, 66.14, 59.19, 27.72, 27.60, 25.94, 17.76,−4.50, −4.66; LRMS m/z at 480 for $[M + H]^+$.

(±)-(1′*β*,2′*β*,3′*β*,4′*β*)-1′-(4-Amino-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2′,3′-(dihydroxy)-4′-(*N*-hydroxyl)amino-cyclopentane (30). A solution of 300 mg (0.63 mg) of **29** in 10 mL of 6 N HCl was stirred for 6 h and then concentrated by lyophilization to give 216 mg of a white foam: R_f (36% pyridine/33% EtOAc/20% acetic acid/11% water) 0.64; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.8 (bs, 2H), 11.1 (bs, 1H), 9.9 (bs, 1H), 8.95 (bs, 1H), 8.55 (s, 1H), 8.46 (s, 1H), 5.08 (m, 1H,), 4.44 (dd, J = 8.7, 5.7 Hz, 1H), 4.20 (dd, J = 5.7, 2.7 Hz, 1H), 3.66 (td, J = 8.7, 2.7 Hz, 1H), 2.45 (m, 1H), 2.23 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.83, 151.05, 147.00, 135.54, 99.45, 74.11, 69.24, 63.28, 59.42, 26.93; LRMS m/z at 266 for $[M + H]^+$.

(±)-(1′*β*,2′*β*,3′*β*,4′*β*)-1′-(4-Amino-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2′,3′-(dihydroxy)-4′-amino-cyclopentane (31). A mixture of 207 mg (0.65 mmol) of **30** and 100 mg of 10% Pd-(C) in 4 mL of 1:1 DMF was stirred under 1 atm of hydrogen for 24 h. Water (50 mL) was added, and solvent was removed by lyophilization to give a tan foam. A solution of the foam in MeOH/EtOAc was treated with Et_2O to give 214 mg of a white solid: R_f (36% pyridine/33% EtOAc/20% acetic acid/11% water) 0.64; ^{1}H NMR (500 MHz, CD_3OD) δ 8.13 (s, 1H), 8.11 (s, 1H), 5.17 (m, 1H), 4.31 (m, 2H), 3.64 (t, 1H) 2.82 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD/D_2O) δ 158.5, 154.8, 153.6, 134.6, 101.8, 76.2, 75.4, 62.1, 55.9, 32.0; LRMS m/z at 251 for [M + H]. Long-range coupling between H(1′) and C(7a) in the HMBC experiment confirmed alkylation at N(1). The all-cis stereochemistry was confirmed by NOE effects observed between proton pairs H(1′)−H(4′), H(1′)−H(5′α), H(4′)−H(5′α), H(1′)−H(2′), and H(3′)−H(4′).

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