1,2-isopropylidene-3-*O*-benzyl-*sn*-glycerol, 16495-03-7; 3-*O*-benzyl-*sn*-glycerol, 56552-80-8; palmitoyl chloride, 112-67-4; 1,2-*O*-dipalmitoyl-3-*O*-benzyl-*sn*-glycerol, 30403-51-1; *rac*-3-*O*-benzylglycerol, 13071-59-5; 1,2-*O*-isopropylidene-3-*O*-palmitoyl-*sn*-glycerol, 57416-03-2; 3-*O*-palmitoyl-*sn*-glycerol, 5309-46-6; 1-*O*-trityl-3-*O*-palmitoyl-*sn*-glycerol, 30563-15-6; 1-*O*-trityl-2,3-*O*-dipalmitoyl-*sn*-glycerol, 30563-16-7; ara-CMP morpholidate, 69467-87-4.

Synthesis and Antiviral Evaluation of 6′-Substituted Aristeromycins: Potential Mechanism-Based Inhibitors of *S*-Adenosylhomocysteine Hydrolase[1,2]

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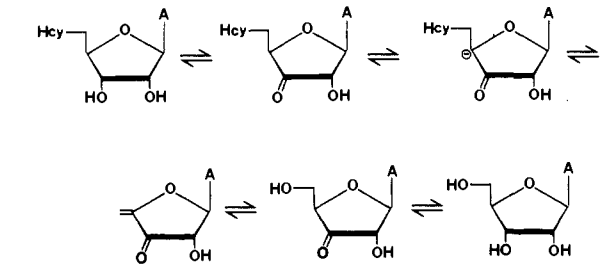
New carbocyclic adenosine analogues substituted at the 6′-position with fluorine, hydroxyl, methylene, or hydroxymethyl have been synthesized as potential mechanism-based inhibitors of *S*-adenosylhomocysteine (AdoHcy) hydrolase. The synthetic routes began with a functionalized (±)-azidocyclopentane **2**, which was elaborated to the adensoine analogue, or with functionalized cyclopentane epoxides **11**, **20**, and **27**, which were opened directly with adenine in the presence of base. The 6′-α-fluoro (**24**), 6′-β-fluoro (**10**), and 6′-methylene (**30**) carbocyclic adenosine analogues were potent inhibitors of AdoHcy hydrolase. None of the compounds displayed significant activity against herpes simplex virus type 1 or type 2, but several demonstrated potent inhibition of vaccinia virus replication.

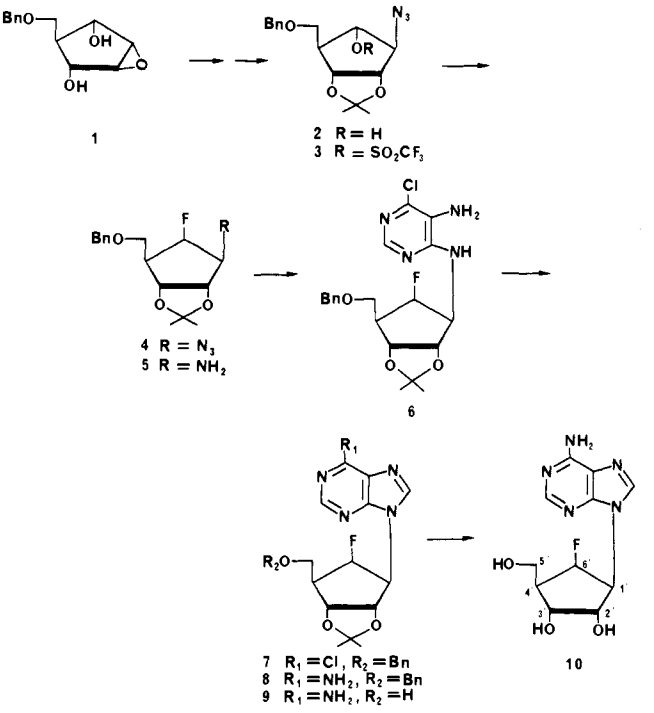
The antiviral activities of the carbocyclic adenosine analogues have been shown to be due, at least in part, to their inhibition of *S*-adenosylhomocysteine (AdoHcy) hydrolase.[6] For example, aristeromycin (the carbocyclic analogue of adenosine) shows activity against vaccinia virus[7] and inhibits AdoHcy hydrolase with a K_i of 5 nM.[8] Neplanocin A also inhibits vaccinia virus and has a K_i of 8 nM,[9] while the carbocyclic analogue of 3-deazaadenosine inhibits the growth of reo, measles, parainfluenza, vesicular stomatitis, herpes simplex-1, and vaccinia viruses[10,11] and displays a K_i value of 1 nM.[10] This relationship can be ratonalized by the fact that many viruses rely upon *S*-adenosylmethionine-dependent methylations to provide the methylated 5′-cap structure on their mRNAs. Since *S*-adenosylhomocysteine is a product and feedback inhibitor of these methylations, its accumulation via the inhibition of AdoHcy hydrolase will curtail viral mRNA capping. This, in turn, leads to inhibition of virus replication.[6b,c]

The mechanism by which AdoHcy hydrolase catalyzes the hydrolysis of AdoHcy to adenosine and homocysteine has been elegantly elucidated.[12–15] As shown in Scheme I, the first step involves oxidation of the 3′-hydroxyl group of AdoHcy by enzyme-bound NAD followed by β-elimi-

Scheme I



Scheme II



(1) Contribution 273 from the Institute of Bio-Organic Chemistry.
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(5) Current address: Bristol-Myers Company, Pharmaceutical Research and Development Division, Wallingford, CT 06492-7660.
(6) (a) De Clercq, E.; Cools, M. *Biochem. Biophys. Res. Commun.* **1985**, *129*, 306. For recent reviews, see: (b) Marquez, V. E.; Lim, M. *Med. Res. Rev.* **1986**, *6*, 1. (c) De Clercq, E.; Bergstrom, D. E.; Holy, A.; Montgomery, J. A. *Antiviral Res.* **1984**, *4*, 119.
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(13) Palmer, J. L.; Abeles, R. H. *J. Biol. Chem.* **1979**, *254*, 1217.
(14) Parry, R. J.; Askanas, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 1417.

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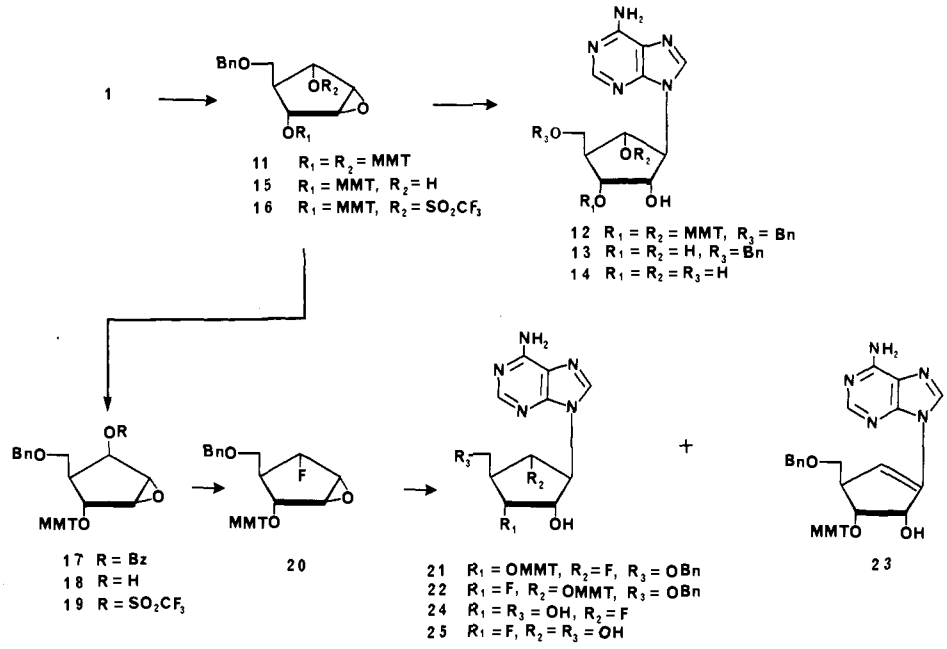
Scheme III



nation of L-homocysteine to give the α,β-unsaturated ketone. Michael addition of water to this intermediate affords 3′-ketoadenosine, which is then reduced by NADH to adenosine.

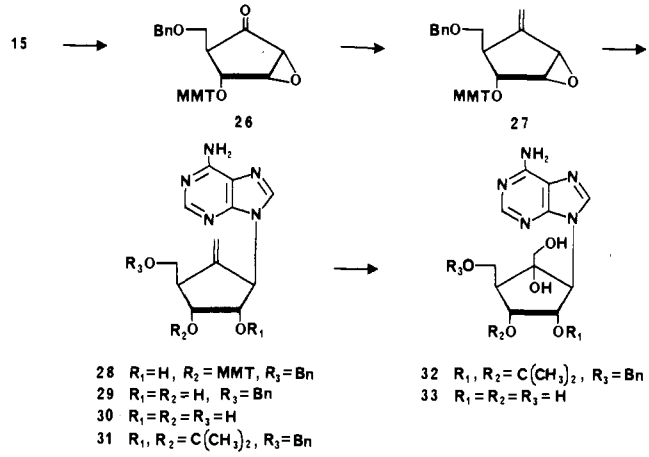
The carbocyclic nucleosides appear to act as substrate analogues of AdoHcy and are oxidized in a similar manner at 3′. This process depletes enzyme-bound NAD, and the enzyme can no longer initiate catalysis.[8,16-19] Whether or not an electrophilic intermediate capable of covalently binding to the enzyme is also produced is subject to conjecture.

Our design of AdoHcy hydrolase inhibitors is based on the fact that the enzyme catalyzed elimination step proceeds via a carbanion mechanism.[13] A common strategy for construction of suicide enzyme inactivators involves the attachment of a fluorine atom adjacent to a position of carbanion formation. Such an intermediate will undergo facile elimination of fluorine to generate a powerful Michael acceptor capable of alkylating the enzyme.[20] We have synthesized a number of aristeromycin analogues in which the 6′-position[21] is substituted with a fluorine, or other functionality, in the hope of obtaining an irreversible inhibitor of AdoHcy hydrolase and enhanced antiviral activity.

Chemistry

Recently, we have described a synthesis of aristeromycin wherein cyclopentadiene is efficiently transformed first to the epoxy diol **1** and then to the (±) azido alcohol **2**.[22] The present work utilizes these two intermediates as starting materials for 6′-substituted aristeromycins.[23]

Scheme IV



As shown in Scheme II, (±)-6′β-fluoroaristeromycin (**10**) was elaborated from **2**. The hydroxyl of **2** was converted to the corresponding triflate, which was immediately treated with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF)[24] to give the inverted fluoride **4** in 80% overall yield. Reduction of the azide of **4**, elaboration of the 9-adeninyl substituent, and final deprotection to afford **10**, paralleled our earlier aristeromycin synthesis.[22] Confirmation of structure was provided by the ^{1}H NMR spectrum in which the 1′-proton contained very large (30 Hz) trans coupling to the 6′-fluorine.

At this point it was felt that the other derivatives could be made more efficiently by opening appropriately sub-

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(20) Rando, R. R. *Pharmacol. Rev.* **1984**, *36*, 111.
(21) For simplicity, the numbering of the carbocyclic nucleosides is consistent with that for adenosine and in accord with ref 22. We also use this numbering system in the Experimental Section to facilitate comparison of the NMR spectra, although the title compounds are named according to IUPAC nomenclature.
(22) Madhavan, G. V. B.; Martin, J. C. *J. Org. Chem.* **1986**, *51*, 1287.
(23) The syntheses of carbocyclic 2′-deoxy-6′-fluorouridines via a different route has recently been described: Biggadike, K.; Borthwich, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youds, P.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 255.
(24) (a) Middleton, W. J. U.S. Pat. 3940402. (b) Card, P. J.; Hitz, W. D. *J. Am. Chem. Soc.* **1984**, *106*, 5348.

Table I. Antiviral, Cytotoxic, and AdoHcy Hydrolase Inhibitory Activity of 6′-Substituted Aristeromycins

compd	HSV-1 (F) VR[a]	HSV-1 (F) ED_{50},[b] μM	HSV-2 (G) VR	HSV-2 (G) ED_{50}, μM	vaccinia VR	vaccinia ED_{50}, μM	cytotoxicity,[c] μM	AdoHcy'ase inhibition: IC_{50},[d] nM
10	0.4	10	0.4	10	0.8	0.50	320	8
14	0.6	100	0.3	100	0.8	18	>320	28000
24	0.1	90	0.1	90	0.4	63	>320	180
25	0.0	225	0.0	225			225	
30	0.0	16	0.3	5	0.9	0.55	50	80
33	0.0	>500	0.0	>500			>500	
DHPG	1.4	<1.0	1.6	<1.0			>3200	
adenosine dialdehyde			0.0	>3200	1.3	0.50	100	40

[a] Viral rating (VR) determined according to Sidwell and Huffmann.[27] [b] Concentration of the compound at which 50% of the virus-induced cytopathic effects are inhibited. [c] Lowest concentration at which complete toxicity to HEP-2 cells was observed. [d] See the Experimental Section for details.

stituted cyclopentane epoxides directly with adenine. Thus, the epoxy diol **1**, after protection as the bis(monomethoxytrityl ether) **11**, was heated with adenine in DMSO in the presence of potassium carbonate (Scheme III). The condensed product **12** was isolated in 32% yield. Removal of the trityl protecting groups with acid followed by transfer hydrogenation[25] furnished (±)-6′α-hydroxyaristeromycin (**14**).

The epoxy diol **1** was also monotritylated to furnish the useful intermediate **15** in which the remaining hydroxyl provides potential access to a variety of 6′-substituted aristeromycins. Conversion of the alcohol **15** to the triflate **16**, followed by benzoate displacement, and then hydrolysis afforded the epimeric alcohol **18** in 59% overall yield. Trifluoromethanesulfonation followed, this time, by reaction with TBAF furnished the (±)-α-fluoro epoxide **20**. On heating the epoxide **20** with adenine in DMSO in the presence of potassium carbonate, the protected (±)-6′α-fluoroaristeromycin **21** was obtained in 31% yield along with the isomeric (±)-3′α-fluoroaristeromycin[26] **22** (16% yield) and a small amount (3% yield) of the (±)-1′-olefin **23**. The two fluoro nucleoside analogues were deprotected as described above. The direction of epoxide opening was evident from the ^1H NMR spectrum of **24**, which contained a large (21 Hz) cis coupling between the 1′-proton and the 6′-fluorine.

Lastly, some aristeromycin analogues having an exocyclic carbon at 6′ were constructed (Scheme IV). Oxidation of **15** with Me_2SO/DCC furnished the ketone **26** in 84% yield, which reacted with methyltriphenylphosphorus ylide to give the exocyclic olefin **27** in 57% yield. On heating **27** with the sodium salt of adenine in DMF, epoxide opening occurred in the desired direction to give a 74% yield of the (±)-6′-methylenearisteromycin derivative **28**. Detritylation using acetic acid gave the diol **29** in 62% yield, and transfer hydrogenation[25] afforded the free nucleoside **30**.

The acetonide of **29** was then made and oxidized with osmium tetroxide providing the (±)-6′-hydroxy-6′-hydroxymethyl derivative **32**. Deprotection via transfer hydrogenation followed by acid hydrolysis then gave the very polar pentol **33**. The configuration at the 6′-position of **33** is assigned on the basis of ^1H NOE subtraction experiments.

Biological Results and Discussion

The deprotected, racemic nucleoside analogues prepared above were assayed for antiviral activity in vitro. The results are summarized in Table I. Tests were carried out on herpes simplex virus-1 (HSV-1) (F strain), HSV-2 (G), and vaccinia virus, and cytotoxicity was evaluated on monolayer cultures of HEP-2 cells. Antiviral activity is expressed as a viral rating (VR),[27] which takes into account both inhibition of viral growth and host cell toxicity. A VR > 1.0 indicates significant activity with 2.0 being the maximum value. Additionally, a 50% effective dose (ED_{50}) value was determined for inhibition of the virally induced cytopathic effects. 9-[(1,3-Dihydroxy-2-propoxy)-methyl]guanine (DHPG, ganciclovir) was used as a positive control in the antiherpes evaluations, while adenosine dialdehyde[28] served as a control for the vaccinia trials.

Except for the 6′-hydroxy-6′-hydroxymethyl derivative **33**, all the analogues exhibited activity against both HSV-1 and HSV-2. The most potent, but also the most toxic, compound was the olefin **30**. The 6′β-fluoro-**10** was nearly as active and much less toxic, resulting in moderate viral ratings (HSV-1 and HSV-2 VR = 0.4). The 6′α-fluoro-**24** was 9 times less active than the β-fluoro-**10** against HSV and also showed lower toxicity. The 6′α-hydroxy-**14** was very similar in activity to the α-fluoro-**24**. Lastly, the 3′-fluoro analogue **25** was only weakly active.

The lack of selective antiherpetic activity for these analogues is consistent with that of other carbocyclic adenosine analogues such as aristeromycin[6c] and carbocyclic 3-deazaadenosine.[11] Our data show that as the compounds become increasingly suppressive to HSV growth they also become more cytotoxic. It is likely that rather than having a direct inhibitory effect on viral growth, these analogues are merely thwarting the host cells' ability to support virus replication.

Against vaccinia virus, the aristeromycin derivatives were consistantly more inhibitory than against herpes. The 6′β-fluoro-**10**, 6′-methylene-**30**, and adenosine dialdehyde (control) showed the greatest potencies, having ED_{50}'s of 0.5 μM. The 6′α-hydroxy-**14** and 6′α-fluoro-**24** were 36 and 130 times less active, respectively. Because of their strong inhibition of vaccinia growth, the viral ratings are in the moderate to good range for this virus. Thus, the anti-vaccinia activity of these analogues is consistent with that shown by other carbocyclic nucleosides.

The four analogues in this series that showed the greatest antiviral activity (**10**, **14**, **24**, and **30**) were examined for inhibition of AdoHcy hydrolase. Adenosine dialdehyde[29] was included as a positive control. The results, listed in Table I, are expressed as a 50% inhibitory concentration (IC_{50}).

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(26) In order to maintain the pictorial analogy with adenosine, structures **22** and **25** depict the opposite enantiomer than that drawn for the other racemic compounds.
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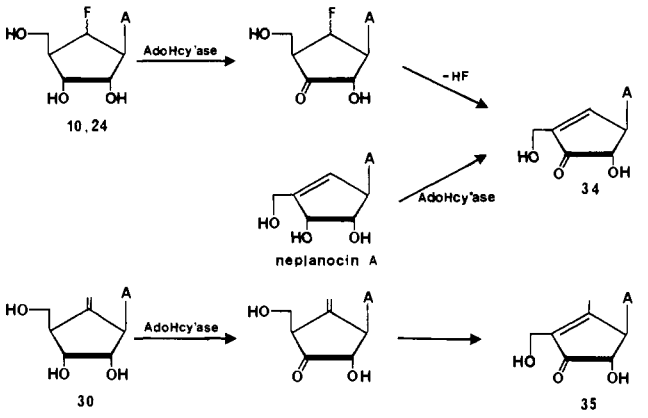
Scheme V



The carbocyclic adenosine analogues substituted at 6' with fluorine or methylene were extremely potent inhibitors of AdoHcy hydrolase. The 6'β-fluoro-**10** was the most potent with an IC_{50} of 8 nM while the 6'α-fluoro-**24** was approximately 20 times less inhibitory (IC_{50} = 180 nM). Midway between the activities of the fluoro analogues was the 6'-methylene-**30** (IC_{50} = 80 nM). The weakest inhibitor of this group was the 6'α-hydroxy analogue **14** (IC_{50} = 28 μM). The control compound, adenosine dialdehyde, produced an IC_{50} of 40 nM in this assay.

Three of the analogues examined, **10**, **24**, and **30**, inhibit AdoHcy hydrolase at similar concentrations to adenosine dialdehyde. This places them among the most potent inhibitors of this enzyme such as neoplanocin A, 3-deazaneplanocin A, and 3-deazaaristeromycin.

The superior enzyme inhibition shown by compounds **10**, **24**, and **30** may be a result of the 6'-substituent facilitating the enzymatically induced formation of a reactive intermediate capable of binding covalently to the enzyme. The two fluoro epimers, **10** and **24**, once oxidized at the 3'-position by enzyme-associated NAD, should easily undergo fluoride elimination[20] to give **34** (Scheme V). This is the same intermediate produced by the action of AdoHcy hydrolase on neplanocin,[17,19] an irreversible inhibitor of the enzyme. The fluoro analogues, however, may be better initial substrates than neplanocin for AdoHcy hydrolase because the 4'-carbon is sp^3 like adenosine rather than sp^2 as in neplanocin A. In the case of the 6'-methylene-**30**, NAD oxidation at 3' could be followed by a rearrangement to afford the reactive species **35**.[30]

The same mechanistic rationale may explain the poor inhibition shown by compound **14**. The 6'-hydroxyl of **14** would not be expected to eliminate as easily as a fluorine, and, therefore, the intermediate **34** may not form.

Although AdoHcy hydrolase inhibition by the analogues ranged from excellent to moderate, their antiherpetic activity was uniformly poor. In fact, there appears to be no correlation between enzyme inhibition and herpes virus inhibition in this study. This is not surprising in light of the fact that the antiviral activity of most AdoHcy hydrolase inhibitors is confined to viruses such as vaccinia, vasicular stomatitis, and reo.[31] Only a few examples of AdoHcy hydrolase inhibitors that are active against herpes viruses exist. These include 5'-deoxy-5'-*S*-isobutyladenosine (SIBA)[32] aristeromycin,[6c] and Ara-A.[6c] The latter drug undoubtedly exerts its antiherpetic effects via a mechanism other than AdoHcy hydrolase inhibition. The other two may also act through a different mechanism.

In contrast to the results with herpes viruses, the AdoHcy hydrolase inhibition shown by these compounds parallels their antivaccinia virus potency. This would be expected since vaccinia virus encodes methyltransferases which are involved in the 5'-capping of viral mRNA.[33] Interference with this capping by inhibitors of AdoHcy hydrolase should impede virus replication. Other investigators[6a,31] have shown that a close correlation exists between the potency of a series of AdoHcy hydrolase inhibitors and their antiviral activity against vesicular stomatitus virus (VSV). Like vaccinia, VSV encodes its own methyltransferases and requires methylated mRNA for replication.

In summary, a number of new carbocyclic adenosine analogues have been shown to be potent inhibitors of AdoHcy hydrolase. These compounds efficiently repress vaccinia virus replication but lack significant antiherpetic activity. A detailed investigation of the enzyme inhibition produced by these compounds will be published elsewhere.

Experimental Section

General Methods. Nuclear magnetic resonance spectra were recorded on a Bruker WM-300 (^{1}H NMR, 300 MHz) spectrometer, and chemical shifts are reported in parts per million downfield from internal tetramethylsilane.[21] Mass spectra (MS) were recorded on Finnigan MAT CH7 and MAT 311A spectrometers operating in the direct inlet mode. UV spectra were recorded on a Hewlett-Packard 8450A spectrophotometer. Elemental analyses were obtained by Syntex Analytical Research. Column chromatography utilized 70–230-mesh silica gel 60 from E. Merck, while preparative thin-layer chromatography was performed on 20 × 20 cm, silica gel GF plates from Analtech. Melting points were determined on a hot-stage microscope and are corrected.

(±)-(1β,2α,3α,4β,5β)-2,3-(Dimethylmethylenedioxy)-5-fluoro-4-[(phenylmethoxy)methyl]-1-cyclopentyl Azide (4). A solution of **2**[22] (6.38 g, 20.0 mmol), trifluoromethanesulfonic anhydride (3.80 mL, 22.6 mmol), and pyridine (2.7 mL, 29 mmol) in CH_2Cl_2 (30 mL) was kept at room temperature for 1 h. The solution was diluted with CH_2Cl_2 (60 mL), washed with 0.1 N $NaHCO_3$ and H_2O, dried (Na_2SO_4), and evaporated. To a solution of the residue in THF (40 mL) was added TASF (6.9 g, 25 mmol). After 14 h at room temperature, the mixture was poured onto ice (400 g) and extracted with EtOAc (600 mL). The extract was washed with H_2O, dried (Na_2SO_4), and concentrated to an oil, which was purified by column chromatography (1:19 EtOAc/hexane) to give 5.14 g (80%) of **4** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.26–7.36 (m, 5 H, Ph), 5.20 (ddd, 1 H, 6), 4.69 (dd, 1 H, 2), 4.56 (s, 2 H, benzylic), 4.49 (ddd, 1 H, 3), 3.66–3.68 (m, 3 H, 1 and 5), 2.40–2.59 (m, 1 H, 4), 1.51 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3). Anal. ($C_{16}H_{20}FN_3O_3$) C, H, N.

(±)-(1β,2α,3α,4β,5β)-2,3-(Dimethylmethylenedioxy)-5-fluoro-4-[(phenylmethoxy)methyl]-1-cyclopentanamine (5). A mixture of **4** (5.0 g, 16 mmol) and Lindlar catalyst (0.50 g) in MeOH (70 mL) was shaken under H_2 (1 atm) for 48 h. After filtration, the mixture was evaporated to dryness, and the residue was purified by column chromatography (1:19 CH_3OH/CH_2Cl_2) to give 2.59 g (56%) of **5** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.29–7.36 (m, 5 H, Ph), 4.99 (ddd, 1 H, 6), 4.57 (s, 2 H, benzylic), 4.43 (dd, 1 H, 3), 4.35 (dd, 1 H, 2), 3.66 (d, 2 H, 5), 3.30 (ddd, 1 H, 1), 2.46 (m, 1 H, 4), 1.55 (s, 2 H, NH_2), 1.50 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3). Anal. ($C_{16}H_{22}FNO_3$) C, H, N.

(±)-(1β,2α,3α,4β,5β)-1-[(5-Amino-6-chloro-4-pyrimidinyl)-amino]-2,3-(dimethylmethylenedioxy)-5-fluoro-4-[(phenylmethoxy)methyl]cyclopentane (6). A solution of **5** (4.00 g, 13.6 mmol), 5-amino-4,6-dichloropyrimidine (4.46 g, 27.2 mmol), and triethylamine (14 mL, 0.1 mmol) in *n*-BuOH (15 mL) was heated at 105 °C under N_2 for 48 h. The solvent was evaporated, and a solution of the residue in EtOAc was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and reevaporated. Purification of the residue by column chromatography (2:3 EtOAc/hexane) and then

(30) We wish to thank a referee for bringing this structure to our attention.

(31) De Clercq, E. *Biochem. Pharmacol.* **1987**, *36*, 2567.
(32) Jacquemont, B.; Huppert, J. *J. Virol.* **1977**, *22*, 160.
(33) Martin, S. A.; Moss, B. *J. Biol. Chem.* **1975**, *250*, 9330.

crystallization from EtOAc/hexane left 3.55 g (62%) of **6**: mp 172–173 °C; UV λ_{max} (MeOH) 264 nm (ϵ 8480), 298 (9850); ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1 H, 2), 7.30–7.40 (m, 5 H, Ph), 5.45 (d, 1 H, NH), 5.32 (ddd, 1 H, 6′), 4.75–4.89 (m, 1 H, 1′), 4.52–4.64 (m, 4 H, 2′,3′ and benzylic), 3.71 (m, 2 H, 5′), 3.31 (br s, 2 H, NH_2), 2.64 (m, 1 H, 4′), 1.54 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3). Anal. ($C_{20}H_{24}ClFN_4O_3$) C, H, N.

(±)-(1β,2α,3α,4β,5β)-1-(6-Chloro-9*H*-purin-9-yl)-2,3-(dimethylmethylenedioxy)-5-fluoro-4-[(phenylmethoxy)methyl]cyclopentane (7). A solution of **6** (3.0 g, 7.1 mmol) in diethoxymethyl acetate (10 mL) was heated at reflux for 12 h and then evaporated to dryness. The residue was purified by column chromatography (3:7 EtOAc/hexane) and crystallized from EtOAc/hexane to give 2.40 g (78%) of **7**: mp 145–146 °C; UV λ_{max} (MeOH) 264 nm (ϵ 8150); ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1 H, 2), 8.34 (d, 1 H, 8), 7.30–7.37 (m, 5 H, Ph), 5.40 (ddd, 1 H, 6′), 5.14–5.27 (m, 2 H, 1′ and 2′), 4.66 (dd, 1 H, 3′), 4.59 (s, 2 h, benzylic), 3.76 (d, 2 H, 5′), 2.80 (m, 1 H, 4′), 1.60 (s, 3 H, CH_3) 1.35 (s, 3 H, CH_3). Anal. ($C_{21}H_{22}ClFN_4O_3$) C, H, N.

(±)-(1β,2α,3α,4β,5β)-1-Adenin-9-yl-2,3-(dimethylmethylenedioxy)-5-fluoro-4-[(phenylmethoxy)methyl]cyclopentane (8). A solution of **7** (2.0 g, 4.6 mmol) in methanolic ammonia (20 mL, saturated at 0 °C) was heated in a Parr bomb at 90 °C for 12 h. The solvent was removed by evaporation, and the residue was chromatographed (1:99 MeOH/CH_2Cl_2) and then crystallized from EtOAc/hexane to give 1.13 g (59%) of **8**: mp 178–179 °C; UV λ_{max} (MeOH) 259 nm (ϵ 15100); ^{1}H NMR (Me_2SO-d_6) δ 8.27 (d, 1 H, 8), 8.17 (s, 1 H, 2), 7.35 (m, 5 H, Ph), 7.30 (s, 2 H, NH_2), 5.47 (dd, 1 H, 2′), 5.29 (ddd, 1 H, 6′), 5.06 (ddd, 1 H, 1′), 4.64 (dd, 1 H, 3′), 4.54 (s, 2 H, benzylic), 3.67 (m, 2 H, 5′), 2.79 (m, 1 H, 4′), 1.50 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3). Anal. ($C_{21}H_{24}FN_5O_3$) C, H, N.

(±)-(1α,2α,3β,4β,5β)-3-Adenin-9-yl-4-fluoro-5-(hydroxymethyl)-1,2-cyclopentanediol (10). A solution of **8** (0.80 g, 1.9 mmol) and 20% $Pd(OH)_2$/C (0.80 g) in cyclohexene (6 mL) and EtOH (10 mL) was heated at reflux for 48 h and then filtered through Celite. The filtrate was evaporated to dryness, and the residue was purified by column chromatography (1:9 CH_3OH/CH_2Cl_2) and crystallized from EtOAc to give 0.50 g (80%) of **9** (mp 132–133 °C). A solution of **9** (100 mg, 0.310 mmol) in 10% HCl (3.0 mL) was heated at 70 °C for 0.25 h and then evaporated to dryness. The residue was coevaporated with 0.5 N NH_4OH (10 mL) and then crystallized from H_2O to give 80 mg (91%) of **10**: mp 280–281 °C; UV λ_{max} (H_2O) 258 nm (ϵ 12100); ^{1}H NMR (Me_2SO-d_6) δ 8.20 (s, 1 H, 8), 8.15 (s, 1 H, 2), 7.24 (br s, 2 H, NH_2), 5.20 (d, J = 5 Hz, 1 H, OH), 5.12 (ddd, $J_{1',6'} = J_{4',6'}$ = 3 Hz, $J_{6',F}$ = 57 Hz, 1 H, 6′), 4.96 (d, J = 4 Hz, 1 H, OH), 4.83 (ddd, $J_{1',2'}$ = 10 Hz, $J_{1',6'}$ = 3 Hz, $J_{1',F}$ = 30 Hz, 1 H, 1′), 4.62–4.71 (m, 1 H, 2′), 3.83 (m, 1 H, 3′), 3.61 (m, 2 H, 5′), 2.33 (m, 1 H, 4′); MS 283 (M^+), 135 (base). Anal. ($C_{11}H_{14}FN_5O_3$) C, H, N.

(1α,2α,3β,4α,5α)-2,4-Bis(*p*-anisyldiphenylmethoxy)-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane (11). A solution of **1**[22] (2.36 g, 10.0 mmol), *p*-anisylchlorodiphenylmethane (9.26 g, 30.0 mmol), triethylamine (10 mL), and 4-(dimethylamino)pyridine (366 mg, 3 mmol) in dry CH_2Cl_2 (50 mL) was stirred at room temperature for 3 days. More *p*-anisylchlorodiphenylmethane (4.63 g, 15.0 mmol) was added, and stirring was continued for another 2 days before evaporation of solvents. The residue was purified by column chromatography (1:4 EtOAc/hexane) to give **11** as a gum, which was then precipitated from hot EtOH, affording 4.43 g (57%) of **11** as an amorphous white solid: ^{1}H NMR ($CDCl_3$) δ 6.74–7.57 (m, 33 H, Ph), 4.03 (s, 2 H, benzylic), 3.69 (s, 6 H, OCH_3's), 3.65 (d, 2 H, 5), 3.51 (d, 2 H, 3 and 6), 2.40 (ddt, 1 H, 4), 2.26 (s, 2 H, 1 and 2). Anal. ($C_{53}H_{48}O_6$) C, H.

(±)-(1α,2β,3α,4β,5α)-2-Adenin-9-yl-3,5-bis(*p*-anisyldiphenylmethoxy)-4-[(phenylmethoxy)methyl]-1-cyclopentanol (12). A mixture of **11** (1.56 g, 2.00 mmol), adenine (540 mg, 4.00 mmol), and K_2CO_3 (552 mg, 4.00 mmol) in Me_2SO (20 mL) was stirred and heated at 140 °C under N_2 for 4 days. The resulting black mixture was diluted with EtOAc (150 mL) and washed with brine (3 × 80 mL). After drying ($MgSO_4$), the solvent was removed in vacuo, and the residue was purified by column chromatography (4% MeOH in 1:9 acetone/CH_2Cl_2). Crystallization of the product from CH_2Cl_2/hexane afforded 578 mg (32%) of **12**: mp 218–219 °C; UV λ_{max} (EtOH) 263 nm (ϵ 16900); ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1 H, 8), 6.81–7.70 (m, 36 H, 2, NH_2, and Ph), 6.40 (d, 1 H, Ar), 5.48 (m, 1 H, 1′), 4.36 (m, 1 H, 2′), 4.12 (dd, 1 H, 6′), 4.05 (d, 1 H, benzylic), 3.93 (d, 1 H, benzylic), 3.92 (s, 1 H, 3′), 3.75 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.39 (dd, 1 H, 5′), 1.65 (dd, 1 H, 5′), 0.92 (br s, 1 H, 4′). Anal. ($C_{58}H_{53}N_5O_6$) C, H, N.

(±)-(1α,2α,3β,4α,5β)-3-Adenin-9-yl-5-[(phenylmethoxy)methyl]-1,2,4-cyclopentanetriol (13). A solution of **12** (500 mg, 0.546 mmol) in HCOOH (2 mL), MeOH (2 mL), and CH_2Cl_2 (4 mL) was kept at room temperature for 3 h before being evaporated to dryness. The residue was purified on a short (8 cm) chromatography column (CH_2Cl_2, and then 15% CH_3OH in CH_2Cl_2) to give a crystalline solid, which was recrystallized from 50% EtOH, affording 189 mg (93%) of **13**: mp 230–231 °C; UV (0.1 N HCl) λ_{max} 259 nm (ϵ 14600); ^{1}H NMR (Me_2SO-d_6) δ 8.10 and 8.09 (s, 2 H, 2 and 8), 7.26–7.42 (m, 5 H, Ph), 7.14 (s, 2 H, NH_2), 5.26 (d, 1 H, OH), 4.94 (d, 1 H, OH), 4.76 (d, 1 H, OH), 4.55 (s, 2 H, benzylic), 4.46 (dd, 1 H, 1′), 4.38 (m, 1 H, 2′), 4.30 (m, 1 H, 3′), 3.91 (m, 1 H, 6′), 3.59 (m, 2 H, 5′), 1.99 (m, 1 H, 4′). Anal. ($C_{18}H_{21}N_5O_4$) C, H, N.

(±)-(1α,2α,3β,4α,5β)-3-Adenin-9-yl-5-(hydroxymethyl)-1,2,4-cyclopentanetriol Hemihydrate (14). A mixture of **13** (148 mg, 0.400 mmol) and 20% $Pd(OH)_2$/C (100 mg) in cyclohexene (2 mL), EtOH (6 mL), and H_2O (3 mL) was heated at reflux for 7 h and then filtered through Celite. After removal of the solvents by evaporation, the residue was crystallized from H_2O to give 103 mg (89%) of **14**: mp 240–241 °C; UV λ_{max} (0.1 N HCl) 258 nm (ϵ 14000); λ_{max} (0.1 N NaOH) 261 (ϵ 14400); ^{1}H NMR (Me_2SO-d_6) δ 8.10 and 8.11 (s, 2 H, 2 and 8), 7.14 (s, 2 H, NH_2), 5.16 (d, J = 6 Hz, 1 H, OH), 4.91 (d, J = 7 Hz, 1 H, OH), 4.65 (m, 2 H, OH's), 4.48 (dd, $J_{1',2'} = J_{1',6'}$ = 9 Hz, 1 H, 1′), 4.31 (m, 1 H, 2′), 4.18 (m, 1 H, 3′), 3.88 (m, 1 H, 6′), 3.47–3.63 (m, 2 H, 5′), 1.82 (m, 1 H, 4′), MS 282 $(M + H)^+$. Anal. ($C_{11}H_{15}N_5O_4 \cdot {}^1/_2H_2O$) C, H, N.

(±)-(1α,2α,3β,4α,5α)-2-(*p*-Anisyldiphenylmethoxy)-4-hydroxy-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane (15). A solution of **1**[22] (12 g, 51 mmol) and *p*-anisylchlorodiphenylmethane (21.4 g, 69 mmol) in dry pyridine (300 mL) was stirred at room temperature for 2 days. After removal of the pyridine by evaporation, the residue was dissolved in CH_2Cl_2 and washed with 0.1 N hydrochloric acid followed by saturated $NaHCO_3$ solution. After the organic phase was dried ($MgSO_4$) and evaporated, the residue was purified by column chromatography (1:3 EtOAc/hexane) to give 15.5 g (60%) of **15** as a foam: ^{1}H NMR (Me_2SO-d_6) δ 6.87–7.53 (m, 19 H, Ph), 5.06 (d, 1 H, OH), 4.30 (s, 2 H, benzylic), 3.70 (s, 3 H, OCH_3), 3.65–3.68 (m, 2 H, 3 and 6), 3.56 (br s, 2 H, 5), 3.19 (dd, 1 H, 1), 2.16 (d, 1 H, 2), 1.83 (m, 1 H, 4). Anal. ($C_{33}H_{32}O_5$) C, H.

(±)-(1α,2α,3β,4β,5α)-2-(*p*-Anisyldiphenylmethoxy)-4-(benzoyloxy)-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane (17). A solution of trifluoromethanesulfonic anhydride (0.46 mL, 2.7 mmol) in CH_2Cl_2 (10 mL) was slowly added with stirring to an ice-cold solution of **15** (1.15 g, 2.26 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.60 g, 2.7 mmol) in CH_2Cl_2 (30 mL). The solution was stirred for 10 min at 0 °C and then for 45 min at room temperature, before being poured into an equal volume of cold, saturated $NaHCO_3$ solution. The organic phase was separated, washed with H_2O, dried ($MgSO_4$), and evaporated, leaving the triflate intermediate as a syrup. A solution of the syrup and lithium benzoate (0.90 g, 7.0 mmol) in DMF (20 mL) was stirred at room temperature for 3 h. After evaporation of solvent, the residue was taken up in CH_2Cl_2, filtered, and reevaporated. Column chromatography (1:4 EtOAc/hexane) of the residue afforded a foam, which crystallized from EtOAc/hexane to give 0.87 g (63%) of **17**: mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 6.83–7.82 (m, 24 H, Ph), 5.57 (d, 1 H, 6), 4.37 (d, 1 H, benzylic), 4.27 (d, 1 H, benzylic), 3.87 (dd, 1 H, 3), 3.79 (s, 3 H, OCH_3), 3.54 (dd, 1 H, 5), 3.41 (dd, 1 H, 5), 3.40 (d, 1 H, 1), 2.68 (m, 1 H, 4), 2.52 (d, 1 H, 2). Anal. ($C_{40}H_{36}O_6$) C, H.

(±)-(1α,2α,3β,4β,5α)-2-(*p*-Anisyldiphenylmethoxy)-4-hydroxy-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane (18). To a solution of **17** (1.50 g, 2.45 mmol) in dioxane (15 mL) was added a solution of ammonia in methanol (saturated at 0 °C, 70 mL) and concentrated ammonium hydroxide (10 mL). The resulting milky solution was stirred at room temperature for 3.5 days, during which time the solution clarified. After evapo-

ration of solvents, the residue was chromatographed (1:4 EtOAc/hexane and then 2:3 EtOAc/hexane) to affordd 1.17 g (94%) of 18 as a white foam: ^{1}H NMR ($CDCl_3$) δ 6.82–7.58 (m, 19 H, Ph), 4.28–4.38 (m, 3 H, 6 and benzylic), 4.02 (dd, 1 H, 3), 3.78 (m, 4 H, 5 and OCH_3), 3.61 (dd, 1 H, 5), 3.93 (d, 1 H, OH), 3.26 (d, 1 H, 1), 2.59 (d, 1 H, 2), 2.31 (m, 1 H, 4). Anal. ($C_{33}H_{32}O_5$) C, H.

(±)-(1α,2α,3β,4α,5α)-2-(p-Anisyldiphenylmethoxy)-4-fluoro-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexane (20). A solution of trifluoromethanesulfonic anhydride (0.41 mL, 2.4 mmol) in dichloromethane (10 mL) was slowly added with stirring to an ice-cold solution of 18 (1.02 g, 2.00 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.60 g, 2.7 mmol) in dichloromethane (30 mL). After being stirred at 0 °C for 10 min and at room temperature for 30 min, the reaction mixture was washed with cold saturated $NaHCO_3$ solution and then H_2O. The organic phase was dried ($MgSO_4$), and the solvent evaporated, leaving the triflate intermediate as a colorless syrup. This syrup and tetrabutylammonium fluoride trihydrate (3.0 g, 9.5 mmol) were dissolved in dry THF and kept at room temperature for 3 h before the solvent was removed by evaporation. The residue was dissolved in toluene, washed with H_2O, and reevaporated to a syrup, which was purified by column chromatography (1:9 EtOAc/hexane and then 1:4 EtOAc/hexane) to give 763 mg (74%) of **20** as a foam: ^{1}H NMR ($CDCl_3$) δ 6.82–7.60 (m, 19 H, Ph), 4.79 (dd, 1 H, 6), 4.28 (s, 2 H, benzylic), 3.82 (d, 1 H, 3), 3.75 (s, 3 H, OCH_3), 3.62 (dd, 1 H, 5), 3.53 (dd, 1 H, 5), 3.39 (br s, 1 H, 1), 2.51 (br s, 1 H, 2), 2.33 (m, 1 H, 4). Anal. ($C_{33}H_{31}O_4F$) C, H.

(±)-(1α,2β,3α,4β,5α)-2-Adenin-9-yl-5-(p-anisyldiphenylmethoxy)-3-fluoro-4-[(phenylmethoxy)methyl]-1-cyclopentanol (21), (±)-(1α,2β,3α,4β,5α)-2-Adenin-9-yl-3-(p-anisyldiphenylmethoxy)-5-fluoro-4-[(phenylmethoxy)methyl]-1-cyclopentanol (22), and (±)-(1α,4β,5α)-2-Adenin-9-yl-5-(p-anisyldiphenylmethoxy)-4-[(phenylmethoxy)methyl]-2-cyclopenten-1-ol (23). A solution of **20** (511 mg, 1.00 mmol), adenine (270 mg, 2.00 mmol), and K_2CO_3 (276 mg, 2.00 mmol) in Me_2SO (10 mL) was heated at 135 °C for 6 h. After dilution with EtOAc (50 mL), the mixture was washed repeatedly with brine, dried ($MgSO_4$), and evaporated to a foam. The foam was chromatographed on thin layer (1 mm) silica gel preparative plates with 5% MeOH in CH_2Cl_2 containing 1% concentrated NH_4OH as eluent. Three major bands were isolated. The most polar isolate was **22**, which crystallized from EtOAc/hexane (106 mg, 16%): mp 188–189 °C; UV λ_{max} (MeOH) 234 nm (ε 14 800), 262 (12 400); ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1 H, 8), 6.45–7.33 (m, 20 H, 2 and Ph), 5.57 (br s, 2 H, NH_2), 4.95 (dd, 1 H, 1'), 4.93 (dd, 1 H, 3'), 4.73 (dd, 1 H, 2'), 4.56 (dd, 1 H, 6'), 4.33 (d, 1 H, benzylic), 4.24 (d, 1 H, benzylic), 3.66 (s, 3 H, OCH_3), 3.19 (dd, 1 H, 5'), 2.70 (m, 2 H, 4' and 5'). Anal. ($C_{38}H_{36}FN_5O_4$) C, H, N.

The middle band was **21** and crystallized from EtOAc/hexane to give 202 mg (31%): mp 167–169 °C; UV λ_{max} (MeOH) 234 nm (ε 15 900), 262 (15 600); ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1 H, 8), 7.79 (s, 1 H, 2), 6.79–7.58 (m, 19 H, Ph), 5.70 (br s, 2 H, NH_2), 5.16 (ddd, 1 H, 6'), 5.11 (dd, 1 H, 1'), 4.31 (m, 4 H, 2', 3', and benzylic), 3.76 (s, 3 H, OCH_3), 3.28 (dd, 1 H, 5'), 3.12 (dd, 1 H, 5'), 2.04 (m, 1 H, 4'). Anal. ($C_{38}H_{36}FN_5O_4$) C, H, N.

The least polar isolate was the olefin **23**, which crystallized from EtOAc/hexane to give 20 mg (3%): mp 100–101 °C; UV λ_{max} (MeOH) 231 nm (ε 33 800); ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1 H, 8), 8.03 (s, 1 H, 2), 6.53–7.55 (m, 19 H, Ph), 5.63 (br s, 2 H, NH_2), 4.22–4.33 (m, 5 H, 2', 3', 6' and benzylic), 3.79 (s, 3 H, OCH_3), 3.67 (br s, 1 H, OH), 3.38 (dd, 1 H, 5'), 3.16 (dd, 1 H, 5'), 3.04 (br s, 1 H, 4'). Anal. ($C_{38}H_{35}N_5O_4$) C, H, N.

(±)-(1α,2α,3β,4α,5β)-3-Adenin-9-yl-4-fluoro-5-(hydroxymethyl)-1,2-cyclopentanediol (24). A solution of **21** (150 mg, 0.23 mmol) in MeOH (2 mL), $CHCl_3$ (1 mL), and formic acid (1 mL) was kept at room temperature for 24 h. After evaporation of solvents, the residue was dissolved in MeOH and extracted repeatedly with hexane. The MeOH phase was evaporated to a syrup, which was heated at 80 °C for 5.5 h with EtOH (1 mL), cyclohexene (0.5 mL), and 20% palladium hydroxide on carbon (150 mg). The filtered reaction mixture was applied directly to preparative, silica gel thin layer plates, which were eluted with 1:4 MeOH/$CHCl_3$. The major band was isolated and crystallized from H_2O/EtOH to give 56 mg (85%) of **24**: mp 224–225 °C; UV λ_{max} (0.1 N HCl) 258 nm (ε 14 000), λ_{max} (0.1 N NaOH) 260 nm (ε 14 200); ^{1}H NMR (Me_2SO-d_6) δ 8.23 (s, 1 H, 8), 8.12 (s, 1 H, 2), 7.23 (br s, 2 H, NH_2), 5.29 (ddd, $J_{1',6'}$ = 7 Hz, $J_{4',6'}$ = 5 Hz, $J_{F,6'}$ = 55 Hz, 1 H, 6'), 5.22 (d, J = 7 Hz, 1 H, 2'-OH), 5.03 (d, J = 4 Hz, 1 H, 3'-OH), 4.98 (ddd, $J_{1',2'}$ = 10 Hz, $J_{1',6'}$ = 7 Hz, $J_{1',F}$ = 21 Hz, 1 H, 1'), 4.96 (s, 1 H, 5'-OH), 4.38 (m, 1 H, 2'), 3.87 (br s, 1 H, 3'), 3.61 (m, 2 H, 5'), 2.17 (m, 1 H, 4'); MS 284 $(M + H)^+$. Anal. ($C_{11}H_{14}FN_5O_3$) C, H, N.

(±)-(1α,2β,3α,4α,5β)-2-Adenin-9-yl-4-fluoro-5-(hydroxymethyl)-1,3-cyclopentanediol (25). Compound **22** (75 mg, 0.116 mmol) was deprotected as described for **21**, with the exception that chromatography was unnecessary. The final filtered solution was evaporated to a solid, which was crystallized from 80% EtOH affording 24 mg (73%) of **25**: mp 237–238 °C; UV λ_{max} (0.1 N HCl) 259 nm (ε 15 600), λ_{max} (0.1 N NaOH) 260 nm (ε 14 100); ^{1}H NMR (Me_2SO-d_6) δ 8.15 (s, 1 H, 8), 8.11 (s, 1 H, 2), 7.18 (br s, 2 H, NH_2), 5.45 (m, 2 H, 2' and 6' OH), 4.95 (t, J = 5 Hz, 1 H, 5'-OH), 4.78 (dd, $J_{2',3'}$ = 4 Hz, $J_{3',F}$ = 55 Hz, 1 H, 3'), 4.50 (m, 2 H, 1' and 2'), 4.22 (m, 1 H, 6'), 3.65 (m, 1 H, 5'), 3.48 (m, 1 H, 5'), 2.07 (m, 1 H, 4'); MS 284 $(M + H)^+$. Anal. ($C_{11}H_{14}FN_5O_3$) C, H, N.

(±)-(1α,3β,4α,5α)-4-(p-Anisyldiphenylmethoxy)-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]hexan-2-one (26). Methylphosphonic acid (400 mg, 3.0 mmol) was added to a 0 °C solution of **15** (15.5 g, 30.5 mmol) and 1,3-dicyclohexylcarbodiimide (25.0 g, 121 mmol) in Me_2SO (150 mL). After the mixture was stirred for 16 h at room temperature, a solution of oxalic acid (20 g) in H_2O (200 mL) was added, and stirring was continued for 2 h. The mixture was filtered, and the filtrate was diluted with EtOAc (400 mL) and extracted 3 times with brine. The EtOAc phase was dried ($MgSO_4$) and chromatographed (3:1 hexane/EtOAc) to afford 13.0 g (84%) of **26** as a white foam. An analytical sample was prepared by crystallization from MeOH: mp 50–52 °C; ^{1}H NMR ($CDCl_3$) δ 6.83–7.61 (m, 19 H, Ph), 4.35 (dd, 1 H, 3), 4.25 (s, 2 H, benzylic), 3.84 (dd, 1 H, 5), 3.77 (s, 3 H, OCH_3), 3.48 (dd, 1 H, 5), 3.23 (d, 1 H, 1), 2.71 (ddd, 1 H, 4), 2.62 (br s, 1 H, 2). Anal. ($C_{33}H_{30}O_5 \cdot {}^1/_2H_2O$) C, H.

(±)-(1α,3β,4α,5α)-4-(p-Anisyldiphenylmethoxy)-2-methylene-3-[(phenylmethoxy)methyl]-6-oxabicyclo[3.1.0]-hexane (27). To a solution of methyltriphenylphosphonium bromide (1.45 g, 4.0 mmol) in THF (20 mL) at −78 °C and under N_2 was added *n*-butyllithium (2.7 mL of 1.6 M in hexanes, 4.3 mmol). The solution was brought to room temperature, kept at 21 °C for 20 min, and then recooled to −78 °C. To this cold solution was slowly added a solution of **26** (1.03 g, 2.0 mmol) in THF (10 mL). After allowing the mixture to come to room temperature, it was diluted with H_2O (50 mL) and extracted with Et_2O. The ether extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (1:3 EtOAc/hexane) to give 580 mg (57%) of **27** as a foam: ^{1}H NMR ($CDCl_3$) δ 6.81–7.60 (m, 19 H, Ph), 5.25 (d, 1 H, =CH), 5.06 (d, 1 H, =CH), 4.37 (d, 1 H, benzylic), 4.24 (d, 1 H, benzylic), 3.79 (d, 1 H, 3), 3.77 (s, 3 H, OCH_3), 3.60 (dd, 1 H, 5), 3.48 (d, 1 H, 1), 3.41 (d, 1 H, 5), 2.75 (m, 1 H, 2), 2.70 (m, 1 H, 4). Anal. ($C_{34}H_{32}O_4$) C, H.

(±)-(1α,2β,4β,5α)-2-Adenin-9-yl-5-(p-anisyldiphenylmethoxy)-3-methylene-4-[(phenylmethoxy)methyl]-1-cyclopentanol (28). A suspension of adenine (4.42 g, 32.7 mmol) and sodium hydride (50% oil dispersion, 1.05 g, 21.9 mmol) in DMF (50 mL) was heated with stirring at 120 °C for 15 min. The epoxide **27** (5.50 g, 10.9 mmol) was added, and heating was continued for 2 h, before the mixture was cooled to room temperature and the solvent evaporated off. A filtered solution of the residue in CH_2Cl_2 was concentrated by evaporation and purified by column chromatography (EtOAc) to give 5.20 g (74%) of **28** as a foam: UV λ_{max} (MeOH) 233 nm (ε 17 700), 260 (16 300); ^{1}H NMR (Me_2SO-d_6) δ 8.13 (s, 1 H, 8), 7.95 (s, 1 H, 2), 6.84–7.64 (m, 19 H, Ph), 5.69 (d, 1 H, OH), 5.52 (d, 1 H, 1'), 4.85 (br s, 1 H, =CH), 4.60 (m, 1 H, 2'), 4.46 (br s, 1 H, =CH), 4.27 (s, 2 H, benzylic), 4.08 (d, 1 H, 3'), 3.73 (s, 3 H, OCH_3), 3.19 (m, 2 H, 5'), 1.75 (br s, 1 H, 4'). Anal. ($C_{39}H_{37}N_5O_4$) C, H, N.

(±)-(1α,2α,3β,5β)-3-Adenin-9-yl-4-methylene-5-[(phenylmethoxy)methyl]-1,2-cyclopentanediol (29). A solution of **28** (4.50 g, 7.03 mmol) in 80% acetic acid (50 mL) was stirred at room temperature for 4.5 h. After the solvent was removed by evaporation, the residue was chromatographed (1:9 MeOH/CH_2Cl_2) to furnish 1.60 g (62%) of **29** after crystallization from EtOAc:

mp 173–174 °C; UV λ_{max} (MeOH) 260 nm (ϵ 14 800); ^{1}H NMR (Me_2SO-d_6) δ 8.06 (s, 1 H, 8), 8.05 (s, 1 H, 2), 7.30 (m, 5 H, Ph), 7.17 (br s, 2 H, NH_2), 5.23 (d, 1 H, 1′), 5.15 (d, 1 H, OH), 5.04 (d, 1 H, OH), 4.95 (br s, 1 H, =CH), 4.48 (m, 4 H, 2′, =CH, and benzylic), 3.99 (br s, 1 H, 3′), 3.61 (m, 2 H, 5′), 2.78 (br s, 1 H, 4′). Anal. ($C_{19}H_{21}N_5O_3$) C, H, N.

(±)-(1α,2α,3β,5β)-3-Adenin-9-yl-5-(hydroxymethyl)-4-methylene-1,2-cyclopentanediol (30). A mixture of **29** (100 mg, 0.272 mmol), palladium hydroxide on carbon (20%, 25 mg), cyclohexene (2 mL), and EtOH (10 mL) was heated at reflux for 1.5 h. After it was cooled and the catalyst filtered off, the solution was evaporated, and the residue was purified with a 2-mm silica gel rotor on a Chromatatron (Harrison Research). Elution with 15% MeOH in CH_2Cl_2 provided 27 mg (27%) of unreacted starting material (**29**) and 26 mg (35%) of **30** as a brittle glass. A portion of the glass was crystallized from EtOAc/MeOH: mp 121–123 °C; UV λ_{max} (0.1 N HCl) 259 nm (ϵ 12 900); ^{1}H NMR (Me_2SO-d_6) δ 8.29 (s, 1 H, 8), 8.16 (s, 1 H, 2), 7.21 (br s, 2 H, NH_2), 5.25 (d, $J_{1',2'}$ = 10 Hz, 1 H, 1′), 5.19 (br s, 1 H, OH), 5.07 (dd, $J_{gem} = J_{4',7'}$ = 2 Hz, 1 H, =CH), 5.03 (br s, 1 H, OH), 4.87 (br s, 1 H, OH), 4.53 (m, 1 H, 2′), 4.49 (dd, $J_{gem} = J_{4',7'}$ = 2 Hz, 1 H, =CH), 4.04 (m, 1 H, 3′), 3.61 (m, 2 H, 5′), 2.63 (m, 1 H, 4′); MS (M^+) 277.117291, calcd for $C_{12}H_{15}N_5O_3$ 277.117489.

(±)-(1β,2α,3α,4β)-1-Adenin-9-yl-2,3-(dimethylmethylenedioxy)-5-methylene-4-[(phenylmethoxy)methyl]cyclopentane (31). Perchloric acid (70%, 0.21 mL) was added to a stirred suspension of **29** (515 mg, 1.40 mmol) in dry acetone (20 mL) and 2,2-dimethoxypropane (20 mL), causing immediate clarification. After 4 h at room temperature, the solution was neutralized by addition of concentrated NH_4OH and evaporated to dryness. The residue was purified by chromatography (1:19 MeOH/CH_2Cl_2) to give 570 mg (100%) of **31** as a foam: UV λ_{max} (MeOH) 260 nm (ϵ 11 300); ^{1}H NMR (Me_2SO-d_6) δ 8.13 (s, 1 H, 8), 8.10 (s, 1 H, 2), 7.30–7.37 (m, 5 H, Ph), 7.26 (br s, 2 H, NH_2), 5.37 (m, 1 H, 1′), 5.12 (br s, 1 H, =CH), 5.07 (dd, 1 H, 2′), 4.69 (dd, 1 H, 3′), 4.57 (s, 1 H, benzylic), 4.56 (d, 1 H, benzylic), 4.49 (br s, 1 H, =CH), 3.72 (m, 2 H, 5′), 3.08 (br s, 1 H, 4′), 1.51 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3).

(±)-(1α,2β,3α,4α,5β)-2-Adenin-9-yl-3,4-(dimethylmethylenedioxy)-1-(hydroxymethyl)-5-[(phenylmethoxy)methyl]-1-cyclopentanol (32). Osmium tetroxide (4 wt % in C_6H_6, 50 μL) and *tert*-butyl hydroperoxide (90%, 0.5 mL) were added, with stirring, to a solution of **31** (570 mg, 1.40 mmol) and tetraethylammonium hydroxide (25 wt % in H_2O, 0.30 mL) in *t*-BuOH (10 mL) and THF (3 mL). After 5 days at room temperature, the reaction mixture was diluted with EtOAc and washed with 1 N aqueous $NaHSO_3$, H_2O, and brine. The dried ($MgSO_4$) EtOAc solution was concentrated by evaporation and purified by column chromatography (6% MeOH in CH_2Cl_2) to give 220 mg (36%) of **32** as an amorphous solid. Also, 123 mg (22%) of unreacted **31** was recovered. **33**: UV λ_{max} (MeOH) 260 nm (ϵ 15 500); ^{1}H NMR (Me_2SO-d_6) δ 8.26 (s, 1 H, 8), 8.13 (s, 1 H, 2), 5.29 (dd, 1 H, 2′), 5.21 (s, 1 H, OH), 5.07 (t, 1 H, OH), 4.84 (d, 1 H, 1′), 4.55 (m, 3 H, 3′ and benzylic), 3.73 (m, 1 H, 5′), 3.57 (m, 1 H, 5′), 3.21 (m, 1 H, C*H*OH), 2.82 (m, 1 H, C*H*OH), 2.62 (m, 1 H, 4′), 1.45 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3). Anal. ($C_{22}H_{27}N_5O_5$) C, H, N.

(±)-(1α,2α,3β,4α,5β)-3-Adenin-9-yl-4,5-bis(hydroxymethyl)-1,2,4-cyclopentanetriol (33). A mixture of **32** (50 mg, 0.11 mmol) and 20% $Pd(OH)_2$/C (15 mg) in cyclohexene (1 mL) and EtOH (5 mL) was heated at reflux for 5 h and then filtered through Celite. The filtrate was concentrated by evaporation to an oil, which was dissolved in 90% trifluoroacetic acid (1 mL). After 0.25 h at room temperature, the solvent was evaporated and the residue was purified by preparative thin-layer chromatography (1:4 MeOH/CH_2Cl_2) to give 5.4 mg (15%) of **33** as an amorphous solid: ^{1}H NMR (Me_2SO-d_6) δ 8.12 (s, 2 H, 2 and 8), 7.26 (br s, 2 H, NH_2), 5.10 (s, 1 H, OH), 4.90 (m, 2 H, OH's), 4.50–4.80 (m, 4 H, 1′, 2′ and OH's), 3.55–3.99 (m, 3 H, 3′ and 5′), 3.23 and 3.01 (m, 2 H, 6′-C*H*$_2$OH), 2.17 (m, 1 H, 4′), NOE subtraction with irradiation at 2.17 (4′H) causes loss of resonances at 3.23 and 3.01 (6′-C*H*$_2$OH); MS (M^+) 311.122345, calcd for $C_{12}H_{17}N_5O_5$ 311.122969.

Biological Methods. AdoHcy hydrolase from rabbit erythrocytes was obtained from Sigma. The assay for enzyme activity measures the formation of [^{3}H]-*S*-adenosylhomocysteine from [^{3}H]adenosine and homocysteine. Enzyme (16 ng) was mixed with 1 μM [8-^{3}H]adenosine, 10 mM homocysteine, 150 mM KH_2PO_4, pH 7.6, 2 mM dithiothreitol, 1 mM EDTA, and test compound in a total volume of 25 μL. After incubation for 7 min at 37 °C, 8 μL of 150 mM HCl was added to each sample to stop the reaction. Fifteen microliters of each sample was spotted on Whatman LHP-KDF high-performance thin-layer chromatography plates, which were then developed in butanol/acetic acid/water at 12:3:5. *S*-Adenosylhomocysteine spots were identified by fluorescence of internal standards, scraped, and counted for tritium. AdoHcy'ase IC_{50} values were extrapolated from drug concentration (−log M) vs percent control inhibition curves (not shown). Each value is the mean of three determinations.

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