Conformationally Locked Nucleoside Analogues. Synthesis of Dideoxycarbocyclic Nucleoside Analogues Structurally Related to Neplanocin C

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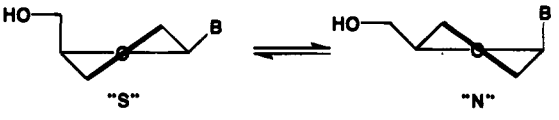
The glycon moiety of nucleosides in solution is known to exist in a rapid dynamic equilibrium between extreme northern and southern conformations as defined by the pseudorotation cycle. The concept of preparing rigid nucleoside analogues with the glycon conformation locked in one of these two extremes was tested with the synthesis of some cyclopropane-fused dideoxycarbocyclic nucleosides, similar to the well-known class of anti-HIV active dideoxynucleosides. The new compounds described here are dideoxynucleoside analogues of the fermentation product neplanocin C (**6**) which exhibits a typical northern geometry for its 6-oxabicyclo[3.1.0]hexane pseudosugar moiety. However, in view of the lability of the epoxide ring in this system, the equivalent cyclopropane-fused bicyclo[3.1.0]hexane system was used instead to prepare the corresponding dideoxynucleoside analogues bearing all the common bases [(±)-**9**–**13**]. Due to the well-documented preference of unrestricted bicyclo[3.1.0]hexane systems to exist exclusively in a boat conformation, the resulting nucleosides are structurally locked in a typical northen conformation similar to that of neplanocin C. The locked northern conformation in these nucleosides remained unchanged in solution in the 20–80 °C temperature range according to variable temperature ^{1}H NMR studies. For the synthesis of these compounds, racemic *trans*-1-[(benzyloxy)methyl]-4-hydroxybicyclo[3.1.0]hexane [(±)-**18**] was prepared by a samarium-promoted cyclopropanation reaction with the antecedent cyclopentenol. All of the bases were incorporated under Mitsunobu conditions and converted to the desired final products following a standard methodology. Anti-HIV evaluation revealed that only the adenosine analogue (±)-**9** possessed enough activity to warrant resolution into its optical antipodes. This was realized by chiral HPLC chromatography to give the individual enantiomers (−)-**32** and (+)-**33**. Adenosine deaminase was used to identify isomer (+)-**33** as the enantiomer with the "natural" configuration which was solely responsible for the observed biological activity and toxicity of (±)-**9**. It is possible that the exclusive northern conformation adopted by these nucleosides reduces their substrate affinity for the various activating kinases, except in the case of the adenosine analogue.

Introduction

The anti-HIV activity of dideoxynucleosides is often modulated by the nature and stereochemical disposition of specific functional groups on the sugar moiety.[1] Such functional groups have a profound effect on the conformation and puckering of the dideoxyribose ring,[2–4] and to a certain extent, they are able to control the outcome of reactions between these prodrugs and the specific enzymes involved in the activation sequence leading to the formation of the active triphosphate metabolites.[5–9] However, the problem in attempting to correlate a conformational preference demanded by a specific enzyme in the activation pathway with a particular sugar conformation is that the dideoxyribose ring is very flexible and its conformation in solution can differ sharply from that determined in the solid state.[10,11] For example, the crystal structures of dideoxyadenosine (ddA, **1**; $P = 190.5°$, $\nu_{max} = 36.5°$)[12] and dideoxycytidine (ddC, **2**; $P = 207.5°$ [13] or $208.0°$ [12], $\nu_{max} = 33.9°$ [13] or $34.4°$ [12]), both potent anti-HIV agents, show exclusively a southern-type (S) geometry as determined by the value of P of the pseudorotation cycle (Figure 1) described by Altona and Sundaralingam.[14] This geometry, however, is not the one preferred in solution,[10,11] since the major pseudorotamer (75–80%), in each case, corresponds to a northern-type (N) furanose geometry: $P = 1.4°$, $\nu_{max} = 34.2°$ for ddA and $P = 10.9°$, $\nu_{max} = 34.7°$ for ddC.[11] Consequently, any conformation–activity study based exclusively on solid-state conformational parameters would be flawed unless both solution and solid-state conformations are known to be equivalent.



1, B = adenine

2, B = cytosine

In a comparative structural study performed on [3.1.0]-fused 2′,3′-dideoxynucleosides, it was concluded that a fused cyclopropane, or epoxide ring, can impart significant rigidity to the sugar portion of the molecule to the extent that the resulting nucleosides indeed show identical conformations in the solid state and in solution.[15] This conclusion was supported by the lack of change observed for the relevant coupling constants in

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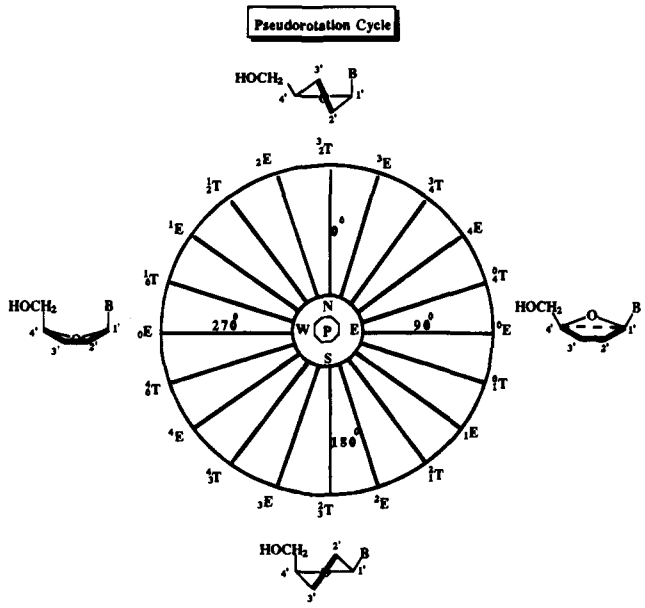
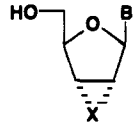


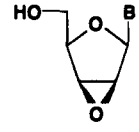
Figure 1. Pseudorotation cycle of the furanose ring in nucleosides. E and T represent envelope and twist conformations that alternate every 18°. Representative conformers for the four cardinal points are indicated.

the ^{1}H NMR spectra of these compounds at various temperatures.[15] Consequently, the furanose ring in these compounds does not appear to be involved in a conformational N ⇌ S equilibrium in solution as is the case for conventional nucleosides.[14,16]

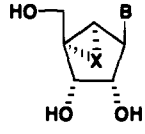


3, B = uracil, X = CH_2

4, B = adenine, X = O

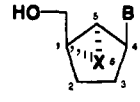


5, B = thymine



6, B = adenine, X = O (neplanocin C)

7, B = adenine, X = CH_2



8, B = adenine, X = O

9, B = adenine, X = CH_2

10, B = guanine, X = CH_2

11, B = thymine, X = CH_2

12, B = uracil, X = CH_2

13, B = cytosine, X = CH_2

In addition to the resulting rigidity, the orientation of the fused three-membered ring—whether *exo* (α-face) or *endo* (β-face)—appears to have a profound effect in determining the extent of ring puckering (ν_{max}).[14] For example, when the three-membered ring is fused to the α-face of the ribose in a uridine analogue (i.e., 2′,3′-dideoxy-2′,3′-α-methyleneuridine, **3**), the ring puckering is virtually eliminated ($\nu_{max} = 8.8°$),[15] resulting instead in a nearly planar sugar moiety when compared to the parent nucleoside uridine ($\nu_{max} = 40.6–41.6°$).[15] Although a puckered structure should in principle be preferred, the steric repulsion between the CH_2OH and the uracil base in this 2′,3′-α-fused system is minimized by the flattening of the ribose ring. A similar flattening effect on the furanose ring is brought about by the epoxide ring in 2′,3′-O-anhydroadenosine (**4**; $\nu_{max} = 8.1–9.3°$) when compared to adenosine ($\nu_{max} = 36.8°$).[15] On the other hand, if the stereochemistry of the three-membered ring is inverted, as in 1-(2′,3′-*O*-anhydro-β-D-lyxofuranosyl)thymine (**5**), a significant degree of puckering is again reestablished ($\nu_{max} = 29.2–33.1°$).[15]

The problem with the 2′,3′-fusion, however, is that the resulting conformation of the sugar moiety is rigidly fixed very much outside the pseudorotational range characteristic of typical nucleosides according to the value of the phase angle of pseudorotation (*P*).[15] This deviation from the natural N-type ($P = -1–34°$)[16] and S-type ($P = 137–194°$)[16] sugar conformations may explain the observed inactivity of these compounds as anti-HIV agents.[15,17] As a corollary, other types of [3.1.0]-bicyclics capable of generating similarly rigid systems, but with typical N or S conformations characteristic of conventional nucleosides, became attractive targets for chemical synthesis to explore a possible relationship between conformation and activity.[18,19]

The natural product neplanocin C (**6**), whose structure has been solved by X-ray analysis,[20] presented itself as a good prototype because the calculated pseudorotational parameters from the crystal structure ($P = 338.03°$ and $\nu_{max} = 21.89°$) were in the expected normal range for a nucleoside in the N hemisphere. These values imply that neplanocin C is approximately in the $_2$E conformation, closer to the typical $^3T_2$ ($P = 0°$) conformation observed for nucleosides with pure N-type geometry (Figure 1). Such a preference for the N hemisphere of neplanocin C is not surprising since the 6-oxabicyclo[3.1.0]hexane system (cyclopentene oxide) has been shown spectroscopically, as well as by *ab initio* molecular orbital calculations, to exist exclusively in the boat conformation,[21] which corresponds exactly to an N hemisphere conformation for the pseudosugar moiety. The alternate, but unattainable, chair conformation corresponds, in turn, to a pseudosugar moiety in the S hemisphere.

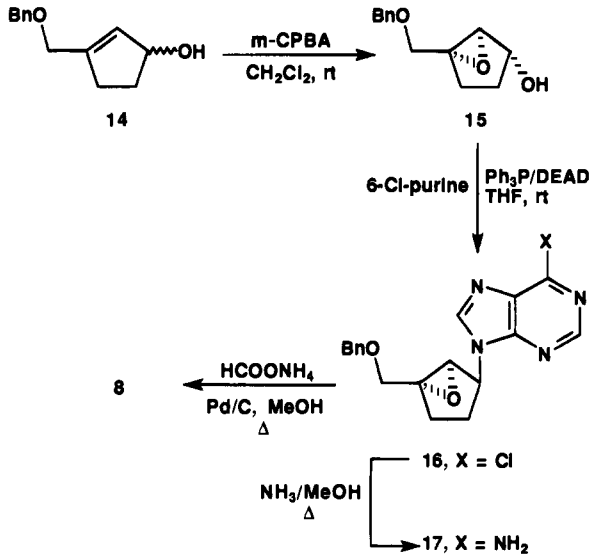
Since the corresponding dideoxyneplanocin C (**8**) proved to be an unstable compound (*vide infra*), we surmised that an equivalent conformational bias for the N hemisphere could be achieved by constructing the nucleosides on a bicyclo[3.1.0]hexane template (compounds **7** and **9**–**13**). Indeed, electron diffraction microwave spectroscopy,[22] as well as *ab initio* calculations,[23–26] has also demonstrated that the boat form for the bicyclo[3.1.0]hexane system is the only stable conformation.

If in fact the bicyclo[3.1.0]hexane system were to generate rigid dideoxynucleoside analogues with conformations typical of N hemisphere geometry, it was of interest to explore synthetic methods to attach all of the common nucleoside bases to this bicyclic system.[19] The present manuscript presents a detailed account of the syntheses of these compounds, together with the conformational evaluation and measured biological activity against HIV.

Synthesis

The synthetic plan envisioned the utilization of a convergent approach[27] to incorporate the heterocyclic bases onto the carbocyclic moiety in one step. Hence, the Mitusnobu reaction[28] became particularly attractive

Scheme 1



for this purpose, and the key intermediates (±)-**15** and (±)-**18** were selected as direct targets. Epoxidation of cyclopentenol (±)-**14**[29] was directed by the alcohol functionality to give the epoxy alcohol (±)-**15** as predicted by the Hembest rule[30] (Scheme 1, only one enantiomer is drawn). Coupling of this epoxy alcohol with 6-chloropurine under Mitsunobu conditions[28,31,32] gave a low but reproducible yield of the desired carbocyclic nucleoside (±)-**16**. Ammonolysis of the chloropurine intermediate produced the adenosine analogue as expected. However, removal of the benzyl protection under catalytic transfer hydrogenation conditions gave only a fleeting dideoxyneplanocin C target [(±)**8**] which decomposed rapidly on standing at room temperature.

Due to the instability shown by the dideoxyneplanocin C nucleoside, attention was directed toward the synthesis of the corresponding cyclopropane-fused carbocycles (±)-**9**−**13**. The requisite *trans*-1-[(benzyloxy)-methyl]-4-hydroxybicyclo[3.1.0]hexane [(±)-**18**] was obtained in excellent yield by a "hydroxyl-directed" cyclopropanation reaction performed on the same cyclopentenol (±)-**14** via an intermediate samarium(2+) carbenoid[33,34] (Scheme 2). The resulting alcohol (±)-**18** was somewhat unstable, but the corresponding acetate (±)-**19** proved to be a reasonably stable compound. Proton assignments for (±)-**19** were determined on the basis of single-frequency decoupling experiments and corroborated by one- and two-dimensional NOE data (Figure 2). A strong positive enhancement was observed at H-5 and at the methylene protons ($BnOCH_2$-) tethered to C-1 upon irradiation of H-6_{exo}. Conversely, irradiation of H-6_{endo} caused enhancement of H-6_{exo} but had no effect on H-4. A positive NOE was observed for H-5 after perturbing H-4 and vice versa. These data allowed us to conclude that H-4, H-5, and the side chain were on the same face of the molecule. In accord with the expected mechanism of reaction, these NOE measurements confirm that the cyclopropane ring and the hydroxyl group in compound (±)-**18** are indeed on the same side of the five-membered ring.

Mitsunobu coupling[28,31,32] of (±)-**18** with 6-chloropurine afforded a 28% yield of a mixture of N-9/N-7 isomers in a 3:1 ratio favoring the desired N-9 isomer (±)-**20** (Scheme 2). The two isomers were easily separated by column chromatography, and although the

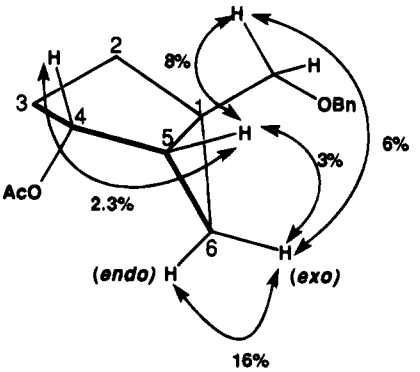
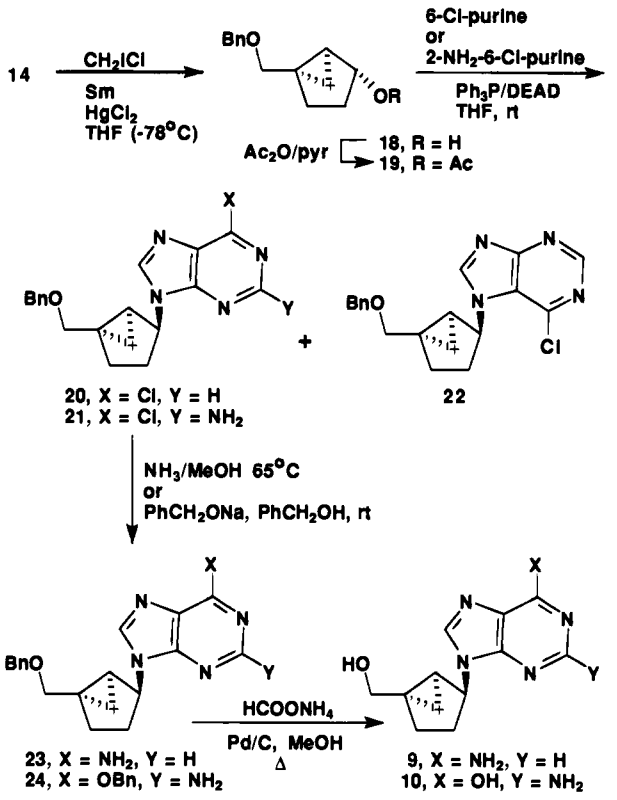


Figure 2. Conformation of compound (±)-**19** as deduced by ^1H NMR. The double arrows represent reciprocal positive enhancements in a one-dimensional NOE difference experiment.

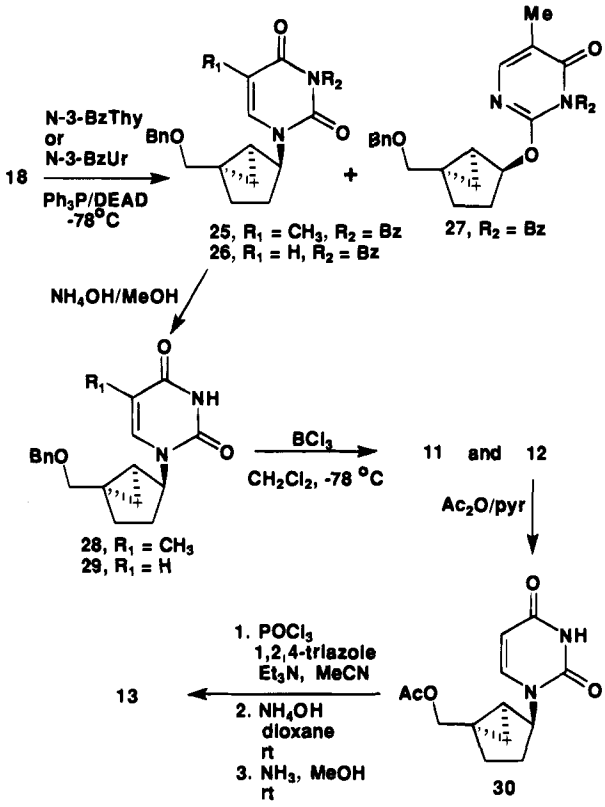
Scheme 2



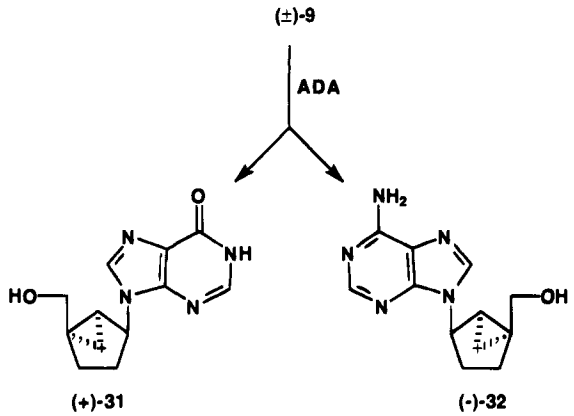
yield was low, this one-step condensation approach was still more desirable than the lengthy linear approach[27] of constructing the purine base in a stepwise fashion. The yield obtained from the condensation using 2-amino-6-chloropurine was better (38%), and only the desired N-9 isomer (±)-**21** appeared to have been formed under these conditions. Compound (±)-**20** was transformed into the adenosine derivative (±)-**23**, and following removal of the benzyl group by catalytic transfer hydrogenation, the target adenosine analogue (±)-**9** was obtained. For the guanosine analogue, compound (±)-**21** was converted into the 6-*O*-benzyl ether derivative (±)-**24**, which upon treatment with boron trichloride afforded the desired target compound (±)-**10**.

The pyrimidine derivatives were also obtained under Mitsunobu conditions[28,31,32] and in comparable yields to those of the purines using either protected *N*-3-benzoylthymine[35] or *N*-benzoyluracil[35] (Scheme 3). With *N*-benzoylthymine, a separable **1:1** mixture of N- and O-alkylated products [(±)-**25** and (±)-**27**] was obtained,

Scheme 3



Scheme 4



and removal of both the *N*-benzoyl and *O*-benzyl groups from (±)-**25** produced the thymidine target (±)-**11**. When *N*-3-benzoyluracil was used, no O-alkylation product was observed, and use of a similar deprotection protocol provided the corresponding uridine target (±)-**12**. The cytosine target (±)-**13** was prepared from (±)-**12** via formation of a triazole intermediate according to published methods.[36]

Adenosine Deaminase Reaction and HPLC Resolution of the Adenosine Analogue (±)-9

The anti-HIV screening (*vide infra*) indicated that only the adenosine analogue (±)-**9** possessed a level of activity that warranted an attempt to resolve the compound into its optically individual enantiomers. Initially, compound (±)-**9** was incubated with adenosine deaminase (ADA; Scheme 4), and deamination occurred readily at room temperature to a point where half of the starting material was consumed. This is consistent with the supposition that the enzyme would deaminate

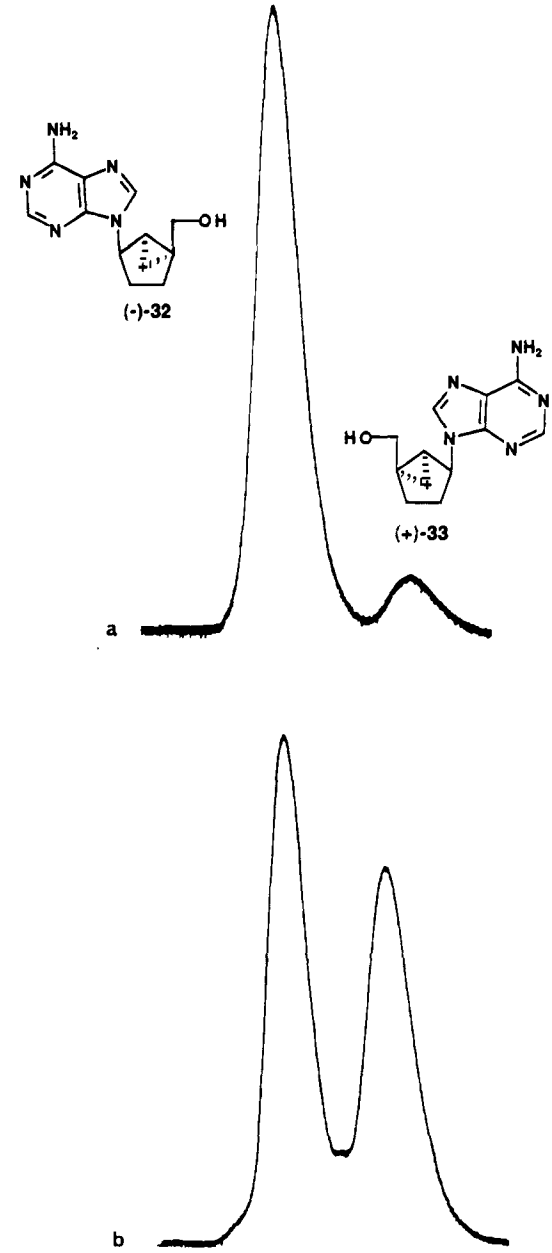


Figure 3. HPLC resolution of (±)-**9** after partial deamination with ADA (a). HPLC resolution of (±)-**9** into its optical antipodes, (−)-**32** and (+)-**33** (b). Both experiments were conducted using a Chiracel OD column with hexane:isopropyl alcohol:diethylamine (86:14:0.1) as eluant; flow rate 3.0 mL/min. Retention times were 22.18 and 26.3 min, respectively, in a and 21.35 and 25.18 min, respectively, in b.

preferentially the enantiomer resembling natural adenosine.[37] However, the midpoint of the reaction could not be very accurately determined since in most instances the reaction was never complete, and chiral HPLC analysis of the remaining "unnatural" enantiomer (−)-**32** always revealed a small amount of the still non-deaminated "natural" enantiomer (+)-**33** (Figure 3a). When analyzed under the same chiral HPLC conditions, the isolated inosine analogue (+)-**31** was enantiomerically homogeneous (ee >99%; data not shown). The ADA reaction was therefore very useful in proving the identity of (+)-**33** as the enantiomer with the "natural" configuration equivalent to that of adenosine. Under identical semipreparative chiral HPLC conditions, separation of (±)-**9** into its optical antipodes, (−)-**32** and (+)-**33** (Figure 3b), was achieved. Both

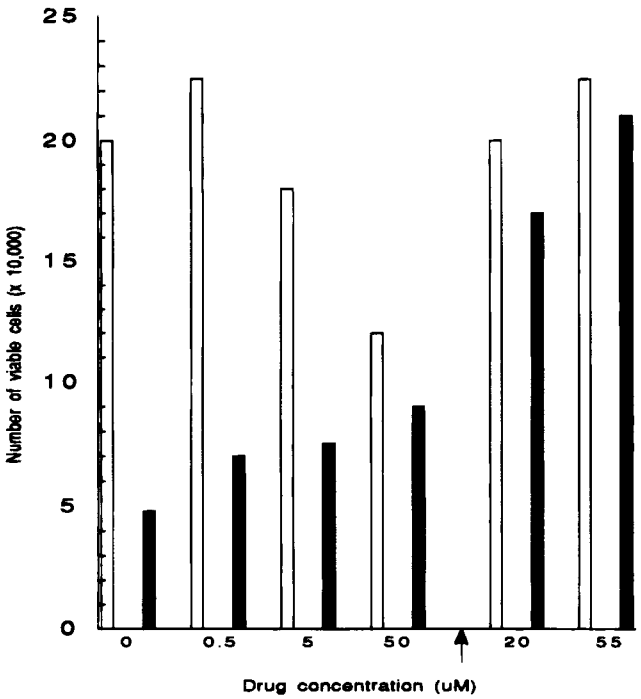


Figure 4. Inhibition of the cytopathic effect of HIV (HIV-$1_{I,AI}$, 200 $TCID_{50}$) by (±)-**9** in ATH8 cells and a reference active compound (dideoxyinosine, ddI) used at known active concentrations (after the arrow). Infected ATH8 cells (3×10^5) were exposed to various concentrations of the drugs (filled columns). Control cells (open columns) were similarly treated but not exposed to the virus.

compounds were isolated in optically pure form as confirmed by chiral HPLC analysis and optical rotation measurements (see the Experimental Section).

Anti-HIV Evaluation

All final target compounds [(±)-**9**–(±)-**13**] were evaluated against the HIV virus (HIV-$1_{I,AI}$) in infected ATH8 cells according to a standard protocol.[38] Only the adenosine analogue (±)-**9** displayed a moderate dose-dependent level of activity in the 0.5–50 μM range. However, the protection achieved by administering this compound was opposed by an equally dose-dependent toxicity to the ATH8 cells in the same concentration range (Figure 4). Antiviral evaluation of the individual enantiomers (−)-**32** and (+)-**33** revealed that the low level of activity observed for (±)-**9** in this cell system was associated exclusively with the compound in the "natural" configuration (data not shown). Although the sugar conformation is obviously not the sole determinant of anti-HIV activity or cellular toxicity, it is possible that the N conformation adopted by this nucleoside leads to a successful interaction with the kinases responsible for the formation of the required nucleotide triphosphate metabolite. Interaction between the viral enzyme reverse transcriptase (RT) and the triphosphate metabolite, on the other hand, would be an unlikely discriminating step since RT is known to interact fairly well with a wide range of nucleoside triphosphates, including those corresponding to nucleosides found to be inactive in cell culture experiments.[39,40] The difference observed between the adenosine analogue [(±)-**9** or (+)-**33**] and the rest of the series [(±)-**10**–(±)-**13**] bearing the other bases is possibly due to a different conformational demand required by the different activating kinases. This may result in a reduced affinity for the latter group when these substrates exist exclusively in an N conformation. Formation of nucleotide metabolites is generally expected to lead to either anti-HIV activity or cellular toxicity, both of which were lacking in the (±)-**10**–(±)-**13** series.

Conformational Studies

Molecular modeling was employed to measure the pseudorotational parameters of the intended target compounds. The program QUANTA version 3.2.4 using CHARMm version 2.1 with the standard parameter set was employed. When the oxygen of the epoxide ring of neplanocin C (**6**) was replaced with a carbon, the minimized conformation for the resulting structure (**7**) showed that the pseudorotational parameters (P = 342.17° and ν_{max} = 29.62°) were quite comparable to those corresponding to the crystal structure of neplanocin C[20] (P = 338.03° and ν_{max} = 21.89°). The dideoxyneplanocin C analogue with a cyclopropane fusion [compound (±)-**9**, or more correctly (+)-**33**] was then derived from **7** by removing both hydroxyl groups. The calculated pseudorotational parameters for this structure approximated very closely the parameters measured for the N-type geometry conformer of ddA in solution.[11] Indeed, the measured value of P for (+)-**33** (P = 356.67°) is only 4.73° away from the value of P calculated for ddA in solution. In addition, the ν_{max} value of 30.45° suggested that the cyclopropane moiety in this compound could successfully force the cyclopentane ring to adopt a puckering very similar to that found for the dideoxyribose ring of ddA in solution.[11] It is of interest to observe that carbocyclic nucleosides with just a cyclopentane ring, such as aristeromycin[41] and carbathymidine,[42] do not show an N hemisphere conformational preference in the solid state, as only the unusual $_1$E conformation is observed in their crystal structures.

Predicting a preferred conformer based on the QUANTA/CHARMm program was not very reliable for the bicyclo[3.1.0]hexane system described here. For example, the energy difference between the N (boat) and S (chair) conformers of (+)-**33** was calculated to be only 0.6 kcal/mol. On the other hand, in the absence of severe 3,6-interactions, electron diffraction microwave spectroscopy, as well as *ab initio* calculations, always shows that the boat conformer exists exclusively in other bicyclo[3.1.0]hexane systems.[22–26]

In order to use ^{1}H NMR coupling data to corroborate the expected N (boat) conformation of our target nucleosides, the specified torsion angles shown in Figure 5 were measured for compound (+)-**33**, in both N (boat) and S (chair) conformations. For the N (boat) conformer, these values were: H5′–C5′–C4′–H4′ (−86.1°), H4′–C4′–C3′–H3′$_\beta$ (91.3°), and H4′–C4′–C3′–H3′$_\alpha$ (−23.9°). Although the Karplus equation might not apply perfectly well due to the distortion produced by the fused cyclopropane ring, these values suggest that two of the three coupling constants involving the pseudoanomeric proton (H-4′) in the N conformer should be very close to zero. Alternatively, none of the same torsion angles for the S conformer approached 90° (−134.7°, 175.7°, and 60.9°).

With the exception of signals corresponding to the different aglycons, the ^{1}H NMR spectra of our target compounds [(±)-**9**–**13**] were nearly identical and no

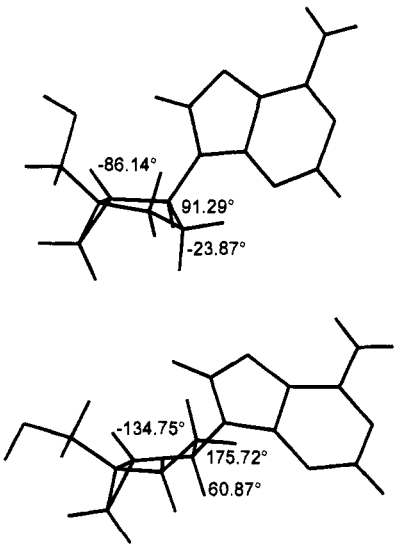


Figure 5. QUANTA-modeled structures of compound (±)-**9** [the enantiomer (+)-**33** is shown] as a northern conformer (boat, $P = 357°$) and a southern conformer ($P = 164°$). The values for the dihedral angles for H5′—C5′—C4′—H4′, H4′—C4′—C3′—H3′$_\beta$, and H4′—C4′—C3′—H3′$_\alpha$ are indicated.

apparent changes in the coupling constants were observed in the 25–80 °C range. This confirmed that all these compounds have similar, highly rigid conformations in solution. Taking compound (±)-**9** as a prototype, the pseudoanomeric signal for H-4′ appeared as a doublet ($J = 6.0$ Hz) centered at δ 4.90 (Figure 6). The same multiplicity for the H-4′ signal was observed for the rest of the target compounds with J values ranging from 5.8 to 6.5 Hz. This multiplicity observed for the pseudoanomeric proton (H-4′) in all these compounds agrees with the torsion angles that were measured above for the N (boat) conformation. In addition, since there are no severe 3,6-interactions in these nucleosides, the proposed N (boat) conformation for these compounds agrees well with what is known about the bicyclo[3.1.0]-hexane system.[43] Indeed, a search for compounds containing unrestricted bicyclo[3.1.0]hexane systems in the Cambridge Structural Data Base[44] revealed that in all seven examples found, the boat conformation was the only form observed.

The compounds described here represent the first examples among nucleosides and pseudonucleosides that appear to exist rigidly in a defined and measurable N geometry conformation that is typical of conventional nucleosides.[45] Given the rigidity observed for these dideoxy systems as N conformers, synthesis of analogous 2′-deoxynucleosides using the bicyclo[3.1.0]hexane pseudosugar as a template will allow the construction of DNA oligomers that will exist exclusively in the A conformation.[46] This should be important for locking the DNA molecule into a specific conformation since it is known that different environmental conditions are able to induce changes between A and B conformations in DNA. Moreover, both A and B regions have been observed *in vivo* within segments of the same DNA molecule, and this could be important for recognition and binding to specific regulatory proteins.[47] In addition, the resulting rigidity of the backbone may lead to a desirable entropic duplex stabilization, a concept that may prove to be useful in antisense oligonucleotide chemotherapy. These and other related aspects aimed at exploiting the rigidity of the bicyclo[3.1.0]hexane system in nucleoside and oligonucleotide research are currently being pursued in our laboratory.

Experimental Section

All chemical reagents were commercially available. Melting points were determined on a Mel-Temp II apparatus, Laboratory Devices, and are uncorrected. Column chromatography was performed on silica gel 60, 230–400 mesh (E. Merck), and analytical TLC was performed on Analtech Uniplates silica gel GF. Proton and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument at 250 and 62.9 MHz, respectively. Spectra were referenced to the solvent in which they were run (7.24 ppm for $CDCl_3$). Following the norm for reporting NMR data in nucleosides, the identity of protons and carbons on the pseudosugar ring (carbocyclic moiety) are indicated by numbers with primes (see corresponding numbering in structures **8**–**13**). When the stereochemistry of the protons is known, this is indicated by the subscripts β (up) and α (down). NOE difference spectra were run at 299 K using the Bruker automated program NOEMULT which allows for multiple irradiation points on each resonance being perturbed. Each resonance was irradiated for a total of 5 s, and spectra were time averaged over 16 cycles for each irradiation point (8 scans/cycle). Percentages were calculated by comparing the ratio of the integrals for peaks in the off-resonance control spectrum with those in the irradiated spectra. Analyses of the integral ratios of peaks in the control spectrum with peaks in the irradiated spectra not showing enhancements were used to calculate an estimated error in the integral measurements of ±2%. Peaks which showed positive NOEs in difference spectra but integrated to <2% are not shown. Variable temperature measurements between 290 and 350 K were used for coupling constant analysis, and spectra at 350 K were used for assignment purposes since the greatest chemical shift dispersion was seen at this temperature. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained on a VG 7070E mass spectrometer at an accelerating voltage of 6 kV and a resolution of 2000. Glycerol was used as the sample matrix, and ionization was effected by a beam of xenon atoms. UV spectra were recorded in a Shimadzu Model UV-2101PC spectrometer. HPLC analysis was performed on a Shimadzu chromatograph with a solvent delivery system, Model LC-6A, and a variable wavelength detector, Model SPD-6AV. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

(±)-***trans*-1-[(Benzyloxy)methyl]-4-hydroxy-6-oxabicyclo[3.1.0]hexane (15).** A solution of *m*-chloroperbenzoic acid (2.715 g, 80%) in CH_2Cl_2 (30 mL) was added dropwise to a solution of alcohol **14** (2.20 g, 10.8 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at room temperature for 2 h and then extracted with a saturated solution of Na_2CO_3 (2 × 150 mL) and water (2 × 150 mL). The organic layer was dried ($MgSO_4$), and removal of the solvent produced 2.193 g (92%) of epoxide **15** as an oil which was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ **1.34** (m, 1 H, H-3$_a$), 1.73 (m, 1 H, H-2$_a$), 2.06 (m, 2 H, H-2$_b$, H-3$_b$), 2.41 (s, 1 H, −O*H*), 3.44 (d, $J = 1.1$ Hz, 1 H, H-5), 3.62 (d, $J = 11.4$ Hz, 1 H, $PhCH_2OCHH$), 3.76 (d, $J = 11.4$ Hz, 1 H, $PhCH_2OCHH$), 4.28 (dt, $J = 8.9$, 1.1 Hz, 1 H, H-4), 4.57 (AB q, $J = 18.5$ Hz, 2 H, $PhCH_2O$), 7.3 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.31 (C-3), 28.22 (C-2), 62.57 (C-5), 65.37 (C-1), 69.74 ($PhCH_2OCH_2$), 73.16 (C-4, $PhCH_2O$), 127.65 (Ph), 127.71 (Ph), 128.36 (Ph), 137.78 (Ph).

(±)-***cis*-1-[(Benzyloxy)methyl]-4-(6-chloro-9-purinyl)-6-oxabicyclo[3.1.0]hexane (16).** A suspension of 6-chloropurine (0.88 g, 5.76 mmol) and triphenylphosphine (1.50 g, 5.76 mmol) in anhydrous THF (15 mL) was treated with diethyl azodicarboxylate (1.02 mL, 6.48 mmol) under argon. The resulting mixture was vigorously stirred for 10 min, and immediately after, a solution of epoxy alcohol **15** (1.32 g, 6 mmol) in THF (5 mL) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue was adsorbed on silica gel and purified by column chromatography using hexane:EtOAc (70:30) as eluant. A second chromatography using CH_2Cl_2:isopropyl alcohol (98.5:1.5) as eluant produced 0.600 g

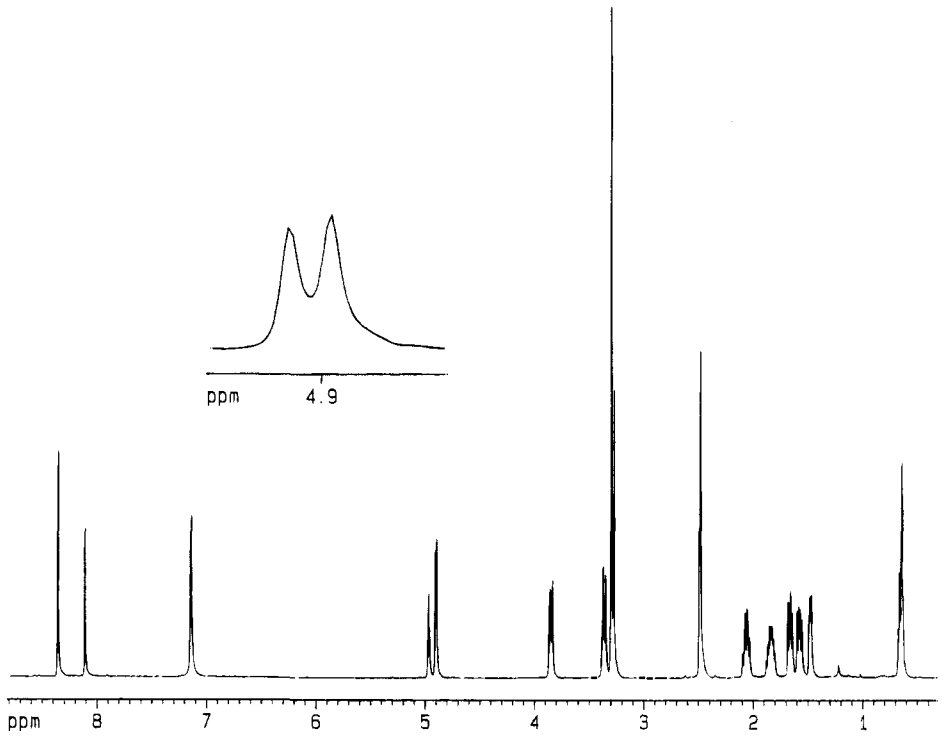


Figure 6. ^{1}H NMR (500 MHz) spectrum of (±)-**9** at 350 K (DMSO-d_6) showing the characteristic doublet at δ 4.90 (J = 6.0 Hz) which confirms the exclusive presence of the northern (boat) conformer.

(28%) of pure compound **16** as a white solid: mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 1 H, H-3′$_a$), 1.90 (m, 1 H, H-2′$_a$), 2.23 (m, 2 H, H-2′$_b$, H-3′$_b$), 3.63 (s, 1 H, H-5′), 3.87 (s, 2 H, $PhCH_2OCH_2$), 4.63 (s, 2 H, $PhCH_2O$), 5.25 (d, J = 6.0 Hz, 1 H, H-4′), 7.3–7.4 (m, 5 H, Ph), 8.24 (s, 1 H, H-8), 8.72 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 26.23 (C-3′), 29.11 (C-2′), 55.42 (C-4′), 60.71 (C-5′), 67.81 (C-1′), 68.75 ($PhCH_2OCH_2$), 73.49 ($PhCH_2O$), 127.66 (Ph), 127.92 (Ph), 128.48 (Ph), 129.66 (C-5), 131.68 (Ph), 137.41 (Ph), 143.50 (C-8), 151.22 (C-4), 151.39 (C-6), 151.93 (C-2); FAB MS (m/z, relative intensity) 357 (MH^+, 85), 91 (100). Anal. ($C_{18}H_{17}ClN_4O_2 \cdot {}^1/_3H_2O$) C, H, N, Cl.

(±)-***cis*-1-[(Benzyloxy)methyl]-4-(6-amino-9-purinyl)-6-oxabicyclo[3.1.0]hexane (17).** Compound **16** (0.240 g, 0.67 mmol) was treated with methanolic ammonia (5 mL, saturated at −78 °C) and heated in a sealed tube at 70 °C for 7 h. The mixture was allowed to cool to room temperature, and the solvent was evaporated. The residue was purified by flash chromatography using CH_2Cl_2:isopropyl alcohol (9:1) as eluant to afford 0.202 g (89%) of pure **17** as a pale yellow solid: mp 138–141 °C dec; UV (MeOH) λ_{max} 261.7 nm; ^{1}H NMR (CD_3OD) δ 1.90 (m, 1 H, H-3′$_a$), 2.20 (m, 3 H, H-3′$_b$, H-2′$_{a,b}$), 3.65 (s, 1 H, H-5′), 3.81 (d, J = 11.2 Hz, 1 H, $PhCH_2OCHH$), 3.96 (d, J = 11.2 Hz, 1 H, $PhCH_2OCHH$), 4.58 (s, 2 H, $PhCH_2O$), 5.12 (d, J = 6.3 Hz, 1 H, H-4′), 8.10 (s, 1 H, H-8), 8.17 (s, 1 H, H-2); ^{13}C NMR (CD_3OD) δ 27.26 (C-3′), 29.88 (C-2′), 56.32 (C-4′), 62.24 (C-5′), 69.23 (C-1′), 70.57 ($PhCH_2OCH_2$), 74.40 ($PhCH_2O$), 128.88 (Ph), 129.46 (Ph), 139.38 (Ph), 140.70 (C-8), 153.87 (C-2); FAB MS (m/z, relative intensity) 338 (MH^+, 100), 136 (b + 2H, 27), 91 (69). Anal. ($C_{18}H_{19}N_5O_2 \cdot {}^1/_2H_2O$) C, H, N.

(±)-***cis*-1-(Hydroxymethyl)-4-(6-amino-9-purinyl)-6-oxabicyclo[3.1.0]hexane (8).** A mixture of compound **17** (0.080 g, 0.24 mmol), ammonium formate (1 g), and palladium on charcoal (10%, 0.150 g) in methanol (10 mL) was refluxed for 2 h under argon. The mixture was cooled to room temperature and filtered through Celite. The filtrate was collected, and the solvent was evaporated. The residue was dissolved in water and adsorbed on a small column of Bio-Rad AG-50WX4 (H^+) resin. After washing thoroughly with water, the compound was eluted with 1 N NH_4OH to afford 8 mg of compound **8** which decomposed on standing: ^{1}H NMR (CD_3OD) δ 1.95 (m, 1 H, H-3′$_a$), 2.40 (m, 3 H, H-3′$_b$, H-2′$_{a,b}$), 3.78 (s, 1 H, H-5′), 3.91 (d, J = 12.8 Hz, 1 H, CHHOH), 4.00 (d, J = 12.8 Hz, 1 H, CHHOH), 5.14 (d, J = 6.0 Hz, 1 H, H-4′), 8.11 (s, 1 H, H-8), 8.22 (s, 1 H, H-2).

(±)-***trans*-1-[(Benzyloxy)methyl]-4-hydroxybicyclo[3.1.0]hexane (18).** Samarium metal (5.04 g, 33.6 mmol) was placed in a flask and dried with a flame under a stream of argon. Anhydrous THF (50 mL) and a solution of mercuric chloride (0.88 g, 3.2 mmol) in 10 mL of THF were added, and the mixture was stirred for 10 min prior to the addition of alcohol **14** (1.52 g, 7.45 mmol). The reaction mixture was cooled to −78 °C and treated with chloroiodomethane (2.32 mL, 32 mmol). The resulting mixture was continuously stirred starting at −78 °C and allowing the temperature to reach ambient conditions during the course of the night. The following day, the reaction was quenched with a saturated solution of Na_2CO_3 (300 mL) and the mixture extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extract was washed with brine, dried (Mg_2SO_4), filtered, and evaporated to give nearly pure compound **18** quantitatively as a colorless oil. Due to its instability, this product was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 0.47 (dd, J = 8, 5.2 Hz, 1 H, H-6$_{exo}$), 0.85 (distorted t, 1 H, H-6$_{endo}$), 1.17 (m, 2 H, H-2), 1.40 (m, 1 H, H-5), 1.85 (m, 2 H, H-3), 3.42 (s, 2 H, $PhCH_2OCH_2$), 4.50 (s, 2 H, $PhCH_2O$), 4.55 (m, 1 H, H-4), 7.25–7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 8.93 (C-6), 27.17 (C-5), 27.51 (C-3), 28.25 (C-1), 29.64 (C-2), 72.39 ($PhCH_2OCH_2$), 73.60 (C-4), 74.42 ($PhCH_2O$), 127.36 (Ph), 128.17 (Ph), 138.35 (Ph); FAB MS (m/z, relative intensity) 201 ([MH − H_2O]$^+$, 9), 91 (100), 71 (98).

(±)-***trans*-1-[(Benzyloxy)methyl]-4-acetoxybicyclo[3.1.0]hexane (19).** A solution of compound **18** (0.109 g, 0.5 mmol) in anhydrous pyridine (3 mL) was treated with acetic anhydride (2 mL), and the mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue was purified by flash chromatography using hexane:EtOAc (4:1) as eluant to give 0.130 g (100%) of compound **19**: ^{1}H NMR ($CDCl_3$) δ 0.54 (dd, J = 8.0, 5.4 Hz, 1 H, H-6$_{exo}$), 0.85 (distorted t, 1 H, H-6$_{endo}$), 1.28 (m, 1 H, H-3$_a$), 1.53 (m, 1 H, H-5), 1.88 (m, 2 H, H-2$_{a,b}$), 2.02 (s, 3 H, $COCH_3$), 2.04 (m, 1 H, H-3$_b$), 3.43 (s, 2 H, $PhCH_2OCH_2$), 4.50 (s, 2 H, $PhCH_2O$), 5.30 (dt, J = 8.2, 4.7 Hz, 1 H, H-4), 7.30 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 9.99 (C-6), 21.12 ($COCH_3$), 24.49 (C-5), 26.36 (C-3), 27.05 (C-2), 28.50 (C-1), 72.52 ($PhCH_2OCH_2$), 74.19 ($PhCH_2O$), 76.77 (C-4), 127.41 (Ph), 128.23 (Ph), 138.32 (Ph), 171.23 (CO); FAB MS (m/z, relative intensity) 261 (MH^+, 2), 201 (14), 153 (31), 91 (100). Anal. ($C_{16}H_{20}O_3$) C, H.

(±)-*cis*-1-[(**Benzyloxy**)**methyl**]-4-(**6-chloro-9-purinyl**)-**bicyclo[3.1.0]hexane** (**20**). A suspension of 6-chloropurine (0.148 g, 0.96 mmol) and triphenylphosphine (0.25 g, 0.96 mmol) in anhydrous THF (3 mL) was treated with diethyl azodicarboxylate (0.206 g, 1.08 mmol) under argon. The resulting mixture was vigorously stirred for 10 min, and immediately after, a solution of alcohol **18** (0.218 g, 1 mmol) in THF (5 mL) was added in one portion. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue was adsorbed on silica gel and purified by column chromatography using hexane:EtOAc (3:2) as eluant to afford 0.075 g (21% yield) of pure compound **20** and 0.024 g of the N-7 derivative (compound **22**).

Compound 20: mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 0.76 (m, 2 H, H-6′$_{a,b}$), 1.56 (dd, J = 8.2, 4.3 Hz, 1 H, H-5′), 1.65–2.00 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.25 (m, 1 H, H-2′$_\beta$), 3.29 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 3.95 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 4.63 (s, 2 H, $PhCH_2O$), 5.22 (d, J = 5.5 Hz, 1 H, H-4′), 7.36 (m, 5 H, Ph), 8.74 (s, 1 H, H-8), 9.00 (s, 1 H, H-2); ^{13}C NMR ($CDCl_3$) δ 12.30 (C-6′), 26.22 (C-5′), 26.28 (C-3′), 30.26 (C-2′, C-1′), 56.94 (C-4′), 72.86 ($PhCH_2OCH_2$), 73.20 ($PhCH_2$), 127.49 (Ph), 127.64 (Ph), 128.52 (Ph), 131.74 (C-5), 137.95 (Ph), 144.78 (C-8), 150.65 (C-4), 151.30 (C-6), 151.51 (C-2); FAB MS (*m/z*, relative intensity) 357 (12), 355 (MH^+, 35), 247 (11), 155 (b + 2H, 34), 91 (100). Anal. ($C_{19}H_{19}ClN_4O$) C, H, N, Cl.

Compound 22: pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 2 H, H-6′$_{a,b}$), 1.67 (dd, J = 3.9, 8.6 Hz, 1 H, H-5′), 1.70–2.05 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.15 (m, 1 H, H-2′$_\beta$), 3.34 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 3.97 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 4.63 (s, 2 H, $PhCH_2O$), 5.49 (d, J = 5.4 Hz, 1 H, H-4′), 7.36 (m, 5 H, Ph), 8.87 (s, 1 H, H-8), 9.18 (s, 1 H, H-2); FAB MS (*m/z*, relative intensity) 357 (7), 355 (MH^+, 21), 155 (b + 2H, 13), 91 (100).

(±)-*cis*-1-[(**Benzyloxy**)**methyl**]-4-(**6-amino-9-purinyl**)-**bicyclo[3.1.0]hexane** (**23**). Compound **20** (0.215 g) was treated with methanolic ammonia (5 mL, saturated at −78 °C) and heated in a sealed tube to 70 °C overnight. The mixture was allowed to cool to room temperature, and the solvent was evaporated. The residue was purified by flash chromatography using CH_2Cl_2:isopropyl alcohol (9:1) as eluant to afford 0.109 g of compound **23** (54%) as a white solid: mp 170 °C; ^{1}H NMR (CD_3OD) δ 0.76 (d, J = 6.1 Hz, 2 H, H-6′$_{a,b}$), 1.59 (distorted t, 1 H, H-5′), 1.65–2.00 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.20 (m, 1 H, H-2′$_\beta$), 3.40 (d, J = 10.0 Hz, 1 H, $PhCH_2OCHH$), 3.97 (d, J = 10.0 Hz, 1 H, $PhCH_2OCHH$), 4.57 (s, 2 H, $PhCH_2O$), 5.02 (d, J = 5.7 Hz, 1 H, H-4′), 7.20–7.40 (m, 5 H, Ph), 8.18 (s, 1 H, H-8), 8.60 (s, 1 H, H-2); ^{13}C NMR (CD_3OD) δ 12.72 (C-6′), 27.27 (C-5′), 27.54 (C-3′), 31.12 (C-2′), 31.36 (C-1′), 57.96 (C-4′), 74.23 ($PhCH_2OCH_2$), 74.80 ($PhCH_2O$), 120.06 (C-5), 128.64 (Ph), 128.70 (Ph), 129.50 (Ph), 139.80 (Ph), 141.08 (C-8), 149.99 (C-4), 153.50 (C-2), 157.27 (C-6). Anal. ($C_{19}H_{21}N_5O$) C, H, N.

(±)-*cis*-1-(**Hydroxymethyl**)-4-(**6-amino-9-purinyl**)**bicyclo-[3.1.0]hexane** (**9**). Palladium on charcoal (10%, 0.300 g) was flushed with argon for 15 min. Compound **23** (0.050 g) was dissolved in methanol (5 mL) and added to the catalyst. Immediately after, ammonium formate (1 g) was added and the reaction was refluxed for a total of 3 h. The mixture was allowed to cool to room temperature and filtered and the solvent evaporated. The residue was purified by reverse phase column chromatography using a Spe-ed cartridge (C-18 octadecyl/18, 2 g) from Applied Separations, Inc., and eluting with water to afford 0.012 g (33%) of pure compound **9** as a pale yellow solid: mp 251 °C dec; UV (MeOH) λ_{max} 260.7 nm (ϵ 15 200); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.66 (m, 2 H, H-6′$_{a,b}$), 1.48 (dd, J = 8.3, 3.9 Hz, 1 H, H-5′), 1.58 (dd, J = 14.3, 8.2 Hz, 1 H, H-2′$_\alpha$), 1.67 (dd, J = 12.5, 8.0 Hz, 1 H, H-3′$_\beta$), 1.84 (m, 1 H, H-3′$_\alpha$), 2.07 (dt, J = 12.0, 8.0 Hz, 1 H, H-2′$_\beta$), 3.37 (dd, J = 11.4, 5.1 Hz, 1 H, $CHHOH$), 3.86 (dd, J = 11.4, 5.1 Hz, 1 H, $CHHOH$), 4.80 (t, J = 5.2 Hz, 1 H, OH), 4.90 (d, J = 6.0 Hz, 1 H, H-4′), 7.17 (s, 2 H, NH_2), 8.11 (s, 1 H, H-8), 8.37 (s, 1 H, H-2); ^{13}C NMR (CD_3OD–D_2O) δ 12.51 (C-6′), 26.88 (C-5′), 27.11 (C-3′), 30.95 (C-2′), 32.99 (C-1′), 58.34 (C-4′), 66.21 (CH_2OH), 119.84 (C-5), 141.05 (C-8), 149.57 (C-4), 153.25 (C-2), 156.84 (C-6); FAB MS (*m/z*, relative intensity) 338 ([MH + glycerine]$^+$, 12), 246 (MH^+, 100), 136 (b + 2H, 84). Anal. ($C_{12}H_{15}N_5O$) C, H, N.

(±)-*cis*-1-[(**Benzyloxy**)**methyl**]-4-(**2-amino-6-chloro-9-purinyl**)**bicyclo[3.1.0]hexane** (**21**). A suspension of 2-amino-6-chloropurine (1.720 g, 10.16 mmol) and triphenylphosphine (2.672 g, 10.24 mmol) in anhydrous THF (60 mL) was treated with diethyl azodicarboxylate (1.76 mL, 11.26 mmol) under argon. The resulting mixture was vigorously stirred for 10 min, and immediately after, a solution of alcohol **18** (0.670 g, 3.07 mmol) in THF (5 mL) was added in one portion. The reaction mixture was stirred for 18 h at room temperature. The solvent was evaporated, and the residue was adsorbed on silica gel and purified by column chromatography using hexane:EtOAc (3:2) as eluant to afford 0.435 g (38%) of pure compound **21** as a white solid: mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 0.69 (m, 2 H, H-6′$_{a,b}$), 1.50 (dd, J = 8.4, 3.9 Hz, 2 H, H-5′), 1.60–1.92 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.23 (m, 1 H, H-2′$_\beta$), 3.30 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 3.88 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 4.60 (s, 2 H, $PhCH_2O$), 4.95 (d, J = 5.3 Hz, 1 H, H-4′), 5.05 (s, 2 H, NH_2), 7.35 (m, 5 H, Ph), 8.56 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) δ 12.21 (C-6′), 26.29 (C-5′), 26.46 (C-3′), 30.19 (C-2′)*, 30.26 (C-1′)*, 56.26 (C-4′), 73.00 ($PhCH_2OCH_2$), 73.17 ($PhCH_2O$), 125.54 (C-5), 127.65 (Ph), 127.75 (Ph), 128.51 (Ph), 138.09 (Ph), 141.83 (C-8), 150.99 (C-4), 153.29 (C-2), 158.76 (C-6); FAB MS (*m/z*, relative intensity) 370 (MH^+, 42), 170 (b + 2H, 43), 91 (100). Anal. ($C_{19}H_{20}ClN_5O \cdot {}^2/_3H_2O$) C, H, N, Cl.

(±)-*cis*-1-[(**Benzyloxy**)**methyl**]-4-[**2-amino-6-(benzyloxy**)-**9-purinyl**]**bicyclo[3.1.0]hexane** (**24**). Anhydrous benzyl alcohol (3 mL) was treated with sodium metal (0.1 g), and the resulting suspension was vigorously stirred under argon with gentle warming until the metal was completely dissolved. Compound **21** (0.174 g, 0.47 mmol) was reacted with 1.5 mL of the above solution, and the reaction mixture was stirred for 10 min. After the reaction was quenched with water (25 mL), the mixture was extracted with CH_2Cl_2 (30 mL). The organic layer was washed with water until the washings reached a neutral pH; it was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography using hexane:EtOAc (1:1) as eluant to give 0.161 g (77%) of pure compound **24** as a white solid: mp 171 °C; ^{1}H NMR ($CDCl_3$) δ 0.66 (m, 2 H, H-6′$_{a,b}$), 1.49 (dd, J = 8.4, 3.8 Hz, 1 H, H-5′), 1.62–1.95 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.20 (m, 1 H, H-2′$_\beta$), 3.36 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 3.82 (d, J = 9.9 Hz, 1 H, $PhCH_2OCHH$), 4.58 (AB q, J = 12.5 Hz, 2 H, $PhCH_2OCH_2$), 4.84 (s, 2 H, NH_2), 4.93 (d, J = 5.2 Hz, 1 H, H-4′), 5.58 (AB q, J = 12.4 Hz, 2 H, $PhCH_2O$-purine), 7.26–7.54 (m, 10 H, Ph), 8.24 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) δ 12.16 (C-6′), 26.47 (C-3′), 26.70 (C-5′), 30.26 (C2′, C-1′), 55.78 (C-4′), 67.91 ($PhCH_2$-purine), 73.09 ($PhCH_2OCH_2$), 73.23 ($PhCH_2OCH_2$), 115.69 (C-5), 127.56 and 127.63 (Ph), 127.45 and 128.18 (Ph), 128.30 and 128.45 (Ph), 136.61 (C-8), 138.21 and 138.63 (Ph), 153.65 (C-4), 158.90 (C-2), 160.90 (C-6); FAB MS (*m/z*, relative intensity) 442 (MH^+, 49), 242 (b + 2H, 34), 91 (100). Anal. ($C_{26}H_{27}N_5O_2$) C, H, N.

(±)-*cis*-1-(**Hydroxymethyl**)-4-(**2-amino-1,9-dihydro-6*H*-6-oxopurin-9-yl**)**bicyclo[3.1.0]hexane** (**10**). A solution of compound **24** (0.154 g, 0.35 mmol) in anhydrous CH_2Cl_2 (35 mL) was cooled to −78 °C under argon, treated with boron trichloride (1.0 M in hexane, 3.00 mL), and stirred at −78 °C for 6 h. Methanol (4 mL) was added while the temperature was still at −78 °C, and the mixture was allowed to reach room temperature. The solvent was removed, and additional amounts of methanol (6 × 4 mL) were added and evaporated successively. The residue was purified by column chromatography using C-18 (octadecyl, 40 μm) reverse phase silica gel from J. T. Baker, Inc., with water as eluant to give 0.050 g (55%) of pure compound **10** as a white solid: mp >300 °C; UV (MeOH) λ_{max} 254.4 nm (ϵ 10 500); ^{1}H NMR (DMSO-d_6) δ 0.60 (m, 2 H, H-6′$_{a,b}$), 1.40 (dd, J = 8.1, 3.7 Hz, 1 H, H-5′), 1.45–1.90 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.00 (m, 1 H, H-2′$_\beta$), 3.45 (dd, J = 11.4, 4.8 Hz, 1 H, $CHHOH$), 3.81 (dd, J = 11.4, 4.8 Hz, 1 H, $CHHOH$), 4.64 (d, J = 5.8 Hz, 1 H, H-4′), 4.95 (t, J = 5.2 Hz, 1 H, OH), 6.60 (s, 2 H, NH_2), 7.94 (s, 1 H, H-8), 10.66 (s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 11.03 (C-6′), 25.50 (C-3′), 25.87 (C-5′), 29.73 (C-1′), 31.89 (C-2′), 55.31 (C-4′), 63.80 (CH_2OH), 116.52 (C-5),

135.19 (C-8), 150.44 (C-4), 153.53 (C-2), 156.79 (C-6); FAB MS (*m/z*, relative intensity) 354 ([MH + glycerine]$^+$, 14), 262 (MH$^+$, 100), 152 (b + 2H, 66). Anal. ($C_{12}H_{15}N_5O_2{}^{1}/_{6}H_2O$) C, H, N.

(±)-***cis*-1-[(Benzyloxy)methyl]-4-(3-benzoyl-5-methyl-2,4(1*H*,3*H*)-dioxopyrimidin-1-yl)bicyclo[3.1.0]hexane (25).** A solution of triphenylphosphine (1.340 g, 5.10 mmol) in anhydrous THF (16 mL) was treated with diethyl azodicarboxylate (0.870 g, 5.0 mmol) and stirred at 0 °C for 30 min. After cooling to −45 °C, a solution of N^3-benzoylthymine (0.920 g, 4 mmol) and alcohol **18** (0.460 g, 2.10 mmol) in THF (16 mL) was added via cannula over 45 min. The mixture was stirred overnight at −45 °C. The reaction mixture was warmed to room temperature, and the solvent was evaporated. The residue was purified by flash chromatography using hexane:EtOAc (7:3) as eluant to give a mixture of N- and O-alkylated products. This mixture was separated after further chromatography using CH_2Cl_2:ether (97.5:2.5) to afford 0.330 g (36%) of the desired N-alkylated product (compound **25**) as a white solid and 0.400 g (44%) of the undesired O-alkylated product (compound **27**) as an oil. In this solvent system, compound **25** eluted faster than compound **27**.

Compound 25: mp 182−184 °C; ^{1}H NMR ($CDCl_3$) δ 0.58 (dd, J = 5.7, 3.90 Hz, 1 H, H-6′$_{exo}$), 0.71 (distorted t, 1 H, H-6′$_{endo}$), 1.32 (dd, J = 8.8, 3.7 Hz, 1 H, H-5′), 1.55 (d, J = 0.8 Hz, 3 H, C*H*$_3$), 1.60−1.90 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.25 (m, 1 H, H-2′$_\beta$), 3.26 (d, J = 9.9 Hz, 1 H, PhCH$_2$OC*H*H), 4.05 (d, J = 9.9 Hz, 1 H, PhCH$_2$OCH*H*), 4.57 (AB q, J = 11.5 Hz, 2 H, PhC*H*$_2$O), 4.98 (d, J = 5.8 Hz, 1 H, H-4′), 7.35 (m, 5 H, *Ph*CH$_2$), 7.50 (t, J = 7.4 Hz, 2 H, *Ph*CO), 7.62 (t, J = 7.4 Hz, 1 H, *Ph*CO), 7.91 (d, J = 7.4 Hz, 2 H, *Ph*CO), 8.00 (d, J = 0.8 Hz, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ 11.77 (*C*H$_3$), 12.18 (C-6′), 25.71 (C-3′), 26.31 (C-5′), 30.34 (C-2′), 31.02 (C-1′), 57.48 (C-4′), 73.53 (PhCH$_2$O*C*H$_2$)*, 73.65 (Ph*C*H$_2$OCH$_2$)*, 110.25 (C-5), 127.99 (Ph), 128.53 (Ph), 129.00 (Ph), 130.37 (Ph), 134.73 (Ph), 137.90 (C-6), 138.19 (Ph), 149.95 (C-2), 162.90 (C-4), 169.46 (Ph*C*O); FAB MS (*m/z*, relative intensity) 431 (MH$^+$, 30), 323 (6), 231 (b + 2H, 13), 105 (100), 91 (79). Anal. ($C_{26}H_{26}N_4O_4{}^{1}/_{10}CH_2Cl_2$) C, H, N.

Compound 27: oil; ^{1}H NMR ($CDCl_3$) δ 0.51 (distorted t, H-6′$_{exo}$), 0.70 (dd, J = 8.7, 5.5 Hz, 1 H, H-6′$_{endo}$), 1.54 (m, 1 H, H-5′), 1.65 (m, 1 H, H-3′$_a$), 1.90−2.20 (m, 3 H, H-3′$_b$, H-2′$_{a,b}$), 3.37 (d, J = 10.3 Hz, 1 H, PhCH$_2$OC*H*H), 3.78 (d, J = 10.3 Hz, 1 H, PhCH$_2$OCH*H*), 4.55 (AB q, J = 12.2 Hz, 2 H, PhC*H*$_2$O), 5.33 (d, J = 4.9 Hz, 1 H, H-4′), 7.30 (m, 5 H, *Ph*CH$_2$), 7.50−70 (m, 3 H, *Ph*CO), 8.20 (m, 2 H, *Ph*CO), 8.40 (s, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ 12.13 (C-6′), 26.31 (C-3′), 28.05 (C-5′), 28.99 (C-2′), 29.22 (C-1′), 72.48 (PhCH$_2$O*C*H$_2$), 74.59 (Ph*C*H$_2$), 81.10 (C-4′), 115.32 (C-5), 127.39 (Ph), 127.62 (Ph), 128.27 (Ph), 128.38 (Ph), 128.69 (Ph), 130.42 (Ph), 134.17 (Ph), 138.59 (Ph), 161.65 (C-6), 163.20 (C-4), 163.84 (C-2), 165.26 (Ph*C*O).

(±)-***cis*-1-[(Benzyloxy)methyl]-4-(5-methyl-2,4(1*H*,3*H*)-dioxopyrimidin-1-yl)bicyclo[3.1.0]hexane (28).** Compound **25** (0.150 g, 0.35 mmol) was suspended in 100 mL of methanol and treated with concentrated ammonia (4 mL). The reaction mixture was stirred at room temperature for 16 h, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), and the organic layer was washed with saturated $NaHCO_3$ (3 × 30 mL) and water (2 × 30 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography using CH_2Cl_2:isopropyl alcohol (97:3) as eluant to give 0.105 g (92%) of **28** as a white solid: mp 205−207 °C; ^{1}H NMR ($CDCl_3$) δ 0.57 (dd, J = 5.6, 4.0 Hz, 1 H, H-6′$_{exo}$), 0.68 (m, 1 H, H-6′$_{endo}$), 1.27 (m, 1 H, H-5′), 1.54 (d, J = 1.0 Hz, 3 H, C*H*$_3$), 1.65−1.90 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.20 (m, 1 H, H-2′$_\beta$), 3.34 (d, J = 9.9 Hz, 1 H, PhCH$_2$OC*H*H), 4.01 (d, J = 9.9 Hz, 1 H, PhCH$_2$OCH*H*), 4.55 (AB q, J = 11.6 Hz, 2 H, PhC*H*$_2$O), 4.98 (d, J = 6.1 Hz, 1 H, H-4′), 7.34 (m, 5 H, Ph), 7.88 (d, J = 1.0 Hz, 1 H, H-6), 8.15 (br s, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 11.78 (*C*H$_3$), 12.14 (C-6′), 25.78 (C-3′), 26.34 (C-5′), 30.25 (C-2′), 30.96 (C-1′), 57.16 (C-4′), 73.47 (PhCH$_2$O*C*H$_2$)*, 73.63 (Ph*C*H$_2$OCH$_2$)*, 110.22 (C-5), 127.92 (Ph), 128.50 (Ph), 128.56 (Ph), 137.94 (C-6), 138.39 (Ph), 151.01 (C-2). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

(±)-***cis*-1-(Hydroxymethyl)-4-(5-methyl-2,4(1*H*,3*H*)-dioxopyrimidin-1-yl)bicyclo[3.1.0]hexane (11).** A solution of compound **28** (0.085 g) in anhydrous CH_2Cl_2 (20 mL) was cooled to −78 °C under argon and treated with boron trichloride (1.0 M in hexane, 1.80 mL). The reaction mixture was stirred at −78 °C for 6 h, after which time methanol (4.0 mL) was added while maintaining the same temperature. The mixture was then allowed to warm up to room temperature, and the solvent was evaporated to dryness. Methanol (6 × 4 mL) was added and evaporated after each addition. The residue was purified by reverse phase column chromatography using a Spe-ed cartridge (C-18 octadecyl/18, 2 g) from Applied Separations, Inc., and eluting with water to give 0.028 g (46%) of pure compound **11** as a white solid: mp 83−84 °C; UV (MeOH) λ_{max} 272.7 nm (ϵ 9400); ^{1}H NMR (DMSO-d_6) δ 0.50 (distorted t, 1 H, H-6′$_{exo}$), 0.59 (m, 1 H, H-6′$_{endo}$), 1.20 (dd, J = 8.5, 3.4 Hz, 1 H, H-5′), 1.45−1.85 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 1.74 (s, 3 H, C*H*$_3$), 2.00 (m, 1 H, H-2′$_\beta$), 3.25 (dd, J = 11.4, 5.0 Hz, 1 H, C*H*HOH), 3.88 (dd, J = 11.4, 5.0 Hz, 1 H, CH*H*OH), 4.72 (d, J = 6.5 Hz, 1 H, H-4′), 5.03 (t, J = 5.0 Hz, 1 H, O*H*), 7.88 (s, 1 H, H-6), 11.17 (s, 1 H, N*H*); ^{13}C NMR (CD_3OD) δ 12.38 (*C*H$_3$), 12.50 (C-6′), 26.56 (C-5′), 27.07 (C-3′), 31.07 (C-1′), 34.07 (C-2′), 58.96 (C-4′), 66.00 (*C*H$_2$OH), 110.91 (C-5), 140.22 (C-6), 152.93 (C-2), 166.49 (C-4); FAB MS (*m/z*, relative intensity) 237 (MH$^+$, 96), 219 (19), 127 (b + 2H, 100). Anal. ($C_{12}H_{16}N_2O_3{}^{1}/_{6}H_2O$) C, H, N.

(±)-***cis*-1-[(Benzyloxy)methyl]-4-(3-benzoyl-2,4(1*H*,3*H*)-dioxopyrimidin-1-yl)bicyclo[3.1.0]hexane (26).** A solution of triphenylphosphine (0.857 g, 3.26 mmol) in anhydrous THF (10 mL) was treated with diethyl azodicarboxylate (0.557 g, 3.2 mmol) and stirred at 0 °C for 30 min. After cooling to −78 °C, a solution of N^3-benzoyluracil (0.550 g, 2.56 mmol) and alcohol **18** (0.280 g, 1.27 mmol) in THF (25 mL) was added via cannula over a period of 10 min. The mixture was stirred overnight at −50 °C. The reaction mixture was allowed to reach room temperature, and the solvent was evaporated. The residue was purified by flash column chromatography using CH_2Cl_2:Et_2O (98:2) as eluant to give 0.150 g (28%) of pure compound **26** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.61 (dd, J = 5.7, 3.9 Hz, 1 H, H-6′$_{exo}$), 0.74 (m, 1 H, H-6′$_{endo}$), 1.31 (dd, J = 8.5, 3.5 Hz, 1 H, H-5′), 1.60−1.90 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.20 (m, 1 H, H-2′$_\beta$), 3.28 (d, J = 9.9 Hz, 1 H, PhCH$_2$OC*H*H), 4.07 (d, J = 9.9 Hz, 1 H, PhCH$_2$OCH*H*), 4.54 (AB q, J = 11.3 Hz, 2 H, PhC*H*$_2$O), 4.95 (d, J = 5.4 Hz, 1 H, H-4′), 5.42 (d, J = 8.1 Hz, 1 H, H-5), 7.30−7.40 (m, 5 H, Ph), 7.47 (t, J = 7.4 Hz, 2 H, *Ph*CO), 7.62 (m, 1 H, *Ph*CO), 7.92 (m, 2 H, *Ph*CO), 8.26 (d, J = 8.1 Hz, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ 12.25 (C-6′), 25.29 (C-3′), 26,18 (C-5′), 30.22 (C-2′), 30.98 (C-1′), 57.83 (C-4′), 73.28 (PhCH$_2$O*C*H$_2$)*, 73.59 (Ph*C*H$_2$O)*, 101.35 (C-5), 127.45 (Ph), 127.88 (Ph), 128.44 (Ph), 128.98 (Ph), 130.30 (Ph), 131.55 (Ph), 134.80 (Ph), 137.95 (Ph), 142.45 (C-6), 149.88 (C-2), 162.14 (C-4), 169.14 (Ph*C*O). Anal. ($C_{25}H_{24}N_2O_4$) C, H, N.

(±)-***cis*-1-[(Benzyloxy)methyl]-4-(2,4(1*H*,3*H*)-dioxopyrimidin-1-yl)bicyclo[3.1.0]hexane (29).** A solution of compound **26** (0.120 g, 0.29 mmol) in methanol (60 mL) was treated with concentrated ammonia (4 mL), and the mixture was stirred for 16 h at room temperature. The solvent was evaporated, and the residue was purified by flash chromatography using CH_2Cl_2:isopropyl alcohol (97:3) as eluant to give 0.077 g (86%) of compound **29** as a white solid: mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 0.59 (distorted t, 1 H, H-6′$_{exo}$), 0.72 (distorted t, 1 H, H-6′$_{endo}$), 1.26 (dd, J = 8.7, 3.8 Hz, 1 H, H-5′), 1.58−1.90 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 2.15 (m, 1 H, H-2′$_\beta$), 3.27 (d, J = 9.9 Hz, 1 H, PhCH$_2$OC*H*H), 4.04 (d, J = 9.9 Hz, 1 H, PhCH$_2$OCH*H*), 4.52 (AB q, J = 11.3 Hz, 2 H, PhC*H*$_2$O), 5.00 (d, J = 5.8 Hz, 1 H, H-4′), 5.37 (dd, J = 8.0, 1.4 Hz, 1 H, H-5), 8.11 (d, J = 8.0 Hz, 1 H, H-6), 9.90 (br s, 1 H, N*H*); ^{13}C NMR ($CDCl_3$) δ 12.19 (C-6′), 25.42 (C-3′), 26.24 (C-5′), 30.16 (C-2′), 30.92 (C-1′), 57.35 (C-4′), 73.25 (PhCH$_2$O*C*H$_2$)*, 73.62 (PhC-H$_2$O)*, 101.59 (C-5), 127.39 (Ph), 127.83 (Ph), 128.42 (Ph), 137.96 (Ph), 142.58 (C-6), 151.21 (C-2), 163.74 (C-4). Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

(±)-***cis*-1-(Hydroxymethyl)-4-(2,4(1*H*,3*H*)-dioxopyrimidin-1-yl)bicyclo[3.1.0]hexane (12).** A solution of compound **29** (0.067 g, 0.21 mmol) in anhydrous methylene chloride (16 mL) was cooled to −78 °C under argon and treated with boron trichloride (1.0 M in hexane, 1.50 mL). The mixture was stirred for 6 h at −78 °C, and workup of the reaction proceeded

as described for compound 11. The residue was purified by flash chromatography using CH_2Cl_2:isopropyl alcohol (9:1) as eluant to give 0.041 g (87%) of pure compound **12** as a white solid: mp 207 °C; UV (MeOH) λ_{max} 267.8 nm (ϵ 10 450); ^{1}H NMR (DMSO-d_6) δ 0.51 (m, 1 H, H-6′$_{exo}$), 0.61 (dd, J = 8.6, 5.2 Hz, 1 H, H-6′$_{endo}$), 1.21 (dd, J = 8.6, 3.5 Hz, 1 H, H-5′), 1.55 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 1.96 (m, 1 H, H-2′$_\beta$), 3.29 (d, J = 11.4 Hz, 1 H, C*H*HOH), 3.81 (d, J = 11.4 Hz, 1 H, CH*H*OH), 4.76 (d, J = 6.4 Hz, 1 H, H-4′), 4.92 (s, 1 H, O*H*), 5.53 (dd, J = 8.0, 2.1 Hz, 1 H, H-5), 7.88 (d, J = 8.0 Hz, 1 H, H-6), 11.20 (d, J = 2.1 Hz, 1 H, N*H*); ^{13}C NMR (CD_3OD) δ 12.44 (C-6′), 26.38 (C-3′), 27.19 (C-5′), 30.93 (C-2′), 34.10 (C-1′), 59.36 (C-4′), 65.95 (*C*H$_2$OH), 101.99 (C-5), 144.26 (C-6), 152.81 (C-2), 166.37 (C-4); FAB MS (*m/z*, relative intensity) 315 ([MH + glycerine]$^+$, 26), 223 (MH$^+$, 100), 205 (13), 113 (b + 2H, 78). Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

(±)-***cis*-1-(Hydroxymethyl)-4-(4-amino-2(1*H*)-oxopyrimidin-1-yl)bicyclo[3.1.0]hexane (13).** Compound **9** (0.120 g, 0.54 mmol) was dissolved in anhydrous pyridine (3 mL) and treated with acetic anhydride (2 mL) at room temperature overnight. Evaporation of the solvent gave the monoacetyl derivative **30** in almost theoretical yield: ^{1}H NMR ($CDCl_3$) δ 0.62 (m, 1 H, H-6′$_{exo}$), 0.78 (m, 1 H, H-6′$_{endo}$), 1.30 (dd, J = 8.9, 3.6 Hz, 1 H, H-5′), 2.05 (s, 3 H, COC*H*$_3$), 1.60–2.00 (m, 4 H, H-2′$_{a,b}$, H-3′$_{a,b}$), 3.90 (d, J = 11.9 Hz, 1 H, AcOC*H*H), 4.51 (d, J = 11.9 Hz, 1 H, AcOCH*H*), 4.96 (d, J = 5.4 Hz, 1 H, H-4′), 5.66 (d, J = 8.1 Hz, 1 H, H-5), 7.62 (d, J = 8.1 Hz, 1 H, H-6), 9.85 (s, 1 H, N*H*). This compound was used in the next step without further purification. Triethylamine (540 μL, 3.88 mmol) was added to a stirred mixture of 1,2,4-triazole (0.280 g, 4.05 mmol), phosphorus oxychloride (81 μL, 0.867 mmol), and anhydrous acetonitrile (2.3 mL) under argon. Compound **30** (0.100 g, 0.45 mmol) dissolved in acetonitrile (2 mL) was added to this mixture, and the reaction mixture was stirred at room temperature for 24 h. An additional amount of triethylamine (375 μL, 2.67 mmol) and water (97 μL, 5.42 mmol) was added, and the mixture was stirred for 10 min more before removing all volatiles under vacuum. The residue was partitioned between CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (50 mL), and the organic layer was separated. The aqueous layer was extracted further with CH_2Cl_2 (2 × 50 mL), and the combined organic extract was dried ($MgSO_4$) and reduced to dryness to give the triazole intermediate, which was used directly in the following step: ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H, COC*H*$_3$), 3.95 (d, J = 11.9 Hz, 1 H, AcOC*H*H), 4.67 (d, J = 11.9 Hz, 1 H, AcOCH*H*), 5.21 (d, J = 5.6 Hz, 1 H, H-4′), 7.03 (d, J = 7.2 Hz, 1 H, H-5), 8.13 (s, 1 H, triazole), 8.38 (d, J = 7.2 Hz, 1 H, H-6), 9.29 (s, 1 H, triazole). The residue was dissolved in dioxane (10 mL) and stirred with ammonium hydroxide (d = 0.9, 1.6 mL) overnight at room temperature. The solvent was evaporated, and the residue was treated with methanolic ammonia (saturated at −70 °C) and stirred for 20 h at room temperature. The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, Analtech, 2000 μM) using CH_2Cl_2:isopropyl alcohol:triethylamine (70:30:1) as eluant to give 0.031 g (37%) of pure compound **13** as a white solid: mp 222–224 °C; UV (MeOH) λ_{max} 276.5 nm (ϵ 8400); ^{1}H NMR (DMSO-d_6) δ 0.50 (distorted t, 1 H, H-6′$_{exo}$), 0.60 (dd, J = 8.6, 5.1 Hz, 1 H, H-6′$_{endo}$), 1.15 (dd, J = 8.6, 3.7, 1 H, H-5′), 1.35–1.80 (m, 3 H, H-3′$_{a,b}$, H-2′$_\alpha$), 1.90 (m, 1 H, H-2′$_\beta$), 3.32 (dd, J = 11.4, 4.1 Hz, 1 H, C*H*HOH), 3.78 (dd, J = 11.4, 4.1 Hz, 1 H, CH*H*OH), 4.77 (d, J = 6.3 Hz, 1 H, H-4′), 4.89 (t, J = 5.0 Hz, 1 H, O*H*), 5.67 (d, J = 7.3 Hz, 1 H, H-5), 7.08 (br s, 2 H, N*H*$_2$), 7.86 (d, J = 7.3 Hz, 1 H, H-6); ^{13}C NMR (DMSO-d_6) δ 11.07 (C-6′), 24.85 (C-3′), 25.75 (C-5′), 29.70 (C-2′), 32.51 (C-1′), 57.11 (C-4′), 63.78 (*C*H$_2$OH), 92.99 (C-5), 142.72 (C-6), 154.88 (C-2), 164.59 (C-4); FAB MS (*m/z*, relative intensity) 314 ([MH + glycerine]$^+$, 9), 222 (MH$^+$, 90), 152 (7), 112 (b + 2 H, 100). Anal. ($C_{11}H_{15}N_2O_3 \cdot {}^1/_3H_2O$) C, H, N.

(+)-(1***S*,4*S*,5*S*)-1-(Hydroxymethyl)-4-(1,9-dihydro-6*H*-6-oxopurin-9-yl)bicyclo[3.1.0]hexane (31).** Compound (±)-**9** (0.060 g, 0.25 mmol) was dissolved in water (10 mL), and the pH was adjusted to 7.5 with dilute aqueous ammonia (1:10). Commercial adenosine deaminase (100 μL, EC 3.5.4.4, calf intestine ca. 2000 units/mL, Boehringer Mannheim) was taken in a 0.5 mL Eppendorf tube and centrifuged. The supernatant was removed, and the pellet was dissolved in water (100 μL) and added to the aqueous solution of (±)-**9**. The reaction mixture was stirred for 3 h, and during the course of the reaction, the pH was maintained below 7.7 by the addition of diluted formic acid (1:100). The solution was lyophilized, and the residue was purified by preparative TLC (silica gel, Analtech, 2000 μm) using $CHCl_3$:MeOH (4:1) as eluant. Extraction of the more polar band afforded 0.010 g (33%) of pure compound **31** as a white solid: mp >280 °C; UV (MeOH) λ_{max} 250.5 nm (ϵ 9700); $[\alpha]^{25}_D$ = +12.8° (c 0.2, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.66 (m, 2 H, H-6′$_{a,b}$), 1.47 (dd, J = 7.4, 4.8 Hz, 1 H, H-5′), 1.52–1.70 (m, 1 H, H-2′$_\alpha$, H-3′$_\beta$), 1.84 (m, 1 H, H-3′$_\alpha$), 2.05 (m, 1 H, H-2′$_\beta$), 3.35 (dd, J = 11.4, 5.0 Hz, 1 H, C*H*HOH), 3.85 (dd, J = 11.4, 5.0 Hz, 1 H, CH*H*OH), 4.88 (d, J = 6.0 Hz, 1 H, H-4′), 4.98 (t, J = 5.0 Hz, 1 H, O*H*), 8.01 (s, 1 H, H-2), 8.34 (s, 1 H, H-8), 12.25 (s, 1 H, N*H*); ^{13}C NMR (DMSO-d_6) δ 11.15 (C-6′), 25.57 (C-3′), 25.80 (C-5′), 29.85 (C-1′), 31.94 (C-2′), 56.15 (C-4′), 63.79 (*C*H$_2$OH), 123.98 (C-5), 138.11 (C-8), 145.27 (C-2), 147.68 (C-4), 156.71 (C-6); FAB MS (*m/z*, relative intensity) 247 (MH$^+$, 83), 137 (b + 2H, 100). On the basis of HPLC analysis using a chiral column (*vide infra*), this compound was enantiomerically pure (ee >99%). Extraction of the less polar band afforded the nonnatural isomer of the carbocyclic adenosine analogue (compound **32**) as a white solid (ee 88%). The ^{1}H NMR spectrum of this compound was identical to that of racemate **9**.

Resolution of Racemate (±)-9 into Both Enantiomers: (−)-(1*R*,4*R*,5*R*)-1-(Hydroxymethyl)-4-(6-amino-9-purinyl)bicyclo[3.1.0]hexane (32) and (+)-(1*S*,4*S*,5*S*)-1-(Hydroxymethyl)-4-(6-amino-9-purinyl)bicyclo[3.1.0]hexane (33). Racemate **9** was resolved into its individual enantiomers by HPLC employing a semipreparative chiral column, Chiracel OD (250 × 10 mm, particle size 10 μm), as a stationary phase and a solvent system consisting of isopropyl alcohol:hexanes:diethylamine (86:14:0.1) as the mobile phase with a flow rate of 3.00 mL/min. The sample (ca. 0.5 mg per injection) was dissolved in isopropyl alcohol (300 μL) before injection. Each peak was collected individually, and after 25 injections, the solvent was evaporated to afford 5 mg of (−)-**32** [retention time 21.35 min, mp 244–245 °C, $[\alpha]^{25}_D$ = −26.3° (c 0.3, MeOH), ee >98%] and 5 mg of (+)-**33** [retention time 25.18 min, mp 234–236 °C, $[\alpha]^{25}_D$ = +26.3° (c 0.2, MeOH), ee >99%]. The enantiomeric excess for each sample was determined by HPLC using a similar analytical chiral column, Chiracel OD (250 × 4.6 mm, 10 μm particle size), under the same conditions with a flow rate of 1.00 mL/min.

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