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Construction of the Bicyclo[3.1.0]hexane Template of a Conformationally Locked Carbocyclic Adenosine via an Olefin Keto-Carbene Cycloaddition

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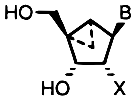
An intramolecular olefin keto-carbene cycloaddition reaction created the bicyclo[3.1.0]hexane template **10** that was necessary for the synthesis of carbocyclic amine **15**. This amine is a direct precursor to a family of rigid nucleosides that are conformationally locked in the Southern hemisphere of the pseudorotational cycle. The synthesis of the conformationally locked adenosine analogue is reported herein as an illustrative example of the methodology. The racemic (South)-methanocarba adenosine analogue (±)-**4** is the first example of a conformationally locked ribonucleoside version in the Southern hemisphere.

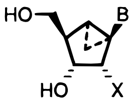
Introduction

Carbocyclic nucleosides have been devised to overcome cleavage of the glycosyl bond, an event that occurs readily in conventional nucleosides by chemical or enzymatic means.[1,2] Although the expected similarity in bond lengths and bond angles between the tetrahydrofuran and cyclopentane rings allows carbocyclic nucleosides to be recognized as substrates or inhibitors of various enzymes, these two classes of rings are far from being identical. First and foremost, the removal of the 4′-oxygen completely abolishes the anomeric effect, and also important gauche interactions between the furan oxygen and the 2′- and 3′-hydroxyl groups, when present, are missing.[3,4] These interactions are responsible for determining the shape and conformation of the tetrahydrofuran ring, which generally adopts a ring pucker close to a 2′-*exo*/3′-*endo* ($^{3}T_{2}$, North, $P = 0^\circ$) or 2′-*endo*/3′-*exo* ($^{2}T_{3}$, South, $P = 180^\circ$) conformation, as defined in the pseudorotational cycle (Figure 1).[3−5] In the solid state, one of these forms usually predominates, whereas in solution the two conformations appear to exist in a rapid dynamic equilibrium between a range of North (${}_{2}E \rightarrow {}^{3}T_{2} \rightarrow {}^{3}E$, $P = 0^\circ \pm 18^\circ$) and opposing South (${}^{2}E \rightarrow {}^{2}T_{3} \rightarrow {}_{3}E$, $P = 180^\circ \pm 18^\circ$) conformations.[3−5] In the absence of the aforementioned forces, the cyclopentane ring in carbocyclic nucleosides adopts an unusual 1′-*exo* (${}_{1}E$, $P = 126^\circ$) conformation that is relatively far from the characteristic North or South conformations observed in the typical nucleosides.[6,7] This conformational deviation from the norm may explain the generally observed weaker biological potency of carbocyclic nucleosides relative to the corresponding nucleoside counterparts.[2]

For the past several years we have synthesized a number of purine and pyrimidine carbocyclic nucleosides built on a rigid bicyclo[3.1.0]hexane template, a system that mimics extremely well either the North envelope (${}_{2}E$) conformation (e.g., compounds **1** and **2**), or the South envelope (${}_{3}E$) conformation (e.g., compounds **3** and **4**) of conventional nucleosides, depending on the point of attachment of the base relative to the position of the fused cyclopropane ring.[8] Since the bicyclo[3.1.0]hexane



1, X = H
2, X = OH



3, X = H
4, X = OH

[†] National Institutes of Health.

[‡] Naval Research Laboratory.

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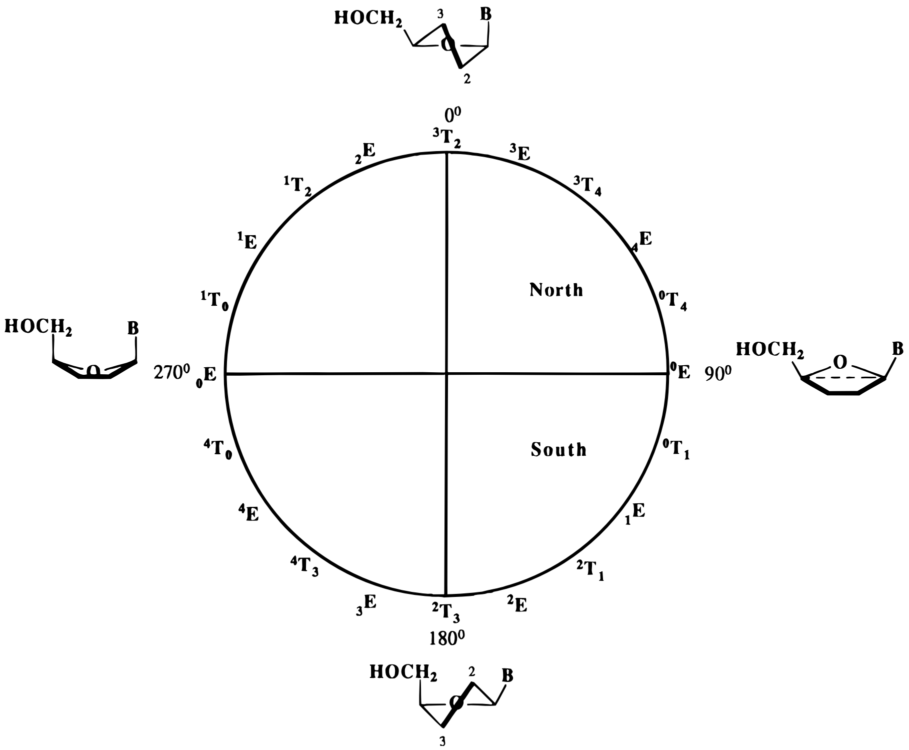


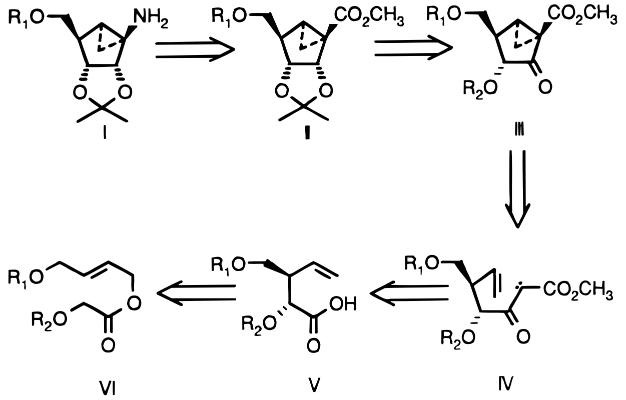
Figure 1. Pseudorotational cycle displaying all the puckering modes (*P*) in conventional nucleosides.

template is known to exist rigidly in a pseudoboat shape, these compounds are able to maintain identical conformations in the solid state and in solution.[8-10] Several studies with these methanocarba nucleosides, mostly in their 2′-deoxyribo configuration, have helped defined the role of sugar puckering in nucleosides by stabilizing the active receptor-bound conformation, and thereby identifying the biologically favored sugar conformer.[8b,d,e,g,h,j-m,o] Thus far, the only compound with the ribo configuration that has been synthesized and studied is the North adenosine analogue (**2**, B = adenine),[8d] and until now, no South ($_3$E)-ribo version has yet been synthesized. Therefore, in the present work, we wish to report a novel approach to these types of carbocyclic nucleosides based on an intramolecular cyclopropanation reaction that culminated with the successful synthesis of the South ($_3$E)-ribo version of adenosine (**4**, B = adenine).

Results and Discussion

Synthesis. The intramolecular cyclopropanation of alkenes to generate bicyclo[3.1.0]hexane systems has been extensively studied in natural product syntheses.[11] However, the key to using this approach successfully in carbocyclic nucleoside chemistry relies on the proper choice of starting materials to make the synthesis adaptable to all types of purine and pyrimidine nucleosides. The retrosynthetic analysis that fulfills such a premise is outline in Scheme 1. Carbocyclic amine I represents a common intermediate to all purines and pyrimidine nucleosides by means of conventional linear approaches.[12-14] The choice of isopropylidene protection is convenient but other protective groups are possible. As in the case of the synthesis of the South ($_3$E)-2′-deoxyribo version,[8c,h] the ester in II could be conveniently transformed into the amine I after hydrolysis to the acid and Curtius rearrangement. The precursor of II is the keto intermediate III, where hydride reduction is anticipated to occur from the less hindered side of the bicyclic system to give the *cis*-diol. The critical bicyclic system III is envisioned to arise from an intramolecular carbene insertion on the olefin in IV following thermolysis of the progenitor diazo compound.[11] The diazo precursor is expected to be readily accessible from the corresponding β-ketoester, which can be obtained from acid V after

Scheme 1



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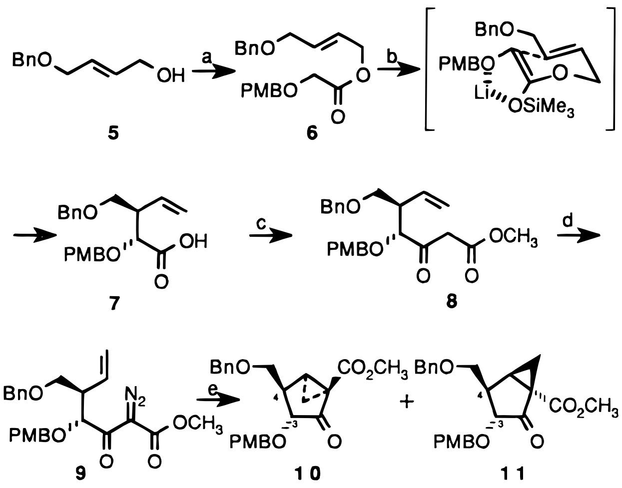
Scheme 2[a]

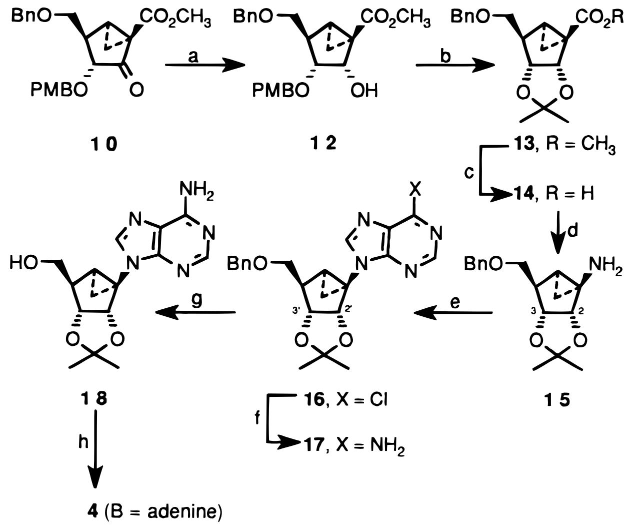


[a] (a) PMBOCH$_2$COOH, DCC, DMAP, CH$_2$Cl$_2$ (99%); (b) (i) LDA, THF; (ii) TMSCl, Et$_3$N (91%); (c) (i) carbonyldiimidazole, THF; (ii) LiCH$_2$CO$_2$CH$_3$, THF (90%); (d) TsN$_3$, Et$_3$N, CH$_3$CN (95%); (e) cupric acetylacetonate, cyclohexane (**10**, 52%; **11**, 26%).

Dieckmann condensation of the activated acid with methyl 2-lithioacetate. Finally, acid V can be conceived as being generated by an enolate [3,3]-sigmatropic rearrangement[15,16] of VI [R$_1$ = Bn and R$_2$ = *p*-methoxybenzyl (PMB)], which in turn can be prepared, in one step, from known (*E*)-4-(benzyloxy)but-2-en-1-ol[17] and *p*-methoxybenzyloxyacetic acid.[18]

The synthesis was realized as planned, and the reagents and conditions employed are shown in Schemes 2 and 3. DCC-catalyzed esterification of (*E*)-butenol **5** and *p*-methoxybenzyloxyacetic acid gave the glycolate ester **6**, which, as expected, underwent an enolate Claisen−Ireland rearrangement[15,16] in the presence of LDA and Me$_3$SiCl with excellent diastereoselectivity to give the desired (2*R**,3*R**)-γ,δ-unsaturated acid **7** in a 95:5 ratio over the (2*S**,3*R**)-isomer. This favorable outcome can be explained by a chairlike transition state that is controlled by the *trans*-geometry of the starting olefin and the local geometry of the enolate induced by the coordinated metal, as illustrated in Scheme 2.[15,16] Activation of the acid with carbonyldiimidazole followed by Dieckmann condensation with methyl 2-lithioacetate[19] produced the β-ketoester **8**, which following diazo transfer with tosyl azide in the presence of triethylamine gave the diazo compound **9** in good yield. Thermolysis of **9** was investigated with a couple of soluble catalysts, such as copper(II) acetylacetonate and rhodium(II) acetate dimer, and copper (II) sulfate as a heterogeneous catalyst. Copper(II) acetylacetonate gave the best results, forming the corresponding bicyclo[3.1.0]hexane system in 78% yield as a separable, 2:1 mixture of diastereoisomers (**10** and **11**) favoring **10**. The initial tentative assignment of structures **10** and **11** was made on the basis of the predictable dihedral angles for a rigid bicyclo[3.1.0]-hexane template,[8] which even with the presence of an sp^2 carbonyl still maintains a pseudoboat conformation.[20] Therefore, the singlet at δ 3.67 ($J = 0$) for the H$_3$ proton signal in the ^{1}H NMR spectrum of one of the isomers was diagnostic of a H$_3$−C$_3$−C$_4$−H$_4$ dihedral angle of ~90° which is only possible in isomer **10**.

Scheme 3[a]



[a] (a) NaBH$_4$, MeOH/CH$_2$Cl$_2$ (2:1) (91%); (b) CuSO$_4$, cat. H$_2$SO$_4$, acetone (93%); (c) 1 N NaOH, MeOH (100%); (d) (i) (PhO)$_2$PON$_3$, Et$_3$N, benzene; (ii) 2 N NaOH, THF (64%); (e) (i) 5-formamido-4,6-dichloropyrimidine, Et$_3$N, THF (78%); (ii) CH$_3$CO$_2$CH(OEt)$_2$ (93%); (f) NH$_3$/MeOH (99%); (g) Pd black, 4.4% HCO$_2$H/MeOH (86%); (h) 80% AcOH (76%).

Additional confirmation of this assignment was obtained after the hydride reduction of the keto group in diastereoisomer **10**, which in diol **12** and all the products derived from it (i.e., **13**−**18** and **4**, Scheme 3) displayed NMR signals for H$_3$ and H$_2$ (**12**−**15**) and H$_{3'}$ and H$_{2'}$ (**16**−**18** and **4**) as doublets, thus confirming a value of ~90° for the H$_3$−C$_3$−C$_4$−H$_4$ torsion angle. Full confirmation of this assignment, however, was obtained later from the X-ray structure of the final adenosine analogue **4** (B = adenine, vide infra). Simultaneous deprotection of the PMB group and acetonide formation occurred in the presence of Cu(II) sulfate and catalytic amounts of sulfuric acid to give **13** (Scheme 3). Saponification of ester **13** was followed by a modified Curtius rearrangement of the resulting acid **14** with diphenylphosphoryl azide[21] in refluxing benzene to give a rather stable isocyanate intermediate that required further hydrolysis with sodium hydroxide to generate the corresponding amine **15**. Finally, the purine base was constructed as shown in Scheme 3 following the same approach that was used for the South ($_3$E)-2′-deoxyribo version (**3**).[8c,h]

Crystal Structure and Conformational Analysis. The X-ray structure of compound **4** (B = adenine, Figure 2) confirmed the fitness of the synthetic approach to construct the rigid, South ($_3$E)-ribo version of the requisite carbocyclic amine **15** and the interpretation of the ^{1}H NMR spectra of the intermediates leading to it (vide supra). The conformation of the pseudosugar ring in **4** (B = adenine) is nearly identical to that of the South ($_3$E)-2′-deoxyribo version of **3** (B = adenine).[8m,o] It has a *P*

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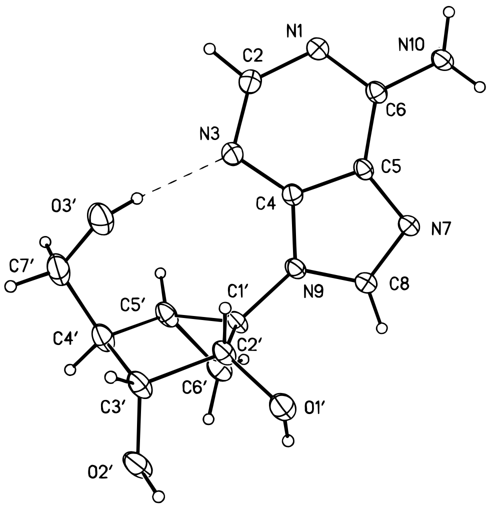

Figure 2. The molecular structure and numbering scheme for **4** (B = adenine, polymorph c). The hydrate is omitted. The dashed line is an intramolecular hydrogen bond.

value of 201.16° and a ν_{max} of 28.63°, which indicates that the conformation is nearly a perfect $_3$E envelope (P = 198°). In the unit cell of the chiral compound **3** (B = adenine), there were two molecules that, although identical relative to the value of P, had different χ torsion angles corresponding to both *anti*- and *syn*-conformers.[8m,o] In the case of (±)-**4** (B = adenine), the cell contains both hands, but the torsion angle χ in both structures is firmly in the *syn* range ($\chi = +58.2°$). The intramolecular hydrogen bond, which may help stabilize the *syn*-conformation in the crystal structure, also fixes the torsion angle γ in the +*sc* range (+47.5°). All of these values are in the normal range of torsion angles found in conventional nucleosides, except that the sugar ring (pseudosugar ring) is confined to the Southern hemisphere. Therefore, this compound represents a useful tool to study of the conformational preferences of adenosine-metabolizing enzymes. Preliminary results indicate that **4** (B = adenine) is an extremely poor substrate for adenosine deaminase (ADA). Indeed, initial attempts to use ADA to resolve the racemate failed. A variant of this approach designed to obtain the chiral, D-ribo version of carbocyclic amine **15** is in progress, as well as the synthesis of other purine and pyrimidine analogues with a South-constrained pseudosugar conformation.

Conclusions

A new and efficient approach for the synthesis of carbocyclic amine **15** based on an intramolecular olefin keto-carbene cycloaddition reaction was successful in creating the requisite bicyclo[3.1.0]hexane template. Amine **15** represents a common intermediate for the synthesis of all purine and pyrimidine analogues, which can be accessed by various linear approaches. The synthesis of the adenosine analogue **4** (B = adenine) represents the first example of a conformationally rigid, South ($_3$E)-ribonucleoside version built on a bicyclo[3.1.0]hexane template. The structure of **4** (B = adenine) was confirmed by X-ray analysis.

Experimental Section

X-ray Crystallography. The adenosine nucleoside **4** was recrystallized by evaporation from methanol/water (10:1) and from 2-butanone/water (3:1) as hydrates to form two polymorphs (p and c), a primitive and C-centered monoclinic, respectively. The conformation of the molecule in the two polymorphs is essentially identical and differs only with respect to the location of the hydroxyl and water hydrogens. There are five hydrogen bonds in the primitive cell and six in the C-centered cell. The additional hydrogen bond in the C-centered cell involves the water, which acts as a donor to the hydroxy methyl oxygen.

Single-Crystal X-ray Diffraction Analysis of 4 (B = adenine). (p) $C_{12}H_{15}N_5O_3 \cdot H_2O$, fw = 295.31, monoclinic space group $P2_1/c$, $a = 15.200(2)$, $b = 7.802(1)$, $c = 11.432(1)$ Å, $\beta = 91.01(1)°$, $V = 1355.5(2)$ Å^3, $Z = 4$, $\rho_{calc} = 1.477$ mg mm^{-3}, λ(Cu Kα) = 1.54184 Å, $\mu = 0.936$ mm^{-1}, $F(000) = 624$, $T = 295$°K.

(c) $C_{12}H_{15}N_5O_3 \cdot H_2O$, fw = 295.31, monoclinic space group $C2/c$, $a = 32.029(2)$, $b = 7.983(1)$, $c = 11.332(3)$ Å, $\beta = 109.44(1)°$, $V = 2732.2(4)$ Å^3, $Z = 8$, $\rho_{calc} = 1.436$ mg mm^{-3}, λ(Cu Kα) = 1.54184 Å, $\mu = 0.928$ mm^{-1}, $F(000) = 1248$, $T = 295$°K. The following parameters are common to p and c, and where different they are indicated by enclosure in brackets [ ] for c.

A clear colorless 0.02 × 0.20 × 0.24 [0.06 × 0.44 × 0.52] mm crystal was used for data collection on an automated Bruker P4 diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from 42 [52] centered reflections within $14° < 2\theta < 50°$ [$6° < 2\theta < 60°$]. The data collection range of hkl was $-16 \le h \le 16$, $-1 \le k \le 8$, $0 \le l \le 12$, [$-34 \le h \le 34$, $-8 \le k \le 0$, $-11 \le l \le 11$], with $\{(\sin\theta)/\lambda\}_{max} = 0.55$. Three standards, monitored after every 97 reflections, exhibited random variations with deviations up to ±2.5% [1.3%] during the data collection. A set of 2396 [3849] reflections was collected in the $\theta/2\theta$ scan mode, with scan width $[2\theta(K_{\alpha 1}) - 1.0]°$ to $[2\theta(K_{\alpha 2}) + 1.0]°$ and ω scan rate (a function of count rate) from 5.0°/min [7.5°/min] to 30.0°/min. There were 1862 [1863] unique reflections, and 1294 [1646]were observed with $F_o > 4\sigma(F_o)$. The structure was solved and refined with the aid of the SHELX-97[22] system of programs. The full-matrix least-squares refinement varied 222 [221] parameters: atom coordinates and anisotropic thermal parameters for all non-H atoms. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C−H distances set to 0.96−0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2 U_{eq}(C)]. The amine, hydroxyl, and water hydrogens coordinates were refined with fixed isotropic thermal values. Final residuals were $R1 = 0.071$ [0.052] with final difference Fourier excursions of 0.53 and −0.44 [0.41 and −0.46] e Å^{-3}.

Tables of coordinates, bond distances and bond angles, and anisotropic thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge, CB2, 1EW, England.

General Procedures. All chemical reagents were commercially available. Melting points were determined on a Fisher−Johns melting point apparatus and are uncorrected. Column chromatography was performed on silica gel 60, 230−400 mesh (E. Merk), and analytical TLC was performed on Analtech Uniplates silica gel GF. Routine IR and ^{1}H and ^{13}C NMR spectra were recorded using standard methods. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained 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. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

(*E*)-4-(Phenylmethoxy)but-2-en-1-ol (5). A stirred solution of LAH (0.45 g, 12 mmol) in anhydrous THF (50 mL) was maintained at −20 °C and treated with 3.5 g (20 mmol) of 4-(phenylmethoxy)but-2-yn-1-ol,[17] which was added slowly and allowed to react further for 2 h at 0 °C. The cold reaction mixture was quenched by the careful addition of water (1 mL),

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[22] Sheldrick, G. M. *SHELXTL* Version 5.1; Bruker Analytical X-ray Instruments: Madison, WI, 1997.

15% NaOH (1 mL), and water (3 mL). After further stirring at room temperature, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Flash column chromatography (25% EtOAc in hexane) gave 3.2 g of the (*E*)-isomer (**5**) as a clear oil.[17]

(*E*)-4-(Phenylmethoxy)but-2-enyl 2-[(4-Methoxyphenyl)methoxy]acetate (6). To a stirred solution of **5** (8.5 g, 48 mmol) in CH_2Cl_2 (140 mL) were added 2-[(4-methoxyphenyl)methoxy]acetic acid (12.1 g, 62 mmol), 1,3-dicyclohexylcarbodiimide (DCC, 11.8 g, 57 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.3 g, 2.5 mmol) at 0 °C. The reaction was allowed to warm slowly to room temperature. After being stirred for 20 h, the reaction mixture was filtered to remove the precipitated urea, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether, filtered, and reconcentrated under reduced pressure. Flash column chromatography (10% → 20% EtOAc in hexane) gave 16.9 g (99.6%) of ester **6** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.43−7.44 (m, 5 H), 7.39 (d, 2 H, J = 8.5 Hz), 6.97 (d, 2 H, J = 8.5 Hz), 6.00 (m, 2 H), 4.76 (d, 2 H, J = 4.2 Hz), 4.66 (s, 2 H), 4.61 (s, 2 H), 4.17 (s, 2 H), 4.12 (d, 2 H, J = 3.7 Hz), 3.86 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.94, 159.35, 137.96, 131.44, 129.65, 129.01, 128.28, 127.58, 127.55, 125.86, 113.76, 72.87, 72.31, 69.58, 66.73, 64.47, 55.17; IR (neat) 1753 cm^{-1}; FAB MS m/z (relative intensity) 356 (M^+, 4.3), 195 (17), 121 (100), 91 (44). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.55; H, 6.83.

(2*R,3*R**)-2-[(4-Methoxyphenyl)methoxy]-3-[(phenylmethoxy)methyl]pent-4-enoic Acid (7).** Ester **6** (10.3 g, 29 mmol) was added slowly to a stirred solution of lithium diispropylamide (LDA, 3.4 g, 32 mmol) in anhydrous THF (100 mL) at −78 °C. After 1 h, 8.3 mL of a clear, 1:1 solution of Me_3SiCl and Et_3N was added, and the mixture was stirred for an additional 1 h at −78 °C. During the course of the ensuing 18 h, the reaction mixture was allowed to reach room temperature. The solution was poured into 5% NaOH, stirred for 15 min, and extracted twice with ether. The aqueous layer was acidified to pH 5 with concentrated HCl at 0 °C and extracted thrice with CH_2Cl_2. The combined organic extract was dried ($MgSO_4$) and concentrated under reduced pressure to give 7.6 g of **7** (91.2% based on recovery of 2 g of starting material from the ether extract) as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 11.18 (br s, 1 H), 7.30−7.50 (m, 7 H), 6.96 (d, 2 H, J = 8.5 Hz), 5.84−6.00 (m, 1 H), 5.25 (m, 2 H), 4.78 (d, 1 H, J = 11.1 Hz), 4.58 (d, 2 H, J = 3.9 Hz), 4.49 (d, 1 H, J = 11.1 Hz), 4.19 (d, 1 H, J = 5.1 Hz), 3.88 (s, 3 H), 3.78 (dd, 1 H, J = 6.9, 9.3 Hz), 3.70 (dd, 1 H, J = 5.6, 9.3 Hz), 3.03 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.18, 159.29, 138.08, 134.85, 129.65, 129.08, 128.16, 127.39, 127.35, 118.04, 113.69, 72.99, 72.57, 69.19, 67.80, 55.18, 46.85; IR (neat) 1720 cm^{-1}; FAB MS m/z (relative intensity) 357 (MH^+, 1.6), 121 (100), 91 (33). Anal. Calcd for $C_{21}H_{24}O_5 \cdot 0.2H_2O$: C, 70.06; H, 6.83. Found: C, 70.10; H, 6.79.

(4*R,5*R**)-Methyl 4-[(4-Methoxyphenyl)methoxy]-3-oxo-5-[(phenylmethoxy)methyl]hept-6-enoate (8).** Carbonyldiimidazole (3.1 g, 19 mmol) was added to a stirred solution of acid **7** (6.2 g, 17.5 mmol) in THF at 0 °C. The temperature was maintained at 0 °C for 30 min and then allowed to reach room temperature after 2 h. This solution was added via cannula to a −78 °C solution of $LiCH_2COOCH_3$ obtained from MeOAc (4.2 mL, 52 mmol) and LDA (5.6 g, 52 mmol) in anhydrous THF (100 mL) after 1 h at −78 °C. After the addition, the reaction was stirred further for 1.5 h at −78 °C, quenched with 1 N HCl solution (53 mL), allowed to reach 0 °C, acidified to pH 3 with additional HCl, and extracted with EtOAc. The combined organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in hexane) to give 6.4 g (89.5%) of the β-ketoester **8** as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.35−7.40 (m, 5 H), 7.33 (d, 2 H, J = 8.5 Hz), 6.97 (d, 2 H, J = 8.5 Hz), 5.79−5.92 (m, 1 H), 5.21−5.29 (m, 2 H), 4.66 (d, 1 H, J = 11.0 Hz), 4.45−4.68 (m, 3 H), 4.10 (d, 1 H, J = 5.1 Hz), 3.86 (s, 3 H), 3.73−3.83 (m, 2 H), 3.74 (s, 3 H), 3.62 (dd, 1 H, J = 5.0, 9.1 Hz), 3.54 (d, 1 H, J = 15.9 Hz), 2.93−3.11 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 204.15, 167.78, 159.32, 137.96, 134.92, 129.48, 129.25, 128.19, 127.49, 127.41, 117.92, 113.72, 84.41, 73.21, 72.91, 68.92, 55.16, 52.00, 47.04, 45.30; IR (neat) 1748 cm^{-1}; FAB MS m/z (relative intensity) 413 (MH^+, 0.6), 276 (1.4), 121 (100), 91 (24.5). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.73; H, 6.80.

(4*R,5*R**)-Methyl2-Diazo-4-[(4-methoxyphenyl)methoxy]-3-oxo-5-[(phenylmethoxy)methyl]hept-6-enoate (9).** To a stirred solution of β-ketoester **8** (6.1 g, 15 mmol) in CH_3CN (30 mL) maintained at 0 °C were added Et_3N (4 mL, 29 mmol) and *p*-toluenesulfonyl azide (2.96 g, 15 mmol). The reaction solution was allowed to reach room temperature and stirred overnight. After partitioning between ether and 2 N NaOH under vigorous stirring for 10 min, the ether layer was separated, washed successively with 2 N NaOH and brine, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a crude product, which was purified by flash column chromatography (10% EtOAc in hexane) to afford 6.2 g (94.9%) of the diazo compound **9** as an oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.29−7.31 (m, 5 H), 7.25 (d, 2 H, J = 8.5 Hz), 6.85 (d, 2 H, J = 8.5 Hz), 5.81−5.96 (m, 1 H), 5.12−5.27 (m, 2 H), 4.93 (d, 1 H, J = 5.1 Hz), 4.57 (d, 1 H, J = 11.2 Hz), 4.48 (d, 1 H, J = 11.7 Hz), 4.41 (d, 1 H, J = 11.7 Hz), 4.35 (d, 1 H, J = 11.2 Hz), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.69 (dd, 1 H, J = 5.8, 9.3 Hz), 3.62 (dd, 1 H, J = 5.6, 9.3 Hz), 2.86−2.93 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 191.07, 161.33, 159.19, 138.25, 135.67, 129.63, 128.10, 127.49, 127.40, 127.30, 117.57, 113.51, 81.00, 75.59, 73.02, 72.46, 69.41, 55.14, 52.17, 47.16; FAB MS m/z (relative intensity) 439 (MH^+, 2), 121 (100). The thermal instability of this sample produced an inaccurate elemental analysis.

(1*R,3*R**,4*R**,5*S**)-Methyl 3-[(4-Methoxyphenyl)methoxy]-2-oxo-4-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexanecarboxylate (10).** A stirred solution of diazoester **9** (4.0 g, 9 mmol) in cyclohexane (100 mL) was treated with copper(II) acetylacetonate (2.4 g, 9 mmol), and the reaction mixture was placed in a preheated oil bath (115−120 °C). After 5 h, the insolubles were removed by filtration through Celite, and the solid cake was washed with ether. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (20% → 33% EtOAc in hexane) to give 1.9 g (52%) of pure bicyclic compound **10** as an oil and its isomer **11** (0.9 g, ca. 26%), which coeluted with another contaminant.

Compound **10**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.28−7.45 (m, 7 H), 6.93 (d, 2 H, J = 8.5 Hz), 4.75 (d, 1 H, J = 11.2 Hz), 4.56 (d, 1 H, J = 11.2 Hz), 4.55 (s, 2 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.67 (s, 1 H), 3.57 (d, 2 H, J = 5.6 Hz), 2.40−2.55 (m, 2 H), 2.13 (dd, 1 H, J = 4.7, 7.9 Hz), 1.98 (uneven triplet, 1 H, J 5.2 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.04, 168.57, 159.22, 137.67, 129.63, 129.21, 128.24, 127.54, 127.30, 113.68, 81.59, 73.11 (CH_2), 72.05 (CH_2), 71.07 (CH_2), 55.16, 52.30, 42.15, 36.87, 33.08, 22.47 (CH_2); IR (neat) 1736 cm^{-1}; FAB MS m/z (relative intensity) 411 (MH^+, 2.8), 121 (100), 91 (33). Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 69.97; H, 6.50.

Compound **11**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.25−7.50 (m, 7 H), 6.93 (d, 2 H, J = 8.8 Hz), 5.05 (d, 1 H, J = 11.2 Hz), 4.45−4.65 (m, 3 H), 3.85 (s, 6H), 3.79 (d, 1 H, J = 8.6 Hz), 3.72 (dd, 1 H, J = 3.3, 9.5 Hz), 3.57 (dd, 1 H, J = 5.8, 9.5 Hz), 2.70 (m, 2 H), 2.05 (m, 1 H), 1.70 (uneven triplet, 1 H, $J \cong 5.1$ Hz).

(1*R,2*S**,3*R**,4*R**,5*S**)-Methyl 2-Hydroxy-3-[(4-methoxyphenyl)methoxy]-4-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexanecarboxylate (12).** A stirred solution of bicyclic ketoester **10** (1.8 g, 4 mmol) in a 2:1 mixture of $MeOH/CH_2Cl_2$ (30 mL) was cooled to − 20 °C and treated with $NaBH_4$ (0.17 g, 4.5 mmol). The temperature was allowed to reach 0 °C, and stirring was continued for 30 min before quenching of the reaction with 1 N H_2SO_4 (3 mL). The resulting solution was extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and reduced to dryness under vacuum. Purification by flash column chromatography (25% EtOAc in hexane) afforded the corresponding alcohol **12** (1.6 g, 91%) as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.36−7.45 (m, 5 H), 7.29 (d, 2 H, J = 8.7 Hz), 6.94 (d, 2 H, J = 8.7 Hz), 5.06 (d, 1 H, J = 6.8 Hz), 4.59 (d, 1 H, J = 11.2 Hz), 4.57 (s, 2 H), 4.45 (d, 1 H, J = 12.2 Hz), 3.87 (br s, 4 H), 3.77 (s, 3 H), 3.50 (dd, 1 H, J = 5.5, 9.2 Hz), 3.40 (dd, 1 H, J = 6.7, 9.2 Hz), 2.92 (br s, 1 H), 2.51 (uneven t, 1 H, $J \cong 6$ Hz), 1.85 (dd, 1 H, J = 5.3, 8.5 Hz), 1.63 (uneven t, 1 H, $J \cong 5$ Hz), 1.51 (ddd, 1 H, $J \cong 1$, 4.2, 8.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.46, 159.23, 137.99, 129.41, 129.36, 128.24, 127.48, 127.27, 113.75, 80.81, 73.07 (CH_2), 72.09, 71.98 (CH_2), 71.47 (CH_2), 55.17, 51.90, 45.01, 36.13, 30.54, 16.78 (CH_2); IR (neat) 3526, 1719 cm^{-1}; FAB MS *m/z* (relative intensity) 413 (MH^+, 0.7), 411 ($MH^+ - H_2$, 2), 121 (100), 91 (27). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.86; H, 6.91.

(1*R,2*S**,3*R**,4*R**,5*S**)-Methyl 2,3-*O*-Isopropylidene-4-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexanecarboxylate (13).** A stirred solution of bicyclic alcohol **12** (0.72 g, 1.7 mmol) in acetone (35 mL) was cooled to 0 °C and treated with anhydrous $CuSO_4$ (0.12 g, 0.7 mmol) and 4 drops of concentrated H_2SO_4. The reaction mixture was stirred overnight at room temperature, and the solid material was removed by filtration through a pad of Celite. The filtrate was neutralized with saturated $NaHCO_3$ solution and extracted with ether. The organic solution was washed with brine, dried ($MgSO_4$), and reduced to dryness under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in hexane) to give **13** (0.5 g, 93%) as a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35−7.45 (m, 5 H), 5.43 (d, 1 H, J = 6.8 Hz), 4.61 (d, 1 H, J = 6.8 Hz), 4.59 (s, 2 H), 3.77 (s, 3 H), 3.45−3.62 (m, 2 H), 2.54 (t, 1 H, J = 5.3 Hz), 2.12 (dd, 1 H, J = 6.2, 8.5 Hz), 1.51−1.67 (m, 2H), 1.58 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.05, 137.99, 128.19, 127.43, 127.17, 110.86, 85.32, 80.54, 73.01(CH_2), 71.84 (CH_2), 51.95, 44.59, 37.60, 36.29, 26.18, 24.12, 19.87 (CH_2); IR (neat) 1723 cm^{-1}; FAB MS *m/z* (relative intensity) 333 (MH^+, 7), 275 (10), 91 (100). Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28. Found: C, 68.83; H, 7.39.

(1*R,2*S**,3*R**,4*R**,5*S**)-2,3-*O*-Isopropylidene-4-[(phenylmethoxy)methyl]-bicyclo[3.1.0]hexanecarboxylic Acid (14).** To a stirred solution of the bicyclic ester **13** (0.08 g, 0.25 mmol) in MeOH (1 mL) was added 1 N NaOH (0.5 mL). After heating to 50 °C for 2 h, the cooled solution was treated with 1 N HCl to pH 5 and extracted with CH_2Cl_2. The organic extract was washed with brine, dried ($MgSO_4$), and reduced to dryness under reduced pressure to give acid **14** (0.08 g, 100%) as a white solid, mp 129−130 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 11.90 (br s, 1 H), 7.33−7.46 (m, 5 H), 5.43 (d, 1 H, J = 6.8 Hz), 4.61 (d, 1 H, J = 6.8 Hz), 4.60 (s, 2H), 3.55 (d, 2 H, J = 5.3 Hz), 2.56 (t, 1 H, J = 5.2 Hz), 2.20 (dd, 1 H, J = 6.3, 8.5 Hz), 1.75 (m, 1 H), 1.59 (overlapped s and m, 4 H), 1.37 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 179.45, 137.86, 128.25, 127.49, 127.30, 110.97, 85.23, 80.18, 73.05 (CH_2), 71.60 (CH_2), 44.67, 37.56, 37.26, 26.18, 24.11, 20.41 (CH_2); IR (KBr) 3752, 1686 cm^{-1}; FAB MS *m/z* (relative intensity) 319 (MH^+, 24), 261 (42), 91 (100). Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.68; H, 7.12.

(1*R,2*S**,3*R**,4*R**,5*S**)-1-Amino-2,3-*O*-isopropylidene-4-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexane (15).** A stirred solution of bicyclic acid **14** (0.08 g, 0.25 mmol) in anhydrous benzene (3 mL) was treated with Et_3N (0.1 mL, 0.75 mmol) and diphenylphosphoryl azide (0.16 mL, 0.75 mmol). The reaction mixture was heated at reflux temperature overnight and then concentrated under reduced pressure. The crude isocyanate was treated with 2 N NaOH (2 mL) and THF (5 mL) and stirred for 20 min at room temperature. The resulting solution was extracted twice with CH_2Cl_2, and the organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the crude (EtOAc) gave the bicyclic amine **15** (0.04 g, 64%) as a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36−7.42 (m, 5 H), 4.76 (dd, 1 H, J = 1.3, 6.9 Hz), 4.62 (s, 2 H), 4.54 (d, 1 H, J = 6.9 Hz), 3.55 (AB m, 2 H), 2.34 (t, 1 H, J = 5.1 Hz), 1.93 (br s, 2 H), 1.58 (s, 3 H), 1.39 (dd, 1 H, J = 4.6, 9.3 Hz), 1.34 (s, 3 H), 1.07 (uneven t, 1 H, $J \cong 5$ Hz), 0.95 (ddd, 1 H, J = 1.6, 4.9, 9.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.20, 128.25, 127.47, 127.35, 110.65, 88.29, 84.76, 73.10 (CH_2), 72.42 (CH_2), 48.24, 44.91, 31.96, 26.25, 24.29, 18.13 (CH_2); IR (neat) 3364 cm^{-1}; FAB MS *m/z* (relative intensity) 290 (MH^+, 70), 232 (12), 91 (100). Anal. Calcd for $C_{17}H_{23}NO_3 \cdot 0.25H_2O$: C, 69.69; H, 8.05; N, 4.78. Found: C, 69.86; H, 7.93; N, 4.66.

(1*R,2*S**,3*R**,4*R**,5*S**)-1-(6-Chloropurin-9-yl)-2,3-*O*-isopropylidene-4-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexane (16).** To a stirred solution of bicyclic amine **15** (0.04 g, 0.14 mmol) in dioxane (3 mL) were added 4,6-dichloro-5-formamidopyrimidine (0.027 g, 0.14 mmol) and Et_3N (0.08 mL, 0.6 mmol). The reaction mixture was heated at reflux for 24 h. After cooling to room temperature, the solution was filtered to remove the precipitated salt, and the filtrate was reduced to dryness under reduced pressure. The residue was purified by flash chromatography (50% EtOAc in hexane) to give 0.05 g (78%) of the 4-chloro-5-formamidopyrimidin-6-yl intermediate as a thick oil. This compound was immediately treated with diethoxymethyl acetate (1 mL, 6 mmol) and heated to 120 °C for 20 h. After cooling, the excess diethoxymethyl acetate was evaporated under reduced pressure, and the residue was purified by flash chromatography to give **16** (0.04 g, 93%) as a thick oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 8.22 (s, 1 H), 7.29−7.36 (m, 5 H), 5.03 (d, 1 H, J = 6.8 Hz), 4.66 (br s, 3 H), 3.85 (m, 2 H), 2.59 (t, 1 H, J = 5.7 Hz), 2.06 (dd, 1 H, J = 5.5, 9.9 Hz), 1.75 (uneven t, 1 H, J 6 Hz), 1.60 (s, 3 H), 1.53−1.57 (m, 1 H), 1.26 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.30, 151.91, 150.59, 145.96, 137.53, 131.55, 128.33, 127.78, 127.71, 111.69, 84.77, 84.33, 73.40 (CH_2), 71.46 (CH_2), 48.42, 44.60, 31.08, 26.27, 24.02, 16.43 (CH_2); IR (neat) 1560, 1493 cm^{-1} ; FAB MS *m/z* (relative intensity) 427 (MH^+, 100), 91 (88). Anal. Calcd for $C_{22}H_{23}ClN_4O_3$: C, 61.25; H, 5.49; N, 12.99. Found: C, 61.32; H, 5.58; N, 12.54.

(1*R,2*S**,3*R**,4*R**,5*S**)-1-(6-Aminopurin-9-yl)-2,3-*O*-isopropylidene-4-[(phenylmethoxy)methyl]bicyclo[3.1.0]hexane (17).** A steel pressure vessel containing a solution of chloropurine **16** (0.94 g, 2 mmol) in saturated methanolic ammonia (43 mL) was heated at 80 °C for 18 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (EtOAc → 20% acetone in EtOAc) to give **17** (0.88 g, 99%) as a white solid, mp 65−67 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.92 (s, 1 H), 7.35−7.43 (m, 5 H), 6.58(br s, 2 H), 5.14 (d, 1 H, J = 6.8 Hz), 4.70 (br s, 3 H), 3.91 (m, 2 H), 2.62 (t, 1 H, J = 6.2 Hz), 2.04 (dd, 1 H, J = 5.4, 9.3 Hz), 1.73 (uneven t, 1 H, $J \cong 6$ Hz), 1.65 (s, 3 H), 1.56 (dd, 1 H, J = 6.1, 9.7 Hz), 1.31 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.60, 153.00, 150.60, 140.97, 137.79, 128.34, 127.75, 127.72, 119.55, 111.54, 84.85, 84.29, 73.36 (CH_2), 71.57 (CH_2), 48.01, 44.84, 30.95, 26.31, 24.06, 16.29 (CH_2); IR (KBr) 3325, 1648 cm^{-1}; FAB MS *m/z* (relative intensity) 408 (MH^+, 100), 350 (3), 228 (7), 136 (15), 91 (49). Anal. Calcd for $C_{22}H_{25}N_5O_3$: C, 64.85; H, 6.18; N, 17.19. Found: C, 64.61; H, 6.28; N, 17.02.

(1*R,2*S**,3*R**,4*R**,5*S**)-1-(6-Aminopurin-9-yl)-2,3-*O*-isopropylidene-4-hydroxy-methyl]bicyclo[3.1.0]hexane (18).** A stirred solution of the protected bicyclic aminopurine **17** (0.75 g, 1.8 mmol) in 5% HCO_2H/MeOH (52 mL) was treated with palladium black (150 mg) and allowed to react overnight. The suspension was filtered through Celite, and the filter cake was washed with MeOH. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (10% EtOAc in hexane) to give **18** (0.5 g, 86%) as a white solid, mp 230−232 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 7.97 (s, 1 H), 6.70 (br s, 2 H), 5.03 (dd, 1 H, J = 1.1, 6.7 Hz), 4.90 (dd, 1 H, J = 1.1, 6.7 Hz), 4.11 (d, 1 H, J = 11.8 Hz), 3.91 (dd, 1 H, J = 2.9, 11.8 Hz), 2.54 (br d, 1 H, J = 2.9 Hz), 2.02 (dd, 1 H, J = 4.5, 9.1 Hz), 1.71 (uneven t, 1 H, J 5.5 Hz), 1.63 (s, 3 H), 1.36 (m, 2 H), 1.32 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.88, 152.34, 149.59, 141.40, 119.26, 111.21, 85.07, 84.47, 65.18, 48.46, 46.35 (CH_2), 30.54, 26.32, 24.12, 16.31 (CH_2); IR (KBr) 3752, 3177, 1654 cm^{-1}; FAB MS *m/z* (relative intensity) 318 (MH^+, 100), 260 (5.6), 136 (21). Anal. Calcd for $C_{15}H_{19}N_5O_3 \cdot 0.25H_2O$: C, 55.98; H, 6.11; N, 21.76. Found: C, 56.14; H, 6.03; N, 21.47.

(1*R,2*S**,3*R**,4*R**,5*S**)-1-(6-Aminopurin-9-yl)-4-(hydroxymethyl)bicyclo-[3.1.0]hexane-2,3-diol (4).** A stirred solution of **18** (0.6 g, 1.8 mmol) in 80% aqueous AcOH was heated to 100 °C for 3.5 h. After cooling, the solvent was removed under reduced pressure, and the residue was purified by reversed phase (Octadecyl-C_{18}) chromatography ($H_2O \rightarrow$ 2% THF in H_2O) to give **4** (0.39 g, 76%) as a white lyophilized powder, mp 249−251 °C, and a second solid (0.09 g, 15%), which according to ^{1}H NMR corresponded to the monoacetate of **4** at the primary alcohol position. Compound **4**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.17 (s, 1 H), 8.07 (s, 1H), 7.37 (br s, 2 H), 5.53 (dd, 1 H, $J = 3.6, 8.3$ Hz, D_2O exchangeable), 4.86 (d, 1 H, $J = 8.1$ H, D_2O exchangeable), 4.69 (d, 1 H, $J = 3.2$ Hz, D_2O exchangeable), 4.57 (t converted to a d after D_2O exchange, 1 H, $J = 5.9$ Hz), 3.90 (br d converted to a d after D_2O exchange, 1 H, $J = 5.9$ Hz), 3.80 (m, 2 H), 2.15 (t, 1 H, $J = 4.7$ Hz), 1.75 (dd, 1 H, $J = 4.8, 8.5$ Hz), 1.70 (uneven t, 1 H, $J \cong 4.4$ Hz), 1.25−1.29 (m, 1 H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 156.01, 152.04, 149.54. 141.70, 118.93, 75.25, 71.67, 63.47 (CH_2), 49.84, 46.92, 23.82, 13.81 (CH_2); IR (KBr) 3605, 3211, 1642 cm^{1}; FAB MS m/z (relative intensity) 278 (MH^+, 100), 136 (23). Anal. Calcd for $C_{12}H_{15}N_5O_3 \cdot H_2O$: C, 48.81; H, 5.80; N, 23.72. Found: C, 49.11; H, 5.81; N, 23.46.

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Supporting Information Available: Crystal data and structure refinement, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, torsion angles, and hydrogen bonds for both polymorphs (p and c) of structure **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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