Synthesis of Cyclopropyl-Fused Carbocyclic Nucleosides via the Regioselective Opening of Cyclic Sulfites†

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The syntheses of some carbocyclic nucleosides that are conformationally locked as "northern" mimics of antiviral active, ring-expanded oxetanocin analogues are reported. The target compounds derived their rigid conformation from a common bicyclo[3.1.0]hexane template. The uracil (**3a**), cytosine (**3b**), and adenine (**3c**) analogues were synthesized from an intermediate cyclic sulfite (**12a**) that underwent selective ring opening with nucleophiles. Reaction of **12a** with sodium azide provided access to the uracil and cytosine analogues (**3a** and **3b**) after construction of the pyrimidine rings, and reaction with the sodium salt of adenine provided an efficient convergent approach to **3c**. The preponderance of the undesired N-7 regioisomer obtained from the coupling of **12a** with 2-amino-6-chloropurine was unanticipated. Hence, the diol derivative **11** was selectively protected and coupled under Mitsunobu conditions to give, after deprotection, the desired guanine analogue **3d**. With the exception of the guanine analogue, the cyclic sulfite chemistry described here represents a useful alternative as a general approach to carbocyclic nucleosides. None of the target nucleosides **3a**−**d** demonstrated significant antiviral activity against HIV-1, HSV-1, HSV-2, and HCMV. Relative to other conformationally rigid, northern carbocyclic analogues that have shown good anti-HSV and anti-HCMV activities, it is concluded that the hydroxymethyl group is a poor substitute for the hydroxyl group in these rigid bicyclic nucleoside templates.

Introduction

The rationale for the synthesis of carbocyclic nucleosides in which the furanose ring oxygen of 4′-oxonucleosides is substituted by a methylene group was to stabilize the hydrolytically and enzymatically scissile glycosyl bond with minimal structural disturbances.[1−4] However, the fact that most conventional carbocyclic nucleosides have generally exhibited poorer biological potencies than the corresponding 4′-oxonucleosides would suggest that the conformational differences between furanose and cyclopentane rings might be partially responsible for the observed differences in biological potency. Judging from the published X-ray structures of some carbocyclic nucleosides, they appear to crystallize with an unusual ring pucker relative to 4′-oxonucleosides.[5−7] For example, thymidine shows a characteristic 2′-endo/3′-exo ring pucker ($^2T_3$) resulting from the dominant gauche effect interaction between the 4′-oxygen and the 3′-hydroxyl group over the anomeric effect.[8] Loss of the furanose oxygen in carbathymidine, however, abolishes these two effects, causing the carbocyclic ring to adopt a rare 1′-exo pucker ($_1$E, $P = 126°$).[5] In solution, 4′-oxonucleosides exist in equilibrium between a 2′-endo/3′-exo ($^2T_3$, southern, $P = 180°$) conformation and a 2′-exo/3′-endo ($^3T_2$, northern, $P = 0°$) conformation separated by an energy barrier in the range of 3−4 kcal/mol. However, when a nucleoside or nucleotide binds to its target enzyme, only one form of the two possible conformations takes part in drug−receptor interactions.[10] Since it is known that a favorable energy difference of as low as 1.3 kcal/mol can result in a 10-fold decrease in the binding constant of a ligand with its receptor,[11] differences in binding can vary between 100- to 1000-fold, depending on the preferred conformation of the nucleoside ligand. This conformational difference between 4′-oxonucleosides and the corresponding carbocyclic nucleosides may explain why carbocyclic nucleosides, in general, show less potent biological activity than their nucleoside counterparts.

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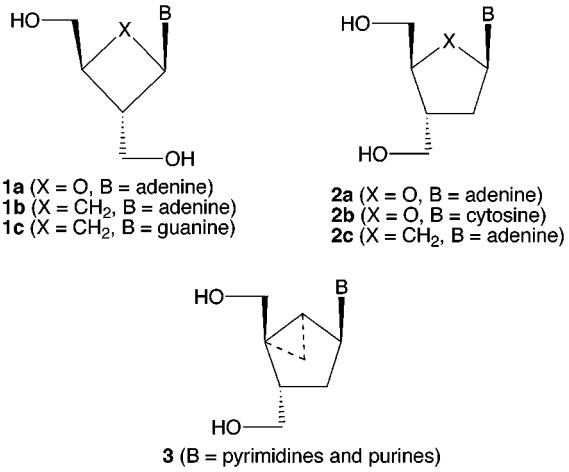

Figure 1.

Therefore, one can hypothesize that if a carbocyclic nucleoside with a 1′-exo ring pucker was forced to take a more conventional southern or northern conformation, biological potency could be recovered.

Oxetanocin A [9-(2*R*,3*R*,4*S*)-3,4-bis(hydroxymethyl)-2-oxetanyl)adenine (**1a**)][12,13] (Figure 1) was the first reported naturally occurring nucleoside containing a four-membered sugar ring. Oxetanocin A, as well as the carbocyclic analogues, cyclobutyl-A (**1b**) and cyclobutyl-G (**1c**), showed potent anti-HIV activity in ATH8 cells.[14,15] In addition, cyclobutyl-G (lobucavir) has shown excellent activity against HSV-1, HSV-2, HCMV, murine CMV, and HBV, and clyclobutyl-A appears to be more potent than acyclovir against VZV.[15−17]

A ring-expanded analogue of oxetanocin A, 2′,3′-dideoxy-3′-*C*-hydroxymethyl adenosine (**2a**), was later shown to have anti-HIV activity comparable to that of **1a**,[18] and the similarly branched cytosine analogue **2b** was also reported to be a very effective antiviral agent.[19] In support of these observations, a molecular modeling study revealed that the more stable northern conformer of **2a** superimposed well on **1a** and that the disposition of the hydroxymethyl substituents was almost coincident. This allowed the hydroxyl groups in **1a** and **2a** to be in an almost identical location as in a natural 2′-deoxy nucleoside.[18] However, the corresponding carbocyclic, ring-expanded analogue **2c** was totally devoid of anti-HIV activity in either CEM or ATH8 cells, probably because of the unfavorable sugar conformation of the cyclopentane ring.[20,21]

One of the strategies that can be used in carbocyclic nucleosides to regain the ring pucker characteristic of typical nucleosides is to construct them on a rigid bicyclic system employing either oxirane or cyclopropane rings fused to the five-member cyclopentane moiety.[22−24] In this report, we present the results of the cyclopropane-fused alternative utilizing a bicyclo[3.1.0]hexane system to generate analogues of ring-expanded oxetanocins carrying different purine and pyrimidine bases. The selected targets (**3**) represent conformationally rigid northern conformers equivalent in conformation to the antivirally active ring-enlarged oxetanocins **2a** and **2b**. The synthesis of the target nucleosides was achieved linearly for the pyrimidine analogues through a completely regioselective ring-opening reaction of an intermediate cyclic sulfite with sodium azide or directly, in a convergent manner, by a similar reaction with the appropriate purine base.

Results and Discussion

The strategy for these syntheses was to utilize cyclic sulfites[25] as epoxide surrogates for the preparation of the desired nucleosides. All syntheses started from our versatile cyclopentenone **4**, which underwent quantitative reduction to the allylic alcohol **5** (Scheme 1).[26] Simmons-Smith cyclopropanation of **5** produced the bicyclo[3.1.0]hexane intermediate **6** in 90% yield.[23] Acid-catalyzed equilibration of **6** in acetone produced the isomeric acetonide **7** (57%) with recovered starting material (42%). Repeated isomerization afforded the desired product **7** almost quantitatively. Oxidation of **7** with tetrapropylammonium perruthenate(VII) (TPAP)[27] and *N*-methylmorpholine *N*-oxide (NMO) gave ketone **8** (100%), which was converted to the 2-ylidene **9** (90%) after Wittig reaction with methyltriphenylphosphonium bromide and *n*-butyllithium at 0 °C. Hydroboration−oxidation[28] of **9** proceeded through the favored attack of the borane from the less hindered convex *β*-side to give preferentially **10a** over **10b** by a 10:1 ratio. The primary hydroxyl group of **10a** was treated with benzyl bromide to give the corresponding benzyl ether (88%), which was followed by the quantitative removal of the acetonide to give the cis-diol **11**. Compound **11** was converted to the cyclic sulfite **12a**, which served as a pseudo-glycosyl donor for the synthesis of the target carbocyclic nucleosides. Because cyclic sulfates are better leaving groups than the cyclic sulfites, the cyclic sulfate **12b** was also synthesized and tested as an epoxide surrogate.[29,30]

In addition to the cyclic sulfite/sulfate method, an alternative approach shown in Scheme 2 was attempted.

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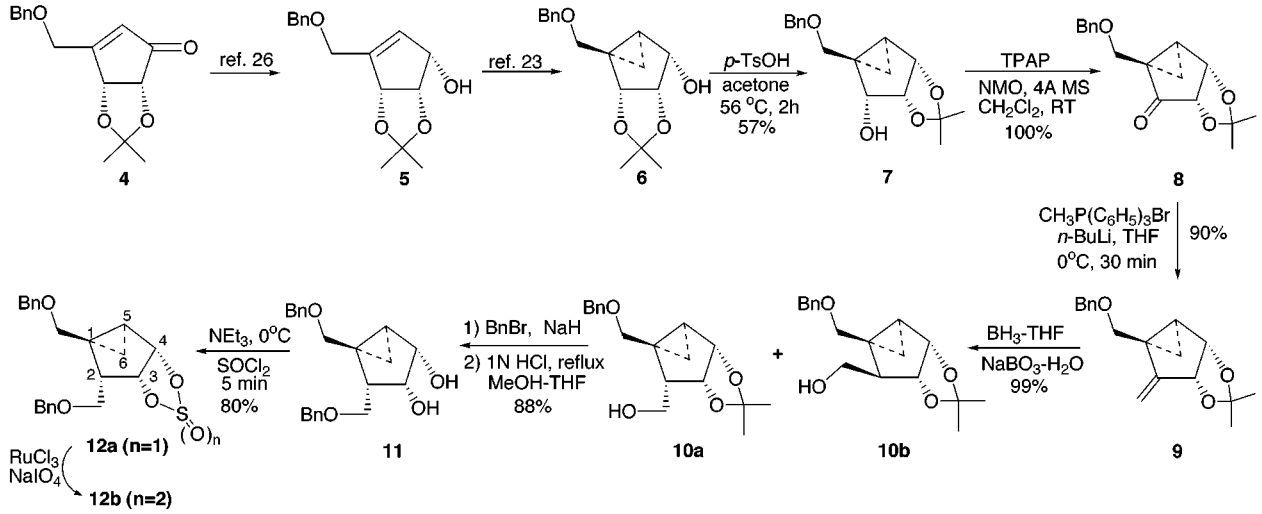
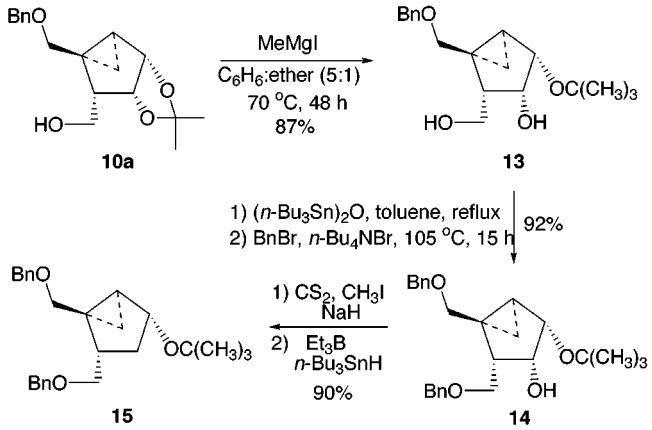
Scheme 1



Scheme 2



This method relied on the regioselective cleavage of acetonide **10a** to the diol derivative **13** after treatment with methylmagnesium iodide (87%).[31] Selective benzyl protection of diol **13** to the monobenzylate **14** was achieved using organotin chemistry (92%),[32] and Barton deoxygenation[33] of the secondary alcohol in **14** afforded the corresponding carbocyclic sugar **15** (90%). Unfortunately, removal of the *tert*-butyl ether group from **15** under a variety of conditions led to extensive decomposition, possibly through an unstable carbocation intermediate. For that reason, this methodology was abandoned in favor of the cyclic sulfite/sulfate approach.

In a model reaction to test the regioselective opening of the cyclic sulfite versus the cyclic sulfate, the less reactive cyclic sulfite **12a** was treated with sodium azide in DMF at 100 °C (Scheme 3), whereas the more reactive cyclic sulfate **12b** was reacted at 0 °C in the same solvent. The cyclic sulfite provided a clean carbocyclic azide product **16** in 81% yield, but the cyclic sulfate gave only a 47% yield of the same product after hydrolytic cleavage of the resulting sulfate with dilute sulfuric acid. This result may reflect the greater instability of **12b** even under mild reaction conditions.[34,35] Therefore, cyclic sulfite **12a** was used throughout this work as the preferred pseudo-glycosyl donor, despite its poorer leaving group capability. Besides its synthetic utility, **12a** proved to be a very stable and easy reagent to store. The rigid boat conformation of the bicyclo[3.1.0]hexane system, which for these class of compounds has been extensively confirmed by X-ray crystallography and NMR analysis,[22−24,36] makes the assignment of the stereochemistry particularly straightforward. The simplicity of the NMR spectrum of the anticipated azide regioisomer **16**, where two H−C−C−H dihedral angles are close to 90°, allows for an easy characterization. For example, irradiation of the H-2 multiplet at δ 2.79 caused the H-3 doublet at δ 4.28 to coalesce into a singlet. This situation could not be the case for the alternative regioisomer (Figure 2). It is important to emphasize that this type of assignment works only in this system and could not be applied to the flexible, carbocyclic counterparts.

The uracil derivative **3a** was synthesized following a linear approach from the carbocyclic azide **16** obtained from cyclic sulfite **12a** (Scheme 3). Silyl protection of the carbocyclic azide **16** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (96%), followed by catalytic hydrogenation, gave the amino derivative **17** (100%). The uracil ring was constructed from **17** according to published methods[37] to give **18**. Before deoxygenation of the secondary alcohol in **18**, the N^3-position of the uracil moiety was protected as the N^3-benzoyl derivative (94%). Following removal of the silyl ether group (90%), the secondary alcohol was removed under Barton deoxygenation conditions[33] to give **19** (44%). Sequential removal of the N^3-benzoyl group with sodium methoxide and the benzyl ethers by catalytic transfer hydrogenation provided the target uracil nucleoside **3a** (50%). This compound was converted to the cytosine derivative **3b** in the conventional manner.[38]

For the synthesis of the adenine derivative **3c** (Scheme 3), the adenine anion generated with NaH/18-crown-6 in DMF at 80 °C was successfully condensed with cyclic sulfite **12a** at 120 °C to give **20** (50%), along with

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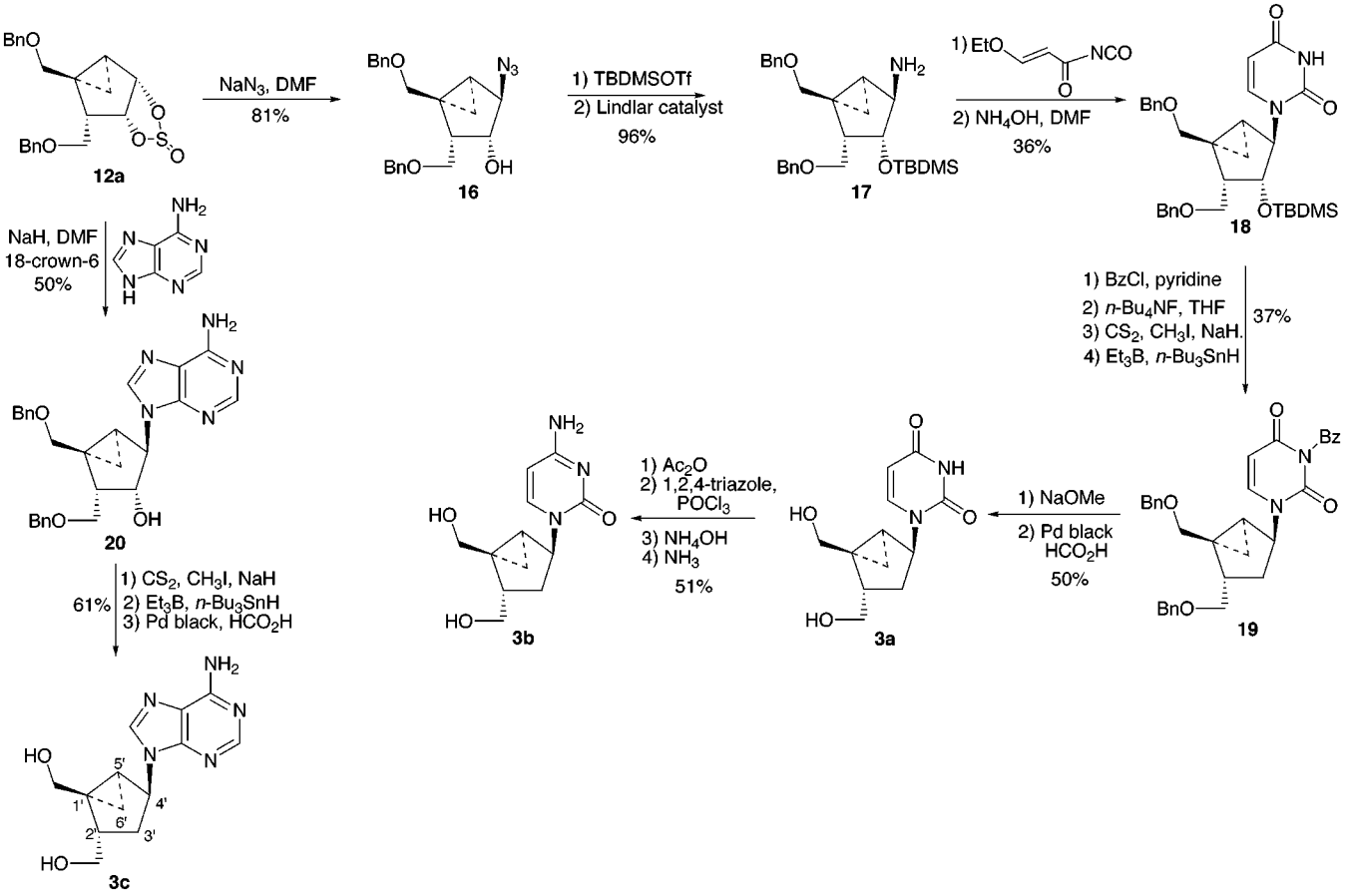
Scheme 3



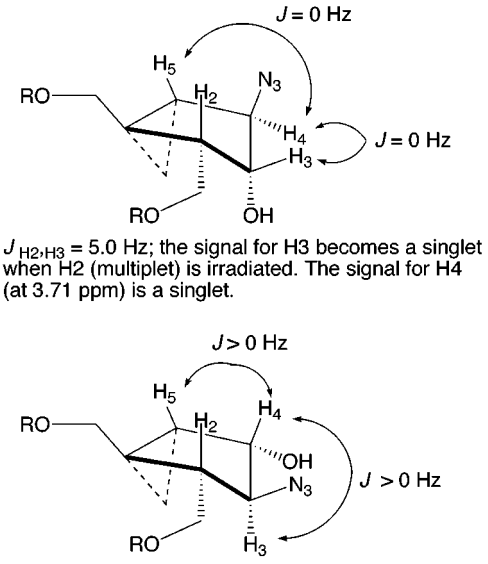


Figure 2.

recovered starting material **12a** and diol **11** (ca. 40−50%). As before, the ring-opening reaction proceeded with complete regioselectivity. Proton NMR spectroscopy of **20** also confirmed the structure unambiguously by virtue of the same diagnostic coupling constants typical of the boat conformation of the bicyclo[3.1.0]hexane system. Indeed, irradiation of the H-2′ multiplet at δ 3.05 caused the H-3′ doublet at δ 4.12 to coalesce into a singlet. The secondary hydroxyl group of **20** was deoxygenated under Barton conditions[33] (73%), and removal of the benzyl ethers under catalytic transfer hydrogenation conditions, as in the case of the uracil analogue, provided the target adenosine analogue **3c** (83%).

Condensation of cyclic sulfite **12a** with 2-amino-6-chloropurine to obtain the guanine derivative resulted in a very low yield (10−15%) of the desired product in favor of the N-7 isomer. Therefore, the guanine derivative **3d** was approached differently as shown in Scheme 4. The diol **11** was selectively protected with *tert*-butyldiphenylsilyl chloride at 10 °C to give **21** (100%). Deoxygenation of **21** under Barton conditions[33] (44%), followed by desilylation with *n*-tetrabutylammonium fluoride, gave the hydroxy derivative **22** (85%). Mitsunobu coupling[39] of **22** with 2-acetamido-6-chloropurine for 15 h at 65 °C afforded the protected nucleoside **23** (38%). Base-catalyzed hydrolysis of the 6-chloro substituent with concomitant loss of the *N*-acetyl group gave the protected guanine derivative **24** (81%). As before, removal of the benzyl ethers by catalytic transfer hydrogenation afforded the final target guanine analogue **3d** (93%). The ^{1}H NMR spectrum of the target guanine analogue **3d** also conformed to the expected pattern observed and discussed previously for **3c**.

The antiviral activity of the target nucleosides **3a**−**d** against HIV-1, HSV-1, HSV-2, and HCMV was investigated. Unfortunately, all the compounds were neither antivirally active nor cytotoxic to the host cells up to concentrations of 100 μg/mL. To become biologically active, nucleosides require conversion to the triphosphate stage prior to interacting with target cellular or viral

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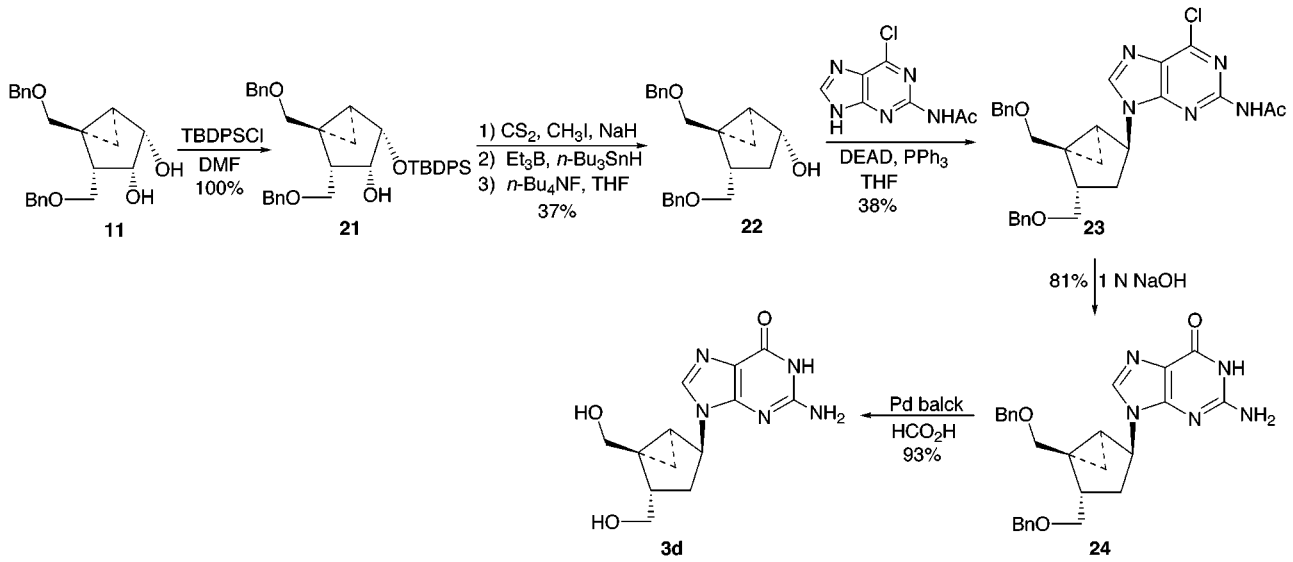
Scheme 4



enzymes. It was presumed that the rigid northern conformation in these nucleosides (**3a**−**d**) might make them good substrates for the various cellular or viral kinases responsible for nucleotide formation by virtue of their conformational similarity with **1a** and the most stable conformers of **2a**,**b**. However, with just the negative antiviral results, it is impossible to know at which stage the compounds failed as substrates. Relative to other conformationally rigid northern carbocyclic analogues that showed good anti-HSV and anti-HCMV activities,[40] it is safe to conclude at this moment that the hydroxymethyl group is a poor substitute for the hydroxyl group in these rigid bicyclic nucleoside templates.

In summary, we have accomplished the synthesis of several cyclopropyl-fused carbocyclic nucleosides using a cyclic sulfite intermediate as an epoxide surrogate. Although cyclic sulfites have been sparsely used in organic syntheses, they proved to be stable and sufficiently reactive to warrant a more extensive application as alternatives to epoxides. In addition, the operation is simpler than with cyclic sulfates, which require additional cleavage of the resulting sulfate. It can be concluded that the cyclic sulfite described here represents a useful alternative as a general approach to the synthesis of carbocyclic nucleosides.[41]

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR data were recorded on either 250 or 300 MHz NMR spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm (δ), and coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), q (quartet), t (triplet), dd (doublet of doublet), td (triplet of doublet), and br s (broad singlet). Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA and Ewha Womans University, general instrument laboratory, Seoul, Korea. Anhydrous benzene, methylene chloride, and THF were distilled over CaH_2, P_2O_5, and Na/benzophenone prior to use, respectively.

(1*S*,2*R*,3*R*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-2-hydroxy-3,4-(isopropylidenedioxy)bicyclo[3.1.0]hexane (7). A solution of **6**[23] (5.0 g, 17.2 mmol) and *p*-TsOH·H_2O (1.63 g, 8.59 mmol) in acetone (100 mL) was refluxed for 2 h. NEt_3 was added to neutralize the mixture, and volatiles were removed. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to give **7** (2.85 g, 57%) as a colorless syrup, together with recovered **6** (2.0 g): $[\alpha]^{25}_D = 8.3°$ (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.61 (dd, 1 H, *J* = 5.4, 8.3 Hz), 1.12 (pseudo t, 1 H, *J* = 4.1, 5.1 Hz), 1.29 (s, 3 H), 1.52 (s, 3 H), 1.60 (quintet, 1 H, *J* = 4.5, 8.8 Hz), 2.33 (br s, 1 H), 3.12 (d, 1 H, *J* = 10.3 Hz), 3.77 (d, 1 H, *J* = 10.3 Hz), 4.51 (m, 3 H), 4.59 (pseudo t, 1 H, *J* = 5.9, 7.0 Hz), 4.82 (pseudo t, 1 H, *J* = 5.7, 6.1 Hz), 7.25−7.39 (m, 5 H). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.33; H, 7.63. Found: C, 70.27; H, 7.60.

(1*R*,3*S*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-3,4-(isopropylidenedioxy)-2-oxo-bicyclo[3.1.0]hexane (8). To a solution of **7** (3.0 g, 0.01 mol), *N*-methylmorpholine *N*-oxide (1.83 g, 0.015 mol), and molecular seives (0.5 g/mmol, 5.19 g) in CH_2Cl_2 (2 mL/mmol) (20.7 mL) was added TPAP (0.18 g, 0.5 mmol) at ambient temperature, and the mixture was stirred for 40 min. The dark mixture was filtered through a short silica gel pad, washed with CH_2Cl_2, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to give **8** (3.0 g, 100%) as a colorless syrup: $[\alpha]^{25}_D = 33.2°$ (*c* 0.37, $CHCl_3$); IR (neat) 1740 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 1 H), 1.25 (s, 3 H), 1.49 (s, 3 H), 1.50 (m, 1 H), 2.31 (m, 1 H), 3.21 (d, 1 H, *J* = 10.9 Hz), 4.08 (d, 1 H, *J* = 10.9 Hz), 4.15 (d, 1 H, *J* = 8.1 Hz), 4.50 (m, 2 H), 4.92 (m, 1 H), 7.20−7.39 (m, 5 H). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.82; H, 6.99. Found: C, 70.80; H, 7.04.

(1*S*,3*R*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-3,4-(isopropylidenedioxy)-2-*C*-methylenebicyclo[3.1.0]hexane (9). To a suspension of methyltriphenylphosphonium bromide (4.3 g, 12.0 mmol) in THF (20 mL) was added *n*-BuLi (7.5 mL, 1.6 M in hexane, 12.0 mmol) at 0 °C, followed by the dropwise addition of **8** (2.0 g, 6.9 mmol). The mixture was stirred further at 0 °C for 30 min. Ether was added, and a white solid precipitated out. The mixture was filtered through a short silica gel pad, washed with ether, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to give **9** (1.8 g, 90%) as a colorless syrup: $[\alpha]^{25}_D = 43.3°$ (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.01 (dd, 1 H, *J* = 4.8, 8.4 Hz), 1.25 (t, 1 H, *J* = 4.5 Hz), 1.29 (s, 3 H), 1.49 (s, 3 H), 1.85 (m, 1 H), 3.42 (d, 1 H, *J* = 10.5 Hz), 3.65 (d, 1 H, *J* = 10.5 Hz), 4.50 (s, 2 H), 4.85 (m, 2 H), 5.29 (s, 2 H), 7.20−7.39 (m, 5 H). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.41; H, 7.77.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-2-hydroxymethyl-3,4-(isopropylidenedioxy)bicyclo[3.1.0]hexane (10a) and Its C-2 Epimer (10b). To a solution of **9** (2.4 g, 8.36 mmol) in THF (30 mL) was added BH_3·THF (16.72 mL,

(40) Siddiqui, M. A.; Ford, H., Jr.; George, C.; Marquez, V. E. *Nucleosides Nucleotides* **1996**, *15*, 235.

(41) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.

1 M in THF, 16.72 mmol) at 0 °C. The mixture was stirred further at 0 °C for 4 h. $NaBO_3 \cdot H_2O$ (2.75 g, 27.59 mmol) and H_2O (15 mL) were added carefully, and the mixture was stirred at ambient temperature for 12 h. The mixture was diluted with CH_2Cl_2 and H_2O. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give **10a** (2.30 g, 90%) and **10b** (0.24 g, 9%) as colorless syrups.

Compound 10a: $[\alpha]^{25}_D = 0.6°$ (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.70 (m, 1 H), 1.15 (m, 1 H), 1.20 (s, 3 H), 1.45 (s, 3 H), 1.52 (m, 1 H), 2.01 (m, 1 H), 3.08 (d, 1 H, $J = 9.9$ Hz), 3.50 (br s, 1 H), 3.61 (d, 1 H, $J = 9.9$ Hz), 3.72 (m, 2 H), 4.50 (dd, 2 H, $J = 11.9$, 14.8 Hz), 4.69 (pseudo t, 1 H, $J = 6.9$, 8.0 Hz), 4.85 (pseudo t, 1 H, $J = 5.6$, 6.2 Hz), 7.25−7.48 (m, 5 H). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.94. Found: C, 71.09; H, 7.99.

Compound 10b: $[\alpha]^{25}_D = 20.9°$ (*c* 1.27, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.62 (dd, 1 H, $J = 4.6$, 8.6 Hz), 1.00 (pseudo t, 1 H, $J = 4.4$, 4.6 Hz), 1.25 (s, 3 H), 1.42 (s, 3 H), 1.75 (quintet, 1 H, $J = 4.6$, 9.0 Hz), 2.25 (m, 1 H), 2.90 (d, 1 H, $J = 10.7$ Hz), 3.48 (br s, 1 H), 3.55 (m, 1 H), 3.82 (m, 1 H), 3.92 (d, 1 H, $J = 10.7$ Hz), 4.49 (s, 2 H), 4.60 (d, 1 H, $J = 7.0$ Hz), 4.90 (pseudo t, 1 H, $J = 6.4$, 6.5 Hz), 7.25−7.48 (m, 5 H). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.94. Found: C, 70.95; H, 7.99.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1,2-Di[(benzyloxy)methyl]-3,4-dihydroxy-bicyclo[3.1.0]hexane (11). To a solution of **10a** (1.3 g, 4.3 mmol) in THF (30 mL) was added NaH (60% in oil) (0.21 g, 5.16 mmol) at 0 °C, followed by BnBr (0.77 mL, 6.45 mmol) and *n*-Bu_4NI (0.24 g, 6.45 mmol), and the mixture was refluxed for 15 h. Glacial AcOH was added to reach neutrality, and the mixture was diluted with ether and H_2O. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7:1) to give 1,2-dibenzyloxymethyl-3,4-(isopropylidenedioxy) bicyclo[3.1.0]hexane (1.50 g, 88%) as a colorless syrup: $[\alpha]^{25}_D = 13.9°$ (*c* 0.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.52 (dd, 1 H, $J = 4.7$, 8.8 Hz), 1.00 (pseudo t, 1 H, $J = 4.6$, 6.4 Hz), 1.22 (s, 3 H), 1.48 (s, 3 H), 1.60 (m, 1 H), 2.91 (quintet, 1 H, $J = 7.5$, 9.6 Hz), 3.09 (d, 1 H, $J = 10.1$ Hz), 3.82 (m, 3 H), 4.43 (s, 2 H), 4.50 (s, 2 H), 4.67 (pseudo t, 1 H, $J = 6.8$, 6.9 Hz), 4.88 (pseudo t, 1 H, $J = 5.6$, 6.1 Hz), 7.25−7.39 (m, 10 H). Anal. Calcd for $C_{35}H_{30}O_4$: C, 76.12; H, 7.66. Found: C, 76.03; H, 7.68.

A solution of 1,2-dibenzyloxymethyl-3,4-(isopropylidenedioxy)bicyclo[3.1.0]hexane (1.50 g, 3.80 mmol) and 1 N HCl (10 mL) in THF/MeOH (30 mL, 1:1) was refluxed for 10 h. The mixture was evaporated and coevaporated with toluene. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) to give **11** (1.35 g, 100%) as a colorless syrup: $[\alpha]^{25}_D = 51.4°$ (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.36 (m, 1 H), 1.23 (t, 1 H, $J = 4.6$ Hz), 1.49 (quintet, 1 H, $J = 4.4$, 8.6 Hz), 2.55 (br s, 1 H), 2.61 (br s, 1 H), 2.75 (m, 1 H), 3.23 (d, 1 H, $J = 10.4$ Hz), 3.49 (d, 1 H, $J = 10.4$ Hz), 3.75 (m, 2 H), 4.18 (t, 1 H, $J = 6.2$ Hz), 4.42−4.58 (m, 5 H), 7.25−7.50 (m, 10 H). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.51; H, 7.44. Found: C, 74.46; H, 7.39.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1,2-Di[(benzyloxy)methyl]-3,4-sulfinyldioxy-bicyclo[3.1.0]hexane (12a). To a solution of **11** (0.70 g, 1.97 mmol) in CH_2Cl_2 (3 mL) were added NEt_3 (1.1 mL, 7.88 mmol) and $SOCl_2$ (0.22 mL, 2.96 mmol) at 0 °C. The mixture was stirred further at 0 °C for 5 min. After the addition of ether (100 mL) and H_2O (50 mL), the organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to give a diasteromeric mixture of sulfoxides **12a** (0.63 g, 80%) as a colorless syrup: ^1H NMR ($CDCl_3$) δ 0.65 (m, 1 H), 0.81 (m, 1 H), 1.65 (m, 1 H), 3.09 (m, 2 H), 3.23 (m, 1 H), 3.68 (m, 2 H), 4.48 (m, 4 H), 5.09 (t, 1 H, $J = 7.2$ Hz), 5.37 (t, 1 H, $J = 6.7$ Hz), 5.48 (t, 1 H, $J = 7.2$ Hz), 5.61 (t, 1 H, $J = 6.1$ Hz), 7.25−7.39 (m, 10 H). Anal. Calcd for $C_{22}H_{24}O_5S$: C, 65.98; H, 6.04; S, 8.01. Found: C, 65.91; H, 6.07; S, 8.07.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1,2-Di[(benzyloxy)methyl]-3,4-sulfonyldioxy-bicyclo[3.1.0]hexane (12b). To a solution of **12a** (0.10 g, 0.25 mmol) in CCl_4 (1 mL), CH_3CN (1 mL), and H_2O (1.5 mL) were added $NaIO_4$ (0.080 g, 0.38 mmol) and $RuCl_3 \cdot 3H_2O$ (2 mg), and the mixture was stirred at ambient temperature for 15 min. After the addition of ether (80 mL) and H_2O (40 mL), the organic layer was washed first with brine and then with $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated. The residue was filtered through a silica gel pad using ether as eluant to give **12b** (0.07 g, 67%), which was immediately used for the next reaction because of its unstable nature.

(1*S*,2*S*,3*R*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-4-*tert*-butyloxy-3-hydroxy-2-hydroxymethylbicyclo[3.1.0]hexane (13). To a solution of **10a** (1.0 g, 3.28 mmol) in benzene/ether (5:1) (60 mL) was added MeMgI (6.6 mL, 3 M in ether, 19.8 mmol) at ambient temperature, and the mixture was heated to 70 °C for 48 h. Following the careful addition of 1 N HCl (5 mL), the mixture was stirred further for 10 min at ambient temperature before the addition of CH_2Cl_2 (100 mL) and H_2O (40 mL). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give **13** (0.91 g, 87%) as a colorless syrup: $[\alpha]^{25}_D = 31.6°$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.50 (m, 1 H), 1.10 (br s, 1 H), 1.20 (s, 9 H), 1.29 (m, 1 H), 1.35 (m, 1 H), 2.46 (m, 1 H), 2.75 (br s, 1 H), 3.20 (d, 1 H, $J = 10.0$ Hz), 3.57 (d, 1 H, $J = 10.0$ Hz), 3.82 (m, 2 H), 3.90 (t, 1 H, $J = 6.3$ Hz), 4.31 (t, 1 H, $J = 5.9$ Hz), 4.51 (s, 2 H), 7.25−7.48 (m, 5 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.80. Found: C, 71.15; H, 8.80.

(1*S*,2*S*,3*R*,4*S*,5*S*)-4-*tert*-Butyloxy-1,2-di[(benzyloxy)-methyl]-3-hydroxy-bicyclo[3.1.0]hexane (14). A solution of **13** (0.85 g, 2.66 mmol) and bistributyltin oxide (1.01 mL, 2.0 mmol) in toluene (30 mL) was refluxed for 15 h using a Dean−Stark apparatus. BnBr (0.41 mL, 3.46 mmol) and *n*-Bu_4NBr (0.43 g, 1.33 mmol) were added, and the mixture was heated to 105 °C for 15 h. The mixture was evaporated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1 to 8:1) to give **14** (1.00 g, 92%) as a colorless syrup: $[\alpha]^{25}_D = 12.0°$ (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.35 (m, 1 H), 1.25 (s, 9 H), 1.31 (m, 1 H), 1.62 (m, 1 H), 2.75 (m, 1 H), 3.12 (d, 1 H, $J = 10.2$ Hz), 3.61−3.85 (m, 3 H), 3.97 (t, 1 H, $J = 6.2$ Hz), 4.32 (t, 1 H, $J = 5.4$ Hz), 4.40−4.61 (m, 4 H), 7.15 (br s, 1 H), 7.21−7.48 (m, 10 H). Anal. Calcd for $C_{26}H_{34}O_4 \cdot 0.5CH_2Cl_2$: C, 70.26; H, 7.78. Found: C, 70.07; H, 8.14.

(1*R*,2*S*,4*R*,5*S*)-4-*tert*-Butyloxy-1,2-di[(benzyloxy)methyl]-bicyclo[3.1.0]hexane (15). To a solution of **14** (0.47 g, 1.15 mmol) in THF (15 mL) were added CS_2 (1.04 mL, 17.25 mmol) and NaH (0.11 g, 60% suspension in oil, 2.88 mmol), and the mixture was stirred at ambient temperature for 1 h. MeI (2.16 mL, 34.5 mmol) was added, and the mixture was stirred at ambient temperature for another 2 h. The mixture was neutralized with AcOH and evaporated. The residue was diluted with CH_2Cl_2 (100 mL) and H_2O (30 mL), and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7:1) to give the intermediate xanthate (0.50 g, 88%) as a yellow solid: ^1H NMR ($CDCl_3$) δ 0.50 (m, 1 H), 0.85 (m, 1 H), 1.18 (s, 9 H), 1.35 (m, 1 H), 2.50 (s, 3 H), 3.05 (m, 1 H), 3.20 (d, 1 H, $J = 10.2$ Hz), 3.49 (pseudo t, 1 H, $J = 8.1$, 9.1 Hz), 3.65 (m, 1 H), 3.68 (d, 1 H, $J = 10.2$ Hz), 4.31−4.65 (m, 5 H), 6.25 (t, 1 H, $J = 6.4$ Hz), 7.25−7.48 (m, 10 H).

To a solution of the xanthate (0.46 g, 0.92 mmol) in benzene (15 mL) were added Et_3B (1.10 mL, 1 M in hexane, 1.1 mmol) and *n*-Bu_3SnH (0.39 mL, 1.38 mmol), and the mixture was stirred at ambient temperature for 2 h. TLC showed no difference between starting material and product. The mixture was evaporated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to give **15** (0.33 g, 90%) as a colorless syrup: ^1H NMR ($CDCl_3$) δ 0.35 (m, 1 H), 0.90 (m, 1 H), 1.18 (s, 9 H), 1.25 (m, 1 H), 1.32 (m, 1 H), 1.98 (m, 1 H), 2.55 (m, 1 H), 3.21 (d, 1 H, $J = 10.2$ Hz), 3.33 (pseudo t, 1 H, $J = 8.0$, 9.1 Hz), 3.61 (m, 1 H), 3.68 (d, 1 H, $J = 10.2$ Hz), 4.31 (m, 1 H), 4.48 (s, 4 H), 7.25−7.48 (m, 10 H). Anal. Calcd for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.44; H, 8.48.

(1*S*,2*S*,3*R*,4*R*,5*S*)-4-Azido-1,2-di[(benzyloxy)methyl]-3-hydroxybicyclo[3.1.0]hexane (16). Method A. To a solution of **12a** (0.70 g, 1.75 mmol) in DMF (10 mL) was added NaN_3 (0.23 g, 3.5 mmol), and the mixture was heated to 100 °C for 10 h. After the addition of EtOAc (200 mL) and H_2O (50 mL), the organic layer was washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to give **16** (0.56 g, 81%) as a colorless syrup: $[\alpha]^{25}_D = -59.1°$ (*c* 0.44, MeOH); IR (neat) 2094 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 0.61 (m, 1 H, H_a-6), 1.25 (m, 1 H, H_b-6), 1.40 (m, 1 H, H-5), 2.79 (m, 1 H, H-2), 3.38 (d, 1 H, J = 10.5 Hz, BnOCH_a), 3.48 (d, 1 H, J = 10.5 Hz, BnOCH_b), 3.68 (pseudo t, 1 H, J = 9.3, 9.5 Hz, BnOCH_{aa}), 3.71 (s, 1 H, H-4), 3.90 (dd, 1 H, J = 5.4, 9.5 Hz, BnOCH_{bb}), 4.28 (d, 1 H, J = 5.0 Hz, H-3), 4.48 (m, 4 H, 2 × $C_6H_5CH_2$), 7.28−7.39 (m, 10 H, 2 × C_6H_5). Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.47; H, 6.61; N, 10.96.

Method B. To a solution of **12b** (0.07 g, 0.17 mmol) in DMF (3 mL) was added NaN_3 (0.027 g, 0.43 mmol) at 0 °C, and the solution was stirred at the same temperature for 30 min. DMF was evaporated, and the residue was treated with a mixture of 1 N H_2SO_4 (1 mL) and THF (5 mL) and was left stirring overnight at ambient temperature. After treatment with $CHCl_3$ (200 mL) and H_2O (50 mL), the organic layer was washed with brine (100 mL) and $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to give **16** (0.03 g, 47%) as a colorless syrup identical to that obtained from method A.

(1*S*,2*S*,3*R*,4*R*,5*S*)-4-Amino-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy)methyl]bicyclo[3.1.0]hexane (17). (1) Preparation of 4-Azido-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy) methyl]bicyclo[3.1.0]hexane. To a solution of **16** (0.681 g, 1.79 mmol) and pyridine (0.16 mL, 1.98 mmol) in anhydrous methylene chloride (16 mL) was added TBDMSOTf (0.45 mL, 1.96 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h, diluted with methylene chloride (150 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to give the 4-azido-3-(*tert*-butyldimethylsilyloxy)-1,2-di-[(benzyloxy)methyl]bicyclo[3.1.0]hexane (0.852 g, 96%) as a syrup: ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.05 (s, 3 H), 0.58 (m, 1 H), 0.85 (s, 9 H), 1.21 (m, 1 H), 1.39 (m, 1 H), 2.75 (m, 1 H), 3.42 (d, 1 H, J = 10.2 Hz), 3.58 (s, 1 H), 3.65 (m, 3 H), 4.15 (d, 1 H, J = 6.2 Hz), 4.45 (m, 4 H), 7.27−7.35 (m, 10 H). This compound was used without further purification in the next step.

(2) Reduction. To a solution of 4-azido-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy)methyl] bicyclo[3.1.0]hexane (0.852 g, 1.73 mmol) in methylene chloride (8 mL) and methanol (8 mL) was added Lindlar's catalyst (0.05 g). The resulting mixture was stirred overnight at ambient temperature under hydrogen, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give **17** (0.807 g, 100%) as a syrup: ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.42 (m, 1 H), 0.82 (s, 2 H), 1.18 (s, 9 H), 2.33 (br s, 2 H), 2.89 (m, 1 H), 3.11 (s, 1 H), 3.22 (d, 1 H, J = 10.0 Hz), 3.62 (d, 2 H, J = 6.7 Hz), 3.71 (d, 1 H, J = 10.0 Hz), 3.98 (d, 1 H, J = 5.4 Hz), 4.44 (m, 4 H), 7.20−7.38 (m, 10 H). Anal. Calcd for $C_{28}H_{41}NO_3Si$: C, 71.90; H, 8.84; N, 2.99. Found: C, 71.88; H, 8.92; N, 3.26.

(1*S*,2*S*,3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-1,2-di-[(benzyloxy)methyl]-4-(2,4(1*H*,3*H*)-dioxopyrimidin-1-yl)-bicyclo[3.1.0]hexane (18). A mixture of ethyl β-ethoxyacrylate (2.99 g, 20.74 mmol) and 2 N sodium hydroxide (11.3 mL, 22.6 mmol) was refluxed for 1 h and cooled to 0 °C. The mixture was filtered, and the filter cake was treated with 2 N sodium hydroxide and evaporated to give the sodium β-ethoxyacrylate (1.516 g, 53%). To a solution of sodium β-ethoxyacrylate (1.516 g, 10.99 mmol) in anhydrous ethyl ether (20 mL) was added thionyl chloride (2 mL, 27.42 mmol), and the mixture was refluxed for 4 h, kept overnight, and evaporated. The residue was distilled to give the β-ethoxyacryloyl chloride (0.35 g). To a solution of silver cyanate (0.819 g, 5.46 mmol) in anhydrous benzene (4 mL) was added a solution of β-ethoxyacryloyl chloride (0.294 g, 6.00 mmol) in anhydrous benzene (3.8 mL) at 10 °C, and the mixture was stirred at the same temperature for 30 min and then filtered. To this filtrate was added a solution of **17** (0.807 g, 1.73 mmol) in anhydrous benzene (3 mL) at 10 °C, and the mixture was stirred at the same temperature for 30 min and then evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 42:1) to give the (1*S*,2*S*,3*R*,4*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy)methyl]-4-[(3-ethoxyacryloyl)ureido]bicyclo [3.1.0]hexane (0.964 g, 92%) as a syrup.

To a solution of (1*S*,2*S*,3*R*,4*R*,5*S*)-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy)methyl]-4-[(3-ethoxyacryloyl)ureido]-bicyclo[3.1.0]hexane (0.266 g, 0.44 mmol) in anhydrous DMF (5.5 mL) was added ammonium hydroxide (3 mL), and the mixture was stirred overnight at 100 °C. The reaction mixture was evaporated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1.5:1) to give **18** (0.096 g, 39%) as a syrup: UV (MeOH) λ_{max} 260 nm; ^1H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.19 (s, 3 H), 0.63 (m, 1 H), 0.88 (s, 9 H), 1.25 (m, 1 H), 1.44 (t, 1 H, J = 4.3 Hz), 2.84 (m, 1 H), 3.10 (d, 1 H, J = 9.9 Hz), 3.58 (dd, 1 H, J = 6.6, 9.0 Hz), 3.67 (dd, 1 H, J = 6.8, 9.0 Hz), 3.97 (dd, 1 H, J = 1.5, 6.3 Hz), 4.20 (d, 1 H, J = 9.9 Hz), 4.44 (d, 1 H, J = 11.0 Hz), 4.45 (d, 1 H, J = 11.7 Hz), 4.50 (d, 1 H, J = 11.0 Hz), 4.56 (d, 1 H, J = 11.7 Hz), 4.74 (s, 1 H), 5.28 (dd, 1 H, J = 2.0, 8.0 Hz), 7.25−7.37 (m, 10 H), 7.91 (br s, 1 H), 8.24 (d, 1 H, J = 8.0 Hz). Anal. Calcd for $C_{32}H_{42}N_2O_5Si$: C, 68.29; H, 7.52; N, 4.98. Found: C, 68.35; H, 7.61; N, 4.96.

(1*S*,2*S*,4*S*,5*S*)-4-[N^3-Benzoyl-2,4-(1H)-dioxopyrimidin-1-yl]-1,2-di[(benzyloxy)methyl]bicyclo[3.1.0]hexane (19). (1) Preparation of (1*S*,2*S*,3*R*,4*S*,5*S*)-4-[N^3−Benzoyl-2,4-(1H)-dioxopyrimidin-1-yl]-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy)methyl]bicyclo[3.1.0]hexane. To a solution of **18** (0.108 g, 0.19 mmol) in anhydrous pyridine (3 mL) was added benzoyl chloride (0.11 mL, 0.95 mmol), and the mixture was stirred overnight at 70 °C. After the mixture was allowed to reach ambient temperature, methanol (1 mL) was added and stirred for 10 min, before reducing to dryness. The residue was diluted with ethyl acetate (100 mL), washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and evaporated. Purification by silica gel column chromatography (hexane/ethyl acetate=4:1) gave (1*S*,2*S*,3*R*,4*S*,5*S*)-4-[N^3-benzoyl-2,4-(1*H*)-dioxopyrimidin-1-yl]-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy)methyl]bicyclo [3.1.0]hexane (0.120 g, 94%) as a syrup.

(2) Preparation of (1*S*,2*S*,3*R*,4*R*,5*S*)-4-[N^3−Benzoyl-2,4-(1H)-dioxopyrimidin-1-yl]-1,2-di [(benzyloxy)methyl]-3-hydroxybicyclo[3.1.0]hexane. To a solution of (1*S*,2*S*,3*R*,-4*S*,5*S*)-4-[N^3-benzoyl-2,4-(1H)-dioxopyrimidin-1-yl]-3-(*tert*-butyldimethylsilyloxy)-1,2-di[(benzyloxy)methyl]bicyclo[3.1.0]-hexane (0.116 g, 0.16 mmol) in anhydrous THF (4 mL) was added *n*-tetrabutylammonium fluoride (0.19 mL, 1.0 M solution in THF, 0.19 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give (1*S*,2*S*,3*R*,4*R*,5*S*)-4-[N^3-benzoyl-2,4-(1*H*)-dioxopyrimidin-1-yl]-1,2-di[(benzyloxy)-methyl]-3-hydroxybicyclo[3.1.0]hexane (0.087 g, 90%) as a syrup: ^1H NMR ($CDCl_3$) δ 0.77 (m, 1 H), 0.90 (m, 1 H), 1.35 (m, 1 H), 2.36 (br s, 1 H), 2.95 (m, 1 H), 3.13 (d, 1 H, J = 10.1 Hz), 3.66−3.77 (m, 2 H), 4.07 (d, 1 H, J = 10.1 Hz), 4.14 (d, 1 H, J = 6.6 Hz), 4.47−4.57 (m, 4 H), 4.98 (s, 1 H), 5.41 (d, 1 H, J = 8.1 Hz), 7.26−7.92 (m, 15 H), 8.28 (d, 1 H, J = 8.1 Hz). Anal. Calcd for $C_{33}H_{32}N_2O_6$: C, 71.72; H, 5.84; N, 5.07. Found: C, 72.01; H, 6.04; N, 5.04.

(3) Preparation of the Xanthate. A solution of (1*S*,2*S*,3*R*,-4*R*,5*S*)-4-[N^3-benzoyl-2,4-(1*H*)-dioxopyrimidin-1-yl]-1,2-di[(benzyloxy)methyl]-3-hydroxybicyclo[3.1.0]hexane (0.090 g, 0.16 mmol), carbon disulfide (0.1 mL, 1.66 mmol), and methyl iodide (0.1 mL, 1.61 mmol) in anhydrous THF (3 mL) was treated with sodium hydride (0.008 g, 60% suspension in mineral oil, 0.19 mmol) at 0 °C, and the mixture was stirred at that temperature for 1 h. After neutralization with acetic acid and evapora-

tion of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give the xanthate (0.066 g, 63%) as a syrup.

(4) Deoxygenation. To a solution of the xanthate (0.063 g, 0.10 mmol) in anhydrous benzene (3 mL) were added triethylborane (0.15 mL, 1.0 M solution in hexanes, 0.15 mmol) and tributyltin hydride (0.04 mL, 0.15 mmol), and the mixture was stirred at ambient temperature for 30 min. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2:1) to give **19** (0.037 g, 70%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 0.83−0.94 (m, 2 H), 1.35 (m, 1 H), 1.53 (m, 1 H), 1.84 (dd, 1 H, J = 8.2, 15.1 Hz), 2.95 (m, 1 H), 3.19 (d, 1 H, J = 9.9 Hz), 3.41 (dd, 1 H, J = 6.3, 9.2 Hz), 3.57 (dd, 1 H, J = 6.6, 9.2 Hz), 4.23 (d, 1 H, J = 9.9 Hz), 4.46−4.58 (m, 4 H), 4.94 (d, 1 H, J = 6.8 Hz), 5.41 (d, 1 H, J = 8.0 Hz), 7.26−7.50 (m, 10 H), 7.60−7.93 (m, 5 H), 8.35 (d, 1 H, J = 9.6 Hz). Anal. Calcd for $C_{33}H_{32}N_2O_5$: C, 73.86; H, 6.01; N, 5.22. Found: C, 73.76; H, 6.25; N, 5.24.

(1*S*,2*S*,4*S*,5*S*)-4-[2,4-(1*H*,3*H*)-Dioxopyrimidin-1-yl]-1,2-dihydroxymethyl-bicyclo[3.1.0]hexane (3a). (1) Preparation of (1*S*,2*S*,4*S*,5*S*)-1,2-Di[(benzyloxy)methyl]-4-[2,4-(1*H*,3*H*)-dioxopyrimidin-1-yl]bicyclo[3.1.0]hexane. To a solution of **19** (0.050 g, 0.09 mmol) in anhydrous methanol (2 mL) was added 1 N sodium methoxide (0.02 mL, 0.02 mmol), and the mixture was stirred at ambient temperature for 1 h and neutralized with AcOH. The reaction mixture was evaporated, and the residue was diluted with ethyl acetate (50 mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1.5) to give the (1*S*,2*S*,4*S*,5*S*)-1,2-di[(benzyloxy)methyl]-4-[2,4-(1*H*,3*H*)-dioxopyrimidin-1-yl]bicyclo[3.1.0]hexane (0.020 g, 50%) as a syrup: UV (MeOH) λ_{max} 262 nm; ^{1}H NMR ($CDCl_3$) δ 0.67 (m, 1 H), 0.69 (m, 1 H), 1.29 (dd, 1 H, J = 6.4, 12.6 Hz), 1.45−1.58 (m, 1 H), 1.77 (dd, 1 H, J = 8.6, 15.5 Hz), 2.82−2.95 (m, 1 H), 3.17 (d, 1 H, J = 9.9 Hz), 3.41 (dd, 1 H, J = 6.1, 9.2 Hz), 3.55 (dd, 1 H, J = 6.6, 9.2 Hz), 4.20 (d, 1 H, J = 9.9 Hz), 4.46 (d, 1 H, J = 19.9 Hz), 4.47 (d, 1 H, J = 11.3 Hz), 4.54 (d, 1 H, J = 11.3 Hz), 4.54 (d, 1 H, J = 19.9 Hz), 4.93 (d, 1 H, J = 6.7 Hz), 5.31 (dd, 1 H, J = 2.5, 8.1 Hz), 7.18−7.39 (m, 10 H), 7.98 (br s, 1 H), 8.22 (d, 1 H, J = 8.1 Hz).

(2) Debenzylation. To a suspension of palladium black (0.044 g) in methanol (2 mL) was added (1*S*,2*S*,4*S*,5*S*)-1,2-di-[(benzyloxy)methyl]-4-[2,4-(1*H*,3*H*)-dioxopyrimidin-1-yl]bicyclo-[3.1.0]hexane (0.022 g, 0.05 mmol) in methanol (2 mL) and formic acid (0.12 mL). The mixture was stirred at 50 °C for 1 h and filtered through a Celite pad. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 10:1) to give **3a** (0.013 g, 100%) as a hygroscopic solid: $[\alpha]^{25}_D$ = 270.0° (*c* 0.02, MeOH); UV (H_2O) λ_{max} 265 nm (ϵ 7 990); ^{1}H NMR (DMSO-d_6) δ 0.65−0.73 (m, 2 H), 1.35 (dd, 1 H, J = 3.6, 8.4 Hz), 1.47−1.63 (m, 1 H), 1.71 (dd, 1 H, J = 8.0, 14.6 Hz), 3.35−3.59 (m, 4 H), 3.92 (dd, 1 H, J = 5.1, 11.4 Hz), 4.72 (t, 1 H, J = 5.1 Hz), 4.79 (d, 1 H, J = 6.6 Hz), 5.11 (t, 1 H, J = 5.0 Hz), 5.65 (d, 1 H, J = 8.0 Hz), 8.01 (d, 1 H, J = 8.0 Hz), 11.29 (s, 1 H). Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.22; H, 6.14; N,11.03.

(1*S*,2*S*,4*S*,5*S*)-4-(4-Amino-2(1H)-oxopyrimidin-1-yl)-1,2-dihyroxymethyl-bicyclo[3.1.0]hexane (3b). A solution of **3a** (0.012 g, 0.05 mmol) in anhydrous pyridine (2 mL) was treated with acetic anhydride (0.05 mL, 0.53 mmol), and the mixture was stirred at ambient temperature for 5 h. The residue obtained after evaporation of all the volatiles was diluted with ethyl acetate (50 mL); washed with diluted HCl, saturated $NaHCO_3$ solution and brine; dried ($MgSO_4$); filtered; and evaporated. The residue was used in the next step without further purification.

A solution of 1,2,4-triazole (0.079 g, 1.14 mmol) and phosphorus oxychloride (0.09 mL, 0.97 mmol) in acetonitrile (3 mL) was treated with triethylamine (0.13 mL, 0.93 mmol) and the above residue in acetonitrile (1 mL). The mixture was stirred at ambient temperature for 15 h. Additional triethylamine (0.1 mL) and water (0.3 mL) were added, and the reaction mixture was stirred at ambient temperature for 10 min. After the addition of methylene chloride (50 mL), the mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and evaporated. The residue was used in the next step without further purification. To a solution of this residue in 1,4-dioxane (2 mL) was added ammonium hydroxide (28%, 0.5 mL), and the mixture was stirred at ambient temperature for 15 h. After removal of all volatiles, the residue was dissolved in methanolic ammonia (3 mL) and stirred overnight at ambient temperature. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (methylene chloride/methanol = 4:1) to give **3b** (0.006 g, 51%) as a solid: mp 231 °C; $[\alpha]^{25}_D$ = 48.1° (*c* 0.1, MeOH); UV (H_2O) λ_{max} 276 nm (ϵ 7 950); ^{1}H NMR (DMSO-d_6) δ 0.56−0.71 (m, 2 H), 1.28 (m, 1 H), 1.48−1.65 (m, 2 H), 3.35−3.54 (m, 4 H), 3.86 (dd, 1 H, J = 5.1, 11.7 Hz), 4.74 (t, 1 H, J = 5.1 Hz), 4.82 (d, 1 H, J = 6.3 Hz), 5.11 (t, 1 H, J = 7.3 Hz), 5.76 (d, 1 H, J = 7.3 Hz), 7.00 (br s, 1 H), 7.05 (br s, 1 H), 7.95 (d, 1 H, J = 7.3 Hz). Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.38; H, 6.73; N, 16.32.

(1*S*,2*S*,3*R*,4*R*,5*S*)-4-(6-Amino-9-purinyl)-1,2-di[(benzyloxy)methyl]-3-hydroxy-bicyclo[3.1.0]hexane (20). A suspension of adenine (0.13 g, 0.96 mmol), 18-crown-6 (0.21 g, 0.80 mmol), and NaH (60% in oil, 0.032 g, 0.80 mmol) in DMF (10 mL) was heated to 80 °C for 3 h. After a solution of **12a** (0.13 g, 0.32 mmol) was added, the mixture was heated to 120 °C for 72 h. The mixture was poured into H_2O (30 mL), extracted with EtOAc (200 mL), dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30:1) to give a single regioisomer **20** (0.075 g, 50%) as a colorless syrup, plus recovered **11** (0.035 g) and **12a** (0.03 g): $[\alpha]^{25}_D$ = 4.44° (*c* 0.18, MeOH); UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 0.70 (m, 1 H, H_a-6′), 1.45 (m, 1 H, H_b-6′), 1.57 (m, 1 H, H-5′), 3.05 (m, 1 H, H-2′), 3.15 (d, 1 H, J = 10.1 Hz, BnOCH_a), 3.69 (d, 2 H, J = 7.3 Hz, BnOCH_2), 3.90 (d, 1 H, J = 10.1 Hz, BnOCH_b), 4.12 (d, 1 H, J = 6.5 Hz, H-3′), 4.45 (s, 2 H, $C_6H_5CH_2$), 4.59 (s, 2 H, $C_6H_5CH_2$), 4.99 (s, 1 H, H-4′), 6.09 (br s, 2 H, NH_2), 7.20−7.39 (m, 10 H, 2 x C_6H_5), 8.32 (s, 1 H, H-2), 8.60 (s, 1 H, H-8). Anal. Calcd for $C_{27}H_{29}O_3N_5$: C, 68.77; H, 6.20; N, 14.85. Found: C, 68.49; H, 6.27; N, 14.65.

(1*S*,2*S*,4*S*,5*S*)-4-(6-Amino-9-purinyl)-1,2-dihydroxymethylbicyclo[3.1.0]hexane (3c). To a suspension of **20** (0.10 g, 0.21 mmol) in THF (15 mL) were added CS_2 (0.25 mL, 4.2 mmol) and NaH (0.025 g, 60% suspension in oil, 0.63 mmol), and the mixture was stirred at ambient temperature for 1.5 h. MeI (0.26 mL, 4.2 mmol) was added at 0 °C, and the mixture was further stirred at 0 °C for 1 h. Following neutralization with AcOH and evaporation of all volatiles, the residue was diluted with CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30:1) to give the xanthate (0.070 g) as a yellow solid, which was used for the next reaction.

To a solution of the xanthate (0.07 g, 0.12 mmol) in benzene (2 mL) were added Et_3B (0.15 mL, 1 M in hexane, 0.15 mmol) and *n*-Bu_3SnH (0.05 mL, 0.18 mmol), and the mixture was stirred at ambient temperature for 15 min. The mixture was evaporated, and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30:1) to give 4-(6-amino-9-purinyl)-1,2-di[(benzyloxy)methyl]bicyclo[3.1.0]hexane (0.070 g, 73%) as a colorless syrup, but contaminated with an impurity: ^{1}H NMR ($CDCl_3$) δ 0.70 (m, 1 H), 1.30 (m, 1 H), 1.57 (m, 2 H), 1.81 (m, 1 H), 2.98 (m, 1 H), 3.20 (d, 1 H, J = 9.9 Hz), 3.30 (dd, 1 H, J = 6.4, 9.1 Hz), 3.55 (dd, 1 H, J = 6.4, 9.2 Hz), 4.05 (d, 1 H, J = 9.9 Hz), 4.41 (s, 2 H), 4.59 (s, 2 H), 5.08 (d, 1 H, J = 6.8 Hz), 5.90 (br s, 2 H), 7.20−7.41 (m, 10 H), 8.32 (s, 1 H), 8.69 (s, 1 H).

A suspension of 4-(6-amino-9-purinyl)-1,2-di[(benzyloxy)-methyl]bicyclo[3.1.0]hexane (0.04 g, 0.088 mmol) and palladium black (0.050 g) in 5% HCO_2H in MeOH (20 mL) was stirred at ambient temperature for 72 h. The mixture was filtered, washed with MeOH, and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH

= 8:1) to give **3c** (0.020 g, 83%) as a white solid: mp 232 °C; $[\alpha]^{25}_D = -10.7°$ (*c* 0.15, MeOH); UV (H_2O) λ_{max} 260 nm (ϵ 16 880); ^{1}H NMR (CD_3OD) δ 0.79 (m, 1 H, H_a-6′), 0.85 (m, 1 H, H_b-6′), 1.65 (m, 2 H, H-5′ and H_a-3′), 1.90 (dd, 1 H, J = 8.1, 14.8 Hz, H_b-3′), 2.75 (m, 1 H, H-2′), 3.60 (m, 3 H, CH_2OH and CH_aOH), 3.92 (d, 1 H, J = 11.7 Hz, CH_bOH), 4.99 (d, 1 H, J = 6.4 Hz, H-4′), 8.20 (s, 1 H, H-2), 8.50 (s, 1 H, H-8); ^{13}C NMR (CD_3OD) δ 10.6, 28.0, 35.5, 42.2, 57.3, 64.2, 65.9, 80.0, 120.3, 141.0, 150.1, 153.6, 157.3. Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.22; N, 25.44. Found: C, 56.80; H, 6.27; N, 25.65.

(1*S*,2*S*,3*R*,4*S*,5*S*)-4-(*tert*-Butyldiphenylsilyloxy)-1,2-di[(benzyloxy)methyl]-3-hydroxybicyclo[3.1.0]hexane (21). To a solution of **11** (0.314 g, 0.89 mmol) and imidazole (0.145 g, 2.13 mmol) in anhydrous methylene chloride (10 mL) was added *tert*-butyldiphenylsilyl chloride (0.28 mL, 1.08 mmol) at 0 °C, and the mixture was stirred at 10 °C for 5 h. The reaction mixture was diluted with ethyl acetate (100 mL); washed with diluted HCl (15 mL × 2), saturated $NaHCO_3$ solution, and brine; dried ($MgSO_4$); filtered; and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1) to give **21** (0.525 g, 100%) as a syrup; ^{1}H NMR ($CDCl_3$) δ 0.32 (dd, 1 H, J = 5.2, 8.3 Hz), 1.08 (s, 9 H), 1.15 (dd, 1 H, J = 4.3, 8.3 Hz), 1.41 (t, 1 H, J = 4.6 Hz), 2.63 (pseudo q, 1 H, J = 6.6, 6.9, 7.1 Hz), 2.96 (s, 1 H), 3.05 (d, 1 H, J = 10.2 Hz), 3.57 (d, 1 H, J = 10.2 Hz), 3.70 (dd, 1 H, J = 6.3, 9.2 Hz), 3.82 (pseudo t, 1 H, J = 8.2, 9.1 Hz), 4.03 (t, 1 H, J = 6.1 Hz), 4.34 (d, 1 H, J = 12.5 Hz), 4.39 (d, 1 H, J = 12.5 Hz), 4.48−4.54 (m, 2 H), 4.61 (d, 1 H, J = 12.2 Hz), 7.19−7.43 (m, 20 H). Anal. Calcd for $C_{38}H_{44}O_4Si$: C, 76.99; H, 7.48. Found: C, 76.59; H, 7.09.

(1*S*,2*S*,4*R*,5*S*)-1,2-Di[(benzyloxy)methyl]-3-hydroxybicyclo[3.1.0]hexane (22). (1) Preparation of the Xanthate. To a suspension of sodium hydride (0.013 g, 60% suspension in oil, 0.33 mmol) in anhydrous THF (2 mL) was added a solution of **21** (0.123 g, 0.21 mmol) in THF (3 mL) at 0 °C, and the mixture was stirred at the same temperature for 5 min and then at ambient temperature for 10 min. To this mixture were added carbon disulfide (0.13 mL, 2.16 mmol) and methyl iodide (0.13 mL, 2.10 mmol) at ambient temperature, and the reaction mixture was stirred at the same temperature for 1 h before it was reduced to dryness. The xanthate was used in the next step without further purification.

(2) Deoxygenation. To a solution of the xanthate in anhydrous benzene (15 mL) were added triethylborane (0.32 mL, 1.0 M solution in hexanes, 0.32 mmol) and tributyltin hydride (0.09 mL, 0.33 mmol), and the mixture was stirred overnight at ambient temperature. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9:1) to give the 4-(*tert*-butyldiphenylsilyloxy)-1,2-di[(benzyloxy)methyl]bicyclo[3.1.0]-hexane (0.038 g, 44%) as a syrup with recovered starting material (0.034 g): ^{1}H NMR ($CDCl_3$) δ 0.38 (dd, 1 H, J = 5.4, 8.0 Hz), 0.99 (m, 1 H), 1.03 (s, 9 H), 1.11 (pseudo td, 1 H, J = 2.3, 8.6 Hz), 1.18−1.28 (m, 1 H), 1.98 (td, 1 H, J = 7.7, 13.2 Hz), 2.39−2.51 (m, 1 H), 3.16 (d, 1 H, J = 10.3 Hz), 3.34 (dd, 1 H, J = 7.6, 9.1 Hz), 3.56 (d, 1 H, J = 10.3 Hz), 3.62 (dd, 1 H, J = 5.9, 9.1 Hz), 4.39 (s, 2 H), 4.47 (s, 2 H), 4.47−4.56 (m, 1 H), 7.22−7.69 (m, 10 H).

(3) Desilylation. To a solution of 4-(*tert*-butyldiphenylsilyloxy)-1,2-di[(benzyloxy)methyl]-bicyclo[3.1.0]hexane (0.13 g, 0.23 mmol) in THF (3 mL) was added *n*-tetrabutylammonium fluoride (0.34 mL, 0.34 mmol, 1.0 M solution in THF), and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL), washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1.5:1) to give **22** (0.065 g, 85%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 0.43 (dd, 1 H, J = 5.6, 7.9 Hz), 0.88−0.98 (m, 2 H), 1.38 (d, 1 H, J = 5.8 Hz), 1.46−1.52 (m, 1 H), 2.14 (td, 1 H, J = 7.9, 13.3 Hz), 2.56−2.69 (m, 1 H), 3.27 (d, 1 H, J = 10.3 Hz), 3.38 (dd, 1 H, J = 7.2, 9.2 Hz), 3.62 (dd, 1 H, J = 6.0, 9.2 Hz), 3.68 (d, 1 H, J = 10.3 Hz), 4.48 (s, 2 H), 4.49 (s, 2 H), 4.54−4.59 (m, 1 H), 7.26−7.35 (m, 10 H). Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.47; H, 7.47.

(1*S*,2*S*,4*S*,5*S*)-4-(2-Acetamido-6-chloro-purin-9-yl)-1,2-di[(benzyloxy)methyl]bicyclo[3,1,0]hexane (23). To a suspension of triphenylphospine (0.15 g, 0.58 mmol) and 2-acetamino-6-chloropurine (0.122 g, 0.58 mmol) in anhydrous THF (4 mL) was added diethyl azodicarboxylate (0.1 mL, 0.64 mmol) at ambient temperature, and the mixture was vigorously stirred at the same temperature for 10 min. To this reaction mixture was added a solution of **22** (0.065 g, 0.19 mmol) in anhydrous THF (3 mL), and the mixture was refluxed overnight. Hexanes (5 mL) was added to the reaction mixture, and the precipitate was filtered off. The organic layer was evaporated, and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 1:1.5) to give **23** (0.039 g, 38%) as a syrup: ^{1}H NMR ($CDCl_3$) δ 0.70 (dd, 1 H, J = 6.1, 8.5 Hz), 0.81 (dd, 1 H, J = 4.0, 6.1 Hz), 1.57−1.69 (m, 2 H), 1.84 (dd, 1 H, J = 7.6, 14.7 Hz), 2.55 (s, 3H), 2.92−3.04 (m, 1 H), 3.15 (d, 1 H, J = 10.0 Hz), 3.41 (dd, 1 H, J = 6.4, 9.3 Hz), 3.55 (dd, 1H, J = 6.2, 9.3 Hz), 4.06 (d, 1 H, J = 10.0 Hz), 4.46 (s, 2 H), 4.56 (d, 1 H, J = 12.5 Hz), 4.62 (d, 1 H, J = 12.5 Hz), 5.05 (d, 1 H, J = 6.1 Hz), 7.28−7.38 (m, 10 H), 8.01 (s, 1 H), 8.93 (s, 1 H). Anal. Calcd for $C_{29}H_{30}ClN_5O_3$: C, 65.47; H, 5.68; N, 13.16. Found: C, 65.23; H, 5.39; N, 13.09.

(1*S*,2*S*,4*S*,5*S*)-1,2-Di[(benzyloxy)methyl]-4-guanin-9-yl-bicyclo[3.1.0]hexane (24). To a solution of **23** (0.023 g, 0.04 mmol) in 1,4-dioxane (3 mL) was added 1 N sodium hydroxide (0.43 mL, 0.43 mmol), and the mixture was stirred at 95 °C for 7 h. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (methylene chloride:methanol = 20:1) to give **24** (0.017 g, 81%) as a syrup: UV (MeOH) λ_{max} 254 nm; ^{1}H NMR (DMSO-d_6) δ 0.74 (dd, 1 H, J = 5.4, 8.3 Hz, H_a-6′), 0.89 (dd, 1 H, J = 4.1, 5.4 Hz, H_b-6′), 1.63−1.67 (m, 2 H, H-5′ and H_a-3′), 1.79 (dd, 1 H, J = 7.5, 14.3 Hz, H_b-3′), 2.87−2.97 (m, 1 H, H-2′), 3.41−3.49 (m, 2 H, BnOCH_a and BnOCH_{aa}), 3.69 (dd, 1 H, J = 6.5, 9.3 Hz, BnOCH_{bb}), 4.06 (d, 1 H, J = 10.0 Hz, BnOCH_b), 4.55 (s, 2 H, $C_6H_5CH_2$), 4.61 (s, 2 H, $C_6H_5CH_2$), 4.75 (d, 1 H, J = 5.9 Hz, H-4′), 6.57 (br s, 2 H, NH_2), 7.33−7.46 (m, 10 H, 2 x C_6H_5), 8.09 (s, 1 H, H-8), 10.71 (br s, 1 H, NH). Anal. Calcd for $C_{27}H_{29}N_5O_3$: C, 68.77; H, 6.20; N, 14.85. Found: C, 68.99; H, 6.08; N, 15.11.

(1*S*,2*S*,4*S*,5*S*)-1,2-Dihydroxymethyl-4-guanin-9-yl-bicyclo[3.1.0]hexane (3d). To a suspension of **24** (0.017 g, 0.04 mmol) and palladium black (0.015 g) in methanol (3 mL) was added formic acid (0.7 mL, 18.55 mmol) at ambient temperature, and the mixture was stirred at 50 °C for 30 min. The reactiom mixture was allowed to cool to ambient temperature and filtered, and the solvent was evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol = 5:1) to give **3d** (0.010 g, 93%) as a white solid: mp 231 °C; $[\alpha]^{25}_D = 14.3°$ (*c* 0.1, MeOH); UV (H_2O) λ_{max} 254 nm (ϵ 14 850); ^{1}H NMR (DMSO-d_6) δ 0.67 (dd, 1 H, J = 5.5, 8.3 Hz, H_a-6′), 0.79 (dd, 1 H, J = 4.0, 5.5 Hz, H_b-6′), 1.49−1.62 (m, 2 H, H-5′ and H_a-3′), 1.74 (dd, 1 H, J = 7.3, 14.3 Hz, H_b-3′), 3.39−3.60 (m, 4 H, H-2′, CH_2OH and CH_aOH), 3.91 (dd, 1 H, J = 5.0, 11.3 Hz, CH_bOH), 4.70 (d, 1 H, J = 6.1 Hz, H-4′), 4.76 (t, 1 H, J = 5.1 Hz, OH), 5.16 (t, 1 H, J = 5.0 Hz, OH), 6.61 (br s, 2 H, NH_2), 8.08 (s, 1 H, H-8), 10.73 (br s, 1 H, NH); ^{13}C NMR (DMSO-d_6) δ 9.60, 26.40, 34.12, 34.56, 54.70, 62.72, 63.70, 104.68, 116.83, 135.67, 150.91, 153.60, 157.23. Anal. Calcd for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.39; H, 5.96; N, 23.98.

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