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Synthesis of Nucleoside Analogues Bearing the Five Naturally Occurring Nucleic Acid Bases Built on a 2-Oxabicylo[3.1.0]hexane Scaffold†

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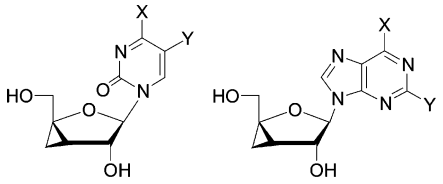

13 (X = OH, Y = H)
14 (X = OH, Y = CH_3)
15 (X = NH_2, Y = H)

17 (X = NH_2, Y = H)
18 (X = OH, Y = NH_2)

Hitherto unknown nucleoside analogues incorporating the five naturally occurring nucleic acid bases built on a 2-oxabicyclo[3.1.0]hexane template were synthesized. The synthesis of these new conformationally restricted nucleoside analogues involved the preparation of a suitable sugar precursor bearing the 2-oxabicyclo[3.1.0]hexane scaffold. This sugar was readily obtained from [(3a*S*,6a*S*)-2,2-dimethyl-3a,6a-dihydrofuro[2,3-*d*][1,3]dioxol-5-yl]methyl benzyl ether (**4**) following a Simons−Smith-type cyclopropanation reaction. Finally, glycosylation reactions and deprotection provided the nucleoside analogues. Using nucleoside **14** bearing thymine base as a model, we found that the conformation of such nucleoside analogue was restricted toward a $^0T_1$ conformation.

Introduction

Over several decades, a large number of nucleoside analogues have been synthesized, and some of them have been shown to present potent antiviral or antitumoral activities.[1,2] To become active, such compounds, generally have to be metabolized by cellular kinases to their 5′-triphosphate forms, which finally interact with viral or cellular polymerases. To discover new nucleoside derivatives endowed with biological activities, modifications of the base and/or sugar moiety of natural nucleosides can be attempted.[3,4] In recent years, the conformational behavior of natural and modified nucleosides, and in particular the sugar puckering, has been considered as of great importance all along their metabolic pathway as well as in the final interaction with the target polymerases. The sugar puckering of natural ribo- and deoxy-ribonucleosides are known to exist in a dynamic equilibrium between two major conformers, the North (N) and the South (S) types (Figure 1).[5] Conformational studies of nucleosides in solution indicate that the North/South interconversion is rapid on a NMR time scale;[6] however, when a nucleoside or a nucleotide binds to an activating enzyme or its pharmacological target, only one form is expected to be present at the active site. Even if the binding conformation is likely modified by the enzyme to achieve optimal fitting,[7] any conformation-activity study would be very helpful in order to identify conformational preferences of nucleoside- or nucleotide-converting enzymes and to study the interactions of the nucleosides or nucleotides with the enzymatic targets. For these reasons, conformationally restricted nucleosides have drawn considerable attention because they can adopt a determined conformation that can be useful tools in a

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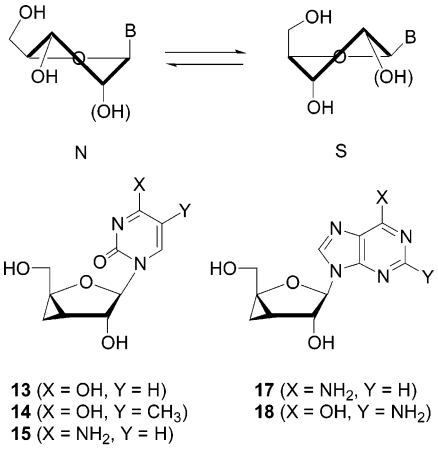

FIGURE 1. Conformational equilibrium. Nucleoside analogues incorporating the five naturally occurring nucleic acid bases built on a 2-oxabicyclo[3.1.0]hexane scaffold.

such evaluation. For instance, the use of conformationally locked carbocyclic nucleosides built on a bicyclo[3.1.0]-hexane template has demonstrated conformational preferences for a number of enzymes[8−11] and subtypes of adenosine receptors.[12−16] For our part, we chose to introduce modifications on the sugar able of restricting the dynamic equilibrium between the northern-type and southern-type geometry that normally characterize the sugar moiety of standard nucleosides in solution. In this respect, we have synthesized new conformationally locked nucleoside analogues built on a 2-oxabicyclo[3.1.0.]hexane scaffold[17] bearing purine and pyrimidine bases. Assuming that the conformation and puckering of the glycon moiety of nucleosides play a critical role in modulating biological activity, such new conformationally restricted nucleoside analogues, could be used to obtain further information regarding the correlation between sugar ring conformation and biological activity. Herein, we will report on the synthesis of such compounds (Figure 1).

Results and Discussion

Retrosynthetic Pathway. The synthesis of the target nucleosides was achieved through glycosylation reactions between a suitable sugar precursor **a** bearing appropriate protecting groups and the heterocyclic bases. For the preparation of the sugar precursor **a**, a Simmons−Smith-type cyclopropanation reaction[18] should be straightforward from a furanose substrate **b** having a double bond in position 3,4. The stereoselective control of the methylene insertion on the α face of **b** might be induced from the steric hindrance of the 1,2-*O*-isopropylidene group on the sugar β face. The unsaturated sugar **b** should be easily synthesized following a β-elimination reaction from 1,2-*O*-isopropylidene L-xylose (Figure 2).

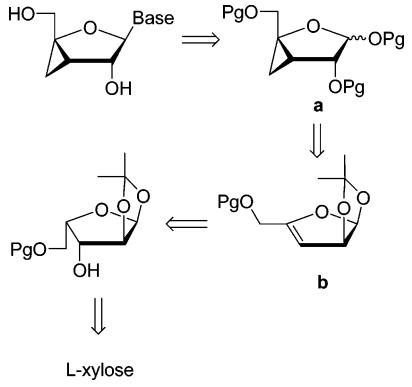

FIGURE 2. Retrosynthetic pathway. Pg = variable protecting group

Chemical Synthesis. As an appropriate carbohydrate precursor, commercially available L-xylose was chosen as starting material. L-Xylose (**1**) was converted to 5-*O*-benzyl-1,2-*O*-isopropylidene-α-L-xylofuranose (**2**) following a similar protocol established in the literature for the synthesis of the D-counterpart (Scheme 1).[19]

Compound **2** was reacted with triflic anhydride (Tf_2O) in a pyridine/dichloromethane mixture at −15 °C[20] to provide sugar **3**, which was subjected to a β-elimination reaction using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile under reflux. Compound (**4**) was obtained in 93% yield after purification by silica gel column chromatography. The cyclopropanation reaction of compound **4** was accomplished via a Simmons−Smith-type reaction following Furukawa's procedure[21,22] to afford a mixture of compounds **5a** and **5b**. Separation was readily achieved by silica gel column chromatography to provide pure **5a** and **5b**, with 91% and 1.5% yield, respectively. As expected, compound **5a** with a methylene *exo* was obtained as the major compound. Stereoselective control of this reaction is obtained on a sterically constrained substrate like compound **4** where the isopropylidene group directs the methylene insertion on the α face, the

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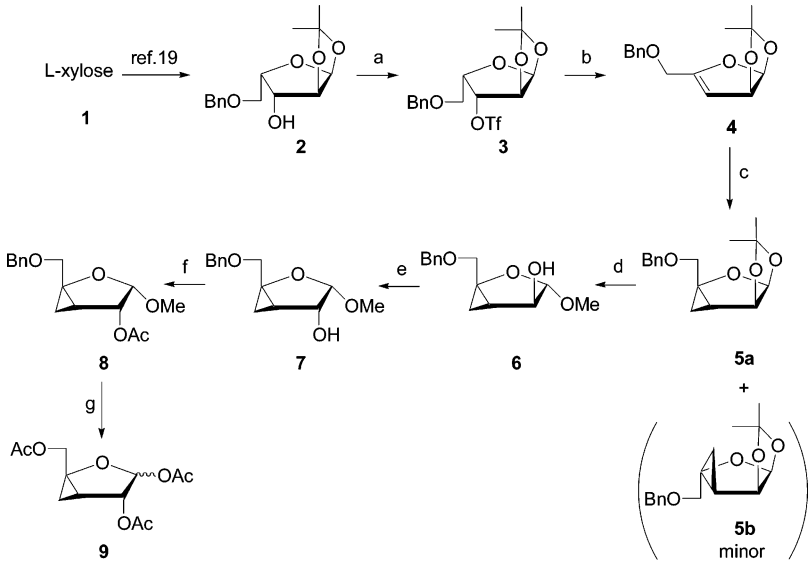
SCHEME 1[a]



[a] Reagents and conditions: (a) Tf_2O, pyridine/CH_2Cl_2, −15 °C; (b) DBU, CH_3CN, 80 °C; (c) $ZnEt_2$, CH_2I_2, toluene, 0 °C; (d) 4 N HCl/dioxane, 0 °C; (e) (i) CrO_3, Ac_2O, pyridine/CH_2Cl_2, 0 °C, (ii) $NaBH_4$/EtOH, rt; (f) Ac_2O/pyridine, rt; (g) AcOH, Ac_2O, H_2SO_4, 0 °C to rt.

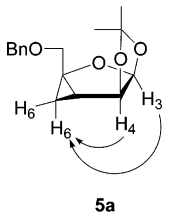


FIGURE 3. NOE effects on compound **5a**.

less hindered face of the compound, providing as a major compound sugar **5a** with a D-like configuration. Structural assignments were based upon ^{1}H NMR spectra, COSY homonuclear experiments, and NOE effects. In the case of **5a**, the H-4 signal appeared as a doublet with a coupling constant $^3J_{H4-H3} = 4.1$ Hz. In the case of **5b**, H-4 signal appeared as a pseudo-triplet with a coupling constant $^3J_{H4-H3}$ and $^3J_{H4-H5}$ of 5.2 and 4.7 Hz, respectively. Furthermore, using NOE-difference spectroscopy, NOE effects were observed for **5a** between the H-6 methylene protons and H-4 (8.8%) as well as H-6 methylene protons and H-3 (4.6%) (Figure 3).

No significant NOE effect was seen for compound **5b**. All of these observations are in agreement with a methylene insertion mainly on the α face of sugar **4** during the cyclopropanation reaction. To obtain the nucleoside analogues with the β-configuration and owing to an anchimeric participation of a 4-*O*-acyl-type protective group during glycosylation reactions, compound **5a** with an arabino-like configuration has to be converted to a sugar with a ribo-like configuration. In this regard, hydrolysis of **5a** with HCl in a dioxane−methanol mixture afforded, as a single isomer, the α-anomer of methyl furanoside **6** in a high yield. Later, a chromium-mediated oxidation of **6** provided the corresponding ketone, which was not isolated but directly reduced with sodium boronhydride to give, after purification on silica gel column chromatography, the sugar epimer **7** with 74% yield. Inversion of configuration at C-4 was established by taking account of ^{1}H NMR spectra of compounds **6** and **7**. In the case of α-methyl furanoside **6**, H-3 signal appears as a singlet while H-3 signal of compound **7** appears as a doublet with a coupling constant $^3J_{H3-H4} = 5.8$ Hz, confirming a ribo-like configuration for **7**. Compound **7** was converted into the suitable peracylated sugar precursor **9** in a two-step procedure. First, an acetylation reaction afforded **8**, which was later reacted with AcOH/Ac_2O/H_2SO_4 to give, after purification by silica gel column chromatography, an anomeric mixture (ratio **9**α/**9**β, 9/91) of 3-(acetyloxy)-1-[(acetyloxy)methyl]-2-oxabicyclo[3.1.0]hex-4-yl acetate with 81% yield. Afterward, sugar **9** was used for the condensation reactions with the heterocyclic bases and provided in each case only the β anomers of the protected nucleosides owing to 4-*O*-acyl-type participating group. The syntheses of the pyrimidines **13**−**15** and purine **17** and **18** nucleosides are depicted in Scheme 2.

Briefly, glycosylation reaction with uracil, thymine or N_4-benzoyl cytosine and sugar **9**, under Vorbrüggen conditions[23] using (trimethylsilyl) trifluoromethane sulfonate (TMSOTf) as a catalyst in anhydrous acetonitrile at 0 °C, afforded compounds **10**−**12**. The target nucleosides **13**−**15** were obtained from **10**−**12** following treatment with methanolic ammonia after purification on silica gel column chromatography. A glycosylation reaction with adenine and **9** using tin(IV) chloride ($SnCl_4$) as a catalyst[24] in anhydrous acetonitrile afforded protected nucleoside **16**, which upon treatment with sodium methoxide in methanol gave the desired nucleoside **17** in 61% yield after purification. To prepare the guanosine analogue (**18**), a condensation reaction of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine with **9** following Robins' procedure[25] was achieved. The crude coupling product was directly treated with methanolic ammonia to give nucleoside **18**.

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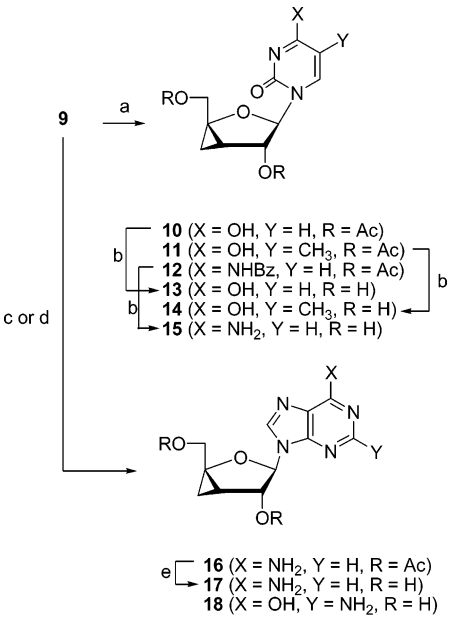
SCHEME 2[a]



[a] Reagents: (a) silylated pyrimidine, TMSOTf, CH_3CN, 0°; (b) MeOH/NH_3, rt; (c) adenine, $SnCl_4$, CH_3CN, rt; (d) (i) silylated 2-*O*-acetyl-6-*O*-(diphenylcarbamoyl)guanine, BSA, toluene, 80 °C, (ii) MeOH/NH_3, rt; (e) MeONa/MeOH, rt.

Conformational Analysis. Briefly, the definition of the conformational behavior of natural and modified nucleosides involves the determination of at least three structural parameters.[5] The glycosidic torsion angle χ determines the syn or anti disposition of the base relative to the sugar moiety (syn when the C-2 carbonyl of pyrimidines or N-3 of purine lies over the sugar ring, anti when these atoms are oriented in the opposite direction). The torsion angle γ determines the orientation of the 5′-OH with respect to C-3′ as represented by the three main rotamers $\gamma+$, γt and $\gamma-$. The conformation of the furanose ring and its deviation from planarity are described by the pseudorotational phase angle P and the maximal puckering amplitude ν_{max}. For conformational studies, we chose as a model compound the nucleoside **14**, and its conformation was analyzed by simple modeling. An ab initio calculation was performed on **14**, i.e., a geometry optimization at the 3-21 G level using basis set as implemented in the HyperChem 7.5 software. A root-mean-square gradient termination cutoff of 0.05 kcal $Å^{-1}$ mol^{-1} was used for geometry optimization with the Polak−Ribiere conjugate gradient algorithm. The torsion angles γ and χ on the nucleoside structure were initially located in the $\gamma-$ and anti ranges, respectively. The calculations provided a geometry optimized structure close to a $^0T_1$ conformation ($P = 107.2°$) ($\nu_2 = -5.1°$) and $\nu_{max} = 17.2°$. As established, the 2-oxabicyclo[3.1.0]hexane scaffold seems to restrict the sugar moiety toward a C1′-*exo* type of conformation according to the standard conformational description of nucleosides. Such kind of *S*-type conformation has been previously reported for nucleoside analogues bearing various *exo* fused ring, such as azetidine,[26] oxetane,[27] and propylene ring.[28] However, in our case, a flatter ring pucker was observed.

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Conclusion

Nucleoside analogues **13**−**15**, **17**, and **18** incorporating the five naturally occurring nucleic acid bases built on a 2-oxabicyclo[3.1.0]hexane scaffold were synthesized through glycosylation reactions between heterocyclic bases and a suitable sugar precursor bearing the 2-oxabicyclo[3.1.0]hexane structure. Using compound **14** as model, we found that the conformation of such nucleoside analogue was restricted toward a $^0T_1$ conformation. Biological evaluations of nucleoside analogues **13**−**15**, **17**, and **18** against a broad range of viruses are currently in progress. These new nucleoside analogues built on a 2-oxabicyclo[3.1.0]hexane scaffold might find wider applicability to probe conformational preferences of nucleoside/nucleotide-converting enzymes and receptors.

Experimental Section

5-*O*-Benzyl-1,2-*O*-isopropylidene-α-L-xylofuranose (2). Compound **2** was prepared in 75% yield from commercially available L-xylose following a similar protocol established in the literature for the synthesis of its D-counterpart:[19] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 5H), 6.01 (d, 1H, $J = 3.7$ Hz), 4.68 (d, 1H, $J = 11.9$ Hz), 4.59 (d, 1H, $J = 11.9$ Hz), 4.54 (m, 1H), 4.28 (m, 2H), 3.97 (m, 2H), 3.66 (d, 1H, $J = 3.5$ Hz), 1.37 (s, 3H), 1.23 (s, 3H). Compound **2** was directly used in the next step without further purification.

5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-triflyl-α-L-xylofuranose (3). Compound **2** (58.7 g, 0.21 mol) was coevaporated with dry pyridine and dissolved in a mixture of dry CH_2Cl_2 (500 mL) and dry pyridine (80 mL). The mixture was cooled to −15 °C, then Tf_2O (70.5 mL, 0.42 mol) in CH_2Cl_2 (500 mL) was added dropwise, and the resulting mixture was stirred for 1 h at room temperature. The mixture was poured into cold saturated $NaHCO_3$ solution and washed with water (3 × 200 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was dissolved in hot hexane, filtered, and coevaporated with dry toluene to give compound **3** as a white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32 (m, 5H), 6.02 (d, 1H, $J = 3.7$ Hz), 5.31 (d, 1H, $J = 2.6$ Hz), 4.76 (d, 1H, $J = 3.7$ Hz), 4.64−4.54 (m, 3H), 3.86−3.65 (m, 2H), 1.52 (s, 3H), 1.36 (s, 3H); FAB-MS (>0) *m/z* 413 $(M + H)^+$. Compound **3** was directly used in the next step without further purification.

[(3a*S*,6a*S*)-2,2-Dimethyl-3a,6a-dihydrofuro[2,3-*d*][1,3]-dioxol-5-yl]methyl Benzyl Ether (4). DBU (59.8 mL, 0.4 mol) was added to a solution of compound **3** (82 g, 0.2 mol) in dry CH_3CN (1 L) and the mixture was heated under reflux 1 h. After cooling, the solution was carefully adjusted to pH 7.5−8 with 2 N HCl solution and dissolved in CH_2Cl_2 (300 mL). The organic phase was washed with water (3 × 100 mL) and dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ether (9:1) as eluent to give compound **4** (48.5 g, 92%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 5H), 6.11 (d, 1H, $J = 5.2$ Hz), 5.33 (m, 1H), 5.26 (m, 1H), 4.62 (s, 2H), 4.08 (s, 2H), 1.50 (s, 3H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 138−128.2, 112.6, 106.8, 100.3, 83.9, 73.5, 65.2, 28.5, 28.3; FAB-MS (>0) *m/z* 263 $(M + H)^+$. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.81; H, 6.98.

[(3a*S*,4a*S*,5a*S*,5b*S*)-2,2-Dimethyltetrahydro-4a*H*-cyclopropa[4,5]furo[2,3-*d*][1,3]dioxol-4a-yl]methyl Benzyl Ether (5a) and [(3a*S*,4a*R*,5a*R*,5b*S*)-2,2-Dimethyltetrahydro-4a*H*-cyclopropa[4,5]furo[2,3-*d*][1,3]dioxol-4a-yl]methyl Benzyl Ether (5b). To a stirred solution of

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4 (6.0 g, 22.9 mmol) in dry toluene (115 mL) at 0 °C was added dropwise diethyl zinc [1 M in hexane] (60 mL, 60 mmol) and diiodomethane (4.8 mL, 59.6 mmol). After 15 min, the mixture was allowed to reach room temperature and stirring was continued for 4 h. Saturated NH_4Cl solution was carefully added and the resulting mixture was extracted with CH_2Cl_2 (3 × 120 mL), washed successively with a saturated $NaHCO_3$ solution (100 mL) and water (100 mL), and dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ether (4:1) as eluent to give successively, as colorless oil, compound **5a** (5.8 g, 91%) and compound **5b** (0.1 g, 1.5%). Compound **5a**: $[\alpha]^{20}_D$ −50.9 (*c* 1.06, DMSO); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.30 (m, 5H), 5.56 (d, 1H, J = 4.1 Hz), 4.79 (d, 1H, J = 4.1 Hz), 4.70 (d, 1H, J = 12.1 Hz), 4.62 (d, 1H, J = 12.1 Hz), 3.90 (d, 1H, J = 11.3 Hz), 3.76 (d, 1H, J = 11.3 Hz), 1.78 (dd, 1H, J = 5, 10 Hz), 1.61 (s, 3H), 1.4 (s, 3H), 0.83 (dd, 1H, J = 5, 6.7 Hz), 0.54 (dd, 1H, J = 6.7, 10 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6−128, 114.5, 107.8, 84.5, 73.4, 71.5, 69.4, 28.7, 28.3, 23.8, 15.3; FAB-MS (>0) *m/z* 277 (M + H)$^+$. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.66; H, 7.37. Compound **5b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40−7.30 (m, 5H), 5.92 (d, 1H, J = 4.6 Hz), 4.93 (t, 1H, J = 4.6 Hz), 4.58 (d, 1H, J = 12.2 Hz), 4.52 (d, 1H, J = 12.2 Hz), 3.79 (d, 1H, J = 11.8 Hz), 3.39 (d, 1H, J = 11.8 Hz), 1.72 (m, 1H), 1.47 (s, 3H), 1.40 (dd, 1H, J = 4.8, 6.1 Hz), 1.21 (s, 3H), 0.91 (dd, 1H, J = 6.1, 9.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2−127.5, 111.9, 110.6, 81.5, 74.1, 73, 71.7, 26.5, 26.5, 24.2, 18.3; FAB-MS *m/z* 277 (M + H)$^+$.

(1*S*,3*S*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-3-methoxy-2-oxabicyclo[3.1.0]hexan-4-ol (6). HCl (4 N) in dioxane (2.2 mL) was added to a solution of **5a** (3.76 g, 13.6 mmol) in MeOH (100 mL) at 0 °C. The mixture was allowed to reach room temperature and stirring was continued overnight. The solution was neutralized with a saturated $NaHCO_3$ solution and then concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ether (1:1) as eluent to give compound **6** (3.05 g, 89%) as a colorless syrup: $[\alpha]^{20}_D$ +11.2 (*c* 1.07, DMSO); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.18 (m, 5H), 4.89 (s, 1H), 4.60 (d, 1H, J = 12.1 Hz), 4.54 (d, 1H, J = 12.1 Hz), 3.97 (s, 1H), 3.89 (d, 1H, J = 11.6 Hz), 3.47 (d, 1H, J = 11.6 Hz), 3.23 (s, 3H), 3.08 (br s, 1H), 1.40 (dd, 1H, J = 5, 10 Hz), 1.12 (dd, 1H, J = 5, 6.5 Hz), 0.62 (dd, 1H, J = 6.5, 10 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3−128, 113.6, 77.9, 73.5, 71.8, 69.5, 55.8, 25.5, 15.4; FAB-MS (>0) *m/z* 251 (M + H)$^+$; FAB-MS (<0) *m/z* 249 (M − H)$^-$. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.96; H, 7.41.

(1*S*,3*S*,4*R*,5*S*)-1-[(Benzyloxy)methyl]-3-methoxy-2-oxabicyclo[3.1.0]hexan-4-ol (7). To a mixture of dry CH_2Cl_2 (150 mL) and dry pyridine (6 mL) at 0 °C were added CrO_3 (3.72 g, 37.2 mmol) and acetic anhydride (3.6 mL, 38.1 mmol). The resulting mixture was stirred for 30 min. A solution of **6** (3 g, 12 mmol) in dry CH_2Cl_2 (30 mL) was added and the solution was stirred for 4 h at room temperature. The mixture was poured into cold ether and filtered through silica with ether/pyridine (99:1). The filtrate was evaporated and coevaporated with dry toluene. The resulting residue was dissolved in absolute ethanol (90 mL) and $NaBH_4$ (1.37 g, 36.2 mmol) in absolute ethanol (30 mL) was added dropwise. Then the reaction mixture was neutralized with 2 N HCl solution, extracted with CH_2Cl_2 (3 × 30 mL), and washed with water. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ether (3:2) as eluent to give compound **7** (2.25 g, 74%) as a colorless syrup: $[\alpha]^{20}_D$ +4.5 (*c* 1.1, DMSO); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.20 (m, 5H), 4.87 (d, 1H, J = 5.8 Hz), 4.65−4.52 (m, 2H,), 3.71 (d, 1H, J = 11.6 Hz), 3.49 (d, 1H, J = 11.6 Hz), 3.34 (s, 3H), 2.67 (d, 1H, J = 9.3 Hz), 1.63 (m, 1H), 1.33 (t, 1H, J = 5.6 Hz), 0.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5−128, 103.8, 74.1, 73.4, 71.9, 67.9, 56.6, 24.3, 15.3; FAB-MS (>0) *m/z* 251 (M + H)$^+$; FAB-MS (<0) *m/z* 249 (M − H)$^-$. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.04; H, 7.40.

(1*S*,3*S*,4*R*,5*S*)-1-[(Benzyloxy)methyl]-3-methoxy-2-oxabicyclo[3.1.0]hex-4-yl Acetate (8). To a solution of the compound **7** (380 mg, 1.52 mmol) in pyridine (7 mL) was added acetic anhydride (1.4 mL, 14.8 mmol). After stirring for 2 h, the solution was evaporated and coevaporated with toluene and the crude product was purified by silica gel column chromatography using petroleum ether/ether (3:2) as eluent to give compound **8** (405 mg, 91%) as a colorless syrup: $[\alpha]^{20}_D$ +23.2 (*c* 0.86, DMSO); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.2 (m, 5H), 5.22 (m, 1H), 5.06 (d, 1H, J = 5.6 Hz), 4.57 (d, 1H, J = 12.2 Hz), 4.53 (d, 1H, J = 12.2 Hz), 3.75 (d, 1H, J = 11.6 Hz), 3.52 (d, 1H, J = 11.6 Hz), 3.26 (s, 3H), 2.03 (s, 3H), 1.64 (m, 1H), 1.50 (t, 1H, J = 5.4 Hz), 0.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 138.5−128, 103.4, 76.1, 73.5, 71.7, 67.1, 56.8, 21.2, 15.9; FAB-MS (>0) *m/z* 293 (M + H)$^+$; FAB-MS (<0) *m/z* 291 (M − H)$^-$. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 66.00; H, 7.03.

(1*S*,3*R*,4*R*,5*S*)-3-(Acetyloxy)-1[(acetyloxy)methyl]-2-oxabicyclo[3.1.0]hex-4-yl Acetate (9α) and (1*S*,3*S*,4*R*,5*S*)-3-(Acetyloxy)-1-[(acetyloxy)methyl]-2-oxabicyclo[3.1.0]-hex-4-yl Acetate (9*β*). Acetic anhydride (1.2 mL, 12.7 mmol) was added to a solution of compound **8** (356 mg, 1.22 mmol) in acetic acid (6 mL) at 0 °C. Sulfuric acid (0.025 mL) was then added dropwise. The reaction mixture was stirred at room temperature overnight then diluted with a mixture of ice and water. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were successively washed with a saturated $NaHCO_3$ solution and water (3 × 30 mL) and dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ether (3:2) as eluent to give an anomeric mixture of compounds **9**α/**9***β* (269 mg, 81%, ratio α/*β*, 9/91) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.35 (d, 1H, J = 5.6 Hz), 5.84 (s, 1H), 5.43 (t, 1H, J = 5.6 Hz), 5.25 (d, 1H, J = 6.3 Hz), 4.38 (d, 1H, J = 12.8 Hz), 4.34 (d, 1H, J = 12.7 Hz), 4,19 (d, 1H, J = 12.7 Hz), 4.15 (d, 1H, J = 12.8 Hz), 2.11 (m, 1H), 2.05−2.00 (m, 18H), 1.87 (m, 1H), 1.58 (dd, 1H, J = 5.1, 6.8 Hz), 1.26 (t, 1H, J = 5.6 Hz), 0.94 (dd, 1H, J = 6.4, 9.6 Hz), 0.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2−169.4, 105.5, 95.0, 79.8, 74.9, 73.3, 65.8, 65.4, 24.2, 21.4−20.9, 19.2, 16.2; FAB-MS (>0) *m/z* 273 (M + H)$^+$; FAB-MS (<0) *m/z* 271 (M − H)$^-$. Anal. Calcd for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 52.54; H, 6.26.

[(1*S*,3*R*,4*R*,5*S*)-4-(Acetyloxy)-3-(2,4-dioxo-3,4-dihydro-1(2*H*)-pyrimidinyl)-2-oxabicyclo[3.1.0]hex-1-yl]methyl Acetate (10). A mixture of uracil (350 mg, 3.12 mmol), HMDS (15 mL), and a catalytic amount of ammonium sulfate was refluxed for 14 h. The resultant clear solution was concentrated to dryness under reduced pressure. TMSOTf (0.47 mL, 2.6 mmol) was added at 0 °C to a solution of compound **9** (380 mg, 1.40 mmol) and silylated base in dry acetonitrile (14 mL). The reaction mixture was stirred for 30 min, poured into a saturated $NaHCO_3$ solution, and filtered through Celite. The resulting mixture was coevaporated, extracted with CH_2Cl_2 (3 × 30 mL), washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using dichloromethane/methanol (97:3) as eluent to give the compound **10** (360 mg, 80%) as a white foam: UV (EtOH 95%) λ_{max} = 260 nm (ϵ = 9800); $[\alpha]^{20}_D$ −101 (*c* 1.00, DMSO); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.38 (br s, 1H), 7.66 (d, 1H, J = 8.0 Hz), 5.71 (d, 1H, J = 8.0 Hz), 5.61 (m, 2H), 4.39 (d, 1H, J = 12.7 Hz), 4.28 (d, 1H, J = 12.7 Hz), 1.93 (m, 7H), 1.30 (t, 1H, J = 5.7 Hz), 1.00 (1H, dd, J = 6.7, 9.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.2, 163.0, 150.0, 142.0, 102.1, 90.7, 78.5, 69.5, 65.1, 21.7, 20.6, 14.2; FAB-MS (>0) *m/z* 325 (M + H)$^+$; FAB-MS (<0) *m/z* 323 (M − H)$^-$. Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.69; H, 5.05, N, 8.35.

[(1*S*,3*R*,4*R*,5*S*)-4-(Acetyloxy)-3-(5-methyl-2,4-dioxo-3,4-dihydro-1(2*H*)-pyrimidinyl)-2-oxabicyclo[3.1.0]hex-1-yl]-methyl Acetate (11). A mixture of thymine (100 mg, 0.79 mmol), HMDS (5 mL), and a catalytic amount of ammonium sulfate was refluxed for 14 h. The resultant clear solution was concentrated to dryness under reduced pressure. TMSOTf (0.08 mL, 0.44 mmol) was added at 0 °C to a solution of **9** (110 mg, 0.40 mmol) and silylated base in dry acetonitrile (4 mL). The reaction mixture was stirred for 30 min, poured into a saturated $NaHCO_3$ solution, and filtered through Celite. The resulting mixture was coevaporated, extracted with CH_2Cl_2 (3 × 30 mL), washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using dichloromethane/methanol (97:3) as eluent to give the compound **11** (90 mg, 67%) as a white foam: UV (EtOH 95%) λ_{max} = 263 nm (ϵ = 8600); $[\alpha]^{20}_D$ −101.9 (*c* 1.02, DMSO); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.38 (br s, 1H), 7.53 (d, 1H, *J* = 1.2 Hz), 5.66 (d, 1H, *J* = 4.5 Hz), 5.58 (t, 1H, *J* = 5.8 Hz), 4.40 (d, 1H, *J* = 12.6 Hz), 4.30 (d, 1H, *J* = 12.6 Hz), 2.08 (7H, m), 1.80 (d, 3H, *J* = 1.2 Hz), 1.33 (t, 1H, *J* = 5.4 Hz), 1.00 (dd, 1H, *J* = 6.7, 9.0 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.2, 163.6, 150.0, 137.1, 110.0, 89.3, 78.4, 69.1, 65.1, 21.5, 20.6, 14.0, 12.0; FAB-MS (>0) *m/z* 339 (M + H)$^+$; FAB-MS (<0) *m/z* 337 (M − H)$^-$. Anal. Calcd for $C_{15}H_{14}N_2O_7$: C, 53.25; H, 5.36 N, 8.28. Found: C, 53.09; H, 5.36, N, 8.09.

[(1*S*,3*R*,4*R*,5*S*)-4-(Acetyloxy)-3-(4-(benzoylamino)-2-oxo-1(2*H*)-pyrimidinyl)-2-oxabicyclo[3.1.0] hex-1-yl]methyl Acetate (12). A mixture of N_4-benzoyl cytosine (300 mg, 1.39 mmol), HMDS (7 mL), and a catalytic amount of ammonium sulfate was refluxed for 14 h. The resultant clear solution was concentrated to dryness under reduced pressure. TMSOTf (0.2 mL, 1.1 mmol) was added at 0 °C to a solution of **9** (160 mg, 0.59 mmol) and silylated base in dry acetonitrile (5.9 mL). The reaction mixture was stirred for 30 min, poured into a saturated $NaHCO_3$ solution, and filtered through Celite. The resulting mixture was coevaporated, extracted with CH_2Cl_2 (3 × 30 mL), washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting yellow powder was washed with ethanol to give compound **12** (190 mg, 75%) as a white solid: mp 190−192 °C; UV (EtOH 95%) λ_{max} = 260 nm (ϵ = 27000); $[\alpha]^{20}_D$ −70.5 (*c* 0.61, DMSO); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (br s, 1H), 7.84−7.41 (m, 7H), 5.70 (d, 1H, *J* = 3.5 Hz), 5.54 (dd, 1H, *J* = 3.5, 6.1 Hz), 4.49 (d, 1H, *J* = 12.9 Hz), 4.27 (d, 1H, *J* = 12.9 Hz), 2.12 (m, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 1.32 (dd, 1H, *J* = 5.4, 6.7 Hz), 0.94 (dd, 1H, *J* = 6.7, 9.4 Hz);^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 163.0, 154.7, 145.4, 133.7−128.1, 97.5, 93.8, 80.5, 72.0, 65.8, 23.3, 21.3, 16.1; FAB-MS (>0) *m/z* 428 (M + H)$^+$; FAB-MS (<0) *m/z* 426 (M − H)$^-$. Anal. Calcd for $C_{21}H_{21}N_3O_7$: C, 59.01; H, 4.95; N, 9.83. Found: C, 59.11; H, 4.99, N, 9.93.

1-[(1*S*,3*R*,4*R*,5*S*)-4-Hydroxy-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-2,4(1*H*,3*H*)-pyrimidinedione (13). A solution of **10** (150 mg, 0.46 mmol) in methanolic ammonia (10 mL, previously saturated at −10 °C and tightly stoppered) was stirred at room temperature for 15 h, then concentrated to dryness. The residue was purified by silica gel column chromatography using dichloromethane/methanol (9:1) as eluent to give the compound **13** (71 mg, 64%) as a white foam that was crystallized from absolute ethanol: mp 169−171 °C; UV (EtOH 95%) λ_{max} = 260 nm (ϵ = 8600); $[\alpha]^{20}_D$ −147.2 (*c* 0.92, DMSO); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.4 (br s, 1H), 7.79 (d, 1H, *J* = 8.0 Hz), 5.79 (d, 1H, *J* = 8.0 Hz), 5.60 (d, 1H, *J* = 4.8 Hz), 5.51 (d, 1H, *J* = 5.5 Hz), 4.98 (t, 1H, *J* = 4.8 Hz), 4.65 (m, 1H), 3.91 (dd, 1H, *J* = 5.9, 12.6 Hz), 3.57 (1H, dd, *J* = 4.5, 12.6 Hz), 1.81 (1H, m), 1.27 (1H, t, *J* = 5.3 Hz), 0.74 (1H, dd, *J* = 6.3, 9.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.2, 152.5, 143.6, 104.5, 92.5, 78.3, 73.6, 64.4, 25.0, 14.4; FAB-MS (>0) *m/z* 241 (M + H)$^+$; FAB-MS (<0) *m/z* 239 (M − H)$^-$. Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.89; H, 5.24, N, 11.42.

1-[(1*S*,3*R*,4*R*,5*S*)-4-Hydroxy-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (14). A solution of **11** (150 mg, 0.45 mmol) in methanolic ammonia (10 mL, previously saturated at −10 °C and tightly stoppered) was stirred at room temperature for 15 h and then concentrated to dryness. The residue was purified by silica gel column chromatography using chloroform/methanol (9:1) as eluent and then lyophylizated from water to give the compound **14** (101 mg, 88%) as a white powder: UV (EtOH 95%) λ_{max} = 264 nm (ϵ = 9700); $[\alpha]^{20}_D$ −113.8 (*c* 1.01, DMSO); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.30 (br s, 1H), 7.56 (s, 1H,), 5.51 (d, 1H, *J* = 5.0 Hz), 5.40 (1H, d, *J* = 6.7 Hz), 4.92 (1H, t, *J* = 4.8 Hz), 4.55 (m, 1H), 3.80 (dd, 1H, *J* = 6.2, 12.5 Hz), 3.48 (dd, 1H, *J* = 5.1, 12.5 Hz), 1.79 (s, 3H), 1.71 (m, 1H), 1.16 (t, 1H, *J* = 5.6 Hz), 0.72 (dd, 1H, *J* = 6.4, 9.1 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.7, 150.4, 136.9, 109.9, 89.6, 75.9, 71.1, 62.2, 22.8, 12.1; FAB-MS (>0) *m/z* 255 (M + H)$^+$. Anal. Calcd for $C_{11}H_{14}N_2O_5 \cdot 0.65H_2O$: C, 49.68; H, 5.80 N, 10.53. Found: C, 50.01; H, 5.77, N, 10.27.

4-Amino-1-[(1*S*,3*R*,4*R*,5*S*)-4-hydroxy-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-2(1*H*)-pyrimidinone (15). A solution of **12** (150 mg, 0.35 mmol) in methanolic ammonia (10 mL, previously saturated at −10 °C and tightly stoppered) was stirred at room temperature for 15 h and then concentrated to dryness. The residue was purified by silica gel column chromatography using chloroform/methanol (97:3) as eluent to give the compound **15** (71 mg, 85%). Analysis was made on the corresponding chlorohydrate salt prepared from ethanol 95% (0.5 mL) and 2 N HCl (0.25 mL): UV (EtOH 95%) λ_{max} = 270 nm (ϵ = 9500); $[\alpha]^{20}_D$ −80.3 (*c* 0.56, DMSO); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.80 (br s, 1H), 8.70 (br s, 1H), 8.12 (d, 1H, *J* = 7.8 Hz), 6.18 (d, 1H, *J* = 7.8 Hz), 5.52 (d, 1H, *J* = 4.2 Hz), 4.59 (m, 1H), 3.85 (d, 1H, *J* = 12.6 Hz), 3.47 (d, 1H, *J* = 12.6 Hz), 1.79 (m, 1H), 1.19 (t, 1H, *J* = 5.2 Hz), 0.77 (dd, 1H, *J* = 6.3, 9.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.3, 147.9, 146.0, 95.4, 93.0, 77.6, 73.8, 62.9, 24.1, 13.8; FAB-MS (>0) *m/z* 240 (M − Cl)$^+$. Anal. Calcd for $C_{10}H_{14}ClN_3O_4$: C, 43.28; H, 5.10; Cl, 13.41 N, 15.41. Found: C, 43.01; H, 5.05, Cl, 13.55, N, 14.99.

[(1*S*,3*R*,4*R*,5*S*)-4-(Acetyloxy)-3-(6-amino-9*H*-purin-9-yl)-2-oxabicyclo[3.1.0]hex-1-yl]methyl Acetate (16). Tin-(IV) chloride (0.1 mL, 0.85 mmol) was added cautiously to a stirred suspension of adenine (60 mg, 0.44 mmol) and compound **9** (100 mg, 0.37 mmol) in dry acetonitrile (3 mL) at room temperature. After 1 h, pyridine (1 mL) was added to the resultant solution. The white precipitate was filtered and washed with chloroform. The combined filtrates were washed with saturated $NaHCO_3$ solution (100 mL) and water (10 mL), dried over sodium sulfate, and concentrated to dryness. The residue was purified by silica gel column chromatography using chloroform/methanol (96:4) as eluent to give the compound **16** (78 mg, 61%), which was crystallized from acetonitrile: mp 109−111 °C; UV (EtOH 95%) λ_{max} = 260 nm (ϵ = 13800); $[\alpha]^{20}_D$ −173.7 (*c* 0.98, DMSO); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.31 (s, 1H), 8.17 (s, 1H), 7.34 (br s, 1H), 6.15 (1H, dd, *J* = 3.9, 6.0 Hz), 5.92 (1H, d, *J* = 3.9 Hz), 4.32 (m, 2H), 2.33 (m, 1H), 2.05 (s, 3H), 1.94 (s, 3H), 1.40 (t, 1H, *J* = 5.4 Hz), 1.09 (dd, 1H, *J* = 6.5, 9.3 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.9, 154.9, 151.6, 147.8, 138.6, 117.7, 87.8, 77.0, 68.7, 63.7, 21.3, 19.4, 19.3, 13.7; FAB-MS (>0) *m/z* 348 (M + H)$^+$; FAB-MS (<0) *m/z* 346 (M − H)$^-$. Anal. Calcd for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93 N, 20.16. Found: C, 52.00; H, 4.99, N, 20.30.

(1*S*,3*R*,4*R*,5*S*)-3-(6-Amino-9*H*-purin-9-yl)-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-4-ol (17). To a solution of compound **16** (935 mg, 2.69 mmol) in methanol (51 mL) was added sodium methoxide (480 mg, 8.88 mmol). The reaction mixture was stirred at room temperature overnight, neutralized with a 2 N HCl solution, and then concentrated to dryness. The residue was purified by silica gel column chromatography using dichloromethane/methanol (88:12) as eluent to give the compound **17** (432 mg, 61%), which was crystallized from absolute ethanol: mp 213−215 °C; UV (EtOH 95%) λ_{max} = 260 nm (ϵ = 15600); $[\alpha]^{20}_D$ −140.4 (*c* 0.99, DMSO); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.33 (s, 1H), 8.14 (s, 1H), 7.28 (s, 2H),

5.58 (d, 1H, J = 4.8 Hz), 5.52 (d, 1H, J = 5.0 Hz), 5.06 (m, 1H), 4.89 (1H, t, J = 5.5 Hz), 3.75 (dd, 1H, J = 5.5, 12.4 Hz), 3.58 (dd, 1H, J = 5.5, 12.4 Hz), 1.87 (m, 1H), 1.28 (t, 1H, J = 5.3 Hz), 0.82 (dd, 1H, J = 6.4, 9.9 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.9, 152.6, 149.1, 139.7, 118.8, 89.9, 75.8, 71.5, 62.3, 23.0, 12.2; FAB-MS (>0) m/z 264 $(M + H)^+$; FAB-MS (<0) m/z 262 $(M - H)^-$. Anal. Calcd for $C_{11}H_{13}N_5O_3 \cdot 0.1H_2O$: C, 49.85; H, 5.02 N, 26.42. Found: C, 49.53; H, 5.00, N, 26.36.

2-Amino-9-[(1*S*,3*R*,4*R*,5*S*)-4-hydroxy-1-(hydroxymethyl)-2-oxabicyclo[3.1.0]hex-3-yl]-1,9-dihydro-6*H*-purin-6-one (18). BSA (0.56 mL, 2.3 mmol) was added to a suspension of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (340 mg, 0.88 mmol) in dry 1,2-dichloroethane (7.6 mL). After 1 h at reflux, the clear solution was evaporated and compound **9** (200 mg, 0.73 mmol) and TMSOTf (0.23 mL, 1.27 mmol) were successively added to the residue in dry toluene (5 mL). The reaction mixture was stirred at reflux for 2 h and then was allowed to reach room temperature. Ethyl acetate (20 mL) was added and the reaction mixture was quenched with saturated $NaHCO_3$ solution, washed with water, dried (Na_2SO_4), and concentrated to dryness. The crude product was directly treated with methanolic ammonia (15 mL) for 48 h at room temperature. After evaporation to dryness under reduced pressure, the residue was subjected to reverse phase purification (C18) using a stepwise gradient of acetonitrile (0−10%) in water. Appropriate fractions were combined, evaporated, and lyophylizated from water to give the compound **18** (40 mg, 20%) as a white powder: UV (EtOH 95%) λ_{max} = 255 nm (ϵ = 11700); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.67 (br s, 1H), 7.91 (s, 1H), 6.49 (br s, 2H), 5.53 (d, 1H, J = 5.1 Hz), 5.37 (d, 1H, J = 4.9 Hz), 4.90−4.80 (m, 2H), 3.70 (dd, 1H, J = 5.1, 12.3 Hz), 3.56 (dd, 1H, J = 5.5, 12.3 Hz), 1.82 (m, 1H), 1.20 (t, 1H, J = 5.3 Hz), 0.77 (dd, 1H, J = 6.4, 9.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.9, 153.9, 151.2, 135.7, 116.4, 89.0, 76.0, 71.4, 62.3, 23.1, 12.2; FAB-MS (>0) m/z 280 $(M + H)^+$; FAB-MS (<0) m/z 278 $(M - H)^-$; HRMS (FAB >0, m/z) calcd for 280.1046, found 280.1045.

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Supporting Information Available: Experimental details and ^{13}C NMR spectra for compounds **4**, **5a**, **5b**, **6**−**9**, **13**−**15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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