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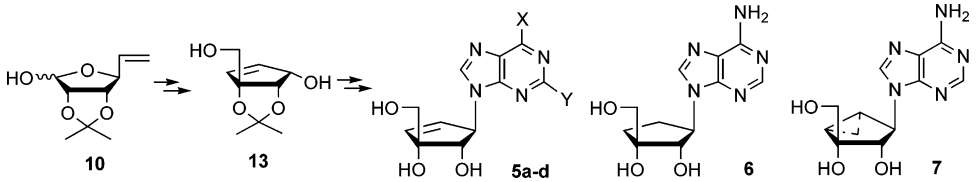
Synthesis of Novel Apio Carbocyclic Nucleoside Analogues as Selective A_3 Adenosine Receptor Agonists

Jeong A Lee,[†] Hyung Ryong Moon,*[,‡] Hea Ok Kim,[†] Kyung Ran Kim,[‡] Kang Man Lee,[†] Bum Tae Kim,[§] Ki Jun Hwang,[§] Moon Woo Chun,[∥] Kenneth A. Jacobson,[⊥] and Lak Shin Jeong*[,†]

Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea, College of Pharmacy, Pusan National University, Pusan 609-735, Korea, Department of Chemistry, Chonbuk National University, Chonju 561-756, Korea, College of Pharmacy, Seoul National University, Seoul 151-742, Korea, and Laboratory of Bioorganic Chemistry, Molecular Recognition Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

lakjeong@ewha.ac.kr

Received February 21, 2005



On the basis of the biological activity of neplanocin A and apio-dideoxyadenosine (apio-ddA), novel apio-neplanocin A analogues **5a**−**d**, combining the properties of two nucleosides, were stereoselectively synthesized. The apio moiety of the target nucleosides **5a**−**d** was stereoselectively introduced by treating lactol **10** with 37% formaldehyde in the presence of potassium carbonate. The carbasugar moiety of neplanocin A was successively built by exposing diene **12** on a Grubbs catalyst in methylene chloride. The final nucleosides **5a**−**d** were synthesized from the condensation of the glycosyl donor **14** with nucleic bases under the standard Mitsunobu conditions. Similarly, apio-aristeromycin **6** and (*N*)-apio-methanocarbaadenosine **7** were derived from the common intermediate **13** using catalytic hydrogenation and Simmons−Smith cyclopropanation as key steps. All of the final nucleosides **5a**−**d**, **6**, and **7** did not show significant inhibitory activity against *S*-adenosylhomocysteine hydrolase (SAH) up to 100 μM, maybe due to the absence of the secondary hydroxyl group at the C3′-position, which should be oxidized by cofactor-bound NAD^+. However, apio-neplanocin A (**5a**) showed potent and highly selective binding affinity ($K_i = 628 \pm 69$ nM) at the A_3 adenosine receptor without any binding affinity at the A_1 and A_{2A} adenosine receptors. In conclusion, we have first developed novel carbocyclic nucleosides with unnatural apio-carbasugars using stereoselective hydroxymethylation and RCM reaction and also discovered a new template of human A_3 adenosine receptor agonist, which play a great role in developing new A_3 adenosine receptor agonist as well as in identifying the binding site of the receptor.

Introduction

Neplanocin A (**1a**)[1] is representative of the carbocyclic nucleosides, which possess inherent stability of the glycosidic bond and exhibit potent biological activity[2] such as antiviral and antitumor activities (Figure 1). Biological activity of neplanocin A is derived from the inhibition of *S*-adenosylhomocysteine hydrolase (SAH), which is essential for viral mRNA capping of most animal-infecting DNA and RNA viruses.[3] However, despite its potent inhibitory activity against SAH, neplanocin A was not

* To whom correspondence should be addressed. Tel: +82 2 3277 3466. Fax: +82 2 3277 2851.
[†] Ewha Womans University.
[‡] Pusan National University.
[§] Chonbuk National University.
[∥] Seoul National University.
[⊥] National Institutes of Health.

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10.1021/jo0503207 CCC: $30.25
Published on Web 05/17/2005

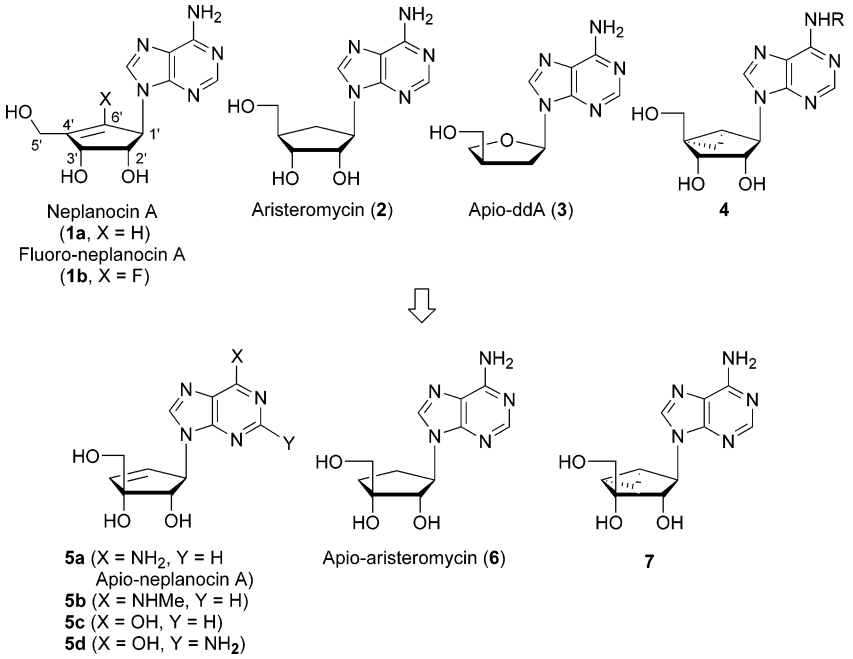

FIGURE 1. Rationale for the design of the target nucleosides.

developed as an antiviral agent because of its high cytotoxicity to the host cells.[4] On the basis of the structure of neplanocin A, many modifications have been made on the carbasugar as well as on the base. As a result, the carbasugar-modified analogue fluoro-neplanocin A (**1b**)[5] was found to be two times more potent than the parent neplnocin A (**1a**) against SAH and to exhibit potent antiviral activity against vesicular stomatitis virus (VSV). The base-modified analogue of neplanocin A, 5-fluorocytosine derivative,[6] exhibited potent anti-West Nile virus activity. A natural product, aristeromycin (**2**),[7] is another representative of carbocyclic nucleosides and also shows potent inhibitory activity against SAH.[8] However, this compound was also cytotoxic and could not be developed as antiviral agent.

Apio nucleosides belong to a unique class of nucleosides in that the 4′-hydroxymethyl group of normal sugar is moved to the C3′ position.[9] Among these, apio-ddA (**3**) has been reported to show potent anti-HIV activity comparable to that of parent 2′,3′-dideoxyadenosine (ddA) and better stability against glycosidic bond hydrolysis than that of ddA.[10]

On the other hand, Jacobson et al.[11] have reported the *N*-methanocarba-*N*^{6}-susbstituted adenosines **4** as potent and selective A_3 adenosine receptor agonists, among which 3-iodobenzyl derivative showed the best binding affinity to the A_3 adenosine receptor, indicating that carbocyclic nucleosides might be also served as a good template for the development of the A_3 adenosine receptor agonists.

Therefore, on the basis of these findings, it is interesting to design and synthesize apio-neplanocin A (**5a**), apio-aristeromycin (**6**), and apio-*N*-methanocarbaadenosine (**7**), combining the properties of **1a**, **2**, and **4** and apio-ddA (**3**), respectively, and evaluate their inhibitory activity against SAH (Figure 1). It is also of great interest to synthesize other purine analogues **5b**−**d** and to measure binding affinity to the A_3 adenosine receptor. All synthesized final nucleosides **5a**−**d**, **6**, and **7** are the first example of the carbocyclic nucleosides with unnatural five-membered apio-carbasugars. During this work, we have discovered novel apio-carbocyclic nucleoside with highly selective binding affinity at the A_3 adenosine receptor, which can be regarded as a novel template in searching of novel A_3 adenosine receptor ligands. In this article, we wish to report the full accounts of apio-carbocyclic nucleosides **5a**−**d**, **6**, and **7** which were synthesized using ring-closing metathesis (RCM), stereoselective hydroxymethylation, and modified Simmons−Smith cyclopropanation as key reactions and their selective A_3 adenosine receptor agonistic activity, since we have previously reported the preliminary accounts[12,13] of apio-neplanocin A (**5a**) and its inhibitory activity against SAH.

Results and Discussion

Chemistry. First, the hydroxymethyl substituent was stereoselectively introduced at the C2-position, as shown in Scheme 1. 2,3-Isopropylidene-D-ribose (**8**),[14] easily

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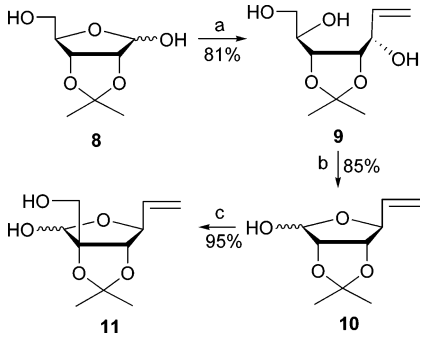
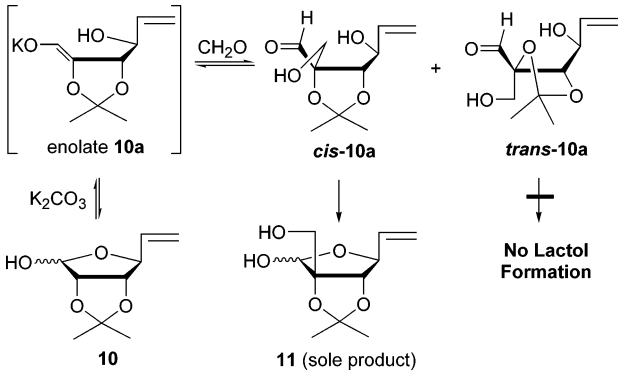
SCHEME 1[a]



[a] Reagents and conditions: (a) CH_2=$CHMgBr$, THF, −78 to 0 °C, 3 h; (b) $NaIO_4$, H_2O, CH_2Cl_2, rt, 0.5 h; (c) 37% CH_2O, K_2CO_3, MeOH, 80 °C, 36 h.

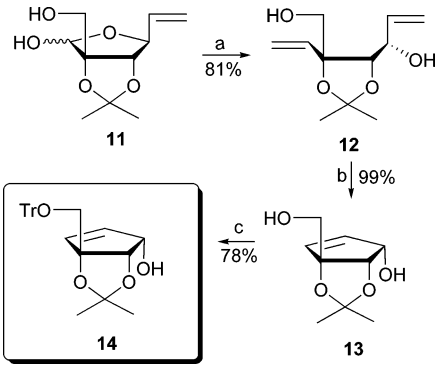
SCHEME 2



prepared from D-ribose, was subjected to a Grignard reaction using vinylmagnesium bromide in THF to give diol **9** as a single product.[15] Oxidative cleavage of diol **9** with sodium metaperiodate afforded vinyl lactol **10**.[15] Treatment of **10** with 37% formaldehyde solution in MeOH in the presence of potassium carbonate gave C2-hydroxymethyl lactol **11** in a purely stereoselective manner.[16]

The sole formation of **11** in the mixed aldol condensation might be mechanistically explained as illustrated in Scheme 2. Treatment of **10** with K_2CO_3 in MeOH followed by the addition of 37% formaldehyde to the resultant enolate **10a** might produce two possible adducts, *trans*-**10a** and *cis*-**10a**. However, under the equilibrium conditions, *trans*-**10a** could not be converted to a lactol due to high ring strain, but underwent the reverse aldol reaction, going back to the enolate **10a**, while *cis*-**10a** was smoothly converted to the thermodynamically stable lactol **11**.

SCHEME 3[a]



[a] Reagents and conditions: (a) CH_3PPh_3Br, KO-*t*-Bu, THF, rt, 15 h; (b) second generation Grubbs catalyst, CH_2Cl_2, rt, 2 h; (c) TrCl, DMAP, pyridine, rt, 20 h.

Second, the key intermediate, glycosyl donor **14**, was synthesized from C2-hydroxylmethyl lactol **11**, using ring-closing metathesis (RCM)[17,18] as a key reaction (Scheme 3). Compound **11** was subjected to a Wittig reaction with the use of methyltriphenylphosphonium bromide and potassium *tert*-butoxide to afford diene **12**. Exposure of **12** to a Grubbs catalyst in CH_2Cl_2 produced the apiocyclopentenol **13** in almost quantitative yield. The primary hydroxyl group of **13** was selectively protected with a trityl group to give the key intermediate **14**.

Synthesis of apio-neplanocin A analogues **5a**−**d** from the key intermediate **14** was achieved using a Mitsunobu reaction as the key step, as illustrated in Scheme 4. Condensation of **14** with 6-chloropurine and 2-acetamido-6-chloropurine under the standard Mitsunobu conditions gave the protected N^9-isomers 6-chloropurine derivative **15** [UV (CH_2Cl_2) λ_{max} 264 nm] and 2-acetamido-6-chloropurine derivative **16** [UV (CH_2Cl_2) λ_{max} 292 nm], respectively. In both cases, no N^7-isomers were detected on Mitsunobu condensation, and the N^9-regioisomers were easily confirmed on the basis of the UV literature data.[19] Treatment of **15** with methanolic ammonia and 40% methylamine in MeOH at 80 °C yielded adenosine and N^6-methyladenosine derivatives, whose protecting groups were removed on stirring with 3 N HCl in THF to give apio-neplanocin A (**5a**) and its N^6-methyl derivative **5b**, respectively. The inosine derivative **5c** was synthesized by heating **15** with 3 N HCl in THF. The guanosine derivative **5d** was also prepared from 2-acetamido-6-chloropurine derivative **16**, using the same conditions.

Synthesis of apio-aristeromycin (**6**) was accomplished starting from the common intermediate **13** (Scheme 5). The cyclopentenol **13** was reduced with palladium on

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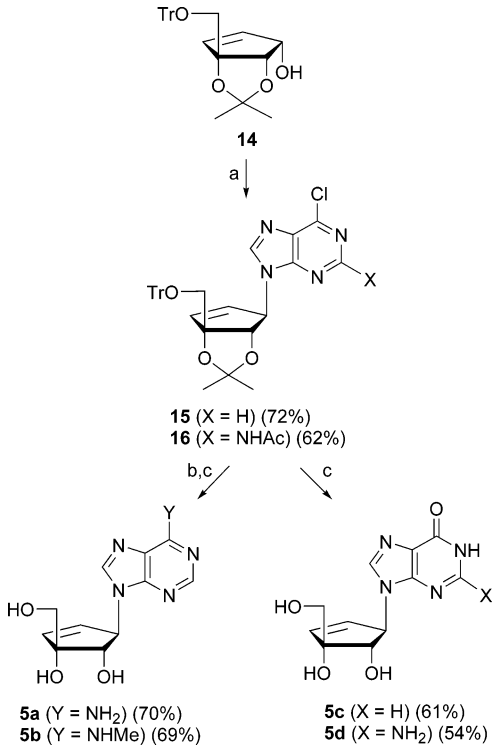
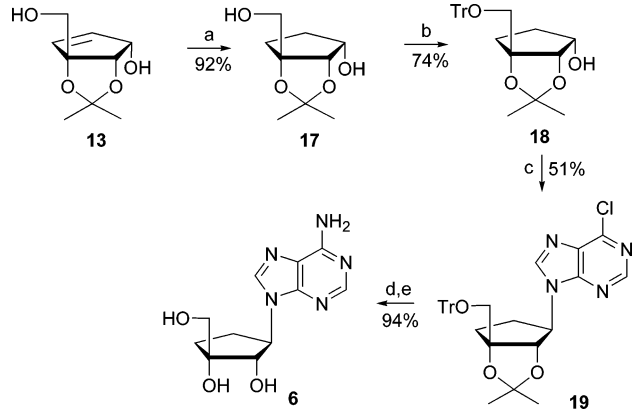
SCHEME 4[a]



[a] Reagents and conditions: (a) 6-chloropurines, Ph_3P, DEAD, THF, rt; (b) NH_3 or 40% $MeNH_2$, MeOH, 80 °C; (c) 3 N HCl, THF.

SCHEME 5[a]

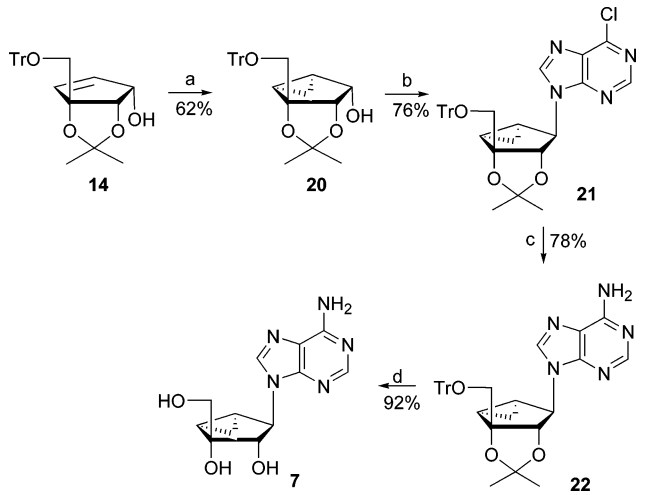


[a] Reagents and conditions: (a) 10% Pd/C, H_2, MeOH, rt, 4 h; (b) TrCl, pyridine, DMAP, rt, 5 d; (c) 6-chloropurine, Ph_3P, DEAD, THF, 48 °C, 10 d; (d) NH_3, MeOH, 80 °C, 30 h; (e) 30% aq CF_3CO_2H, THF, rt, 3 d.

carbon to give cyclopentanol **17** in good yield. The primary hydroxyl group of **17** was selectively protected as trityl ether **18**, which was condensed with 6-chloropurine under the Mitsunobu conditions to give the protected N^9-isomer **19**[19] without the formation of N^7-isomer, but the reaction was sluggish unlike in the case of apio-neplanocin A, giving only 51% yield with recovered starting material (26%). Conversion of 6-chloro group of **19** into 6-amino group followed by the removal of the protecting group with 30% aqueous trifluoroacetic acid afforded the final nucleoside **6** in 94% yield.

Synthesis of apio-*N*-methanocarbaadenosine (**7**) was achieved using modified Simmons−Smith cyclopropanation as a key step, as shown in Scheme 6. Simmons−Smith cyclopropanation of the cyclopentenol **14** gave the cyclopropyl-fused cyclopentanol **20** in 62% yield. Condensation of **20** with 6-chloropurine under the standard Mitsunobu conditions afforded the N^9-isomer **21**[19] as a sole product, which was treated with methanolic ammonia to give **22**. Removal of the protecting groups in **22** using 50% aqueous trifluoroacetic acid gave the final nucleoside **7**.

SCHEME 6[a]



[a] Reagents and conditions: (a) CH_2I_2, Et_2Zn, CH_2Cl_2, rt, overnight; (b) 6-chloropurine, PPh_3, DEAD, THF, rt, 4 h; (c) NH_3, MeOH, 80 °C, 6 h (d) 50% aq CF_3CO_2H, THF, rt, 6 d.

Enzyme Inhibition Assay. Inhibition of SAH by the synthesized compounds **5a**−**d**, **6**, and **7** was measured using pure recombinant enzyme from human placenta.[5] The residual activity of the enzyme was determined in the synthetic direction toward *S*-adenosylhomocysteine using adenosine and L-homocysteine. Unfortunately, none of compounds showed the inhibitory activity against SAH up to 100 μM. Lack of enzyme inhibitory activity might be due to the presence of the tertiary hydroxyl group at the C3′-position, which could not be oxidized by cofactor-bound NAD^+.

Binding Affinity at the Adenosine Receptors. The final nucleosides **5a**−**d**, **6**, and **7** were subjected to competitive radioligand binding assays.[20] Binding at the human A_3 adenosine receptor was performed using [^{125}I]I-AB-MECA (1.0 nM) as radioligand, and bindings at human A_1 and A_{2A} adenosine receptors were carried out using [^{3}H]CPX (0.5 nM, recombinant human A_1 AR) and [^{3}H]ZM241385 CPX (2 nM, recombinant human A_{2A} AR) as radioligands, respectively.[20] Among the compounds tested, apio-neplanocin A (**5a**) was found to be a potent and highly selective A_3 adenosine receptor agonist (K_i = 628 ± 69 nM), while compound **5a** did not show any binding affinity at human A_1 and A_{2A} receptors (percentage inhibitions at 10 μM: 8% and 0%, respectively). The efficacy of compound **5a** at the human A_3 adenosine receptor was also examined by measuring its effect on the inhibition of forskolin-stimulated cyclic AMP ac-

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cumulation at 10 μM in CHO cells stably expressing the human A_3 adenosine receptor. Compound **5a** maximally inhibited the forskolin-stimulated cyclic AMP production, like the known potent and selective A_3 adenosine receptor agonists, N^6-(3-iodobenzyl)-5′-*N*-methylcarbamoyladenosine (IB-MECA)[21] and 2-chloro-N^6-(3-iodobenzyl)-5′-*N*-methylcarbamoyladenosine (Cl-IB-MECA),[21] indicating it is a full agonist. Although compound **5a** did not show excellent binding affinity at the human A_3 adenosine receptor like IB-MECA and Cl-IB-MECA, no binding affinity at the human A_1 and A_{2A} receptors guarantees that apio-carbocyclic nucleosides can be regarded as a new and novel template for the development of A_3 adenosine receptor agonists.

Conclusions

Synthesis of novel apio-carbocyclic nucleoside analogues of neplanocin A, aristeromycin, and *N*-methanocarbaadenosine was accomplished, starting from D-ribose. To the best of our knowledge, apio-carbocyclic nucleosides developed here are the first example of the carbocyclic nucleosides with unnatural apio-carbasugars. In addition to the synthetic procedure highlighted by stereoselective hydroxymethylation and RCM reaction, we have also discovered a new template, which shows potent and selective binding affinity at the human A_3 adenosine receptor. This template will play a great role in developing new A_3 adenosine receptor agonist as well as in identifying the binding site of the receptor.

Experimental Section

General Methods. Melting points are uncorrected. NMR data were recorded on 200, 400, and 500 MHz NMR spectrometers using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are reported in ppm (δ). Coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), dd (doublet of doublet), br s (broad singlet). All the reactions described below were performed under argon or nitrogen atmosphere and monitored by thin-layer chromatography (TLC). All anhydrous solvents were distilled over CaH_2 or Na/benzophenone prior to use.

(−)-(1*R*)-1-[(4*R*,5*S*)-5-((1*S*)-1-Hydroxyallyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]ethane-1,2-diol (9). To a stirred solution of acetonide **8** (1.018 g, 5.35 mmol) in THF (40 mL) was added dropwise vinylmagnesium bromide (24 mL, 24 mmol, 1.0 M solution in THF) at −78 °C, and the reaction mixture was stirred at 0 °C for 3 h. After water (8 mL) was added to the mixture at 0 °C, the resulting precipitate was removed through a pad of Celite. The filtrate was extracted by ethyl acetate (80 mL × 2), dried, filtered, and evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography using hexane and ethyl acetate (1:2.5) as the eluent to afford triol **9** (949 mg, 81%) as a white solid: mp 73−74 °C; $[\alpha]^{25}_D$ −29.8 (*c* 1.23, $CHCl_3$); ^{1}H NMR (MeOH-d_4) δ 5.97 (m, 1 H), 5.31 (td, 1 H, J = 1.6, 17.2 Hz), 5.17 (td, 1 H, J = 1.6, 10.8 Hz), 4.24 (m, 1 H), 4.11 (dd, 1 H, J = 5.6, 9.6 Hz), 3.96 (dd. 1 H, J = 5.2, 9.6 Hz), 3.84 (m, 1 H), 3.77 (dd, 1 H, J = 2.4, 11.2 Hz), 3.59 (dd, 1 H, J = 6.0, 11.2 Hz), 1.35 (s, 3 H), 1.28 (s, 3 H). Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.97; H, 8.44.

(3a*S*,4*R*,6S,6a*S*)- and (3a*S*,4*S*,6*S*,6a*S*)-2,2-Dimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (10). To a stirred solution of triol **9** (2.75 g, 12.6 mmol) in methylene chloride (47 mL) was added dropwise an aqueous solution of $NaIO_4$ (29.1 mL, 18.92 mmol, 0.65 M solution) at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. After the addition of water (30 mL), the mixture was extracted with methylene chloride (100 mL × 2), dried, filtered, and evaporated under reduced pressure to give an oil, which was purified by silica gel column chromatography using hexane and ethyl acetate (2:1) as the eluent to give vinyl lactol **10** (2.00 g, 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddd, 1 H, J = 7.6, 10.4, 17.2 Hz), 5.77 (ddd, 1 H, J = 4.8, 10.8, 17.2 Hz), 5.47 (s, 1 H), 5.37 (td, 1 H, J = 1.6, 17.6 Hz), 5.30−5.25 (m, 2 H), 5.20 (td, 1 H, J = 1.6, 10.8 Hz), 5.15 (td, 1 H, J = 1.6, 10.0 Hz), 4.67−4.53 (m, 6 H), 3.85 (br s, 2 H), 1.56 (s, 3 H), 1.48 (s, 3 H), 1.37 (s, 3 H), 1.31 (s, 3 H); LRMS (FAB+) *m/z* 187 (M^+ + 1). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.47; H, 7.89.

(3a*S*,4*R*,6*S*,6a*S*)- and (3a*S*,4*S*,6*S*,6a*S*)-3a-Hydroxymethyl-2,2-dimethyl-6-vinyl-tetrahydrofuro[3,4-*d*][1,3]-dioxol-4-ol (11). To a stirred suspension of K_2CO_3 (0.7 g) in MeOH (17 mL) was added 37% aqueous formaldehyde (7 mL), and the solution was stirred until the pH became 10. The clear solution (10 mL) was added to vinyl lactol **10** (1.901 g, 10.21 mmol), and the reaction mixture was refluxed for 36 h. The mixture was partitioned between water (5 mL) and ethyl acetate (80 mL × 2), and the organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (1:1.5) as the eluent to give diol **11** (2.096 g, 95%) as a colorless oil: ^{1}H NMR (400 MHz, MeOH-d_4) δ 6.05 (ddd, 1 H, J = 7.2, 10.8, 17.6 Hz), 5.89 (ddd, 1 H, J = 5.2, 10.4, 16.4 Hz), 5.37−5.28 (m, 3 H), 5.20 (td, 1 H, J = 1.6, 10.4 Hz), 5.14 (td, 1 H, J = 1.6, 10.8 Hz), 5.10 (s, 1 H), 4.56−4.51 (m, 2 H), 4.44 (d, 1 H, J = 1.2 Hz), 4.41 (d, 1 H, J = 2.0 Hz), 3.80 (d, 1 H, J = 12.4 Hz), 3.72 (d, 1 H, J = 12.4 Hz), 3.66 (d, 1 H, J = 12.0 Hz), 3.58 (d, 1 H, J = 12.0 Hz), 1.56 (s, 3 H), 1,48 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (100 MHz MeOH-d_4) δ 139.6, 136.9, 117.1, 117.0, 115.9, 114.6, 105.9, 98.8, 92.6, 91.2, 88.4, 88.3, 86.9, 83.1, 64.0, 62.8, 28.5, 28.2, 27.8, 27.6; LRMS (FAB+) *m/z* 199 ($M^+ + 1 - H_2O$). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.26; H, 7.39.

(−)-(1*S*)-1-[(4*S*,5*S*)-5-Hydroxymethyl-2,2-dimethyl-5-vinyl[1,3]dioxolan-4-yl]prop-2-en-1-ol (12). To a stirred suspension of methyltriphenylphosphonium bromide (11.631 g, 32.56 mmol) in THF (90 mL) was added potassium *tert*-butoxide (4.189 g, 32.56 mmol, 95%) at 0 °C, and the mixture was stirred at room temperature for 1 h to give a yellow suspension. To this stirred solution was added a solution of diol **11** (2.346 g, 10.85 mmol) in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was partitioned between water (20 mL) and ethyl acetate (100 mL × 2), and the organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (1.5:1) as the eluent to give diene **12** (1.889 g, 81%) as a colorless oil: $[\alpha]^{25}_D$ −14.0 (*c* 1.57, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, 1 H, J = 10.8, 16.8 Hz), 6.04 (ddd, 1 H, J = 5.6, 10.4, 17.6 Hz), 5.55 (dd, 1 H, J = 1.6, 17.2 Hz), 5.39 (td, 1 H, J = 1.2, 17.6 Hz), 5.34 (dd, 1 H, J = 2.0, 11.2 Hz). 5.27 (td, 1 H, J = 1.2, 10.4 Hz), 4.20−4.16 (m, 1 H), 3.94 (d, 1 H, J = 8.8 Hz), 3.71 (d, 1 H, J = 11.6 Hz), 3.65 (d, 1 H, J = 11.6 Hz), 1.98 (br s, 2 H), 1.52 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 140.7, 137.9, 117.3, 115.6, 109.8, 87.8, 82.6, 72.3, 67.6, 28.3, 27.0; LRMS (FAB+) *m/z* 215 (M^+ + 1). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.71; H, 8.55.

(+)-(3a*S*,4*S*,6a*S*)-6a-Hydroxymethyl-2,2-dimethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (13). To a stirred solution of diene **12** (1.766 g, 8.24 mmol) in CH_2Cl_2 (30 mL) was added second-generation Grubbs catalyst (10 mg, 0.01 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h and evaporated in vacuo to give

(21) Kim, H. O.; Ji, X.-d.; Siddiqi, S. M.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. *J. Med. Chem.* **1994**, *37*, 3614.

brown residue. The residue was applied on silica gel column chromatography using hexane and ethyl acetate (1:1.5) as the eluent to give cyclopentenol **13** (1.524 g, 99%) as a white solid: mp 29.2−29.4 °C; $[\alpha]^{25}_D$ +46.7 (*c* 0.45, MeOH); ^{1}H NMR (400 MHz, MeOH-d_4) δ 5.83 (d, 1 H, J = 6.0 Hz), 5.73 (dd, 1 H, J = 1.2, 6.0 Hz), 4.57 (dd, 1 H, J = 1.6, 4.8 Hz), 4.48 (d, 1 H, J = 5.2 Hz), 3.65 (d, 1 H, J = 11.6 Hz). 3.53 (d, 1 H, J = 11.6 Hz), 1.39 (s, 6 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 137.4, 134.3, 113.3, 96.3, 82.1, 76.0, 65.1, 28.5, 28.0; LRMS (FAB+) *m/z* 187 (M^+ + 1). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.98; H, 7.72.

(+)-(3a*S*,4*S*,6a*S*)-2,2-Dimethyl-6a-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-ol (14). A solution of cyclopentenol **13** (1.469 g, 7.89 mmol), trityl chloride (4.39 g, 15.78 mmol), and 4-(dimethylamino)pyridine (193 mg, 1.58 mmol) in pyridine (10 mL) was stirred at room temperature for 20 h. The reaction mixture was partitioned between water (30 mL) and ethyl acetate (150 mL), and the organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (5:1) as the eluent to give trityl ether **14** (2.622 g, 78%) as a white solid: mp 93.3−94.4 °C; $[\alpha]^{25}_D$ +39.4 (*c* 2.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 15 H), 5.88 (d, 1 H, J = 6.0 Hz), 5.77 (d, 1 H, J = 5.6 Hz). 4.63−5.59 (m, 1 H), 4.47 (d, 1 H, J = 5.6 Hz), 3.28 (d, 1 H, J = 9.2 Hz), 3.24 (d, 1 H, J = 9.6 Hz), 2.66 (d, 1 H, J = 10.4 Hz), 1.40 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 136.4, 134.0, 128.9, 128.0, 127.3, 112.7, 93.9, 87.0, 80.9, 75.1, 65.9, 28.3, 27.9; LRMS (FAB+) *m/z* 429 (M^+ + 1). Anal. Calcd for $C_{28}H_{28}O_4$: C, 78.48; H, 6.59. Found: C, 78.64; H, 6.78.

6-Chloro-9-[(3a*S*,4*R*,6a*S*)-2,2-dimethyl-6a-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-yl]-9*H*-purine (15). To a stirred solution of cyclopentenol **14** (688 mg, 1.61 mmol), triphenylphosphine (1.278 g, 4.87 mmol), and 6-chloropurine (745 mg, 4.82 mmol) in tetrahydrofuran (20 mL) was added dropwise diethyl azodicarboxylate (0.80 mL, 5.08 mmol) at 0 °C, and the reaction mixture was stirred at room-temperature overnight. The volatiles were evaporated in vacuo and the resulting residue was purified by silica gel column chromatography using hexane and ethyl acetate (2.5:1) as the eluent to give the protected 6-chloropurine nucleoside **15** (655 mg, 72%) as a colorless oil: UV (CH_2Cl_2) λ_{max} 264.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 7.75 (s, 1 H), 7.37−7.20 (m, 15 H), 6.33 (dd, 1 H, J = 1.2, 5.6 Hz), 5.94 (dd, 1 H, J = 2.0, 5.6 Hz), 5.64 (br s, 1 H), 4.39 (s, 1 H), 3.45 (d, 1 H, J = 10.0 Hz), 3.35 (d, 1 H, J = 10.0 Hz), 1.49 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 151.7, 151.3, 143.5, 143.3, 141.5, 132.2, 128.8, 128.2, 128.1, 127.5, 113.5, 95.4, 87.3, 86.3, 66.8, 66.2, 28.4, 28.1. Anal. Calcd for $C_{33}H_{29}ClN_4O_3$: C, 70.14; H, 5.17; N, 9.92. Found: C, 69.85; H, 5.20; N, 10.06.

***N*-[6-Chloro-9-[(3a*S*,4*R*,6a*S*)-2,2-dimethyl-6a-trityloxymethyl-4,6a-dihydro-3a*H*-cyclopenta[1,3]dioxol-4-yl]-9*H*-purin-2-yl]acetamide (16).** Cyclopentenol **14** (203 mg, 0.47 mmol) was converted to the protected 2-acetamido-6-chloropurine nucleoside **16** (183 mg, 62%) as a colorless oil, according to the same procedure used in the preparation of **15**: UV (CH_2Cl_2) λ_{max} 292.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1 H), 7.59 (s, 1 H), 7.40−7.20 (m, 15 H), 6.30 (dd, 1 H, J = 2.0, 6.0 Hz), 5.96 (dd, 1 H, J = 2.8, 6.0 Hz), 5.53 (br s, 1 H), 4.37 (s, 1 H), 3.37 (d, 1 H, J = 10.0 Hz), 3.29 (d, 1 H, J = 10.0 Hz), 2.53 (s, 3 H), 1.46 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 152.5, 152.3, 151.5, 143.4, 142.3, 141.4, 129.8, 128.7, 128.3, 128.1, 127.5, 113.3, 95.1, 87.3, 86.4, 66.2, 66.2, 28.3, 28.0, 25.4. Anal. Calcd for $C_{35}H_{32}ClN_5O_4$: C, 67.57; H, 5.18; N, 11.26. Found: C, 67.61; H, 5.12; N, 11.43.

(−)-(1*S*,2*S*,5*R*)-5-(6-Aminopurin-9-yl)-2-hydroxymethylcyclopent-3-ene-1,2-diol (5a). A solution of **15** (150 mg, 0.27 mmol) and saturated methanolic ammonia (7 mL) was heated in a glass bomb at 80 °C overnight, and the volatiles were evaporated in vacuo. To a stirred solution of the resulting residue in tetrahydrofuran (3.0 mL) was added 3 M aqueous HCl solution (3.0 mL), and the reaction mixture was stirred at room temperature 2 d. The reaction mixture was evaporated in vacuo and purified by reversed-phase silica gel column chromatography using 0% → 10% aqueous methanol as the eluent to give the adenine nucleoside **5a** (49 mg, 70%) as a white solid: mp 125.8−127.3 °C; $[\alpha]^{25}_D$ −77.3 (*c* 0.66, MeOH); UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.20 (s, 1 H), 8.14 (s, 1 H), 6.18 (dd, 1 H, J = 2.4, 6.0 Hz), 6.12 (dd, 1 H, J = 1.6, 6.0 Hz), 5.57 (td, 1 H, J = 2.0, 5.6 Hz), 4.31 (d, 1 H, J = 6.0 Hz), 3.65 (d, 1 H, J = 11.2 Hz), 3.59 (d, 1 H, J = 10.8 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) δ 157.5, 153.8, 151.1, 141.1, 138.6, 133.5, 120.4, 82.4, 79.6, 67.2, 66.3; LRMS (FAB+) *m/z* 264 (M^++1).; Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.19; H, 4.98; N, 26.60. Found: C, 50.03; H, 5.02; N, 26.54.

(−)-1*S*,2*S*,5*R*)-2-Hydroxymethyl-5-(6-methylaminopurin-9-yl)cyclopent-3-ene-1,2-diol (5b). A solution of **15** (41 mg, 0.07 mmol) and 40% methylamine (4.4 mL) in methanol (8 mL) was heated at 80 °C for 30 min, and the reaction mixture was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography using methylene chloride and methanol (25:1) as the eluent to give the corresponding 6-methylamino purine nucleoside (37 mg, 91%) as a colorless oil: UV (CH_2Cl_2) λ_{max} 263.5 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.63 (s, 1 H), 7.36−7.19 (m, 16 H), 6.31 (dd, 1 H, J = 0.8, 6.0 Hz), 6.07 (dd, 1 H, J = 2.8, 6.0 Hz), 5.52 (br s, 1 H), 4.38 (s, 1 H), 3.42 (d, 1 H, J = 10.0 Hz), 3.36 (d, 1 H, J = 10.0 Hz), 3.11 (s, 3 H), 1.45 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 153.7, 149.6, 143.6, 140.5, 137.6, 129.1, 128.9, 128.1, 127.4, 120.4, 113.2, 95.3, 87.2, 86.7, 66.6, 66.0, 29.9, 28.4, 28.1. Anal. Calcd for $C_{34}H_{33}N_5O_3$: C, 72.97; H, 5.94; N, 12.51. Found: C, 73.10; H, 5.68; N, 12.25.

To a stirred solution of the above 6-methylamino purine nucleoside (37 mg, 0.07 mmol) in tetrahydrofuran (1.5 mL) was added 3 M aqueous HCl solution (0.7 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated in vacuo, neutralized with K_2CO_3, and purified by reversed-phase silica gel column chromatography using 0% → 12% aqueous methanol as the eluent to give the 6-methylamino purine nucleoside **5b** (14 mg, 76%) as a white solid: mp 117.2−118.2 °C; $[\alpha]^{25}_D$ −10.6 (*c* 1.66, MeOH); UV (H_2O) λ_{max} 266.5 nm; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.24 (s, 1 H), 8.07 (s, 1 H), 6.18 (dd, 1 H, J = 2.0, 6.4 Hz), 6.11 (dd, 1 H, J = 2.0, 6.4 Hz), 5.56 (td, 1 H, J = 2.0, 6.0 Hz), 4.31 (d, 1 H, J = 6.0 Hz), 3.65 (d, 1 H, J = 10.8 Hz), 3.60 (d, 1 H, J = 11.2 Hz), 3.10 (s, 3 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ; 156.9, 153.9, 150.1, 140.5, 138.8, 133.5, 121.0, 82.3, 79.3, 67.2, 66.2, 27.9; LRMS (FAB+) *m/z* 278 (M^+ + 1). Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 52.24; H, 5.78; N, 25.55.

(−)-9-[(1*R*,4*S*,5*S*)-4,5-Dihydroxy-4-hydroxymethylcyclopent-2-enyl]-1,9-dihydropurin-6-one (5c). To a stirred solution of **15** (61 mg, 0.11 mmol) in tetrahydrofuran (1.5 mL) was added 3 M aqueous HCl solution (1.5 mL), and the mixture was stirred at 70 °C overnight. The reaction mixture was evaporated in vacuo, and the residue was purified by reversed phase silica gel column chromatography using 0% → 10% aqueous methanol as the eluent to give the hypoxanthine nucleoside **5c** (17 mg, 61%) as a white solid: mp 118.5−119.5 °C dec; $[\alpha]^{25}_D$ −17.0 (*c* 0.23, H_2O); UV (MeOH) λ_{max} 250.5 nm; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.10 (s, 1 H), 8.04 (s, 1 H), 6.17 (dd, 1 H, J = 2.4, 6.4 Hz), 6.10 (dd, 1 H, J = 1.6, 6.4 Hz), 5.60 (td, 1 H, J = 2.0, 6.0 Hz), 4.31 (d, 1 H, J = 6.0 Hz), 3.65 (d, 1 H, J = 10.8 Hz), 3.59 (d, 1 H, J = 10.8 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) δ 161.7, 153.3, 149.2, 143.1, 141.4, 136.0, 128.1, 84.8, 82.0, 70.0, 68.7; LRMS (FAB+) *m/z* 265 (M^+ + 1). Anal. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.72; H, 4.64; N, 21.08.

(−)-2-Amino-9-[(1*R*,4*S*,5*S*)-4,5-dihydroxy-4-hydroxymethylcyclopent-2-enyl]-1,9-dihydropurin-6-one (5d). To a stirred solution of **16** (82 mg, 0.13 mmol) in tetrahydrofuran (3.0 mL) was added 3 M aqueous HCl solution (3.0 mL), and the mixture was heated at 70 °C for 2 d. The reaction mixture

was evaporated in vacuo, neutralized with triethylamine, and purified by reversed-phase silica gel column chromatography using 0% → 10% aqueous methanol as the eluent to give the guanine nucleoside **5d** (20 mg, 54%) as a white solid: mp 191.5−192.5 °C dec; $[\alpha]^{25}_D$ −7.33 (*c* 0.30, H_2O); UV (H_2O) λ_{max} 254.0 nm; ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.73 (s, 1 H), 6.12 (dd, 1 H, J = 2.4, 6.4 Hz), 6.07 (dd, 1 H, J = 1.6, 6.4 Hz), 5.40 (td, 1 H, J = 2.0, 6.0 Hz), 4.28 (d, 1 H, J = 6.0 Hz), 3.63 (d, 1 H, J = 10.8 Hz), 3.58 (d, 1 H, J = 10.8 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) δ 159.6, 155.3, 153.6, 138.4, 137.9, 133.8, 117.9, 82.3, 79.0, 66.8, 66.1; LRMS (FAB+) *m/z* 280 (M^+ + 1). Anal. Calcd for $C_{11}H_{13}N_5O_4$: C, 47.31; H, 4.69; N, 25.08. Found: C, 47.66; H, 4.70; N, 25.19.

(−)-(3a*S*,4*S*,6a*S*)-6a-Hydroxymethyl-2,2-dimethyltetrahydrocyclopenta[1,3]dioxol-4-ol (17). A solution of cyclopentenol **13** (2.030 g, 10.90 mmol) in methanol (15 mL) was stirred under H_2 gas in the presence of 10% Pd/C (50 mg) at room temperature for 4 h. The reaction mixture was filtered through a pad of Celite, evaporated, and purified by silica gel column chromatography using hexane and ethyl acetate (1:3.5) to give cyclopentanol **17** (1.885 g, 92%) as a white solid: mp 59.6−60.2 °C; $[\alpha]^{25}_D$ −27.4 (*c* 1.9, MeOH); ^{1}H NMR (400 MHz, MeOH-d_4) δ 4.22 (d, 1 H, J = 4.0 Hz), 3.82 (m, 1 H), 3.58 (d, 1 H, J = 11.2 Hz), 3.51 (d, 1 H, J = 10.8 Hz), 1.90−1.54 (m, 4 H), 1.45 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 112.0, 92.0, 83.6, 74.9, 66.9, 31.9, 30.6, 27.8, 27.1; LRMS (FAB+) *m/z* 188 (M^+). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.51; H, 8.73.

(+)-(3a*S*,4*S*,6a*S*)-2,2-Dimethyl-6a-trityloxymethyltetrahydrocyclopenta[1,3]dioxol-4-ol (18). A solution of cyclopentanol **17** (1.885 g, 10.01 mmol) was converted to trityl ether **18** (3.196 g, 74%) as a white solid, according to the same procedure used in the preparation of **14**: mp 132.2−132.8 °C; $[\alpha]^{25}_D$ +3.87 (*c* 1.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.20 (m, 15 H), 4.20 (d, 1 H, J = 4.8 Hz), 3.97−3.89 (m, 1 H), 3.30 (d, 1 H, J = 9.2 Hz), 3.14 (d, 1 H, J = 9.6 Hz), 2.21 (d, 1 H, J = 10.4 Hz), 1.96−1.91 (m, 1 H), 1.77−1.69 (m, 3 H), 1,44 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 128.9, 128.1, 127.3, 111.2, 89.9, 86.9, 82.4, 74.3, 67.0, 31.6, 30.9, 27.4, 26.8; LRMS (FAB+) *m/z* 453 (M^+ + Na). Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 77.89; H, 7.37.

(−)-6-Chloro-9-[(3a*S*,4*R*,6a*S*)2,2-dimethyl-6a-trityloxymethyltetrahydrocyclopenta[1,3]dioxol-4-yl]-9*H*-purine (19). Trityl ether **18** (854 mg, 1.98 mmol) was converted to the protected 6-chloropurine nucleoside **19** (576 mg, 51%) as a colorless sticky oil with unreacted starting material (219 mg), according to the same procedure used in the preparation of **15**: $[\alpha]^{25}_D$ −17.5 (*c* 2.86, $CHCl_3$); UV ($CHCl_3$) λ_{max} 265.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1 H, H-8), 8.01 (s, 1 H), 7.34−7.20 (m, 15 H), 4.91−4.87 (m, 1 H), 4.77 (d, 1 H, J = 2.0 Hz), 3.38 (d, 1 H, J = 10.0 Hz), 3.34 (d, 1 H, J = 9.6 Hz), 2.55−2.47 (m, 1 H), 2.34−2.23 (m, 2 H), 2.07−2.05 (m, 1 H), 1.53 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 152.0, 151.4, 143.8, 143.6, 132.2, 128.8, 128.1, 127.4, 113.2, 91.6, 87.2, 87.1, 66.4, 63.3, 35.1, 29.4, 28.8, 27.8; LRMS (FAB+) *m/z* 567 (M^+ + 1). Anal. Calcd for $C_{33}H_{31}ClN_4O_3$: C, 69.89; H, 5.51; N, 9.88. Found: C, 69.72; H, 5.35; N, 9.90.

(−)-(1*S*,2*S*,3*R*)-3-(6-Aminopurin-9-yl)-1-hydroxymethylcyclopentane-1,2-diol (6). 6-Chloropurine derivative **19** (198 mg, 0.35 mmol) was converted to the corresponding adenine nucleoside (186 mg, 97%), according to the same procedure used in the preparation of **5a**: white solid; mp 180.1−181.4 °C; $[\alpha]^{25}_D$ +0.93 (*c* 1.08, $CHCl_3$); UV ($CHCl_3$) λ_{max} 262.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.71 (s, 1 H), 7.38−7.17 (m, 15 H), 6.39 (br s, 2 H), 4.86−4.83 (m, 1 H), 4.78 (d, 1 H, J = 2.0 Hz), 3.39 (d, 1 H, J = 9.6 Hz), 3.35 (d, 1 H, J = 9.6 Hz), 2.52−2.43 (m, 1 H), 2.34−2.17 (m, 2 H), 2.08−2.01 (m, 1 H), 1.53 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 152.6, 150.2, 143.7, 138.8, 128.8, 128.0, 127.3, 120.1, 112.9, 91.7, 87.3, 87.1, 66.4, 62.5, 35.1, 29.6, 28.7, 27.8. Anal. Calcd for $C_{33}H_{33}CN_5O_3$: C, 72.37; H, 6.07; N, 12.79. Found: C, 72.22; H, 5.84; N, 12.50.

To a stirred solution of the protected adenine nucleoside (158 mg, 0.29 mmol) in tetrahydrofuran (2.0 mL) was added 30% aqueous trifluoroacetic acid (4.0 mL), and the reaction mixture was stirred at room temperature for 3 d. The reaction mixture was evaporated in vacuo and purified by reversed-phase silica gel column chromatography using 0% → 10% aqueous methanol as the eluent to give the adenine nucleoside **6** (74 mg, 97%) as a white hygroscopic solid: $[\alpha]^{25}_D$ −24.2 (*c* 1.12, MeOH); UV (MeOH) λ_{max} 261.0 nm; ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.20 (s, 1 H), 8.16 (s, 1 H), 4.93−4.86 (m, 1 H), 4.51 (d, 1 H, J = 9.6 Hz), 3.60 (d, 1 H, J = 11.6 Hz), 3.55 (d, 1 H, J = 11.2 Hz), 2.40−2.24 (m, 2 H), 2.16−2.09 (m, 1 H), 1.84−1.77 (m, 1 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 157.4, 153.5, 151.2, 142.1, 120.7, 79.3, 77.4, 66.8, 62.6, 31.4, 26.0; LRMS (FAB+) *m/z* 266 (M^+ + 1). Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.65; H, 5.89; N, 26.64.

(+)-(1a*R*,1b*S*,4a*S*,5*S*,5a*S*)-3,3-Dimethyl-1b-trityloxymethylhexahydro-2,4-dioxacyclopropa[*a*]pentalen-5-ol (20). To a stirred solution of cyclopentenol **14** (2.14 g, 4.99 mmol) in CH_2Cl_2 (40 mL) was added diethylzinc (25 mL, 25.00 mmol, 1.0 M soution in hexane) at 0 °C, and the reaction mixture was stirred at the same temperature for 15 min. Diiodomethane (4.0 mL, 50.21 mmol) was added to the reaction mixture at 0 °C and the resulting mixture stirred at room temperature overnight. After aqueous ammonium chloride solution (10 mL) was added, the reaction mixture was partitioned between ethyl acetate and water and the organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (2.5:1) as the eluent to give the corresponding cyclopropane-fused compound **20** (1.38 g, 62%) as a white solid: mp 161.5−162.3 °C; $[\alpha]^{25}_D$ +40.4 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.20 (m, 15 H), 4.51 (br s, 1 H), 4.14 (d, 1 H, J = 6.4 Hz), 3.43 (d, 1 H, J = 9.2 Hz), 3.24 (d, 1 H, J = 9.2 Hz), 2.23 (br s, 1 H), 1.92 (m, 1 H), 1.55 (m, 1 H), 1.51 (s, 3 H), 1.15 (s, 3 H), 1.03 (td, 1 H, J = 4.0, 4.8 Hz), 0.61 (td, 1 H, J = 5.6, 8.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.6, 128.7, 127.8, 127.1, 112.6, 90.5, 86.9, 81.6, 71.5, 67.4, 27.6, 26.8, 25.5, 24.5, 6.7; LRMS (ESI) *m/z* 442 [M + Na]$^+$. Anal. Calcd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83. Found: C, 79.00; H, 6.92.

(+)-6-Chloro-9-((1a*R*,1b*S*,4a*S*,5*R*,5a*S*)-3,3-dimethyl-1b-trityloxymethylhexahydro-2,4-dioxacyclopropa[*a*]pentalen-5-yl)-9*H*-purine (21). To a stirred solution of bicyclo-[3.1.0]hexanol **20** (785 mg, 1.77 mmol), PPh_3 (1395 mg, 5.32 mmol), and 6-chloropurine (822 mg, 5.32 mmol) in anhydrous THF (30 mL) was dropwise added diethyl azodicarboxylate (0.84 mL, 5.32 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexane and ethyl acetate (3.5:1) as the eluent to give the protected 6-chloropurine nucleoside **21** (777 mg, 76%) as a colorless sticky oil: $[\alpha]^{25}_D$ +2.2 (*c* 0.99, $CHCl_3$); UV ($CHCl_3$) λ_{max} 264.0 nm; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.71 (s, 1 H), 7.90 (s, 1 H), 7.54−7.32 (m, 15 H), 5.36 (s, 1 H), 4.36 (s, 1 H), 3.52 (s, 2 H), 2.31−2.21 (m, 1 H), 1.89−1.80 (m, 1 H), 1.70 (s, 3 H), 1.41 (s, 3 H), 1.29−1.07 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.4, 151.6, 151.5, 143.7, 143.2, 132.1, 129.0, 128.3, 127.7, 113.0, 92.4, 90.3, 87.6, 67.7, 60.7, 27.9, 27.3, 26.4, 24.3, 10.2; LRMS (ESI) *m/z* 579 [M + H]$^+$. Anal. Calcd for $C_{34}H_{31}ClN_4O_3$: C, 70.52; H, 5.40; N, 9.68. Found: C, 70.26; H, 5.44; N, 9.82.

(+)-(1a*R*,1b*S*,4a*S*,5*R*,5a*S*)-9-(3,3-Dimethyl-1b-trityloxymethylhexahydro-2,4-dioxacyclopropa[*a*]pentalen-5-yl)-9*H*-purin-6-ylamine (22). The protected 6-chloropurine nucleoside **21** (317 mg, 0.55 mmol) was converted to the corresponding adenine nucleoside **22** (239 mg, 78%) according to the same procedure used in the preparation of **5a**: colorless sticky oil: $[\alpha]^{25}_D$ +3.4 (*c* 0.87, $CHCl_3$); UV (CH_2Cl_2) λ_{max} 259.0 nm; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.28 (s, 1 H), 7.56 (s, 1 H), 7.47−7.20 (m, 15 H), 6.45 (br s, 2 H), 5.09 (s, 1 H), 4.24 (s, 1 H), 3.50 (d, 1 H, J = 10.2 Hz), 3.40 (d, 1 H, J = 10.2 Hz), 2.22−2.12 (m, 1 H), 1.82−1.72 (m, 1 H), 1.61 (s, 3 H), 1.30 (s, 3 H),

1.17−0.98 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.9, 151.8, 149.6, 143.4, 138.6, 128.8, 128.0, 127.3, 119.6, 112.5, 92.0, 90.4, 87.3, 67.5, 59.7, 27.5, 27.0, 26.0, 24.2, 9.8; LRMS (ESI) *m/z* 560 $[M + H]^+$. Anal. Calcd for $C_{34}H_{33}N_5O_3$: C, 72.97; H, 5.94; N, 12.51. Found: C, 72.70; H, 5.71; N, 12.84.

(−)-(1*R*,2*S*,3*S*,4*R*,5*S*)-4-(6-Aminopurin-9-yl)-2-hydroxymethylbicyclo[3.1.0]hexane-2,3-diol (7). To a stirred solution of protected adenine nucleoside **22** (577 mg, 1.03 mmol) in THF (6 mL) was added 50% aqueous trifluoroacetic acid (6 mL), and the reaction mixture was stirred at room temperature for 6 d. After the reaction mixture was concentrated, the residue was purified by reversed phase silica gel column chromatography using 0% → 12% aqueous methanol as the eluent to give the adenine nucleoside **7** (263 mg, 92%) as a white solid: mp 194.5 °C dec; $[\alpha]^{25}_D$ −41.7 (*c* 0.57, DMF); UV (MeOH) λ_{max} 260.0 nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 (s, 1 H), 8.20 (s, 1 H), 7.49 (br s, 2 H), 5.18 (br s, 1 H), 4.81 (br s, 1 H), 4.45 (d, 1 H, J = 5.0 Hz), 4.22 (br s, 1 H), 4.08 (d, 1 H, J = 5.5 Hz), 3.43 (d, 1 H, J = 10.5 Hz), 3.36 (d, 1 H, J = 11.0 Hz), 1.75−1.71 (m, 1 H), 1.65−1.62 (m, 1 H), 0.95 (q, 1 H, J = 4.5 Hz), 0.78 (td, 1 H, J = 5.0, 8.5 Hz); ^{13}C NMR (50 MHz, DMSO-d_6) δ 155.2, 151.3, 149.5, 139.8, 119.2, 79.7, 77.6, 66.3, 63.2, 24.7, 17.9, 9.7; LRMS (EI) *m/z* 277 $(M)^+$. Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.73; H, 5.42; N, 25.46.

Acknowledgment. We thank Dr. Z.-G. Gao (NIDDK) for binding experiments of adenosine receptors. This research was supported by grants from the Korea Science and Engineering Research Foundation (KOSEF-R01-2002-000-00114-0) and the Korea Research Foundation (KRF-2003-042-E20111).

JO0503207