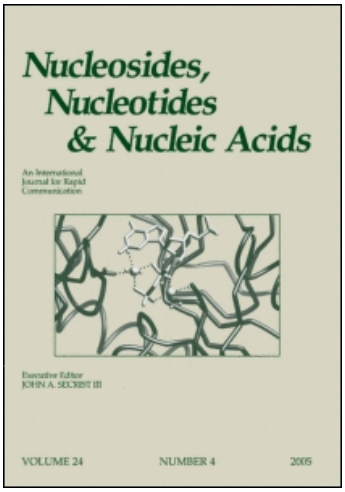

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Facile Synthesis of cis-9-[4-(1,2-Dihydroxyethyl)-cyclopent-2-enyl]guanine and Its Derivative

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Online publication date: 05 November 2010

To cite this Article An, Gwang-Il and Rhee, Hakjune(2000) 'A Facile Synthesis of cis-9-[4-(1,2-Dihydroxyethyl)-cyclopent-2-enyl]guanine and Its Derivative', Nucleosides, Nucleotides and Nucleic Acids, 19: 7, 1111 — 1122
To link to this Article: DOI: 10.1080/15257770008035034
URL: http://dx.doi.org/10.1080/15257770008035034

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(7), 1111–1122 (2000)

A FACILE SYNTHESIS OF *CIS*-9-[4-(1,2-DIHYDROXYETHYL)-CYCLOPENT-2-ENYL]GUANINE AND ITS DERIVATIVE

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ABSTRACT: The synthesis of carbocyclic nucleosides, *cis*-9-[4-(1,2-dihydroxyethyl)-cyclopent-2-enyl]guanine (**3**) and *cis*-2-amino-6-cyclopropylamino-9-[4-(1,2-dihydroxyethyl)-cyclopent-2-enyl]purine (**4**), was achieved from cyclopentadiene (**5**) in five and six steps, respectively. This route involves a hetero Diels-Alder reaction and a Pd(0)-catalyzed coupling reaction.

INTRODUCTION

Carbocyclic nucleosides, *i.e.*, carbocyclic analogues of normal purine or pyrimidine nucleosides, have been obtained much attention for the potential antiviral and antitumor therapeutic agents.[1] The replacement of the furanose oxygen by a carbon gives the nucleoside increased stability to the enzymes that cleave the nucleosidic bonds of the natural nucleosides in addition to modifying the biological activity.[2] Carbocyclic 2',3'-didehydro-2',3'-dideoxyguanosine (carbovir, **1a**)[3] was reported to be an *in vitro* selective inhibitor of HIV-1 and exhibited less toxicity than other agents. The analogue of (-)-carbovir, abacavir (**1b**), which has higher oral bioavailability than carbovir,[4] is currently commercialized for the treatment of HIV infection. Because of the important biological activity of these carbocyclic nucleosides, the synthesis of (-)-carbovir analogues has been focused and reported by several research groups.[5] Recently, we and other groups synthesized an analogue of carbovir, 5'-homocarbovir (**2**).[5a-5e] However, antiviral screening revealed that 5'-homocarbovir (**2**) did

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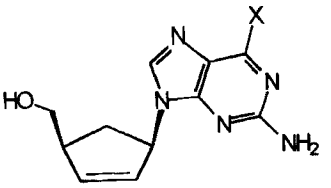
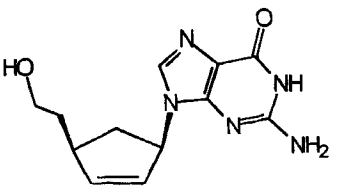
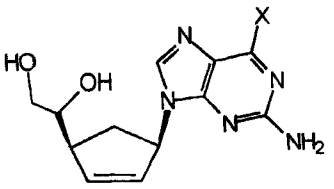
not exhibit any anti-HSV and anti-HIV activity In order to search for more potent anti-HIV agents we have chosen *cis*-9-[4-(1,2-dihydroxyethyl)-cyclopent-2-enyl]guanine (**3**) and *cis*-2-amino-6-cyclopropylamino-9-[4-(1,2-dihydroxyethyl)-cyclopent-2-enyl]purine (**4**) as target compounds. In this paper, we report a short synthetic route for the carbocyclic nucleosides **3** and **4** starting from cyclopentadiene (**5**).



X= OH (Carbovir, **1a**)
X= NH-cyclopropyl (Abacavir, **1b**)



5'-Homocarbovir, **2**

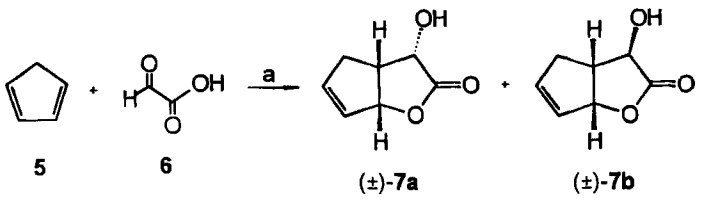


X= OH (**3**)
X= NH-cyclopropyl (**4**)

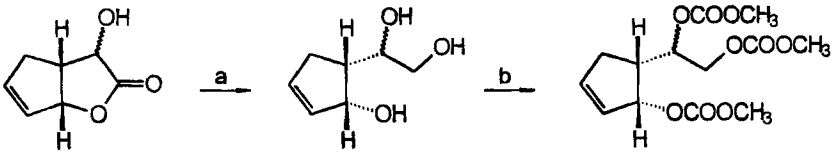
RESULTS AND DISCUSSION

Hetero Diels-Alder reaction of cyclopentadiene (**5**) and glyoxylic acid (**6**) in water was known as a facile method for the synthesis of bicyclic α–hydroxy-γ-lactone **7** (Scheme 1).[3,6] The products of this reaction could be separated by silica gel column chromatography (**7a**:**7b** = 1.72:1).

Endo-hydroxylactone (±)-**7a** and *exo*-hydroxylactone (±)-**7b** could be converted to the corresponding triols (±)-**8a** and (±)-**8b** by lithium aluminum hydride reduction[3,7] (Scheme 2). At this stage, the triols **8a** and **8b** should be carbonated for the Pd(0)-catalyzed coupling reaction with a nucleoside base. Treatment of the triols **8a** and **8b** with methyl chloroformate and 4-dimethylaminopyridine (DMAP) afforded tricarbonates **9a** and **9b**, respectively (Scheme 2).

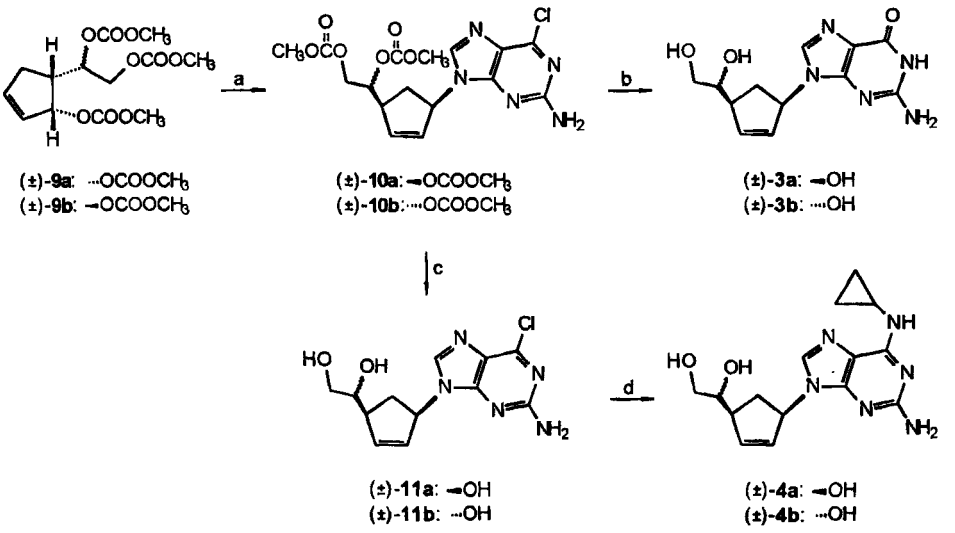


Scheme 1. a. Toluene, H_2O, 40 °C, 2 h, 79 % (**7a**:**7b** = 1.72:1).



Scheme 2. a. $LiAlH_4$, THF, reflux, 2 h (**8a**, 96 %; **8b**, 93 %). b. Methylchloroformate, DMAP, pyridine, $CHCl_3$, 0 °C, 2 h (**9a**, 93 %; **9b**, 97 %).

The key coupling was then effected by treatment of the tricarbonates **9a** and **9b** with 2-amino-6-chloropurine in THF:DMSO in the presence of 5 mol % $Pd[P(OPr^i)_3]_4$.[3] The coupling adducts **10a** and **10b** were separated in 68 and 67 % yields, respectively (Scheme 3). Hydrolysis of compounds **10a** and **10b** with aqueous sodium hydroxide gave a carbovir analogues, (±)-**3a** and (±)-**3b** in good yield. Meanwhile, hydrolysis of compounds **10a** and **10b** with potassium carbonate afforded the chloropurines **11a** and **11b** in 77 and 79 % yields. Treatment of the chloropurines **11a** and **11b** with cyclopropylamine produced abacavir analogues, (±)-**4a** and (±)-**4b** in 73 and 63 % yields, respectively (Scheme 3). In summary, the short synthesis of carbovir analogues, (±)-**3a** and (±)-**3b** was achieved from cyclopentadiene (**5**) in 26 and 15 % overall yields, respectively. Also, the synthesis of abacavir analogues, (±)-**4a** and (±)-**4b** was accomplished from cyclopentadiene (**5**) in 17 and 9 % overall yields, respectively. The antiviral screening of carbocyclic nucleosides, (±)-**3a**, (±)-**3b**, (±)-**4a**, and (±)-**4b** is currently under investigation.



Scheme 3. a. i) $Pd(OAc)_2$, $(i\text{-}PrO)_3P$, THF, rt ii) *n*-BuLi, rt iii) **9** in THF, 2-amino-6-chloropurine, DMSO, rt, 39 h (**10a**, 68 %; **10b**, 67 %). b. 1.0 *N* NaOH, reflux, 2 h (**3a**, 85 %; **3b**, 86 %). c. K_2CO_3, MeOH, $CHCl_3$, H_2O, rt, 6 h (**11a**, 77 %; **11b**, 79 %). d. cyclopropylamine, EtOH, autoclave, 100 °C, 22 h (**4a**, 73 %; **4b**, 63 %).

EXPERIMENTAL

Proton (^1H) NMR spectra were obtained using a Varian Mercury 300 spectrometer (300 MHz) instrument operating in Fourier transform mode. Carbon-13 (^{13}C) NMR spectra were recorded using a Varian Mercury 300 spectrometer (75.5 MHz) instrument. Infrared spectra were recorded on Bio-Rad FTS 6000 FT-IR spectrometer. Uncorrected melting points were determined with a Gallenkamp melting point apparatus. Analytical thin layer chromatography (TLC) was conducted on E. Merck 60 F254 aluminum backed silica gel plates (0.2 mm) with a fluorescent indicator. Developed plates were visualized under UV light, with iodine staining, or by dipping in 2.0 % phosphomolybdic acid solution and then heating. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) under positive pressure of air according to the procedure of Still.[8] Reagents and solvents were of reagent grade, and solvents were purified by the known procedure[9] before use.

(±)-4-*endo* and *exo*-Hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one ((±)-7a and (±)-7b). A white solid (±)-**7a** and a colorless oil (±)-**7b** were prepared by a known procedure.[3,6] Compound (±)-7a: m.p. 66-69 °C ($CHCl_3$/Hexane) (m.p.[lit.] 63-64 °C);[6] IR (thin film) 3445, 3057, 2958, 2925, 2851, 1748, 1443, 1388, 1347, 1271, 1040, 909, 792 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (ddd, J = 5.5, 2.7, 1.8 Hz, 1H), 5.95 (dd, J = 7.0, 5.2 Hz, 1H), 5.35 (dd, J = 4.8, 2.1 Hz, 1H), 4.72 (d, J = 9.6 Hz, 1H), 3.24 (dd, J = 9.3, 6.4 Hz, 1H), 2.83 (br s, 1H), 2.76 (ddd, J = 17.8, 5.9, 1.8 Hz, 1H), 2.49 (ddd, J = 17.8, 9.3, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 177.05, 141.04, 127.47, 86.52, 69.28, 40.63, 30.89. Compound (±)-7b: IR (thin film) 3454, 3067, 2961, 2855, 1751, 1657, 1561, 1447, 1391, 1273, 1043, 983, 722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.09 (dd, J = 5.4, 3.7 Hz, 1H), 5.92 (ddd, J = 7.2, 7.0, 5.4 Hz, 1H), 5.55 (ddd, J = 7.3, 3.7, 1.8 Hz, 1H), 4.15 (d, J = 7.0 Hz, 1H), 3.18 (br s, 1H), 3.08 (dd, J = 7.5, 1.8 Hz, 1H), 2.78 (ddd, J = 17.7, 9.3, 1.8 Hz, 1H), 2.61 (dd, J = 17.7, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 177.67, 136.60, 129.34, 87.43, 74.44, 44.22, 36.78.

(1*R,5*S**)-5-[(1*S**)-1,2-Dihydroxyethyl]-cyclopent-2-en-1-ol and (1*S**,5*R**)-5-[(1*R**)-1,2-dihydroxyethyl]-cyclopent-2-en-1-ol ((±)-8a).** Triol (±)-**8a** was prepared from *endo*-hydroxylactone (±)-**7a** by a known procedure:[3,7] IR (thin film) 3398, 3056, 2937, 2839, 1615, 1334, 1234, 1073, 1007, 878, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.00 (m, 1H), 5.87 (m, 1H), 4.86 (m, 1H), 4.78 (m, 1H), 4.70 (m, 1H), 4.34 (m, 1H), 3.87 (br s, 1H), 3.66 (m, 1H), 3.52 (m, 1H), 2.12-2.22 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 134.99, 132.08, 75.91, 72.34, 65.50, 44.22, 33.24.

(1*R,5*S**)-5-[(1*R**)-1,2-Dihydroxyethyl]-cyclopent-2-en-1-ol and (1*S**,5*R**)-5-[(1*S**)-1,2-dihydroxyethyl]-cyclopent-2-en-1-ol ((±)-8b).** Triol (±)-**8b** was prepared from *exo*-hydroxylactone (±)-**7b** by the same method: IR (thin film) 3407, 3058, 2927, 2849, 2724, 1641, 1443, 1423, 1343, 1318, 1072, 1005, 915, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 (dd, J = 3.2, 1.8 Hz, 1H), 5.84 (dd, J = 3.6, 1.8 Hz, 1H), 4.74 (m, 1H), 4.25 (br s, 1H), 4.11 (m, 1H), 3.98 (br s, 1H), 3.52-3.77 (m, 3H), 2.58 (m, 1H), 2.17-2.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 135.89, 132.23, 77.59, 71.84, 65.98, 43.47, 31.73.

Methyl (1*R,5*S**)-5-[(1*S**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl carbonate and (1*S**,5*R**)-5-[(1*R**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl carbonate ((±)-9a).** To a solution of triol (±)-**8a** (2.00 g, 13.9 mmol) in anhydrous $CHCl_3$ (50 mL) was added pyridine (10.8 mL, 139 mmol) and DMAP (0.170 g, 1.38 mmol) at 0 °C. Then, methyl chloroformate (16.1 mL, 208 mmol) in anhydrous $CHCl_3$ (20 mL) was slowly added by dropping funnel at 0 °C. After being stirred for 2 h, the reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with brine solution (20 mL). The aqueous phase was extracted with $CHCl_3$ (20 mL x 3). The organic phase was collected, dried with anhydrous $MgSO_4$ and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (Et_2O:Hexane = 1:2, v/v) to give a colorless oil (±)-**9a** (R_f = 0.22; 4.07 g, 93 %): IR (thin film) 3485, 3017, 2968, 2859, 1737, 1467, 1237, 1102, 1075, 944, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.19 (m, 1H), 5.99 (m, 1H), 5.58 (m, 1H), 5.12 (m, 1H), 4.59 (m, 1H), 4.14 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 2.70 (m, 1H), 2.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 155.26, 154.82, 154.65, 137.88, 128.97, 81.07, 74.18, 67.42, 54.93, 54.80, 54.54, 41.79, 33.07.

Methyl (1*R,5*S**)-5-[(1*R**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl carbonate and (1*S**,5*R**)-5-[(1*S**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl carbonate ((±)-9b).** Tricarbonate (±)-**9b** was prepared from triol (±)-**8b** (1.37 g, 9.51 mmol) by the same method (R_f = 0.25, Et_2O:Hexane = 1:2, v/v; 2.91 g, 97 %): IR (thin film) 3480, 3006, 2961, 2857, 1746, 1443, 1335, 1308, 1122, 944, 789 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.19 (m, 1H), 5.98 (m, 1H), 5.48 (m, 1H), 5.20 (m, 1H), 4.50 (m, 1H), 4.21 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.70 (m, 1H), 2.49-2.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 155.00, 154.92, 154.82, 138.49, 128.55, 81.66, 74.86, 67.44, 54.96, 54.92, 54.66, 41.25, 34.03.

(1*R,4*S**)–2-Amino-6-chloro-9-[4-[(1*S**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl]purine and (1*S**,4*R**)-2-amino-6-chloro-9-[4-[(1*R**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl]purine ((±)-10a).** Triisopropyl phosphite (0.37 mL, 1.5 mmol) was added at ambient temperature to a solution of $Pd(OAc)_2$ (0.083 g, 0.37 mmol) in anhydrous THF (5.0 mL)

under argon. After being stirred for 15 min, *n*-BuLi (1.6 *N* in hexane, 0.46 mL, 0.73 mmol) was added at ambient temperature. The resulting mixture was stirred for 15 min to obtain tetrakis(triisopropylphosphite)palladium (0) catalyst. The *in situ* prepared Pd(0) catalyst was added to a solution of 2-amino-6-chloropurine (1.63 g, 9.61 mmol) in anhydrous DMSO (7.0 mL) *via* cannula at ambient temperature. Then, a solution of tricarbonate (±)-**9a** (2.30 g, 7.23 mmol) in anhydrous THF (15 mL) was added to the reaction mixture. After being stirred for 39 h, the reaction mixture was diluted with ethyl acetate (10 mL) and washed with brine solution (15 mL). The aqueous phase was extracted with ethyl acetate (10 mL x 3). The organic phase was collected, dried with anhydrous $MgSO_4$ and concentrated by rotary-evaporation. The residue was purified by flash column chromatography (EtOAc:Hexane = 3:2, v/v) to give a white solid (±)-**10a** (R_f = 0.23; 2.02 g, 68 %) with starting tricarbonate (±)-**9a** (0.019 g, 8 %): m.p. 129-131 °C ($CHCl_3$/Hexane); IR (thin film) 3437, 3323, 3306, 2964, 2871, 1743, 1562, 1444, 1268, 1236, 907, 733 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.97 (s, 1H), 6.84 (s, 2H), 6.12 (m, 1H), 6.02 (m, 1H), 5.48 (m, 1H), 5.01 (m, 1H), 4.38 (m, 1H), 4.24 (m, 1H), 3.68-3.71 (br s, 6H), 3.14 (m, 1H), 2.70 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.36, 154.74, 154.70, 153.43, 149.18, 140.85, 135.06, 130.81, 123.62, 77.17, 66.99, 59.08, 54.89, 54.84, 44.96, 33.11.

(1*R,4*S**)-2-Amino-6-chloro-9-[4-[(1*R**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl]purine and (1*S**,4*R**)-2-amino-6-chloro-9-[4-[(1*S**)-1,2-dimethoxycarbonyloxyethyl]-cyclopent-2-enyl]purine ((±)-10b).** Compound (±)-**10b** was prepared from tricarbonate (±)-**9b** (2.00 g, 6.28 mmol) by the same method (R_f = 0.25, EtOAc:Hexane = 3:2, v/v; 1.73 g, 67 %): IR (thin film) 3447, 3376, 3321, 3207, 3005, 2958, 1750, 1615, 1510, 1463, 1295, 940, 787 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.94 (s, 1H), 6.86 (s, 2H), 6.08 (m, 1H), 6.01 (m, 1H), 5.48 (m, 1H), 5.06 (m, 1H), 4.42 (m, 1H), 4.23 (m, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.16 (m, 1H), 2.68 (m, 1H), 1.77 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.43, 154.72, 154.58, 153.43, 149.22, 140.66, 135.37, 131.06, 123.50, 76.43, 66.94, 58.87, 54.91, 54.86, 45.73, 32.30.

(1*R,4*S**)-9-[4-[(1*S**)-1,2-Dihydroxyethyl]-cyclopent-2-enyl]guanine and (1*S**,4*R**)-9-[4-[(1*R**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]guanine ((±)-3a)**. The coupling adduct (±)-**10a** (0.050 g, 0.12 mmol) was added to 1.0 *N* aqueous NaOH (10 mL, 10 mmol). The mixture was stirred at reflux temperature for 2 h. Then, the reaction mixture was neutralized to *p*H 7-8 with diluted HCl. After removal of water by rotary-evaporation, the residue was diluted with methanol (20 mL). Silica gel (~ 2.0 g) was added to this solution and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography ($CHCl_3$:MeOH = 3:1, v/v), a white solid (±)-**3a** (R_f = 0.25; 0.029 g, 85 %) was obtained: m.p. 234 °C ($CHCl_3$/MeOH; decomp.); IR (thin film) 3348, 3127, 1690, 1610, 1531, 1374, 1179, 1052, 779 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.54 (br s, 1H), 7.25 (s, 1H), 6.43 (s, 2H), 5.81 (m, 1H), 5.45 (m, 1H), 4.95 (m, 1H), 4.51 (m, 1H), 4.32 (m, 1H), 2.80-3.20 (m, 4H), 2.23 (m, 1H), 1.23 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 156.61, 153.58, 150.49, 137.27, 134.93, 129.41, 116.38, 73.87, 64.43, 58.37, 47.55, 34.65.

(1*R,4*S**)-9-[4-(1*R**)-1,2-Dihydroxyethyl]-cyclopent-2-enyl]guanine and (1*S**,4*R**)-9-[4-[(1*S**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]guanine ((±)-3b)**. Compound (±)-**3b** was prepared from the coupling adduct (±)-**10b** (0.108 g, 0.26 mmol) by the same method (R_f = 0.29, $CHCl_3$:MeOH = 3:1, v/v; 0.063 g, 86 %): m.p. 206-209 °C ($CHCl_3$/MeOH); IR (thin film) 3346, 3138, 1690, 1612, 1575, 1532, 1475, 1407, 1373, 1177, 1025, 780 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.52 (br s, 1H), 7.20 (s, 1H), 6.42 (br s, 2H), 5.64 (m, 1H), 5.40 (m, 1H), 4.90 (m, 1H), 4.41 (d, *J* = 4.5 Hz, 1H), 4.31 (d, *J* = 4.5 Hz, 1H), 3.15 (m, 1H), 2.91 (m, 2H), 2.75 (m, 1H), 2.10 (m, 1H), 1.34 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 156.65, 153.61, 150.48, 138.55, 135.04, 129.23, 116.33, 72.70, 64.36, 58.23, 47.86, 32.18.

(1*R,4*S**)-2-Amino-6-chloro-9-[4-[(1*S**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine and (1*S**,4*R**)-2-amino-6-chloro-9-[4-[(1*R**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine ((±)-11a)**. The coupling adduct (±)-**10a** (0.55 g, 1.3 mmol) in mixed solvent (MeOH/$CHCl_3$/H_2O = 7:3:3, v/v/v; 13mL) was added K_2CO_3 (0.56 g, 3.7 mmol) at 0 °C. After being stirred for 6 h at ambient

temperature, the reaction mixture was neutralized to *p*H 7-8 with diluted HCl. After removal of water by rotary-evaporation, the residue was diluted with methanol (30 mL). Silica gel (~ 2.5 g) was added to this solution and then the resulting suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography ($CHCl_3$:MeOH = 8:1, v/v), a white solid (±)-**11a** (R_f = 0.22; 0.30 g, 77 %) was obtained: m.p. 168-171 °C ($CHCl_3$/MeOH); IR (thin film) 3407, 3337, 3106, 2922, 2867, 1632, 1610, 1567, 1460, 1218, 1061, 911, 645 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.06 (s, 1H), 6.88 (br s, 2H), 6.22 (m, 1H), 5.89 (m, 1H), 5.43 (m, 1H), 4.79 (m, 1H), 4.58 (m, 1H), 3.39 (br s, 2H), 3.35 (m, 1H), 2.91 (m, 1H), 2.63 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.43, 153.46, 149.05, 141.09, 137.73, 129.00, 123.37, 73.71, 64.38, 58.86, 47.55, 34.24.

(1*R,4*S**)-2-Amino-6-chloro-9-[4-[(1*R**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine and (1*S**,4*R**)-2-amino-6-chloro-9-[4-[(1*S**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine ((±)-11b)**. Compound (±)-**11b** was prepared from the coupling adduct (±)-**10b** (0.27 g, 0.65 mmol) by the same method (R_f = 0.25, $CHCl_3$:MeOH = 8:1, v/v; 0.15 g, 79 %): m.p. 181-183 °C ($CHCl_3$/MeOH); IR (thin film) 3327, 3212, 2924, 1611, 1564, 1446, 1405, 1203, 910, 784 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.97 (s, 1H), 6.81 (s, 2H), 6.03 (m, 1H), 5.80 (m, 1H), 5.36 (m, 1H), 4.66 (m, 1H), 4.51 (m, 1H), 3.23-3.27 (br s, 2H), 3.08 (m, 1H), 2.87 (m, 1H), 2.45 (m, 1H), 1.73 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 159.43, 153.41, 149.02, 141.11, 139.26, 128.68, 123.32, 72.44, 64.31, 58.73, 47.83, 31.54.

(1*R,4*S**)-2-Amino-6-cyclopropylamino-9-[4-[(1*S**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine and (1*S**,4*R**)-2-amino-6-cyclopropylamino-9-[4-[(1*R**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine ((±)-4a)**. Cyclopropylamine (0.11mL, 1.5 mmol) was added to a solution of the compound (±)-**11a** (0.080 g, 0.27 mmol) in ethanol (5.0 mL) and then the reaction mixture was stirred at 100 °C in autoclave. After being stirred for 10 h, the more cyclopropylamine (0.11 mL, 1.5 mmol) was added to reaction mixture and stirred for 12 h. The reaction mixture was concentrated by rotary-evaporation. The crude reaction mixture was washed with chloroform (3 mL x 3) and was diluted with methanol (30 mL). Silica gel (~ 1.5 g) was added to this solution and then the resulting

suspension was dried under the reduced pressure. By the pre-loaded silica gel column chromatography ($CHCl_3$:MeOH = 7:1, v/v), a white solid (±)-**4a** (R_f = 0.22; 0.062 g, 73 %) was obtained: m.p. 176-178 °C ($CHCl_3$/MeOH); IR (thin film) 3322, 3237, 1559, 1444, 1384, 1294, 1246, 967, 785, 742, 652 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.64 (s, 1H), 7.28 (m, 1H), 6.17 (m, 1H), 5.83 (m, 1H), 5.81 (s, 2H), 5.38 (m, 1H), 4.88 (m, 1H), 4.58 (m, 1H), 3.37 (br s , 2H), 3.03 (m, 1H), 2.88 (m, 1H), 2.59 (m, 1H), 1.63 (m, 1H), 0.57-0.66 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 159.75, 155.68, 150.68, 136.85, 134.98, 129.76, 113.45, 73.94, 64.42, 58.15, 47.54, 34.46, 23.88, 6.51.

(1*R,4*S**)-2-Amino-6-cyclopropylamino-9-[4-[(1*R**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine and (1*S**,4*R**)-2-amino-6-cyclopropylamino-9-[4-[(1*S**)-1,2-dihydroxyethyl]-cyclopent-2-enyl]purine ((±)-4b)**. Compound (±)-**4b** was prepared from compound (±)-**11b** (0.09 g, 0.30 mmol) by the same method (R_f = 0.24, $CHCl_3$:MeOH = 7:1, v/v; 0.060 g, 63 %): m.p. 186-189 °C ($CHCl_3$/MeOH); IR (thin film) 3320, 3207, 2927, 1597, 1480, 1389, 1353, 1258, 964, 790, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.63 (s, 1H), 7.26 (m, 1H), 6.04 (m, 1H), 5.79-5.81 (m, 3H), 5.37 (m, 1H), 4.78 (m, 1H), 4.58 (m, 1H), 3.57 (m, 1H), 3.42 (m, 1H), 3.32 (m, 1H), 3.03 (m, 1H), 2.92 (m, 1H), 1.77 (m, 1H), 0.57-0.65 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 159.75, 155.66, 150.67, 138.12, 135.02, 129.57, 113.39, 72.74, 64.34, 57.97, 47.82, 31.90, 23.86, 6.50.

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Received 3/13/00
Accepted 5/16/00