Synthesis of Carbocyclic 2′,3′-Dideoxy-2′-*C*-hydroxymethyl Nucleosides as Potential Inhibitors of HIV

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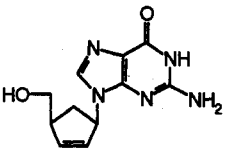
The synthesis of the enantiomerically pure carbocyclic 2′,3′-dideoxy-2′-*C*-hydroxymethyl derivatives of adenosine and guanosine is described. *trans*-(1*R*,2*R*)-1,2-Bis(methoxycarbonyl)-4-oxocyclopentane (**4**) was reacted with the zinc–dibromomethane–titanium tetrachloride mixed reagent to give an exocyclic olefin. Hydroboration followed by oxidation gave the *C*-2 symmetric hydroxymethyl diester **6**. The two ester groups in **6** were differentiated by lactonization to give lactone **7**. The lactone **7** was opened with ammonia, and the remaining carboxylic acid group was reduced. Hofmann rearrangement of the amide gave (1*R*,2*R*,4*R*)-2,4-bis(acetoxymethyl)-1-[(*tert*-butoxycarbonyl)amino]-cyclopentane (**9**), which after deprotection was converted to the adenosine derivative **12** and the guanosine derivative **15**. Compounds **12** and **15** were evaluated for activity against human immunodeficiency virus (HIV).

Introduction

Since the first description of AIDS in the early 1980's and the discovery of the causative agent, the human immunodeficiency virus (HIV), there has been intense research aimed at identifying substances effective against HIV.[1] Nucleoside analogues having anti-HIV activity were developed early on as promising drug candidates and today there are three nucleosides approved for the treatment of HIV infection. These compounds, 3′-azido-3′-deoxythymidine (AZT)[2], 2′,3′-dideoxyinosine (DDI)[3], and 2′,3′-dideoxycytidine (DDC)[4] are, *in vivo*, metabolized to their corresponding 5′-triphosphates and are, as such, inhibitors of viral reverse transcriptase and/or chain terminators of viral DNA synthesis. Recently, the discovery of clinical resistance of HIV toward AZT has emerged as a major concern with effectiveness of long term treatment.[5] Strategies to overcome this include the administration of cocktails of antiviral agents, to induce multiple mutations in the HIV and eventually render the virus uninfective or dead.[6] This and other similar combination therapies call for the continued development of new, and possibly more effective, antiviral drugs.

Carbocyclic nucleosides,[7] wherein the furanose oxygen has been replaced by a carbon denoted as C-6′, have emerged as a potentially promising class of nucleosides and some show potent anti-HIV activity. Two such compounds are carbovir[8] (**1**) and carbocyclic oxetanocin G[9] (**2**). Substitution of the furanose oxygen by carbon not



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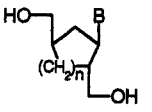

2 n=0 B=guanine
3 n=1

only modulates the antiviral properties of the parent nucleoside but sometimes confers antiviral activity to a carbocyclic analogue where none exists for the parent nucleoside.[10] Carbocyclic nucleosides also have greater metabolic stability to the phosphorylase enzymes that cleave the glycosidic bond of the parent nucleoside.[11,12] The higher lipophilicity of carbocyclic nucleosides is potentially beneficial for oral availability and cell wall penetration.

During recent years, the syntheses of different types of hydroxymethyl-branched nucleosides have been reported from our group,[13] as well as other groups.[14] In order to further evaluate the structure–activity relationship of hydroxymethyl-substituted nucleosides, we have synthesized enantiomerically pure, carbocyclic 2′,3′-dideoxy-2′-

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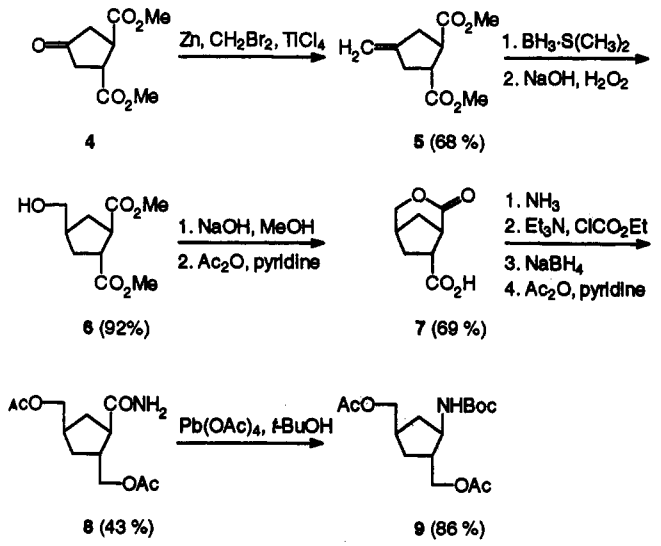
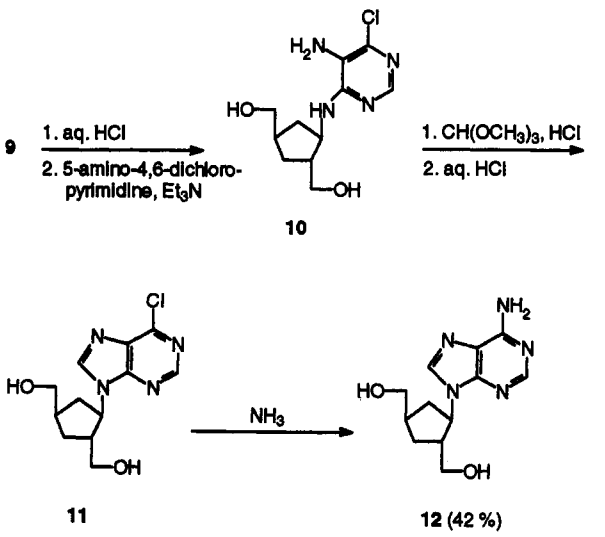
Scheme 1



Scheme 2



hydroxymethyl nucleosides in the purine series. These nucleosides (**3**) can be viewed as structural homologues of carbocyclic oxetanocin G (**2**).

Results and Discussion

The starting material used was enantiomerically pure keto diester **4**, which was prepared by a method recently developed in our laboratory.[15] Compound **4** was extended by one carbon using the zinc–dibromomethane–titanium tetrachloride mixed reagent[16] (Scheme 1). The isolated yield of the resulting methylene diester **5**, after purification by silica gel column chromatography, was 68%. Attempts to methylenate the ketone using Wittig type reagents were not successful, giving only 10–20% of the isolated desired product. Enolization of the keto group is a probable explanation of the low yields obtained using this approach.[17] Hydroboration of the exocyclic double bond in **5**, using borane–dimethyl sulfide in tetrahydrofuran, followed by oxidation of the resulting alkylborane with alkaline peroxide,[18] afforded enantiomerically pure *C*-2 symmetric hydroxymethyl diester **6** in 92% yield. The two ester groups in **6** could be differentiated by formation of the lactone **7**. This was accomplished by hydrolysis of the diesters in **6** using aqueous sodium hydroxide in methanol followed by lactonization using acetic anhydride in pyridine at room temperature[19] to give the lactone **7** in 69% yield from **6**. The lactonization step was sensitive to the pH adjustment following the hydrolysis step. When the hydrolysis mixture was treated with Dowex H^+ to pH 3, evaporated, and reacted with acetic anhydride–pyridine, a 1:1 mixture of the desired lactone **7** and the diacid having the acetylated hydroxyl group was obtained. If the pH was adjusted to 8 prior to evaporation, the lactone **7** was the major product formed and only a trace of the diacid was detected, which indicates that **7** is formed as a result of the mixed anhydride being esterified by the unreacted hydroxyl group. Reacting **7** with methanolic ammonia at 100 °C in a steel vessel gave the corresponding amide. The remaining carboxylic acid group was activated to the corresponding mixed anhydride using ethyl chloroformate and triethylamine[20] in dimethylformamide. Sodium borohydride reduction of the mixed anhydride[20] afforded the diol, which was acetylated with acetic anhydride in pyridine at room temperature, giving **8** in 43% yield from **7**. Hofmann rearrangment of **8** using lead tetraacetate in dimethylformamide containing *tert*-butyl alcohol[21] gave compound **9** in 86% yield. The protective groups were removed using aqueous methanolic hydrochloric acid to give the free amino diol, which was further reacted to give the desired derivatives **12** and **15**, using established procedures.[11,12,19] Thus, coupling of the amino diol with 5-amino-4,6-dichloropyrimidine in refluxing butanol in the presence of triethylamine under an argon atmosphere afforded the diamine **10** (Scheme 2). Cyclization of **10** with triethyl orthoformate under acidic conditions in dimethylformamide, followed by treatment with aqueous hydrochloric acid to liberate the derivatized hydroxyl groups, gave the 6-chloropurine **11**, which was treated with methanolic ammonia to give the adenosine derivative **12** in 42% yield from **9**, after silica gel column chromatography. For the synthesis of **15**, the amino diol was coupled to 2-amino-4,6-dichloropyrimidine following the same protocol as above to give **13** (Scheme 3). Diazotization of **13** using (4-chlorophenyl)diazonium chloride, followed by reduction of the resulting yellow diazo compound with zinc, afforded **14**, which was used without further purification. Treatment of **14** with triethyl orthoformate under acidic conditions in dimethylformamide, followed by

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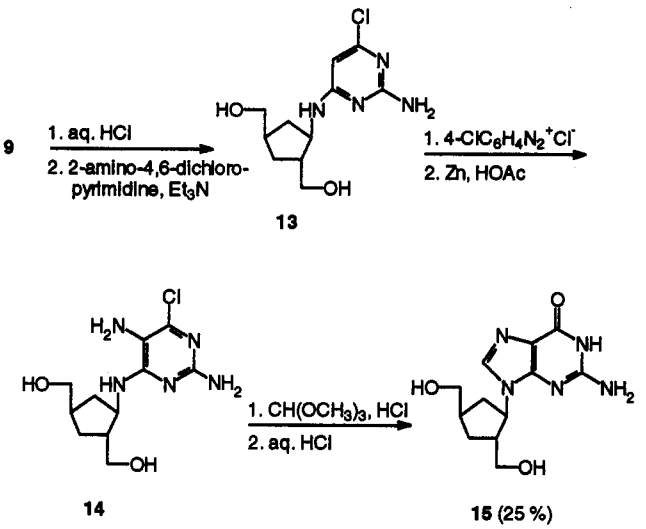
Scheme 3



hydrolytic cleavage of the 6-chloro moiety and the derivatized hydroxyl groups, gave the guanosine derivative **15** in 25% yield from **9**, after purification by HPLC.

Compounds **12** and **15** were tested for inhibition of HIV multiplication in the XTT assay on M4 cells,[22] and both were found to be inactive.

Experimental Section

Removal of solvents was performed under reduced pressure. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX-100 instrument using $CDCl_3$, DMSO-d_6, or acetone-d_6 as solvents with TMS as internal standard. The shifts are reported in ppm (δ scale). TLC analyses were performed on Merck precoated 60 F-254 plates. The spots were visualized by UV light and/or charring with ethanol/sulfonic acid/*p*-anisaldehyde, 90:3:1:2. Column chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck). HPLC analyses were performed on a prepacked steel column (250 × 25 mm) using Polygosil 60-7, C-18 (Macherey-Nagel). Organic phases were dried over anhydrous magnesium sulfate. Optical rotations were measured in $CHCl_3$ or DMSO solutions at room temperature using a Perkin-Elmer 141 instrument.

***trans*-(1*R*,2*R*)-1,2-Bis(methoxycarbonyl)-4-methylenecyclopentane (5).** A 100-mL three-necked round-bottomed flask was flame-dried, connected to argon, and charged with activated zinc powder (2.88 g, 44.1 mmol), dry tetrahydrofuran (25 mL), and dry dibromomethane (1.0 mL). Freshly distilled titanium tetrachloride (1.15 mL, 10.5 mmol) was added dropwise over a period of 15 min at −40 °C, and the reaction mixture was stirred at 5 °C (in a cold room) for 3 days under argon to give a gray slurry. To the slurry, diluted with dry dichloromethane (5.0 mL), was added slowly a solution of *trans*-(1*R*,2*R*)-1,2-bis(methoxycarbonyl)-4-oxocyclopentane[15] (**4**) (2.0 g, 10.0 mmol) in dry dichloromethane (8.0 mL) at 0 °C over a period of 10 min. After 1.5 h stirring at room temperature, the resulting dark mixture was diluted with ethyl acetate (40 mL) and quenched by careful addition of aqueous sodium hydrogen carbonate (5 g in 10 mL) over a period of 1 h. The organic layer was decanted off, and the residue was washed twice with ethyl acetate. The combined organic phase was dried (sodium hydrogen carbonate, 4 g; magnesium sulfate, 20 g) and concentrated. Purification by flash chromatography (toluene–ethyl acetate, 6:1) of the residue gave compound **5** (1.35 g, 68%) as a colorless syrup: $[\alpha]^{22}_D$ −74.6° (*c* 0.52, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 2.41–2.84 (m, 4 H, H-3, H-5), 3.04–3.29 (m, 2 H, H-1, H-2), 3.70 (s, 6 H, 2 × CO_2CH_3), 4.86–4.95 (quin, 2 H, CH_2=); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 36.1 (C-3, C-5), 46.6 (C-1, C-2), 51.9 (2 × CO_2CH_3), 107.2 (CH_2=), 146.7 (C-4), 173.9 (2 × CO_2CH_3). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.65; H, 7.17.

***trans*-(1*R*,2*R*)-4-(Hydroxymethyl)-1,2-bis(methoxycarbonyl)cyclopentane (6).** A 100-mL three-necked round-bottomed flask was flame-dried, connected to argon, and charged with compound **5** (1.22 g, 6.15 mmol) and dry tetrahydrofuran (28 mL). To the mixture was added dropwise borane–dimethyl sulfide (1.53 mL of a 2 M solution in tetrahydrofuran, 3.06 mmol) at −10 °C over 10 min. The reaction mixture was stirred at −10 °C for 1 h and at 0 °C for 2 h before it was cooled to −10 °C, and methanol (1.52 mL), aqueous sodium hydroxide (3 M, 0.61 mL), and 30% hydrogen peroxide (0.92 mL) were added. After stirring for 2 h at 40–50 °C the mixture was cooled to room temperature and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried, concentrated, and purified by flash column chromatography (toluene–ethyl acetate, 1:1) to give compound **6** (1.22 g, 92%) as a colorless syrup: $[\alpha]^{22}_D$ −58.05° (*c* 1.12, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.43–2.47 (m, 6 H, H-3, H-4, H-5, OH), 3.04–3.32 (m, 2 H, H-1, H-2), 3.52–3.58 (d, 2 H, CH_2OH), 3.69 (s, 6 H, 2 × CO_2CH_3); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 32.5, 33.2 (C-3, C-5), 41.05 (C-4), 46.1, 46.9 (C-1, C-2), 52.0 (2 × CO_2CH_3), 65.6 (CH_2OH), 174.8 (2 × CO_2CH_3). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.38; H, 7.54.

(1*R*,5*R*,7*R*)-3-Oxabicyclo[3.2.1]octan-2-one-7-carboxylic Acid (7). A mixture of compound **6** (0.78 g, 3.6 mmol), methanol (19.5 mL), and 1 M sodium hydroxide (14.7 mL) was stirred at room temperature for 3 h. The mixture was treated with Dowex 50W × 8 (H^+) to pH 8–9, filtered, concentrated, and codistilled twice with toluene to give the corresponding diacid. The diacid was dissolved in pyridine (13.8 mL), and acetic anhydride (8.9 mL) was added, after which the mixture was stirred at room temperature for 14 h. Concentration, codistillation with toluene, and purification by flash chromatography (toluene–ethyl acetate–acetic acid, 6:8:1) gave compound **7** (0.42 g, 69%) as a white solid. Attempts to crystallize compound **7** led to opening of the lactone: $[\alpha]^{22}_D$ −66.10° (*c* 1.05, DMSO); ^1H NMR (100 MHz, acetone-d_6) δ 1.88–2.31 (m, 4 H, H-3, H-5), 2.59 (b, 1 H, H-4), 2.94–3.09 (m, 2 H, H-1, H-2), 3.96–4.39 (m, 2 H, CH_2OCO), 7.65 (b, 1 H, COO*H*); ^{13}C NMR (25.05 MHz, acetone-d_6) δ 30.41, 32.87 (C-3, C-5), 34.86 (C-4), 46.29, 47.76 (C-1, C-2), 76.76 (CH_2OCO), 171.91 (CH_2OCO), 174.84 (*C*OOH). The numbering system of the NMR data is in accordance with the one used for the other substances. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.20; H, 5.79.

(1*R*,2*R*,4*R*)-2,4-Bis(acetoxymethyl)cyclopentane-1-carboxamide (8). A cold (−40 °C) solution of compound **7** (0.42 g, 2.5 mmol) in dry methanol (4.0 mL) was saturated with ammonia (g), after which the reaction mixture was heated at 100 °C in a bomb for 24 h. The ammonia was evaporated off under a stream of argon, and the resulting mixture was concentrated. To the residue were added triethylamine (1.03 mL, 7.4 mmol) and dimethylformamide (9.4 mL) followed by dropwise addition of ethyl chloroformate (0.71 mL, 7.4 mmol) over a period of 10 min at −7 °C. After stirring for an additional 30 min at this temperature, the white precipitate of triethylammonium chloride was removed by filtration and washed with tetrahydrofuran (3 × 1.0 mL). The filtrate was cooled to 0 °C, sodium borohydride (0.28 g, 7.4 mmol) and methanol (3.2 mL) were added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched by acidification with acetic acid (1.0 mL) before the solvent was removed in vacuo (oil pump, 30 °C) to give the crude diol. The diol was dissolved in pyridine (8.4 mL) and acetic anhydride (5.4 mL), and the solution was stirred at room temperature for 14 h. After concentration, codistillation with toluene, and purification by flash chromatography (chloroform–methanol, 10:1), the pure amide **8** (0.27 g, 43%) was obtained as a colorless syrup: $[\alpha]^{22}_D$ −23.56° (*c* 1.02, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 1.55–2.71 (m, 7H, H-1, H-2, H-3, H-4, H-5), 2.05 (s, 3H, $OCOCH_3$), 2.07 (s, 3H, $OCOCH_3$), 3.98–4.16 (m, 4H, 2 × CH_2OAc), 6.20–6.47 (d, 2H, NH_2); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 20.9 (2 $OCOCH_3$), 31.8, 34.2, 37.6 (C-3, C-4, C-5), 41.5 (C-2), 48.3 (C-1), 66.0, 67.3 (2 × CH_2OAc), 170.8, 171.0 (2 × $OCOCH_3$), 176.4 ($CONH_2$). Anal. Calcd for $C_{12}H_{19}O_5N \times 0.4\,H_2O$: C, 54.49; H, 7.54; N, 5.29. Found: C, 54.54; H, 7.26; N, 5.34.

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(1*R*,2*R*,4*R*)-2,4-Bis(acetoxymethyl)-1-[(*tert*-butoxycarbonyl)amino]cyclopentane (9). A solution of compound 8 (0.23 g, 0.89 mmol), *tert*-butyl alcohol (4.9 mL), and dimethylformamide (2.6 mL) was heated to 40 °C. Lead tetraacetate (2.0 g, 4.5 mmol) was added in one portion, and the reaction mixture was refluxed for 30 min. After cooling to room temperature and concentration, the crude product was passed through a short column of silica gel using diethyl ether as eluant. The combined fractions containing the product were washed twice with 10% sodium hydroxide and water, dried, and concentrated to give pure compound 9 (0.25 g, 86%) as a colorless syrup: $[\alpha]^{22}_D$ −24.70° (*c* 0.98, $CHCl_3$); ^1H NMR (100 MHz, $CDCl_3$) δ 0.87–2.35 (m, 6H, H-2, H-3, H-4, H-5), 1.43 [s, 9 H, $OCOC(CH_3)_3$], 2.06 (s, 6 H, 2 × $OCOCH_3$), 3.69–3.81 (m, 1 H, H-1), 3.95–4.25 (m, 4 H, 2 × CH_2OAc), 4.74–4.83 (d, 1H, NH); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 20.86 (2 × $OCOCH_3$), 28.3 [$OCOC(CH_3)_3$], 30.1, 34.6, 36.6 (C-3, C-4, C-5), 43.9 (C-2), 54.0 (C-1), 65.8, 67.7 (2 × CH_2OAc), 79.1 [$OCOC(CH_3)_3$], 155.1 [$OCOC(CH_3)_3$], 170.7 (2 × $OCOCH_3$). Anal. Calcd for $C_{16}H_{27}O_6N$: C, 58.32; H, 8.27; N, 4.25. Found: C, 58.27; H, 8.15; N, 4.17.

(1*R*,2*R*,4*R*)-6-Amino-9-[2,4-bis(hydroxymethyl)cyclopentyl]-9*H*-purine (12). A solution of compound 9 (96 mg, 0.29 mmol), methanol (1.1 mL), and 2 M hydrochloric acid (1.1 mL) was refluxed for 1 h. The solvent was evaporated, and the residue was dissolved in methanol (2.0 mL), neutralized with Amberlite IRA-400 (OH^-), filtered, and concentrated to give the free amine. To a solution of the amine in triethylamine (0.2 mL) and 1-butanol (3.0 mL), 5-amino-4,6-dichloropyrimidine (72 mg, 0.44 mmol) was added, and the mixture was refluxed for 50 h under argon. After concentration the residue was purified by column chromatography (chloroform–methanol, 3:1) to give compound 10. A solution of compound 10 in triethyl orthoformate (1.3 mL, 8.0 mmol), dimethylformamide (0.67 mL), and concentrated hydrochloride acid (0.06 mL) was stirred at room temperature overnight. The solvents were removed in vacuo (oil pump, 30 °C), and the residue was dissolved in 0.5 M hydrochloric acid (2.7 mL). After stirring for 30 min at room temperature, the mixture was neutralized with Amberlite IRA-400 (OH^-), filtered, and concentrated. Methanol was repeatedly added and distilled off to give crude 6-chloropurine 11. A solution of 6-chloropurine 11 in dry methanol (3.0 mL) was saturated with ammonia (g) and then heated in a bomb at 100 °C for 48 h. The ammonia was evaporated off under a stream of argon, and the resulting solution was concentrated and purified by column chromatography (chloroform–methanol, 3:1) to give compound 12 (34.5 mg, 42%): $[\alpha]^{22}_D$ −29.00° (*c* 0.74, DMSO); ^1H NMR (100 MHz, DMSO-d_6) δ 1.48–2.39 (m, 6 H, H′-2, H′-3, H′-4, H′-5), 3.11–3.72 (m, 4 H, 2 CH_2OH), 4.31–4.79 (m, 3 H, H′-1, 2 × OH), 7.18 (s, 2 H, NH_2), 8.11 (s, 1 H, H-2), 8.20 (s, 1 H, H-8); ^{13}C NMR (25.05 MHz, DMSO-d_6) δ 29.8, 35.55, 38.2 (C′-3, C′-4, C′-5), 45.0 (C′-2), 56.9 (C′-1) 61.8, 64.2 (2 × CH_2OH), 118.8 (C-5), 139.6 (C-8), 149.0 (C-4), 151.6 (C-2), 155.5 (C-6). Anal. Calcd for $C_{12}H_{17}O_2N_5 \cdot 1.0H_2O$: C, 51.23; H, 6.80; N, 24.89. Found: C, 51.41; H, 6.21; N, 24.60.

(1*R*,2*R*,4*R*)-2-Amino-9-[2,4-bis(hydroxymethyl)cyclopentyl]-9*H*-purin-6(1*H*)-one (15). A solution of compound 9 (126 mg, 0.38 mmol) in methanol (1.4 mL) and 2 M hydrochloric acid (1.4 mL) was refluxed for 1 h. The solvent was evaporated, and the residue was dissolved in methanol (2.5 mL), neutralized with Amberlite IRA-400 (OH^-), filtered, and concentrated to give the free amine. To a solution of the amine in triethylamine (0.26 mL) and 1-butanol (3.2 mL) was added 2-amino-4,6-dichloropyrimidine (94 mg, 0.57 mmol), and the mixture was refluxed for 50 h under argon. After concentration the residue was purified by column chromatography (chloroform–methanol, 3:1) to give compound 13. A cold solution of 4-chlorobenzenediazonium chloride, prepared from *p*-chloroanilin (49 mg, 0.38 mmol) in a mixture of water (0.64 mL), hydrochloric acid (0.22 mL), and sodium nitrite (28 mg, 0.40 mmol) in water (0.3 mL), was added dropwise to a solution of compound 13 in water (1.7 mL), acetic acid (1.7 mL), and sodium acetate trihydrate (0.72 g). The reaction mixture was stirred overnight at room temperature before it was cooled to 0 °C. The yellow precipitate of 5-[(*p*-chlorophenyl)azo]pyrimidine was collected by filtration, washed with ice–water until the eluate had pH ≈ 7, and dried in vacuo over phosphoruspentoxide. A mixture of 5-[(*p*-chlorophenyl)-azo]pyrimidine, water (5.4 mL), ethanol (5.4 mL), acetic acid (0.11 mL), and zinc dust (0.21 g) was refluxed under argon for 3 h. The warm mixture was filtered, cooled to room temperature, and evaporated. To the residue was added ethanol and repeatedly distilled off. The product was purified by column chromatography (chloroform–methanol, 3:1) to give compound 14. To a stirred mixture of compound 14, triethyl orthoformate (1.2 mL, 7.2 mmol), and dimethylformamide (0.6 mL) was added concentrated hydrochloric acid (0.09 mL), and the mixture was stirred at room temperature overnight. The solvent was removed in vacuo (oil pump, 30 °C), and the residue was dissolved in 0.6 M hydrochloric acid (1.7 mL). The mixture was stirred at room temperature for 2 h, and under reflux for additional 2 h. After cooling to room temperature the pH was adjusted to 7 with 2 M sodium hydroxide. Concentration, filtration through a column of Amperlite LH-20 (water), and purification by HPLC (water–methanol, 80:20, v/v) gave compound 15 (28.7 mg, 25%): $[\alpha]^{22}_D$ −33.95° (*c* 0.62, DMSO); ^1H NMR (100 MHz, DMSO-d_6) δ 1.53–2.36 (m, 6 H, H′-2, H′-3, H′-4, H′-5), 3.13–3.61 (m, 4 H, 2 × CH_2-OH), 4.24–4.78 (m, 3H, H′-1, 2 × OH), 6.54 (s, 2 H, NH_2), 7.79 (s, 1 H, H-8), 10.68 (b, 1 H, NH); ^{13}C NMR (25.05 MHz, DMSO-d_6) δ 29.7, 35.8, 38.1 (C′-3, C′-4, C′-5), 45.1 (C′-2), 55.9 (C′-1), 61.6, 64.8 (2 × CH_2OH), 116.3 (C-5), 135.5 (C-8), 150.8 (C-4), 152.85 (C-2), 156.45 (C-6). Anal. Calcd for $C_{12}H_{17}O_3N_5$: C, 51.61; H, 6.13; N, 25.08. Found: C, 51.72; H, 6.53; N, 24.70.

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