Synthesis of 5-[2-(Guanin-9-yl)- and 5-[2-(2-Aminopurin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetrahydroxybutyl)-1,3-dioxane

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Stereoselective synthesis of 5-[2-(guanin-9-yl)- and 5-[2-(2-aminopurin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetrahydroxybutyl)-1,3-dioxane, **2-5**, as potential prodrugs of penciclovir, has been accomplished in six steps from readily available 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-ribose (**6**) and the 1,3-diol **7**. It has been demonstrated that the use of boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) in dichloromethane along with excess anhydrous copper(II) sulfate was crucial for the efficient formation of cyclic acetal **8**. In addition, the chromatographic separation of *cis* and *trans* isomers of the cyclic acetal at the bromide stage **10** was feasible, which was requisite for the successful stereoselective synthesis of the ribosyl derivatives **2-5**.

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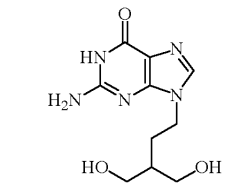
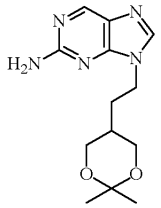
An acyclonucleoside 9-(4-hydroxy-3-hydroxymethyl-but-1-yl)guanine (penciclovir) is a potent and selective inhibitor of members of the herpesvirus family including herpes simplex virus type 1 and type 2, varicella-zoster virus, and Epstein-Barr virus both in cell cultures and in animal models [1], and of hepatitis B virus and duck hepatitis B virus in cell cultures [2]. The advantage of penciclovir over 9-(2-hydroxyethoxymethyl)guanine (acyclovir) is that its antiviral activity in cell culture is more persistent than that of acyclovir because penciclovir triphosphate has a much greater stability than acyclovir triphosphate within virus-infected cells [1b,3]. However, like other acycloguanosine analogues such as acyclovir [4] and 9-(1,3-dihydroxy-2-propoxymethyl)guanine (ganciclovir) [5], penciclovir was poorly absorbed when given orally to rodents [6]. Therefore, the search for a prodrug that is orally well absorbed and then readily converted to penciclovir is of high priority [6a,7].



penciclovir



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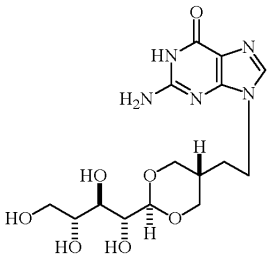

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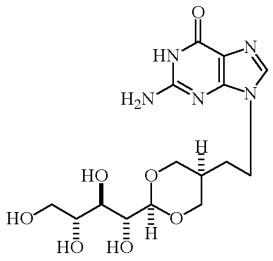

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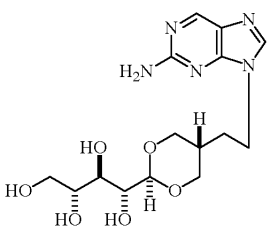

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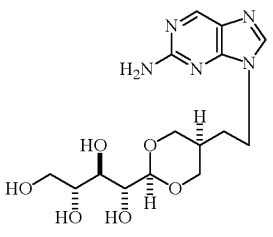

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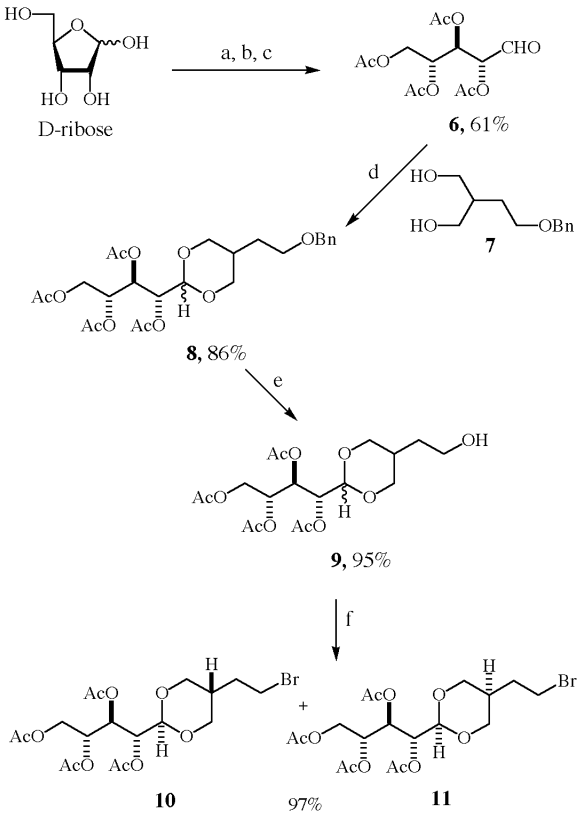
It has been reported that the amino acid esters of the above-mentioned acycloguanosine antiviral agents significantly increased their oral bioavailability [7a,7c,8]. Especially, the naturally occurring branched chain amino acid, L-valyl, had a profound effect on the efficiency of prodrug absorption. However, no prodrug approach utilizing carbohydrates for such antiviral agents has been reported to date. Harnden *et al.* reported that the cyclic acetal derivative of 6-deoxypenciclovir, **1**, was absorbed much more efficiently and provided maximum concentration of penciclovir in the blood that was 7 times higher than that obtained after administration of the equivalent oral dose of penciclovir to mice [6a]. On the basis of these findings, we have synthesized the D-ribosyl cyclic acetal derivatives of penciclovir and 6-deoxypenciclovir, **2-5**, to evaluate their potential as prodrugs of penciclovir.

The requisite bromides, **10** and **11**, were prepared from 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-ribose (**6**) [9] and the 1,3-diol **7** [10] as shown in Scheme 1, which were readily available from known procedures. Synthesis of compound **6** from D-ribose was carried out according to the well-documented three-step reaction sequence where the formation of dithioacetal, acetylation and oxidative removal of dithioacetal group are involved. Roberts and his coworkers reported the synthesis of compound **6** in a somewhat low overall yield of 19% [9a]. Fortunately, it was possible to improve the overall yield of compound **6** to

Scheme 1



[a] EtsH, c-HCl, rt, then Na_2CO_3, continuous extraction with EtOAc; [b] Ac_2O, DMAP, pyridine, 0° for 1 h, then rt for 1 h; [c] NBS, $CdCO_3$, acetone-water (97:3, v/v), 0°, 1 h, then $Na_2S_2O_3$, $NaHCO_3$, 0°, 2h; [d] BF_3•OEt_2, anh. CuSO4, CH_2Cl_2, rt, 2h; [e] H_2 (50 psi), 10% Pd/C (10 wt%), THF, rt, 2h; [f] CBr_4, PPh_3, DMF, 0°, 2h.

61% by utilizing the continuous extraction technique for dithioacetal forming step and *N*-bromosuccinimide for oxidative removal of dithioacetal group. It should be noted that the use of cadmium carbonate was beneficial for the reaction with *N*-bromosuccinimide, providing a higher yield of 85% compared to that (54%) without cadmium carbonate.

Unexpectedly, the formation of cyclic acetal **8** from compounds **6** and **7** under acidic conditions turned out to be very challenging. Thin layer chromatography analyses showed that all the reactions under various acidic conditions were rather complex, and the only identifiable compound was the diacetate of diol **7** which was produced *via* intermolecular acetyl transfer between compounds **6** and **7** under acidic reaction conditions. Thus, it was reasoned that the use of a milder Lewis acid could suppress the undesired reactions, and this turned out to be the case. When a catalytic amount of boron trifluoride diethyl etherate (0.1 equivalent) was tried as a Lewis acid in tetrahydrofuran, the desired product **8** was isolated in 65% yield. After several attempts to optimize the reaction conditions, the best yield (86%) of compound **8** was realized with a slight excess amount of boron trifluoride diethyl etherate (1.2 equivalents) in anhydrous dichloromethane at room temperature in the presence of excess anhydrous copper(II) sulfate. As was expected, compound **8** was formed as a mixture of *cis* and *trans* isomers, slightly favoring the *trans* isomer in a ratio of 1:1.77 by ^{1}H nmr. Since they were not separable by chromatographic purification on silica gel, compound **8** was subjected to further transformations as a mixture. Hydrogenolysis of compound **8** in tetrahydrofuran was carried out under Parr condition to afford the alcohol **9** as a mixture of isomers in 95% yield.

Conversion of compound **9** to the bromide, **10** and **11**, proceeded smoothly by using carbon tetrabromide and triphenylphosphine in *N*,*N*-dimethylformamide at 0° in 97% yield. At this stage, it was possible to separate the *cis* and *trans* isomers of the resulting bromide by careful column chromatography on silica gel using ethyl acetate/hexane as eluent. Each isomerically pure **10** and **11** was fully characterized, and the relative stereochemistry was assigned based on ^{1}H nmr analysis. As shown in Figure 1, conformer (**A**) of the *trans* isomer **10** is by

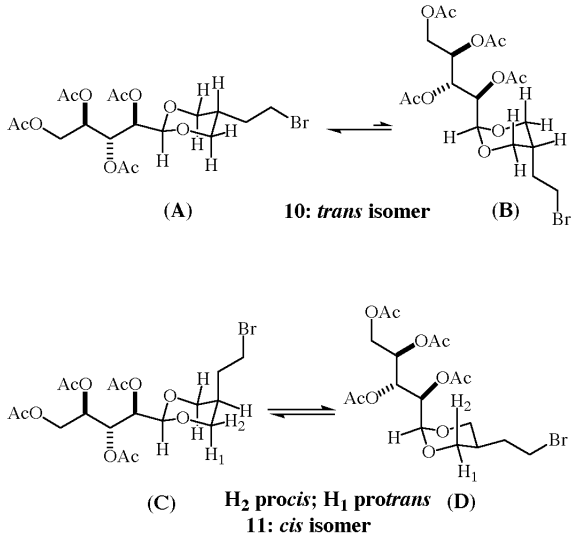


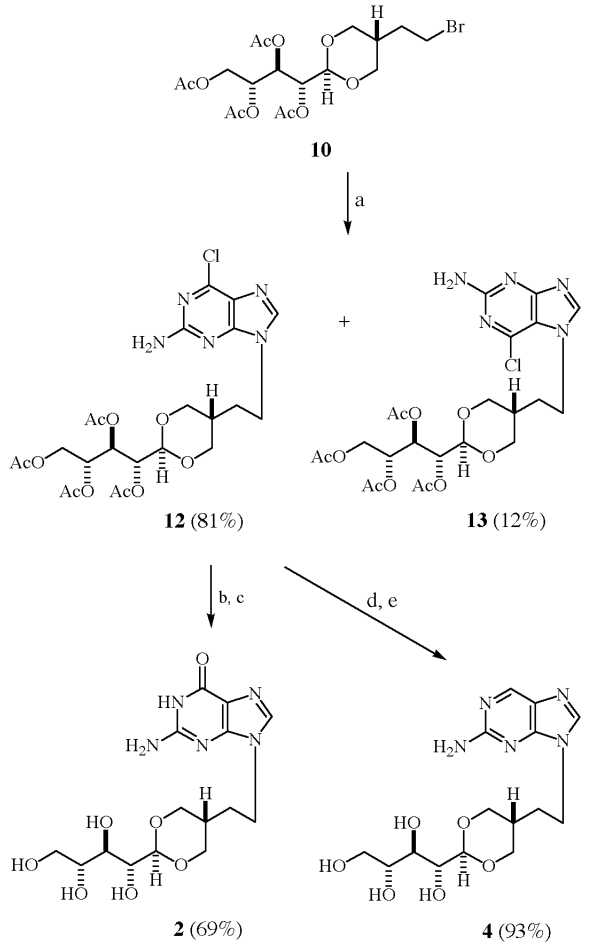
Figure 1. Conformational analysis of compounds **10** and **11**.

far favored over conformer (**B**) since it disposes two alkyl groups at the equatorial positions, thus avoiding the 1,3-diaxial interactions. Due to this anancomeric behavior [11] and the chirality of the molecule, the axial and equatorial protons of C-4 and C-6 became diastereotopic and distinct from each other, showing big differences in the chemical shifts and splitting patterns. Its ^{1}H nmr spectrum in benzene-d_6 revealed that the diastereotopic axial protons appeared as two triplets at 2.76 and 2.73 ppm with a typical large coupling constant of geminal and diaxial couplings ($J_{gem} = J_{ax,5} = 11.4$ Hz), and two signals were also obtained for the

diastereotopic equatorial ones as two doublet of doublet of doublets at 3.66 and 3.63 ppm with expected coupling constants including a long range coupling between equatorial protons (J_{gem} = 11.4 Hz, $J_{eq,5}$ = 6.6 Hz and $J_{4,6}$ = 2.1 Hz). In contrast, there would be no preference over any of two conformers, (**C**) and (**D**), of *cis*-isomer **11** because both of them were expected to have similar 1,3-diaxial interactions. Thus, any typical diaxial couplings could not be observed in the ^{1}H nmr spectrum of *cis*-isomer **11** due to the rapid conformational exchanges between (**C**) and (**D**) at room temperature. Since the protons of C-4 and C-6 are diastereotopic as a consequence of the chirality and sterically different despite the ring flipping (pro*cis* and pro*trans*), the ^{1}H nmr spectrum of compound **11** in benzene-d_6 exhibited four different signals, as expected, at 3.27 (dd, J_{gem} = 12.0 Hz, J = 2.7 Hz), 3.32 (dd, J_{gem} = 12.0 Hz, J = 3.0 Hz), 3.44 (br d, J_{gem} = 12.0 Hz), and 3.50 ppm (br d, J_{gem} = 12.0 Hz) without showing any typical diaxial couplings.

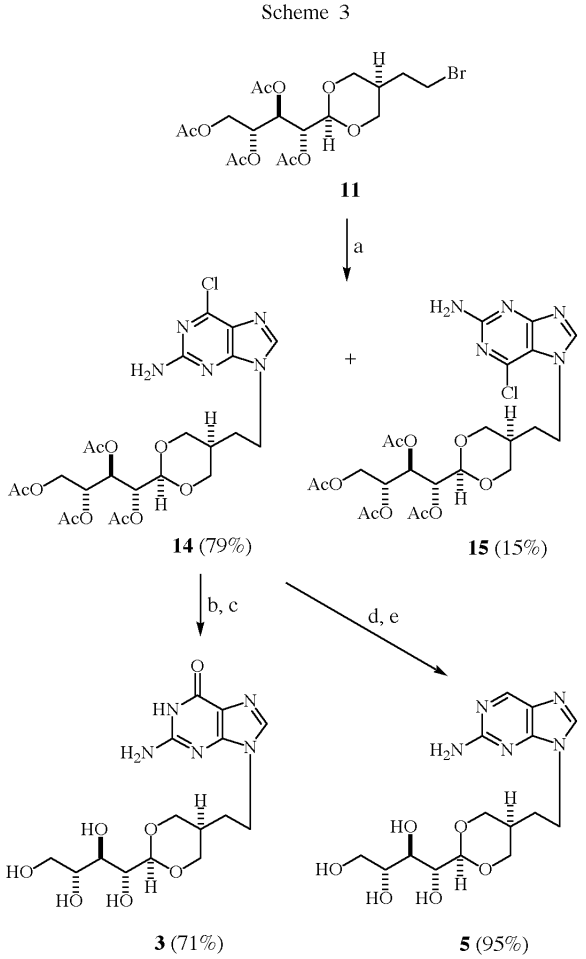
Each isomerically pure bromide, **10** and **11**, was transformed to the target compounds **2-5** according to Schemes 2 and 3. As detailed in Scheme 2, compound **10** was reacted with 2-amino-6-chloropurine using anhydrous potassium carbonate in *N*,*N*-dimethylformamide at room temperature, and the desired N-9 alkylated product **12** was obtained in 81% yield along with N-7 product **13** in 12% after column chromatographic purification on silica gel. Direct conversion of compound **12** to the guanine derivative **2** was first attempted by using sodium hydroxide aqueous solution under reflux, but the reaction was rather sluggish probably due to its low solubility. Therefore, the four acetyl groups of compound **12** were first removed using potassium carbonate in methanol at room temperature, and the resulting intermediate, without isolation, was further treated with 0.5 *N* sodium hydroxide aqueous solution under reflux to afford the desired guanine product **2** in 69% yield after chromatographic purification on C_{18} reverse-phase silica gel. Preparation of the purine derivative **4** from compound **12** was performed smoothly by a one-pot, two-step reaction sequence. Removal of the

Scheme 2



[a] 2-amino-6-chloropurine, anh. K_2CO_3, DMF, rt, 24 h; [b] anh. K_2CO_3, MeOH, rt, 2h; [c] 0.5 N NaOH, reflux, 16 h; [d] H_2 (1 atm), 10% Pd/C (10 wt%), Et_3N, MeOH, rt, 16 h; [e] anh. K_2CO_3, rt, 24 h.

Scheme 3



Reagents and conditions: See corresponding footnotes of Scheme 2.

chloro atom of compound **12** was carried out in methanol at room temperature under catalytic hydrogenolysis conditions in the presence of triethylamine as a hydrogen chloride scavenger, and the subsequent treatment of the reaction mixture with potassium carbonate produced the desired 2-aminopurine compound **4** in 93% yield after chromatographic purification on C_{18} reverse-phase silica gel. As shown in Scheme 3, other target compounds, **3** and **5**, were efficiently prepared from the *cis*-bromide **11** by using the identical sequence of reactions as those used for the synthesis of compounds, **2** and **4**.

As was expected, compounds **2-5** showed remarkable increases in aqueous solubility (>50 mg/ml) compared with that of penciclovir (3.2 mg/ml). However, the oral bioavailability of the compounds **2-5** in mice (2-5%) was only comparable to that of penciclovir (3%), presumably due to their highly polar nature resulting from the multiple hydroxyl groups present.

In conclusion, the present work described stereoselective synthesis of the ribosyl derivatives of penciclovir and 6-deoxypenciclovir, **2-5**, as potential prodrugs of penciclovir, where the efficient formation of cyclic acetal **8** from 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-ribose (**6**) and the 1,3-diol **7** was the key step. This synthetic approach should also be applicable to the synthesis of other nucleoside derivatives with a sugar moiety.

EXPERIMENTAL

Melting points were determined on either a Thomas-Hoover or a Mettler melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian Unity 300 spectrometer. Spectra were recorded in deuteriochloroform, dimethyl sulfoxide-d_6, benzene-d_6 or deuterium oxide, and chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. The ^{13}C nmr spectra (^{1}H noise-decoupled) were recorded on a Varian Unity 300 spectrometer at 75.4 MHz. When deuteriochloroform or dimethyl sulfoxide-d_6 was used as solvent, it served as the internal standard at δ 77.0 or 39.5, respectively. When deuterium oxide was used, sodium 4,4-dimethyl-4-silapentane-1-sulfonate (0.05%, w/w) was added as the internal standard. Electron-impact mass spectra (EI-MS) and fast-atom bombardment mass spectra (FAB-MS) were obtained on a VG Quattro mass spectrometer. Optical rotations were taken with a Perkin-Elmer 241 polarimeter, and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Analytical thin layer chromatography was performed on Merck silica gel 60F-254 glass plates. Medium-pressure chromatography (MPLC) was performed using Merck silica gel 60 (230-400 mesh) with a VSP-2200 ceramic pump (Eyela). Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

cis/trans-5-(2-Benzyloxyethyl)-2-D-*ribo*-(1',2',3',4'-tetraacetoxybutyl)-1,3-dioxane (**8**).

To a stirred mixture of 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-ribose (**6**) (11.25 g, 35.35 mmoles), diol **7** (6.76 g, 32.15 mmoles), and anhydrous copper(II) sulfate (15.40 g, 96.49 mmoles) in dry dichloromethane (100 ml) was added boron trifluoride diethyl etherate (4.8 ml, 39.03 mmoles) in one portion at room temperature, and the resulting mixture was stirred at room temperature for 2 hours under a nitrogen atmosphere. The reaction mixture was filtered into a filtering flask charged with saturated aqueous sodium bicarbonate solution (300 ml) and then extracted with dichloromethane (2 x 200 ml). The combined extracts were dried (magnesium sulfate) and evaporated under reduced pressure to leave a yellow oil, which was purified by column chromatography on silica gel using ethyl acetate-hexane (1:2, v/v) as eluent to afford the *cis/trans*-1,3-dioxane **8** (14.11 g, 86%) as a colorless oil; ir (neat): 1760 and 1740 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.29-1.36 (m, 1.28H, CHC*H*$_2$CH$_2$O), 1.60-1.77 (m, 0.36H, 5-H), 1.96-2.01 (m, 0.72H, CHC*H*$_2$CH$_2$O), 2.03-2.12 (6 x s, 12H, 4 x COCH$_3$), 2.12-2.22 (m, 0.64H, 5-H), 3.27-3.37 (m, 1.28H, OCH$_{ax}$), 3.44 (t, J = 6.3 Hz, 1.28H, CH$_2$C*H*$_2$O), 3.57 (t, J = 6.0 Hz, 0.72H, CH$_2$C*H*$_2$O), 3.80-3.96 (m, 1.44H, 0.72 x OCH$_{ax}$ and 0.72 x OCH$_{eq}$), 4.10-4.18 (m, 2.28H, 4'-H and 1.28 x OCH$_{eq}$), 4.40 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 2.7 Hz, 1H, 4'-H), 4.46 (s, 1.28H, OC*H*$_2$Ph), 4.49 (s, 0.72H, OC*H*$_2$Ph), 4.59 (d, $J_{2,1'}$ = 4.8 Hz, 0.64 H, 2-H), 4.68 (d, $J_{2,1'}$ = 4.5 Hz, 0.36H, 2-H), 5.14-5.19 (m, 1H, 1'-H), 5.41-5.48 (m, 2H, 2'-H and 3'-H), 7.25-7.37 (m, 5H, ArH); ^{13}C nmr (deuteriochloroform): δ 20.7, 20.82, 20.84, 28.3, 29.2, 30.9, 32.3, 62.14, 62.16, 67.66, 67.69, 69.5, 69.6, 69.8, 69.9, 70.0, 70.2, 71.0, 71.1, 71.8, 71.9, 72.8, 73.0, 98.48, 98.54, 99.0, 127.53, 127.55, 127.6, 128.3, 128.4, 138.1, 138.4, 169.3, 169.5, 169.7, 169.8, 170.6; ms: m/z (FAB) 511 (MH$^+$).

Anal. Calcd. for $C_{25}H_{34}O_{11}$: C, 58.82; H, 6.71. Found: C, 58.95; H, 6.66.

Use of other acidic reagent such as glacial acetic acid, methanesulfonic acid, pyridinium *p*-toluenesulfonate, anhydrous hydrogen chloride and an acidic ion exchange resin (Amberlyst-15) in an aprotic solvent (toluene, dichloromethane, chloroform, or tetrahydrofuran) along with excess anhydrous copper(II) sulfate (3.0 equivalents) turned out to be unsuccessful.

cis/trans-5-(2-Hydroxyethyl)-2-D-*ribo*-(1',2',3',4'-tetraacetoxybutyl)-1,3-dioxane (**9**).

A solution of the benzyl ether **8** (13.20 g, 25.86 mmoles) in tetrahydrofuran (90 ml) was vigorously agitated in the presence of 10% palladium on carbon (1.32 g) at room temperature for 2 hours under a hydrogen atmosphere (50 psi). The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated under reduced pressure to leave a yellowish oil, which was purified by column chromatography on silica gel using ethyl acetate-hexane (4:1, v/v) as eluent to afford the *cis/trans*-alcohol **9** (10.31 g, 95%) as a colorless oil; ir (neat): 3478 (OH), 1749 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.25-1.32 (m, 1.28H, CHC*H*$_2$CH$_2$O), 1.58-1.67 (m, 0.36H, 5-H), 1.83-2.02 (m, 0.72H, CHC*H*$_2$CH$_2$O), 2.04-2.14 (4 x s, 12H, 4 x COCH$_3$), 2.10-2.22 (m, 0.64H, 5-H), 3.29-3.39 (m, 1.28H, OCH$_{ax}$), 3.64 (t, J = 6.0 Hz, 1.28H, CH$_2$C*H*$_2$O), 3.79 (br t, 0.72H, CH$_2$C*H*$_2$O), 3.83-4.04 (m, 1.44H, 0.72 x OCH$_{ax}$ and 0.72 x OCH$_{eq}$), 4.11-4.18 (m, 2.28H, 4'-H and 1.28 x OCH$_{eq}$), 4.38-4.45 (m, 1H, 4'-H), 4.62 (d, $J_{2,1'}$ = 4.8 Hz, 0.64H, 2-H), 4.71 (d, $J_{2,1'}$ = 4.2 Hz, 0.36H, 2-H), 5.15-5.18 (m, 1H, 1'-H), 5.44-5.51 (m, 2H, 2'-H and 3'-H); ^{13}C nmr (deuteriochloroform): δ 20.68, 20.77, 20.80, 20.85, 30.9, 31.0, 31.7, 32.8, 60.0, 60.4, 62.13, 62.16, 69.5, 69.6, 69.9, 70.0, 70.27, 70.34, 71.01, 71.04, 71.79, 71.81, 98.5, 98.6, 98.9, 169.37, 169.40, 169.6, 169.86, 169.92, 170.6; ms: m/z (FAB) 421 (MH$^+$).

Anal. Calcd. for $C_{18}H_{28}O_{11}$: C, 51.43; H, 6.71. Found: C, 51.61; H, 6.65.

cis/trans-5-(2-Bromoethyl)-2-D-*ribo*-(1',2',3',4'-tetraacetoxybutyl)-1,3-dioxane (**10**) and (**11**).

To a cooled (0°) and stirred solution of the alcohol **9** (7.57 g, 18.01 mmoles) and carbon tetrabromide (8.96 g, 27.02 mmoles) in anhydrous *N*,*N*-dimethylformamide (60 ml) was added triphenylphosphine (7.08 g, 26.99 mmoles) in one portion, and the resulting yellow solution was stirred at 0° for 2 hours under a nitrogen atmosphere. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (2 x 200 ml). The combined extracts were dried (magnesium sulfate) and evaporated under reduced pressure to leave a yellow oil, which was purified by careful column chromatography on silica gel using ethyl acetate-hexane (1:2, v/v) as eluent to afford the isomerically pure *trans*-bromide **10** (2.35 g, 27%) as a solid, *cis*-isomer **11** (2.70 g, 31%) as a solid, and a mixture of isomers (3.39 g, 39%) as a colorless oil.

trans-Isomer (**10**); mp 75.6-77.1° (diethyl ether-hexane); $[\alpha]_D^{25}$ = +15.1 (c = 1.0, methanol); ir (potassium bromide): 1748 (C=O) cm^{-1}; ^1H nmr (benzene-d_6): δ 0.79 (td, J = 7.5 Hz, J = 6.9 Hz, 2H, CHCH_2CH_2Br), 1.71 (s, 3H, $COCH_3$), 1.72 (s, 3H, $COCH_3$), 1.74 (s, 3H, $COCH_3$), 1.75-1.84 (m, 1H, 5-H), 1.79 (s, 3H, $COCH_3$), 2.49 (t, J = 7.5 Hz, 1H, CH_2CH_2Br), 2.73 (t, J = 11.4 Hz, 1H, OCH_{ax}), 2.76 (t, J = 11.4 Hz, 1H, OCH_{ax}), 3.63 (ddd, J_{gem} = 11.4 Hz, $J_{eq,5}$ = 6.6 Hz, $J_{4,6}$ = 2.1 Hz, 1H, OCH_{eq}), 3.66 (ddd, J_{gem} = 11.4 Hz, $J_{eq,5}$ = 6.6 Hz, $J_{4,6}$ = 2.1 Hz, 1H, OCH_{eq}), 4.37 (dd, J_{AB} = 12.3 Hz, $J_{3',4'}$ = 7.5 Hz, 1H, 4'-H), 4.62 (d, $J_{2,1'}$ = 5.1 Hz, 1H, 2-H), 4.78 (dd, J_{AB} = 12.3 Hz, $J_{3',4'}$ = 5.4 Hz, 1H, 4'-H), 5.66 (dd, $J_{2,1'}$ = 5.1 Hz, $J_{1',2'}$ = 4.2 Hz, 1H, 1'-H), 5.92-5.98 (m, 2H, 2'-H and 3'-H); ^{13}C nmr (deuteriochloroform): δ 20.7 (2C), 20.8, 20.9, 29.2, 31.3, 33.1, 62.1, 69.6, 69.8, 70.9, 71.0 (2C), 98.6, 169.3, 169.5, 169.8, 170.6; ms: m/z (EI) 483 (M^+).

Anal. Calcd. for $C_{18}H_{27}BrO_{10}$: C, 44.73; H, 5.63. Found: C, 44.62; H, 5.80.

cis-Isomer (**11**); mp 73.1-74.4° (diethyl ether-hexane); $[\alpha]_D^{25}$ = +11.5 (c = 1.0, methanol); ir (potassium bromide): 1742 (C=O) cm^{-1}; ^1H nmr (benzene-d_6): δ 0.99-1.07 (m, 1H, 5-H), 1.68 (s, 3H, $COCH_3$), 1.69 (s, 3H, $COCH_3$), 1.73 (s, 3H, $COCH_3$), 1.79 (s, 3H, $COCH_3$), 1.95 (dt, J = 7.2 Hz, J = 6.6 Hz, 2H, CHCH_2CH_2Br), 3.04 (t, J = 6.6 Hz, 2H, CH_2CH_2Br), 3.27 (dd, J_{gem} = 12.0 Hz, J = 2.7 Hz, 1H, OCH), 3.32 (dd, J_{gem} = 12.0 Hz, J = 3.0 Hz, 1H, OCH), 3.44 (br d, J_{gem} = 12.0 Hz, OCH), 3.50 (br d, J_{gem} = 12.0 Hz, OCH), 4.33 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 7.5 Hz, 1H, 4'-H), 4.64 (d, $J_{2,1'}$ = 5.1 Hz, 1H, 2-H), 4.73 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 2.7 Hz, 1H, 4'-H), 5.57 (dd, $J_{2,1'}$ = 5.1 Hz, $J_{1',2'}$ = 4.5 Hz, 1H, 1'-H), 5.85-5.93 (m, 2H, 2'-H and 3'-H); ^{13}C nmr (deuteriochloroform): δ 20.7 (2C), 20.80, 20.84, 31.8, 32.1, 32.4, 62.2, 69.4, 69.48, 69.49, 69.9, 71.1, 99.1, 169.4, 169.5, 169.8, 170.6; ms: m/z (EI) 483 (M^+).

Anal. Calcd. for $C_{18}H_{27}BrO_{10}$: C, 44.73; H, 5.63. Found: C, 44.61; H, 5.77.

General Procedure for the Synthesis of 2-Amino-6-chloropurine Derivatives (**12-15**).

A suspension of 2-amino-6-chloropurine (0.66 g, 3.89 mmoles), bromide **10** or **11** (1.97 g, 4.08 mmoles), and anhydrous potassium carbonate (0.80 g, 5.79 mmoles) in anhydrous *N*,*N*-dimethylformamide (20 ml) was stirred at room temperature for 24 hours under a nitrogen atmosphere. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting residue was partitioned between water (50 ml) and ethyl acetate (50 ml). The aqueous layer was extracted with ethyl acetate (2 x 50 ml), and the combined extracts were dried (magnesium sulfate) and evaporated under reduced pressure to leave a yellow solid, which was purified by column chromatography on silica gel using methanol-chloroform (5:95, v/v) as eluent to afford the desired N-9 product **12** or **14** along with N-7 isomer **13** or **15**.

trans-5-[2-(2-Amino-6-chloropurin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetraacetoxybutyl)-1,3-dioxane (**12**).

This compound was obtained from **10** in 81% yield as a white foam; $[\alpha]_D^{25}$ = +18.7 (c = 5.0, methanol); ir (neat): 3474 and 3373 (NH_2), 1754 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.61 (td, J = 7.5 Hz, J = 6.6 Hz, 2H, CHCH_2CH_2N), 2.04-2.14 (m, 1H, 5-H), 2.04 (s, 3H, $COCH_3$), 2.07 (s, 6H, 2 x $COCH_3$), 2.12 (s, 3H, $COCH_3$), 3.36 (t, J = 11.1 Hz, 1H, OCH_{ax}), 3.39 (t, J = 11.1 Hz, 1H, OCH_{ax}), 4.06 (t, J = 7.5 Hz, 2H, CH_2CH_2N), 4.08-4.22 (m, 3H, 4'-H and 2 x OCH_{eq}), 4.42 (dd, J_{AB} = 12.3 Hz, $J_{3',4'}$ = 2.1 Hz, 1H, 4'-H), 4.63 (d, $J_{2,1'}$ = 4.8 Hz, 1H, 2-H), 5.16 (dd, $J_{2,1'}$ = 4.8 Hz, $J_{1',2'}$ = 3.9 Hz, 1H, 1'-H), 5.24 (br s, 2H, NH_2), 5.43-5.48 (m, 2H, 2'-H and 3'-H), 7.74 (s, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 20.7 (2C), 20.8, 20.9, 28.5, 31.8, 40.9, 62.1, 69.6, 69.8, 70.9, 71.1 (2C), 98.6, 125.2, 141.7, 151.4, 153.7, 159.1, 169.3, 169.5, 169.9, 170.6; ms: m/z (EI) 571 (M^+).

Anal. Calcd. for $C_{23}H_{30}ClN_5O_{10}$: C, 48.30; H, 5.29; N, 12.24. Found: C, 48.13; H, 5.44; N, 12.05.

trans-5-[2-(2-Amino-6-chloropurin-7-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetraacetoxybutyl)-1,3-dioxane (**13**).

This compound was obtained from **10** in 12% yield as a white solid; mp 184.5–187.0° dec (ethyl acetate); $[\alpha]_D^{25}$ = +20.8 (c = 1.0, methanol); ir (potassium bromide): 3407 and 3321 (NH_2), 1746 and 1736 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.53 (td, J = 6.6 Hz, J = 6.0 Hz, 2H, CHCH_2CH_2N), 1.78-1.95 (m, 1H, 5-H), 1.98 (s, 3H, $COCH_3$), 2.017 (s, 3H, $COCH_3$), 2.021 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 3.38 (t, J = 11.1 Hz, 1H, OCH_{ax}), 3.40 (t, J = 11.1 Hz, 1H, OCH_{ax}), 4.01-4.13 (m, 3H, 4'-H and 2 x OCH_{eq}), 4.28 (t, J = 6.6 Hz, 2H, CH_2CH_2N), 4.31 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 2.4 Hz, 1H, 4'-H), 4.64 (d, $J_{2,1'}$ = 5.1 Hz, 1H, 2-H), 5.01 (dd, $J_{2,1'}$ = 5.1 Hz, $J_{1',2'}$ = 3.3 Hz, 1H, 1'-H), 5.25-5.27 (m, 2H, 2'-H and 3'-H), 6.62 (br s, 2H, NH_2), 8.43 (s, 1H, 8-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.38, 20.41, 20.5, 20.6, 29.2, 31.5, 43.5, 61.4, 68.8, 69.0, 70.1, 70.3, 70.4, 97.7, 114.6, 142.1, 149.3, 159.9, 164.3, 169.08, 169.11, 169.3, 170.0; ms: m/z (EI) 571 (M^+).

Anal. Calcd. for $C_{23}H_{30}ClN_5O_{10}$: C, 48.30; H, 5.29; N, 12.24. Found: C, 48.18; H, 5.42; N, 12.15.

cis-5-[2-(2-Amino-6-chloropurin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetraacetoxybutyl)-1,3-dioxane (**14**).

This compound was obtained from **11** in 79% yield as a white foam; $[\alpha]_D^{25}$ = +11.4 (c = 5.0, methanol); ir (neat): 3468, 3369 and 3334 (NH_2), 1756 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.36-1.44 (m, 1H, 5-H), 2.04 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.31 (q, J = 7.2 Hz, 2H, CHCH_2CH_2N), 3.88 (dd, J = 12.0 Hz, J = 5.4 Hz, 1H, OCH_{eq}), 3.89 (dd, J = 12.0 Hz, J = 5.4 Hz, 1H, OCH_{eq}), 4.03 (dd, J = 12.3 Hz, J = 12.0 Hz, 2H, 2 x OCH_{ax}), 4.14 (dd, J_{AB} = 12.3 Hz, $J_{3',4'}$ = 6.9 Hz, 1H, 4'-H), 4.21 (t, J = 7.2 Hz, 2H,

CH_2CH_2N), 4.46 (dd, J_{AB} = 12.3 Hz, $J_{3',4'}$ = 2.1 Hz, 1H, 4'-H), 4.72 (d, $J_{2,1'}$ = 4.5 Hz, 1H, 2-H), 5.17 (dd, $J_{2,1'}$ = 4.5 Hz, $J_{1',2'}$ = 3.6, Hz, 1H, 1'-H), 5.25 (br s, 2H, NH_2), 5.49-5.54 (m, 2H, 2'-H and 3'-H), 7.87 (s, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 20.7 (2C), 20.79, 20.83, 29.6, 31.4, 41.6, 62.2, 69.5, 69.59, 69.63, 70.0, 71.1, 99.1, 125.2, 142.2, 151.3, 153.9, 159.0, 169.4, 169.5, 169.9, 170.6; ms: m/z (EI) 571 (M^+).

Anal. Calcd. for $C_{23}H_{30}ClN_5O_{10}$: C, 48.30; H, 5.29; N, 12.24. Found: C, 48.14; H, 5.41; N, 12.12.

c*is*-5-[2-(2-Amino-6-chloropurin-7-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetraacetoxybutyl)-1,3- dioxane (**15**).

This compound was obtained from **11** in 15% yield as a white solid; mp 166.0-168.5° dec (ethyl acetate); $[\alpha]_D^{25}$ = +11.2 (c = 1.0, methanol); ir (potassium bromide): 3466 and 3345 (NH_2), 1749 and 1738 (C=O) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.36-1.45 (m, 1H, 5-H), 1.98 (s, 6H, 2 x $COCH_3$), 2.02 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.12 (td, J = 6.9 Hz, J = 6.6 Hz, 2H, $CHCH_2CH_2N$), 3.85-3.95 (m, 4H, 2 x OCH_{eq} and 2 x OCH_{ax}), 4.10 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 6.9 Hz, 1H, 4'-H), 4.32 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 2.1 Hz, 1H, 4'-H), 4.39 (t, J = 6.9 Hz, 2H, CH_2CH_2N), 4.72 (d, $J_{2,1'}$ = 4.8 Hz, 1H, 2-H), 5.01 (dd, $J_{2,1'}$ = 4.8 Hz, $J_{1',2'}$ = 4.5 Hz, 1H, 1'-H), 5.27-5.33 (m, 2H, 2'-H and 3'-H), 6.61 (br s, 2H, NH_2), 8.41 (s, 1H, 8-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.37, 20.42, 20.43, 20.5, 30.7, 30.9, 44.4, 61.4, 68.7, 69.0, 69.2, 69.3, 70.5, 98.1, 114.8, 142.2, 149.2, 159.9, 164.2, 169.1 (2C), 169.3, 170.0; ms: m/z (EI) 571 (M^+).

Anal. Calcd. for $C_{23}H_{30}ClN_5O_{10}$: C, 48.30; H, 5.29; N, 12.24. Found: C, 48.22; H, 5.39; N, 12.15.

General Procedure for the Synthesis of Guanine Derivatives (**2**) and (**3**).

A suspension of compound **12** or **14** (0.80 g, 1.40 mmoles) and anhydrous potassium carbonate (0.58 g, 4.20 mmoles) in methanol (7 ml) was stirred at room temperature for 2 hours and then filtered. The filtrate was evaporated under reduced pressure, and the resulting residue was dissolved in 0.5 *N* aqueous sodium hydroxide (6 ml). The reaction mixture was heated under reflux for 16 hours, after which it was cooled and neutralized with acetic acid. The mixture was purified by column chromatography on C_{18} reverse-phase silica gel using water followed by methanol-water (10:90, v/v) as eluent to afford the guanine product **2** or **3**.

trans-5-[2-(Guanin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetrahydroxybutyl)-1,3-dioxane (**2**).

This compound was obtained from **12** in 69% yield as a white solid; mp 227.0-228.5° dec (water-ethanol); $[\alpha]_D^{25}$ = -0.5 (c = 1.0, methanol); ir (potassium bromide): 3425, 3407 and 3335 (NH and OH), 1684 (C=O) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.62 (dt, J = 6.9 Hz, J = 6.6 Hz, 2H, $CHCH_2CH_2N$), 1.95-2.15 (m, 1H, 5-H), 3.54 (t, J = 11.4 Hz, 1H, OCH_{ax}), 3.56 (t, J = 11.4 Hz, 1H, OCH_{ax}), 3.65 (dd, J_{AB} = 11.7 Hz, $J_{3',4'}$ = 6.9 Hz, 2H, 4'-H), 3.71-3.83 (m, 2H, 1'-H and 2'-H), 3.86-3.91 (m, 1H, 3'-H), 4.05 (t, J = 6.9 Hz, 2H, CH_2CH_2N), 4.08-4.18 (m, 2H, 2 x OCH_{eq}), 4.79 (d, $J_{2,1'}$ = 2.7 Hz, 1H, 2-H), 7.80 (s, 1H, 8-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 27.8, 31.7, 40.6, 62.7, 70.4, 70.6, 71.4, 72.2, 72.8, 100.7, 116.5, 137.3, 151.1, 153.5, 156.8; ms: m/z (FAB) 386 (MH^+).

Anal. Calcd. for $C_{15}H_{23}N_5O_7$: C, 46.75; H, 6.02; N, 18.17. Found: C, 46.67; H, 6.13; N, 18.08.

cis-5-[2-(Guanin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetrahydroxybutyl)-1,3-dioxane (**3**).

This compound was obtained from **14** in 71% yield as a white solid; mp 229.0-230.0° dec (water-ethanol); $[\alpha]_D^{25}$ = -1.7 (c = 1.0, methanol); ir (potassium bromide): 3413 and 3334 (NH and OH), 1684 (C=O) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.48 (br t, J = 6.9 Hz, 1H, 5-H), 2.22 (dt, J = 7.2 Hz, J = 6.9 Hz, 2H, $CHCH_2CH_2N$), 3.65 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 6.9 Hz, 1H, 4'-H), 3.71-3.82 (m, 3H, 1'-H, 2'-H and 4'-H), 3.89-3.92 (m, 1H, 3'-H), 3.98-4.07 (m, 4H, 2 x OCH_{ax} and 2 x OCH_{eq}), 4.16 (t, J = 7.5 Hz, 2H, CH_2CH_2N), 4.87 (d, $J_{2,1'}$ = 2.7 Hz, 1H, 2-H), 7.81 (s, 1H, 8-H); ^{13}C nmr δ (dimethyl sulfoxide-d_6): 29.7, 31.0, 40.7, 62.7, 68.9, 69.1, 71.3, 72.3, 73.0, 101.2, 116.5, 137.4, 151.2, 153.5, 156.8; ms: m/z (FAB) 386 (MH^+).

Anal. Calcd. for $C_{15}H_{23}N_5O_7$: C, 46.75; H, 6.02; N, 18.17. Found: C, 46.83; H, 5.95; N, 18.23.

General Procedure for the Synthesis of 2-Aminopurine Derivatives (**4**) and (**5**).

A solution of compound **12** or **14** (0.80 g, 1.40 mmoles) and triethylamine (0.59 ml, 4.20 mmoles) in methanol (7 ml) was vigorously agitated in the presence of 10% palladium on carbon (80 mg) at room temperature for 16 hours under a hydrogen atmosphere (1 atm). Anhydrous potassium carbonate (0.39 g, 2.82 mmoles) was added to the reaction mixture and then it was stirred at room temperature for an additional 24 hours. The reaction mixture was filtered, and the filtrate was neutralized with acetic acid. The reaction mixture was evaporated under reduced pressure, and the resulting residue was purified by column chromatography on C_{18} reverse-phase silica gel using water followed by methanol-water (30:70, v/v) as eluent to afford the 2-aminopurine product **4** or **5**.

trans-5-[2-(2-Aminopurin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetrahydroxybutyl)-1,3-dioxane (**4**).

This compound was obtained from **12** in 93% yield as a white solid; mp 157.0-158.6° (methanol-ethanol); $[\alpha]_D^{25}$ = +0.5 (c = 2.0, methanol); ir (potassium bromide): 3346 and 3220 (NH and OH), 1616 (C=N) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.65 (dt, J = 6.9 Hz, J = 6.6 Hz, 2H, $CHCH_2CH_2N$), 2.01-2.16 (m, 1H, 5-H), 3.60 (t, J = 11.4 Hz, 1H, OCH_{ax}), 3.61 (t, J = 11.4 Hz, 1H, OCH_{ax}), 3.72 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 7.2 Hz, 2H, 4'-H), 3.68-3.89 (m, 2H, 1'-H and 2'-H), 3.92-3.99 (m, 1H, 3'-H), 4.11 (t, J = 6.9 Hz, 2H, CH_2CH_2N), 4.14-4.26 (m, 2H, 2 x OCH_{eq}), 4.85 (d, $J_{2,1'}$ = 2.7 Hz, 1H, 2-H), 8.08 (s, 1H, 8-H), 8.50 (s, 1H, 6-H); ^{13}C nmr (deuterium oxide): δ 30.0, 34.3, 43.3, 65.1, 73.6, 73.7, 74.2, 74.4, 74.8, 102.9, 129.3, 146.9, 151.5, 155.2, 162.2; ms: m/z (FAB) 370 (MH^+).

Anal. Calcd. for $C_{15}H_{23}N_5O_6$: C, 48.78; H, 6.28; N, 18.96. Found: C, 48.97; H, 6.19; N, 18.84.

cis-5-[2-(2-Aminopurin-9-yl)ethyl]-2-D-*ribo*-(1',2',3',4'-tetrahydroxybutyl)-1,3-dioxane (**5**).

This compound was obtained from **14** in 95% yield as a white solid; mp 151.0-152.2° (methanol-ethanol); $[\alpha]_D^{25}$ = -1.8 (c = 2.0, methanol); ir (potassium bromide): 3385 and 3337 (NH and OH), 1648 and 1614 (C=N) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 1.51-1.60 (m, 1H, 5-H), 2.27 (td, J = 7.2 Hz, J = 6.6 Hz, 2H, $CHCH_2CH_2N$), 3.74 (dd, J_{AB} = 12.0 Hz, $J_{3',4'}$ = 6.9 Hz, 1H, 4'-H), 3.80-3.91 (m, 3H, 1'-H, 2'-H and 4'-H), 3.94-4.02 (m, 1H, 3'-H), 4.04-4.15 (m, 4H, 2 x OCH_{ax} and 2 x OCH_{eq}), 4.22 (t, J =

7.5 Hz, 2H, CH_2CH_2N), 4.95 (d, $J_{2,1'}$ = 2.7 Hz, 1H, 2-H), 8.10 (s, 1H, 8-H), 8.49 (s, 1H, 6-H); ^{13}C nmr (deuterium oxide): δ 31.7, 33.9, 44.1, 65.0, 72.3, 72.5, 74.1, 74.7, 74.9, 103.3, 129.3, 147.0, 151.3, 155.2, 162.2; ms: m/z (FAB) 370 (MH^+).

Anal. Calcd. for $C_{15}H_{23}N_5O_6$: C, 48.78; H, 6.28; N, 18.96. Found: C, 48.67; H, 6.34; N, 18.78.

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