Synthesis of 9-[2-(2-Hydroxymethyl-2-methyl-, -(2-Acetoxymethyl-2-methyl-, -(2,2-Di(hydroxymethyl)-, and -(2,2-Di(acetoxymethyl)-1,3-dioxan-5-yl)ethyl] Derivatives of Guanine and 2-Aminopurine

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Synthesis of 9-[2-(2-hydroxymethyl-2-methyl-, -(2-acetoxymethyl-2-methyl-, -(2,2-di(hydroxymethyl)-, and -(2,2-di(acetoxymethyl)-1,3-dioxan-5-yl)ethyl] derivatives of guanine and 2-aminopurine, **2-9**, has been accomplished in seven to eight step sequences from readily available 1-(*tert*-butyldiphenylsilyloxy)-acetone, 1,3-di(*tert*-butyldiphenylsilyloxy)acetone, and the diol **10**. Formation of cyclic ketals **11** and **12** was carried out successfully under an acidic condition using a catalytic amount of methanesulfonic acid along with excess anhydrous copper(II) sulfate in toluene. Subsequent reactions of desilylation, acetylation, hydrogenolysis, and bromination afforded the key intermediates **19** and **20**, which were coupled with 2-amino-6-chloropurine to produce the purine compounds **21** and **22** in good yields. Guanine derivatives **2-5** were obtained from **21** and **22** by hydrolysis and acetylation, while the dechlorination and hydrolysis of **21** and **22** yielded the 2-aminopurine compounds **6-9**.

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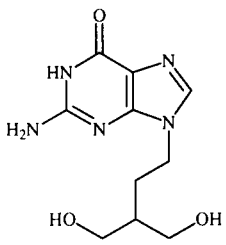
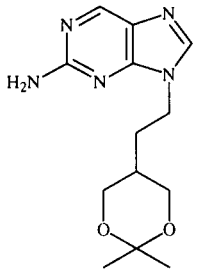
An acyclonucleoside 9-(4-hydroxy-3-hydroxymethyl-but-1-yl)guanine (penciclovir) is a potent and selective inhibitor of members of the herpesvirus family including herpes simplex virus type 1 and type 2, varicella-zoster virus, and Epstein-Barr virus [1]. The advantage of penciclovir over 9-(2-hydroxyethoxymethyl)guanine (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,2]. However, like other acycloguanosine analogues such as acyclovir [3] and 9-(1,3-dihydroxy-2-propoxymethyl)guanine (ganciclovir) [4], penciclovir was poorly absorbed when given orally to rodents [5]. Therefore, the search for a prodrug that is orally well absorbed and then readily converted to penciclovir is of high priority [5a,6].



penciclovir



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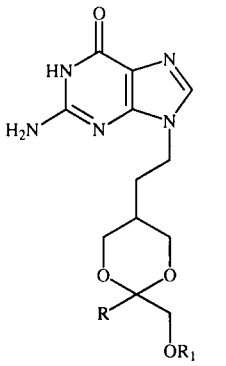
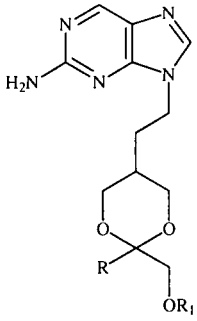


2: R = Me, R_1 = H
3: R = CH_2OH, R_1 = H
4: R = Me, R_1 = Ac
5: R = CH_2OAc, R_1 = Ac



6: R = Me, R_1 = H
7: R = CH_2OH, R_1 = H
8: R = Me, R_1 = Ac
9: R = CH_2OAc, R_1 = Ac

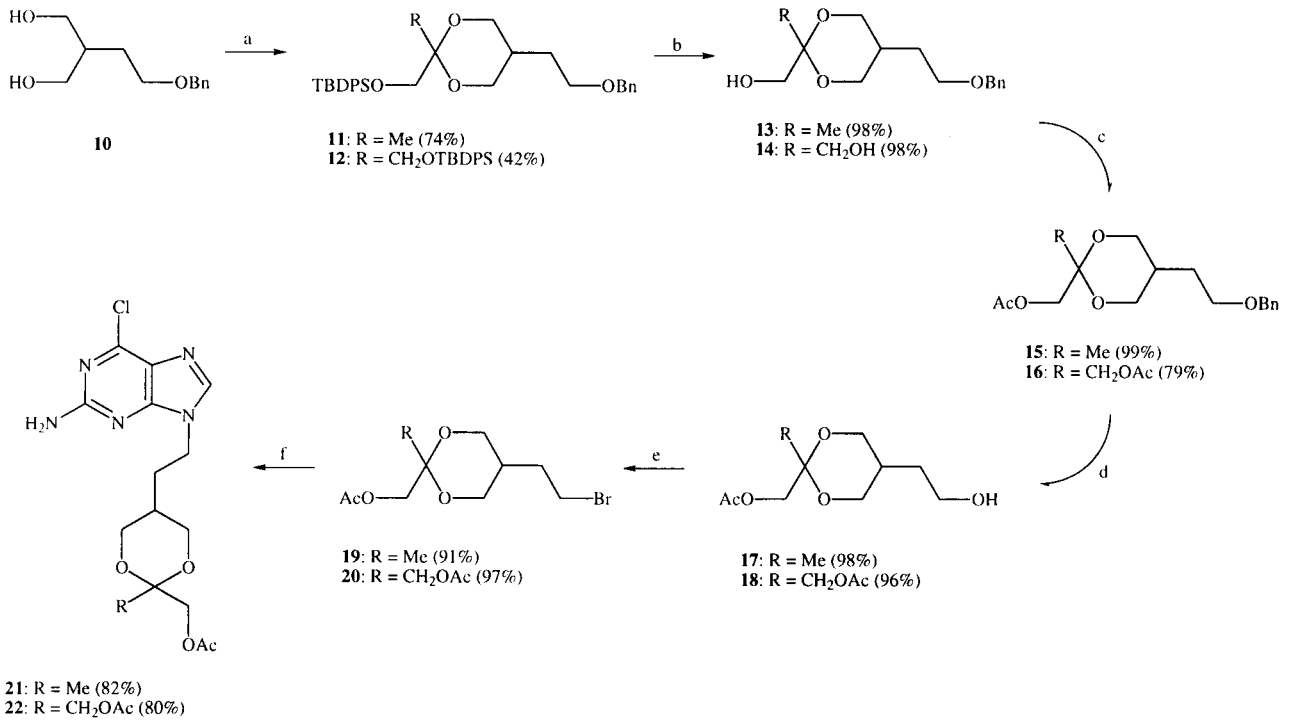
Harnden *et al.* reported that the isopropylidene derivative of 6-deoxypenciclovir, **1**, was absorbed much more efficiently and provided maximum concentration of penciclovir in the blood that was 7 times higher than that obtained after administration of the equivalent oral dose of penciclovir to mice [5a]. On the basis of this finding, it was our interest to find out whether the introduction of one or two hydroxyl groups to the isopropylidene moiety could increase their oral penciclovir bioavailability. Therefore, in this report we have synthesized the 1-hydroxy or 1,3-dihydroxyacetone derivatives of penciclovir and 6-deoxypenciclovir, **2-9**, to evaluate their potential as prodrugs of penciclovir.

Two requisite bromides, **19** and **20**, were prepared by reacting 1-(*tert*-butyldiphenylsilyloxy)acetone [7] and 1,3-di(*tert*-butyldiphenylsilyloxy)acetone [8] with the known 1,3-diol **10** [9] as shown in Scheme 1. By adopting the identical reaction conditions developed by us [7], the formation of cyclic ketal **11** from 1-(*tert*-butyldiphenylsilyloxy)acetone and the diol **10** proceeded smoothly in 74% yield using a catalytic amount of methanesulfonic acid and excess amounts of anhydrous copper(II) sulfate (3.0 equiva-

lents) in anhydrous toluene at 45°. As was expected, compound **11** was formed as a 1:1 mixture of *cis* and *trans* isomers by ^{1}H nmr. Since they were not separable by chromatographic purification on silica gel, the ketal **11** was subjected to further transformations as a mixture of isomers. On the other hand, a similar reaction with 1,3-di-(*tert*-butyldiphenylsilyloxy)acetone under the identical conditions was rather sluggish and complex probably due to the steric bulkiness of the two *tert*-butyldiphenylsilyl (TBDPS) groups, producing the desired ketal **12** in a somewhat low yield of 42%. When 1,3-diacetoxyacetone or 1,3-dichloroacetone were used in place of 1,3-di(*tert*-butyldiphenylsilyloxy)acetone under acidic conditions using methanesulfonic acid, camphorsulfonic acid or boron trifluoride diethyl etherate, the reactions were also rather complicated, and the only identifiable compounds were the mono- or diacetate of diol **10** which was produced *via* intermolecular acetyl transfer between the diol **10** and 1,3-diacetoxyacetone.

It was first planned that the TBDPS group could be carried on to the late stage of the synthesis since it is known as a pretty robust protecting group under various reaction conditions. To our surprise, it was observed that hydrogenolysis of the benzyl moiety in the ketals **11** and **12** under Parr condition (10% palladium on carbon, 50 psi of hydrogen, tetrahydrofuran) was extremely slow and the TBDPS groups were also cleaved off. Therefore, the silyl protecting groups of compounds **11** and **12** were removed quantitatively by using tetrabutylammonium fluoride in tetrahydrofuran, and the resulting alcohols **13** and **14** were converted to the corresponding acetates **15** and **16** in 99% and 79% yields, respectively, under a typical acetylation condition (acetic anhydride/4-dimethylaminopyridine). In contrast with compounds **11** and **12**, hydrogenolysis of the acetates **15** and **16** proceeded smoothly even under rather mild reaction condition (10% palladium on carbon, 1 atmosphere of hydrogen, room temperature, tetrahydrofuran) to afford the alcohols **17** and **18** in high yields of 96-98%.

Scheme 1

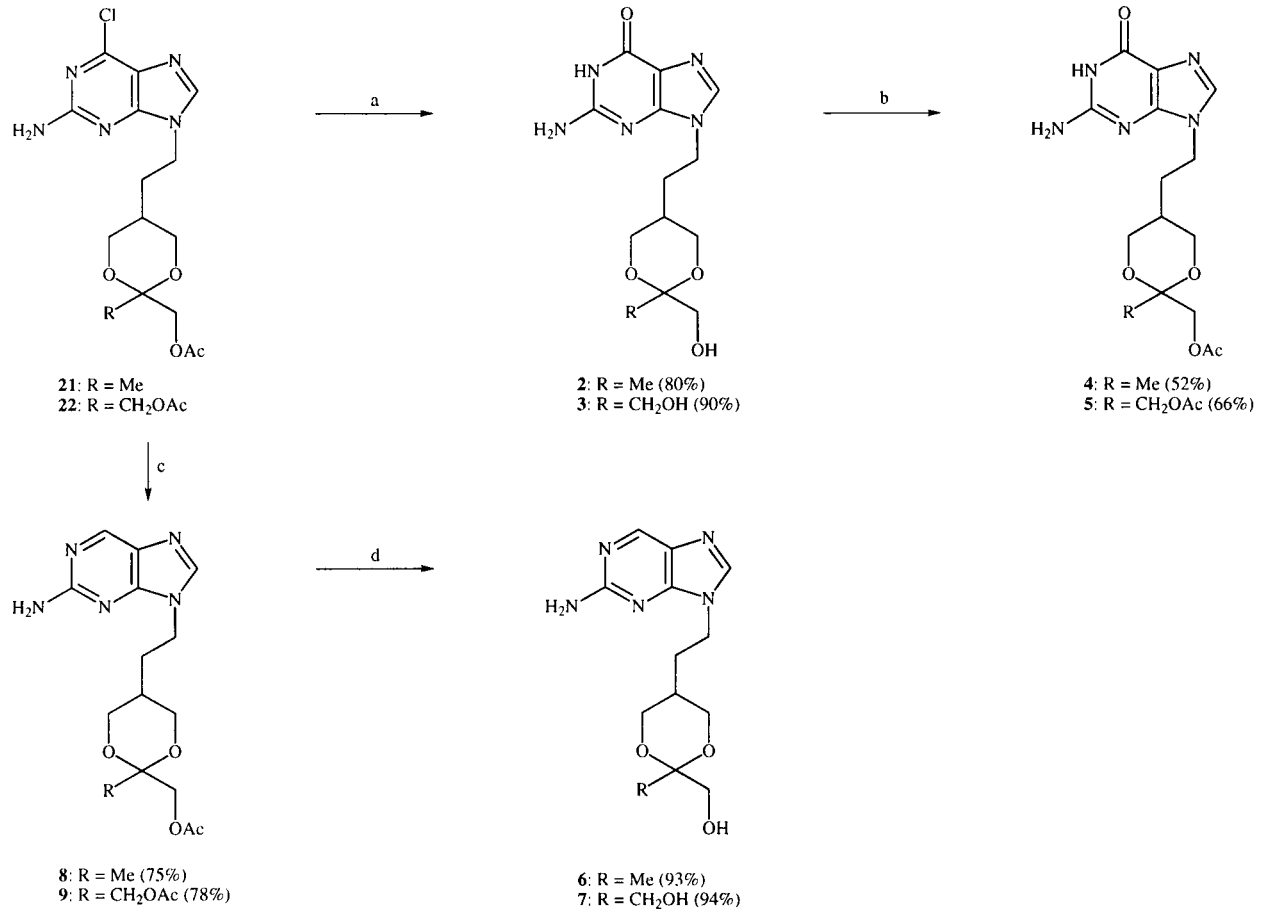


[a] 1-(*tert*-Butyldiphenylsilyloxy)acetone (for **11**) or 1,3-di(*tert*-butyldiphenylsilyloxy)acetone (for **12**) (1.0 equivalent), anhydrous $CuSO_4$ (3.0 equivalents), $MeSO_3H$ (catalytic), anhydrous toluene, 45°, 4 days, N_2 atmosphere; [b] Tetrabutylammonium fluoride (1.0 *M* solution in THF, 1.5 equivalents), THF, room temperature, 16 hours; [c] Ac_2O, (3.0 equivalents), 4-DMAP (0.1 equivalent), anhydrous CH_2Cl_2, 0° to room temperature, 1 hour, N_2 atmosphere; [d] H_2 (1 atmosphere), 10% Pd/C (10 wt%), THF, room tmeperature, 3 hours; [e] (i) CBr_4 (1.5 equivalents), PPh_3 (1.5 equivalents), anhydrous DMF, 0°, 2 hours, N_2 atmosphere, (ii) saturated $NaHCO_3$ solution, H_2O; [f] 2-Amino-6-chloropurine (1.0 equivalent), anhydrous K_2CO_3 (1.5 equivalents), anhydrous DMF, room temperature, 18 hours, N_2 atmosphere.

Treatment of compounds **17** and **18** with carbon tetrabromide and triphenylphosphine in *N,N*-dimethylformamide at 0° produced the bromides **19** and **20** in 91% and 97% yields, respectively. Alkylations of 2-amino-6-chloropurine with the bromides **19** and **20** were performed using anhydrous potassium carbonate in *N,N*-dimethylformamide at room temperature [1a], and the desired N-9 products **21** and **22** were isolated in 80-82% yields after column chromatographic purification on silica gel. It should be pointed out again that the 2-amino-6-chloropurine derivative **21** was formed as a mixture of *cis* and *trans* isomers with a ratio of 1:1 by ^{1}H nmr. Since several attempts to separate two stereoisomers of **21** either by HPLC or repeated recrystallization have failed, compound **21** was transformed into the target compounds as a mixture of isomers.

Transformations of the 2-amino-6-chloropurine derivatives **21** and **22** to the target compounds **2-9** were detailed as shown in Scheme 2. In the first place, the direct conversions of **21** and **22** to the guanine derivatives **2** and **3** were attempted by using sodium hydroxide aqueous solution under reflux, but the reaction was rather sluggish probably due to their low solubility in aqueous medium. Therefore, the acetyl groups of **21** and **22** were first removed by using potassium carbonate in methanol at room temperature, and the resulting intermediates, without isolation, were further treated with 0.5 *N* sodium hydroxide aqueous solution under reflux to afford the desired guanine products **2** and **3** in 80% and 90% yields, respectively, after chromatographic purification on C_{18} reverse-phase silica gel using methanol/water mixture as eluent. Acetylation of **2** and **3** with acetic anhydride in

Scheme 2



21: R = Me
22: R = CH_2OAc

2: R = Me (80%)
3: R = CH_2OH (90%)

4: R = Me (52%)
5: R = CH_2OAc (66%)

8: R = Me (75%)
9: R = CH_2OAc (78%)

6: R = Me (93%)
7: R = CH_2OH (94%)

[a] (i) Anhydrous K_2CO_3 (1.0 equivalent), MeOH, room temperature, 4 hours, (ii) 0.5 *N* NaOH, reflux, 21 hours; [b] Ac_2O (2.0 equivalents), 4-DMAP (0.1 equivalent), DMF, 0° to room temperature 22 hours; [c] H_2 (1 atmosphere), 10% Pd/C (10 wt%), Et_3N (3 equivalents), MeOH, room temperature, 4 hours; [d] Anhydrous K_2CO_3 (1.0 equivalent), MeOH, room temperature, 2 hours.

N,N-dimethylformamide in the presence of a catalytic amount of 4-dimethylaminopyridine provided two other guanine derivatives **4** and **5** in 52-66% yields. Preparations of purine derivatives **6-9** from compounds **21** and **22** were performed smoothly by dechlorination and hydrolysis reactions. Removal of the chloro atom of **21** and **22** was carried out in methanol at room temperature under catalytic hydrogenolysis conditions (10% palladium on carbon, 1 atmosphere of hydrogen) in the presence of triethylamine as a hydrochloric acid scavenger to give the desired 2-aminopurine compounds **8** and **9** in 75-78% yields. Subsequent treatment of the acetates **8** and **9** with potassium carbonate in methanol at room temperature produced the hydroxy compounds **6** and **7** in 93-94% yields after chromatographic purification on C_{18} reverse-phase silica gel.

It was rather disappointing that the mean urinary recovery of penciclovir over a 24 hour period after a single oral administration (0.2 mmole/kg) of the compounds **2-9** to mice (3-6%) was only comparable to that of penciclovir (3%). These results indicated that the introduction of one or two hydroxyl groups to the isopropylidene moiety was not very effective at increasing the oral penciclovir bioavailability of the compounds **2-9**.

In conclusion, the present work described the efficient synthesis of guanine and 2-aminopurine derivatives, **2-9**, as potential prodrugs of penciclovir, which has been accomplished in seven to eight steps from readily available 1-(*tert*-butyldiphenylsilyloxy)acetone, 1,3-di(*tert*-butyldiphenylsilyloxy)acetone, and the diol **10**.

EXPERIMENTAL

Melting points were determined on either a Thomas-Hoover or a Mettler FP62 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. The ^{1}H nmr spectra were determined on a Varian Unity 300 spectrometer. Spectra were recorded in deuteriochloroform or dimethyl sulfoxide-d_6, and chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Electron-impact mass spectra (EI-MS) and fast-atom bombardment mass spectra (FAB-MS) were obtained on a VG Quattro mass spectrometer. Analytical tlc 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 analyzer.

General Procedure for the Formation of 1,3-Dioxanes **11** and **12**.

A suspension of 1-(*tert*-butyldiphenylsilyloxy)acetone or 1,3-di-(*tert*-butyldiphenylsilyloxy)acetone (35.05 mmoles), diol **10** (7.37 g, 35.05 mmoles), anhydrous copper(II) sulfate (16.78 g, 105.15 mmoles), and a catalytic amount of methanesulfonic acid (5 drops) in anhydrous toluene (100 ml) was stirred at 45° for 4 days under a nitrogen atmosphere. The resulting mixture was cooled to room temperature, and anhydrous potassium carbonate (0.49 g, 3.52 mmoles) was added to the mixture. The reaction mixture was filtered through a Celite pad, and the filtered solids were washed well with dichloromethane. The combined filtrates were evaporated *in vacuo* to leave a yellowish oil, which was purified by column chromatography on silica gel (gradient, 5:95 to 1:4 ether/hexane, v/v) to afford the 1,3-dioxane **11** or **12**.

5-(2-Benzyloxyethyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-2-methyl-1,3-dioxane (**11**).

This compound was obtained from 1-(*tert*-butyldiphenylsilyloxy)-acetone in 74% yield as a colorless syrup; ir (neat): 2930, 1428, 695 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.07 (s, 9H, $C(CH_3)_3$), 1.40-1.46 (m, 1H, $CHCH_2CH_2O$), 1.44 (s, 1.5H, CH_3), 1.46 (s, 1.5H, CH_3), 1.50-1.57 (m, 1H, $CHCH_2CH_2O$), 1.88-2.00 (m, 1H, CH), 3.35-3.44 (m, 3H, OCH_{ax} and CH_2CH_2O), 3.58 (dd, J = 12.0 Hz, J = 7.8 Hz, 1H, OCH_{ax}), 3.64 (s, 1H, CH_2OSi), 3.74 (s, 1H, CH_2OSi), 3.83 (dd, J = 12.0 Hz, J = 4.5 Hz, 2H, 2 x OCH_{eq}), 4.44 (s, 1H, OCH_2Ph), 4.47 (s, 1H, OCH_2Ph), 7.24-7.42 (m, 11H, ArH), 7.67-7.71 (m, 4H, ArH); ms: m/z (FAB) 505 (MH^+).

Anal. Calcd. for $C_{31}H_{40}O_4Si$: C, 73.77; H, 7.99. Found: C, 73.89; H, 7.90.

5-(2-Benzyloxyethyl)-2,2-di(*tert*-butyldiphenylsilyloxymethyl)-1,3-dioxane (**12**).

This compound was obtained from 1,3-di(*tert*-butyldiphenylsilyloxy)acetone in 42% yield as a colorless syrup; ir (neat): 2931, 1428, 703 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.06 (s, 18H, 2 x $C(CH_3)_3$), 1.36-1.43 (m, 2H, $CHCH_2CH_2O$), 1.88-1.92 (m, 1H, CH), 3.29 (dd, J = 11.7 Hz, J = 7.5 Hz, 2H, 2 x OCH_{ax}), 3.37 (t, J = 6.3 Hz, 2H, CH_2CH_2O), 3.71 (dd, J = 11.7 Hz, J = 4.8 Hz, 2H, 2 x OCH_{eq}), 3.85 (s, 2H, CH_2OSi), 3.95 (s, 2H, CH_2OSi), 4.43 (s, 2H, OCH_2Ph), 7.20-7.38 (m, 17H, ArH), 7.71-7.74 (m, 8H, ArH); ms: m/z (FAB) 759 (MH^+).

Anal. Calcd. for $C_{47}H_{58}O_5Si_2$: C, 74.36; H, 7.70. Found: C, 74.15; H, 7.81.

General Procedure for the Preparation of Alcohols **13** and **14** *via* Desilylation.

To a solution of TBDPS ether **11** or **12** (20.23 mmoles) in tetrahydrofuran (70 ml) at room temperature was added tetrabutylammonium fluoride (1.0 *M* in tetrahydrofuran, 30.4 ml, 30.35 mmoles), and the reaction mixture was stirred at ambient temperature for 16 hours. The resulting mixture was evaporated *in vacuo* to leave a yellowish oil, which was purified by column chromatography on silica gel (gradient, 5:95 to 1:4 ether/hexane for **13** or 5:95 methanol/chloroform for **14**, v/v) to afford the alcohol **13** or **14**.

5-(2-Benzyloxyethyl)-2-(hydroxymethyl)-2-methyl-1,3-dioxane (**13**).

This compound was obtained from **11** in 98% yield as a colorless oil; ir (neat): 3456, 2862, 1096 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 1.5H, CH_3), 1.41 (s, 1.5H, CH_3), 1.41-1.47 (m, 1H, $CHCH_2CH_2O$), 1.73-1.79 (m, 1H, $CHCH_2CH_2O$), 1.83-1.92 (m, 1.5H, 0.5 x CH and OH), 2.03-2.17 (m, 0.5H, CH), 3.48 (t, J = 6.0 Hz, 1H, CH_2CH_2O), 3.49 (s, 1H, CH_2OH), 3.53 (t, J = 6.0 Hz, 1H, CH_2CH_2O), 3.57 (s, 1H, CH_2OH), 3.60-3.68 (m, 2H, 2 x OCH_{ax}), 3.90 (dd, J = 12.0 Hz, J = 5.1 Hz, 1H, OCH_{eq}), 4.04 (dd, J = 12.0 Hz, J = 3.6 Hz, 1H, OCH_{eq}), 4.48 (s, 1H,

OCH_2Ph), 4.49 (s, 1H, OCH_2Ph), 7.26-7.36 (m, 5H, ArH); ms: m/z (FAB) 267 (MH^+).

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.61; H, 8.42.

5-(2-Benzyloxyethyl)-2,2-di(hydroxymethyl)-1,3-dioxane (**14**).

This compound was obtained from **12** in 98% yield as a needle, mp 73.8-75.2° (ethyl acetate-hexane); ir (potassium bromide): 3312, 2933, 1047 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.53-1.60 (m, 2H, $CHCH_2CH_2O$), 1.85 (br t, J = 5.1 Hz, 1H, OH), 1.98 (br t, J = 6.0 Hz, 1H, OH), 2.02-2.14 (m, 1H, CH), 3.50 (t, J = 6.3 Hz, 2H, CH_2CH_2O), 3.65 (dd, J = 12.0 Hz, J = 9.0 Hz, 2H, 2 x OCH_{ax}), 3.70 (d, J = 6.0 Hz, 2H, CH_2OH), 3.81 (d, J = 5.1 Hz, 2H, CH_2OH), 3.99 (dd, J = 12.0 Hz, J = 4.5 Hz, 2H, 2 x OCH_{eq}), 4.48 (s, 2H, OCH_2Ph), 7.26-7.40 (m, 5H, ArH); ms: m/z (FAB) 283 (MH^+).

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.95; H, 7.80.

General Procedure for the Preparation of Acetates **15** and **16**.

To a solution of alcohol **13** or **14** (18.72 mmoles) and 4-dimethylaminopyridine (0.23 g, 1.87 mmoles) in anhydrous dichloromethane (50 ml) at 0° was added acetic anhydride (56.16 mmoles for **13** or 112.32 mmoles for **14**), and the reaction mixture was warmed gradually to room temperature for 1 hour. The resulting mixture was cooled to 0°, quenched with methanol (5 ml), and was evaporated *in vacuo* to leave a yellowish oil, which was purified by column chromatography on silica gel (1:4 ethyl acetate/hexane for **15** or 2:1 ethyl acetate/hexane for **16**, v/v) to afford the acetate **15** or **16**.

2-(Acetoxymethyl)-5-(2-benzyloxyethyl)-2-methyl-1,3-dioxane (**15**).

This compound was obtained from **13** in 99% yield as a colorless oil; ir (neat): 2859, 1734, 1221 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.41 (s, 1.5H, CH_3), 1.42 (s, 1.5H, CH_3), 1.51-1.63 (m, 2H, $CHCH_2CH_2O$), 1.95-2.10 (m, 1H, CH), 2.10 (s, 1.5H, $COCH_3$), 2.11 (s, 1.5H, $COCH_3$), 3.49 (t, J = 6.0 Hz, 2H, CH_2CH_2O), 3.59-3.67 (m, 2H, 2 x OCH_{ax}), 3.94 (dd, J = 11.7 Hz, J = 4.5 Hz, 2H, 2 x OCH_{eq}), 4.11 (s, 1H, CH_2OAc), 4.24 (s, 1H, CH_2OAc), 4.78 (s, 2H, OCH_2Ph), 7.27-7.36 (m, 5H, ArH); ms: m/z (FAB) 309 (MH^+).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.38; H, 7.80.

5-(2-Benzyloxyethyl)-2,2-di(acetoxymethyl)-1,3-dioxane (**16**).

This compound was obtained from **14** in 79% yield as a colorless oil; ir (neat): 2864, 1745, 1247 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.51-1.63 (m, 2H, $CHCH_2CH_2O$), 2.00-2.10 (m, 1H, CH), 2.09 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 3.49 (t, J = 6.0 Hz, 2H, CH_2CH_2O), 3.65 (dd, J = 12.0 Hz, J = 8.4 Hz, 2H, 2 x OCH_{ax}), 3.98 (dd, J = 12.0 Hz, J = 4.5 Hz, 2H, 2 x OCH_{eq}), 4.21 (s, 2H, CH_2OAc), 4.34 (s, 2H, CH_2OAc), 4.74 (s, 2H, OCH_2Ph), 7.25-7.40 (m, 5H, ArH); ms: m/z (FAB) 367 (MH^+).

Anal. Calcd. for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.15; H, 7.19.

General Procedure for the Preparation of Alcohols **17** and **18** by Hydrogenolysis.

A solution of the benzyl ether **15** or **16** (17.36 mmoles) in tetrahydrofuran (100 ml) was vigorously stirred in the presence of 10% palladium on carbon (10 wt%) at room temperature for 3 hours under a hydrogen atmosphere (1 atmosphere). The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated *in vacuo* to leave a yellowish oil, which was purified by column chromatography on silica gel (2:1 ethyl acetate/hexane, v/v) to afford the alcohol **17** or **18**.

2-(Acetoxymethyl)-5-(2-hydroxyethyl)-2-methyl-1,3-dioxane (**17**).

This compound was obtained from **15** in 98% yield as a colorless oil; ir (neat): 3447, 2938, 1740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (s, 1.5H, CH_3), 1.43 (s, 1.5H, CH_3), 1.49-1.63 (m, 2H, $CHCH_2CH_2O$), 1.89-2.08 (m, 1H, CH), 2.11 (s, 3H, $COCH_3$), 3.62-3.74 (m, 4H, 2 x OCH_{ax} and CH_2OH), 3.97 (dd, J = 12.0 Hz, J = 4.8 Hz, 1H, OCH_{eq}), 3.99 (dd, J = 12.0 Hz, J = 4.5 Hz, 1H, OCH_{eq}), 4.13 (s, 1H, CH_2OAc), 4.23 (s, 1H, CH_2OAc); ms: m/z (FAB) 219 (MH^+).

Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.25; H, 8.25.

2,2-Di(acetoxymethyl)-5-(2-hydroxyethyl)-1,3-dioxane (**18**).

This compound was obtained from **16** in 96% yield as a colorless oil; ir (neat): 3512, 2938, 1743 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.52-1.59 (m, 2H, $CHCH_2CH_2O$), 2.00-2.10 (m, 1H, CH), 2.10 (s, 6H, 2 x $COCH_3$), 3.68 (dd, J = 12.0 Hz, J = 8.1 Hz, 2H, 2 x OCH_{ax}), 3.69 (t, J = 6.3 Hz, 2H, CH_2CH_2OH), 4.01 (dd, J = 12.0 Hz, J = 4.5 Hz, 2H, 2 x OCH_{eq}), 4.22 (s, 2H, CH_2OAc), 4.34 (s, 2H, CH_2OAc); ms: m/z (FAB) 277 (MH^+).

Anal. Calcd. for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 52.44; H, 7.20.

General Procedure for the Preparation of Bromides **19** and **20**.

To a cooled (0°) and stirred solution of the alcohol **17** or **18** (16.29 mmoles) and carbon tetrabromide (8.11 g, 24.44 mmoles) in anhydrous *N,N*-dimethylformamide (80 ml) was added triphenylphosphine (6.41 g, 24.44 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 (100 ml), and extracted with ethyl acetate (3 x 100 ml). The combined extracts were dried (magnesium sulfate) and was evaporated *in vacuo* to leave a yellowish oil, which was purified by column chromatography on silica gel (1:4 ethyl acetate/hexane, v/v) to afford the bromide **19** or **20**.

2-(Acetoxymethyl)-5-(2-bromoethyl)-2-methyl-1,3-dioxane (**19**).

This compound was obtained from **17** in 91% yield as a colorless oil; ir (neat): 2961, 1734, 1214 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.41 (s, 1.5H, CH_3), 1.43 (s, 1.5H, CH_3), 1.88-2.08 (m, 3H, $CHCH_2CH_2O$), 2.11 (s, 3H, $COCH_3$), 3.42 (t, J = 6.9 Hz, 1H, CH_2CH_2Br), 3.45 (t, J = 6.6 Hz, 1H, CH_2CH_2Br), 3.60-3.67 (m, 2H, 2 x OCH_{ax}), 4.00 (dd, J = 12.0 Hz, J = 4.5 Hz, 1H, OCH_{eq}), 4.02 (dd, J = 12.0 Hz, J = 3.6 Hz, 1H, OCH_{eq}), 4.17 (s, 1H, CH_2OAc), 4.18 (s, 1H, CH_2OAc); ms: m/z (FAB) 281 (MH^+).

Anal. Calcd. for $C_{10}H_{17}BrO_4$: C, 42.72; H, 6.09. Found: C, 42.57; H, 6.02.

5-(2-Bromoethyl)-2,2-di(acetoxymethyl)-1,3-dioxane (**20**).

This compound was obtained from **18** in 97% yield as a colorless oil; ir (neat): 2969, 1744, 1247 cm^{-1}; ^1H nmr (deuterio-

chloroform): δ 1.93-1.99 (m, 2H, $CHCH_2CH_2O$), 2.00-2.10 (m, 1H, CH), 2.10 (s, 6H, 2 x $COCH_3$), 3.42 (t, J = 6.6 Hz, 2H, CH_2CH_2Br), 3.68 (dd, J = 12.0 Hz, J = 6.9 Hz, 2H, 2 x OCH_{ax}), 4.04 (dd, J = 12.0 Hz, J = 4.2 Hz, 2H, 2 x OCH_{eq}), 4.28 (s, 2H, CH_2OAc), 4.29 (s, 2H, CH_2OAc); ms: m/z (FAB) 339 (MH^+).

Anal. Calcd. for $C_{12}H_{19}BrO_6$: C, 42.49; H, 5.65. Found: C, 42.31; H, 5.71.

General Procedure for the Preparation of 2-Amino-6-chloropurine Derivatives **21** and **22**.

A suspension of 2-amino-6-chloropurine (2.04 g, 11.79 mmoles), bromide **19** or **20** (12.38 mmoles), and anhydrous potassium carbonate (2.44 g, 17.69 mmoles) in anhydrous *N,N*-dimethylformamide (50 ml) was stirred at room temperature for 18 hours under a nitrogen atmosphere. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness *in vacuo* to leave a yellow residue, which was purified by column chromatography on silica gel (gradient, 5:95 to 10:90 methanol/chloroform, v/v) to afford the desired N-9 product **21** or **22**.

2-Amino-6-chloro-9-[2-(2-acetoxymethyl-2-methyl-1,3-dioxan-5-yl)ethyl]purine (**21**).

This compound was obtained from **19** in 82% yield as a white solid, mp 142.6-142.8° (ethanol-ethyl acetate-hexane); ir (potassium bromide): 3427, 3336, 3222, 1733, 1246 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (s, 3H, CH_3), 1.64-1.85 (m, 1H, CH), 1.87-2.03 (m, 2H, $CHCH_2CH_2N$), 2.11 (s, 3H, $COCH_3$), 3.68 (t, J = 12.0 Hz, 1H, OCH_{ax}), 3.71 (t, J = 12.0 Hz, 1H, OCH_{ax}), 3.98 (t, J = 3.6 Hz, 1H, CH_2CH_2N), 4.02 (t, J = 3.6 Hz, 1H, CH_2CH_2N), 4.03-4.17 (m, 2H, 2 x OCH_{eq}), 4.16 (s, 1H, CH_2OAc), 4.20 (s, 1H, CH_2OAc), 5.16 (br s, 2H, NH_2), 7.76 (s, 1H, H-8); ms: m/z (FAB) 370 (MH^+).

Anal. Calcd. for $C_{15}H_{20}ClN_5O_4$: C, 48.72; H, 5.45; N, 18.94. Found: C, 48.97; H, 5.35; N, 18.77.

2-Amino-6-chloro-9-[2-[2,2-di(acetoxymethyl)-1,3-dioxan-5-yl]-ethyl]purine (**22**).

This compound was obtained from **20** in 80% yield as a white solid, mp 128.5-130.0° (ethyl acetate-hexane); ir (potassium bromide): 3464, 3352, 3236, 1747, 1251 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.77-1.86 (m, 1H, CH), 1.92-2.00 (m, 2H, $CHCH_2CH_2N$), 2.10 (s, 6H, 2 x $COCH_3$), 3.73 (dd, J = 12.0 Hz, J = 7.2 Hz, 2H, 2 x OCH_{ax}), 4.04 (dd, J = 12.0 Hz, J = 4.2 Hz, 2H, 2 x OCH_{eq}), 4.13 (t, J = 7.2 Hz, 2H, CH_2CH_2N), 4.26 (s, 2H, CH_2OAc), 4.31 (s, 2H, CH_2OAc), 5.26 (br s, 2H, NH_2), 7.76 (s, 1H, H-8); ms: m/z (EI) 427 (M^+).

Anal. Calcd. for $C_{17}H_{22}ClN_5O_6$: C, 47.73; H, 5.18; N, 16.37. Found: C, 47.51; H, 5.36; N, 16.59.

General Procedure for the Preparation of Guanine Derivatives **2-5**.

A suspension of compound **21** or **22** (4.06 mmoles) and anhydrous potassium carbonate (0.28 g, 2.03 mmoles) in methanol (20 ml) was stirred at room temperature for 4 hours, after which it became almost clear. The reaction mixture was evaporated to dryness *in vacuo*, and the resulting residue was dissolved in 0.5 *N* aqueous sodium hydroxide (17 ml). The reaction mixture was heated under reflux for 21 hours, after which it was cooled to room temperature and neutralized with acetic acid (0.6 ml) to give a mass of white precipitates. The resulting solids were filtered, which were 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 guanine product **2** or **3**.

To a suspension of **2** or **3** (1.59 mmoles) and 4-dimethylaminopyridine (20 mg, 0.16 mmole) in anhydrous *N,N*-dimethylformamide (10 ml) at 0° was added dropwise acetic anhydride (3.18 mmoles for **2** or 4.77 mmoles for **3**), and the reaction mixture was warmed to room temperature immediately. After 22 hours stirring at room temperature, the resulting mixture was cooled to 0°, quenched with methanol (1 ml), and was evaporated *in vacuo* to leave a yellowish solid, which was purified by column chromatography on silica gel (gradient, 1:9 to 1:4 methanol/chloroform, v/v) to afford the acetate **4** or **5**.

9-[2-(2-Hydroxymethyl-2-methyl-1,3-dioxan-5-yl)ethyl]guanine (**2**).

This compound was obtained from **21** in 80% yield as a white solid, mp 243-244° dec (ethanol-methanol-water); ir (potassium bromide): 3466, 3316, 3190, 1722, 1626 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.23 (s, 1.5H, CH_3), 1.29 (s, 1.5H, CH_3), 1.49-1.77 (m, 3H, $CHCH_2CH_2N$), 3.26 (d, J = 6.3 Hz, 1H, CH_2CH_2OH), 3.44 (d, J = 6.3 Hz, 1H, CH_2CH_2OH), 3.50-3.58 (m, 2H, 2 x OCH_{ax}), 3.75 (dd, J = 11.4 Hz, J = 3.3 Hz, 1H, OCH_{eq}), 3.80 (dd, J = 11.4 Hz, J = 4.2 Hz, 1H, OCH_{eq}), 3.92-3.98 (m, 2H, CH_2CH_2N), 4.63 (t, J = 6.3 Hz, 0.5H, OH), 4.68 (t, J = 6.3 Hz, 0.5H, OH), 6.41 (br s, 2H, NH_2), 7.71 (s, 1H, H-8), 10.53 (br s, 1H, NH); ms: m/z (FAB) 310 (MH^+).

Anal. Calcd. for $C_{13}H_{19}N_5O_4$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.32; H, 6.25; N, 22.78.

9-[2-[2,2-Di(hydroxymethy)-1,3-dioxan-5-yl]ethyl]guanine (**3**).

This compound was obtained from **22** in 90% yield as a white solid, mp 252-255° dec (water); ir (potassium bromide): 3538, 3322, 3191, 1722, 1625 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.57-1.73 (m, 3H, $CHCH_2CH_2N$), 3.37 (s, 2H, CH_2CH_2OH), 3.51-3.58 (m, 4H, 2 x OCH_{ax} and CH_2CH_2OH), 3.78 (dd, J = 11.7 Hz, J = 3.9 Hz, 2H, 2 x OCH_{eq}), 3.95 (t, J = 6.9 Hz, 2H, CH_2CH_2N), 4.45 (br s, 2H, 2 x OH), 6.41 (br s, 2H, NH_2), 7.72 (s, 1H, H-8), 10.53 (br s, 1H, NH); ms: m/z (FAB) 326 (MH^+).

Anal. Calcd. for $C_{13}H_{19}N_5O_5$: C, 48.00; H, 5.89; N, 21.53. Found: C, 47.71; H, 5.92; N, 21.60.

9-[2-(2-Acetoxymethyl-2-methyl-1,3-dioxan-5-yl)ethyl]guanine (**4**).

This compound was obtained from **2** in 52% yield as a white solid, mp 241-242° dec (ethanol-methanol); ir (potassium bromide): 3466, 3316, 3190, 1722, 1626 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.26 (s, 1.5H, CH_3), 1.33 (s, 1.5H, CH_3), 1.54-1.76 (m, 3H, $CHCH_2CH_2N$), 2.02 (s, 1.5H, $COCH_3$), 2.03 (s, 1.5H, $COCH_3$), 3.54-3.62 (m, 2H, 2 x OCH_{ax}), 3.79-3.86 (m, 2H, 2 x OCH_{eq}), 3.95 (t, J = 6.3 Hz, 2H, CH_2CH_2N), 3.97 (s, 1H, CH_2OAc), 4.17 (s, 1H, CH_2OAc), 6.42 (br s, 2H, NH_2), 7.71 (s, 1H, H-8), 10.53 (br s, 1H, NH); ms: m/z (FAB) 352 (MH^+).

Anal. Calcd. for $C_{15}H_{21}N_5O_5$: C, 51.28; H, 6.02; N, 19.93. Found: C, 51.42; H, 5.88; N, 19.88.

9-[2-[2,2-Di(acetoxymethyl)-1,3-dioxan-5-yl]ethyl]guanine (**5**).

This compound was obtained from **3** in 66% yield as a white solid, mp 249-251° dec (ethanol); ir (potassium bromide): 3559, 3327, 3200, 1742, 1689, 1629 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.60-1.80 (m, 3H, $CHCH_2CH_2N$), 2.02 (s, 6H, 2 x $COCH_3$), 3.63 (dd, J = 11.7 Hz, J = 7.5 Hz, 2H, 2 x OCH_{ax}),

3.89 (dd, J = 11.7 Hz, J = 3.9 Hz, 2H, 2 x OCH_{eq}), 3.96 (t, J = 6.9 Hz, 2H, CH_2CH_2N), 4.08 (s, 2H, CH_2OAc), 4.27 (s, 2H, CH_2OAc), 6.41 (br s, 2H, NH_2), 7.71 (s, 1H, H-8), 10.51 (br s, 1H, NH); ms: m/z (FAB) 410 (MH^+).

Anal. Calcd. for $C_{17}H_{23}N_5O_7$: C, 49.87; H, 5.66; N, 17.11. Found: C, 49.55; H, 5.82; N, 17.35.

General Procedure for the Preparation of 2-Aminopurine Derivatives **6-9**.

A solution of compound **21** or **22** (4.06 mmoles) and triethylamine (1.7 ml, 12.17 mmoles) in methanol (20 ml) was vigorously stirred in the presence of 10% palladium on carbon (150 mg) at room temperature for 4 hours under a hydrogen atmosphere (1 atmosphere). The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness *in vacuo* to give a white residue, which was purified by column chromatography on silica gel using methanol/chloroform (5:95, v/v) as eluent to afford the 2-aminopurine product **8** and **9**.

A mixture of **8** or **9** (1.46 mmoles) and anhydrous potassium carbonate (202 mg, 1.46 mmoles) in methanol (15 ml) was stirred at room temperature for 2 hours, and the reaction mixture was neutralized with acetic acid. The reaction mixture was evaporated to dryness *in vacuo* to leave a colorless residue, which was purified by column chromatography either on silica gel using methanol/chloroform (5:95, v/v) as eluent (for **6**) or on C_{18} reverse-phase silica gel using methanol/water (3:7, v/v) as eluent (for **7**) to afford the hydroxy product **6** or **7**.

2-Amino-9-[2-(2-acetoxymethyl-2-methyl-1,3-dioxan-5-yl)-ethyl]purine (**8**).

This compound was obtained from **21** in 75% yield as a white solid, mp 123.6-125.0° (ethyl acetate); ir (potassium bromide): 3390, 3333, 3223, 1728, 1639 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (s, 3H, CH_3), 1.67-1.75 (m, 1H, CH), 1.95-2.03 (m, 2H, $CHCH_2CH_2N$), 2.11 (s, 3H, $COCH_3$), 3.72 (dd, J = 11.7 Hz, J = 6.6 Hz, 2H, 2 x OCH_{ax}), 4.00 (dd, J = 11.7 Hz, J = 4.2 Hz, 2H, 2 x OCH_{eq}), 4.17 (t, J = 7.2 Hz, 2H, CH_2CH_2N), 4.17 (s, 1H, CH_2OAc), 4.21 (s, 1H, CH_2OAc), 5.07 (br s, 2H, NH_2), 7.74 (s, 1H, H-8), 8.69 (s, 1H, H-6); ms: m/z (EI) 335 (M^+).

Anal. Calcd. for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.88. Found: C, 53.88; H, 6.20; N, 20.70.

2-Amino-9-[2-[2,2-di(acetoxymethyl)-1,3-dioxan-5-yl]-ethyl]purine (**9**).

This compound was obtained from **22** in 78% yield as a white foam; ir (potassium bromide): 3460, 3367, 3202, 1743, 1689, 1612 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.79-1.89 (m, 1H, CH), 1.92-2.00 (m, 2H, $CHCH_2CH_2N$), 2.10 (s, 6H, 2 x $COCH_3$), 3.73 (dd, J = 12.0 Hz, J = 6.9 Hz, 2H, 2 x OCH_{ax}), 4.03 (dd, J = 12.0 Hz, J = 4.2 Hz, 2H, 2 x OCH_{eq}), 4.13 (t, J = 7.2 Hz, 2H, CH_2CH_2N), 4.26 (s, 2H, CH_2OAc), 4.32 (s, 2H, CH_2OAc), 5.04 (br s, 2H, NH_2), 7.73 (s, 1H, H-8), 8.69 (s, 1H, H-6); ms: m/z (EI) 393 (M^+).

Anal. Calcd. for $C_{17}H_{23}N_5O_6$: C, 51.90; H, 5.89; N, 17.80. Found: C, 51.65; H, 6.01; N, 17.98.

2-Amino-9-[2-(2-hydroxymethyl-2-methyl-1,3-dioxan-5-yl)-ethyl]purine (**6**).

This compound was obtained from **8** in 93% yield as a white solid, mp 163-165.5° (ethanol); ir (potassium bromide): 3398, 3328, 3206, 1647, 1615 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.23 (s, 1.5H, CH_3), 1.29 (s, 1.5H, CH_3), 1.50-1.83 (m, 3H, $CHCH_2CH_2N$), 3.26 (d, J = 6.3 Hz, 1H, CH_2CH_2OH), 3.44 (d, J = 6.3 Hz, 1H, CH_2CH_2OH), 3.52-3.60 (m, 2H, 2 x OCH_{ax}), 3.77 (dd, J = 11.7 Hz, J = 4.2 Hz, 1H, OCH_{eq}), 3.82 (dd, J = 11.7 Hz, J = 4.2 Hz, 1H, OCH_{eq}), 4.06 (t, J = 6.9 Hz, 1H, CH_2CH_2N), 4.07 (t, J = 7.2 Hz, 1H, CH_2CH_2N), 4.63 (t, J = 6.3 Hz, 0.5H, OH), 4.68 (t, J = 6.3 Hz, 0.5H, OH), 6.48 (br s, 2H, NH_2), 8.09 (s, 1H, H-8), 8.57 (s, 1H, H-6); ms: m/z (EI) 293 (M^+).

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.88. Found: C, 53.45; H, 6.38; N, 23.70.

2-Amino-9-[2-[2,2-di(hydroxymethyl)-1,3-dioxan-5-yl]-ethyl]purine (**7**).

This compound was obtained from **9** in 94% yield as a white solid, mp 205-207.5° dec (ethanol-water); ir (potassium bromide): 3538, 3322, 3191, 1722, 1625 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.56-1.70 (m, 1H, CH), 1.72-1.80 (m, 2H, $CHCH_2CH_2N$), 3.38 (s, 2H, CH_2CH_2OH), 3.54-3.61 (m, 4H, 2 x OCH_{ax} and CH_2CH_2OH), 3.81 (dd, J = 11.7 Hz, J = 4.2 Hz, 2H, 2 x OCH_{eq}), 4.07 (t, J = 7.2 Hz, 2H, CH_2CH_2N), 4.44 (t, J = 6.0 Hz, 1H, OH), 4.49 (t, J = 6.3 Hz, 1H, OH), 6.48 (br s, 2H, NH_2), 8.10 (s, 1H, H-8), 8.57 (s, 1H, H-6); ms: m/z (EI) 309 (M^+).

Anal. Calcd. for $C_{13}H_{19}N_5O_4$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.22; H, 6.32; N, 22.88.

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