Analogues of the Antiviral Acyclonucleoside 9-(4-Hydroxy-3-hydroxymethylbutyl)guanine. Part 2.[1] Substitutions on C-1′ and C-3′ of the Acyclic N-9 Substituent

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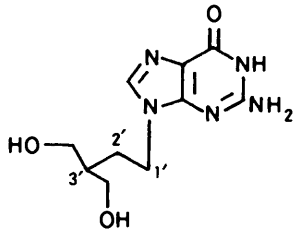
Syntheses of 9-[3,3-bis(hydroxymethyl)butyl]guanine (**2**), 9-(3-benzyloxymethyl-4-hydroxy-3-hydroxymethylbutyl)guanine (**3**), 9-(3,4-dihydroxy-3-hydroxymethylbutyl)guanine (**4**), 9-(3-fluoro-4-hydroxy-3-hydroxymethylbutyl)guanine (**5**), and 9-[4-hydroxy-3,3-bis(hydroxymethyl)butyl]guanine (**6**) are described. These 3′-substituted analogues of the antiviral acyclonucleoside 9-(4-hydroxy-3-hydroxymethylbutyl)guanine (**1**) were like the 2′-substituted analogues reported in Part 1 of this series, synthesized by a route involving alkylation of 2-amino-6-chloropurine with protected bromides (**8a—d**) derived from the appropriately substituted partially protected alcohols (**7a—d**). Subsequent hydrolysis and deprotection afforded the required 9-substituted guanines.

The preparation of 9-(4-hydroxy-3-hydroxymethyl-1-methoxybutyl)guanine (**28**) is also described. This 1′-substituted analogue (**28**) of (**1**) and its N-7 substituted isomer (**29**) were synthesized by Lewis acid-catalysed alkylation of trimethylsilylated 2-*N*-acetylguanine with a hydroxy-protected α-chloro ether (**25**) and subsequent deprotection of both the hydroxy groups and the 2-amino substituent. All of these acyclonucleosides (**2**)—(**6**), (**28**), and (**29**), were tested for antiviral activity in cell cultures. The most active compound was the 3′-fluoro derivative (**5**), which was *ca.* 3-fold less active than the lead compound (**1**) against the herpes viruses.

In continuation of our studies[1,2] on the synthesis and antiviral evaluation of analogues of the highly selective antiherpes virus acyclonucleoside 9-(4-hydroxy-3-hydroxymethylbutyl)guanine (**1**),[3–9] we have prepared a series of compounds bearing additional atoms or groups, with varying steric and electronic



(**1**)

properties, on the acyclic N-9 substituent at the carbon atom designated as C-3′. Also, following our recently reported studies on the synthesis and antiviral evaluation of 1′-methoxy substituted pyrimidine,[10] and purine[11] acyclonucleosides, we have prepared the 1′-methoxy analogue of (**1**) and its N-7 isomer.

Results and Discussion

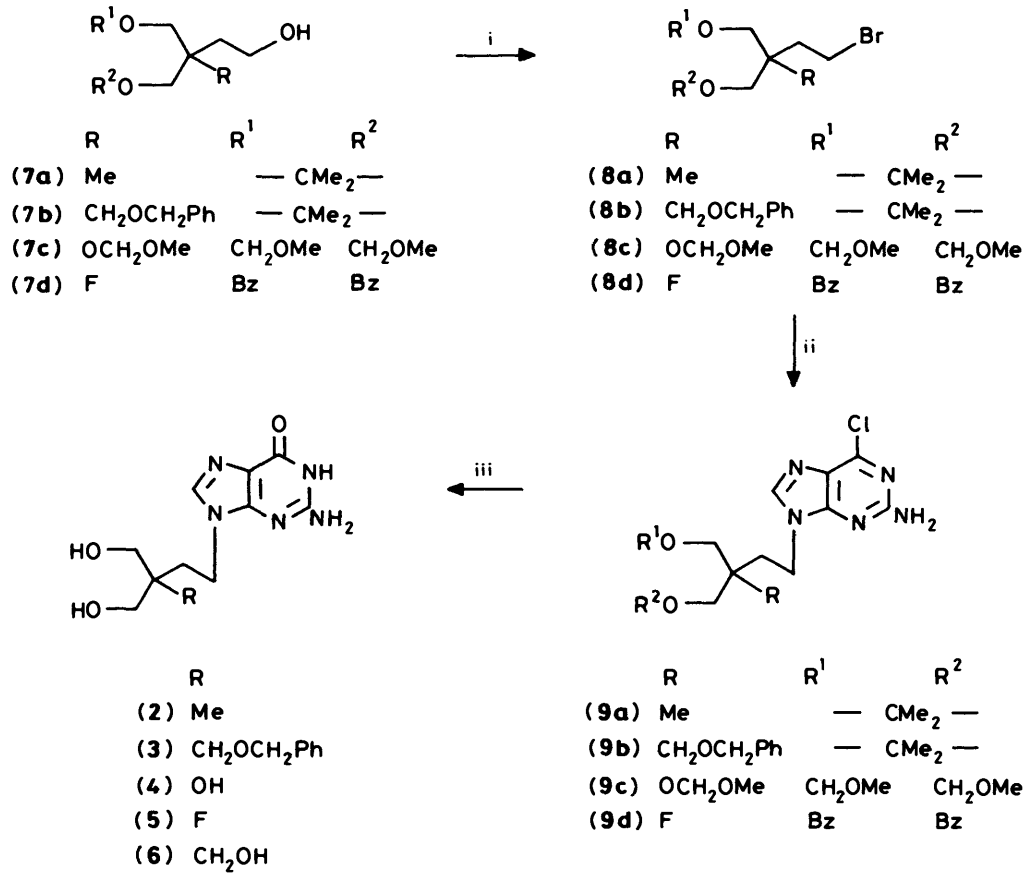
The novel guanine derivatives (**2**)—(**6**) were prepared by a route involving alkylation at N-9 of 2-amino-6-chloropurine with protected bromides (**8a—d**). The bromides were synthesized by reaction of partially protected alcohols (**7a—d**) with triphenylphosphine–carbon tetrabromide (Scheme 1).

The alcohols (**7a—d**) were prepared as shown in Schemes 2 and 3. In our published synthesis of (**1**),[3] an efficient route to such alcohol precursors was described (Scheme 2, R = H). This procedure proved suitable for the preparation of the alcohols (**7a**) and (**7b**). The triester precursors (**11a**) and (**11b**) were obtained by reaction of the anion of triethyl ethane-1,1,2-tricarboxylate (**10**) with iodomethane or benzyl chloromethyl ether, respectively. Reduction of (**11a**) with sodium borohydride or lithium aluminium hydride gave the triol (**12a**) in quantitative and 58% yield, respectively. Reduction of (**11b**) with lithium aluminium hydride afforded triol (**12b**) in 73% yield. Protection of the 1,3-diol system in (**12a**) and (**12b**) by acetonide formation was accomplished with little selectivity. In addition to the required alcohols (**7a**) and (**7b**), their isomeric 7-membered ring acetonides (**13a**) and (**13b**) were obtained in appreciable quantities. These isomeric products were separated by column chromatography and the required alcohols (**7a**) and (**7b**) isolated as clear oils.

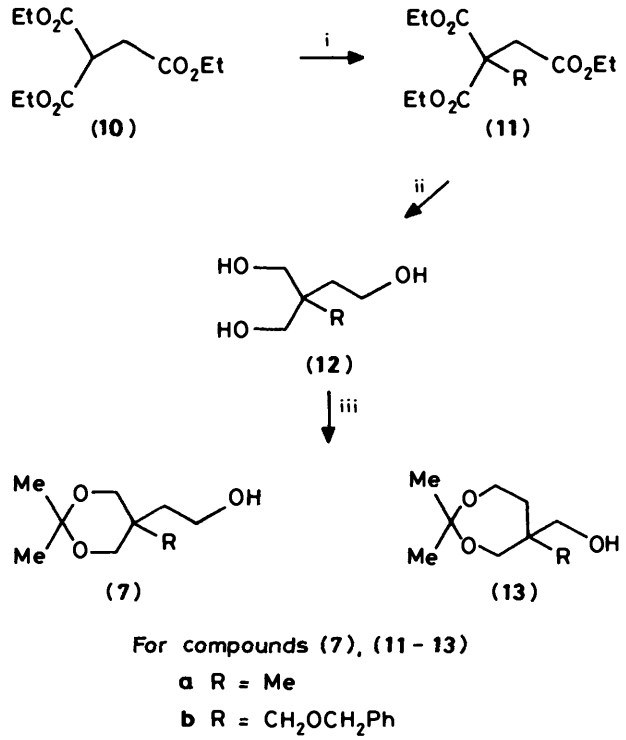
Preparation of the alcohol precursor (**7c**) was achieved by reaction of the anion of diethyl acetoxymalonate (**14**) with benzyl 2-bromoethyl ether (Scheme 3). The triester (**15**) was reduced with lithium aluminium hydride, affording the crude triol (**16**) in 88% yield. Treatment of (**16**) with chloromethyl methyl ether and di-isopropylethylamine at room temperature, gave only the dialkylated product, with the tertiary hydroxy unsubstituted. Further reaction at elevated temperature, however, gave the trimethoxymethyl derivative (**17**) in 84% yield. Catalytic hydrogenolysis of (**17**) at atmospheric pressure over palladium on carbon then afforded the required alcohol (**7c**) in 74% yield.

The conversion of the triol (**16**) into its dibenzoate ester (**18**) was achieved in 67% yield by treatment with 2.2 equiv. of benzoyl chloride in pyridine. An appreciable quantity (17%) of the monobenzoate was also isolated. Fluorination of the tertiary hydroxy group in (**18**) was carried out using diethylaminosulphur trifluoride (DAST) in dichloroethane containing an inorganic base, affording (**19**) in 89% yield. The fluoro alcohol (**7d**) was obtained in 90% yield by catalytic hydrogenolysis of (**19**) in acetic acid–ethanol over palladium on carbon.

The 9-substituted 2-amino-6-chloropurines (**9d—d**) were



Scheme 1. *Reagents:* i, CBr_4, Ph_3P, DMF or CH_2Cl_2; ii, 2-amino-6-chloropurine, K_2CO_3, DMF; iii, 2M HCl, 100 °C

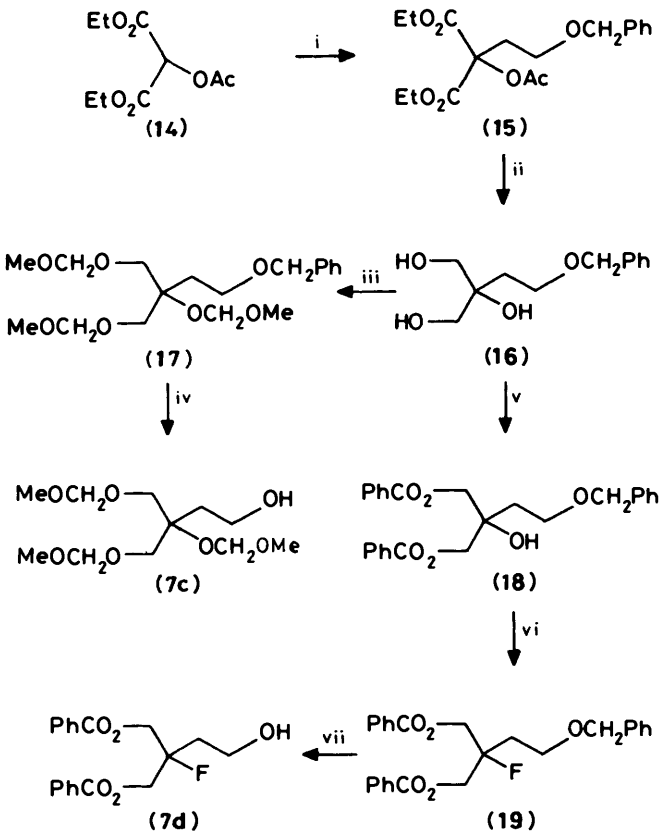


Scheme 2. *Reagents:* i, NaH, DMF, RX; ii, $NaBH_4$, Bu^{t}OH, MeOH or $LiAlH_4$, THF; iii, $Me_2C(OMe)_2$, *p*-$MeC_6H_4SO_3H$, Me_2CO

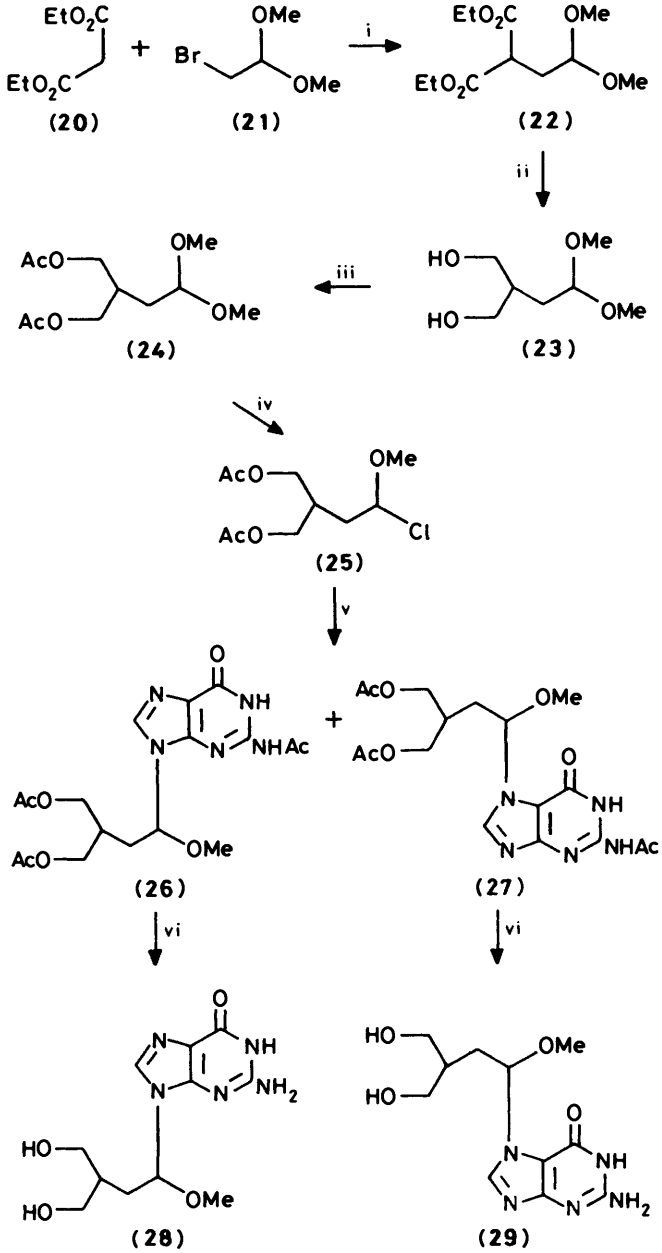
prepared in yields in the range 30—69% by alkylation of 2-amino-6-chloropurine with bromides (**8a—d**). Although no 7-substituted purines were isolated during these alkylations, the low yields of some of the 9-substituted products may have been due to competing alkylation reactions.

Conversion of (**9a—d**) into the guanine derivatives (**2**)—(**6**) was accomplished by acidic hydrolysis (Scheme 1). When the isopropylidene derivatives (**9a**) and (**9b**) were treated with 2M hydrochloric acid at 100 °C, hydrolysis of the 6-chloro group occurred with concomitant removal of the acetonide protecting group affording (**2**) and (**3**) directly. Hydrogenolysis of (**3**) over palladium on carbon in acidic medium gave the 3′-hydroxymethyl derivative (**6**) in 86% yield. Removal of the three methoxymethyl groups and hydrolysis of the 6-chloro group in (**9c**) was accomplished by heating in 2M hydrochloric acid. The deprotected acyclonucleoside (**4**)[12] was isolated in low (16%) yield by preparative high-pressure liquid chromatography (h.p.l.c.) Treatment of the protected fluoro compound (**9d**) with 2.3M hydrochloric acid at 100 °C followed by preparative h.p.l.c. afforded the fluoro substituted acyclonucleoside (**5**) in 28% yield. The guanine derivatives (**2**)—(**6**) were all recrystallised from water.

Synthesis of the 1′-methoxy derivatives (**28**)—(**29**) commenced from diethyl malonate (**20**) and bromoacetaldehyde dimethyl acetal (**21**). Reaction of the anion of (**20**) with (**21**) in *N*,*N*-dimethylformamide gave the diester (**22**) in 64% yield. Reduction of (**22**) was carried out using lithium aluminium hydride in ether, affording the diol (**23**) in 61% yield. Treatment of (**23**) with acetic anhydride in pyridine gave the diacetate (**24**) in 50% yield. Reaction of (**24**) with acetyl chloride and thionyl chloride in dichloromethane, gave the α-chloro ether (**25**) in



Scheme 3. *Reagents:* i, NaH, DMF, $PhCH_2O(CH_2)_2Br$; ii, $LiAlH_4$, THF; iii, $(Me_2CH)_2NEt$, $MeO(CH_2)_2OMe$, $MeOCH_2Cl$; iv, H_2, Pd/C, EtOH, H_2O; v, PhCOCl, pyridine; vi, Et_2NSF_3(DAST), $CaCO_3$, $(CH_2)_2Cl_2$; vii, H_2, Pd/C, EtOH, H_2O



Scheme 4. *Reagents:* i, NaH, DMF; ii, $LiAlH_4$, ether; iii, Ac_2O, pyridine; iv, AcCl, $SOCl_2$, CH_2Cl_2; v, N^2-acetylguanine, $(Me_3Si)_2NH$, Me_3SiCl, $(NH_4)_2SO_4$, $SnCl_4$, CH_3CN; vi, $H_2NNH_2{\cdot}H_2O$, EtOH

97% yield. Trimethylsilylated 2-*N*-acetylguanine was treated with crude (**25**) in acetonitrile using tin(IV) chloride as catalyst, providing a mixture of 7- and 9-alkylation products. These were separated by column chromatography, affording the N-9 isomer (**26**) and the N-7 isomer (**27**) in 16 and 22% yield, respectively. Treatment of (**26**) and (**27**) with hydrazine hydrate in refluxing ethanol, gave the deprotected nucleosides (**28**) and (**29**) in 89 and 82% yield, respectively.

Biological Data.—The acyclonucleosides prepared in this study were tested at concentrations up to 100 μg ml^{-1} for antiviral activity in cell cultures. The most active new compound was the fluoro analogue (**5**), for which the 50% inhibitory concentration (IC_{50}) against herpes simplex virus type 1 (SC-16) strain and herpes simplex virus type 2 (MS strain) in MRC-5 (human fibroblast) cells was 2.0 and 3.6 μg ml^{-1}, respectively, compared with IC_{50} values of 0.8 and 1.0 μg ml^{-1} obtained in the same tests with 9-(4-hydroxy-3-hydroxymethylbutyl)guanine (**1**). Slight activity was also noted with the methyl (**2**), hydroxy (**4**), and hydroxymethyl (**6**) substituted compounds which had IC_{50} values of 30, 10, and > 100 μg ml^{-1}, respectively, against the type 1 virus and 51, 60, and 26 μg ml^{-1}, respectively, against the type 2 virus. Additionally, at concentrations up to 100 μg ml^{-1} none of the compounds (**2**)—(**6**) or (**28**) and (**29**), inhibited the replication of influenza A (HK/1/68) virus or of parainfluenza type 1 (Sendai) virus in Madin-Darby canine kidney cells. In none of these antiviral tests was toxicity for the cell monolayer observed at compound concentrations up to 100 μg ml^{-1}.

Experimental

M.p.s were determined using a Reichert Kofler apparatus and are uncorrected. U.v. spectra were recorded with a Cary 219 spectrometer. I.r. spectra were recorded with a Perkin-Elmer 197 or 580 spectrometer. ^1H N.m.r. spectra were carried out on a Varian EM-390 90 MHz or a JEOL GX-270 270 MHz spectrometer. Mass spectrometry was performed using a V.G. 70-70F instrument operating at 70 eV and accurate mass measurements were determined using a VG ZAB instrument. Elemental analysis was carried out on a Carlo Erba model 1106 analyzer. Chromatography was performed on Merck 7736 60H silica gel and h.p.l.c. using Waters 6000A/660 equipment and a μ-Bondapak C_{18} column. All compounds were homogeneous by t.l.c. on silica gel $60F_{254}$ coated aluminium sheets.

Triethyl Propane-1,2,2-*tricarboxylate* (**11a**).—Triethyl ethane-1,1,2-tricarboxylate (**10**) (1 g, 4.1 mmol) was dissolved in *N,N*-dimethylformamide (6 ml) and treated at 25 °C under nitrogen with 50% sodium hydride dispersion in oil (0.22 g, 4.4 mmol). The reaction was stirred at 25 °C for 1 h before being cooled to 0 °C and treated with iodomethane (1 ml, 16 mmol). The mixture was stirred at 25 °C for 1 h and poured into ice–water (30 ml) and ethyl acetate (50 ml). The aqueous layer was further extracted with ethyl acetate (3 × 50 ml). The ethyl acetate solutions were combined, dried (Na_2SO_4), and evaporated under reduced pressure to leave a yellow oil. The oil was distilled *in vacuo*, affording the substituted triester (**11a**) (1.02 g, 97%) as a pale lemon oil; $\nu_{max.}$(film) 1 735 cm^{-1}; $\delta_H(CDCl_3)$ 1.30 (9 H, t, *J* 7 Hz, 3 × CH_2CH_3), 1.52 (3 H, s, CH_3), 2.9 (2 H, s, CH_2CO_2Et), and 4.19 (6 H, m, 3 × CH_2CH_3) (Found: C, 55.1; H, 7.6%; M^+, 260.1261; $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.75%; M^+, 260.1260).

2-*Hydroxymethyl*-2-*methylbutane*-1,4-*diol* (**12a**).—A solution of the triester (**11a**) (2 g, 7.7 mmol) in tetrahydrofuran (10 ml) was added dropwise over 1 h to a stirred suspension of lithium aluminium hydride (1.44 g, 38 mmol) in dry distilled tetrahydrofuran (25 ml) under nitrogen at 0 °C. The reaction was stirred at 0 °C for 2 h and then at 25 °C for 4 h. A mixture of tetrahydrofuran–water (2:1; 20 ml) was added dropwise to the reaction mixture and the inorganic salts were filtered off and washed with methanol (30 ml). The solvents were removed under reduced pressure and the residue dissolved in methanol (25 ml). The solution was filtered, the filtrate evaporated, and the residual oil distilled *in vacuo*, affording the triol (**12a**) (600 mg, 58%) as a clear oil; $\nu_{max.}$(film) 3 300 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 0.76 (3 H, s, CH_3), 1.39 (2 H, t, *J* 7 Hz, CH_2CH_2OH), 3.20 (4 H, s, 2 × CH_2OH), 3.48 (2 H, t, *J* 7 Hz, CH_2CH_2OH), and 4.42 (3 H, br s, D_2O exchangeable, 3 × OH) (Found: C, 53.7; H, 10.8%. $C_6H_{14}O_3$ requires C, 53.7; H, 10.5%).

2-*Hydroxymethyl*-2-*methylbutane*-1,4-*diol* (**12a**).—A refluxing solution of the triester (**11a**) (27 g, 104 mmol) and sodium borohydride (10.5 g, 278 mmol) in t-butyl alcohol (200 ml) was treated with methanol (15 ml) in 3 portions over 0.5 h. The solution was boiled under reflux for a further 0.5 h and allowed to cool. 5M Hydrochloric acid was carefully added (exothermic) to neutralise the solution, which was then filtered. The residue was extracted three times with ethanol and the solvent evaporated under reduced pressure, affording the triol (**12a**) (14 g, quantitative) as a clear oil. A small sample was distilled *in vacuo*; $\nu_{max.}$(film) 3 300 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 0.79 (3 H, s, CH_3), 1.40 (2 H, t, *J* 7 Hz, CH_2CH_2OH), 3.21 (4 H, m, 2 × CH_2OH), 3.50 (2 H, t, *J* 7 Hz, CH_2CH_2OH), and 4.43 (3 H, br s, D_2O exchangeable, 3 × OH) (Found: C, 54.2; H, 10.3. $C_6H_{14}O_3$ requires C, 53.7; H, 10.5%).

5-(2-*Hydroxyethyl*)-2,2,5-*trimethyl*-1,3-*dioxane* (**7a**).—A solution of the triol (**12a**) (14 g, 104 mmol) in acetone (250 ml) containing 2,2-dimethoxypropane (13 g, 125 mmol) and toluene-*p*-sulphonic acid monohydrate (1 g, 5.3 mmol, 5 mol%) was stirred for 1 h at 25 °C. The reaction was neutralised by addition of triethylamine and the solvent removed under reduced pressure, affording an oil (14 g), which was chromatographed on silica gel eluting with hexane–acetone (3:1), to afford (**7a**) (7.0 g, 38%) as a clear oil; $\nu_{max.}$(film) 3 420 cm^{-1}; $\delta_H(CDCl_3)$ 0.88 (3 H, s, CH_3), 1.42 [3 H, s, $C(CH_3)_2$], 1.44 [3 H, s, $C(CH_3)_2$], 1.69 (2 H, t, *J* 6.2 Hz, CH_2CH_2OH), 2.58 (1 H, br s, D_2O exchangeable, OH), 3.63 [4 H, s, 2 × $CH_2OC(CH_3)_2$], and 3.83 (2 H, t, *J* 6.2 Hz, CH_2OH); *m/z* 175 (MH^+, 6%) (Found: C, 61.8; H, 10.7%. $C_9H_{18}O_3$ requires C, 62.0; H, 10.4%), and (**13a**) (3.6 g, 20%); $\nu_{max.}$(film) 3 450 cm^{-1}; $\delta_H(CDCl_3)$ 0.87 (3 H, s, CH_3), 1.33 [3 H, s, $C(CH_3)_2$], 1.34 [3 H, s, $C(CH_3)_2$], 1.52 (2 H, m, CH_2CH_2O), 1.66 (1 H, br s, D_2O exchangeable, OH), and 3.45—3.81 [6 H, m, 2 × $CH_2OC(CH_3)_2$ and CH_2OH]; *m/z* (isobutane c.i.) 175 (MH^+) (Found: C, 62.2; H, 10.4. $C_9H_{18}O_3$ requires C, 62.0; H, 10.4%).

5-(2-*Bromoethyl*)-2,2,5-*trimethyl*-1,3-*dioxane* (**8a**).—A solution of the alcohol (**7a**) (2.3 g, 13.2 mmol) and carbon tetrabromide (6.3 g, 18.6 mmol) in dry *N,N*-dimethylformamide (30 ml) was cooled to 0 °C and treated with triphenylphosphine (4.9 g, 18.6 mmol). The cooling bath was removed and the reaction mixture stirred for 2 h at 25 °C. The solvent was removed under reduced pressure and the residue dissolved in chloroform (100 ml) and washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml) and water (100 ml). The chloroform solution was dried (Na_2SO_4) and the solvent evaporated to give a semisolid residue. This was chromatographed on silica gel, eluting with hexane–acetone (3:1), to afford the bromo compound (**8a**) (3 g, 95%) as an oil; $\delta_H(CDCl_3)$ 0.92 (3 H, s, CH_3), 1.31 [3 H, s, $C(CH_3)_2$], 1.40 [3 H, s, $C(CH_3)_2$], 2.07 (2 H, m, CH_2CH_2Br), 3.46 (2 H, m, CH_2Br), and 3.55 [4 H, s, 2 × $CH_2OC(CH_3)_2$]; *m/z* 221 (M^+ − CH_3, 33%).

2-*Amino*-6-*chloro*-9-[2-(2,2,5-*trimethyl*-1,3-*dioxan*-5-*yl*)-*ethyl*]*purine* (**9a**).—2-Amino-6-chloropurine (386 mg, 2.3 mmol) and then potassium carbonate (320 mg, 2.3 mmol) were added to a solution of (**8a**) (490 mg, 2.07 mmol) in *N,N*-dimethylformamide (7 ml) and the suspension was stirred at 25 °C for 3 days. The solvent was evaporated under reduced pressure and the residue extracted several times with ethyl acetate. The ethyl acetate solution was dried (Na_2SO_4) and evaporated and the residue was chromatographed on silica gel, eluting with ethyl acetate to afford the 9-alkylated purine (**9a**) (200 mg, 30%), m.p. 171—173 °C; $\nu_{max.}$(Nujol) 3 420, 3 380, 3 330, 3 220, 3 180, 1 650, and 1 610 cm^{-1}; $\delta_H(CDCl_3)$ 0.91 (3 H, s, CH_3), 1.38 [3 H, s, $C(CH_3)_2$], 1.42 [3 H, s, $C(CH_3)_2$], 2.00 (2 H, m, CH_2CH_2N), 3.61 (4 H, s, 2 × CH_2O), 4.16 (2 H, m, CH_2N), 5.27 (2 H, br s, D_2O exchangeable, NH_2), and 7.77 (1 H, s, 8-H) (Found: C, 49.95; H, 6.2; N, 20.8%; M^+, 325.1291. $C_{14}H_{20}ClN_5O_2 \cdot 0.5H_2O$ requires C, 50.2; H, 6.3; N, 20.9%; M^+, 325.1305).

9-[3,3-*Bis*(*hydroxymethyl*)*butyl*]*guanine* (**2**).—A solution of (**9a**) (150 mg, 0.46 mmol) in 2M hydrochloric acid (3 ml) was boiled under reflux for 2 h. The hot solution was neutralised with 10% aqueous sodium hydroxide and allowed to cool. The solid was filtered off, washed well with cold water, and recrystallised from hot water, affording the guanine (**2**) (110 mg, 89%) as a white solid, m.p. 284—287 °C; $\lambda_{max.}(H_2O)$ 253 nm (ε 11 500); $\nu_{max.}$(KBr) 3 390, 3 330, 3 190, 3 140, 1 730, 1 690, and 1 625 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 0.80 (3 H, s, CH_3), 1.66 (2 H, m, CH_2CH_2N) 3.25 (4 H, d, *J* 6 Hz, 2 × CH_2OH), 3.93 (2 H, m, CH_2N), 4.44 (2 H, t, *J* 6 Hz, D_2O exchangeable, 2 × OH), 6.37 (2 H, br s, D_2O exchangeable, NH_2), 7.66 (1 H, s, 8-H), and 10.50 (1 H, br s, D_2O exchangeable, 1-NH) (Found: C, 46.0; H, 6.6; N, 24.6%; M^+, 267.1326. $C_{11}H_{17}N_5O_3 \cdot H_2O$ requires C, 46.3; H, 6.7; N, 24.6%; M^+, 267.1331).

Triethyl 1-*Benzyloxymethylethane*-1,1,2-*tricarboxylate* (**11b**).—A hexane-washed 50% sodium hydride dispersion (4.4 g, 91.7 mmol) in *N,N*-dimethylformamide (200 ml) was treated with triethyl ethane-1,1,2-tricarboxylate (**10**) (20 g, 81.3 mmol) under nitrogen and the reaction mixture stirred for 1 h at room temperature. The reaction was cooled to 0 °C, treated with benzyl chloromethyl ether (14 g, 89.4 mmol), and then stirred at room temperature for 2 h. The mixture was poured into ice–water (500 ml) and ethyl acetate (800 ml) and the aqueous layer extracted with ethyl acetate (3 × 300 ml). The combined ethyl acetate solutions were dried (Na_2SO_4) and evaporated under

reduced pressure to a yellow oil, which was chromatographed on silica gel, eluting with hexane–ethyl acetate (15:1), to afford the substituted triester (**11b**) (16 g, 53%) as a clear oil; $\nu_{max.}$(film) 2 980, 1 760, 1 740, 1 460, 1 370, and 1 300 cm^{-1}; $\delta_H(CDCl_3)$ 1.22 (9 H, t, *J* 7 Hz, 3 × $CH_3CH_2CO_2$), 3.14 (2 H, s, CH_2CO_2Et), 3.98 (2 H, s, CH_2OCH_2Ph), 4.20 (6 H, q, *J* 7 Hz, 3 × $CH_3CH_2CO_2$), 4.50 (2 H, s, CH_2Ph), and 7.38 (5 H, m, ArH); *m/z* 367 (MH^+, 0.5%), 2.75 (2), 91 (100) (Found: C, 62.5; H, 7.0%; MH^+, 367.1748; $C_{19}H_{26}O_7$ requires C, 62.3; H, 7.15%; MH^+, 367.1756).

2-Benzyloxymethyl-2-hydroxymethylbutane-1,4-*diol* (**12b**).—A solution of triester (**11b**) (8.9 g, 24.3 mmol) in dry tetrahydrofuran (100 ml) was added over 1 h to a suspension of lithium aluminium hydride (2.8 g, 73 mmol) in dry tetrahydrofuran (100 ml) cooled to 0 °C. The cooling bath was removed and the reaction stirred at room temperature for 3 h. A tetrahydrofuran–water mixture (2:1; 50 ml) was then added. The inorganic salts were filtered off and well washed with ethanol. The solvents were evaporated under reduced pressure and the residue dissolved in ethyl acetate, and the solution dried (Na_2SO_4) and evaporated under reduced pressure to give a yellowish oil. The oil was chromatographed on silica gel, eluting with ethyl acetate–methanol (20:1) to afford the triol (**12b**) (4.0 g, 73% as a clear oil; $\nu_{max.}$(film) 3 350, 2 950, 2 900, 1 500, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.64 (2 H, t, *J* 6 Hz, CH_2CH_2OH), 3.43 (2 H, s, CH_2OCH_2Ph), 3.45—3.76 (9 H, m, 3 × CH_2OH), 4.48 (2 H, s, CH_2Ph), and 7.30 (5 H, m, ArH); *m/z* 222 ($M^+ - H_2O$, 4%), 107 (18), and 91 (100) (Found: C, 64.8; H, 8.45%; $M^+ - H_2O$, 222.1241. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4% $M^+ - H_2O$, 222.1256).

5-Benzyloxymethyl-5-(2-hydroxyethyl)-2,2-dimethyl-1,3-*dioxane* (**7b**) *and 5-Benzyloxymethyl-5-hydroxymethyl-2,2-dimethyl*-1,3-*dioxepane* (**13b**).—A mixture of (**12b**) (7.05 g, 31 mmol), 2,2-dimethoxypropane (3.94 g, 38 mmol), and toluene-*p*-sulphonic acid monohydrate (0.72 g, 3.8 mmol) was stirred in acetone (100 ml) at 0 °C for 1 h. The solution was neutralised with triethylamine and evaporated to afford a yellowish oil. The oil was chromatographed on silica gel, eluting with hexane–acetone (3:1) and two products were isolated as clear oils. The first compound to be eluted was (**13b**) (2.45 g, 28%); $\nu_{max.}$(film) 3 450, 3 020, 2 980, 2 850, 1 705, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.31 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 1.48 (2 H, m, CCH_2CH_2), 2.56 (1 H, br s, D_2O exchangeable, OH), 3.43 (2 H, s, CH_2OCH_2Ph), 3.60—3.71 (6 H, m, 2 × CH_2O + CH_2OH), 4.50 (2 H, s, CH_2Ph), and 7.25 (5 H, m, ArH) (Found: C, 68.3; H, 8.6%. $C_{16}H_{24}O_4$ requires C, 68.55; H, 8.6%).

The second component to be eluted was (**7b**) (3.45 g, 39%); $\nu_{max.}$(film) 3 430, 3 030, 2 980, 2 940, 2 850, 1 480, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.39 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.59 (2 H, t, *J* 5 Hz, CH_2CH_2OH), 3.21 (1 H, br m, D_2O exchangeable, OH), 3.53 (2 H, s, CH_2OCH_2Ph), 3.65 [2 H, d, J_{AB} 12 Hz, $CH_2OC(CH_3)_2$], 3.68 (2 H, m, CH_2OH), 3.79 [2 H, d, J_{AB} 12 Hz, $CH_2OC(CH_3)_2$], 4.57 (2 H, s, CH_2Ph), and 7.27 (5 H, m, ArH) (Found: C, 68.5; H, 8.5%; $M^+ - CH_3$ 265.1430. $C_{16}H_{24}O_4$ requires C, 68.55; H, 8.6%; $M^+ - CH_3$ 265.1440).

5-Benzyloxymethyl-5-(2-bromoethyl)-2,2-dimethyl-1,3-*dioxane* (**8b**).—A solution of (**7b**) (1.7 g, 6.07 mmol) and carbon tetrabromide (2.82 g, 8.50 mmol) in dichloromethane (50 ml) was cooled to 0 °C and stirred during the addition of triphenylphosphine (2.23 g, 8.5 mmol) in portions. The cooling bath was removed and the reaction mixture stirred for 2 h at 25 °C. After this the solution was washed with saturated aqueous sodium hydrogen carbonate (3 × 50 ml) and water (50 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was extracted with ether and the ether solution were filtered and evaporated under reduced pressure. The residue was adsorbed on silica gel and subjected to flash chromatography on silica, eluting with hexane–acetone (15:1) to give (**8b**) (500 mg, 25%) as an unstable oil; $\nu_{max.}$(film) 3 060, 3 030, 2 980, 2 940, 2 860, 1 480, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.4 (6 H, m, 2 × CH_3), 1.96 (2 H, m, CH_2CH_2Br), 3.40 (2 H, m, CH_2Br), 3.44 (2 H, s, CH_2OCH_2Ph), 4.48 (2 H, s, CH_2Ph), and 7.27 (5 H, m, ArH).

2-Amino-9-[2-(5-benzyloxymethyl-2,2-dimethyl-1,3-*dioxan*-*5-yl)ethyl]-6-chloropurine* (**9b**).—2-Amino-6-chloropurine (251 mg, 1.48 mmol) and then potassium carbonate (205 mg, 1.48 mmol) were added to a solution of (**8b**) (460 mg, 1.34 mmol) in dry *N*,*N*-dimethylformamide (7 ml), and the mixture then stirred at 25 °C for 7 days. The solvent was evaporated under reduced pressure and the residue continuously extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and the solvent evaporated under reduced pressure, leaving an oil, which was chromatographed on silica gel, eluting with ethyl acetate to give the 9-alkylpurine (**9b**) (400 mg, 69%) as a white solid, m.p. 148—150 °C; $\lambda_{max.}$(MeOH) 223 (ε 28 000) and 310 nm (ε 7 670); $\nu_{max.}$(KBr) 3 390, 3 340, 3 220, 2 990, 2 940, 2 860, 1 650, 1 615, 1 565, 1 520, 1 470, 1 455, and 1 410 cm^{-1}; $\delta_H(CDCl_3)$ 1.40 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.94 (2 H, m, CH_2CH_2N), 3.52 (2 H, s, CH_2OCH_2Ph), 3.67 [2 H, d, J_{AB} 12 Hz, $(CH_3)_2COCH_2$], 3.76 [2 H, d, J_{AB} 12 Hz, $(CH_3)_2COCH_2$], 4.15 (2 H, m, CH_2N), 4.54 (2 H, s, CH_2Ph), 5.22 (2 H, br s D_2O exchangeable, NH_2), 7.32 (5 H, m, ArH), and 7.68 (1 H, s, 8-H); *m/z* 431 (M^+, 7%) 416 (30), 340 (25), 325 (15), 266 (30), 169 (27), 134 (23), and 91 (100) (Found: C, 58.3; H, 6.0; N, 16.1%; M^+, 431.1720. $C_{21}H_{26}ClN_5O_3$ requires C, 58.4; H, 6.1; N, 16.2%; M^+, 431.1724).

9-(3-Benzyloxymethyl-4-hydroxy-3-hydroxymethylbutyl)-guanine (**3**).—A solution of (**9b**) (150 mg, 0.35 mmol) in 2M hydrochloric acid (4 ml) was heated at 100 °C for 5 h. The hot solution was neutralised with 10% aqueous sodium hydroxide and then refrigerated. The solid which was precipitated was collected and washed well with cold water, affording (**3**) (90 mg, 92%), m.p. 235—240 °C; $\lambda_{max.}$(MeOH) 254 nm (ε 13 000); $\nu_{max.}$(Nujol) 3 350, 3 150, 2 930, 2 730, 1 730, 1 690, 1 640, 1 600, 1 580, and 1 540 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.76 (2 H, m, CH_2CH_2N), 3.36 (2 H, s, CH_2OCH_2Ph), 3.38 (2 H, s, CH_2OH), 3.40 (2 H, s, CH_2OH), 4.03 (2 H, m, CH_2N), 4.45 (2 H, s, CH_2Ph), 4.47 (2 H, m, D_2O exchangeable, 2 × OH), 6.36 (2 H, br s, D_2O exchangeable, NH_2), 7.33 (5 H, m, ArH), 7.61 (1 H, s, 8-H), and 10.50 (1 H, br s, NH); *m/z* 373 (M^+, 5%); 282 (16), 236 (16), 151 (21), 108 (32), and 91 (100) (Found: M^+, 373.1743. $C_{18}H_{23}N_5O_4$ requires M^+, 373.1750).

9-[4-Hydroxy-3,3-bis(hydroxymethyl)butyl]guanine (**6**).—The guanine (**3**) (140 mg, 0.38 mmol) was suspended in ethanol (2 ml) and water (2 ml) and 5M hydrochloric acid added dropwise until dissolution occurred. 10% Palladium-on-charcoal (70 mg) was added and the mixture hydrogenated under atmospheric pressure for 3 h. The mixture was filtered, the catalyst washed with 5M hydrochloric acid, and the filtrate evaporated under reduced pressure to remove ethanol. Neutralisation of the solution with 25% aqueous sodium hydroxide and refrigeration gave a white solid which was collected and recrystallised from hot water, affording (**6**) (91 mg, 86%) as the hemihydrate, m.p. 295—299 °C (decomp.); $\lambda_{max.}(H_2O)$ 252 nm (ε 11 700); $\nu_{max.}$(KBr) 3 340, 3 200, 2 940, 2 880, 2 740, 1 725, 1 690, 1 630, 1 605, 1 570, 1 540, and 1 485 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.69 (2 H, m, CH_2CH_2N), 3.35 (6 H, m, 3 × CH_2OH), 4.03 (2 H, m, CH_2N), 4.35 (3 H, t, *J* 5.2 Hz, D_2O exchangeable, 3 × OH), 6.37 (2 H, br s, D_2O exchangeable, NH_2), 7.63 (1 H, s, 8-H), and 10.46 (1 H, br s, D_2O exchangeable, NH); *m/z* (f.a.b. +ve ion; thioglycerol/DMSO) 284 (MH^+, 100%) and 152 (33) (Found: C, 45.0; H, 6.3; N, 23.8. $C_{11}H_{17}N_5O_4 \cdot 0.5H_2O$ requires C, 45.05; H, 6.2; N, 24.0%).

Diethyl Acetoxy(2-benzyloxyethyl)malonate (**15**).—Diethyl acetoxymalonate (**14**) (12.4 g, 56.9 mmol) was added to a hexane-washed dispersion of 60% sodium hydride (2.57 g = 1.54 g NaH, 64.3 mmol) in dry *N,N*-dimethylformamide (100 ml) under nitrogen, and the mixture was stirred for 1 h at 25 °C. It was then cooled to 0 °C, treated dropwise with benzyl bromoethyl ether (12.4 g, 57.7 mmol), and then stirred at 25 °C for 16 h. The solution was poured into a mixture of ice–water (150 ml) and ethyl acetate (150 ml) and the aqueous layer extracted with further ethyl acetate (3 × 150 ml). The extract was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give a yellow oil, which was chromatographed on silica gel, eluting with hexane–ethyl acetate (5:1) to give (**15**) (16 g, 80%) as a pale yellow oil; $\nu_{max.}$(film) 3 060, 3 030, 2 970, 2 940, 2 900, 2 870, 1 750, 1 460, and 1 440 cm^{-1}; $\delta_H(CDCl_3)$ 1.20 (6 H, t, *J* 7 Hz, 2 × CH_3CH_2), 2.11 (3 H, s, CH_3CO_2), 2.57 (2 H, t, *J* 6 Hz, $CH_2CH_2OCH_2Ph$), 3.55 (2 H, t, *J* 6 Hz, CH_2OCH_2Ph), 4.20 (4 H, q, *J* 7 Hz, 2 × CH_3CH_2), 4.39 (2 H, s, CH_2Ph), and 7.29 (5 H, m, ArH); *m/z* 309 ($M^+ - CH_3CO$, 3%) (Found: C, 59.1; H, 7.0% $M^+ - CH_3CO$ 309.1345. $C_{18}H_{24}O_7 \cdot 0.8H_2O$ requires C, 58.9; H, 7.0%; $M^+ - CH_3CO$ 309.1338).

4-*Benzyloxy*-2-*hydroxymethylbutane*-1,2-*diol* (**16**).—A solution of the diester (**15**) (15.9 g, 45.17 mmol) in tetrahydrofuran (100 ml) was added dropwise to an ice-cold suspension of lithium aluminium hydride (5.32 g, 140 mmol) in tetrahydrofuran (140 ml) under nitrogen. The ice-bath was removed and the reaction mixture stirred at 25 °C for 2 h. Water (0.45 ml), 10% aqueous sodium hydroxide (0.45 ml), and water (1.4 ml) were added dropwise after which the reaction mixture was evaporated under reduced pressure. The residue was then dissolved in methanol–water (1:1) and neutralised with Amberlite IR-120 (H) ion exchange resin. The resin was filtered off, washed with a little methanol, and the solvents removed under reduced pressure. The residual oil was dissolved in ethyl acetate, filtered, and the solvent removed under reduced pressure to give (**16**) (9 g, 88%) as an oil; $\nu_{max.}$(film) 3 350, 3 030, 2 940, 2 870, 1 500, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 1.76 (2 H, t, *J* 6 Hz, $CH_2CH_2OCH_2Ph$), 3.50 (4 H, s, 2 × CH_2OH), 3.52 (3 H, br m, D_2O exchangeable, 3 × OH), 3.64 (2 H, t, *J* 6 Hz, CH_2OCH_2Ph), 4.46 (2 H, s, CH_2Ph), and 7.31 (5 H, m, ArH); *m/z* 226 (M^+, 1%) (Found: M^+, 226.1202. $C_{12}H_{18}O_4$ requires M^+, 226.1205).

1-*Benzyloxy*-3-*methoxymethoxymethyl*-3,4-*bismethoxymethoxybutane* (**17**).—A solution of (**16**) (8.6 g, 38.05 mmol) in 1,2-dimethoxyethane (50 ml) was treated with di-isopropylethylamine (24.6 g, 34 ml, 190 mmol) and then cooled to 0 °C before the slow addition of chloromethyl methyl ether (15.32 g, 14.5 ml, 190 mmol), The cooling bath was removed and the reaction mixture was heated under reflux for 2 h. It was then poured into water (1 l) and ethyl acetate (500 ml) and the aqueous layer extracted with further ethyl acetate (3 × 500 ml). The organic layer was washed with 2M hydrochloric acid (3 × 500 ml), saturated aqueous sodium hydrogen carbonate (2 × 200 ml), and water (200 ml) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the title product (**17**) (11.4 g, 84%) as an oil; $\nu_{max.}$(film) 3 100, 3 060, 3 030, 2 940, 2 880, 2 820, 1 500, and 1 470 cm^{-1}; $\delta_H(CDCl_3)$ 2.0 (2 H, t, *J* 6 Hz, $CH_2CH_2OCH_2Ph$), 3.27 (9 H, s, 3 × CH_3), 3.61 (4 H, s, 2 × CH_2OCH_2OMe), 3.64 (2 H, t, *J* 6 Hz, CH_2OCH_2Ph), 4.44 (2 H, s, CH_2Ph), 4.53 (4 H, s, 2 × CH_2OCH_3), 4.76 (2 H, s, CH_2OCH_3), and 7.25 (5 H, m, ArH); *m/z* 313 [($M^+ - CH_2OCH_3$)$^+$, 1%], 281 (1), 251 (6), 237 (3), 207 (17), 107 (3), and 91 (100) (Found: C, 59.3; H, 8.4. $C_{18}H_{30}O_7 \cdot 0.4H_2O$ requires C, 59.1; H, 8.5%).

3-*Methoxymethoxymethyl*-3,4-*bismethoxymethoxybutanol* (**7c**).—A solution of (**17**) (11.3 g, 31.5 mmol) in ethanol (100 ml) and water (2 ml) was treated with 10% palladium-on-charcoal (1 g) and hydrogenated under atmospheric pressure for 2 h. The catalyst was filtered off, the solvents removed under reduced pressure, and the residual oil chromatographed on silica gel, eluting with ethyl acetate–hexane (2:1) to give the alcohol (**7c**) (6.2 g, 74%) as an oil; $\nu_{max.}$(film) 3 500, 2 950, 2 900, 2 830, 2 780, and 1 470 cm^{-1}; $\delta_H(CDCl_3)$ 1.98 (2 H, t, *J* 6 Hz, CH_2CH_2OH), 2.69 (1 H, br s, D_2O exchangeable, OH), 3.38 (9 H, s, 3 × CH_3), 3.67 (4 H, s, 2 × CH_2OCH_2OMe), 3.80 (2 H, t, *J* 6 Hz, CH_2OH), 4.60 (4 H, s, 2 × CH_2OCH_3), and 4.81 (2 H, s, CH_2OCH_3); *m/z* 237 [($M^+ - OCH_3$)$^+$, 0.5%]; (f.a.b. + ve ion; thioglycerol) 269 (MH^+, 100%) (Found: C, 49.0; H, 9.05. $C_{11}H_{24}O_7$ requires C, 49.2; H, 9.0%).

1-*Bromo*-3,4-*bismethoxymethoxy*-3-*methoxymethoxymethylbutane* (**8c**).—Carbon tetrabromide (3.75 g, 11.3 mmol) was added to a solution of (**7c**) (2.0 g, 7.46 mmol) in *N,N*-dimethylformamide (45 ml) and the solution cooled to 0 °C during the addition of triphenylphosphine (2.96 g, 11.3 mmol). The mixture was stirred at 0 °C for 2 h after which more carbon tetrabromide (1 g, 3 mmol) and triphenylphosphine (0.75 g, 3 mmol) were added: the mixture was then stirred for a further 2 h at 0 °C. Saturated aqueous sodium hydrogen carbonate (45 ml) was added and the mixture extracted with hexane (3 × 70 ml). The combined extracts were washed with water (100 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with hexane–ethyl acetate (5:2) to give the bromo compound (**8c**) (1.5 g, 61%) as a volatile liquid; $\nu_{max.}$(film) 1 470, 1 440, and 1 400 cm^{-1}; $\delta_H(CDCl_3)$ 2.29 (2 H, m, CH_2CH_2Br), 3.37 (6 H, s, 2 × CH_3), 3.39 (3 H, s, CH_3), 3.53 (2 H, m, CH_2Br), 3.60 (2 H, s, $CH_2OCH_2OCH_3$), 3.61 (2 H, s, $CH_2OCH_2OCH_3$), 4.63 (4 H, s, 2 × CH_2OCH_3), and 4.82 (2 H, s, CH_2OCH_3).

2-*Amino*-6-*chloro*-9-(3,4-*bismethoxymethoxy*-3-*methoxymethoxymethylbutyl*)*purine* (**9c**).—A solution of (**8c**) (1.4 g, 4.2 mmol) in dry *N,N*-dimethylformamide (30 ml) was treated with 2-amino-6-chloropurine (1.2 g, 7.08 mmol) and potassium carbonate (0.94 g, 6.80 mmol) and the reaction mixture was stirred for 3 days at 25 °C. It was then filtered, the solvent removed under reduced pressure, and the residue adsorbed on silica gel and chromatographed; elution with ethyl acetate gave the 9-alkylpurine (**9c**) (0.66 g, 37%) as a white solid, m.p. 90—92 °C; $\lambda_{max.}$(MeOH) 224 (ε 29 200), 248 (ε 5 620) and 310 nm (ε 7 860); $\nu_{max.}$(KBr) 3 380, 3 330, 3 220, 1 645, 1 615, 1 560, 1 530, and 1 475 cm^{-1}; $\delta_H(CDCl_3)$ 2.20 (2 H, m, CH_2CH_2N), 3.35 (6 H, s, 2 × CH_3), 3.39 (3 H, s, CH_3), 3.65 (4 H, s, 2 × $CH_2OCH_2OCH_3$), 4.28 (2 H, m, CH_2N), 4.63 (4 H, s, 2 × CH_2OCH_3), 4.84 (2 H, s, CH_2OCH_3), 5.36 (2 H, br s, D_2O exchangeable, NH_2), and 7.81 (1 H, s, 8-H); *m/z* 419 (M^+, 2.7%) (Found: C, 45.5; H, 6.3; N, 16.3%; M^+, 419.1577. $C_{16}H_{26}ClN_5O_6$ requires C, 45.8; H, 6.2; N, 16.7%; M^+, 419.1572).

9-(3,4-*Dihydroxy*-3-*hydroxymethylbutyl*)*guanine* (**4**).—A solution of (**9c**) (100 mg, 0.24 mmol) in 2M hydrochloric acid (2.2 ml) was heated under reflux for 6 h and then neutralised with 40% aqueous sodium hydroxide. Preparative h.p.l.c. (7.8 mm × 30 cm μ-Bondapak C_{18}, eluted with 5% aqueous MeOH at 3 ml min^{-1} and u.v. detection at 250 nm) of this solution afforded the guanine (**4**) (10 mg, 16%), m.p. 285—290 °C (decomp.) (from water); $\lambda_{max.}(H_2O)$ 252 nm (ε 12 600); $\nu_{max.}$(KBr) 3 420, 3 340, 1 680, 1 600, 1 545, 1 390, and 1 040 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.83 (2 H, m, CH_2CH_2N), 3.31 (4 H, m, 2 × CH_2OH), 4.04 (2 H, m, CH_2N), 4.23 (1 H, br s, D_2O exchangeable, OH), 4.51 (2 H, br s, D_2O exchangeable, 2 × OH), 6.44 (2 H, s, D_2O exchangeable, NH_2), 7.63 (1 H, s, 8-H), and 10.55 (1 H, br s, D_2O exchangeable, NH) (Found: C,

43.8; H, 5.6; N, 25.3. $C_{10}H_{15}N_5O_4 \cdot 0.3H_2O$ requires C, 43.7; H, 5.7; N, 25.5%).

4-Benzyloxy-2-benzoyloxymethyl-2-hydroxybutyl Benzoate (**18**).—A solution of (**16**) (3.95 g, 17.48 mmol) in dry pyridine (80 ml) was treated dropwise with benzoyl chloride (5.36 g, 4.5 ml, 38.14 mmol) at 0 °C and the mixture then stirred at 25 °C for 2 h. It was then diluted with water (80 ml) and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with 2M hydrochloric acid (2 × 100 ml), saturated aqueous sodium hydrogen carbonate (2 × 100 ml), and water (100 ml) and dried (Na_2SO_4). The solvent was evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate–hexane (1:3). The first compound to be eluted was (**18**) (5.0 g, 67%) isolated as a clear oil; $\nu_{max.}$(film) 3 470, 1 720, 1 600, 1 580, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 2.07 (2 H, t, *J* 6 Hz, $CH_2CH_2OCH_2Ph$), 3.80 (2 H, t, *J* 6 Hz, CH_2OCH_2Ph), 3.98 (1 H, br s, D_2O exchangeable, OH), 4.44 (4 H, s, 2 × CH_2O_2CPh), 4.54 (2 H, s, CH_2Ph), and 7.25—8.2 (15 H, m, ArH) (Found: C, 71.6; H, 6.0. $C_{26}H_{26}O_6$ requires C, 71.9; H, 6.0%).

The second compound to be eluted was 4-benzyloxy-2-hydroxy-2-hydroxymethylbutyl benzoate (1.0 g, 17%); $\nu_{max.}$ 3 450, 1 720, 1 450, 1 260, and 1 110 cm^{-1}; $\delta_H(CDCl_3)$ 1.92 (2 H, m, $CH_2CH_2OCH_2Ph$), 2.89 (2 H, br s, D_2O exchangeable, 2 × OH), 3.52 (2 H, s, CH_2OH), 3.72 (2 H, t, *J* 6 Hz, CH_2OCH_2Ph), 4.27 (2 H, s, CH_2O_2CPh), 4.46 (2 H, s, CH_2Ph), and 7.2—8.1 (10 H, m, ArH).

4-Benzyloxy-2-benzoyloxymethyl-2-fluorobutyl Benzoate (**19**).—A solution of (**18**) (4.6 g, 10.6 mmol) in 1,2-dichloroethane (40 ml) was treated with dried (120 °C) calcium carbonate (6 g, 60 mmol) and cooled to −35 °C during the addition by syringe of diethylaminosulphur trifluoride (2.6 g, 2 ml, 15.9 mmol). The cooling bath was removed and the reaction mixture stirred at 25 °C for 2 h: it was then slowly diluted with water (30 ml). The aqueous layer was extracted with 1,2-dichloroethane (3 × 50 ml) and the combined extracts washed with water (100 ml), dried ($MgSO_4$), and evaporated to leave an oil which was chromatographed on silica gel, eluting with hexane–ethyl acetate (3:1) to afford the fluoro compound (**19**) (4.1 g, 89%) as a clear oil; $\nu_{max.}$(film) 1 730, 1 600, 1 580, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 2.27 (2 H, dt, J_{HH} 6.1 Hz, J_{HF} 19.5 Hz, $CFCH_2CH_2$), 3.72 (2 H, t, *J* 6.1 Hz, CH_2OCH_2Ph), 4.52 (2 H, s, CH_2Ph), 4.64 (4 H, m, 2 × CH_2O_2CPh), and 7.20—8.10 (15 H, m, ArH); *m/z* 436 (M^+, 1%) (Found: C, 71.4; H, 5.75%; M^+, 436.1683. $C_{26}H_{25}FO_5$ requires C, 71.55; H, 5.8%; M^+, 436.1685).

2-Benzoyloxymethyl-2-fluoro-4-hydroxybutyl Benzoate (**7d**).—A solution of (**19**) (4 g, 9.17 mmol) in a mixture of ethanol (80 ml), water (8 ml), and acetic acid (2 ml) was hydrogenated at atmospheric pressure over 10% palladium-on-charcoal (0.8 g) for 2 days. The catalyst was filtered off, the solvents removed under reduced pressure, toluene (20 ml) added to the residue, and the mixture then evaporated. The latter procedure was repeated and the residue obtained was dissolved in chloroform (50 ml), dried ($MgSO_4$), and evaporated to give the fluoro alcohol (**7d**) (2.85 g, 90%) as a clear oil; $\nu_{max.}$(film) 3 500, 1 720, 1 600, 1 580, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 2.21 (2 H, dt, J_{HH} 6.2 Hz, J_{HF} 19.5 Hz, $CFCH_2CH_2OH$), 2.59 (1 H, br s, D_2O exchangeable, OH), 3.93 (2 H, t, *J* 6.2 Hz, CH_2OH), 4.65 (4 H, d, J_{HF} 19.5 Hz, 2 × CH_2O_2CPh), and 7.2—8.2 (10 H, m, ArH).

2-Benzoyloxymethyl-4-bromo-2-fluorobutyl Benzoate (**8d**).—A solution of (**7d**) (1.05 g, 3 mmol) in *N,N*-dimethylformamide (25 ml) was treated with carbon tetrabromide (3.1 g, 9 mmol) and the reaction mixture then cooled to 0 °C during the addition of triphenylphosphine (2.4 g, 9 mmol). The reaction mixture was stirred at 25 °C for 2.5 h, quenched by the addition of saturated aqueous sodium hydrogen carbonate (25 ml) and then extracted with hexane (3 × 50 ml). The combined extracts were washed with water (2 × 50 ml), dried ($MgSO_4$), and evaporated to leave a residue which was chromatographed on silica gel, eluting with hexane–ethyl acetate (3:1) to afford the title compound (**8d**) (625 mg, 50%) as a clear oil; $\nu_{max.}$(film) 1 725, 1 600, 1 580, and 1 450 cm^{-1}; $\delta_H(CDCl_3)$ 2.50 (2 H, dt, J_{HH} 8.1 Hz, J_{HF} 18.9 Hz, $CFCH_2CH_2Br$), 3.53 (2 H, t, *J* 8.1 Hz, CH_2Br), 4.54 (4 H, d, J_{HF} 16.8 Hz, 2 × CH_2O_2CPh), and 7.2—8.2 (10 H, m, ArH) (Found: C, 54.5; H, 4.6%; M^+, 408.0389. $C_{19}H_{18}BrFO_4 \cdot 0.5H_2O$ requires C, 54.5; H, 4.55%; M^+, 408.0373).

2-Amino-9-(4-benzoyloxy-3-benzoyloxymethyl-3-fluorobutyl)-6-chloropurine (**9d**).—A solution of 2-amino-6-chloropurine (280 mg, 1.64 mmol) and anhydrous potassium carbonate (230 mg, 1.64 mmol) in *N,N*-dimethylformamide (7 ml) was treated with a solution of (**8d**) (560 mg, 1.37 mmol) in *N,N*-dimethylformamide (3 ml) at 25 °C. The reaction was stirred at 25 °C for 16 h and then at 55 °C for 6 h; it was then cooled and filtered. The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel, eluting with ethyl acetate–hexane (3:1) to afford the purine (**9d**), which was crystallised from ether (340 mg, 50%), m.p. 139—140 °C; $\lambda_{max.}$(MeOH) 225 (ε 47 500) and 310 nm (7 480); $\nu_{max.}$(KBr) 3 480, 3 400, 3 320, 1 725, 1 615, 1565, and 1 515 cm^{-1}; $\delta_H(CDCl_3)$ 2.49 (2 H, m, CH_2CH_2N), 4.33 (2 H, m, CH_2N), 4.65 (4 H, d, J_{HF} 16.3 Hz, 2 × CH_2O_2CPh), 4.96 (2 H, br s, D_2O exchangeable, NH_2), 7.4—8.1 (10 H, m, ArH), and 7.79 (1 H, s, 8-H); *m/z* 497 (M^+, 11%) (Found: C, 57.9; H, 4.3; N, 13.9%; M^+, 497.1274. $C_{24}H_{21}ClFN_5O_4$ requires C, 57.9; H, 4.25; N, 14.1%; M^+, 497.1266).

9-(3-Fluoro-4-hydroxy-3-hydroxymethylbutyl)guanine (**5**).—A solution of (**9d**) (100 mg, 0.2 mmol) in 2.3M hydrochloric acid (2.5 ml) was held at 100 °C for 6 h after which it was cooled and evaporated under reduced pressure. The residue was suspended in water (4 ml) and brought to pH 4.5 with 1M hydrochloric acid. Preparative h.p.l.c. (C_{18} μ-Bondapak, 5% methanol in 0.05M pH 4.5 ammonium acetate buffer at 3 ml^{-1}) and then recrystallisation from water afforded the guanine (**5**) (15 mg, 28%), m.p. 283—284 °C; $\lambda_{max.}$(MeOH) 254 nm (ε 13 800); $\nu_{max.}$(KBr) 3 420, 3 340, 3 160, 1 695, 1 650, and 1 620 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.10 (2 H, m, CH_2CH_2N), 3.51 (4 H, dd, $J_{H/OH}$ 5.5 Hz, J_{HF} 18.3 Hz, 2 × CH_2OH), 4.08 (2 H, m, CH_2N), 4.93 (2 H, t, *J* 5.5 Hz, D_2O exchangeable, 2 × OH), 6.42 (2 H, br s, D_2O exchangeable, NH_2), 7.67 (1 H, s, 8-H), and 10.52 (1 H, br s, NH); *m/z* 271 (M^+, 10%) (Found: C, 42.5; H, 5.2; N, 24.6%; M^+, 271.1087. $C_{10}H_{14}FN_5O_3 \cdot 0.7H_2O$ requires C, 42.3; H, 5.5; N, 24.7%; M^+, 271.1080).

Diethyl (2,2-Dimethoxyethyl)malonate (**22**).[13]—Diethyl malonate (**20**) (16 g, 0.1 mol) was added to a suspension of 60% dispersion of sodium hydride (4.5 g ≡ 2.7 g NaH, 0.11 mmol) in *N,N*-dimethylformamide (150 ml) under nitrogen and the reaction mixture stirred for 1 h at 25 °C. It was then cooled to 0 °C during the dropwise addition of bromoacetaldehyde dimethyl acetal (**21**) (20 g, 0.12 mol) and then stirred at 100 °C for 4 h. The reaction mixture was then poured into ice–water (500 ml) and the aqueous layer was extracted with ethyl acetate (3 × 500 ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give an oil, which was distilled under high vacuum to afford the diester (**22**) (16.05 g, 64%) as a clear liquid, $\nu_{max.}$(film) 1 740, 1 500, 1 470, and 1 440 cm^{-1}; $\delta_H(CDCl_3)$ 1.30 (6 H, t, *J* 7 Hz, 2 × CH_3CH_2), 2.21 (2 H, q, *J* 6 Hz, $CHCH_2CH$), 3.35 (6 H, s, 2 × OCH_3), 3.50 [1 H, t, *J* 6 Hz, $CH(CO_2Et)_2$], 4.25 (4 H, q, *J* 7 Hz, 2 × CH_3CH_2), and 4.42 [1 H, t, *J* 6 Hz, $CH(OMe)_2$].

2-Hydroxymethyl-4,4-dimethoxybutan-1-ol (**23**).[13]—A solution of (**22**) (8.5 g, 34.3 mmol) in ether (10 ml) was added dropwise to a cooled (−10 °C) suspension of lithium aluminium hydride (2.9 g, 75.5 mmol) in ether (25 ml), and the mixture was stirred at 20 °C for 16 h. The reaction mixture was then diluted with ether (50 ml), and water (7 ml), and 10% aqueous sodium hydroxide (4 ml) added slowly: stirring was then continued for a further 2 h. The solids were filtered off and the filtrate evaporated under reduced pressure. The residue obtained was dissolved in ethyl acetate and the solution dried ($MgSO_4$) and evaporated to afford the diol (**23**) (3.4 g, 61%) as a clear liquid; $\nu_{max.}$(film) 3 400, 1 470, 1 440, and 1 380 cm^{-1}; $\delta_H(CDCl_3)$ 1.72 [3 H, m, $CHCH_2CH(OMe)_2$], 3.10 (2 H, br s, D_2O exchangeable, 2 × OH), 3.34 (6 H, s, 2 × OCH_3), 3.71 (4 H, m, 2 × CH_2OH), and 4.49 [1 H, t, *J* 6 Hz, $CH(OMe)_2$].

2-Acetoxymethyl-4,4-dimethoxybutyl Acetate (**24**).—A solution of (**23**) (3.3 g, 20.3 mmol) in dry pyridine (10 ml) was cooled to 0 °C and acetic anhydride (10 ml) was added dropwise. The cooling bath was removed and the reaction mixture stirred at 25 °C for 16 h: it was then poured into water (50 ml) and ethyl acetate (50 ml). The aqueous layer was extracted with ethyl acetate (3 × 50 ml) and the combined ethyl acetate solutions were washed wtih 2M hydrochloric acid (3 × 100 ml), saturated aqueous sodium hydrogen carbonate (2 × 100 ml), and water (100 ml) and then dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was chromatographed on silica gel, eluting with hexane–ethyl acetate (5:1) to afford the diacetate (**24**) (2.5 g, 50%) as a clear oil; $\nu_{max.}$(film) 1 740, 1 470, and 1 430 cm^{-1}; $\delta_H(CDCl_3)$ 1.60 [2 H, t, *J* 6 Hz, $CH_2CH(OCH_3)_2$], 2.02 (6 H, s, 2 × CH_3CO_2), 1.9—2.2 [1 H, m, $CH(CH_2OAc)_2$], 3.30 (6 H, s, 2 × OCH_3), 4.04 (4 H, d, *J* 6 Hz, 2 × CH_2OAc), and 4.43 [1 H, t, *J* 6 Hz, $CH(OCH_3)_2$] (Found: C, 53.05; H, 8.1. $C_{11}H_{20}O_6$ requires C, 53.2; H, 8.1%).

2-Acetoxymethyl-4-chloro-4-methoxybutyl Acetate (**25**).—A solution of (**24**) (1.11 g, 4.48 mmol) in dry dichloromethane (10 ml) was treated with acetyl chloride (1 g, 12.54 mmol) and a catalytic amount of thionyl chloride (30 µl). The reaction mixture was stirred at 25 °C for 16 h and then evaporated under reduced pressure. A chloroform (5 ml) solution of the residue was dried ($MgSO_4$) and evaporated, affording the α-chloro ether (**25**) as an oil (1.1 g, 97%); $\nu_{max.}$(film) 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.6—2.7 [9 H, m, 2 × CH_3CO_2 + $CH(CH_2OAc)_2$ + $CHCH_2CH$], 3.50 (3 H, s, OCH_3), 4.05 (4 H, d, *J* 6 Hz, 2 × CH_2OAc), and 5.67 (1 H, t, *J* 6 Hz, CHCl). This material (**25**) was contaminated with a small amount of 4-acetoxy-3-acetoxymethylbutanal.

2-N-Acetyl-9-(4-acetoxy-3-acetoxymethyl-1-methoxybutyl)guanine (**26**) *and* *2-N-Acetyl-7-(4-acetoxy-3-acetoxymethyl-1-methoxybutyl)guanine* (**27**).—A mixture of 2-*N*-acetylguanine (0.97 g, 5 mmol), 1,1,1,3,3,3-hexamethyldisilazane (100 ml), trimethylchlorosilane (0.5 ml), and ammonium sulphate (catalytic) was heated under reflux for 16 h. The reaction mixture was evaporated under reduced pressure and the residue was immediately dissolved in dry acetonitrile (50 ml). This solution was then treated with the crude chloro ether (**25**) (1 g, 4 mmol) and cooled to −70 °C under nitrogen during the addition of tin(IV) chloride (0.52 g, 2 mmol). The reaction mixture was allowed to warm to 25 °C and then stirred for 44 h. Saturated aqueous sodium hydrogen carbonate (20 ml) was added and the mixture extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed with water (100 ml), dried (Na_2SO_4), and evaporated to leave an oily residue, which was chromatographed on silica gel, eluting with ethyl acetate–methanol (30:1). The first component to be eluted was the N-7 substituted guanine (**27**) (350 mg, 22%), isolated as yellow foam; $\lambda_{max.}$(MeOH) 255 nm (ε 13 400); $\nu_{max.}$(KBr) 3 430, 1 740, 1 685, 1 615, 1 545, 1 370, and 1 250 cm^{-1}; $\delta_H(CDCl_3)$ 1.9—2.5 [9 H, m, 2 × CH_3CO_2 + $CH(CH_2OAc)_2$ + $CHCH_2CH$], 2.42 (3 H, s, CH_3CONH), 3.36 (3 H, s, CH_3O), 4.11 (4 H, d, *J* 6 Hz, 2 × CH_2OAc), 6.11 (1 H, t, *J* 6 Hz, $CHOCH_3$), 8.04 (1 H, s, 8-H), 11.40 (1 H, br s, D_2O exchangeable, NH), and 12.32 (1 H, br s, D_2O exchangeable, NH) (Found: C, 48.9; H, 5.8; N, 16.7. $C_{17}H_{23}N_5O_7 \cdot H_2O$ requires C, 48.8; H, 5.8; N, 16.7%).

The second component to be eluted was the N-9 substituted guanine (**26**) (250 mg, 16%), isolated as a white solid, m.p. 146—148 °C; $\lambda_{max.}$(MeOH) 259 nm (ε 16 600); $\nu_{max.}$(KBr) 3 440, 1 740, 1 695, 1 680, 1 610, 1 555, 1 475, and 1 250 cm^{-1}; $\delta_H(CDCl_3)$ 1.98 (2 H, m, $CHCH_2CH$), 2.06 (3 H, s, CH_3CO_2), 2.08 (3 H, s, CH_3CO_2), 2.18 [1 H, m, $CH(CH_2OAc)_2$], 2.32 (3 H, s, CH_3CONH), 3.28 (3 H, s, OCH_3), 5.51 (1 H, t, *J* 6 Hz, $CHOCH_3$), 7.83 (1 H, s, 8-H), 9.03 (1 H, br s, D_2O exchangeable, NH), and 11.97 (1 H, br s, D_2O exchangeable, NH) (Found: C, 49.6; H, 5.8; N, 17.5%. $C_{17}H_{23}N_5O_7$ requires C, 49.9; H, 5.7; N, 17.1%).

9-(4-Hydroxy-3-hydroxymethyl-1-methoxybutyl)guanine (**28**).—A solution of (**26**) (110 mg, 0.28 mmol) in ethanol (6 ml) was treated with hydrazine hydrate (1.1 ml) and the reaction mixture was heated under reflux for 16 h. The solvents were removed under reduced pressure, affording a residual gum, which was triturated with acetone to give the guanine (**28**) (70 mg, 89%) as a white solid, m.p. >310 °C; $\lambda_{max.}$(MeOH) 254 nm (ε 13 900); $\nu_{max.}$(KBr) 3 420, 3 330, 1 685, 1 630, 1 600, 1 570, 1 540, 1 480, 1 380, and 1 350 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.42 [1 H, m, $CH(CH_2OH)_2$], 1.92 (1 H, m, $CHCH_2CH$), 2.08 (1 H, m, $CHCH_2CH$), 3.12 (3 H, s, OCH_3), 3.37 (4 H, m, 2 × CH_2OH), 4.40 (2 H, m, D_2O exchangeable, 2 × OH), 5.49 (1 H, t, *J* 7 Hz, $CHOCH_3$), 6.46 (2 H, br s, D_2O exchangeable, NH_2), 7.80 (1 H, s, 8-H), and 10.58 (1 H, br s, D_2O exchangeable, NH); $\delta_C[(CD_3)_2SO]$ 33.2 ($CHCH_2CH$), 38.9 [$CH(CH_2OH)_2$], 55.4 (OCH_3), 61.1 (CH_2OH), 61.2 (CH_2OH), 83.4 ($CHOCH_3$), 116.3 (C-5), 135.1 (C-8) 151.5 (C-4), 153.6 (C-2), and 156.7 (C-6); *m/z* (f.a.b. +ve ion; thioglycerol) 284 (MH^+), and 567 ($2M + H^+$) (Found: C, 46.05; H, 5.8; N, 24.5%. $C_{11}H_{17}N_5O_4$ requires C, 46.6; H, 6.05; N, 24.7%).

7-(4-Hydroxy-3-hydroxymethyl-1-methoxybutyl)guanine (**29**).—A solution of (**27**) (190 mg, 0.48 mmol) in ethanol (10 ml) was treated with hydrazine hydrate (2 ml) and the mixture heated under reflux for 6 h. The solvents were evaporated under reduced pressure and the residue triturated with acetone. The solid thus obtained was recrystallised from ethanol–hexane, affording the guanine (**29**) (112 mg, 82%) as a white solid, m.p. >310 °C; $\lambda_{max.}$(MeOH) 211 (ε 22 600) and 286 nm (7 320); $\nu_{max.}$(KBr) 3 300—3 460, 1 670br, 1 560, 1 470, 1 380, and 1 210 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.38 [1 H, m, $CH(CH_2OH)_2$], 2.01 (2 H, m, $CHCH_2CH$), 3.17 (3 H, s, OCH_3), 3.33 (4 H, m, 2 × CH_2OH), 4.37 (2 H, m, D_2O exchangeable, 2 × OH), 5.90 (1 H, t, *J* 7 Hz, $CHOCH_3$), 6.21 (2 H, br s, D_2O exchangeable, NH_2), 8.13 (1 H, s, 8-H), and 10.88 (1 H, br s, D_2O exchangeable, NH); $\delta_C[(CD_3)_2SO]$ 33.9 ($CHCH_2CH$), 39.5 [$CH(CH_2OH)_2$], 55.5 (OCH_3), 60.7 (CH_2OH), 61.2 (CH_2OH), 86.2 ($CHOCH_3$), 108.1 (C-5), 141.3 (C-8), 152.8 (C-2), 154.4 (C-6), and 159.8 (C-4); *m/z* (f.a.b. +ve ion; thioglycerol) 284 (MH^+) (Found: C, 46.7; H, 6.0; N, 24.5%. $C_{11}H_{17}N_5O_4$ requires C, 46.6; H, 6.05; N, 24.7%).

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