The Potential of Carbocyclic Nucleosides for the Treatment of AIDS: Synthesis of Some Diphosphorylphosphonates Possessing Potent Activity Against HIV-Coded Reverse Transcriptase

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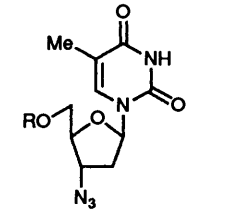
The phosphonates **19**, **20**, **24**, **27** and the diphosphorylphosphonates **10** and **11** have been prepared as mimics of nucleoside-phosphates and -triphosphates respectively. The compounds **10** and **11** were found to be potent inhibitors of human immunodeficiency virus reverse transcriptase (HIV-rt).

Acquired Immune Deficiency Syndrome (AIDS) is a deadly disease that is spreading at an alarming rate. Chemotheurapeutic agents such as azidothymidine (AZT) **1**[1] can have a beneficial effect in prolonging the life-span of persons infected by the causative agent Human Immunodeficiency Virus (HIV). However it is well established that AZT produces severe side effects[2] and a better medicine for the treatment of AIDS is urgently required.

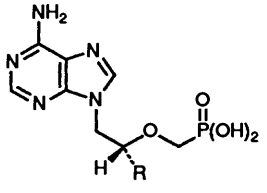
Compounds such as AZT are converted into the corresponding triphosphate **2** *in vivo* and the triphosphate acts as an



1 R = H

2 R = $P(OH)OP(OH)OP(OH)_2$ (O, O, O)

3 R = $P(OH)_2$ (O)



4 R = CH_2OH

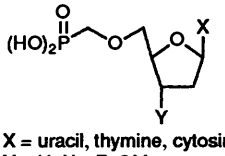
5 R = H

inhibitor of the enzyme reverse transcriptase (rt), a protein that is peculiar to the retrovirus and one that is crucial to the virus for it to continue the production of infectious virions.

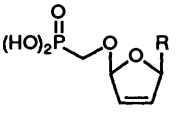
In order to exert anti-viral activity by inhibiting such a key target enzyme in virally infected cells, nucleoside analogues such as AZT require activation through formation of the corresponding triphosphate *via* the monophosphate derivative **3**. The efficiency of this activation process is an important factor in the observed anti-viral activity. A variety of avenues have been explored in an effort to bypass the critical initial phosphorylation step. (Note that nucleotides themselves are too polar to allow penetration into cells at a rate sufficient to produce a significant chemotherapeutic effect).[3]

One approach to the solution of this problem involves the synthesis of derivatives of nucleoside analogues which might enter the cell and subsequently be converted into the corresponding nucleotide. Strategies aimed at the production of such pro-drugs include the preparation of 3′,5′-cyclic phosphates,[4] phosphotriester derivatives,[5] phosphoramidite derivatives[6] as well as cyclic phosphotriesters and phosphoramidite derivatives.[7]

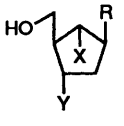
The discovery of (*S*)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine [(*S*)-HPMPA] **4** as a potent broad spectrum anti-viral agent defined a new type of useful nucleotide analogue.[8] Subsequently there have been intensive studies into the design and synthesis of related phosphonomethoxy compounds as potential anti-viral agents and 9-[2-(phosphonomethoxy)-ethyl]adenine (PMEA) **5** and 9-[2-(phosphonomethoxy)ethyl]-guanine were shown to be active against HIV.[9] It has been shown that such PME derivatives are diphosphorylated *in vivo* and it is the resultant diphosphorylphosphonates that act as inhibitors of HIV-rt.[10] The distance between the base moiety and the phosphonomethoxy group has been shown to be critical in maintaining anti-viral activity; compounds such as **6** display reduced levels of biological activity. In contrast compounds of type **7** possessing the correct base-phosphonate interspacial relationship, show potent anti-HIV activity *in vitro*.[11] We felt that the mimicry of a 5′-monophosphate unit by a phosphonomethoxy unit could also be examined by appropriate modification of carbocyclic nucleosides such as **8** and **9** since some of these compounds display anti-HIV activity[12] through inhibition of HIV-rt by the corresponding triphosphates.[13]



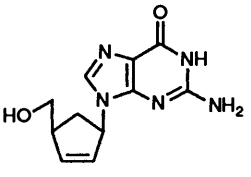
6 X = uracil, thymine, cytosine
Y = H, N_3, F, OMe



7 R = guanine, thymine



8 X = H or F
Y = H or N_3
R = adenine, thymine



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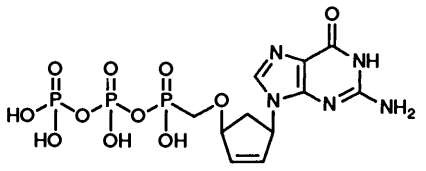
Specifically, we wished to prepare the carbocyclic compounds **10** and **11** to compare the inhibition of HIV-rt by these species with results obtained from the related compounds **2**, **12** and **13** which were known to possess good to excellent inhibitory activity against this enzyme.[14] We report our progress in achieving these targets.

Results and Discussion

6-Oxabicyclo[3.1.0]hex-2-ene **14** was prepared from cyclopentadiene according to a literature procedure.[15] Reaction of this epoxide with 2-amino-6-chloropurine **15** in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0)



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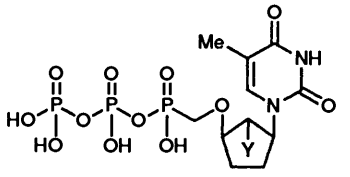
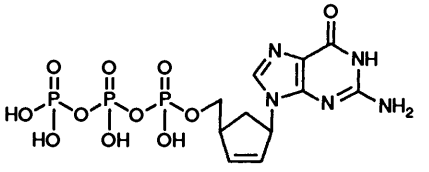


11 Y = H
12 Y = F



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(10 mmol%) gave the alcohol **16** in 91% yield.[16] The latter compound was converted into the methoxy compound **17** using potassium carbonate in methanol (86%). Deprotonation of the alcohol **17** with sodium hydride in tetrahydrofuran (THF) followed by addition of diethyl (*p*-tolylsulfonyloxymethyl)-phosphonate gave the diester **18** in 25% yield.[17] Purification of this diester was accomplished by chromatography over silica and HPLC using an S2-ODS-2 reversed-phase column.

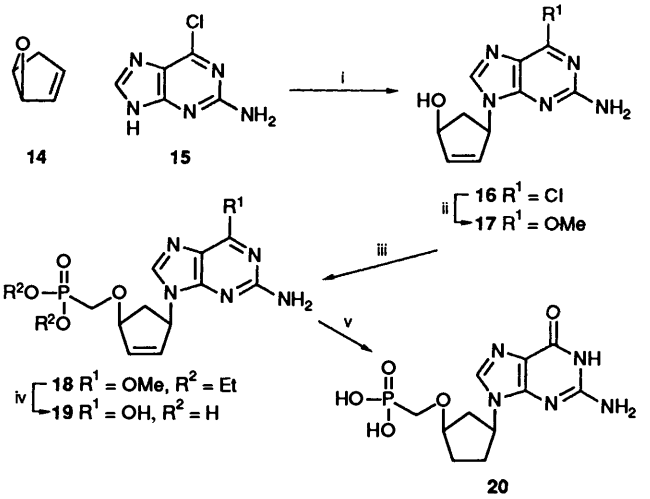
De-esterification of the diethyl phosphonate **18** was achieved by reaction with a large excess of trimethylsilyl iodide in dimethylformamide (DMF), followed by hydrolysis of the resultant silyl ester using an aqueous solution of ammonium hydrogen carbonate.[18] The crude phosphonate **19** was purified using Sephadex LH-20 [eluting with methanol–aqueous formic acid (0.1 mol dm^{-3}) (1:1)] followed by HPLC using a Microsorb reversed-phase column (eluent 10% methanol in water). Note that the 6-methoxypurine unit was converted into the guanine base during the course of the reaction.

Hydrogenation of the phosphonate **19** using palladium on carbon as the catalyst gave the cyclopentane derivative **20** (Scheme 1).

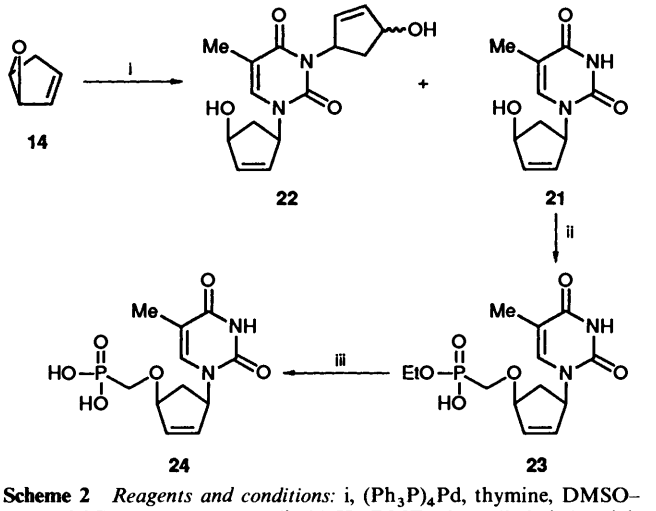
Reaction of the epoxide **14** with thymine in dimethyl sulfoxide (DMSO) and THF in the presence of tetrakis(triphenylphosphine)palladium(0) gave two products (Scheme 2). The major product **21** (25%) was clearly formed through alkylation of thymine at N-1 (λ_{max}/nm 272, pH6 buffer). NMR spectroscopy showed that the minor product contained two cyclopentenol units, and possessed the structure shown in formula **22** (11%).

Deprotonation of the alcohol **21** and reaction with diethyl (*p*-tolylsulfonyloxymethyl)phosphonate in DMF yielded, after work-up and chromatography over Sephadex LH-20, the monoester **23**. Loss of one of the phosphonate ester groups has been observed previously in reactions of this type.[19] The target compound **24** was obtained from the monoester **23** using trimethylsilyl bromide in DMF followed by hydrolysis using ammonium hydrogen carbonate. Purification was effected by chromatography over Sephadex LH-20 [eluent methanol–aqueous formic acid] and Sephadex DEAE-A25 eluting with a linear gradient of water and aqueous ammonium hydrogen carbonate (0 to 0.4 mol dm^{-3}).

Hydrogenation of the alkene **21** in the presence of palladium on carbon gave the hydrogenolysis product **25** (19%) and the



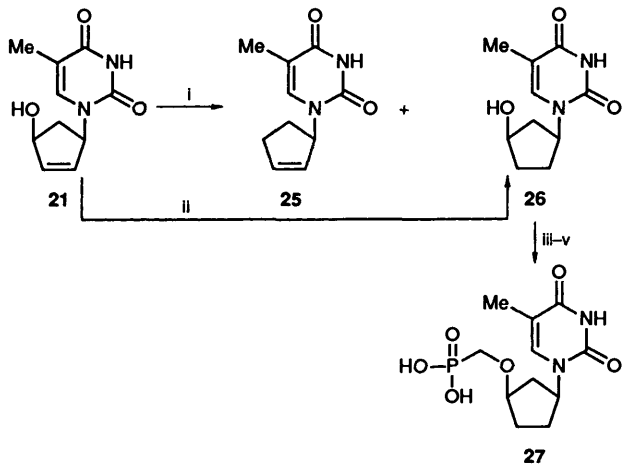
Scheme 1 *Reagents and conditions:* i, $(Ph_3P)_4Pd$, DMSO–THF, 0 °C to room temp.; ii, K_2CO_3, MeOH, heat; iii, NaH, THF, 0.5 h then diethyl (*p*-tolylsulfonyloxymethyl)phosphonate in THF, room temp.; iv, Me_3SiI, DMF, room temp. then NH_4HCO_3, H_2O; v, Pd–C, H_2O, H_2, 6 h, room temp.



Scheme 2 *Reagents and conditions:* i, $(Ph_3P)_4Pd$, thymine, DMSO–THF, 0 °C to room temp.; ii, NaH, DMF, then diethyl (*p*-tolylsulfonyloxymethyl)phosphonate, room temp.; iii, Me_3SiBr, DMF, 0 °C then NH_4HCO_3, H_2O

required *N*-(3-hydroxycyclopentyl)thymine **26** 47%). An indirect sequence involving protection of the hydroxy group proved to be higher yielding (61% overall) for the conversion of **21** into **26** (Scheme 3). The latter compound was transformed into the phosphonate **27** in a standard sequence of reactions.

With the phosphonates **19**, **20**, **24**, and **27** in hand, two of the compounds **19** and **27** were selected for conversion into the corresponding diphosphorylphosphonates. Hence the phosphonate **27** was treated with 1,1′-carbonyldiimidazole to give the intermediate imidazolidate *in situ*.[20] Addition of tributylammonium pyrophosphate gave a crude product which was purified by anion exchange chromatography over Sephadex DEAE-A25 to furnish the *pseudo*-triphosphate **11**. Reaction of the phosphonate **19** under the above conditions was unsuccessful probably due to solubility problems. As a result an alternative method involving the formation of a morpholidate intermediate was devised.[21] Thus the phosphonate **19** was treated with morpholine and 1,3-dicyclohexylcarbodiimide (DCC) in hot aqueous *tert*-butyl alcohol. The crude mixture obtained after an aqueous work-up procedure was rigorously dried and treated with tributylammonium pyrophosphate in dry DMSO.



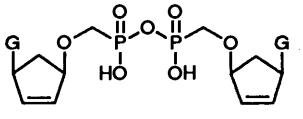
Scheme 3 *Reagents and conditions:* i, Pd–C, H_2, EtOH, room temp.; ii, TBDMSCl, imidazole, DMF, room temp. then *i*, then TBAF, THF room temp.; iii, NaH, DMF, room temp. then diethyl (*p*-tolylsulfonyloxymethyl)phosphonate, room temp.; iv, TMSBr, DMF, 0 °C–room temp.; v, NH_4HCO_3, H_2O, 0 °C–room temp.

Table 1 Activity of nucleotides and analogues against HIV-rt[a]

Compound	IC_{50} (μ mol dm^{-3})
2	0.075
10	0.06
11	0.11
12	0.01
13	0.05

[a] AZT triphosphate and other thymidine derivatives were assayed using (rA)(dT) as the template primer and [^{3}H]dTTP as substrate. Carbovir triphosphate and compound **10** were assayed using (rC)(dG) as the template primer and [^{3}H]dGTP as substrate.

After 4 d the reaction mixture was applied onto a Sephadex DEAE-A25 anion exchange column. The column was eluted with water and then a linear gradient of water and aqueous ammonium hydrogen carbonate (0 → 0.4 mol dm^{-3}). Two UV active products were obtained, the required *pseudo*-triphosphate **10** and a compound tentatively assigned the structure **28**.



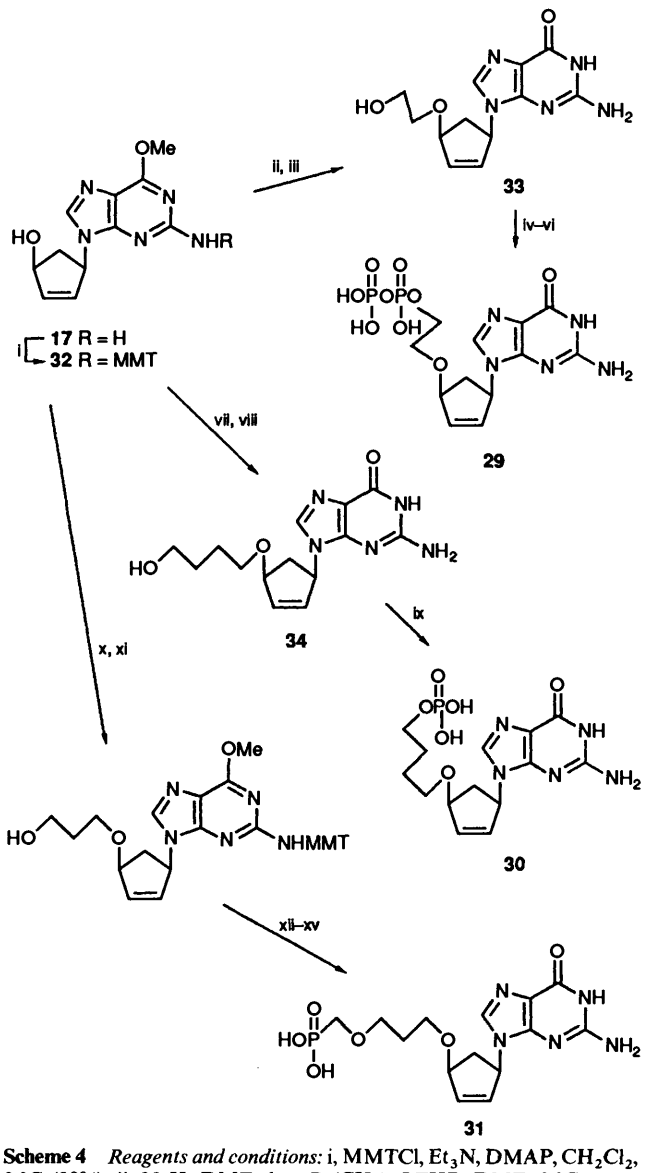
28 G = N-9 guanine

The ^{31}P NMR spectra of the diphosphorylphosphonates **10** and **11** displayed three signals δ *ca.* 9.8 [1 P, d, *J* 25, P(1)], *ca.* −9.5 [1 P, m, P(3)], and *ca.* −22 [1 P, m, P(2)].

The ^{31}P NMR spectrum of compound **28** showed a single signal (δ −8.8) considerably upfield from the corresponding signal from the phosphonate (δ 16.4). Unfortunately, the structure of compound **28** could not be confirmed by FAB-MS—the major signal observed (*m*/*z* 328) corresponded to the phosphonate.

Biological Activities.—The biological activities of the nucleoside triphosphates and analogues under scrutiny are given in Table 1.

The results are striking. The compounds **10** and **11** are as potent inhibitors of HIV-1 reverse transcriptase as the triphosphate derivatives of AZT **2** and carbovir **13**. However neither of the two triphosphates **10**, **11** nor the corresponding phosphonates **19**, **27** displayed activity against HIV-infected cells *in vitro*. While not proven, it seems likely that these triphosphate mimics and also the monophosphate mimics are too polar to cross lipophilic cell walls. In summary, the diphosphorylphosphonates **10**, **11** are excellent inhibitors of HIV-rt but neither they nor the putative metabolic precursors **19**, **27** can gain entry into an infected cell.



Scheme 4 *Reagents and conditions:* i, MMTCl, Et_3N, DMAP, CH_2Cl_2, 0 °C (80%); ii, NaH, DMF then $Br(CH_2)_2OTHP$, DMF, 0 °C–room temp. (59%); iii, aq. HCl (2 mol dm^{-3}), THF, heat; iv, $POCl_3$, $(MeO)_3$ P=O, 0–4 °C (36%); v, morpholine, DCC, aq. Bu^{t}OH, heat; vi, PO_4H_3–NBu_3, pyridine, room temp. (36% for steps v, vi); vii, NaH, DMF then $Cl(CH_2)_4OTHP$, DMF 0 °C–room temp.(34%); viii, aq. HCl (2 mol dm^{-3}), THF, heat (65%); ix, $POCl_3$, $(MeO)_3$ P=O, 0–4 °C (21%); x, NaH, DMF then $Br(CH_2)_3OTBDMS$ (64%); xi, TBAF, THF, room temp. (100%); xii, NaH, THF then $(EtO)_2P(O)CH_2OTs$ (49%); xiii, glacial CH_3CO_2H, heat (80%); xiv, TMSI, DMF, 0 °C to room temp.; xv, aq. NH_4HCO_3, 0 °C–room temp. (43% for steps xiv, xv)

In order to try to increase the lipophilic nature of the side chain it was decided to investigate whether more substantial modification of the triphosphate chain could be made. Three compounds **29**–**31** were prepared as outlined in Scheme 4.

Unfortunately, none of these three compounds showed activity against the reverse transcriptase. However during the course of these investigations a number of nucleosides containing an extended side chain attached to the cyclopentene ring *via* an ether linkage were prepared. One of these analogues **33** displayed activity against HIV (IC_{50} 14 μg cm^{-3}). Homologues

prepared of other nucleosides or analogues have frequently lacked antiviral activity;[22] it is therefore proposed that the presence of the oxygen atom in the ether linkage is responsible for the observed activity. The number of carbon atoms in the side chain has a bearing on the situation since the analogue **34** containing a longer side chain was devoid of activity.

We are continuing to investigate the mimicry of the monophosphate and triphosphate moieties of carbocyclic nucleotides. Other research groups are active in the preparation of nucleotide surrogate species.[23] Different types of anti-HIV nucleotide analogues are continuing to appear in the literature[24] and these data help to define the different structural requirements that are necessary for the requisite biological activity in the nucleoside and carbocyclic nucleoside series.[25]

Experimental

The UV spectra were recorded on a Philips PU8700 spectrometer; the wavelength of the maximum absorbance (λ_{max}) is given in nm with the molar extinction coefficient. The IR spectra were recorded on a Perkin-Elmer 881 spectrometer. The ^1H NMR spectra were recorded on a Bruker AM 250 spectrometer at 250 MHz using deuteriochloroform as the solvent unless otherwise stated. The ^{31}P NMR spectra were recorded on a Varian 400 MHz spectrometer at 161.9 MHz. All chemical shifts are reported as δ values and the coupling constants (J) are quoted in Hz. The m.p.s were determined on a capillary apparatus, and the b.p.s are uncorrected. Light petroleum refers to the fraction of b.p. 60–80 °C. Benzene, ether and tetrahydrofuran (THF) were distilled from $LiAlH_4$ or sodium wire and benzophenone immediately before use. Dichloromethane was distilled from CaH_2 immediately before use. Dimethyl sulfoxides (DMSO), pyridine and triethylamine were distilled from CaH_2 and DMF was distilled from barium oxide and stored over 4 Å molecular sieves.

2-*Amino*-6-*chloro*-9-[(1′β,4′β)-4′-*hydroxycyclopent*-2′-*enyl*]-*purine* **16**.—Tetrakis(triphenylphosphine)palladium(0) (0.288 g, 0.25 mmol) was added to a suspension of 2-amino-6-chloropurine **15** (5.10 g, 30.07 mmol) in dry DMSO (50 cm^3). After being stirred for 2 min at room temp. in the dark under an inert atmosphere the mixture was cooled to 0 °C. A solution of 6-oxabicyclo[3.1.0]hex-2-ene **14** (2.75 g, 33.50 mmol) in dry THF (20 cm^3) was added dropwise, then the yellow suspension was stirred at 0 °C for 3 h then allowed to warm to room temp. slowly and stirred overnight. The orange solution was concentrated under reduced pressure; the dark oil was dissolved in dichloromethane (50 cm^3), filtered through Celite and evaporated under reduced pressure. The resultant oil was purified by chromatography using ethyl acetate as eluent and the *title compound* **16** (6.87 g, 27.30 mmol, 91%) was obtained as a white crystalline solid, m.p. 156–158 °C (from MeOH) (Found: C, 46.4; H, 4.15; N, 27.0. $C_{10}H_{10}ClN_5O + 0.5H_2O$ requires C, 46.1; H, 3.9; N, 26.9%); λ_{max}(pH 6 phosphate buffer)/nm 245.6 and 307.8; ν_{max}(KBr)/cm^{-1} 3600–2700s br (NH, OH), 1610s and 1562s (C=C, C=N); δ_H(250 MHz; [$^2H_6$]-DMSO) 8.03 (1 H, s, 8-H), 6.74 (2 H, s, NH), 6.19 (1 H, ddd, J 5.5, 2, 2, 3′-H), 6.03–5.97 (1 H, m, 2′-H), 5.37–5.27 (1 H, m, 1′-H), 5.24 (1 H, d, J 6, OH), 4.78–4.70 (1 H, m, 4′-H), 2.86 (1 H, ddd, J 14, 8, 7, 5′-αH) and 1.69 (1 H, ddd, J 14, 4, 4, 5′-βH); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 159.59 (C-2), 153.41 (C-6), 149.36 (C-4), 141.16 (C-8), 139.58 (C-3′), 130.32 (C2′), 123.51 (C-5), 73.54 (C-4′), 56.64 (C-1′) and 41.00 (C-5′).

2-*Amino*-9-[(1′β,4′β)-4′-*hydroxycyclopent*-2′-*enyl*]-6-*methoxypurine* **17**.—Potassium carbonate 2.06 g, 14.90 mmol) was added to a solution of the purine **16** (2.50 g, 9.93 mmol) in methanol (90 cm^3). The reaction mixture was refluxed for 0.75 h and then adsorbed onto silica. Chromatography using dichloromethane–methanol (15:1) as eluent yielded the *title compound* **17** (2.12 g, 8.57 mmol, 86%) as an off-white solid, m.p. 152–153 °C (Found: C, 53.3; H, 5.2; N, 27.9. $C_{11}H_{13}N_5O_2$ requires C, 53.4; H, 5.3; N, 28.3%); λ_{max}(pH 6 phosphate buffer)/nm 248.8 and 251.0; ν_{max}(KBr)/cm^{-1} 3600–2800s (NH, OH), 1612s and 1580s (C=C, C=N); δ_H(250 MHz; [$^2H_6$]-DMSO) 7.64 (1 H, s, 8-H), 6.33 (2 H, s, NH_2), 6.16 (1 H, ddd, J 5.5, 2, 2, 3′-H), 5.96 (1 H, ddd, J 5.5, 2, 1, 2′-H), 5.34–5.24 (2 H, m, 1′-H, OH), 4.76–4.66 (1 H, m, 4′-H), 3.80 (3 H, s, OCH_3), 2.85 (1 H, ddd, J 14, 8, 7, 5′-αH) and 1.65 (1 H, ddd, J 14, 4, 4, 5′-βH); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 159.04, 158.02, 151.95, 112.34 (C-2, C-4, C-5, C-6), 137.63, 136.11, 129.10 (C-8, C-2′, C-3′), 71.98 (C-4′), 54.85 (C-1′), 51.49 (OCH_3) and 39.67 (C-5′) (Found (EI): M^+, 247.1069. $C_{11}H_{13}N_5O_2$ requires M, 247.1069].

2-*Amino*-9-[(1′β,4′β)-4′-(*diethylphosphonomethoxy*)*cyclopent*-2′-*enyl*]-6-*methoxypurine* **18**.—A solution of the allylic alcohol **17** (1.002 g, 4.05 mmol) in dry THF (20 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.880 g, 60% in oil *ca.* 22.0 mmol) in dry THF (10 cm^3) under an inert atmosphere. After 0.5 h, a solution of diethyl (*p*-tolylsulfonyloxymethyl)phosphonate (1.909 g, 5.93 mmol) in dry THF (10 cm^3) was added dropwise and the reaction mixture was stirred overnight. After cooling to 0 °C, glacial acetic acid (0.34 cm^3, *ca.* 6.0 mmol) was added dropwise and the resultant brown suspension was filtered through Celite and evaporated under reduced pressure. Chromatography using dichloromethane–methanol (15:1) as eluent afforded two fractions: the first contained the title compound (0.304 g) whilst the second contained the title compound and the starting alcohol. Separation of the mixed fractions was achieved by HPLC (S2-ODS-2 column eluting with 53% methanol in water). The *title compound* **18** (0.404 g, 1.02 mmol, 25%) was obtained as a colourless gum; λ_{max}(pH 6 phosphate buffer)/nm 249.4 and 281.0; ν_{max}($CHCl_3$)/cm^{-1} 3534w, 3426m (NH), 1608s, 1587s (C=C, C=N) and 1246s br (P=O); δ_H(250 MHz; $CDCl_3$) 7.67 (1 H, s, 8-H), 6.31 (1 H, ddd, J 6, 2, 2, 3′-H), 6.06 (1 H, dd, J 6, 2, 2′-H), 5.49–5.39 (1 H, m, 1′-H), 5.00–4.83 (2 H, m, NH_2), 4.77–4.67 (1 H, m, 4′-H), 4.25–4.09 (4 H, m, 4 × H-CHO), 4.07 (3 H, s, OCH_3), 4.01–3.81 (2 H, m, 2 × H-CHO), 2.89 (1 H, ddd, J 15, 7.5, 7.5, 5′-αH), 2.00 (1 H, ddd, J 15, 4, 4, 5′-βH) and 1.40–1.29 (6 H, m, 2 × CH_3CH_2); δ_C(62.9 MHz; $CDCl_3$) 159.30 (C), 138.02, 135.40, 133.96 (C-8, C-2′, C-3′), 84.48 (d, J 11.8 C-4′), 62.81 (d, J 167.6, PCH_2O), 62.50 (d, J 4.5, CH_3CH_2OP), 56.65 (C-1′), 53.82 (OCH_3), 37.90 (C-5′) and 16.47 (d, J 6.1, CH_3CH_2OP); δ_P(161.9 MHz; $CDCl_3$) 21.85 [Found (EI): M^+, 397.1515. $C_{16}H_{24}N_5O_5P$ requires M, 397.1515].

9-[(1′β,4′β)-4′-(*Phosphonomethoxy*)*cyclopent*-2′-*enyl*]*guanine* **19**.—Trimethylsilyl iodide (1.0 cm^3, *ca.* 1.4 g, 7.0 mmol) was added dropwise to stirred solution of the diethyl phosphonate **18** (0.177 g, 0.44 mmol) in dry DMF (5 cm^3) at 0 °C in the dark. The reaction mixture was stirred at room temp. overnight. After cooling to 0 °C ammonium hydrogen carbonate (0.2 mol dm^{-3}; 5 cm^3) was added dropwise and stirring continued for 2.5 h at room temp. Ethanol (75 cm^3) was added and the resultant solution evaporated under reduced pressure; the residue was chromatographed over Sephadex LH-20 using methanol–aqueous formic acid (0.1 mol dm^{-3}) (1:1). The yellow solid obtained (0.086 g) was further purified by HPLC (Microsorb C18, 80-225-C^5 eluting with 10% methanol in water). The *title compound* **19** (0.036 g, 0.11 mmol, 25%) was obtained as a white lyophiliate by lyophilisation of appropriate fractions (Found: C, 37.5; H, 5.1; N, 20.3. $C_{11}H_{14}N_5O_5P + 1.3H_2O$ requires C, 37.7; H, 5.2; N, 20.0%); λ_{max}(pH 6 phosphate buffer)/nm 253.2 and 280.2; ν_{max}(KBr)/cm^{-1} 3600–2600s (NH, OH), 1689s and 1607s (C=O, C=C, C=N); δ_H(250 MHz; D_2O)

8.00 (1 H, s, 8-H), 6.55–6.49 (1 H, m, 3′-H), 6.31–6.24 (1 H, m, 2′-H), 5.52–5.42 (1 H, m, 1′-H), 3.83 (2 H, d, *J* 10, PCH_2O), 3.11 (1 H, ddd, *J* 15, 7.5, 7.5, 5′-αH) and 2.30 (1 H, ddd, *J* 15, 4, 4, 5′-βH); δ_P (161.9 MHz; D_2O) 16.4 (5) [Found (FAB): $M^+ + H$, 328.0811. $C_{11}H_{14}N_5O_5P$ requires (*M* + H), 328.0811].

1-[(1′β,4′β)-4′-(*Phosphonomethoxy*)*cyclopentyl*]*guanine* **20**.—A solution of the alkene **19** (0.020 g, 0.061 mmol) in water (3 cm^3) was added to palladium on carbon (10%, 0.013 g). The suspension was stirred under an atmosphere of hydrogen for 6 h, the catalyst was removed by filtration through Celite and washed with ethanol–ammonia–water (5:1:5). The solution was evaporated under reduced pressure and the residue chromatographed over Sephadex LH-20 [eluent methanol–aqueous formic acid (0.1 mol dm^{-5}) (1:2)]. The *title compound* **20** (0.018 g, 0.055 mmol, 90%) was obtained as a white lyophiliate of lyophilisation of appropriate fractions; $\lambda_{max}(H_2O)$/nm 253.2 (11 860); ν_{max}(KBr)/cm^{-1} 3700–2600s br (NH, OH), 1687s (C=O, guanine), 1607s (C=C, C=N) and 1250–1000 sbr (C–O, P–O–C, P=O); δ_H(250 MHz; D_2O) 8.20 (1 H, s, 8-H), 4.42–4.33 (1 H, m, 4′-H), 3.74 (2 H, d, *J* 9, PCH_2O), 2.70 (1 H, ddd, *J* 15, 8, 6, 5′-H), 2.48–2.34 (1 H, m, 2′-, 3′- or 5′-H), 2.28–2.04 (4 H, m, 4 × 2′-, 3′- or 5′-H) [Found (FAB): $M^+ + H$ 330.097. $C_{11}H_{16}N_5O_5P$ requires (*M* + H) 330.097].

1-[(1′β,4′β)-4′-*Hydroxycyclopent*-2′-*enyl*]-3-[(1″,4″)-4″-*hydroxycyclopent*-2″-*enyl*]*thymine* **22** *and* 1-[(1′β,4′β)-4′-*hydroxycyclopent*-2′-*enyl*]*thymine* **21**.—Tetrakis(triphenylphosphine) palladium(0) (0.097 g, 0.08 mmol) was added to a suspension of thymine (1.120 g, 8.88 mmol) in dry DMSO (10 cm^3) under an inert atmosphere in the dark. After being stirred for 2 min at room temp., the reaction mixture was cooled to 0 °C and a solution of 6-oxabicyclo[3.1.0]hex-2-ene **15** (0.649 g, 7.90 mmol) in dry THF (8 cm^3) was added dropwise over 10 min. The yellow solution was allowed to warm to room temp. over 2 h and then stirred overnight. The solvent was evaporated under reduced pressure and the residue dissolved in dichloromethane (20 cm^3), filtered through Celite and evaporated under reduced pressure. The residue was chromatographed using chloroform–ethanol (15:1) and afforded the *title compound* **22** (0.258 g, 0.89 mmol, 11%) as a colourless oil; λ_{max}(pH 6 phosphate buffer)/nm 273.8; $\nu_{max}(CHBr_3)$/cm^{-1} 3585m (OH), 3550–3200m br (OH), 1689s, 1665s (C=O) and 1630s (C=C); δ_H(250 MHz; $CDCl_3$) 7.18 (1 H, dd, *J* 1, 1, 6-H), 6.26–6.19 (1 H, m, 3′-H), 6.14 (1 H, ddd, *J* 5, 2.5, 2.5, 3″-H), 5.96 (1 H, ddd, *J* 10, 2.5, 2.5, 2″-H), 5.85–5.79 (1 H, m, 1″-H), 5.75 (1 H, ddd, *J* 5.5, 2.5, 2′-H), 5.61–5.50 (1 H, m, 1′-H), 4.93–4.84 (1 H, m, 4′- or 4″-H), 4.75–4.68 (1 H, m, 4′- or 4″-H), 4.30 (1 H, dd, *J* 9, 2, OH), 2.98–2.70 (2 H, m, 5′-, 5″-H), 2.40 (1 H, s, OH), 1.99–1.86 (4 H, m, 5′-CH_3, 5″-H) and 1.57 (1 H, ddd, *J* 15, 4, 4, 5′-H); δ_C(100.58 (MHz; [$^2H_6$]-DMSO) 163.15, 150.74 (C=O), 140.23, 140.18, 136.08, 134.33, 132.20, 132.15, 130.83, 130.78 (C-6), C-2′, C-2″, C-3′, C-3″), 108.76 (C-5), 74.28, 73.44 (C-4′, C-4″), 58.99, 55.61 (C-1′, C-1″), 40.33, 37.68 (C-5′, C-5″) and 12.96 (CH_3–C-5) [Found (EI): M^+, 290.1267. $C_{15}H_{18}N_2O_4$ requires *M*, 290.1267]; and the *title compound* **21** (0.404 g, 1.94 mmol, 25%) as a white crystalline solid, m.p. 196–199 °C (from isopropyl alcohol) (Found: C, 57.55; H, 5.9; N, 13.1. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.8, N, 13.45%); λ_{max}(pH 6 phosphate buffer)/nm 272.0 (10 050); ν_{max}(KBr)/cm^{-1} 3600–3300s br (NH, OH) and 1688s br (C=O, thymine); δ_H(250 MHz; [$^2H_6$]-DMSO) 11.25 (1 H, s, NH), 7.29 (1 H, s, 6-H), 6.13 (1 H, ddd, *J* 6, 2, 2, 3′-H), 5.82–5.76 (1 H, m, 2′-H), 5.43–5.33 (1 H, m, 1′-H), 5.23 (1 H, d, *J* 5, OH), 4.68–4.53 (1 H, m, 4′-H), 2.73 (1 H, ddd, *J* 14, 7, 7, 5′-αH), 1.76 (3 H, s, 5-CH_3) and 1.36 (1 H, ddd, *J* 14, 4.5, 4.5, 5′-βH); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 163.70, 150.73 (C-2, C-4), 139.88, 137.10, 130.78 (C-6, C-2′, C-3′), 109.24 (C-5), 73.29 (C-4′), 57.75 (C-1′), 40.09 (C-5′) and 12.06 (5-CH_3).

1-[(1′β,4′β)-4′-(*Diethylphosphonomethoxy*)*cyclopent*-2′-*enyl*]*thymine and* 1-[(1′β,4′β)-4′(*Ethylphosphonomethoxy*)*cyclopent*-2′-*enyl*]*thymine* **23**.—A solution of the allylic alcohol **21** (0.410 g, 1.97 mmol) in dry DMF (5 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.40 g, 60% in oil, *ca.* 10.0 mmol) in dry DMF (3 cm^3) under an inert atmosphere. After the mixture had been stirred for 0.25 h a solution of diethyl (toluene-*p*-sulfonyloxymethane)phosphonate (0.763 g, 2.38 mmol) in dry DMF (3 cm^3) was added dropwise. The brown solution was stirred overnight at room temperature then cooled to 0 °C. Glacial acetic acid (0.135 cm^3, *ca.* 2.4 mmol) was added dropwise, the reaction mixture was then filtered through Celite and evaporated under reduced pressure. The residue was chromatographed over Sephadex LH-20 using methanol as eluent. Two fractions were collected, both were contaminated with diethyl (*p*-tolylsulfonyloxymethyl)phosphonate: the first contained 1-[(1′β,4′β)-4′-(*diethylphosphonomethoxy*)*cyclopent*-2′-*enyl*]*thymine* and the second contained the *title compound* **23**. An analytical sample of compound **23** was obtained as a colourless gum by further purification over Sephadex LH-20 using methanol as eluent; λ_{max}(MeOH)/nm 272.4 (12 250); ν_{max}3600–3200w (NH, OH), 1686s br (C=O), thymine), 1258s (P=O) and 1055s (P–O–C, C–O); δ_H(250 MHz; [$^2H_4$]-MeOH) 7.40 (1 H, d, *J* 1, 6-H), 6.37 (1 H, ddd, *J* 5, 2, 2, 3′-H), 5.92–5.85 (1 H, m, 2′-H), 5.59–5.50 (1 H, m, 1′-H), 4.62–4.54 (1 H, m, 4′-H), 3.96 (2 H, ddd, *J* 14, 7, 7, OCH_2CH_3), 3.68 (2 H, d, *J* 9, PCH_2O), 2.79 (1 H, ddd, *J* 15, 8, 7, 5′-αH), 1.87 (3 H, d, *J* 1, 5-CH_3), 1.69 (1 H, ddd, *J* 15, 4, 4, 5′-βH) and 1.24 (3 H, t, *J* 7, CH_3CH_2); δ_C(62.9 MHz; [$^2H_4$]-MeOH) 166.45, 152.97 (C-2, C-4), 139.41, 138.10, 133.90 (C-6, C-2′, C-3′), 112.02 (C-5), 85.49 (d, *J* 12.5, C-4′), 66.21 (d, *J* 159, PCH_2O), 61.69 (d, *J* 5.7, CH_2OP), 60.01 (C-1′), 37.94 (C-5′), 17.35 (d, *J* 6.0, CH_3CH_2OP) and 12.52 (5-CH_3) [Found (FAB): M^+ + Na, 353.0878. $C_{13}H_{19}N_2O_6P$ requires (M + Na), 353.0878].

1-[1′β,4′β)-4′-(*Phosphonomethoxy*)*cyclopent*-2′-*enyl*]*thymine* **24**.—Trimethylsilyl bromide (0.2 cm^3, *ca.* 0.230 g, 1.50 mmol) was added dropwise to a stirred solution of the crude monoethyl phosphonate **23** (0.088 g, *ca.* 0.27 mmol) in dry DMF (3 cm^3) at 0 °C. The reaction mixture was stirred at room temp. for 5.25 h then cooled to 0 °C. Aqueous ammonium hydrogen carbonate solution (0.6 mol dm^{-3}; 5 cm^3) was added dropwise and the reaction mixture allowed to stand overnight at room temp. After evaporation under reduced pressure the residue was chromatographed over Sephadex LH-20 using methanol–aqueous formic acid (0.1 mol dm-3) (1:2) as eluent. Appropriate fractions were combined and evaporated under reduced pressure, the residue was chromatographed over Sephadex DEAE-A25 eluting with aqueous ammonium hydrogen carbonate solution (0–0.4 mol dm^{-3} in 600 cm^3). Appropriate fractions were evaporated under reduced pressure, co-evaporated with water (4 × 25 cm^3) and lyophilised to afford the *title compound* **24** (0.022 g, 0.07 mmol, *ca.* 26%) as a white lyophiliate; λ_{max}(pH 6 phosphate buffer)/nm 272.2 (13 610); ν_{max}(KBr)/cm^{-1} 3700–2600s br (NH, OH), 1691s, 1640s (C=O, thymine) and 1260s (P=O); δ_H(250 MHz; D_2O) 7.58 (1 H, s, 6-H), 6.51 (1 H, ddd, *J* 6, 2, 2, 3′-H), 6.11 (1 H, ddd, *J* 6, 1, 1, 2′-H), 5.67–5.57 (1 H, m, 1′-H), 3.84 (2 H, d, *J* 9, PCH_2O), 3.06 (1 H, ddd, *J* 15, 7.5, 7.5, 5′-αH, 2.02 (3 H, s, 5-CH_3) and 1.81 (1 H, ddd, *J* 15, 4.5, 4.5, 5′-βH); δ_P(161.9 MHz; D_2O) 16.44 [Found (FAB): $M^+ + H$, 303.0746. $C_{11}H_{15}N_2O_6P$ requires (M + H) 303.0746].

1-(*Cyclopent*-2′-*enyl*)*thymine* **25** *and* 1-[(1′β,4′β)-4′-*Hydroxycyclopentyl*]*thymine* **26**.—A solution of the allylic alcohol **21** (0.984 g, 4.73 mmol) in ethanol (50 cm^3) was added to palladium on carbon catalyst (10%, 0.197 g) suspended in ethanol (5 cm^3). The reaction mixture was stirred under an atmosphere of hydrogen for 2.5 h; the catalyst was removed by filtration

through Celite and the filtrate evaporated under reduced pressure. Chromatography using dichloromethane–methanol (20:1 followed by 15:1) as eluent yielded the *title compound* **25** (0.170 g, 0.88 mmol, 19%) as a white solid, m.p. 172–174 °C (decomp.); λ_{max}(EtOH)/nm 273.6 (10 200); ν_{max}(KBr)/cm^{-1} 3600–3300w br (NH), 1687s and 1658s (C=O, thymine); δ_H(250 MHz; $CDCl_3$) 9.44 (1 H, s, NH), 7.01 (1 H, d, *J* 1, 6-H), 4.90 (1 H, ddd, *J* 17, 8.5, 8.5, 1′-H) and 2.22–1.48 (11 H, m, 5-CH_3, 2 × 2′-H, 2 × 3′-H, 2 × 4′-H, 2 × 5′-H); δ_C(62.9 MHz; $CDCl_3$) 163.90, 151.34 (C-2, C-4′), 136.78 (C-6), 110.91 (C-5), 56.43 (3-1′), 31.24, 24.18 (C-2′, C-3′, C-4′, C-5′) and 12.58 (5-CH_3) [Found (EI): M^+, 194.1055. $C_{10}H_{14}N_2O_2$ requires *M*, 194.1055]; and the *title compound* **26** (0.471 g, 2.24 mmol, 47%) as a white solid, m.p. 184–186 °C (Found: C, 57.05; H, 6.75; N, 13.2. $C_{10}H_{12}N_2O_3$ requires C, 57.13; H, 6.70; N, 13.32%); λ_{max}(pH 6 phosphate buffer)/nm 273.4 (8360); ν_{max}(KBr)/cm^{-1} 3600–3300m (NH, OH) and 1677s br (C=O, thymine); δ_H(250 MHz; [$^2H_6$]-DMSO) 11.12 (1 H, s, NH), 7.72 (1 H, s, 6-H), 5.0–4.82 (2 H, m, 1′-H, OH), 4.22–4.08 (1 H, m, 4′-H), 2.26–2.11 (1 H, m, 2′-, 3′- or 5′-H), 2.05–1.86 (1 H, m, 2′-, 3′- or 5′-H) and 1.82–1.45 (7 H, m, 5-CH_3, 4 × 2′-, 3′- or 5′-H); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 163.63, 150.96 (C-2, C-4), 138.05 (C-6), 109.19 (C-5), 70.06 (C-4′), 53.40 (C-1′), 40.01, 34.02, 29.40 (C-2′, C-3′, C-5′) and 12.17 (5-CH_3) [Found (CI): M^+ + H, 211.1083. $C_{10}H_{12}N_2O_3$ requires (M + H), 211.1083].

Preparation of 1-[1′β,4′β)-4′-*Hydroxycyclopentyl*]*thymine* **26** via 1-{(1′β,4′β)-4′-tert-*Butyldimethylsilyloxycyclopent*-2′-*enyl*]-*thymine*.—*tert*-Butyldimethylsilyl chloride (1.085 g, 7.20 mmol) was added to a stirred solution of the allylic alcohol **21** (1.370 g, 6.58 mmol) and imidazole (0.939 g, 13.79 mmol) in dry DMF (50 cm^3) under an inert atmosphere. The reaction mixture was stirred at room temp. for 2 h then partitioned between ethyl acetate (100 cm^3) and water (100 cm^3). The aqueous phase was extracted with ethyl acetate (3 × 100 cm^3) and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was partitioned between ether (100 cm^3) and water (100 cm^3), the organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography using light petroleum–ethyl acetate (2:1) as eluent afforded 1-[(1′β,4′β)-4′-tert-*butyldimethylsilyloxycyclopent*-2′-*enyl*]*thymine* (1.573 g, 4.88 mmol, 74%) as a white solid, m.p. 159–160 °C (Found: C, 58.9; H, 8.1; N, 8.3. $C_{16}H_{26}N_2O_3Si$ + 0.25·H_2O requires C, 58.8; H, 8.2; N, 8.6%); λ_{max}(MeOH)/nm 272.1 (11 770); ν_{max}(KBr)/cm^{-1} 3600–3300w (NH), 1704s, 1666s (C=O, thymine) and 1091s (Si–O); δ_H(250 MHz; $CDCl_3$) 9.70 (1 H, s, NH), 7.26 (1 H, s, 6-H), 6.13–6.06 (1 H, m, 3′-H), 5.75 (1 H, dd, *J* 6, 2, 2′-H), 5.67–5.57 (1 H, m, 1′-H), 4.80–4.70 (1 H, m, 4′-H), 2.73 (1 H, ddd, *J* 15, 8, 7, 5′-αH), 1.86 (3 H, s, 5-CH_3), 1.52 (1 H, ddd, *J* 15, 3, 3, 5′-βH), 1.90 [9 H, s, $(CH_3)_3C$] and 0.24–0.00 (6 H, m, 2 × CH_3–Si); δ_C(62.9 MHz; $CDCl_3$) 164.17, 151.33 (C-2, C-4), 139.46, 137.41, 131.47 (C-6, C-2′, C-3′), 111.11 (C-5), 75.05 (C-4′), 58.20 (C-1′), 40.51 (C-5′), 25.77 [$(CH_3)_3C$], 18.00 [$(CH_3)_3C$], 12.34 (5-CH_3), −4.71 and −4.83 (CH_3-Si) [Found (CI): M^+ + H, 323.1791. ($C_{16}H_{26}N_2O_3Si$ requires (M + H), 323.1791].

A solution of the silyloxyalkene (1.250 g, 3.88 mmol) in ethanol (45 cm^3) was added to a suspension of palladium on carbon catalyst (10%, 0.10 g) in ethanol (5 cm^3). The reaction mixture was stirred under an atmosphere of hydrogen for 3 h. The catalyst was removed by filtration through Celite and the solvent evaporated under reduced pressure. The residue was chromatographed using light petroleum–ethyl acetate (2:1) as eluent to yield 1-[(1′β,4′β)-4′-tert-*butyldimethylsilyloxycyclopentyl*]*thymine* (1.226 g, 3.78 mmol, 97%) as a white solid, m.p. 135–137 °C; λ_{max}(MeOH)/nm 273.7 (10 000); ν_{max}(KBr)/cm^{-1} 3600–3300w (NH), 1692s br (C=O, thymine) and 1084s (Si–O); δ_H(250 MHz; $CDCl_3$) 8.96 (1 H, s, NH), 7.62 (1 H, s, 6-H), 5.30–5.15 (1 H, m, 1′-H), 4.39–4.31 (1 H, m, 4′-H), 2.39–2.12 (2 H, m, 2 × 2′-, 3′- or 5′-H), 1.92 (3 H, s, 5-CH_3), 1.99–1.52 (4 H, m, 4 × 2′-, 3′- or 5′-H), 0.94 [9 H, s, $(CH_3)_3$] and 0.12 (6 H, s, 2 × CH_3–Si); δ_C(62.9 MHz; $CDCl_3$) 163.81, 151.37 (C-2, C-4), 138.08 (C-6), 111.25 (C-5), 73.03 (C-4′), 53.68 (C-1′), 41.50, 35.50, 30.58 (C-2′, C-3′, C-5′), 25.87 [$(CH_3)_3C$], 18.11 [$(CH_3)_3$-*C*], 12.36 (5-CH_3), −4.7 and −4.86 (2 × CH_3–Si) [Found (CI): M^+ + H, 325.1947. $C_{16}H_{28}H_2O_3Si$ requires (M + H), 325.1947].

TBAF (5.4 cm^3; 1 mol dm^{-3} solution in THF, 5.40 mmol) was added dropwise to a stirred solution of the above silyl ether (1.201 g, 3.70 mmol) in THF (30 cm^3) and the resultant mixture stirred at room temp. overnight under an inert atmosphere. Methanol (5 cm^3) was added and the reaction mixture adsorbed onto silica. Chromatography using dichloromethane–methanol (20:1) yielded the *title compound* **26** (0.659 g, 3.13 mmol, 85%) as a white solid which was identical with that prepared by the alternative procedure.

1-[(1′β,4′β)-4′-(*Phosphonomethoxy*)*cyclopentyl*]*thymine* **27**.—A solution of the alcohol **26** (0.308 g, 1.47 mmol) in dry DMF (5 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.30 g, 60% in oil, *ca.* 7.30 mol) in dry DMF (3 cm^3) at room temp. under an inert atmosphere. After 1 h a solution of diethyl (*p*-tolylsulfonyloxymethyl)phosphonate (0.709 g, 2.20 mmol) in dry DMF (3 cm^3) was added dropwise. The reaction mixture was stirred overnight at room temperature then cooled to 0 °C. Glacial acetic acid (0.13 cm^3, *ca.* 2.27 mmol) was added dropwise and the brown suspension filtered through Celite and evaporated under reduced pressure. The residue was chromatographed over Sephadex LH-20 using methanol as eluent to yield a brown gum which contained 1-[(1′β,4′β)-4′-(*diethylphosphonylmethoxy*)*cyclopentyl*]-*thymine*.

Trimethylsilyl bromide (0.66 cm^3, *ca.* 0.77 g, 5.03 mmol) was added dropwise to a solution of the above material in dry DMF (5 cm^3) at 0 °C in the dark. The reaction mixture was stirred at room temperature for 4 h then cooled to 0 °C. Aqueous ammonium hydrogen carbonate solution (0.6 mol dm^{-3}; 10 cm^3) was added dropwise; the mixture was allowed to warm to room temp. slowly then left standing overnight. After evaporation of the solvent under reduced pressure the residue was chromatographed over Sephadex LH-20 using methanol–aqueous formic acid (0.1 mol dm^{-3} (1:2) as eluent. Appropriate fractions were combined, evaporated under reduced pressure, co-evaporated under reduced pressure with ethanol (10 cm^3) then lyophilised to afford the *title compound* **27** (0.058 g, 0.19 mmol, 13%) as a white lyophiliate; λ_{max}(H_2O)/nm 274.4 (3530); ν_{max}(KBr)/cm^{-1} 3700–2600s br (NH, OH), 1671s br (C=O, thymine) and 1272s (P=O); δ_H(250 MHz; D_2O) 7.89 (1 H, d, *J* 1, 6-H), 5.18–5.03 (1 H, m, 1′-H), 4.33–4.24 (1 H, m, 4′-H), 3.76 (2 H, dd, *J* 9, 1.5, PCH_2O), 2.56 (1 H, ddd, *J* 15, 9, 4, 2′-, 3′- or 5′-H) and 2.33–1.86 (8 H, m, 5-CH_3, 5 × 2′-, 3′- or 5′-H); δ_P(161.9 MHz; D_2O) 17.0 [Found (FAB): M^+ + H, 305.0902. $C_{11}H_{17}N_2O_6P$ requires (M + H), 305.0902].

1-[(1′β,4′β)-4′-(*Triphosphonomethoxy*)*cyclopentyl*]*thymine*, *Tris*(*ammonium*) *Salt* **11**.—Triethylamine (0.0012 cm^3, *ca.* 0.0087 g, 0.086 mmol) was added to a solution of the phosphonate **27** (0.025 g, 0.082 mmol) in water (1 cm^3). The solution was evaporated under reduced pressure and dried by the addition and evaporation under reduced pressure of dry pyridine (2 × 1 cm^3) and dry DMF (1 cm^3). A solution of 1,1′-carbonyldiimidazole (0.067 g, 0.41 mmol) in dry DMF (1 cm^3) was added dropwise to a stirred solution of the phosphonate **27** in dry DMF (1 cm^3). The reaction mixture was stirred under an inert atmosphere at room temp. for 20 h, then methanol (0.027

cm^3 *ca.* 0.664 mmol) was added and stirring continued for a further 0.5 h. A solution of tributylammonium pyrophosphate (0.164 g, 0.42 mmol) in dry DMF (3 cm^3) was added and the reaction mixture stirred for 24 h. The precipitate was removed by filtration and the solid washed with dry DMF (3 × 1 cm^3). Methanol (9 cm^3) was added to the filtrate and the solvent evaporated under reduced pressure. The residue was chromatographed over Sephadex DEAE-A25 using aqueous ammonium hydrogen carbonate (0–0.4 mol dm^{-3} in 500 cm^3 followed by 0.4 mol dm^{-3}) as eluent. Appropriate fractions were combined, evaporated under reduced pressure, co-evaporated under reduced pressure with water (4 × 25 cm^3) and lyophilised to yield the *title compound* **11** (0.013 g, 0.025 mmol, 30%) as a pale cream solid; $\lambda_{max}(H_2O)$/nm 275.2 (4150); ν_{max}(KBr)/cm^{-1} 3600–2600s br (NH, OH), 1695s br (C=O, thymine), 1217s (P=O) and 901s (P–O–P); δ_H(250 MHz; D_2O) 7.88 (1 H, s, 6-H), 5.17–5.03 (1 H, m, 1′-H), 4.39–4.29 (1 H, m, 4′-H), 3.96 (2 H, dd, *J* 9, 3, PCH_2O), 2.69–2.51 (1 H, m, 2′-, 3′- or 5′-H) and 2.33–1.86 (8 H, m, 5-CH_3, 5 × 2′-, 3′- or 5′-H); δ_P(161.9 MHz; D_2O) 9.8 [1 P, d, *J* 25, P(1)], −7.8––8.8 [1 P, m, P(3)] and −21.5––22.5 [1 P, m, P(2)].

9-[(1′β,4′β)-4′-(*Diphosphonomethoxy*)*cyclopent*-2′-*enyl*]-*guanine*, **10** *Tris*(*ammonium*) *Salt and Bis*(*ammonium*) P^1, P^2-Bis[(1′β,4′β)-4′-(*guanin*-9-*yl*)*cyclopent*-2′-*enyloxymethyl*]*diphosphonate* **28**.—A solution of 1,3-dicyclohexylcarbodiimide (0.165 g, 0.8 mmol) in *tert*-butyl alcohol (3 cm^3) was added dropwise to a stirred refluxing solution of the phosphonate **19** (0.057 g, 0.174 mmol) and morpholine (0.07 cm^3, *ca.* 0.07 g, 0.8 mmol) in *tert*-butyl alcohol–water (3 cm^3, 1:1) over a period of 3 h. After 1 h the solution was cooled and evaporated under reduced pressure. The residue was dissolved in water (5 cm^3) and filtered; the solid was washed with an additional portion of water (5 cm^3). The combined aqueous portions were extracted with ether (3 × 5 cm^3), evaporated under reduced pressure and then co-evaporated under reduced pressure with pyridine (3 × 1 cm^3) and benzene (1 cm^3).

Tributylammonium pyrophosphate (0.282 g, 0.72 mmol) in dry DMSO (2 cm^3) was added to a solution of the above solid, assumed to be the morpholidate, in dry DMSO (1 cm^3). The reaction mixture was stirred at room temp. under an inert atmosphere for 60 h. The solution was applied directly onto a column of Sephadex DEAE-A25, the column was eluted with water (300 cm^3), followed by aqueous ammonium hydrogen carbonate (0–0.4 mol dm^{-3} in 500 cm^3 followed by 0.4 mol dm^{-3}). Appropriate fractions were evaporated under reduced pressure, co-evaporated under reduced pressure with water (4 × 25 cm^3) then lyophilised. *Diammonium salt* **28** (0.073 g, 0.110 mmol, 63%) was obtained as white lyophiliate; $\lambda_{max}(H_2O)$/nm 253.7 (7480); ν_{max}(KBr)/cm^{-1} 3800–2600s br (NH, OH), 1689s (C=O, guanine), 1614w (C=C, C=N), 1156s (P=O) and 911s (P–O–P); δ_H(250 MHz; D_2O) 7.96 (1 H, s, 8-H), 6.54–6.48 (1 H, m, 3′-H) 6.27 (1 H, ddd, *J* 5, 1, 1, 2′-H), 5.51–5.42 (1 H, m, 1′-H), 3.81 (2 H, d, *J* 9 PCH_2O), 3.11 (1 H, ddd, *J* 15, 7.5, 7.5, 5′-αH) and 2.02 (1 H, ddd, *J* 15, 4, 4, 5′-βH); δ_P (161.9 MHz; D_2O) −8.8 (s). *Tris*(*ammonium*) *salt* **10** (0.013 g, 0.024 mmol, 14%) was obtained as a white lyophiliate; λ_{max} (H_2O)/nm 253.9 (15 120); ν_{max}(KBr)/cm^{-1} 3600–2600s br (NH, OH), 1691s (C=O, guanine), 1614w (C=C, C=N), 1237s (P=O) and 905m (P–O–P); δ_H(250 MHz; D_2O) 7.97 (1 H, s, 8-H), 6.56–6.48 (1 H, m, 3′-H), 6.24 (1 H, d, *J* 5, 2′-H), 5.52–5.41 (1 H, m, 1′-H), 5.02–4.93 (1 H, m, 4′-H), 4.02 (2 H, d, *J* 9, PCH_2O), 3.15 (1 H, ddd, *J* 14, 8, 8, 5′-αH) and 2.05 (1 H, ddd, *J* 14, 5, 5, 5′-βH); δ_P(161.9 MHz; D_2O) 9.75 [1 P, d, *J* 28, P(1)], −9.5––10.5 [1 P, m, P(3)] and −21.6––22.7 [1 P, m, P(2)].

9-[(1′β,4′β)-4′-*Hydroxycyclopent*-2′-*enyl*]-6-*methoxy*-2-(N-*monomethoxytriphenylmethylamino*)*purine* **32**.—A solution of monomethoxytriphenylmethyl chloride (1.014 g, 3.28 mmol) in dry dichloromethane (10 cm^3) was added dropwise to a stirred solution of the 6-methoxypurine **17** (0.688 g, 2.78 mmol), triethylamine (1.0 cm^3, *ca.* 7.0 mmol) and DMAP (*ca.* 0.05 g) in dry dichloromethane (15 cm^3) at 0 °C under an inert atmosphere. The reaction mixture was stirred for 0.5 h then evaporated under reduced pressure. The residue was chromatographed using ethyl acetate as eluent to yield the *title compound* **32** (1.157 g, 2.23 mmol, 80%) as a white foam, m.p. 107–112 °C (Found: C, 69.85; H, 5.85; N, 12.6. $C_{31}H_{29}N_5O_3$ + 0.75·H_2O requires C, 69.84; H, 5.77; N, 13.14%); λ_{max}(EtOH)/nm 258.3 (16 590) and 286.7 (16 320); ν_{max}(KBr)/cm^{-1} 3600–3100m br (NH, OH), 1611s and 1590s (C=C, C=N); (250 MHz; $CDCl_3$) 7.58 (1 H, s, 8-H), 7.36–7.11 (12 H, m, H-Ar), 6.79–6.71 (2 H, m, H-Ar), 6.24–6.18 (1 H, m, 3′-H), 6.14 (1 H, s, NH), 5.76 (1 H, dd, *J* 5.5, 2, 2′-H), 5.25 (1 H, s, OH), 5.16–5.06 (1 H, m, 1′-H), 4.83–4.72 (1 H, m, 4′-H), 3.74 (3 H, s, 6-CH_3O), 3.43 (3 H, s, br, CH_3O-Ar), 2.81 (1 H, ddd, *J* 15, 7.5, 7.5, 5′αH) and 2.02–1.90 (1 H, m, 5′-βH); δ_C(62.9 MHz; $CDCl_3$) 160.23, 158.18, 157.42 [C(purine)], 139.18, 138.66, 130.65 (C-8, C-2′, C-3′), 138.12 (C), 130.21, 128.99, 127.60, 126.56 [CH(Ar)], 116.05 (C), 112.94 [CH(Ar)], 74.99 (C-4′), 70.74 [$C(Ar)_3$], 58.91 (C-1′), 55.17, 53.93 (2 × OCH_3) and 40.23 (C-5′) [Found (EI): M^+ + H, 520.2350. $C_{31}H_{29}N_5O_3$ requires (M + H), 520.2348].

9-[1′β,4′β)-4′-(2″-*Diphosphonoethoxy*)*cyclopent*-2′-*enyl*]-*guanine*, *Diammonium Salt* **29**.—A solution of the allylic alcohol **32** (0.299 g, 0.58 mmol) in dry DMF (2 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.043 g, 60% in oil, *ca.* 1.07 mmol) in dry DMF (1 cm^3) at room temp. under an inert atmosphere. After 0.5 h the reaction mixture was cooled to 0 °C and a solution of 1-bromo-2-tetrahydropyranyloxyethane (0.270 g, 1.29 mmol) in dry DMF (2 cm^3) was added dropwise. The reaction mixture was allowed to warm to room temp. slowly then stirred overnight. After cooling to 0 °C water (1 cm^3) was added dropwise, the resultant mixture was partitioned between ethyl acetate (25 cm^3) and water (25 cm^3). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography using light petroleum–ethyl acetate (1:1) yielded 6-*methoxy*-2-(N-*monomethoxytriphenylmethylamino*)-9-{(1′β,4′β)-4′-[2″-(*tetrahydropyranyloxy*)-*ethoxy*]*cyclopent*-2′-*enyl*}*purine* (0.222 g, 0.34 mmol, 59%) as a white foam, m.p. 62–67 °C (Found: C, 69.9; H, 6.6; N, 10.6. $C_{38}H_{41}N_5O_5$ + 0.4·H_2O requires C, 69.7; H, 6.4; N, 10.7%); λ_{max}(EtOH)/nm 258.4 (18 050), 286.1 (17 050); ν_{max}(KBr)/cm^{-1} 1608s, 1585s (C=C, C=N) and 1073s (C–O–C); δ_H(250 MHz; $CDCl_3$) 7.64 (1 H, d, *J* 1.5, 8-H), 7.37–7.16 (12 H, m, H-Ar), 6.80–6.71 (2 H, m, H-Ar), 6.28–6.18 (2 H, m, NH, 5′-H), 5.88 (1 H, d, *J* 4, 2′-H), 5.22–5.08 (1 H, m, 1′-H), 4.64–4.50 (2 H, m, 4′-H, OCHO), 3.90–3.42 [12 H, m, 6-CH_3O, CH_3O-Ar, 2 × 1″-H, 2 × 2″-H, 2 × H-CHO(THP)], 2.76–2.63 [1 H, m, 5′-αH) and 1.84–1.43 (7 H, m, 5′-βH, 6 × H-CH(THP)]; δ_C(62.9 MHz; $CDCl_3$) 158.13, 157.79, 146.07, 146.03, 138.27, 137.78 [C(purine)], 136.29, 136.14, 132.87, 132.71 (C-2′, C-3′), 130.34, 129.11, 127.49, 126.45, 112.82 [CH(Ar)], 99.10 (*O*CHO), 82.59 (C-4′), 70.65 [$C(Ar)_3$], 68.64, 68.56, 66.81, 66.79, 62.33 [C-1″, C-2″, *C*HO(THP)], 56.26 (C-1′), 55.17, 53.77 (2 × OCH_3), 38.74, 38.55, 30.60, 30.57, 25.42 and 19.54 [C-5′, 3 × CH_2(THP)] [Found (EI): M^+, 647.3108. $C_{38}H_{41}N_5O_5$ requires *M*, 647.3108].

A solution of the substituted purine (0.169 g, 0.26 mmol) in THF–aqueous hydrochloric acid (2 mol dm^{-3}; 4 cm^3, 1:1) was refluxed for 1 h. The reaction mixture was evaporated under reduced pressure then co-evaporated under reduced pressure with ethanol (15 cm^3); the residue was chromatographed using chloroform–methanol (4:1) as eluent to afford 9-[(1′β,4′β)-4′-(2″-*hydroxyethoxy*)*cyclopent*-2′-*enyl*]*guanine* **33** (0.072 g, 0.26 mmol, 100%) as a pale cream solid, m.p. 212–213 °C (decomp.);

λ_{max}(MeOH)/nm 255.3 (8130); ν_{max}(KBr)/cm^{-1} 3700–2600s br (NH, OH), 1688s, 1632s br [CO (guanine), C=C, C=N] and 1089s, br (C–O–C); δ_H(250 MHz; [$^2H_6$]-DMSO) 10.46 (1 H, br s, NH), 7.54 (1 H, s, 8-H), 6.46 (2 H, s, NH_2), 6.30 (1 H, ddd, *J* 6, 2, 2, 3′-H), 6.12–6.05 (1 H, m, 2′-H), 5.28–5.18 (1 H, m, 1′-H), 4.64–4.51 (1 H, m, 4′-H, OH), 3.54–3.48 (4 H, m, 2 × 1″-H, 2 × 2″-H), 2.88–2.72 (1 H, m, 5′-αH) and 1.75 (1 H, ddd, *J* 14, 4, 4, 5′-βH); δ_C(62.9 MHz; [$^2H_6$]-DMSO) 161.98, 159.08 (C-2, C-6), 141.41, 140.14, 137.91 (C-8, C-2′, C-3′), 87.15 (C-4′), 75.61, 65.66 (C-1″, C-2″), 61.27 (C-1′) and 43.80 (C-5′) [Found (CI): M^+ 278.1283. $C_{12}H_{15}N_5O_3$ requires (M + H) 278.1253].

Phosphorus oxychloride (0.23 cm^3, *ca.* 0.378 g, 2.47 mmol) was added dropwise to a stirred solution of the alcohol (0.054 g, 0.194 mol) in trimethyl phosphate (2 cm^3) at 0 °C under an inert atmosphere. The reaction mixture was stirred overnight at 4 °C then poured onto ice-cold water (30 cm^3). The resultant mixture was extracted with ether (3 × 25 cm^3); the aqueous phase was neutralised with aqueous ammonia then evaporated under reduced pressure. The residue was applied to a charcoal column, this was eluted with water until a negative test with silver nitrate solution was obtained then ethanol–concentrated ammonia solution–water (10:1:10). The UV-active fractions were evaporated under reduced pressure and chromatographed over Sephadex DEAE-A25 using aqueous ammonium hydrogen carbonate (0–0.4 mol dm^{-3} in 500 cm^3 then 0.4 mol dm^{-3}) as eluent. Appropriate fractions were combined, evaporated under reduced pressure, co-evaporated under reduced pressure with water (2 × 50 cm^3) then lyophilised to yield 9-[(1′β,4′β)-4′-(2″-*phosphonoethoxy)cyclopent-2′-enyl*]*guanine, ammonium salt* (0.026 g, 0.069 mmol, 36%) as a white lyophiliate; λ_{max}(H_2O)/nm 253.7 (15 850); ν_{max}(KBr)/cm^{-1} 3600–3200s br (NH, OH), 1686s br (C=O, guanine) and 1167s br (P=O); δ_H(250 MHz; D_2O) 8.12 (1 H, s, 8-H), 6.57–6.50 (1 H, m, 3′-H), 6.34–6.26 (1 H, m, 2′-H), 5.57–5.47 (1 H, m, 1′-H), 4.18–4.11 (2 H, m, 2 × 1″- or 2″-H), 3.92 (2 H, dd, *J* 5, 5, 2 × 1″- or 2″-H), 3.13 (1 H, ddd, *J* 15, 7.5, 7.5, 5′-αH) and 2.04 (1 H, ddd, *J* 15, 4, 4, 5′-βH); δ_P(161.9 MHz; D_2O) 1.22 [Found (FAB): (M^+ − NH_4^+ + 2 H), 358.0996. $C_{12}H_{19}N_6O_6P$ requires (M − NH_4^+ + 2 H), 358.0916].

Dowex X8(H^+) (*ca.* 12 beads) were added to a solution of the monophosphate (0.038 g, 0.10 mmol) in water (1 cm^3). After being stirred for 10 min the solution was passed through a column of Dowex X8(H^+) (*ca.* 10 beads) washing with water (1 cm^3). *tert*-Butyl alcohol (2 cm^3) and morpholine (0.035 cm^3, *ca.* 0.035 g, 0.40 mmol) were added and the solution refluxed. A solution of 1,3-dicyclohexylcarbodiimide (0.083 g, 0.40 mmol) in *tert*-butyl alcohol (3 cm^3) was added dropwise over 3.5 h. After an additional 1.75 h the reaction mixture was cooled and evaporated under reduced pressure. The residue was dissolved in water (5 cm^3) and filtered, washing the solid with water (5 cm^3). The aqueous filtrate was extracted with ether (3 × 5 cm^3); the aqueous phase was evaporated under reduced pressure then co-evaporated under reduced pressure with pyridine (3 × 1 cm^3) and dissolved in pyridine (0.5 cm^3).

Orthophosphoric acid (85%, 0.017 cm^3, *ca.* 0.29 g, 0.30 mmol) was added to pyridine (1.0 ml) containing tributylamine (0.072 cm^3, *ca.* 0. 056 g, 0.30 mmol). The solution was evaporated under reduced pressure then co-evaporated under reduced pressure with pyridine (2 × 1 cm^3); the residue was dissolved in dry pyridine (0.5 cm^3) and added dropwise to the above solution. The reaction mixture was stirred at room temp. for 24 h under an inert atmosphere then evaporated under reduced pressure. The residue was chromatographed over Sephadex DEAE-A25 eluting with aqueous ammonium hydrogen carbonate (0–0.4 mol dm^{-3} in 500 cm^3 followed by 0.4 mol dm^{-3}). Appropriate fractions were evaporated under reduced pressure, co-evaporated under reduced pressure with water (4 × 25 cm^3) then lyophilised to yield *diammonium salt* **29** (0.017 g, 0.036 mmol, 36%) as a white lyophiliate; λ_{max}(H_2O)/nm 253.0 (13 770); ν_{max}(KBr)/cm^{-1} 3800–2400s br (OH), 1692s br (C=O, guanine) and 1300–1000s br (P=O, C–O–C, P–O–C); δ_H(250 MHz; D_2O) 7.96 (1 H, s, 8-H), 6.55–6.49 (1 H, m, 3′-H), 6.31–6.25 (1 H, m, 2′-H), 5.55–5.45 (1 H, m, 1′-H), 4.27–4.17 (2 H, m, 2 × 1″- or 2″-H), 3.95 (2 H, dd, *J* 5, 2, 2 × 1″- or 2″-H), 3.16 (1 H, ddd, *J* 15, 7.5, 7.5, 5′-αH) and 2.02 (1 H, ddd, *J* 15, 4.5, 4.5, 5′-βH); δ_P(161.9 MHz; D_2O) −9.5– −10 and −10– −10.5 [each m, P(1), P(2)].

9-[(1′β,4′β)-4′-(4″-*Phosphonobutoxy)cyclopent-2′-enyl*]*guanine, Ammonium Salt* **30**.—A solution of the allylic alcohol **32** (0.201 g, 0.39 mmol) in dry DMF (2 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.023 g, 60% in oil, *ca.* 0.57 mmol) in dry DMF (1 cm^3) at room temp. under an inert atmosphere. After 0.5 h a solution of 4-tetrahydropyranyloxybutyl chloride (0.132 g, 0.68 mmol) in dry DMF (2 cm^3) was added dropwise. The reaction mixture was heated at *ca.* 55 °C for 4.5 h then cooled to room temp. Water (1 cm^3) was added dropwise and the resultant mixture partitioned between ethyl acetate (20 cm^3) and water (20 cm^3). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography using light petroleum–ethyl acetate (1:1) followed by ethyl acetate as eluent yielded 6-*methoxy*-2-(N-*monomethoxytriphenylmethylamino*)-9-{(1′β,4′β)-4′-[4″-(*tetrahydropyranyloxy*)*butoxy*]*cyclopent-2′-enyl*}*purine* (0.056 g, 0.083 mmol, 34% based on recovered starting material) as a white foam, m.p. 62–67 °C (Found: C, 69.65; H, 6.8: N, 10.05. $C_{40}H_{45}N_5O_5$ + 0.75·H_2O requires C, 69.70; H, 6.80; N, 10.16%); λ_{max}(EtOH)/nm 258.4 (14 250) and 286.4 (13 300); ν_{max}(KBr)/cm^{-1} 1608s, 1585s (C=C, C=N) and 1075s (C–O–C); δ_H(250 MHz; $CDCl_3$) 7.63 (1 H, s, 8-H), 7.38–7.14 (12 H, m, H-Ar), 6.80–6.75 (2 H, m, H-Ar), 6.27–6.18 (2 H, m, NH, 3′-H), 5.92–5.84 (1 H, m, 2′-H), 5.25–5.07 (1 H, br s, 1′-H), 4.56 (1 H, dd, *J* 3, 3, OCHO), 4.49–4.40 (1 H, m, 4′-H), 3.89–3.33 [12 H, m, 6-CH_3O, CH_3O-Ar, 2 × 1″-H, 2 × 4″-H, 2 × H-CHO(THP)], 2.78–2.58 (1 H, m, 5′-αH) and 1.89–1.43 [11 H, m, 5′-βH, 2 × 2″-H, 2 × 3″-H, 6 × H-CH(THP)]; δ_C(62.9 MHz; $CDCl_3$) 146.03, 138.28 (C), 136.27, 132.53 (C-2′, C-3′), 130.35, 129.12, 127.50, 126.50, 126.45, 112.83 (CH), 98.85 (O*C*HO), 82.17 (C-4′), 70.66 [C(Ar_3)], 69.23, 67.22, 62.29 [C-1″, C-4″, CH_2O(THP)], 56.26 (C-1′), 55.18, 53.79 (2 × OCH_3), 38.82, 30.76, 26.89, 26.52, 25.50 and 19.63 [C-5′, C-2″, C-3″, 3 × CH_2(THP)] [Found (EI): M^+ 675.3421. $C_{40}H_{45}N_5O_5$ requires *M*, 675.3421].

A solution of the substituted purine (0.112 g, 0.17 mmol) in THF–aqueous hydrochloric acid (2 mol dm^{-3}; 4 cm^3, 1:1) was refluxed for 1 h then evaporated under reduced pressure. The residue was chromatographed using dichloromethane–methanol (5:1) as eluent to afford 9-[(1′β,4′β)-4′-(4″-*hydroxybutoxy)cyclopent-2′-enyl*]*guanine* **34** (0.033 g, 0.11 mmol, 65%) as a white solid, m.p. 162–164 °C (decomp.); λ_{max}(MeOH)/nm 254.2 (8880) and 276.3 (5830); ν_{max}(KBr)/cm^{-1} 3700–2800s br (NH, OH), 1685s br (C=O, guanine) and 1079s br (C–O–C); δ_H(250 MHz; [$^2H_4$]-MeOH) 7.71 (1 H, s, 8-H), 6.35 (1 H, ddd, *J* 5.5, 2, 2, 3′-H), 6.08 (1 H, ddd, *J* 5.5, 2, 2′-H), 5.45–5.35 (1 H, m, 1′-H), 4.60–4.52 (1 H, m, m, 4′-H), 3.64–3.52 (4 H, m, 2 × 1″-H, 2 × 4″), 2.86 (1 H, ddd, *J* 14, 8, 7, 5′-αH), 1.84 (1 H, ddd, *J* 14, 3, 3, 5′-βH) and 1.70–1.54 (4 H, m, 2 × 2″-H, 2 × 3″-H); δ_C(62.9 MHz; [$^2H_4$]-MeOH) 137.90, 134.64, 133.40 (C-8, C-2′, 3-3′), 83.64 (C-4′), 70.38, 62.74 (C-1″, C-4″), 58.27 (C-1′), 39.70 (C-5′), 30.43 and 27.58 (C-2″, C-3″) [Found (FAB): M^+, 306.1549. $C_{14}H_{19}N_5O_3$ requires *M*, 306.1566].

Phosphorus oxychloride (0.24 cm^3, *ca.* 0.395 g, 2.57 mmol) was added dropwise to a stirred solution of the alcohol **34** (0.058 g, 0.19 mmol) in trimethyl phosphate (cm^3) at 0 °C under an inert atmosphere. The reaction mixture was stirred at 4 °C overnight then poured onto ice-cold water (30 cm^3). The resultant mixture was extracted with ether (3 × 25 cm^3); the aqueous phase was

neutralised with aqueous ammonia then evaporated under reduced pressure. The residue was applied onto a charcoal column, and eluted with water until a negative test was obtained with silver nitrate solution, then with ethanol–concentrated ammonia solution–water (10:1:10) The UV-active fractions were evaporated under reduced pressure, and chromatographed over Sephadex DEAE-A25 using aqueous ammonium hydrogen carbonate (0–0.4 mol dm^{-3} in 500 cm^3; then 0.4 mol dm^{-3}) as eluent. Appropriate fractions were evaporated under reduced pressure, co-evaporated under reduced pressure with water (2 × 50 cm^3) then lyophilised to afford the *ammonium salt* **30** (0.016 g, 0.04 mmol, 21%) as a white lyophiliate; $\lambda_{max}(H_2O)$/nm 253.6 (17 810); ν_{max}(KBr)/cm^{-1} 3600–2600s br (NH, OH) 1688s br (C=O, guanine), 1612s br (C=C, C=N), 1170s (P=O) and 1082s br (C–O–C); δ_H(250 MHz; D_2O) 8.15 (1 H, s, 8-H), 6.57–6.51 (1 H, m, 3′-H), 6.35–6.28 (1 H, m, 2′-H), 5.57–5.47 (1 H, m, 1′-H), 3.99 (2 H, dd, *J* 6, 6, 2 × 1″- or 4″-H), 3.81–3.73 (2 H, m, 2 × 1″- or 4″-H), 3.10 (1 H, ddd, *J* 15, 7.5, 7.5, 5′-αH), 2.0 (1 H, ddd, *J* 15, 4, 4, 5′-βH) and 1.82–1.72 (4 H, m, 2 × 2″-H, 2 × 3″-H); δ_P(161.9 MHz, D_2O) 2.5; [Found (FAB): $M^+ - NH_4^+ + 2$ H), 386.1196. $C_{14}H_{23}N_6O_6P$ requires (M − NH_4^+ + 2 H), 386.1229].

9-{(1′β,4′β)-4′-[3″-(*Phosphonomethoxy*)*propoxy*]*cyclopent*-2′-*enyl*}*guanine* **31**.—A solution of the allylic alcohol **32** (0.379 g, 0.73 mmol) in dry DMF (2 cm^3) was added dropwise to a stirred suspension of sodium hydride (0.046 g, 60% in oil, *ca.* 1.15 mmol) in dry DMF (1 cm^3) at room temp. under an inert atmosphere. After 0.5 h the reaction mixture was cooled to 0 °C, a solution of 1-bromo-3-*tert*-butyldimethylsilyloxypropane (0.351 g, 1.39 mmol) in dry DMF (2 cm^3) was added dropwise. The reaction mixture was allowed to warm to room temp. slowly then stirred overnight. After cooling to 0 °C water (1 cm^3) was added dropwise, the resultant mixture was partitioned between ethyl acetate (25 cm^3) and water (25 cm^3). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography using light petroleum–ethyl acetate (1:1) as eluent yielded 9-{(1′β,4′β)-4′-[3″-(tert-*butyldimethylsilyloxy*)*propoxy*]*cyclopent*-2′-*enyl*}-6-*methoxy*-2-(N-*monomethoxytriphenylmethylamino*)*purine* (0.325 g, 0.47 mol, 64%) as a white foam, m.p. 58–65 °C; λ_{max}(EtOH)/nm 258.4 (13 460) and 286.5 (12 640); ν_{max}(KBr)/cm^{-1} 1609s, 1586s (C=C, C=N) and 1092s br (C–O–C, Si–O); δ_H(250 MHz; $CDCl_3$) 7.84 (1 H, s, 8-H), 7.39–7.14 (12 H, m, H-Ar), 6.82–674 (2 H, m, H-Ar), 6.27–6.19 (2 H, m, NH, 3′-H), 5.93–5.85 (1 H, m, 2′-H), 5.25–5.05 (1 H, m, 1′-H), 4.49–4.41 (1 H, s, 4′-H), 3.76 (3 H, s, 6-CH_3O), 3.72–3.47 (7 H, m, CH_3O-Ar, 2 × 1″-H, 2 × 3″-H), 2.78–2.59 (1 H, m, 5′-αH), 1.83–1.64 (3 H, m, 5′-βH, 2 × 2″-H), 0.92 [9 H, s, $(CH_3)_3C$] and 0.4 and 0.3 (each 3 H, s, 2 × CH_3-Si); δ_C(62.9 MHz; $CDCl_3$) 158.14, 146.03, 137.63 (C), 136.35, 132.48 (C-2′, C-3′), 130.35, 129.11, 127.50, 126.45, 112.83, [CH(Ar)], 82.26 (C-4′), 70.66 [$C(Ar)_3$], 65.94, 59.68 (C-1″, C-3″), 56.25 (C1′), 55.18, 53.78 (2 × OCH_3), 38.86 (C-5′), 33.13 (C-7′), 25.93 and −5.35 (CH_3) [Found (EI): M^+, 691.3554. $C_{40}H_{49}N_5O_4Si$ requires *M*, 691.3554].

TBAF (0.6 cm^3, 1 mol dm^{-3} solution in THF, 0.6 mmol) was added dropwise to a stirred solution of the silyl ether (0.204 g, 0.30 mmol) in THF (7 cm^3). The reaction mixture was stirred at room temp. for 1.5 h under an inert atmosphere then evaporated under reduced pressure. Chromatography using dichloromethane–methanol (25:1) as eluent yielded 9-[(1′β,4′β)-4′-(3″-*hydroxypropoxy*)*cyclopent*-2′-*enyl*]-6-*methoxy*-2-(N-*monomethoxytriphenylmethylamino*)*purine* (0.172 g, 0.30 mmol, 100%) as a white foam, m.p. 93–98 °C (Found: C, 69.6; H, 6.2; N, 11.8. $C_{34}H_{35}N_5O_4$ + 0.5·H_2O requires C, 69.6; N, 6.2; N, 11.9%); λ_{max}(EtOH)/nm 258.4 (14 410) and 286.4 (13 580); ν_{max}(KBr)/cm^{-1} 3700–3200s br (NH, OH), 1610s, 1587s (C=C, C=N) and 1074s (C–O–C); δ_H(250 MHz; $CDCl_3$) 7.61 (1 H, s, 8-H), 7.38–7.14 (12 H, m, H-Ar), 7.82–7.72 (2 H, m, H-Ar), 6.31 (1 H, s, NH), 6.26–6.19 (1 H, m, 3′-H), 5.95–5.87 (1 H, m, 2′-H), 5.22–5.08 (1 H, m, 1′-H), 4.52–4.42 (1 H, m, 4′-H), 3.79–3.50 (11 H, m, 6-CH_3O, CH_3O-Ar, 2 × 1″-H, 2 × 3″-H, OH), 2.76–2.58 (1 H, m, 5′-αH) and 1.92–1.66 (3 H, m, 5′-βH, 2 × 2″-H); δ_C(62.69 MHz; $CDCl_3$) 158.12, 146.04, 137.63 (C), 136.08, 132.86 (C-2′, C-3′), 130.55, 129.12, 127.50, 126.46, 112.83 [CH(Ar)], 82.40, (C-4′), 70.66 [$C(Ar)_3$], 67.33, 60.86 (C-1″, C-3″), 56.39 (C-1′), 55.19, 53.80 (2 × OCH_3), 38.54 and 32.25 (C-5′, C-2″) (Found (EI): M^+, 577.2689. $C_{34}H_{35}N_5O_4$ requires *M*, 577.2689].

A solution of the alcohol (0.459 g, 0.79 mmol) in dry THF (3 cm^3) was added dropwise to a suspension of sodium hydride (0.107 g, 60% in oil, *ca.* 2.7 mmol) in dry THF (2 cm^3) at room temp. under an inert atmosphere. After 0.5 h the reaction mixture was cooled to 0 °C and a solution of diethyl (*p*-tolylsulfonyloxymethyl)phosphonate (0.495 g, 1.54 mmol) in dry THF (3 cm^3) was added dropwise. The reaction mixture was allowed to warm to room temp. slowly then stirred overnight. After filtration through Celite the solvent was evaporated under reduced pressure. Chromatography using ethyl acetate–ethanol (19:2 followed by 9:1) yielded 9-{(1′β,4′β)-4′-[3″-*diethylphosphonomethoxy*)*propoxy*]*cyclopent*-2′-*enyl*}-6-*methoxy*-2-(N-*monomethoxytriphenylmethylamino*)*purine* (0.191 g, 0.26 mmol, 33%) as a white foam, m.p. 43–50 °C; λ_{max}(EtOH)/nm 258.1 (14 330) and 286.1 (13 410); ν_{max}(KBr)/cm^{-1} 1610s, 1590s (C=C, C=N), 1239s (P=O) and 1108s br (C–O–C, P–O–C); δ_H(250 MHz; $CDCl_3$) 7.60 (1 H, s, 8-H), 7.38–7.12 (12 H, m, H-Ar), 6.82–6.71 (2 H, m, H-Ar), 6.28–6.16 (2 H, m, NH, 3′-H), 5.92–5.84 (1 H, m, 2′-H), 5.25–5.04 (1 H, m, 1′-H), 4.48–4.38 (1 H, m, 4′-H), 4.23–4.05 (4 H, m, 4 × H-CH), 3.79–3.70 (5 H, m, 6-CH_3O, 2 × H-CH), 3.65–3.50 (7 H, m, CH_3O-Ar, 4 × H-CH), 2.74–2.58 (1 H, m, 5′-αH), 1.99–1.88 (2 H, m, 2 × 2″-H), 1.74–1.60 (1 H, m, 5′-βH) and 1.36–1.15 (6 H, m, 2 × C$H_3$$CH_2O$) [Found (CI): M^+ 727.314. $C_{39}H_{46}N_5O_7P$ requires *M* 727.3135]: and 9-{[1′β,4′β]-4′-[(3″-*ethylphosphonomethoxy*)*propoxy*]-*cyclopent*-2′-*enyl*}-6-*methoxy*-2-(N-*monomethoxytriphenylmethylamino*)*purine* (0.094 g, 0.13 mmol, 16%) as a white foam, m.p. 78–84 °C; λ_{max}(EtOH)/nm 258.6 (11 340) and 286.7 (10 870); ν_{max}(KBr)/cm^{-1} 1610s, 1587s (C=C, C=N), 1248s (P=O) and 1180s br (C–O–C, P–O–C); δ_H(250 MHz; $CDCl_3$) 7.62–7.58 (1 H, m, 8-H), 7.38–7.12 (12 H, m, H-Ar), 6.80–6.72 (2 H, m, H-Ar), 6.27–6.17 (2 H, m, NH, 3′-H), 5.92–5.84 (1 H, m, 2′-H), 5.22–5.06 (1 H, m, 1′-H), 4.47–4.37 (1 H, m, 4′-H), 4.25–4.08 (4 H, m, 4 × H-CH), 3.79–3.71 (4 H, m, 6-CH_3O, H-CH), 3.66–3.50 (6 H, m, CH_3O-Ar, 3 × H-CH), 2.78–2.58 (1 H, m, 5′-αH), 2.03 (1 H, s, OH), 1.88 (2 H, ddd, *J* 21, 6, 6, 2 × 2″-H), 1.75–1.63 (1 H, m, 5′-βH) and 1.39–1.21 (3 H, m, 2 × C$H_3$$CH_2O$); *m*/*z* (FAB) 699 ($M^+$, 8%).

A solution of the latter compound (0.087 g, 0.12 mmol) in glacial acetic acid (1 cm^3) was refluxed for 1 h. Ethanol (5 cm^3) was added and the resultant mixture evaporated under reduced pressure. Chromatography using dichloromethane–methanol (25:1 followed by 10:1) as eluent yielded 2-*amino*-9-{(1′β,4′β)-4′-[3″-(*ethylphosphonomethoxy*)*propoxy*]*cyclopent*-2′-*enyl*}-6-*methoxypurine* (0.043 g, 0.10 mmol, 83%) as a white gum; λ_{max}(MeOH)/nm 250.0 (9670) and 283.6 (11 090); $\nu_{max}(CHCl_3)$/cm^{-1} 3530w, 3425m (NH, OH), 1611s, 1587s (C=C, C=N), 1248s br (P=O) and 1043s br (P–O–C, C–O); δ_H(250 MHz; $CDCl_3$) 7.70 (1 H, d, *J* 2, 8-H), 6.30–6.23 (1 H, m, 3′-H), 6.00 (1 H, dd, *J* 5, 1.5, 2′-H), 5.46–5.36 (1 H, m, 1′-H), 5.00 (2 H, s, NH_2), 4.53–4.42 (1 H, m, 4′-H), 4.22–4.03 (6 H, m, 6-CH_3O, 3 × H-CH), 3.77–3.69 (2 H, m, 2 × H-CH), 3.63–3.51 (3 H, m, 3 × H-CH), 3.44 (1 H, s, OH), 2.84 (1 H, ddd, *J* 15, 15, 7.5, 5′-αH), 1.98–1.76 (3 H, m, 5′-βH, 2 × 2″-H) and 1.34–1.12 (3 H, m, C$H_3$$CH_2$).

TMSI (0.18 cm^3, *ca.* 0.253 g, 1.26 mmol) was added dropwise to a solution of the monoprotected phosphonate (0.058 g, 0.14 mmol) in dry DMF (2 cm^3) at 0 °C in the dark. The reaction

mixture allowed to warm to room temp. slowly then stirred overnight. After cooling to 0 °C aqueous ammonium hydrogen carbonate (0.2 mol dm^{-3}; 8 cm^3) was added dropwise, stirring was continued at 0 °C for 0.5 h then at room temp. for 3.5 h. The reaction mixture was filtered and evaporated under reduced pressure. The residue was chromatographed over Sephadex LH-20 using methanol–aqueous formic acid (0.1 mol dm^{-3}) (1:2) as eluent. Appropriate fractions were combined, evaporated under reduced pressure then lyophilised to afford the *title compound* **31** (0.023 g, 0.06 mmol, 43%) as a white lyophiliate; $\lambda_{max}(H_2O)$/nm 250.3 (12 490); ν_{max}(KBr)/cm^{-1} 3600–2600s, br (NH, OH), 1686s br (C=O, guanine), 1614m (C=C, C=N) and 1200–1050s br (P–O–C, C–O, P=O); δ_H(250 MHz; D_2O) 7.89 (1 H, s, 8-H), 6.54–6.47 (1 H, m, 3′-H), 6.33–6.27 (1 H, m, 2′-H), 5.51–5.41 (1 H, m, 1′-H), 3.87–3.62 (6 H, m, 6 × H-CH), 3.08 (1 H, ddd, *J* 17, 7.5, 7.5, 5′-αH) and 2.06–1.90 (3 H, m, 5′-βH, 2 × 2″-H); δ_P(161.9 MHz; D_2O) 16.8 [Found (FAB): $M^+ + H$, 386.1196. $C_{14}H_{20}N_5O_6P$ requires (M + H), 386.1229].

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