Synthesis of [3-(Phosphonomethoxy)pyrrolidin-1-yl] Derivatives of Pyrimidines and Purines: Analogues of 2',3'-Dideoxynucleotides

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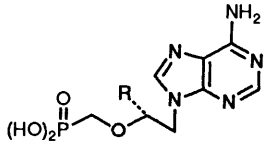
Pyrrolidin-1-yl derivatives of pyrimidines and purines, incorporating the phosphonomethoxy group as a phosphate mimic, were prepared as analogues of 2',3'-dideoxynucleotides. The heterocyclic bases uracil, thymine, cytosine, adenine and hypoxanthine were constructed upon the primary amino group of the *N*-aminopyrrolidine **7**, which was prepared by reaction of the dibromide **6** with hydrazine.

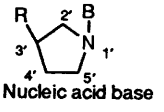
The discovery of the potent antiviral activity of the acyclonucleotide analogues 9-[2-(phosphonomethoxy)ethyl]-adenine (PMEA) **1** and (*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine [(*S*)-HPMPA] **2**[1] has prompted great interest in this class of compounds. The antiviral activity of these phosphonates is not restricted to purine derivatives and the cytosine analogue of **2** has been shown to exhibit potent activity against some members of the herpes virus family.[2,3] The use of the phosphonomethoxy group as a stable isosteric mimic of the (isomeric) phosphate monoester function is now being widely explored in both the acyclic[2–13] and the cyclic[14–17] series of nucleotide analogues.

Recently a new series of dideoxynucleoside analogues of type **3** containing a pyrrolidine ring linked to the base *via* the heteroatom has been developed.[18–20] The pyrrolidine analogues of some 3'-substituted thymidine nucleosides have also been described very recently.[21] In this report we describe the preparation of the [3-(phosphonomethoxy)pyrrolidin-1-yl] derivatives **4** of pyrimidines and purines as novel analogues of 2',3'-dideoxynucleotides.

The reported syntheses of pyrrolidinyl nucleoside analogues used *N*-aminopyrrolidine precursors to pyrimidine nucleosides[18,20,21] or routes *via* the various *N*-amino bases to purine or pyrimidine nucleosides.[19] We elected to employ an *N*-aminopyrrolidine phosphonate as a common intermediate to both pyrimidine and purine nucleotide analogues.



R = H, PMEA **1**
R = CH_2OH, (*S*)-HPMPA **2**



B = Nucleic acid base

R = CH_2OH **3**
R = $OCH_2P(O)(OH)_2$ **4**

Results and Discussion

Arbusov reaction of the α-chloro ether derived from 1,4-dibromobutan-2-ol **5** gave a 51% overall yield of the diethyl phosphonate **6** (Scheme 1). Treatment of dibromide **6** with hydrazine hydrate then gave the unstable 1-aminopyrrolidine **7**, which was converted into the 1-ureidopyrrolidine **8** in 52% yield using trimethylsilyl isocyanate. Attempted condensation of compound **8** with methyl 3,3-dimethoxypropionate, in the presence of either potassium *tert*-butoxide in *tert*-butyl alcohol or sodium hydride in dimethyl sulfoxide (DMSO) failed, probably due to the incompatibility of the phosphonate group with the strongly basic conditions. However, an alternative cyclization method[22,23] avoiding strong base was successfully exploited. Acylation of compound **8** (on the NH_2 group) using 3-ethoxyacryloyl chloride in the presence of pyridine afforded the intermediate acrylamide in 76% yield, which cyclized smoothly upon treatment with sulfuric acid to give the uracil **9** in 87% yield. De-esterification of compound **9** with bromotrimethylsilane afforded the free phosphonic acid **10** in 86% yield.

The uracil **9** was converted into the cytosine **11** in 57% yield *via* the triazolide.[24] De-esterification of compound **11** then gave the phosphonic acid **12** in 79% yield. Acylation of the 1-ureidopyrrolidine **8** with ethyl (*E*)-3-ethoxy-2-methylacryloyl chloride gave the intermediate acrylamide, acid-catalysed cyclization of which gave the thymine derivative **13** in 13% overall yield. Compound **13** was de-esterified to give the phosphonic acid **14** in 84% yield.

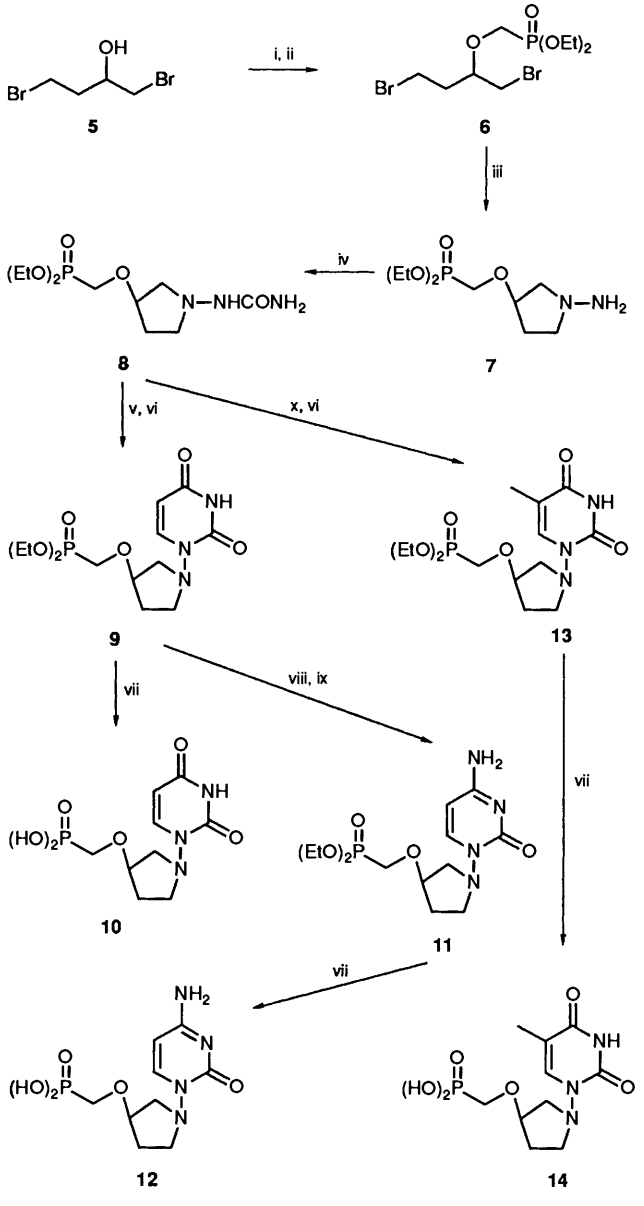
The key intermediate **7** was also progressed to purine derivatives *via* an imidazole intermediate[25,26] (Scheme 2). Treatment of compound **7** with ethyl *N*-(carbamoylcyanomethyl)formimidate gave the imidazole **15** in 28% yield, which was converted into the free phosphonic acid **16** in 56% yield. Compound **15** was converted[27] into the hypoxanthine **17** in 63% yield using triethyl orthoformate, subsequent deprotection of **17** then yielding the phosphonic acid **18** in 73% yield.

The hypoxanthine **17** was successfully transformed in 22% yield into the adenine **19** *via* the 2,4,6-triisopropylbenzenesulfonate (a method previously used for transformation of a guanine derivative into a 2,6-diaminopurine[28]), following unsuccessful attempts *via* the trifluoromethanesulfonate[29] (which appeared to result in decomposition). Attempted conversion of the hypoxanthine **17** into the 6-chloropurine using phosphoryl trichloride and *N*,*N*-diethylaniline[30] caused loss of one of the phosphonate ester groups and so this was not a viable route to the adenine **19**. Treatment of compound **19** with bromotrimethylsilane gave the phosphonic acid **20** in 72% yield.

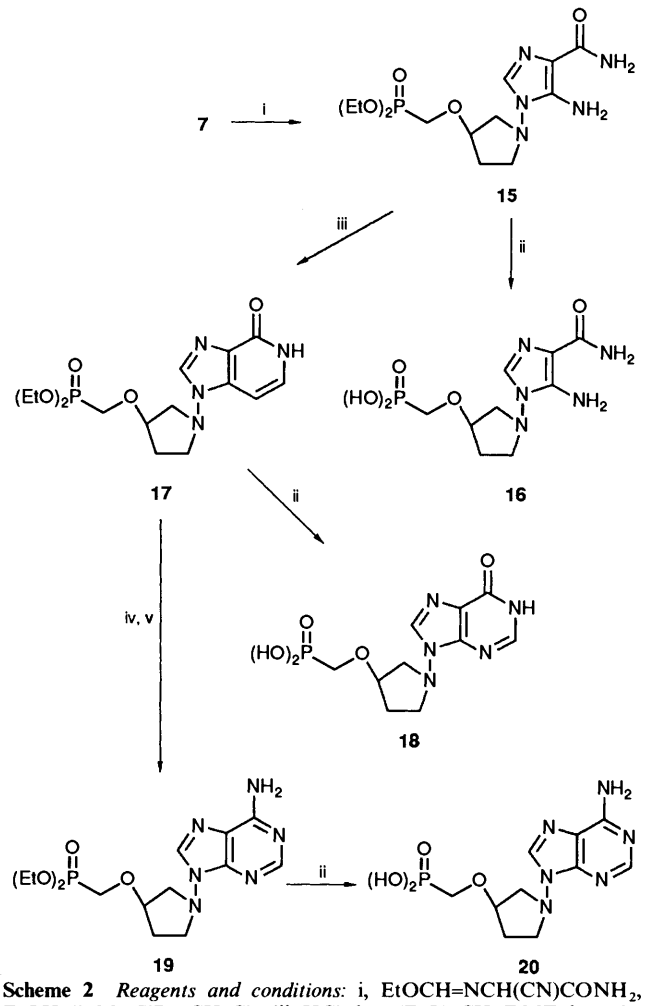
A number of attempts to prepare the guanine derivative from amide **15** were not successful, the phosphonate ester moiety proving to be unstable to a variety of standard reaction conditions for this transformation.

To assess the state of ionization of these novel nucleotide analogues at physiological pH the pK_a profiles were determined for compounds **9** and **14** (Table 1). The pyrrolidine nitrogen has very low basicity (as would be expected for substituted hydrazines of this type*[,31]) and hence it is unlikely to participate in zwitterion formation with the phosphonic acid function. Consistent with this is the lack of any shift in the NMR signals of the C-2' or C-5' pyrrolidine ring protons for compounds **10**, **12**, **14**, **16**, **18** and **20** relative to their respective

* The basic pK_a of acetylhydrazine is 3.24.



Scheme 1 *Reagents and conditions:* i, HCl, $(CH_2O)_n$, $CaCl_2$, CH_2Cl_2; ii, $(EtO)_3P$, heat; iii, H_2NNH_2, EtOH; iv, Me_3SiNCO, CH_2Cl_2; v, EtOCH=CHCOCl, C_5H_5N, CH_2Cl_2; vi, 0.5 mol dm^{-3} H_2SO_4, heat; vii, Me_3SiBr, CH_2Cl_2; viii, 4-$ClC_6H_4OP(O)Cl_2$, 1,2,4-triazole, C_5H_5N; ix, NH_3, MeOH; x, EtOCH=C(Me)COCl, C_5H_5N, CH_2Cl_2



Scheme 2 *Reagents and conditions:* i, EtOCH=NCH(CN)$CONH_2$, EtOH; ii, Me_3SiBr, CH_2Cl_2; iii, HCl then $(EtO)_3CH$, DMF, heat; iv, 2,4,6-$Pr^i_3C_6H_2SO_2Cl$, Et_3N, DMAP, CH_2Cl_2; v, NH_3, EtOH, heat

Table 1 Dissociation constants for compounds **9** and **14**

Compound	Basic pK_a[a]	Acidic pK_a[a]		
		1[b]	2[c]	3[d]
9	<2.0[e]			9.16
14	<0.7[f]	1.75	6.91	9.47

[a] Measured using a Metrohm 670 Titroprocessor or a Hewlett-Packard 845A diode array spectrophotometer. [b] First dissociation constant of the phosphonic acid. [c] Second dissociation constant of the phosphonic acid. [d] Dissociation constant of the pyrimidine moiety. [e] By potentiometric methods no end-point was observed down to pH 2. [f] By potentiometric methods no end-point was observed down to pH 2 and by UV methods no spectral changes were observed over the pH range 3.2–0.7.

diethyl esters **9**, **11**, **13**, **15**, **17** and **19**. Additionally the NMR spectrum of the cytosine derivative **12** does not show the downfield shift and splitting of the NH_2 signal characteristic of protonation at N-3.[32] Therefore, in [$^2H_6$]DMSO, the cytosine moiety of compound **12** must also remain unprotonated. However, the IR bands at 1735 and 1680 cm^{-1} indicate that compound **12** is zwitterionic in the solid state, the N-3 atom being the proton acceptor.[33]

The conformation around the pseudo-glycosidic bond of compound **11** was investigated using NOE experiments. Irradiation of the 6-H signal produced a positive NOE enhancement of similar magnitude (medium) for both of the 2′-H signals, and both of the 5′-H signals. Hence, although these novel nucleotide analogues presumably exist as a mixture of α and β forms due to inversion at the pyrrolidine nitrogen, a significant proportion of the mixture may be in the *anti* conformation characteristic of the natural nucleosides.

The nucleotide analogues **10**, **12**, **14**, **16**, **18** and **20** were tested at concentrations up to 100 μg cm^{-3} for inhibition of virus replication in cell culture. Compound **20** showed good activity against visna virus in sheep choroid plexus cells (minimum inhibitory concentration 3 μg cm^{-3}), compounds **10**, **12**, **14**, **16** and **18**, however, being inactive. All compounds were found to be devoid of activity against herpes simplex virus types 1 and 2, varicella zoster virus and cytomegalovirus in MRC-5 (human fibroblast) cells. In these tests no toxicity to the cell monolayers was observed.

Experimental

M.p.s were determined using a Reichert Kofler apparatus and are uncorrected. NMR spectra were recorded with a JEOL GX-

270 270 MHz spectrometer and *J*-values are given in Hz. NOE difference spectroscopy was performed on a Bruker AMX400 spectrometer using standard software and $CDCl_3$ as solvent. IR spectra were recorded with a Perkin-Elmer 580 spectrometer, and UV spectra with a Uvikon 810 spectrometer. Mass spectra were recorded and accurate masses were measured on a JEOL JMS-SX102 spectrometer. Microanalyses were performed on a Carlo Erba model 1106 analyser. Column chromatography was carried out on Merck 7736 silica gel. All compounds were homogeneous by TLC on silica gel $60F_{254}$-coated glass plates.

Diethyl (1,4-*Dibromobutan*-2-*yloxy*)*methylphosphonate*. **6**.—(*a*) Hydrogen chloride was bubbled into a stirred mixture of 1,4-dibromobutan-2-ol **5** (10.0 g, 43.1 mmol), paraformaldehyde (1.30 g, 43.1 mmol), and anhydrous calcium chloride (20.8 g) in dichloromethane (100 cm^3) for 1.5 h. The mixture was filtered and the solvent was removed to leave a light brown oil (10.6 g) which was used without further purification. ^1H NMR analysis indicated approximately 50% conversion into the desired chloro ether; $\delta_H(CDCl_3)$ 2.20 (2 H, m, CH_2), 3.50 (4 H, m, CH_2Br), 4.10 (1 H, m, $CHOCH_2$) and 5.60 (2 H, s, $CHOCH_2$).

(*b*) A mixture of crude 1,4-dibromo-2-chloromethoxybutane (7.44 g, ~ 13.3 mmol) and triethyl phosphite (4.41 g, 26.5 mmol) was heated at 100 °C for 1.75 h. The mixture was cooled to room temperature and purified by column chromatography on silica gel with ethyl acetate–hexane (1:1) then ethyl acetate as eluent to afford the *phosphonate* **6** as a liquid (6.0 g, 51% from **5**); ν_{max}(film)/cm^{-1} 1255 (P=O); $\delta_H(CDCl_3)$ 1.36 (6 H, t, *J* 7, Me), 2.17 (2 H, m, CH_2), 3.45–3.75 (4 H, m, 2 × CH_2Br), 3.75–4.15 (3 H, m, $CHOCH_2P$) and 4.19 (4 H, pseudo quintet, *J* 7, OCH_2Me); $\delta_C(CDCl_3)$ 16.40 (d, $^3J_{PC}$ 6.8, Me), 29.17 (s, CCH_2C), 33.12 (s, CH_2Br), 36.37 (s, CH_2Br), 62.49 (d, $^2J_{PC}$ 6.1, OCH_2Me), 64.20 (d, $^1J_{PC}$ 166.8, OCH_2P) and 78.74 (d, $^3J_{PC}$ 12.2, $COCH_2P$) (Found: C, 28.6; H, 5.2. $C_9H_{19}Br_2O_4P$ requires C, 28.3; H, 5.0%).

Diethyl (1-*Aminopyrrolidin*-3-*yloxy*)*methylphosphonate* **7**.—To a solution of the phosphonate **6** (2.74 g, 7.20 mmol) in ethanol (12.4 cm^3) was added hydrazine monohydrate (2.88 g, 2.80 cm^3, 57.5 mmol) and the mixture was stirred at room temperature for 18 h before being partitioned between water (75 cm^3) and chloroform (8 × 75 cm^3), and the combined organic portions were dried ($MgSO_4$) and filtered, and the solvent was removed to give diethyl (1-aminopyrrolidin-3-yloxy)methylphosphonate **7** (1.76 g, 97%) as a pale yellow oil which was unstable and was therefore used without further purification; ν_{max}(film)/cm^{-1} 3450 (NH_2), 1615 (NH_2) and 1250 (P=O); $\delta_H(CDCl_3)$ 1.33 (6 H, t, *J* 6, Me), 2.00 (2 H, m, CCH_2C), 2.50–3.00 (4 H, m, CH_2N), 3.73 (2 H, d, *J* 9, OCH_2P) and 4.20 (5 H, m, OCH_2Me and $CHOCH_2$).

Diethyl (1-*Ureidopyrrolidin*-3-*yloxy*)*methylphosphonate* **8**.—To a solution of the 1-aminopyrrolidine **7** (0.66 g, 2.62 mmol) in dry dichloromethane (5.6 cm^3) stirred at room temperature was added trimethylsilyl isocyanate (0.84 g, 0.99 cm^3, 7.29 mmol). After 2.5 h the reaction was quenched by addition of methanol and the solvents were removed to leave an oil, which was purified by column chromatography on silica gel with dichloromethane–methanol (19:1, 4:1) as eluent to afford the 1-*ureidopyrrolidine* **8** as a gum (0.40 g, 52%); ν_{max}(film)/cm^{-1} 3460 (NH/NH_2), 3300 (NH/NH_2), 3200 (NH/NH_2), 1680 (C=O) and 1240 (P=O); $\delta_H[(CD_3)_2SO]$ 1.23 (6 H, t, *J* 7, Me), 1.70 (1 H, m, CCH_2C), 2.02 (1 H, m, CCH_2C), 2.50–3.20 (4 H, br m, CH_2N), 3.75 (2 H, d, *J* 9, OCH_2P), 4.04 (5 H, m, OCH_2Me + $CHOCH_2$), 5.90 (2 H, s, NH_2) and 6.96 (1 H, s, NH); $\delta_C(CDCl_3)$ 16.30 (d, $^3J_{PC}$ 6.8, Me), 30.01 (s, CCH_2C), 54.58 (s, CH_2N), 60.86 (br s, CH_2N), 62.35 (d, $^3J_{PC}$ 6.1, OCH_2Me), 62.80 (d, $^1J_{PC}$ 167.5, OCH_2P), 79.61 (br, s, $COCH_2P$) and 160.08 (s, $HNCONH_2$) (Found: C, 40.5; H, 7.6; N, 14.1%; MH^+, 296.1373. $C_{10}H_{22}N_3O_5P$ requires C, 40.7; H, 7.5; N, 14.2%; *M*H, 296.1375).

1-[3-(*Diethoxyphosphorylmethoxy*)*pyrrolidin*-1-*yl*]*uracil* **9**.—(*a*) 3-Ethoxyacryloyl chloride (0.4 g, 2.97 mmol) was added to a solution of the 1-ureidopyrrolidine **8** (0.76 g, 2.57 mmol) and pyridine (0.24 g, 0.25 cm^3, 3.03 mmol) in dry dichloromethane (5 cm^3) and the mixture was stirred at room temperature for 18 h before being partitioned between water (10 cm^3) and dichloromethane (2 × 10 cm^3). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel with ethyl acetate–methanol (19:1, 7:1) as eluent to give *diethyl* {[1-(3-*ethoxyacryloyl*)*ureido*]*pyrrolidin*-3-*yloxy*}*methylphosphonate* as a gum (0.76 g, 76%); ν_{max}(film)/cm^{-1} 3220 (NH), 3150 (NH), 1715 (C=O), 1678 (C=O), 1615 (C=C) and 1240 (P=O); $\delta_H[(CD_3)_2SO]$ 1.24 (9 H, m, Me), 1.75 (1 H, m, CCH_2C), 2.07 (1 H, m, CCH_2C), 2.70–3.25 (4 H, br m, CH_2N), 3.76 (2 H, d, *J* 9, OCH_2P), 3.90–4.20 (7 H, m, OCH_2Me + $CHOCH_2$), 5.51 (1 H, d, *J* 12, OCH=C*H*), 7.55 (1 H, d, *J* 12, OC*H*=CH), 9.34 (1 H, s, NH) and 10.02 (1 H, s, NH) (Found: MH, 394.1747. $C_{15}H_{28}N_3O_7P$ requires *M*H, 394.1743).

(*b*) A mixture of diethyl {[1-(3-ethoxyacryloyl)ureido]-pyrrolidin-3-yloxy}methylphosphonate (0.61 g, 1.55 mmol) and 0.5 mol dm^{-3} sulfuric acid (11.5 cm^3) was heated at 100 °C for 50 min. The cooled mixture was partitioned between saturated aq. sodium hydrogen carbonate (11 cm^3) and dichloromethane (5 × 40 cm^3). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated to afford *the uracil* **9** as a pale yellow gum (0.47 g, 87%); λ_{max}(EtOH)/nm 262 (ε/dm^3 mol^{-1} cm^{-1} 8590); ν_{max}(film)/cm^{-1} 3000 (NH), 1720 (C^2=O), 1680 (C^4=O), 1240 (P=O); $\delta_H[(CD_3)_2SO]$ 1.24 (6 H, t, *J* 7, Me), 1.80 (1 H, m, 4′-H), 2.15 (1 H, m, 4′-H), 3.20–3.35 (3 H, m, 2′-H and 5′-H_2), 3.49 (1 H, dd, *J* 6 and 10, 2′-H), 3.79 (2 H, d, *J* 9, PCH_2O), 4.05 (4 H, pseudo quintet, *J* 7, CH_2O), 4.20 (1 H, m, 3′-H), 5.43 (1 H, d, *J* 8, 5-H), 7.61 (1 H, d, *J* 8, 6-H) and 11.30 (1 H, s, 3-H) (Found: MH^+, 348.1325. $C_{13}H_{22}N_3O_6P$ requires *M*H, 348.1325).

1-[3-(*Phosphonomethoxy*)*pyrrolidin*-1-*yl*]*uracil* **10**.—Bromotrimethylsilane (0.97 g, 6.33 mmol) was added to a solution of the uracil **9** (110 mg, 0.32 mmol) in dry dichloromethane (5 cm^3) and the mixture was stirred at room temperature for 20 h before being evaporated to dryness, then the residue was azeotroped with methanol (× 3). The residue was purified by column chromatography on C_{18} silica gel with water as eluent to give the *phosphonic acid* **10** as a hygroscopic solid (80 mg, 86%); λ_{max}(EtOH)/nm 263 (ε/dm^3 mol^{-1} cm^{-1} 8465); ν_{max}(KBr)/ cm^{-1} 3420 (H_2O), 3170 (NH), 1715 (C^2=O), 1680 (C^4=O) and 1180 [$(PO_3H)^-$]; $\delta_H[(CD_3)_2SO]$ 1.82 (1 H, m, 4′-H), 2.15 (1 H, m, 4′-H), 3.15–3.35 (3 H, m, 2′-H and 5′-H_2), 3.50 (3 H, m, 2′-H and PCH_2O), 4.23 (1 H, m, 3′-H), 5.44 (1 H, d, *J* 8, 5-H), 7.63 (1 H, d, *J* 8, 6-H) and 11.30 (1 H, s, 3-H) (Found: C, 35.0; H, 5.3; N, 13.3. $C_9H_{14}N_3O_6P{\cdot}H_2O$ requires C, 35.0; H, 5.2; N, 13.6%).

1-[3-(*Diethoxyphosphorylmethoxy*)*pyrrolidin*-1-*yl*]*cytosine* **11**.—To a solution of the uracil **9** (246 mg, 0.71 mmol) in dry pyridine (3.9 cm^3) stirred at room temperature was added 4-chlorophenyl phosphorodichloridate (0.23 g, 0.94 mmol). After 20 min 1,2,4-triazole (130 mg, 1.88 mmol) was added and the mixture was stirred at room temperature for 18 h. To the solution were added ammonia (*d* 0.88 g cm^{-3}; 0.4 cm^3) and methanol (0.8 cm^3), and the mixture was stirred for a further 4 h. The solvent was removed, and the residue was azeotroped with toluene (× 2) before being purified by column chromatography on silica gel with dichloromethane–methanol (9:1, 4:1) as

eluent to afford the *cytosine* **11** as a gum (140 mg, 57%); λ_{max}(EtOH)/nm 273 (ε/dm^3 mol^{-1} cm^{-1} 6957) and 235 (ε 7130); ν_{max}(film)/cm^{-1} 3360 (NH_2), 3220 (NH_2), 1660 (NH_2) and 1270 (P=O); δ_H[$(CD_3)_2SO$] 1.25 (6 H, t, *J* 7, Me), 1.80 (1 H, m, 4′-H), 2.20 (1 H, m, 4′-H), 3.20 (1 H, dd, *J* 4 and 9, 2′-H), 3.29 (2 H, t, *J* 7, 5′-H_2), 3.53 (1 H, dd, *J* 6 and 9, 2′-H), 3.78 (2 H, d, *J* 9, PCH_2O), 4.05 (4 H, pseudo quintet, *J* 7, CH_2O), 4.23 (1 H, m, 3′-H), 5.55 (1 H, d, *J* 7, 5-H), 7.10 (2 H, br s, NH_2) and 7.51 (1 H, d, *J* 7, 6-H) (Found: MH^+, 347.1483. $C_{13}H_{23}N_4O_5P$ requires *M*H, 347.1485).

1-[3-(*Phosphonomethoxy*)*pyrrolidin*-1-*yl*]*cytosine* **12**.—To a solution of the cytosine **11** (120 mg, 0.34 mmol) in dichloromethane (4 cm^3) was added bromotrimethylsilane (0.71 g, 4.64 mmol) and the mixture was stirred at room temperature for 18 h and then evaporated to dryness, and the residue was azeotroped with methanol (× 3) before being purified by column chromatography on C_{18} silica gel with water as eluent to give *the cytosine* **12** as a solid (79 mg, 79%), m.p. 171–172 °C; λ_{max}(EtOH)/nm 274 (ε/dm^3 mol^{-1} cm^{-1} 6725); ν_{max}(KBr)/cm^{-1} 3425 (H_2O), 3187 (NH_2), 3100 (NH_2), 1735 (C=O), 1680 (C=N$^+$) and 1200 [$(PO_3H)^-$]; δ_H[$(CD_3)_2SO$] 1.80 (1 H, m, 4′-H), 2.18 (1 H, m, 4′-H), 3.18 (1 H, dd, *J* 4 and 10, 2′-H), 3.29 (2 H, t, *J* 7, 5′-H_2), 3.50 (3 H, m, 2′-H and PCH_2O), 4.25 (1 H, m, 3′-H), 5.59 (1 H, d, *J* 7, 5-H), 7.30 (2 H, br, NH_2) and 7.57 (1 H, d, *J* 7, 6-H) (Found: C, 36.0; H, 5.9; N, 18.7. $C_9H_{15}N_4O_5{\cdot}0.5H_2O$ requires C, 36.1; H, 6.1; N, 18.7%).

1-[3-(*Diethoxyphosphorylmethoxy*)*pyrrolidin*-1-*yl*]*thymine* **13**.—(*a*) 3-Ethoxy-2-methylacryloyl chloride (0.69 g, 4.64 mmol) was added to a solution of compound **8** (1.19 g, 4.03 mmol) and pyridine (0.38 g, 4.85 mmol) in dichloromethane (7.8 cm^3) and the mixture was stirred at room temperature for 18 h. The mixture was partitioned between water (10 cm^3) and dichloromethane (2 × 10 cm^3). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel with ethyl acetate–methanol (49:1, 9:1) as eluent to afford diethyl {[1-(3-ethoxy-2-methylacryloyl)ureido]pyrrolidin-3-yloxy}methylphosphonate as a gum (0.37 g, 22%); ν_{max}(film)/cm^{-1} 3220 (NH), 1695 (C=O), 1655 (C=O) and 1240 (P=O); δ_H[$(CD_3)_2SO$] 1.24 (9 H, m, *Me*CH_2O), 1.62 (3 H, s, Me), 1.75 (1 H, m, 4′-H), 2.05 (1 H, m, 4′-H), 2.75–3.15 (4 H, br m, 2′- and 5′-H_2), 3.75 (2 H, d, *J* 9, PCH_2O), 4.10 (6 H, m, CH_2O), 7.52 (1 H, s, CH=C), 9.45 (1 H, s, NH) and 9.70 (1 H, s, NH); FABMS (3-nitrobenzyl alcohol/sodium acetate) 430 (MNa^+).

(*b*) A mixture of diethyl {[1-(3-ethoxy-2-methylacryloyl)-ureido]pyrrolidin-3-yloxy}methylphosphonate (0.36 g, 0.88 mmol) and 0.5 mol dm^{-3} sulfuric acid (6.5 cm^3) was heated at 100 °C for 1.8 h. The mixture was cooled, saturated aq. sodium hydrogen carbonate (6.2 cm^3) was added, and the resulting solution was extracted with dichloromethane (5 × 25 cm^3). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel with dichloromethane–methanol (49:1, 19:1) as eluent to afford *the thymine* **13** as a gum (0.19 g, 59%); λ_{max}(EtOH)/nm 267 (ε/dm^3 mol^{-1} cm^{-1} 8870); ν_{max}(film)/cm^{-1} 1700 (C=O) and 1240 (P=O); δ_H[$(CD_3)_2SO$] 1.25 (6 H, t, *J* 7, *Me*CH_2O), 1.72 (3 H, s, Me), 1.80 (1 H, m, 4′-H), 2.14 (1 H, m, 4′-H), 3.15–3.35 (3 H, m, 2′-H and 5′-H_2), 3.48 (1 H, dd, *J* 10 and 6, 2′-H), 3.78 (2 H, d, *J* 9, PCH_2O), 4.05 (4 H, pseudo quintet, *J* 7, CH_2O), 4.22 (1 H, m, 3′-H), 7.53 (1 H, s, 6-H) and 11.28 (1 H, s, 3-H) (Found: MH^+, 362.1478. $C_{14}H_{24}N_3O_6P$ requires *M*H, 362.1481).

1-[3-(*Phosphonomethoxy*)*pyrrolidin*-1-*yl*]*thymine* **14**.—To a solution of the thymine **13** (0.16 g, 0.44 mmol) in dry dichloromethane (5 cm^3) was added bromotrimethylsilane (1.16 g, 7.58 mmol) and the mixture was stirred at room temperature for 18 h. The solution was evaporated and the residue was azeotroped with methanol (× 3). The residue was purified by column chromatography on C_{18} silica gel with water as eluent to afford the *phosphonic acid* **14** as a powder (0.12 g, 84%), m.p. 106–108 °C; λ_{max}(EtOH)/nm 269 (ε/dm^3 mol^{-1} cm^{-1} 8450); ν_{max}(KBr)/cm^{-1} 3420 (H_2O), 3170 (NH), 1705 (C=O) and 1205 [$(PO_3H)^-$]; δ_H[$(CD_3)_2SO$] 1.73 (3 H, s, Me), 1.82 (1 H, m, 4′-H), 2.13 (1 H, m, 4′-H), 3.10–3.35 (3 H, m, 2′-H and 5′-H_2), 3.47 (1 H, dd, *J* 10 and 6, 2′-H), 3.52 (2 H, d, *J* 9, PCH_2O), 7.55 (1 H, s, 6-H) and 11.27 (1 H, s, 3-H) (Found: C, 36.3; H, 5.5; N, 12.7. $C_{10}H_{16}N_3O_6P{\cdot}1.5H_2O$ requires C, 36.15; H, 5.8; N, 12.65%).

Diethyl [1-(5-*Amino*-4-*carbamoylimidazol*-1-*yl*)*pyrrolidin*-3-*yloxy*]*methylphosphonate* **15**.—A mixture of compound **7** (2.63 g, 10.4 mmol) and ethyl *N*-(carbamoylcyanomethyl)formimidate (1.78 g, 10.4 mmol) in ethanol (7 cm^3) was heated under reflux for 5 min, then allowed to cool. The solvent was removed and the residue was purified by column chromatography on silica gel with dichloromethane–methanol (19:1, 9:1) as eluent to afford *the imidazole* **15** as a gum (1.07 g, 28%); λ_{max}(EtOH)/nm 267 (ε/dm^3 mol^{-1} cm^{-1} 11 400); ν_{max}(film)/cm^{-1} 3300 (NH_2), 1650 (C=O) and 1230 (P=O); δ_H[$(CD_3)_2SO$] 1.25 (6 H, t, *J* 7, Me), 2.00 (1 H, m, 4′-H), 2.30 (1 H, m, 4′-H), 3.15–3.30 (3 H, m, 2′-H and 5′-H_2), 3.41 (1 H, dd, *J* 6 and 10, 2′-H), 3.85 (2 H, dd, *J* 9, PCH_2O), 4.07 (4 H, pseudo quintet, *J* 7, CH_2O), 4.25 (1 H, m, 3′-H), 5.57 (2 H, br s, D_2O exchangeable, NH_2), 6.63 (2 H, s, D_2O exchangeable, NH_2) and 7.51 (1 H, s, 2-H) (Found: MH^+, 362.1585. $C_{13}H_{24}N_5O_5P$ requires *M*H, 362.1593).

[1-(5-*Amino*-4-*carbamoylimidazol*-1-*yl*)*pyrrolidin*-3-*yloxy*]-*methylphosphonic Acid* **16**.—To a solution of the imidazole **15** (160 mg, 440 μmol) in dichloromethane (5 cm^3) was added bromotrimethylsilane (1.35 g, 8.56 mmol). The mixture was stirred at room temperature for 18 h. The solution was evaporated off and the residue was azeotroped with methanol (× 3). The residue was purified by column chromatography on C_{18} silica gel with water as eluent to afford the *phosphonic acid* **16** as pale pink crystals (75 mg, 56%), m.p. 142–144 °C; λ_{max}(EtOH)/nm 267 (ε/dm^3 mol^{-1} cm^{-1} 11 700); ν_{max}(KBr)/cm^{-1} 3420 (H_2O) and 1675 (C=O); δ_H[$(CD_3)_2SO$] 2.05 (1 H, m, 4′-H), 2.20 (1 H, m, 4′-H), 3.20 (3 H, m, 2′-H and 5′-H_2) 3.41 (1 H, dd, *J* 6 and 10, 2′-H), 3.57 (2 H, dd, *J* 9, PCH_2O), 4.25 (1 H, m, 3′-H), 5.65 (2 H, br s, D_2O exchangeable, NH_2), 6.70 (2 H, br s, D_2O exchangeable, NH_2) and 7.52 (1 H, s, 2-H) (Found: C, 33.2; H, 5.6; N, 21.6. $C_9H_{16}N_5O_5P{\cdot}H_2O$ requires C, 33.4; H, 5.6; N, 21.7%).

9-[3-(*Diethoxyphosphorylmethoxy*)*pyrrolidin*-1-*yl*]*hypoxanthine* **17**.—To a solution of the imidazole **15** (400 mg, 1.11 mmol) in methanol (4 cm^3) was added 5 mol dm^{-3} hydrochloric acid (0.220 cm^3, 1.10 mmol). The solvent was removed to leave the hydrochloride salt as a light brown gum. To a solution of the hydrochloride salt in *N*,*N*-dimethylformamide (DMF) (3.5 cm^3) was added triethyl orthoformate (1.11 g, 7.51 mmol) and the mixture was heated at 120 °C for 0.25 h. The solution was evaporated and the residue was purified by column chromatography on silica gel with dichloromethane–methanol (49:1, 9:1) as eluent to afford *the hypoxanthine* **17** as a gum (269 mg, 63%); λ_{max}(EtOH)/nm 245 (ε/dm^3 mol^{-1} cm^{-1} 10 235); ν_{max}-($CHCl_3$)/cm^{-1} 1680 (C=O) and 1240 (P=O); δ_H[$(CD_3)_2SO$] 1.25 (6 H, t, *J* 7, Me), 1.95 (1 H, m, 4′-H), 2.30 (1 H, m, 4′-H), 3.50 (3 H, m, 2′-H and 5′-H_2), 3.69 (1 H, dd, *J* 6 and 10, 2′-H), 3.85 (2 H, dd, *J* 9, PCH_2O), 4.10 (4 H, pseudo quintet, *J* 7, CH_2O), 4.35 (1 H, m, 3′-H), 8.02 (1 H, s, 2/8-H), 8.16 (1 H, s, 8/2-H) and 12.35 (1 H, br s, D_2O exchangeable, 1-H) (Found: MH^+, 372.1443. $C_{14}H_{22}N_5O_5P$ requires *M*H, 372.1437).

9-[3-(*Phosphonomethoxy*)*pyrrolidin*-1-*yl*]*hypoxanthine* **18**.—To a solution of the hypoxanthine **17** (110 mg, 300 μmol) in dichloromethane (4 cm^3) was added bromotrimethylsilane (1.16 g, 5.92 mmol) and the mixture was stirred at room temperature for 24 h. The solution was evaporated and the residue was purified by column chromatography on C_{18} silica gel with water as eluent to give the *phosphonic acid* **18** as a solid (69 mg, 73%), m.p. 275–278 °C; λ_{max}(EtOH)/nm 245 (ε/dm^3 mol^{-1} cm^{-1} 5870); ν_{max}(KBr)/cm^{-1} 3420 (H_2O), 1700 (C=O) and 1180 [$(PO_3H)^-$]; δ_H[$(CD_3)_2SO$] 1.97 (1 H, m, 4′-H), 2.30 (1 H, m, 4′-H), 3.47 (3 H, m, 2′-H and 5′-H_2), 3.57 (2 H, d, *J* 9, PCH_2O), 3.70 (1 H, dd, *J* 6 and 10, 2′-H), 4.35 (1 H, m, 3′-H), 8.05 (1 H, s, 2/8-H), 8.17 (1 H, s, 8/2-H) and 12.35 (1 H, br s, D_2O exchangeable, 1-H) (Found: C, 37.4; H, 4.5; N, 22.1. $C_{10}H_{14}N_5O_5P$•0.25H_2O requires C, 37.6; H, 4.6; N, 21.9%).

9-[3-(*Diethoxyphosphorylmethoxy*)*pyrrolidin*-1-*yl*]*adenine* **19**.—To a solution of the hypoxanthine **17** (245 mg, 0.66 mmol) in dichloromethane (7 cm^3) were added triethylamine (100 mg, 1.00 mmol), 2,4,6-triisopropylbenzenesulfonyl chloride (250 mg, 8.25 mmol) and 4-(dimethylamino)pyridine (DMAP) (8 mg, 65 μmol) and the solution was stirred at room temperature for 3 h before being washed with water, then the organic portion was dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in saturated ethanolic ammonia (30 cm^3) and the solution was heated at 80 °C in a stainless steel bomb for 5 h. The solvent was removed, and the residue was partitioned between saturated aq. sodium hydrogen carbonate (20 cm^3) and dichloromethane (4 × 20 cm^3). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography on silica gel with ethyl acetate–methanol (4:1, 2:1) as eluent to give *the adenine* **19** as a gum (53 mg, 22%) which slowly crystallized to a solid, m.p. 122–123 °C; λ_{max}(EtOH)/nm 260 (ε/dm^3 mol^{-1} cm^{-1} 13 670); ν_{max}(KBr)/cm^{-1} 3305 (NH_2), 3145 (NH_2), 1670 (NH_2), 1595 (adenine) and 1250 (P=O); δ_H[$(CD_3)_2SO$] 1.26 (6 H, t, *J* 7, Me), 1.96 (1 H, m, 4′-H), 2.32 (1 H, m, 4′-H), 3.52 (3 H, m, 2′-H and 5′-H_2), 3.75 (1 H, dd, *J* 6 and 10, 2′-H), 3.84 (2 H, d, *J* 9, PCH_2O), 4.07 (4 H, pseudo quintet, *J* 7, CH_2O), 4.35 (1 H, m, 3′-H), 7.25 (2 H, br s, D_2O exchangeable, NH_2), 8.11 (1 H, s, 2/8-H) and 8.16 (1 H, s, 8/2-H) (Found: MH^+, 371.1594. $C_{14}H_{23}N_6O_4P$ requires *M*H, 371.1597).

9-[3-(*Phosphonomethoxy*)*pyrrolidin*-1-*yl*]*adenine* **20**.—To a solution of the adenine **19** (190 mg, 513 μmol) in dichloromethane (8 cm^3) was added bromotrimethylsilane (1.57 g, 10.3 mmol) and the mixture was stirred at room temperature for 16 h. The solvent was removed and the residue was azeotroped with methanol (×3) and acetone–water (1:1) (×3). The residue was purified by column chromatography on C_{18} silica gel with water as eluent to give the adenine **20** as a solid (116 mg, 72%), m.p. 264–266 °C; λ_{max}(MeOH)/nm 260 (ε/dm^3 mol^{-1} cm^{-1} 13 290); ν_{max}(KBr)/cm^{-1} 3330 (NH_2), 3150 (NH_2), 1670 (NH_2) and 1165 [$(PO_3H)^-$]; δ_H(D_2O) 2.20 (1 H, m, 4′-H), 2.40 (1 H, m, 4′-H), 3.45–3.80 (6 H, m, 2′-H_2, 5′-H_2 and PCH_2O), 4.43 (1 H, m, 3′-H), 8.28 (1 H, s, 2/8-H) and 8.44 (1 H, s, 8/2-H) (Found: C, 37.6; H, 4.7; N, 26.05. $C_{10}H_{15}N_6O_4P$•0.4H_2O requires C, 37.4; H, 4.95; N, 26.15%).

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