Preparation of carbocyclic, phosphonate analogues of cyclic adenosine monophosphate (cAMP)

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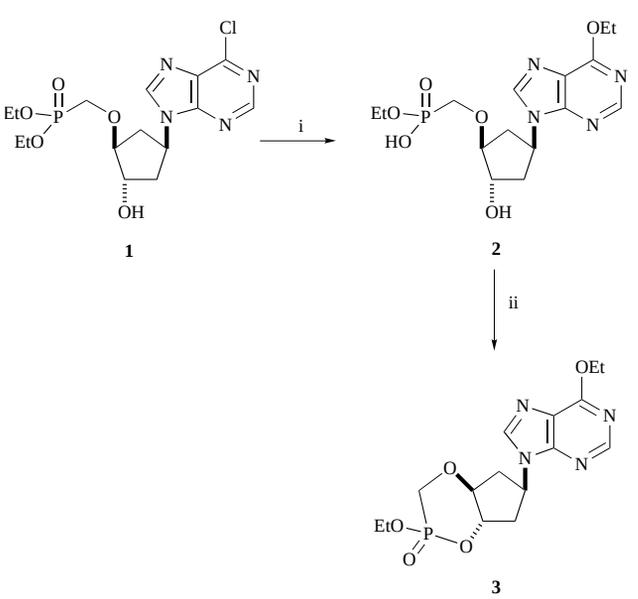
Compounds 2 and 5 have been synthesised and cyclised to form the cyclic 3′,5′-adenosine monophosphate (cAMP) analogues 3, 6 and 7. In a complementary exercise, cyclopentadiene has been converted into the phosphonic acid 16 in six steps. Compound 16 has been deprotected and cyclised to form the cyclic 3′,5′-adenosine monophosphate (cAMP) analogues 18 and 19.

Introduction

Cyclic adenosine monophosphate (cAMP) is the second messenger of a variety of hormones, and numerous derivatives and analogues of cAMP have been synthesised[1] in order to elucidate their molecular interactions with receptor sites,[2–4] as potential agonists or antagonists of cAMP,[2,4,5] to control metabolism,[6] as inhibitors of the proliferation of metastasising tumour cells (*i.e.* anti-cancer treatments),[7] as cardiotonic agents[8] or as prodrugs of antiviral or antitumour nucleosides or nucleotides.[9] During our recent studies we have found a simple strategy for the preparation of a new family of cAMP mimetics.

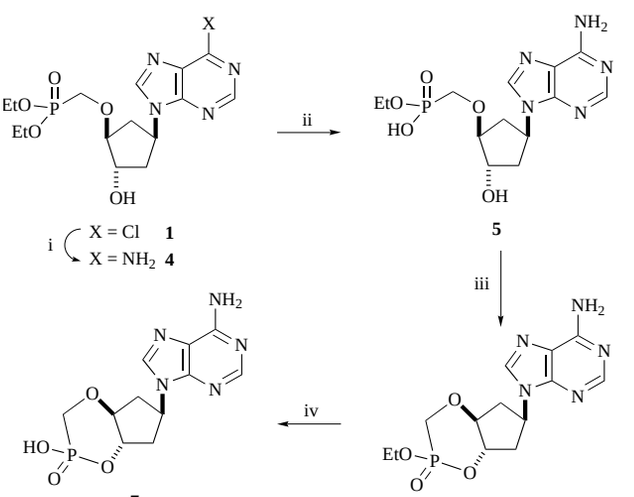
Results and discussion

The carbocyclic nucleotide **1** was synthesised according to a previously published procedure[10] and hydrolysed to yield the monoacid **2** with concomitant replacement of the labile chlorine atom. The monoacid **2** was cyclised in good yield using benzotriazol-1-yloxy(tripyrrolidino)phosphonium hexafluorophosphate (PyBOP)[11] to give only the 3′,4′-cyclic phosphonates **3** (Scheme 1) with a diastereomeric ratio of ~3:1 (*vide infra*). The diastereomers were separated by flash column chromatography.



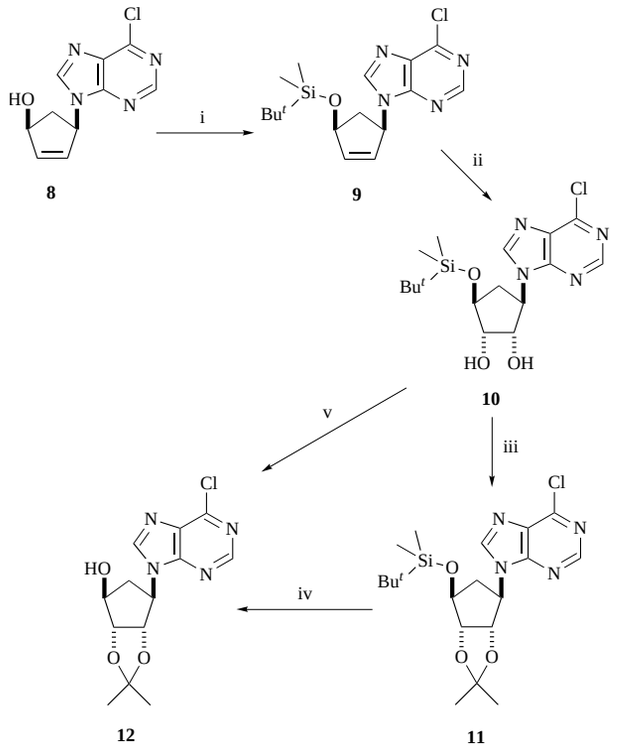
Scheme 1 *Reagents and conditions:* (i) NaOH, EtOH, room temp., 24 h (89%); (ii) PyBOP, DIEA, DMF, room temp., 24 h (80%)

It was not possible to make the deoxy cAMP analogue **6** from the 6-ethoxy compound **3** using liquid ammonia, hence an alternative route was adopted. Conversion of compound **1** into compound **4** was readily achieved as shown in Scheme 2, whereupon reaction with sodium hydroxide in ethanol furnished compound **5**, which was converted into the cyclic compound **6** (~3:1 inseparable mixture of diastereomers).



Scheme 2 *Reagents and conditions:* (i) $NH_{3(l)}$, room temp., 24 h (83%); (ii) NaOH, EtOH, room temp., 24 h (95%); (iii) PyBOP, DIEA, DMF, room temp., 24 h (70%); (iv) TMSBr, DMF, room temp., 72 h (90%)

Trimethylsilyl bromide (TMSBr) cleaved an alkoxy group[12] to afford exclusively the desired product **7**, with no opening of the P-containing ring (Scheme 2). The synthesis of a related cAMP analogue possessing a 2′-hydroxy group was then undertaken (Scheme 3). Compound **8** was prepared using a previously developed strategy.[13] Dihydroxylation of the alkene **8** gave a polar, unstable triol (not shown). However, protection of the alcohol **8** with a *tert*-butyldimethylsilyl (TBDMS) group gave compound **9**, which underwent dihydroxylation in high yield, after a short reaction time and a simple work-up procedure. The diol **10** was protected as the acetonide **11**. Removal of the TBDMS group by using ammonium fluoride in methanol[14] gave the alcohol **12** [Nuclear Overhauser enhancement (NOE) experiments were carried out on the acetonides **11** and **12** to confirm that the dihydroxylation had occurred on the lower (α) face]. Conversion of the diol **10** into the acetonide **11** proceeded with a disappointing yield. On further investigation it was found that some of the diol **10** had been converted

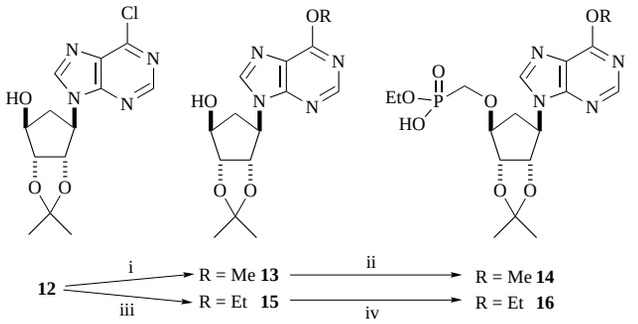


Scheme 3 *Reagents and conditions:* (i) TBDMSCl, imidazole, room temp., 1 h, DMF (97%); (ii) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, Bu′OH–water, room temp., 24 h (85%); (iii) 2,2-DMP, PTSA (cat.), DMF, room temp., 48 h (61%); (iv) NH_4F, MeOH, 60 °C, 3 h (100%); (v) 2,2-DMP, PTSA (1 mol equiv.), DMF, room temp., 48 h (97%)

directly into the acetonide **12**, *i.e.* the toluene-*p*-sulfonic acid (PTSA) had catalysed both protection as the acetonide and removal of the TBDMS group. This was not immediately apparent as compounds **10** and **12** co-elute under the TLC conditions used. When one mol equivalent of PTSA was used, it was possible to convert the diol **10** into the acetonide **12** in almost quantitative yield (Scheme 3).

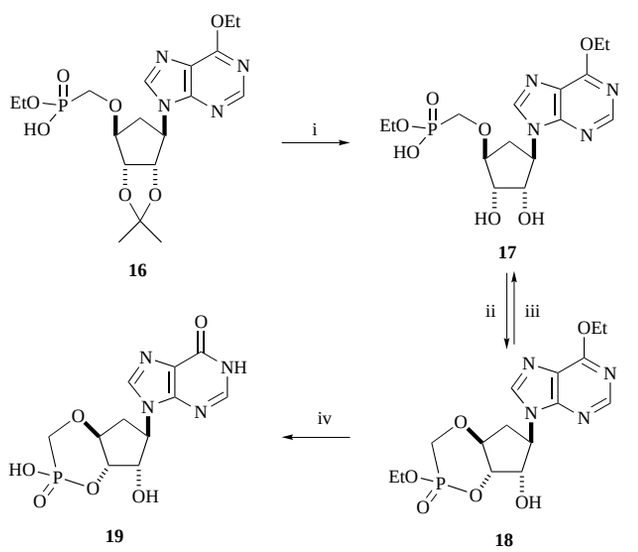
Attempts were made to introduce the phosphonate moiety into compounds **12** and **8** by using sodium hydride and diethyl *p*-tolylsulfonyloxymethanephosphonate [prepared from diethyl (hydroxymethane)phosphonate[15]]; diethyl phosphonomethyltriflate [prepared from diethyl (hydroxymethane)phosphonate[16]] and butyllithium or 4-(dimethylamino)pyridine (DMAP) and pyridine, but no product was isolated from any of these reactions. The problem was probably due to the labile chlorine atom on the purine ring (as this reaction works successfully on nucleoside analogues without a 6-chloropurine base)[15] and hence the chlorine atom of compound **12** was replaced with a methoxy group to give the ether **13** by refluxing compound **12** in methanol in the presence of potassium carbonate. The phosphonate moiety was then introduced into the alcohol **13** by using sodium hydride and the phosphonate monoester $(EtO)(HO)(P{=}O)CH_2OTs$. This monoester[17] was used as it has been shown to give a cleaner reaction than the diester $(EtO)_2(P{=}O)CH_2OTs$ due to the lability of one of the ethoxy groups. However, the yield of the product **14** was only 25%. A small amount of the ethoxy compound **16** was also isolated from the reaction, indicating that, under these conditions, the methoxy group on the purine base is labile. By using the ethoxy compound **15** (prepared by refluxing chloride **12** with K_2CO_3 in EtOH) the yield of the product **16** was increased to 75% (Scheme 4).

Several methods were tried to remove the acetonide unit from compound **16**. Iodine in methanol[18] gave a complex mixture of products, while aq. acetic acid was ineffective. Dowex 50-W gave a low and variable yield (35–61%) while HCl–tetrahydrofuran (THF) (1:1) gave a satisfactory conversion,



Scheme 4 *Reagents and conditions:* (i) MeOH, K_2CO_3, reflux, 2 h (91%); (ii) NaH (95%, dry), $(EtO)(HO)(P{=}O)CH_2OTs$, THF, DMF, room temp., 24 h (25%); (iii) EtOH, K_2CO_3, reflux, 2 h (91%); (iv) NaH (95%, dry), $(EtO)(HO)(P{=}O)CH_2OTs$, THF, DMF, room temp., 24 h (75%)

providing compound **17** in 81% yield. The diol **17** was cyclised by using PyBOP to give compound **18** as a separable mixture of diastereomers (~3:1) (Scheme 5).

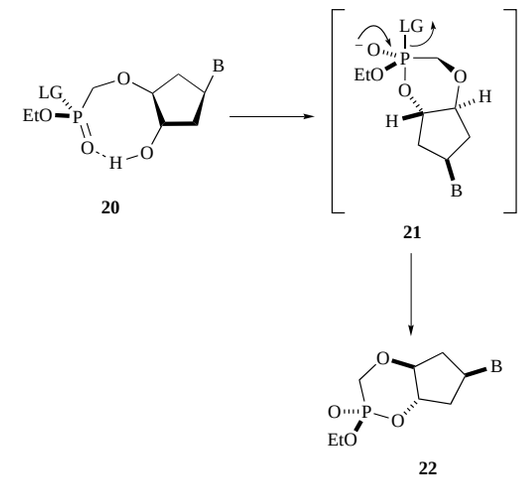


Scheme 5 *Reagents and conditions:* (i) HCl (2M)–THF (1:1), room temp., 24 h (81%); (ii) PyBOP, DIEA, DMF, room temp., 24 h (76%); (iii) NaOH, EtOH, room temp., 1 h; (iv) TMSBr, DMF, room temp., 48 h (87%)

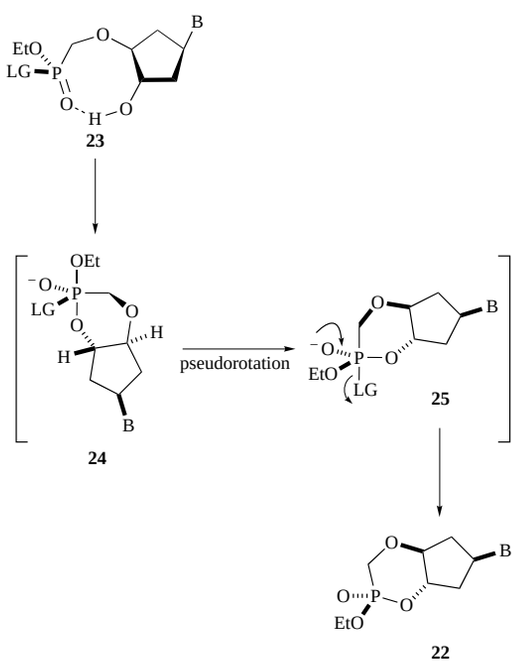
Alkaline hydrolysis (NaOH–EtOH) of compound **18** gave exclusively the ring-opened product **17**. The ethoxy group on the phosphorus could, however, be removed by treatment of compound **18** with TMSBr[12] without any ring opening occurring, to give the cyclic inosine product **19**. Note also that modification of the purine ethoxy group occurred concomitantly.

The monoesters **2**, **5** and **17** were converted into the cyclic AMP analogues **3**, **6** and **18**, respectively, with diastereomeric ratios all ~3:1. While spectroscopic data do not allow identification of the major diastereomer to be made, for mechanistic reasons we tentatively predict that the major product will have the *S* configuration at the phosphorus centre. Thus, after activation by PyBOP to give a good leaving group (LG) on phosphorus, structure **20** (Scheme 6), a favourable hydrogen-bonded conformation for the diastereomer **20** allows the ready formation of the pentacoordinate trigonal bipyramidal intermediate **21**, leading to production of the diastereomer **22**. The other diastereomer of the activated phosphonate, compound **23**, undergoes pseudorotation (**24**→**25**) (Scheme 7) in order to form the same product **22** as the major component of the isolated material.

Although this work was carried out on racemic mixtures, compounds **1**[10] and **8**[13] can be made as single enantiomers [enantiomeric excess (ee) ≥ 95%], thus enabling all the cAMP



Scheme 6



Scheme 7

analogues described in this paper to be made, if required, in optically active form.

Experimental

Analytical-grade solvents were used for flash column chromatography; light petroleum refers to the fraction distilling between 40 and 60 °C. Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl. Anhydrous dichloromethane was obtained by distillation from calcium hydride. Anhydrous dimethylformamide (DMF) was obtained direct from Aldrich. All other solvents employed in reactions were 'Spectrograde' and were used as received. All reagents were used as obtained from commercial sources unless otherwise stated.

TLC was performed on Merck Kieselgel 60 F_{254} 0.25 mm glass-backed plates. The plates were visualised using alkaline potassium permanganate and/or by irradiation under a low-frequency UV lamp. Flash column chromatography was performed using Merck Kieselgel 60, 230–400 mesh.

Mps were measured using an 'Electrothermal' capillary melting point apparatus and are uncorrected.

Optical rotations were measured on an Optical Activity Ltd. AA-1000 polarimeter. $[\alpha]_D$-Values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films, $CHCl_3$ solutions or KBr discs on a Perkin-Elmer 881 grating spectrometer. Absorption maxima were recorded in reciprocal centimetres (cm^{-1}). The following abbreviations are used: s, strong; ms, medium strong; m, medium; mw, medium weak; w, weak; br, broad; str., stretch; def., deformation; sym. def., symmetric deformation; sat., saturated; unsat., unsaturated; sub., substituted; conj., conjugated. UV absorptions were recorded using 1 cm solution cells on a Phillips PU 8720 UV-visible scanning spectrophotometer. Absorption maxima are recorded in nanometres (nm). ^{1}H NMR spectra were recorded on Bruker AM250 (250 MHz), AM300 (300 MHz) or AM400 (400 MHz) spectrometers. Chemical shifts (δ_H) are reported in parts per million (ppm) downfield from tetramethylsilane. Coupling constants (J) are reported in hertz (Hz). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad; and combinations of these. ^{13}C NMR spectra were recorded on Bruker AM250 (62.9 MHz), AM300 (75.5 MHz) or AM400 (100.6 MHz) spectrometers. Chemical shifts (δ_C) are reported in parts per million (ppm) downfield from tetramethylsilane. ^{31}P NMR spectra were recorded on a Bruker AM400 (162.0 MHz) spectrometer. Mass spectra were run on a Kratos Profile HV-3 high-resolution instrument.

Enantiomeric excesses (ees) were determined by ^{1}H NMR spectroscopy using tris-{3-[heptafluoropropyl(hydroxy)methylene]-(+)-camphorato}europium(III).

3,4-Epoxycyclopentan-1-ol was obtained from Cookson Chemicals Ltd.

6-Ethoxy-9-{(1′β,3′α,4′β)-4′-[ethoxy(hydroxy)phosphorylmethoxy]-3′-hydroxycyclopentyl}purine 2

Sodium hydroxide (2 M; 0.8 cm^3) was added to a solution of the diester **1** (71 mg, 0.176 mmol) in EtOH (1 cm^3). The reaction mixture was stirred overnight, and then neutralised to pH 7 with 1 M hydrochloric acid. The solvents were removed *in vacuo* and the resultant oil was purified by chromatography using a reversed-phase C-18 column, eluting with water–CH_3CN (95 : 5). The title compound **2** was isolated as a glass (60 mg, 88%); ν_{max}(film) 3354br, m (O–H str.), 2984m (C–H str.), 1600s (conj. cyclic C=N), 1580m (conj. cyclic C=N), 1460m (C–H def.), 1340m (O–H bend), 1319m (P=O) and 1056s (C–O str. and P–O-alkyl); δ_H(400 MHz; CD_3OD) 1.31 (3 H, t, J 7, CH_3CH_2OP), 1.48 (3 H, t, J 7, CH_3CH_2OAr), 2.14 (1 H, m, 5′-H$^{\beta}$), 2.39 (2 H, m, 2′-H), 2.79 (1 H, ddd, J 15, 9 and 5.5, 5′-H$^{\alpha}$), 3.88 (2 H, m, PCH_2O), 3.97 (1 H, m, 4′-H), 4.11 (2 H, m, CH_3CH_2OP), 4.46 (1 H, m, 3′-H), 4.66 (2 H, q, J 7, CH_3CH_2OAr), 5.37 (1 H, dtd, J 9, 8 and 5, 1′-H), 8.50 (1 H, s, 2- or 8-H) and 8.63 (1 H, br s, 8- or 2-H); δ_C(75.5 MHz; CD_3OD) 14.72 (CH_3CH_2OAr), 17.21 (CH_3, d, $^3J_{CP}$ 6, CH_3CH_2OP), 37.91 (CH_2, 5′-C), 40.49 (CH_2, 2′-C), 53.59 (CH, 1′-C), 61.61 (CH_2, d, $^2J_{CP}$ 6, CH_3CH_2OP), 64.15 (CH_3CH_2OAr), 66.43 (CH_2, d, $^1J_{CP}$ 159, PCH_2O), 75.57 (CH, 3′-C), 88.43 (CH, d, $^3J_{CP}$ 12, 4′-C), 121.90 (C, br), 143.58 (CH, br), 152.82 (CH), 153.19 (C, br) and 161.72 (C); δ_P(162.0 MHz; CD_3OD) 16.76; m/z 385 [(M − H)$^-$, 100%], 357 (6), 163 (7) and 59 (15) [Found (FAB): (M − H)$^-$, 385.1281. $C_{15}H_{22}N_4O_6P$ requires m/z, 385.1277].

3′,4′-Cyclic ester of 6-ethoxy-9-{(1′β,3′α,4′β)-4′-[ethoxy(hydroxy)phosphorylmethoxy]-3′-hydroxycyclopentyl}purine, compound 3

PyBOP (170 mg, 0.327 mmol) was added in a single portion to a solution of the monoacid **2** (60 mg, 0.155 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (190 mm^3, 142 mg, 1.10 mmol) in anhydrous DMF (3.9 cm^3). The reaction mixture was stirred overnight and then diluted with dichloromethane (50 cm^3). Water (50 cm^3) was added and the aqueous phase was extracted with further dichloromethane (2 × 50 cm^3). The combined organic fractions were concentrated *in vacuo*. The residual DMF was azeotropically removed with toluene (3 × 50 cm^3). The resultant oil was purified by flash column chromatography

eluting with CH_2Cl_2–EtOH (95:5) to give the title compound **3** as a mixture of diastereomers (~3:1) (46 mg, 81%). The diastereomers were separated by flash column chromatography eluting with EtOAc–MeOH (95:5) to yield the *faster running diastereomer* as a glass (34 mg, 60%); ν_{max}(film) 2985w (C–H str.), 1598s (conj. cyclic C=N), 1575m (conj. cyclic C=N), 1459m, 1341m and 1251m (P=O), 1050m s (C–O str. and P–O-alkyl) and 980m; δ_H(400 MHz; $CDCl_3$) 1.38 (3 H, t, *J* 7, CH_3CH$_2$OP), 1.51 (3 H, t, *J* 7, CH_3CH$_2$OAr), 2.37 (1 H, td, *J* 13 and 9, 5′-H$^{\beta}$), 2.44 (2 H, m, 2′-H$_2$), 2.58 (1 H, ddd, *J* 13, 9 and 7, 5′-H$^{\alpha}$), 3.85 (1 H, ddd, *J* 13, 9 and 7, 4′-H), 3.94 (1 H, dd, *J* 14 and 2, PCHO), 4.28 (3 H, m, CH$_3$CH_2OP and PCHO), 4.67 (2 H, q, *J* 7, CH$_3$CH_2OAr), 5.10 (1 H, m, 1′-H), 5.57 (1 H, m, 3′-H), 7.89 (1 H, s, 2- or 8-H) and 8.52 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; $CDCl_3$) 14.50 (*C*H$_3$CH$_2$OAr), 16.62 (CH$_3$, d, $^3J_{CP}$ 5, *C*H$_3$CH$_2$OP), 32.74 (CH$_2$, 5′-C), 33.73 (CH$_2$, d, $^3J_{CP}$ 6, 2′-C), 49.00 (CH, 1′-C), 63.19 (CH$_3$*C*H$_2$OAr), 63.39 (CH$_2$, d, $^2J_{CP}$ 6, CH$_3$*C*H$_2$OP), 64.54 (CH$_2$, d, $^1J_{CP}$ 145, PCH$_2$O), 80.29 (CH, d, $^3J_{CP}$ 6.5, 4′-C), 80.51 (CH, d, $^2J_{CP}$ 4.5, 3′-C), 140.58 (CH), 151.33 (C), 152.25 (CH) and 161.02 (C); δ_P(162.0 MHz; $CDCl_3$) 15.40; *m/z* 368 (M^+, 2%), 246 (40) and 165 [(BH + H)$^+$, 100] [Found (EI): M^+, 368.1247. $C_{15}H_{21}N_4O_5P$ requires *M*, 368.1250].

Further elution yielded the *slower running diastereomer* as a glass (12 mg, 21%); ν_{max}(film) 1598s (conj. cyclic C=N), 1575m (conj. cyclic C=N), 1461m (C–H def.), 1341m, 1320m, 1251m (P=O), 1118m, 1098m and 1034m (C–O str. and P–O-alkyl); δ_H(400 MHz; $CDCl_3$) 1.50 (3 H, t, *J* 7, CH_3CH$_2$OP), 1.51 (3 H, t, *J* 7, CH_3CH$_2$OAr), 2.37 (1 H, td, *J* 12.5 and 9, 5′-H$^{\beta}$), 2.45 (2 H, m, 2′-H$_2$), 2.57 (1 H, ddd, *J* 12.5, 9 and 7, 5′-H$^{\alpha}$), 3.84 (1 H, ddd, *J* 12.5, 9 and 7, 4′-H), 3.99 (1 H, d, *J* 15, PCHO), 4.22 (1 H, dd, *J* 15 and 11, PCHO), 4.30 (2 H, m, CH$_3$CH_2OP), 4.67 (2 H, q, *J* 7, CH$_3$CH_2OAr), 5.07 (1 H, qd, *J* 9 and 5, 1′-H), 5.42 (1 H, br q, *J* 9, 3′-H), 7.88 (1 H, s, 2- or 8-H) and 8.51 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; $CDCl_3$) 14.50 (*C*H$_3$CH$_2$OAr), 16.47 (CH$_3$, d, $^3J_{CP}$ 6, *C*H$_3$CH$_2$OP), 32.34 (CH$_2$, 5′-C), 33.56 (CH$_2$, d, $^3J_{CP}$ 6, 2′-C), 49.43 (CH, 1′-C), 62.23 (CH$_2$, d, $^2J_{CP}$ 7, CH$_3$*C*H$_2$OP), 63.23 (CH$_3$*C*H$_2$OAr), 63.44 (CH$_2$, d, $^1J_{CP}$ 142, PCH$_2$O), 80.13 (CH, d, $^3J_{CP}$ 6.5, 4′-C), 81.52 (CH, d, $^2J_{CP}$ 7, 3′-C), 122.48 (C), 140.95 (CH), 152.04 (CH) and 161.08 (C); δ_P(162.0 MHz; $CDCl_3$) 13.69; *m/z* 368 (M^+, 7%), 246 (24) and 165 [(BH + H)$^+$, 100] [Found (EI): M^+, 368.1264].

9-[(1′β,3′α,4′β)-4′-(Diethoxyphosphorylmethoxy)-3′-hydroxycyclopentyl]adenine 4

The chloride **1** (72 mg, 0.178 mmol) was dissolved in liquid ammonia, contained in a sealed steel bomb. The reaction vessel was allowed to warm to room temp. and was left overnight. The ammonia was evaporated off using a stream of nitrogen, and the product was dissolved in methanol and transferred to a round-bottomed flask. The solvent was removed *in vacuo* and the residue was purified using flash column chromatography and elution with CH_2Cl_2–MeOH (9:1) to yield the *title compound* **4** as an oil (57 mg, 83%); R_f 0.09 [EtOAc–MeOH (5:1)]; λ_{max}(MeOH) 262 (ε/1000 cm^3 mol^{-1} 13 645); ν_{max}(film) 3334 and 3180 both br, s (O–H str. and N–H str.), 2983s (C–H str.), 1647s (N–H bend), 1598s (conj. cyclic C=N), 1572s (conj. cyclic C=N), 1476s (C–H def.), 1248s (P=O), 1024s, br (C–O str. and P–O-alkyl) and 754s; δ_H(400 MHz; $CDCl_3$) 1.33 (6 H, 2 × t, *J* 7, 2 × CH_3CH$_2$OP), 2.07 (1 H, m, 5′-H$^{\beta}$), 2.36 (2 H, m, 2′-H$_2$), 2.80 (1 H, ddd, *J* 15, 9 and 5.5, 5′-H$^{\alpha}$), 3.92 (2 H, m, PCH$_2$O), 4.00 (1 H, m, 4′-H), 4.17 (4 H, m, 2 × CH$_3$CH_2OP), 4.53 (1 H, m, 3′-H), 5.28 (1 H, qd, *J* 9 and 5.5, 1′-H), 6.26 (2 H, s, NH$_2$), 8.08 (1 H, s, 2- or 8-H) and 8.30 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; $CDCl_3$) 16.48 (CH$_3$, d, $^3J_{CP}$ 5, 2 × *C*H$_3$CH$_2$OP), 37.31 (CH$_2$, 5′-C), 40.03 (CH$_2$, 2′-C), 51.44 (CH, 1′-C), 62.66 (CH$_2$, d, $^2J_{CP}$ 7, CH$_3$*C*H$_2$OP), 62.82 (CH$_2$, d, $^2J_{CP}$ 7, CH$_3$*C*H$_2$OP), 63.96 (CH$_2$, d, $^1J_{CP}$ 168, PCH$_2$O), 74.91 (CH, 3′-C), 88.12 (CH, d, $^3J_{CP}$ 10, 4′-C), 119.51 (C), 139.33 (CH), 149.90 (C), 152.68 (CH) and 155.65 (C); δ_P(162.0 MHz; $CDCl_3$) 21.93; *m/z* 385 (M^+, 1%), 234 (29), 136 [(BH + H)$^+$, 100] and 60 (88) [Found (EI): M^+, 385.1519. $C_{15}H_{24}N_5O_5P$ requires *M*, 385.1515].

9-{1′β,3′α,4′β)-4′-[Ethoxy(hydroxy)phosphorylmethoxy]-3′-hydroxycyclopentyl}adenine 5

Sodium hydroxide (2 M; 0.6 cm^3) was added to a solution of the diester **4** (56 mg, 0.145 mmol) in EtOH (1 cm^3). The reaction mixture was stirred overnight, and then was neutralised to pH 7 with 1 M hydrochloric acid. The solvents were removed *in vacuo* and the resultant oil was purified by chromatography using a reversed-phase C-18 column, eluting with water–CH_3CN (95:5). The title compound **5** was isolated as a glass (48 mg, 93%); ν_{max}(KBr disc) 3401 and 3190 both br, s (O–H str. and N–H str.), 1648s (N–H bend), 1601s (conj. cyclic C=N), 1573m (conj. cyclic C=N), 1200s [(P=O)OH] and 1047s (C–O str. and P–O-alkyl); δ_H(400 MHz; CD_3OD) 1.26 (3 H, t, *J* 7, CH_3CH$_2$OP), 2.07 (1 H, m, 5′-H$^{\beta}$), 2.34 (2 H, m, 2′-H$_2$), 2.76 (1 H, ddd, *J* 15, 9 and 6, 5′-H$^{\alpha}$), 3.72 (2 H, m, PCH$_2$O), 3.93 (1 H, m, 4′-H), 3.99 (2 H, quin, *J* 7, CH$_3$CH_2OP), 4.45 (1 H, m, 3′-H), 5.25 (1 H, m, 1′-H), 8.19 (1 H, s, 2- or 8-H) and 8.41 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; CD_3OD) 15.91 (CH$_3$, d, $^3J_{CP}$ 6, *C*H$_3$CH$_2$OP), 36.72 (CH$_2$, 5′-C), 39.43 (CH$_2$, 2′-C), 51.93 (CH, 1′-C), 60.26 (CH$_2$, d, $^2J_{CP}$ 6, CH$_3$*C*H$_2$OP), 65.07 (CH$_2$, d, $^1J_{CP}$ 160, PCH$_2$O), 74.32 (CH, 3′-C), 87.15 (CH, d, $^3J_{CP}$ 12, 4′-C), 118.60 (C), 140.34 (CH), 149.27 (C), 152.06 (CH) and 155.81 (C); δ_P(162.0 MHz; CD_3OD) 16.75; *m/z* 735 {[(M − H)$_2$Na]$^+$, 5%}, 378 [(M + Na − 2 H)$^+$, 16] and 356 [(M − H)$^+$, 100] [Found (FAB): (M − H)$^+$, 356.1118. $C_{13}H_{19}N_5O_5P$ requires *m/z*, 356.1124].

3′,4′-Cyclic ester of 9-{(1′β,3′α,4′β)-4′-[ethoxy(hydroxy)phosphorylmethoxy]-3′-hydroxycyclopentyl}adenine, compound 6

PyBOP (150 mg, 0.289 mmol) was added in a single portion to a solution of the monoacid **5** (51 mg, 0.143 mmol) and DIEA (148 mm^3, 110 mg, 0.85 mmol) in anhydrous DMF (3.3 cm^3). The reaction mixture was stirred overnight and was then diluted with dichloromethane (50 cm^3). Water (20 cm^3) was added and the aqueous phase was extracted with further dichloromethane (2 × 50 cm^3). The combined organic fractions were concentrated *in vacuo.* The residual DMF was azeotropically removed with toluene (3 × 50 cm^3). The resultant oil was purified by flash column chromatography eluting with CH_2Cl_2–EtOH (9:1) and then recolumning appropriate fractions, eluting with EtOAc–MeOH (9:1), to give the *title compound* **6** as an oil {inseparable mixture of diastereomers [A:B (~3:1)]} (32 mg, 66%); ν_{max}(film) 3432s, br (N–H str.), 1637s (N–H bend), 1598m (conj. cyclic C=N), 1256 (P=O), 1041m (C–O str. and P–O-alkyl) and 981m; δ_H(400 MHz; CD_3OD) 1.35 (2 H, t, *J* 7, CH_3CH$_2$OP, A), 1.46 (1 H, t, *J* 7, CH_3CH$_2$OP, B), 2.29 (1 H, m, 5′-H$^{\beta}$), 2.42 (2 H, m, 2′-H$_2$), 2.53 (1 H, m, 5′-H$^{\alpha}$), 3.96 (1 H, m, 4′-H), 4.05 (1 H, m, PCHO), 4.25 (3 H, m, PCHO and CH$_3$CH_2OP), 5.19 (1 H, m, 1′-H), 5.44 (0.3 H, br q, *J* 9, 3′-H, B), 5.53 (0.7 H, br q, *J* 9, 3′-H, A), 8.14 (0.3 H, s, 2- or 8-H, B), 8.15 (0.7 H, s, 2- or 8-H, A), 8.21 (0.3 H, s, 8- or 2-H, B) and 8.22 (0.7 H, s, 8- or 2-H, A); δ_C(100.6 MHz; CD_3OD) 15.35 (CH$_3$, d, $^3J_{CP}$ 6, *C*H$_3$CH$_2$OP, B), 15.44 (CH$_3$, d, $^3J_{CP}$ 5, *C*H$_3$CH$_2$OP, A), 31.74 (CH$_2$, 5′-C, B), 31.86 (CH$_2$, 5′-C, A), 32.71 (CH$_2$, d, $^3J_{CP}$ 6, 2′-C, B), 32.89 (CH$_2$, d, $^3J_{CP}$ 6, 2′-C, A), 49.02 (CH, 1′-C, A), 49.17 (CH, 1′-C, B), 62.12 (CH$_2$, d, $^2J_{CP}$ 7, CH$_3$*C*H$_2$OP, B), 62.34 (CH$_2$, d, $^1J_{CP}$ 142, PCH$_2$O, B), 63.59 (CH$_2$, d, $^1J_{CP}$ 144, PCH$_2$O, A), 63.79 (CH$_2$, d, $^2J_{CP}$ 7, CH$_3$*C*H$_2$OP, A), 79.90 (CH, d, $^3J_{CP}$ 6, 4′-C, B), 80.13 (CH, d, $^3J_{CP}$ 6, 4′-C, A), 81.17 (CH, d, $^2J_{CP}$ 5, 3′-C, A), 82.15 (CH, d, $^2J_{CP}$ 7, 3′-C, B), 119.36 (C), 140.51 (CH, A), 140.66 (CH, B), 148.92 (C), 152.14 (CH, B), 152.19 (CH, A) and 155.87 (C); δ_P(162.0 MHz; CD_3OD) 15.80 (0.3 P, B) and 16.52 (0.7 P, A); *m/z* 339 (M^+, 2%), 309 (4), 217 (46) and 136 [(BH + H)$^+$, 100] [Found (EI): M^+, 339.1088. $C_{13}H_{18}N_5O_4P$ requires *M*, 339.1096].

3′,4′-Cyclic ester of 9-[(1′β,3′α,4′β)-4′-(dihydroxyphosphorylmethoxy)-3′-hydroxycyclopentyl]adenine, compound 7

TMSBr (200 mm^3, 233 mg, 1.52 mmol) was added dropwise to a cooled solution (0 °C) of the cyclic compound **6** (15 mg, 0.044 mmol) in anhydrous DMF (0.8 cm^3). The reaction mixture was allowed to warm to room temp. and was stirred for 72 h. After the mixture had been cooled to 0 °C, water (2 cm^3) was added; the mixture was again allowed to warm to room temp., and was stirred for a further 1 h. The solution was neutralised to pH 7 with 2 M sodium hydroxide and the aqueous phase was washed with diethyl ether (2 × 10 cm^3). The solvents were removed *in vacuo* and the resultant solid was purified by chromatography using a reversed-phase C-18 column, eluting with water–CH_3CN (95 : 5). The title compound **7** was isolated as a glass (12 mg, 90%); ν_{max}(KBr disc) 3432m s, br (N–H str.), 1638 (N–H bend), 1598m s (conj. cyclic C=N), 1572m (conj. cyclic C=N), 1252m s, 1209s [(P=O)OH] and 1057s (C–O str. and P–O-alkyl); δ_H(400 MHz; D_2O) 1.99 (1 H, td, *J* 12.5 and 9, 5′-H$^{\beta}$), 2.25 (1 H, ddd, *J* 14, 9 and 3, 2′-H), 2.38 (1 H, dt, *J* 14 and 11, 2′-H), 2.61 (1 H, ddd, *J* 12.5, 8 and 7, 5′-H$^{\alpha}$), 3.80 (1 H, dd, *J* 14 and 2, PCHO), 3.85 (1 H, ddd, *J* 12, 9 and 7, 4′-H), 4.00 (1 H, dd, *J* 14 and 9, PCHO), 4.88 (1 H, m, 3′-H), 5.05 (1 H, m, 1′-H), 8.06 (1 H, s, 2- or 8-H) and 8.20 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; D_2O) 32.22 (CH_2, 5′-C), 32.94 (CH_2, d, $^3J_{CP}$ 6, 2′-C), 48.27 (CH, 1′-C), 65.34 (CH_2, d, $^1J_{CP}$ 141, PCH_2O), 79.68 (CH, d, $^3J_{CP}$ 6.5, 4′-C), 80.04 (CH, d, $^2J_{CP}$ 5, 3′-C), 118.5 (C, br), 140.32 (CH), 148.49 (C), 152.21 (CH) and 155.27 (C); δ_P(162.0 MHz; D_2O) 11.81; *m*/*z* 310 [(M − H)$^+$, 100%], 205 (23), 113 (20) and 80 (4) [Found (FAB): (M − H)$^+$, 310.0709. $C_{11}H_{13}N_5O_4P$ requires *m*/*z*, 310.0705].

9-[(1′β,4′β)-4′-(*tert*-Butyldimethylsiloxy)cyclopent-2′-enyl]-6-chloropurine 9

Imidazole (764 mg, 11.24 mmol) and TBDMSCl (955 mg, 6.32 mmol) were added to a solution of the alcohol **8** (1.25 g, 5.28 mmol) in dry DMF (14 cm^3). The reaction mixture was stirred under an inert atmosphere for 1 h. Dichloromethane (100 cm^3) and water (50 cm^3) were added, and the aqueous portion was extracted with dichloromethane (3 × 100 cm^3). The combined organic fractions were washed with brine (20 cm^3), dried over magnesium sulfate, and the solvent was removed *in vacuo.* Flash column chromatography, eluting first with light petroleum and then light petroleum–EtOAc (1 : 1), gave the *title compound* **9** as a crystalline solid (1.80 g, 97%); mp 68–70 °C; R_f 0.68 (EtOAc) [Found: (EI) M$^+$, 350.1336; C, 54.6; H, 6.6; N, 16.0%. $C_{16}H_{23}ClN_4OSi$ requires *M*, 350.1330; C, 54.8; H, 6.6; N, 16.0%]; ν_{max}(KBr disc) 2957, 2931, 2888 and 2858 all s (all C–H str.), 1589s (conj. cyclic C=N), 1552s (conj. cyclic C=N), 1398s (CH_3 sym. def.), 1332s, 1259s [$Si(CH_3)_2$], 1173s, 1072s and 897s; δ_H(300 MHz; $CDCl_3$) 0.08 (3 H, s, CH_3Si), 0.12 (3 H, s, CH_3Si), 0.89 (9 H, s, ᵗBuSi), 1.84 (1 H, dt, *J* 14.5 and 2.5, 5′-H$^{\beta}$), 2.91 (1 H, ddd, *J* 14.5, 8 and 6.5, 5′-H$^{\alpha}$), 4.91 (1 H, ddd, *J* 6.5, 2.5 and 2, 4′-H), 5.69 (1 H, dtd, *J* 8, 2.5 and 2, 1′-H), 5.80 (1 H, dd, *J* 5.5 and 2.5, 2′-H), 6.24 (1 H, dt, *J* 5.5 and 2, 3′-H), 8.36 (1 H, s, 8-H) and 8.72 (1 H, s, 2-H); δ_C(75.5 MHz; $CDCl_3$) −4.84 (CH_3Si), −4.69 (CH_3Si), 18.02 [C (ᵗBu)], 25.79 [3 × CH_3(ᵗBu)], 41.95 (CH_2, 5′-C), 57.36 (CH, 1′-C), 75.16 (CH, 4′-C), 130.66 (CH, 2′-C), 131.68 (C), 139.86 (CH, 3′-C), 144.62 (CH), 150.83 (C), 151.36 (C) and 151.75 (CH); *m*/*z* 350 (M$^+$, 1%), 335 [(M − CH_3)$^+$, 2], 293 [(M − ᵗBu)$^+$, 100], 211 (34), 139 (68) and 75 (49).

9-[(1′β,2′α,3′α,4′β)-4′-(*tert*-Butyldimethylsiloxy)-2′,3′-dihydroxycyclopentyl]-6-chloropurine 10

To a solution of the olefin **9** (1.80 g, 5.14 mmol) in *tert*-butyl alcohol (120 cm^3) and water (120 cm^3) were added potassium hexacyanoferrate(III) (6.39 g, 19.42 mmol), potassium carbonate (3.67 g, 26.59 mmol) and osmium tetraoxide (1 cm^3, 0.018 mol equiv.; 2.5 wt% solution in BuᵗOH). The mixture was stirred at room temp. for 24 h. Sodium sulfite (2.04 g, 16.19 mmol) was added and the mixture was stirred for a further 3 h. The mixture was filtered through Celite®, which was washed with ethyl acetate. The solvents were removed *in vacuo* and the residue was taken up in water (100 cm^3) and extracted with dichloromethane (3 × 200 cm^3). The combined organic phase was dried over magnesium sulfate, and the solvent was removed *in vacuo* to give the *title compound* **10** as a crystalline solid (1.68 g, 85%); mp 173–175 °C (from EtOAc); R_f 0.42 [MeOH–$CHCl_3$ (1 : 9)] (Found: C, 49.8; H, 6.6; N, 14.4. $C_{16}H_{25}ClN_4O_3Si$ requires C, 49.9; H, 6.55; N, 14.55%); ν_{max}(KBr disc) 3384m, br (O–H str.), 2955, 2931 and 2858 all m (C–H str.), 1592s (conj. cyclic C=N), 1560s (conj. cyclic C=N), 1399ms (CH_3 sym. def.), 1337s (O–H bend), 1256s [$Si(CH_3)_2$], 1077s (C–O str. and P–O-alkyl) and 837m s; δ_H(300 MHz; $CDCl_3$) 0.12 (6 H, s, 2 × CH_3Si), 0.90 (9 H, s, ᵗBuSi), 2.02 (1 H, ddd, *J* 14.5, 6.5 and 2.5, 5′-H$^{\beta}$), 2.99 (1 H, ddd, *J* 14.5, 10 and 6, 5′-H$^{\alpha}$), 3.30 (1 H, br, OH), 4.09 (1 H, m, 3′-H), 4.30 (1 H, dt, *J* 6 and 2.5, 4′-H), 4.63 (1 H, m, 2′-H), 4.70 (1 H, br, OH), 4.97 (1 H, dt, *J* 10 and 6.5, 1′-H), 8.29 (1 H, s, 8-H) and 8.67 (1 H, s, 2-H); δ_C(75.5 MHz; $CDCl_3$) −4.90 (CH_3Si), −4.83 (CH_3Si), 18.01 [C (ᵗBu)], 25.76 [3 × CH_3 (ᵗBu)], 37.69 (CH_2, 5′-C), 60.49 (CH, 1′-C), 75.42 (CH), 77.78 (CH), 78.20 (CH), 131.67 (C), 144.31 (CH), 151.12 (C), 151.60 (CH) and 151.92 (C); *m*/*z* 384 (M$^+$, 4%), 383 [(M − H)$^+$, 11], 369 [(M − CH_3)$^+$, 6], 327 [(M − ᵗBu)$^+$, 89] and 155 [(BH + H)$^+$, 100] [Found: (M − ᵗBu)$^+$, 327.0682. $C_{12}H_{16}ClN_4O_3Si$ requires *m*/*z*, 327.0680; (M − CH_3)$^+$, 369.1148. $C_{15}H_{22}ClN_4O_3Si$ requires *m*/*z*, 369.1150].

9-[(1′β,2′α,3′α,4′β)-4′-(*tert*-Butyldimethylsiloxy)-2′,3′-isopropylidenedioxycyclopentyl]-6-chloropurine 11

To a solution of the diol **10** (65 mg, 0.169 mmol) in dry DMF (0.8 cm^3) were added PTSA (4 mg, 0.02 mmol) and freshly distilled 2,2-dimethoxypropane (2,2-DMP) (1.2 cm^3). The mixture was stirred under an inert atmosphere at room temp. for 48 h, then was diluted with water (8 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The combined organic phase was dried over magnesium sulfate and the solvents were removed *in vacuo* to give an oil. Purification by flash column chromatography eluting with ethyl acetate yielded the *title compound* **11** as a crystalline solid (44 mg, 61%); R_f 0.73 (EtOAc); mp 112–114 °C; ν_{max}(KBr disc) 2932m s (C–H str.), 1589s (conj. cyclic C=N), 1566 and 1560 both m (conj. cyclic C=N), 1259m s [$Si(CH_3)_2$], 1209s, 1135s, 1081s, 877s and 838s; δ_H(300 MHz; $CDCl_3$) 0.10 (3 H, s, CH_3Si), 0.14 (3 H, s, CH_3Si), 0.89 (9 H, s, ᵗBuSi), 1.32 (3 H, s, CH_3C), 1.52 (3 H, s, CH_3C), 2.13 (1 H, dquin, *J* 15 and 1.5, 5′-H$^{\beta}$), 2.81 (1 H, ddd, *J* 15, 8 and 5, 5′-H$^{\alpha}$), 4.47 (1 H, br d, *J* 5, 4′-H), 4.60 (1 H, br d, *J* 5.5, 3′-H), 4.89 (1 H, br d, *J* 5.5, 2′-H), 5.18 (1 H, br d, *J* 8, 1′-H), 8.51 (1 H, s, 8-H) and 8.77 (1 H, s, 2-H); δ_C(62.9 MHz; $CDCl_3$) −4.99 (CH_3Si), −4.90 (CH_3Si), 18.16 [C (ᵗBu)], 24.20 (CH_3C), 25.84 [3 × CH_3 (ᵗBu)], 26.63 (CH_3C), 37.57 (CH_2, 5′-C), 61.41 (CH, 1′-C), 77.74 (CH), 86.03 (CH), 87.34 (CH), 111.70 [$C(CH_3)_2$], 131.63 (C), 145.00 (CH) and 151.89 (CH); *m*/*z* 424 (M$^+$, 1%), 409 [(M − CH_3)$^+$, 9], 369 (62), 368 (41), 367 [(M − ᵗBu)$^+$, 92] and 155 [(BH + H)$^+$, 100] [Found (EI): M$^+$, 424.1678. $C_{19}H_{29}ClN_4O_3Si$ requires *M*, 424.1697].

6-Chloro-9-[(1′β,2′α,3′α,4′β)-4′-hydroxy-2′,3′-isopropylidenedioxycyclopentyl]purine 12

Method A. A solution of the silyl ether **11** (40 mg, 0.094 mmol) and ammonium fluoride (48 mg, 1.30 mmol) in methanol (1.9 cm^3) was stirred at 60 °C for *ca.* 3 h. Silica gel (0.5 g) was added and the mixture was evaporated to a dry powder *in vacuo.* This was added to the top of a pre-packed silica column. The column was eluted with ethyl acetate to yield the title compound **12** as a crystalline solid (28 mg, 100%). Data were consistent with those described below.

Method B. To a solution of the diol **10** (1.56 g, 4.06 mmol) in dry DMF (19 cm^3) were added PTSA (770 mg, 4.05 mmol, 1 mol equiv.) and freshly distilled 2,2-DMP (30 cm^3). The mixture

was stirred under an inert atmosphere at room temp. for 48 h and then was diluted with water (50 cm^3). The aqueous phase was washed with light petroleum (2 × 100 cm^3) and was then extracted with dichloromethane (3 × 100 cm^3). The combined extracts were dried over magnesium sulfate and the solvents were removed *in vacuo*. The residual DMF was azeotropically removed with toluene. The pure *title compound* **12** was thus obtained as a crystalline solid (1.22 g, 97%); R_f 0.34 (EtOAc); mp 170–172 °C [Found: (EI) M^+, 310.0837; C, 50.1; H, 4.9; N, 17.9%. $C_{13}H_{15}ClN_4O_3$ requires *M*, 310.0833; C, 50.25; H, 4.9; N, 18.0%]; ν_{max}(KBr disc) 3380br, m s (O–H str.), 2934m w (C–H str.), 1594s (conj. cyclic C=N), 1564s m (conj. cyclic C=N), 1210s, 1054s (C–O str.) and 635m (C–Cl); δ_H(300 MHz; $CDCl_3$) 1.29 (3 H, s, CH_3C), 1.51 (3 H, s, CH_3C), 2.25 (1 H, dquin, *J* 15 and 1.5, 5′-H^{β}), 2.87 (1 H, ddd, *J* 15, 9 and 5, 5′-H^{α}), 4.47 (1 H, br, OH), 4.56 (1 H, m, 4′-H), 4.72 (1 H, br d, *J* 5.5, 3′-H), 4.89 (1 H, br d, *J* 5.5, 2′-H), 5.11 (1 H, br d, *J* 9, 1′-H), 8.58 (1 H, s, 8-H) and 8.74 (1 H, s, 2-H); δ_C(75.5 MHz; $CDCl_3$) 24.22 (CH_3), 26.70 (CH_3), 36.86 (CH_2, 5′-C), 62.39 (CH, 1′-C), 76.05 (CH), 86.26 (CH), 87.05 (CH), 111.79 [$C(CH_3)_2$], 131.62 (C), 145.81 (CH), 150.95 (C), 151.50 (C) and 151.74 (CH); *m*/*z* 310 (M^+, 5%), 295 [$(M - CH_3)^+$, 24], 252 {$[M - (CH_3)_2CO]^+$, 65}, 235 (64), 181 (100) and 155 $[(BH + H)^+$, 95].

9-[(1′β,2′α,3′α,4′β)-4′-Hydroxy-2′,3′-isopropylidenedioxycyclopentyl]-6-methoxypurine 13

Potassium carbonate (36 mg, 0.261 mmol) was added to a solution of the chloride **12** (40 mg, 0.129 mmol) in anhydrous methanol (2 cm^3). The mixture was heated at reflux for 2 h and then cooled to room temp. The solvent was evaporated off *in vacuo* and water (20 cm^3) was added. The aqueous phase was then extracted with dichloromethane (3 × 50 cm^3). The pure *title compound* **13** was obtained as a solid (36 mg, 91%); R_f 0.26 (EtOAc); mp 167–168 °C; ν_{max}($CHCl_3$ solution) 3257br w (O–H str.), 2997m w (C–H str.), 1603s (conj. cyclic C=N), 1581m (conj. cyclic C=N), 1481m, 1324 (O–H bend) and 1034m s (C–O str.); δ_H(400 MHz; $CDCl_3$) 1.28 (3 H, s, CH_3C), 1.50 (3 H, s, CH_3C), 2.20 (1 H, br d, *J* 15.5, 5′-H^{β}), 2.89 (1 H, br ddd, *J* 15.5, 9.5 and 5.5, 5′-H^{α}), 4.16 (3 H, s, CH_3O), 4.52 (1 H, br d, *J* 5.5, 4′-H), 4.74 (1 H, br d, *J* 5.5, 3′-H), 4.87 (1 H, br d, *J* 5.5, 2′-H), 4.99 (1 H, br d, *J* 9.5, 1′-H), 5.82 (1 H, br, OH), 8.26 (1 H, s, 2- or 8-H) and 8.51 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; $CDCl_3$) 24.37 (CH_3C), 26.89 (CH_3C), 37.58 (CH_2, 5′-C), 54.32 (CH_3O), 62.96 (CH, 1′-C), 75.84 (CH, 4′-C), 86.56 (CH, 2′-C), 87.47 (CH, 3′-C), 111.52 [$C(CH_3)_2$], 121.64 (C), 142.91 (CH), 151.08 (C), 151.75 (CH) and 161.13 (C); *m*/*z* 306 (M^+, 7%), 291 $[(M - CH_3)^+$, 13], 248 {$[M - (CH_3)_2CO]^+$, 46}, 231 (98), 177 (100), 151 $[(BH + H)^+$, 51] and 120 (38) [Found (EI): M^+, 306.1333. $C_{14}H_{18}N_4O_4$ requires *M*, 306.1328].

9-{(1′β,2′α,3′α,4′β)-4′-[Ethoxy(hydroxy)phosphorylmethoxy]-2′,3′-isopropylidenedioxycyclopentyl}-6-methoxypurine 14

A solution of the alcohol **13** (35 mg, 0.114 mmol) in THF (1 cm^3)–DMF (0.2 cm^3) was added dropwise to a suspension of sodium hydride (15 mg, 0.594 mmol; 95%, dry) in THF (1 cm^3). The mixture was stirred for 3 h. A solution of ethyl hydrogen *p*-tolylsulfonyloxymethanephosphonate [(EtO)(HO)(P=O)CH_2OTs] (45 mg, 0.153 mmol) in DMF (0.5 cm^3) was then added dropwise. The reaction mixture was stirred for 24 h at room temp., cooled to 0 °C, and then quenched with glacial acetic acid (0.5 cm^3). The solvents were removed *in vacuo* and the resultant oil was purified by chromatography using a reversed-phase C-18 column, eluting with water–CH_3CN (9:1). The *title compound* **14** was isolated as a glass (12 mg, 25%); ν_{max}(film) 2985m (C–H str.), 1602s (conj. cyclic C=N), 1578m s (conj. cyclic C=N), 1479s (C–H def.), 1211s (P=O) and 1057s (C–O str. and P–O-alkyl); δ_H(400 MHz; CD_3OD) 1.17 (3 H, t, *J* 7, CH_3CH_2OP), 1.30 (3 H, s, CH_3C), 1.50 (3 H, s, CH_3C), 2.33 (1 H, br d, *J* 15, 5′-H^{β}), 2.72 (1 H, ddd, *J* 15, 8 and 5.5, 5′-H^{α}), 3.70 (2 H, m, PCH_2O), 3.93 (2 H, m, CH_3CH_2OP), 4.10 (1 H, m, 4′-H), 4.14 (3 H, s, CH_3O), 4.84 (1 H, m, 3′-H), 4.96 (1 H, br d, *J* 6, 2′-H), 5.10 (1 H, ddd, *J* 8, 3 and 2, 1′-H), 8.49 (1 H, s, 2- or 8-H) and 8.63 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; CD_3OD) 15.80 (CH_3, d, $^3J_{CP}$ 6, CH_3CH_2OP), 23.14 (CH_3C), 25.54 (CH_3C), 34.72 (CH_2, 5′-C), 53.42 (CH_3O), 60.43 (CH_2, d, $^2J_{CP}$ 6, CH_3CH_2OP), 60.59 (CH, 1′-C), 64.96 (CH_2, d, $^1J_{CP}$ 162, PCH_2O), 83.71 (CH, 3′-C), 85.28 (CH, 2′-C), 85.81 (CH, d, $^3J_{CP}$ 12.5, 4′-C), 111.66 [$C(CH_3)_2$], 120.12 (C), 143.40 (CH), 151.71 (CH) and 160.64 (C); *m*/*z* 428 (M^+, 1%), 427 $[(M - H)^+$, 1], 224 (27) and 105 (63) [Found (EI): M^+, 428.1446; $C_{17}H_{25}N_4O_7P$ requires *M*, 428.1461]. Further elution yielded compound **16** (data were consistent with those described below).

6-Ethoxy-9-[(1′β,2′α,3′α,4′β)-4′-hydroxy-2′,3′-isopropylidenedioxycyclopentyl]purine 15

Potassium carbonate (360 mg, 2.61 mmol) was added to a solution of the chloride **12** (400 mg, 1.29 mmol) in anhydrous EtOH (20 cm^3). The mixture was heated at reflux for 2 h and then was cooled to room temp. The solvent was evaporated off *in vacuo*, water (50 cm^3) was added, and the aqueous phase was extracted with dichloromethane (3 × 100 cm^3). The pure *title compound* **15** was obtained as a solid (374 mg, 91%); mp 154–157 °C; ν_{max}($CHCl_3$ solution) 3250br w (O–H str.), 2993m (C–H str.), 1600s (conj. cyclic C=N), 1579m (conj. cyclic C=N), 1459m (C–H def.), 1342m s, 1324m s (O–H bend) and 1033s (C–O str.); δ_H(300 MHz; $CDCl_3$) 1.28 (3 H, s, CH_3C), 1.48 (3 H, t, *J* 7, CH_3CH_2O), 1.50 (3 H, s, CH_3C), 2.19 (1 H, br d, *J* 15.5, 5′-H^{β}), 2.90 (1 H, ddd, *J* 15.5, 10 and 6.5, 5′-H^{α}), 4.52 (1 H, br, 4′-H), 4.63 (2 H, q, *J* 7, CH_3CH_2O), 4.74 (1 H, br d, *J* 5.5, 3′-H), 4.88 (1 H, br d, *J* 5.5, 2′-H), 4.97 (1 H, m, 1′-H), 6.00 (1 H, br, OH), 8.22 (1 H, s, 2- or 8-H) and 8.48 (1 H, s, 8- or 2-H); δ_C(75.5 MHz; $CDCl_3$) 14.48 (CH_3CH_2O), 24.38 (CH_3C), 26.91 (CH_3C), 37.72 (CH_2, 5′-C), 63.11 (CH, 1′-C), 63.35 (CH_3CH_2O), 75.77 (CH, 4′-C), 86.56 (CH, 2′-C), 87.49 (CH, 3′-C), 111.50 [$C(CH_3)_2$], 121.67 (C), 142.77 (CH), 150.96 (C), 151.72 (CH) and 160.89 (C); *m*/*z* 321 $[(M + H)^+$, 6%], 320 (M^+, 1), 262 {$[M - (CH_3)_2CO]^+$, 6}, 245 (14), 191 (21), 136 (32), 109 (36), 81 (60) and 59 {$[(CH_3)_2COH]^+$, 100} [Found (EI): M^+, 320.1483; $C_{15}H_{20}N_4O_4$ requires *M*, 320.1485].

6-Ethoxy-9-{(1′β,2′α,3′α,4′β)-4′-[ethoxy(hydroxy)phosphorylmethoxy]-2′,3′-isopropylidenedioxycyclopentyl}purine 16

A solution of the alcohol **15** (374 mg, 1.17 mmol) in THF (10 cm^3)–DMF (1 cm^3) was added dropwise to a suspension of sodium hydride (90 mg, 3.56 mmol; 95% dry) in THF (10 cm^3). The mixture was stirred for 3 h. A solution of ethyl hydrogen *p*-tolylsulfonyloxymethanephosphonate [(EtO)(HO)(P=O)CH_2-OTs] (400 mg, 1.36 mmol) in DMF (5 cm^3) was then added dropwise. The reaction mixture was stirred for 24 h, cooled to 0 °C, and then quenched with glacial acetic acid (5 cm^3). The solvents were removed *in vacuo* and the resultant oil was purified by chromatography using a reversed-phase C-18 column, eluting with water–CH_3CN (9:1). The title compound **16** was isolated as a glass (385 mg, 75%); ν_{max}($CHCl_3$ solution) 2987m (C–H str.), 1598s (conj. cyclic C=N), 1577m (conj. cyclic C=N), 1457m (C–H def.), 1238s (P=O) and 1057s (C–O str. and P–O-alkyl); δ_H(400 MHz; CD_3OD) 1.16 (3 H, t, *J* 7, CH_3CH_2OP), 1.28 (3 H, s, CH_3C), 1.45 (3 H, t, *J* 7, CH_3CH_2OAr), 1.48 (3 H, s, CH_3C), 2.31 (1 H, br d, *J* 14, 5′-H^{β}), 2.70 (1 H, ddd, *J* 14, 8 and 5.5, 5′-H^{α}), 3.71 (2 H, m, PCH_2O), 3.94 (2 H, quin, *J* 7, CH_3CH_2OP), 4.08 (1 H, m, 4′-H), 4.61 (2 H, q, *J* 7, CH_3CH_2OAr), 4.82 (1 H, br d, *J* 6, 3′-H), 4.94 (1 H, br d, *J* 6, 2′-H), 5.09 (1 H, m, 1′-H), 8.46 (1 H, s, 2- or 8-H) and 8.64 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; CD_3OD) 13.43 (CH_3CH_2-OAr), 15.84 (CH_3, d, $^3J_{CP}$ 6, CH_3CH_2OP), 23.15 (CH_3C), 25.56 (CH_3C), 34.67 (CH_2, 5′-C), 60.37 (CH_2, d, $^2J_{CP}$ 5.5, CH_3CH_2OP), 60.55 (CH, 1′-C), 64.22 (CH_3CH_2OAr), 65.04 (CH_2, d, $^1J_{CP}$ 165, PCH_2O), 83.70 (CH, 3′-C), 85.29 (CH, 2′-C), 85.82 (CH, d, $^3J_{CP}$ 12, 4′-C), 111.57 [$C(CH_3)_2$], 120.11 (C), 143.36 (CH), 151.70 (CH) and 160.33 (C); δ_P(162.0 MHz;

CD_3OD) 12.61; *m/z* 441 [$(M - H)^-$, 100%], 163 (B^+, 56), 134 (27), 79 (36) and 63 (44) [Found (FAB): $(M - H)^+$, 441.1545. $C_{18}H_{26}N_4O_7P$ requires *m/z*, 441.1539].

6-Ethoxy-9-{(1′β,2′α,3′α,4′β)-4′-[ethoxy(hydroxy)phosphoryl-methoxy]-2′,3′-dihydroxycyclopentyl}purine 17

Hydrochloric acid (5 cm^3; 2 M) was added to a solution of the acetonide **16** (200 mg, 0.452 mmol) in THF (5 cm^3). The reaction mixture was stirred overnight, and then was neutralised to pH 7 with sodium hydroxide (2 M). The solvents were removed *in vacuo* and the mixture was purified by using a reversed-phase column, eluent water–CH_3CN (95 : 5). The title compound **17** was isolated as a glass (148 mg, 81%); mp 130–135 °C; ν_{max}(KBr disc) 3393br m (O–H str.), 2984m w (C–H str.), 1602s (conj. cyclic C=N), 1577m (conj. cyclic C=N), 1460m (C–H def.), 1318m (O–H bend), 1233m (P=O) and 1053s (C–O str. and P–O-alkyl); δ_H(400 MHz; D_2O) 1.22 (3 H, t, *J* 7, C$H_3$$CH_2$OP), 1.39 (3 H, t, *J* 7, C$H_3$$CH_2$OAr), 2.06 (1 H, ddd, *J* 14, 8.5 and 4.5, 5′-H^{β}), 2.86 (1 H, ddd, *J* 14, 8.5 and 7.5, 5′-H^{α}), 3.72 (2 H, d, *J* 9, PCH_2O), 3.94 (2 H, m, $CH_3C$$H_2$OP), 3.97 (1 H, m, 4′-H), 4.22 (1 H, dd, *J* 5.5 and 2, 3′-H), 4.40 (2 H, q, *J* 7, $CH_3C$$H_2$OAr), 4.58 (1 H, dd, *J* 8.5 and 5.5, 2′-H), 4.82 (1 H, q, *J* 8.5, 1′-H), 8.21 (1 H, s, 2- or 8-H) and 8.34 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; D_2O) 13.66 (*C*$H_3$$CH_2$OAr), 16.12 ($CH_3$, d, $^3J_{CP}$ 5, *C*$H_3$$CH_2$OP), 33.21 ($CH_2$, 5′-C), 58.38 (CH, 1′-C), 61.42 (CH_2, d, $^2J_{CP}$ 5.5, CH_3*C*H_2OP), 64.31 (CH_3*C*H_2OAr), 64.46 (CH_2, d, $^1J_{CP}$ 158, PCH_2O), 73.65 (CH, 3′-C), 75.56 (CH, 2′-C), 83.88 (CH, d, $^3J_{CP}$ 12, 4′-C), 120.40 (C), 142.63 (CH, br), 151.41 (CH) and 160.20 (C); δ_P(162.0 MHz; D_2O) 18.73; *m/z* 825 {$[(M - H)_2Na]^+$, 6%}, 423 $[(M + Na - 2\ H)^+$, 17], 401 $[(M - H)^+$, 100] and 163 (30) [Found (FAB): $(M - H)^+$, 401.1220. $C_{15}H_{22}N_4O_7P$ requires *m/z*, 402.1226].

3′,4′-Cyclic ester of 6-ethoxy-9-{(1′β,2′α,3′α,4′β)-4′-[ethoxy-(hydroxy)phosphorylmethoxy]-2′,3′-dihydroxycyclopentyl}-purine, compound 18

PyBOP (200 mg, 0.385 mmol) was added in a single portion to a solution of the monoacid **17** (75 mg, 0.187 mmol) and DIEA (220 mm^3, 164 mg, 1.27 mmol) in anhydrous DMF (4.5 cm^3). The reaction mixture was stirred overnight and then was diluted with dichloromethane (50 cm^3). Water (50 cm^3) was added and the aqueous phase was extracted with more dichloromethane (2 × 50 cm^3). The combined organic fractions were concentrated *in vacuo* and the residual DMF was azeotropically removed with toluene (3 × 50 cm^3). The resultant oil was purified by flash column chromatography eluting with EtOAc–MeOH (95 : 5) to give the title compound **18** as a mixture of diastereomers (~3 : 1) (55 mg, 76%). It was possible to separate the diastereomers by flash column chromatography eluting with $CHCl_3$–EtOH (95 : 5) to yield the *faster running diastereomer* as a glass (42 mg, 58%); ν_{max}(film) 3344br m (O–H str.), 2988m (C–H str.), 1600s, (conj. cyclic C=N), 1577s (conj. cyclic C=N), 1460s (C–H def.), 1342s (O–H bend), 1320m s, 1258s (P=O), 1221m s, 1118s, 1053s (C–O str. and P–O-alkyl), 983m s and 753m; δ_H(400 MHz; CD_3OD) 1.38 (3 H, td, *J* 7 and 0.5, C$H_3$$CH_2$OP), 1.48 (3 H, t, *J* 7, C$H_3$$CH_2$OAr), 2.26 (1 H, ddd, *J* 12.5, 11.5 and 9, 5′-H^{β}), 2.59 (1 H, ddd, *J* 12.5, 9 and 7, 5′-H^{α}), 4.06 (1 H, dd, *J* 14 and 1, PCHO), 4.27 (4 H, m, $CH_3C$$H_2$OP, PCHO and 4′-H), 4.39 (1 H, dd, *J* 6 and 1, 2′-H), 4.65 (2 H, q, *J* 7, $CH_3C$$H_2$OAr), 4.89 (1 H, td, *J* 9 and 1, 1′-H), 5.40 (1 H, ddd, $^3J_{HH}$ 10, 6, $^3J_{HP}$ 1.5, 3′-H), 8.31 (1 H, s, 2- or 8-H) and 8.49 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; CD_3OD) 13.35 (*C*$H_3$$CH_2$OAr), 15.39 ($CH_3$, d, $^3J_{CP}$ 5, *C*$H_3$$CH_2$OP), 29.64 ($CH_2$, 5′-C), 60.90 (CH, 1′-C), 62.92 (CH_3*C*H_2OAr), 63.19 (CH_2, d, $^1J_{CP}$ 145, PCH_2O), 63.95 (CH_2, d, $^2J_{CP}$ 7, CH_3*C*H_2OP), 72.23 (CH, d, $^3J_{CP}$ 6, 2′-C), 77.38 (CH, d, $^3J_{CP}$ 6, 4′-C), 82.01 (CH, d, $^2J_{CP}$ 5, 3′-C), 121.25 (C), 142.87 (CH), 151.33 (C), 151.81 (CH) and 160.60 (C); δ_P(162.0 MHz; CD_3OD) 17.12; *m/z* 384 (M^+, 1%), 369 $[(M - CH_3)^+$, 2], 262 (77), 165 $[(BH + H)^+$, 100] and 137 (33) [Found (EI): M^+, 384.1195; $C_{15}H_{21}N_4O_6P$ requires *M*, 384.1199].

Further elution yielded the *slower running diastereomer* as a glass (14 mg, 19%); ν_{max}(film) 3340br w (O–H str.), 2983w (C–H str.), 1597s (conj. cyclic C=N), 1577m (conj. cyclic C=N), 1459m, 1342m (O–H bend), 1318m, 1228m (P=O), 1120m s (C–O str.) and 1029m s (P–O-alkyl); δ_H(400 MHz; CD_3OD) 1.48 (3 H, t, *J* 7, C$H_3$$CH_2$O), 1.49 (3 H, t, *J* 7, C$H_3$$CH_2$O), 2.23 (1 H, ddd, *J* 12.5, 11.5 and 9, 5′-H^{β}), 2.59 (1 H, ddd, *J* 12.5, 9 and 7, 5-H^{α}), 3.99 (1 H, d, *J* 15, PCHO), 4.24 (1 H, ddd, *J* 11.5, 10 and 7, 4′-H), 4.30 (3 H, m, $CH_3C$$H_2$OP and PCHO), 4.37 (1 H, dd, *J* 6 and 1, 2′-H), 4.66 (2 H, q, *J* 7, $CH_3C$$H_2$OAr), 4.88 (1 H, td, *J* 9, 1, 1′-H), 5.33 (1 H, ddd, $^3J_{HH}$ 10, 6, $^3J_{HP}$ 1.5, 3′-H), 8.31 (1 H, s, 2- or 8-H) and 8.50 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; CD_3OD) 13.35 (*C*$H_3$$CH_2$OAr), 15.37 ($CH_3$, d, $^3J_{CP}$ 6, *C*$H_3$$CH_2$OP), 29.53 ($CH_2$, 5′-C), 60.90 (CH, 1′-C), 61.91 (CH_2, d, $^1J_{CP}$ 143, PCH_2O), 62.22 (CH_2, d, $^2J_{CP}$ 7, CH_3*C*H_2OP), 62.92 (CH_3*C*H_2OAr), 72.12 (CH, d, $^3J_{CP}$ 5.5, 2′-C), 77.15 (CH, d, $^3J_{CP}$ 6, 4′-C), 83.11 (CH, d, $^2J_{CP}$ 7, 3′-C), 121.34 (C), 142.99 (CH), 151.32 (C), 151.74 (CH) and 160.64 (C); δ_P(162.0 MHz; CD_3OD) 16.53; *m/z* 384 (M^+, 12%), 262 (30), 191 (47), 178 (35), 165 $[(BH + H)^+$, 100] and 137 (46) [Found (EI): M^+, 384.1181].

3′,4′-Cyclic ester of 9-[(1′β,2′α,3′α,4′b)-2′,3′-dihydroxy-4′-(dihydroxyphosphorylmethoxy)cyclopentyl]inosine 19

TMSBr (540 mm^3, 626 mg, 4.09 mmol) was added dropwise to a cooled solution (0 °C) of the cyclic compound **18** (27 mg, 0.070 mmol) in anhydrous DMF (2 cm^3). The reaction mixture was allowed to warm to room temp. and was stirred for 48 h. After cooling to 0 °C, water (1 cm^3) was added and the mixture was again allowed to warm to room temp., and was stirred for a further 1 h. The solution was then neutralised to pH 7 with 2 M sodium hydroxide and the aqueous phase was washed with diethyl ether (2 × 5 cm^3). The solvents were removed *in vacuo* and the resultant solid was purified by chromatography using a reversed-phase column, eluent water–CH_3CN (95 : 5) to yield the title compound **19** as a glass (20 mg, 87%); λ_{max}(H_2O) 250 (ε/1000 cm^3/mol^{-1} cm^{-1} 9660); ν_{max}(KBr disc) 3422br m (O–H str.), 1683s [(C=O)NH and conj. cyclic C=N], 1214m s (P=O) and 1078m (C–O str. and P–O-alkyl); δ_H(400 MHz; D_2O) 2.10 (1 H, ddd, *J* 12.5, 11 and 9, 5′-H^{β}), 2.64 (1 H, ddd, *J* 12.5, 9 and 6.5, 5′-H^{α}), 3.78 (1 H, dd, *J* 14 and 2, PCHO), 4.00 (1 H, dd, *J* 14 and 9.5, PCHO), 4.11 (1 H, ddd, *J* 11, 10 and 6.5, 4′-H), 4.35 (1 H, dd, *J* 6.5 and 1.5, 2′-H), 4.85 (1 H, td, *J* 9 and 1.5, 1′-H), 4.86 (1 H, ddd, $^3J_{HH}$ 10 and 6.5, $^3J_{HP}$ 2.5, 3′-H), 8.13 (1 H, br s, 2- or 8-H) and 8.15 (1 H, s, 8- or 2-H); δ_C(100.6 MHz; D_2O) 29.95 (CH_2, 5′-C), 59.80 (CH, 1′-C), 64.96 (CH_2, d, $^1J_{CP}$ 141, PCH_2O), 72.68 (CH, d, $^3J_{CP}$ 6, 2′-C), 77.44 (CH, d, $^3J_{CP}$ 5, 4′-C), 80.50 (CH, d, $^2J_{CP}$ 5, 3′-C), 140.88 (CH), 145.94 (CH), 148.85 (C) and 159.14 (C); δ_P(162.0 MHz; D_2O) 12.52; *m/z* 327 $[(M - H)^+$, 23%], 205 {$[(glyc)_2 + Na - 2\ H]^+$, 44} and 113 $[(glyc + Na - 2\ H)^+$, 100] [Found (FAB): $(M - H)^+$, 327.0487. $C_{11}H_{12}N_4O_6P$ requires *m/z*, 327.0494].

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