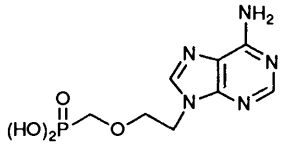
Analogues of Acylonucleoside Diphosphates. The Synthesis of a Series of Diphosphonate Derivatives of Pyrimidines and Purines

Ann Parkin
SmithKline Beecham Pharmaceuticals, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ, England

The synthesis of a series of (hydroxy)(phosphonomethyl)phosphorylmethoxyalkoxy-pyrimidines and -purines is described. The diphosphonate unit was introduced into suitably functionalised alcohols by use of the reagent (diethoxyphosphinoyl)methyldiethoxyphosphine **13**. Mitsunobu coupling of the alcohols **18** and **20** with 1-hydroxypyrimidines and 9-hydroxypurines provided a general route to the protected derivatives **23–26**, **31**, **32**, **36**, **37**, **40** and **41**. Conventional deprotection techniques afforded the pyrimidines **3–8** and purines **9–12** in good overall yields. The antiviral activity of this series of compounds is recorded.

Considerable research effort has recently been directed towards the synthesis and biological evaluation of acyclonucleosides, many of which exhibit antiviral activity.[1-6] Such compounds generally exert their antiviral effect as triphosphates after undergoing a series of phosphorylations by both viral and cellular enzymes. In the case of the herpes viruses, a number of acyclonucleosides owe their antiviral activity to the selective inhibition of virally specified DNA polymerases by their triphosphates.[7-9] It has been recognised that metabolically stable forms of acyclonucleoside mono-, di- and tri-phosphates may also interfere with viral replication.[10]

The phosphonomethoxy group is potentially a metabolically stable bioisosteric replacement for phosphate, and a number of phosphonomethoxyalkyl derivatives of purines and pyrimidines are claimed to exhibit broad spectrum antiviral activity against a range of DNA viruses.[11-14] 9-(2-Phosphonomethoxyethyl)-adenine (PMEA) **1** is reported to have activity against herpes



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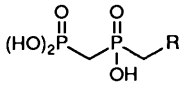

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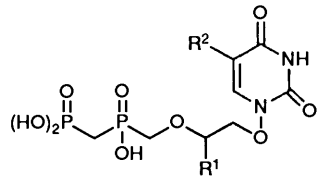
simplex virus type 1 (HSV-1) and against human immunodeficiency virus (HIV), the aetiologic agent in acquired immunodeficiency syndrome (AIDS).[15] These analogues exert their major effect after two phosphorylation steps, becoming nucleoside triphosphate analogues which are active mainly as viral DNA polymerase inhibitors. PMEA diphosphate has also demonstrated activity against HSV-1 encoded ribonucleotide reductase, the enzyme which catalyses the reduction of all four ribonucleoside 5'-diphosphates.[16] We have recently described the synthesis of phosphonomethoxyalkoxypurines [17-19] and pyrimidines[20] which show activity against several strains of herpes virus and against some lentiviruses.

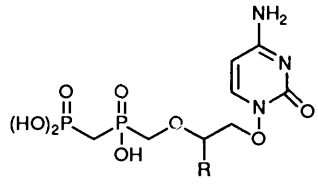
Research into analogues of nucleoside diphosphates has been more limited. Such species have also the potential to interfere with viral replication as inhibitors of the enzyme ribonucleotide reductase or, after metabolic phosphorylation to a triphosphate form, as DNA polymerase inhibitors. A number of bioisosteric replacements for the diphosphate linkage have been suggested, but as yet no antivirally active nucleoside analogues have been reported.[10] Phosphonoformic acid and phosphonoacetic acid exhibit antiherpes activity as viral DNA polymerase inhibitors, by interfering with the pyrophosphate binding site on viral DNA.[21] However, phosphonoformyl or phosphonoacetyl derivatives of nucleosides or acyclonucleosides do not represent metabolically stable species, being prone to cleavage by cellular esterases into the component molecules.[22]

In the phosphonophosphinoyl system **2** a methylene unit replaces the bridging oxygen of a diphosphate unit.[23,24] Isoprenoid (phosphinoylmethyl)phosphonates have been shown to act as inhibitors of squalene synthetase, by virtue of their resemblance to the natural substrate farnesyl diphosphate (FPP).[25,26] By analogy, a similar replacement of diphosphate in a nucleoside diphosphate should afford a stable analogue with the potential for inhibiting enzymes essential for viral replication.

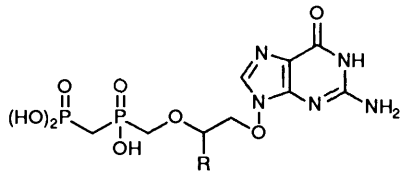
In this publication, the synthesis of a series of (hydroxy)-(phosphonomethyl)phosphorylmethoxyalkoxy-pyrimidines and -purines, **3–12**, novel analogues of acyclonucleoside



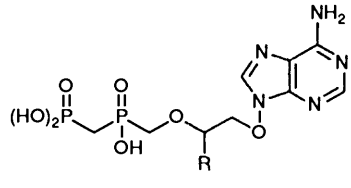
3; R^1 = H, R^2 = H
4; R^1 = CH_2OH, R^2 = H
5; R^1 = H, R^2 = CH_3
6; R^1 = CH_2OH, R^2 = CH_3



7; R = H
8; R = CH_2OH



9; R = H
10; R = CH_2OH



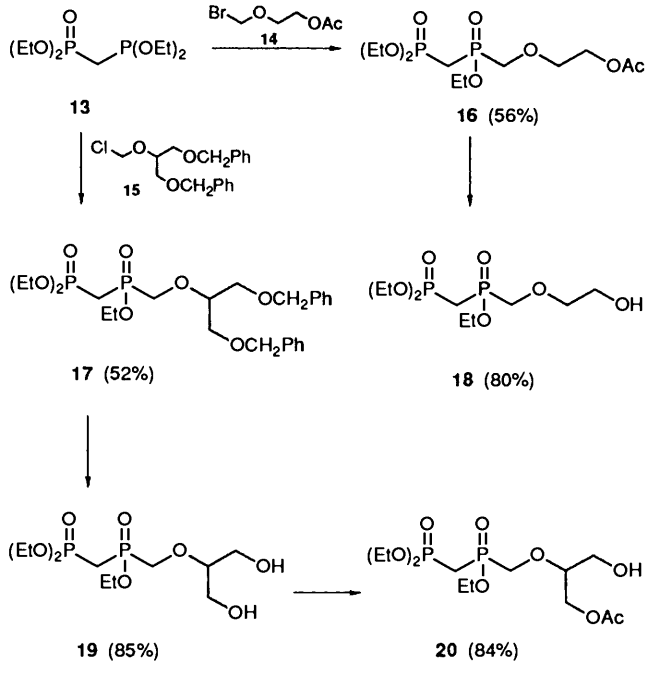
11; R = H
12; R = CH_2OH

diphosphates, is described. A generalised route to these compounds, involving Mitsunobu coupling of suitably functionalised alcohols with 1-hydroxypyrimidines and 9-hydroxypurines has been developed.

Results and Discussion

We have recently developed an efficient synthesis of 1-phosphonomethoxyalkoxypyrimidines by the coupling of functionalised alcohols with 1-hydroxypyrimidines using triphenylphosphine–diethyl azodicarboxylate (DEAD) in *N*,*N*-dimethylformamide (DMF).[20] Under these conditions reasonable yields of 1-alkoxy derivatives are obtained, and it is unusual to see products derived from substitution at other positions on the pyrimidine ring. This synthetic methodology was applied to the preparation of the uracil and thymine derivatives **3**–**6**.

The requisite alcohols **18** and **20** were obtained by means of an Arbuzov reaction of 1-acetoxy-2-bromomethoxyethane[27] **14** or 1,3-dibenzyloxy-2-chloromethoxypropane **15**[17,19] with the air and moisture sensitive reagent (diethoxyphosphinoyl)-methyldiethoxyphosphine **13** (Scheme 1).[25,28] The protected

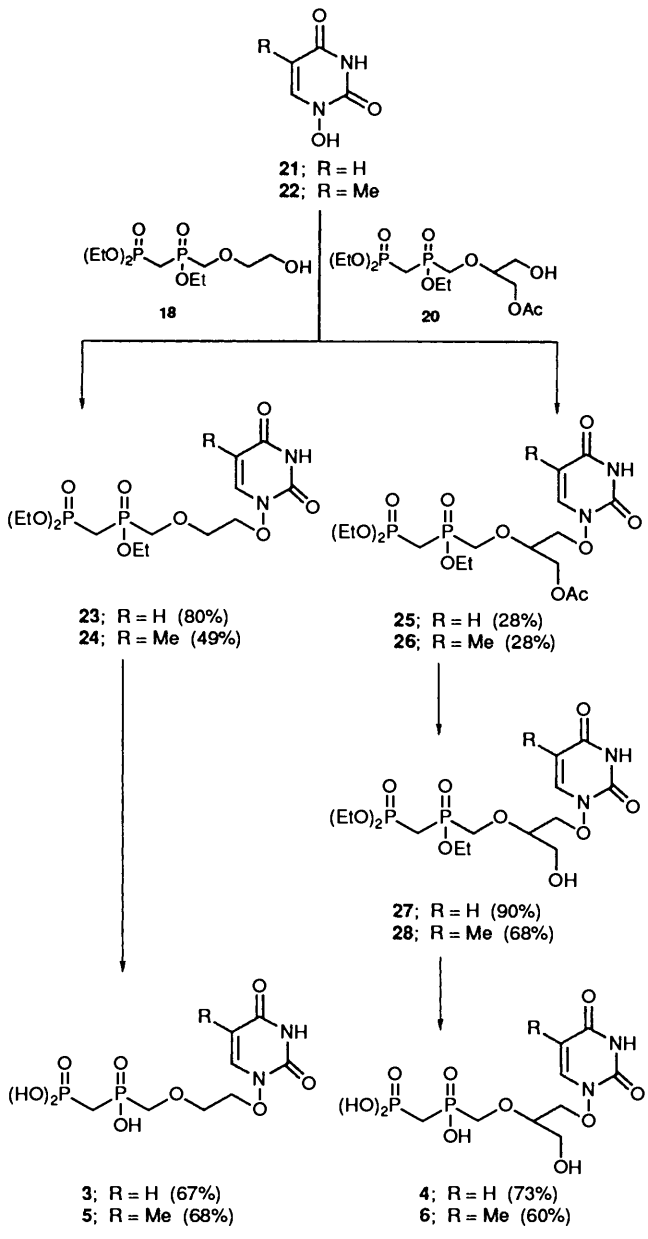


Scheme 1

alcohols **16** and **17** were obtained in 56 and 52% yields respectively. Deprotection of **16** with aqueous ethanolic hydrogen chloride afforded the alcohol **18** in 80% yield. Debenzylation of **17** by catalytic hydrogenolysis afforded an 85% yield of the diol **19** which was converted into the monoacetate **20** in 84% yield by treatment with trimethylorthoacetate and acidic hydrolysis of the intermediate orthoester.

Treatment of 1-hydroxyuracil **21**[29] or 1-hydroxythymine **22**[30] with a 10% excess of the alcohol **18**, triphenylphosphine and DEAD in DMF gave **23** and **24** in yields of 80 and 49% respectively. Under similar conditions the branched chain compounds **25** and **26** were obtained in 28% yields. Deprotection of the acetoxy group in compounds **25** and **26** was carried out using aqueous ethanolic hydrogen chloride. This method afforded compounds **27** and **28** in 90 and 68% yields respectively, and was preferable to the more general techniques of deprotection using catalytic sodium methoxide in methanol or treatment with ammonia,[20] which gave very poor yields of products in this series of compounds. The phosphonic acids **3**–**6** were obtained in 60–73% yields by reaction of **23**, **24**, **27** and **28** with an excess of trimethylsilyl bromide in dichloromethane (Scheme 2).

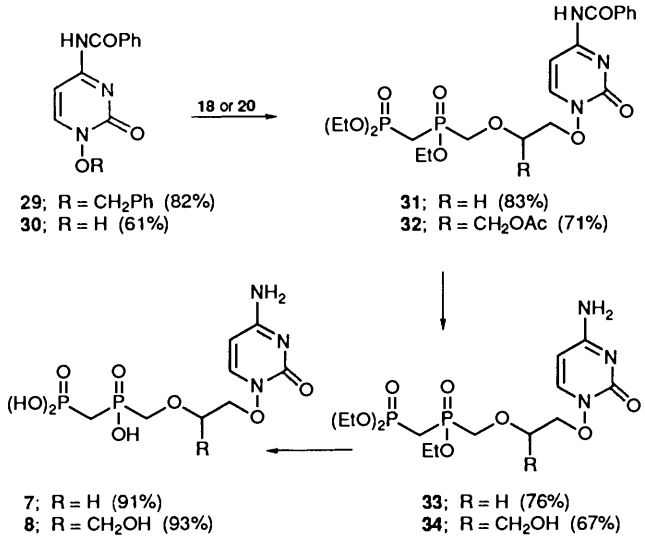
In general, a convenient method for the preparation of cytosine derivatives is treatment of the corresponding uracil



Scheme 2

analogue with 1,2,4-triazole–(4-chlorophenyl)-phosphodichloridate, and ammonolysis of the intermediate 4-triazolo derivatives.[31–33,20] These conditions did not prove suitable for the conversion of **23** into a cytosine analogue, as in each step very low yields of impure products were obtained, with evidence of extensive polymerisation. A method of obtaining a cytosine analogue by direct alkylation was clearly required. Attempted alkylation of 1-hydroxycytosine[34] using Mitsunobu conditions was unsuccessful, but similar treatment of the 4-benzamido derivative **30** (obtained by treatment of 1-benzyloxycytosine[34] with benzoic anhydride followed by hydrogenolysis of **29** over 10% palladium on charcoal) gave compounds **31** and **32** in 83 and 71% yields respectively (Scheme 3). The benzamido group in **31** and **32** was removed by treatment with aqueous ethanolic hydrogen chloride, giving **33**, and (by concomitant removal of the acetoxy group in **32**), **34** in 76 and 67% yields respectively. Treatment of **33** and **34** with trimethylsilyl bromide gave the phosphonic acids **7** and **8** in high yields.

The preparation of 2-(bis-*tert*-butoxycarbonyl)amino-9-hydroxy-6-methoxypurine **35**, and 9-hydroxy-6-phthalimidopurine **39**, and their utility in the synthesis of 9-alkoxy



Scheme 3

derivatives of guanine and adenine both by alkylation with alkyl halides under base catalysed conditions, and with alcohols under Mitsunobu conditions has recently been reported.[35] The latter conditions were applied for the synthesis of this series of purine analogues.

Thus, treatment of **35** with the alcohols **18** and **20** in DMF as described previously (using a 20% excess of reagents) afforded the derivatives **36** and **37** in 50 and 70% yields respectively. Compound **36** was directly converted into the phosphonic acid **9** in 93% yield by treatment with trimethylsilyl bromide in dichloromethane (Scheme 4). Compound **37** was deprotected in two stages, initially by treatment with aqueous ethanolic hydrogen chloride to give **38** in 78% yield, and subsequently with trimethylsilyl bromide to give **10** in 32% yield.

In a similar fashion the protected adenine analogues **40** and **41** were obtained from 9-hydroxy-6-phthalimidopurine **39** in 67 and 78% yields respectively (Scheme 5). It was found to be essential in compound **41** to remove the phthalimido protecting group using basic conditions before carrying out the acidic deprotection of the acetoxy group, since the phthalimido group was prone to partial cleavage even under very mild acidic conditions. The ring-opened amide thus formed was then very resistant to complete deprotection. Thus treatment of **40** and **41** with methylhydrazine afforded **42** and **43** in 67 and 86% yields. The acetoxy group in **43** was removed by treatment with ethanolic hydrogen chloride, giving **44** in 95% yield, and **42** and **44** were deesterified in the usual fashion to afford the phosphonic acids **11** and **12** in 61 and 73% yields respectively.

Compounds **3**–**12** were screened against viruses of the herpes family and visna virus, a lentivirus related to HIV. In the herpes screens the cytosine derivative **8** showed activity against herpes simplex virus type 1 (HSV-1) at 30 μg cm^{-3}, and the guanine analogue **9** showed activity against varicella zoster virus (VZV) at 19 μg cm^{-3}. The adenine derivative **11** was active against visna virus, at 0.3 μg cm^{-3}.

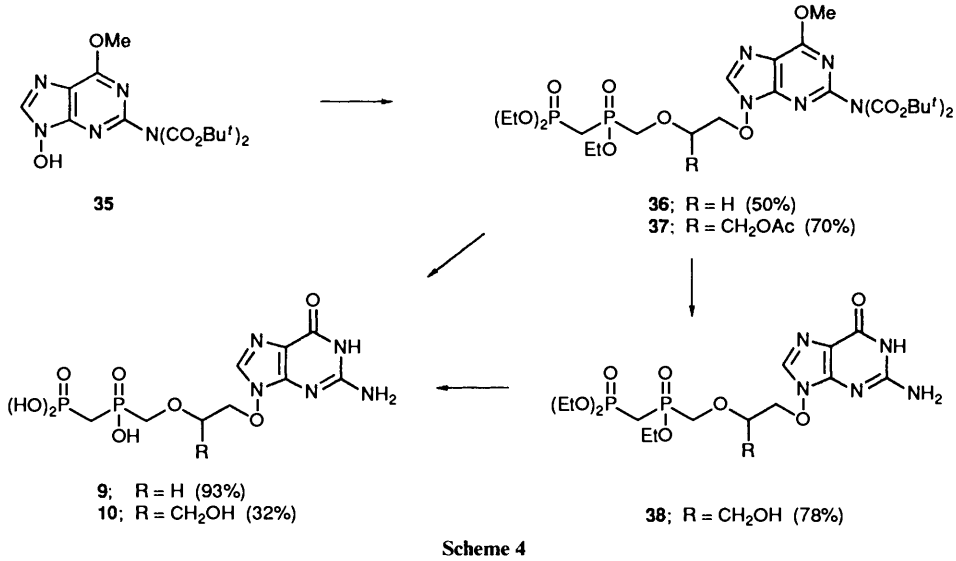
Experimental

IR spectra were recorded on a Perkin-Elmer 580 or Bio-Rad FTS spectrometer; UV spectra were obtained on a Cary 219 spectrometer. NMR spectra were obtained on JEOL GX270 and Bruker AM 400 spectrometers, J values are given in Hz. Mass spectroscopy was performed using a JEOL SX-102 instrument operating at 70 eV. M.p.s were determined using a Reichert-Koffler apparatus and are uncorrected. Elemental analysis was carried out on a CC440 Elemental Analyser. Organic solutions of products were dried using magnesium sulphate and chromatography was performed on Merck 7736 60H silica gel. All compounds were homogeneous by TLC on silica gel $60F_{254}$ coated aluminium sheets.

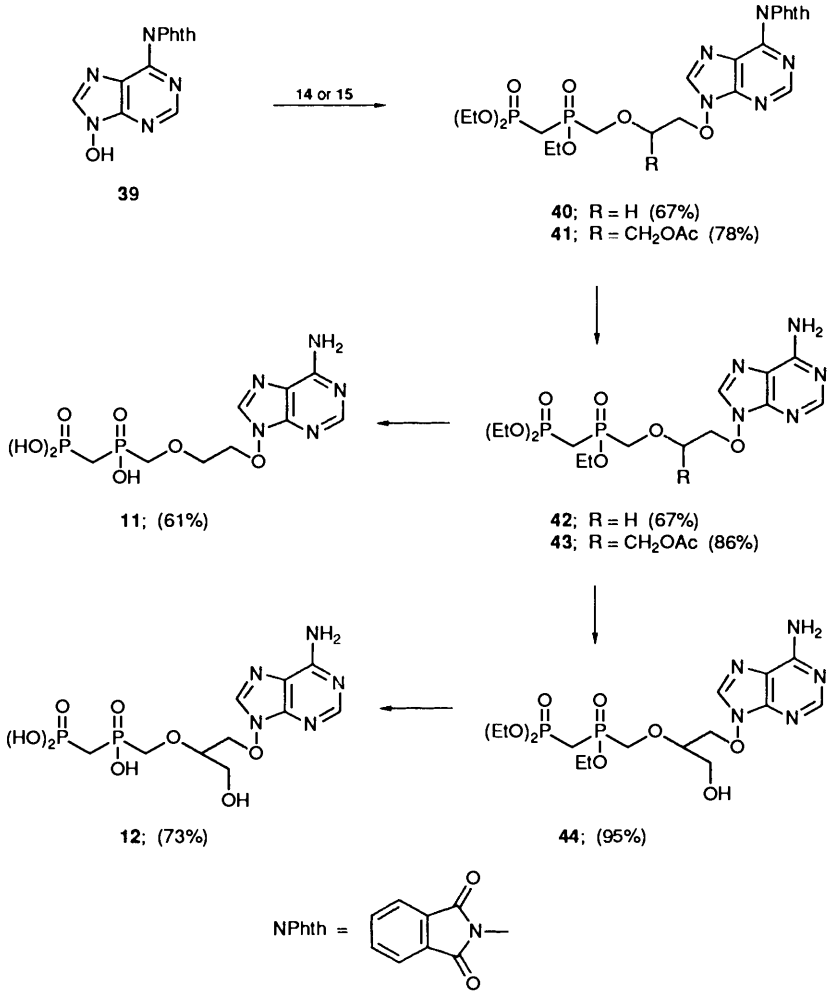
General Procedure for the Preparation of Compounds **16** *and* **17**.—The bromo or chloro ether **14** or **15** (1 mmol) under nitrogen was treated with (diethoxyphosphinoyl)methyldiethoxyphosphine (1 mmol) *via* a septum, with evolution of heat. The mixture was heated at 120 °C under a slow stream of nitrogen for 18 h, and then at 180 °C for 15 min. After cooling, the product was chromatographed on silica gel eluting with chloroform–methanol (30:1).

Diethyl [2-*Acetoxyethoxymethyl*(*ethoxy*)*phosphoryl*]*methylphosphonate* **16** was obtained as an oil in 56% yield (14 mmol scale); ν_{max}(film)/cm^{-1} 3449, 2984, 2940, 2910, 1739, 1654 and 1446; δ_H($CDCl_3$) 1.36 (9 H, t, J 7.1, 3 × CH_3), 2.08 (3 H, s, $OCCH_3$), 2.47 (1 H, ddd, $J_{H,H}$ 15.4, $J_{H,P}$ 20.6 and $J_{H,P}$ 17.9, H_B of PCH_2P), 2.56 (1 H, ddd, $J_{H,H}$ 15.4, $J_{H,P}$ 20.6 and $J_{H,P}$ 16.8, H_A of PCH_2P), 3.82 (2 H, m, CH_2OAc), 3.93 (1 H, ddd, $J_{H,H}$ 13.5, $J_{H,P}$ 7.6 and $J_{H,P}$ 7.7, H_D of PCH_2O), 4.00 (1 H, ddd, $J_{H,H}$ 13.5, $J_{H,P}$ 7.6 and $J_{H,P}$ 7.7, H_C of PCH_2O) and 4.20 (8 H, m, CH_2OCOCH_3 plus 3 × CH_2CH_3) (Found: C, 39.6; H, 7.6%; M^+, 360.1073. $C_{12}H_{26}O_8P_2 \cdot 0.25H_2O$ requires C, 39.5; H, 7.3%; M, 360.1103).

(R,S)-*Diethyl* [2-(*Benzyloxy*-1-*benzyloxymethyl*)*ethoxy methyl*(*ethoxy*)*phosphoryl*]*methylphosphonate* **17** was obtained



Scheme 4



Scheme 5

as an *oil* in 52% yield (30 mmol scale); ν_{max}(film)/cm^{-1} 3453, 3214, 3064, 3033, 2984, 2906, 2867, 1497, 1477 and 1454; δ_H($CDCl_3$) 1.31 (9 H, m, 3 × CH_3), 2.55 (2 H, m, PCH_2P), 3.60 (4 H, m, 2 × CH_2CH), 3.88 (1 H, m, CH), 4.15 (8 H, m, 3 × CH_2, PCH_2O), 4.52 (2 H, s, CH_2Ph), 4.53 (2 H, s, CH_2Ph) and 7.32 (10 H, m, 2 × Ph) (Found: C, 54.2; H, 7.2%; M$^+$, 528.2050. $C_{25}H_{38}O_8P_2$·1.5H_2O requires C, 54.05; H, 7.4%; *M*, 528.2042).

Diethyl [2-*Hydroxyethoxymethyl*(*ethoxy*)*phosphoryl*]*methylphosphonate* **18**.—A solution of compound **16** (1 g, 2.8 mmol) in ethanol (10 cm^3) and hydrochloric acid (2 mol dm^{-3}; 3 cm^3, 6 mmol) was heated at reflux for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel, eluting with chloroform–methanol (20:1) to give the *title compound* **18** as an oil (0.7 g, 80%); ν_{max}(film)/cm^{-1} 3420, 2984, 2935, 2909, 2136, 1654, 1480 and 1445; δ_H($CDCl_3$) 1.36 (9 H, m, 3 × CH_3), 2.49 (1 H, ddd, $J_{H,H}$ 15.1, $J_{H,P}$ 18.7 and 21.2, H_B of PCH_2P), 2.60 (1 H, ddd, $J_{H,H}$ 15.1, $J_{H,P}$ 17.9 and $J_{H,P}$ 20.6, H_A of PCH_2P) and 3.6–4.3 (13 H, m, 4 × CH_2CH_3, CH_2OH, PCH_2O, plus D_2O exchangeable OH) (Found: C, 37.2; H, 7.90%; M$^+$, 318.0998. $C_{10}H_{24}O_7P_2$·0.25H_2O requires C, 37.2; H, 7.65%; *M*, 318.0997).

(R,S)-*Diethyl* (2-*Hydroxy*-1-*hydroxymethyl*)*ethoxymethyl* (*ethoxy*)*phosphoryl*]*methylphosphonate* **19**.—A solution of compound **17** (7.5 g, 14 mmol) in 90% aqueous ethanol (150 cm^3) and hydrochloric acid (5 mol dm^{-3}; 1.5 cm^3) was treated with 10% palladium–charcoal catalyst (500 mg). The mixture was hydrogenated at atmospheric pressure and room temperature for 3 h, filtered through a glass fibre filter pad and then evaporated under reduced pressure. The residue was chromatographed on silica gel to give the *title compound* **19** as an oil (4.2 g, 85%); ν_{max}(film)/cm^{-1} 3380, 2984, 2934, 2909, 1725, 1654, 1479 and 1444; δ_H($CDCl_3$) 1.85 (9 H, m, 3 × CH_3), 2.57 (2 H, m, PCH_2P) and 3.1–4.4 (15 H, m, 3 × CH_2CH_3, PCH_2O, CH, 2 × CH_2OH plus 2 × D_2O exchangeable OH) (Found: C, 37.55; H, 7.55. $C_{11}H_{26}O_8P_2$ requires C, 37.9; H, 7.5%).

(R,S) *Diethyl* [(1-*Acetoxymethyl*-2-*hydroxy*)*ethoxymethyl*-(*ethoxy*)*phosphoryl*]*methylphosphonate* **20**.—A solution of compound **19** (0.85 g, 2.4 mmol) and toluene-4-sulphonic acid (50 mg) in trimethyl orthoacetate (10 cm^3) was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in 50% acetic acid and stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel, eluting with chloroform–methanol (20:1) to give the *title compound* **20** as an oil (0.8 g, 84%); ν_{max}(film)/cm^{-1} 3393, 2984, 2938, 2908, 1740, 1653, 1561, 1479 and 1444; δ_H($CDCl_3$) 1.36 (9 H, m, 3 × CH_3), 2.07 and 2.08 (3 H, 2 × s, OCH_3), 2.55 (2 H, m, PCH_2P) and 3.5–4.53 (14 H, m, 3 × CH_2CH_3, PCH_2O, CH, CH_2OH, CH_2OAc, plus D_2O exchangeable OH) (Found: C, 39.0; H, 7.3%; M$^+$, 390.1211. $C_{13}H_{28}O_9P_2$·0.5H_2O requires C, 39.1; H, 7.3%; *M*, 390.1209).

General Procedure for the Preparation of Compounds **23**, **24**, **25**, **26**, **31**, **32**, **36**, **37**, **40** *and* **41**.—A mixture of compound **21**, **22**,

30, **35** or **39** (1 mmol), alcohol **18** or **20** (1 mmol), and triphenylphosphine (Ph_3P) (1.1–1.5 mmol) in dry DMF or tetrahydrofuran (THF), cooled to 0 °C, was treated with diethyl azodicarboxylate (DEAD) (1.1–1.5 mmol). After being stirred for 18 h at room temperature, the mixture was evaporated under reduced pressure and the residue was purified by chromatography on silica gel.

1-{2-[(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}*uracil* **23**. This compound was obtained as a gum in 80% yield [4.8 mmol scale, solvent DMF (20 cm^3) using 1.2 equiv. of Ph_3P and DEAD] after chromatography, eluting with chloroform; ν_{max}(film)/cm^{-1} 3162, 3050, 2985, 2948, 2907, 2818, 1730, 1686, 1624, 1479, 1446 and 1418; δ_H($CDCl_3$) 1.36 (9 H, m, 3 × CH_3), 2.50 (1 H, ddd, $J_{H,H}$ 15.4, $J_{H,P}$ 17.3 and $J_{H,P}$ 17.6, H_B of PCH_2P), 2.57, (1 H, ddd, $J_{H,H}$ 15.4, $J_{H,P}$ 17.6 and $J_{H,P}$ 17.9, H_A of PCH_2P), 3.89 (2 H, m, CH_2CH_2ON), 4.02 (2 H, d, *J* 7.1, PCH_2O), 4.28 (6 H, m, 3 × CH_2CH_3), 4.38 (2 H, m, CH_2ON), 5.59 (1 H, d, *J* 8, 5-H), 7.80 (1 H, d, *J* 8, 6-H) and 9.01 (1 H, s, D_2O exchangeable NH) (Found: C, 38.2; H, 6.3; N, 6.0. $C_{14}H_{26}N_2O_9$·0.5H_2O requires C, 38.45; H, 6.2; N, 6.4%).

1-{2-[(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}*thymine* **24**. This compound was obtained as a gum in 49% yield [1.8 mmol scale, solvent DMF (10 cm^3), using 1.2 equiv. of Ph_3P and DEAD] after chromatography eluting with chloroform–methanol (50:1); ν_{max}(KBr)/cm^{-1} 3160, 3044, 2985, 2933, 2907, 2816, 1721, 1687, 1460, 1444 and 1418; δ_H($CDCl_3$) 1.37 (9 H, m, 3 × CH_3), 1.93 (3 H, d, *J* 1.1, 5-CH_3), 2.50 (1 H, ddd, $J_{H,H}$ 15.4, $J_{H,P}$ 17.6 and $J_{H,P}$ 20.8, H_B of PCH_2P), 2.58 (1 H, ddd, $J_{H,H}$ 15.4, $J_{H,P}$ 17.5 and $J_{H,P}$ 20.5, H_A of PCH_2P), 3.89 (2 H, m, CH_2CH_2ON), 4.02 (2 H, d, *J* 7.1, PCH_2O), 4.1–4.4 (8 H, m, 3 × CH_2CH_3, CH_2ON), 7.62 (1 H, q, *J* 1.1, 6-H) and 8.82 (1 H, s, D_2O exchangeable NH) (Found: C, 40.7; H, 6.4; N, 6.2. $C_{15}H_{28}N_2O_9P_2$ requires C, 40.7; H, 6.4; N, 6.3%).

(R,S)-1-{2-*Acetoxymethyl*-2-[(*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}*uracil* **25**. This compound was obtained as a gum in 28% yield [0.8 mmol scale, solvent DMF (5 cm^3), using 1.5 equiv. of Ph_3P and DEAD] after chromatography eluting with chloroform–methanol (30:1); ν_{max}(KBr)/cm^{-1} 3463, 3510, 3030, 2988, 2907, 2821, 1735, 1686, 1624, 1445 and 1419; δ_H($CDCl_3$) 1.35 (9 H, m, 3 × CH_3), 2.10 (3 H, s, $OCCH_3$), 2.53 (2 H, m, PCH_2P), 4.23 (13 H, m, 3 × CH_2CH_3, PCH_2O, CH_2ON, CH_2OAc, CH), 5.59 (1 H, d, *J* 8.25, 5-H), 7.81 and 7.94 (1 H, 2 × d, *J* 8.25, 6-H) and 8.67 (1 H, s, D_2O exchangeable NH) (Found: C, 40.5; H, 6.2; N, 5.5. $C_{17}H_{30}N_2O_{11}P_2$ requires C, 40.8; H, 6.0; N, 5.6%).

(R,S)-1-{2-*Acetoxymethyl*-2-[(*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}*thymine* **26**. This compound was obtained as a gum in 28% yield [2.1 mmol scale, solvent DMF (10 cm^3), using 1.1 equiv. of Ph_3P and DEAD] after chromatography eluting with chloroform, increasing polarity to chloroform–methanol (40:1); ν_{max}(KBr)/cm^{-1} 3442, 3163, 3101, 3043, 2989, 2932, 2912, 2815, 1740, 1723, 1685, 1462, 1444 and 1417; δ_H($CDCl_3$) 1.37 (9 H, m, 3 × CH_3), 1.93 (3 H, d, *J* 1.1, 5-CH_3), 2.09 and 2.10 (3 H, 2 × s, $OCCH_3$), 2.53 (2 H, m, PCH_2P), 3.95–4.5 (13 H, m, 3 × CH_2CH_3, PCH_2O, CH_2ON, CH_2OAc, CH), 7.61 and 7.75 (1 H, 2 × q, *J* 1.1, 6-H) and 8.6 (1 H, 2 × br s, D_2O exchangeable NH) (Found: C, 41.1; H, 6.3; N, 5.1. $C_{18}H_{32}N_2O_{11}P_2$·0.5H_2O requires C, 41.3; H, 6.4; N, 5.35%).

4-*Benzamido*-1-{[(2-*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}*uracil* **31**. This compound was obtained as a gum in 83% yield [0.95 mmol scale, solvent DMF (10 cm^3), using 1.1 equiv. of Ph_3P and DEAD] after chromatography eluting with chloroform, increasing polarity to chloroform–methanol (25:1); ν_{max}(KBr)/cm^{-1} 3444, 3218, 3059, 2987, 2907, 2869, 1695, 1677, 1611, 1584, 1560, 1480, 1449 and 1427; δ_H[$(CD_3)_2SO$] 1.25 (9 H, m, 3 × CH_3), 2.68 (2 H, dd, *J* 17.1 and 20.6, PCH_2P), 3.75–4.2 (10 H, m, 3 × CH_2CH_3, PCH_2O, CH_2CH_2ON), 4.38 (2 H, m, CH_2ON), 7.29 (1 H, d, *J* 7.4, 5-H), 7.45–8.05 (5 H, m, C_6H_5), 8.43 (1 H, d, *J* 7.4, 6-H) and 11.28 (1 H, s, D_2O exchangeable NH) (Found: C, 46.7; H, 5.95; N, 7.4. $C_{21}H_{31}N_3O_9P_2$·0.5H_2O requires C, 46.7; H, 6.0; N, 7.8%).

(R,S)-1-{2-*Acetoxymethyl*-2-[(*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}-4-*benzamidouracil* **32**. This compound was obtained as a gum in 71% yield [1.3 mmol scale, solvent DMF (10 cm^3), using 1.1 equiv. of Ph_3P and DEAD] after chromatography eluting with chloroform, increasing polarity to chloroform–methanol (30:1); ν_{max}(KBr)/cm^{-1} 3460, 3191, 3130, 3064, 2983, 2905, 1741, 1685, 1613, 1558, 1482 and 1447; δ_H[$(CD_3)_2SO$] 1.25 (9 H, m, 3 × CH_3), 2.06 (3 H, s, $OCCH_3$), 2.62 (2 H, dd, J_1 = J_2 19, PCH_2P), 3.9–4.5 (13 H, m, 3 × CH_2CH_3, PCH_2O, CH, CH_2OAc, CH_2ON), 7.30 (1 H, d, *J* 7.7, 5-H), 7.45–8.1 (5 H, m, C_6H_5), 8.50 and 8.52 (1 H, 2 × d, *J* 7.7, 6-H) and 11.30 (1 H, s, D_2O exchangeable NH) (Found: C, 46.0; H, 5.6; N, 6.5. $C_{24}H_{35}N_3O_{11}P_2$·H_2O requires C, 46.4; H, 6.0; N, 6.8%).

2-[N,N-*Bis*-(tert-*butoxycarbonyl*)*amino*]-9-{2-[(*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}-6-*methoxypurine* **36**. This compound was obtained as a gum in 50% yield [1.3 mmol scale, solvent DMF (10 cm^3), using 1.2 equiv. of Ph_3P and DEAD] after chromatography eluting with chloroform, increasing polarity to chloroform–methanol (30:1); ν_{max}(KBr)/cm^{-1} 3074, 2983, 2937, 2909, 1793, 1759, 1573, 1447, 1459 and 1424; δ_H($CDCl_3$) 1.4 [27 H, m, 3 × CH_2CH_3 plus 2 × $C(CH_3)_3$], 2.48 (1 H, ddd, $J_{H,H}$ 15, $J_{H,P}$ 18.0 and $J_{H,P}$ 20.8, H_B of PCH_2P), 2.56 (1 H, ddd, $J_{H,H}$ 15, $J_{H,P}$ 17.2 and $J_{H,P}$ 20.5, H_A of PCH_2P), 4.1 (13 H, m, 3 × CH_2CH_3, OCH_3, PCH_2O, CH_2CH_2ON), 4.6 (2 H, m, CH_2ON) and 8.31 (1 H, s, 8-H) (Found: C, 44.6; H, 6.7; N, 10.0. $C_{26}H_{45}N_5O_{12}P_2$·H_2O requires C, 44.6; H, 6.8; N, 10.0%).

(R,S)-9-{2-*Acetoxymethyl*-2-[(*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}-2-[N,N-*bis*-(tert-*butoxycarbonyl*)*amino*]-6-*methoxypurine* **37**. This compound was obtained as a foam in 70% yield [1.3 mmol scale, solvent DMF (10 cm^3), using 1.2 equiv. of Ph_3P and DEAD] after chromatography eluting with chloroform, increasing polarity to chloroform–methanol (40:1); ν_{max}(KBr)/cm^{-1} 3077, 2982, 2937, 1793, 1746, 1594, 1476, 1455 and 1425; δ_H($CDCl_3$) 1.35 (9 H, m, 3 × CH_2CH_3), 1.47 [9 H, s, $(CH_3)_3C$], 2.09 (3 H, s, $OCCH_3$), 2.55 (2 H, m, PCH_2P), 4.05–4.70 (16 H, m, 3 × CH_2CH_3, PCH_2O, CH_2OAc, CH, CH_2ON, OCH_3) and 8.38 and 8.43 (1 H, 2 × s, 8 H) (Found: C, 45.1; H, 6.6; N, 8.9. $C_{29}H_{49}N_5O_{14}P_2$·H_2O requires C, 45.1; H, 6.7; N, 9.1%).

9-{[2-(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}-6-N-*phthalimidopurine* **40**. This compound was obtained as a gum in 67% yield [0.8 mmol scale, solvent THF (10 cm^3), using 1.2 equiv. of Ph_3P and DEAD] after chromatography eluting with acetone–hexane (1:1) of increasing polarity to acetone; ν_{max}(KBr)/cm^{-1} 3465, 3094, 3065, 2984, 2938, 2909, 1792, 1762, 1735, 1661, 1600, 1579, 1456, 1447 and 1405; δ_H($CDCl_3$) 1.36 (9 H, m, 3 × CH_3), 2.56 (2 H, m, PCH_2P), 4.14 (10 H, m, 3 × CH_2CH_3, PCH_2O, CH_2CH_2ON), 4.70 (2 H, m, CH_2ON), 7.87 (2 H, m, ArH), 8.04 (2 H, m, ArH), 8.63 (1 H, s, CH) and 9.07 (1 H, s, CH) (Found: C, 45.45; H, 5.15; N, 11.0. $C_{23}H_{29}N_5O_9P_2$·1.5H_2O requires C, 45.4; H, 5.3; N, 11.5%).

(R,S)-9-{2-*Acetoxymethyl*-2-[(*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}-6-N-*phthalimidopurine* **41**. This compound was obtained as a gum in 78% yield [1.3 mmol scale, solvent THF (10 cm^3), using 1.5 equiv. of Ph_3P and DEAD] after chromatography eluting with acetone–hexane (1:1) of increasing polarity to acetone; ν_{max}(KBr)/cm^{-1} 3502, 3462, 3093, 3063, 2984, 2907, 1791, 1732, 1599, 1578, 1455, 1447 and 1404; δ_H($CDCl_3$) 1.32 (9 H, m, CH_2CH_3), 2.11 (1 H, s,

$OCCH_3$), 2.58 (2 H, m, PCH_2P), 4.03–4.8 (13 H, m, 3 × CH_2CH_3, PCH_2O, CH_2OAc, CH_2ON, CH), 7.95 (4 H, m, C_6H_4), 8.73 and 8.58 (1 H, 2 × s, CH) and 9.07 (1 H, s, CH) (Found: C, 46.7; H, 5.1; N, 10.1. $C_{26}H_{33}N_5O_{11}P_2 \cdot H_2O$ requires C, 46.5; H, 5.25; N, 10.4%).

4-*Benzamido*-1-*benzyloxyuracil* **29**.—A mixture of 1-benzyloxycytosine (4.34 g, 20 mmol) and benzoic anhydride (9 g, 40 mmol) in ethanol (100 cm^3) was heated at reflux for 1.5 h. The mixture was treated with additional benzoic anhydride (9 g, 40 mmol) and heated at reflux for a further 2.5 h. An additional quantity of benzoic anhydride (9 g, 40 mmol) was added and the mixture was left to cool for 18 h. The precipitated product was collected by filtration and washed with dry ether, to give the *title compound* **29** (5.25 g, 82%), m.p. 209–211 °C; ν_{max}(KBr)/cm^{-1} 3411, 3060, 3037, 2995, 1692, 1670, 1615, 1644, 1497, 1483, 1449 and 1418; δ_H[$(CD_3)_2SO$] 5.25 (2 H, s, CH_2Ph), 7.12 (1 H, d, *J* 7.7, 5-H), 7.4–8.1 (10 H, m, 2 × C_6H_5), 8.27 (1 H, d, *J* 7.7, 6-H) and 11.27 (1 H, s, D_2O exchangeable NH) (Found: C, 66.7; H, 4.7; N, 13.0. $C_{18}H_{15}N_3O_3 \cdot 0.25H_2O$ requires C, 66.35; H, 4.78; N, 12.9%).

4-*Benzamido*-1-*hydroxyuracil* **30**.—A solution of compound **29** (1.5 g, 4.7 mmol) in THF (75 cm^3), water (7 cm^3) and saturated methanolic hydrogen chloride (1 cm^3) was treated with 10% palladium–charcoal catalyst (0.15 g). The mixture was hydrogenated at atmospheric pressure and room temperature for 13 min, filtered through a glass fibre pad and then evaporated under reduced pressure. The residue was crystallised from methanol to give the *title compound* **30** as a solid (0.66 g, 61%), m.p. 225–227 °C; ν_{max}(KBr)/cm^{-1} 3434, 3217, 3150, 3107, 3050, 2500, 1699, 1682, 1611, 1602, 1581, 1487 and 1409; δ_H[$(CD_3)_2SO$] 7.26 (1 H, d, *J* 7.4, 5-H), 7.4–8.1 (5 H, m, C_6H_5), 8.36 (1 H, d, *J* 7.4, 6-H), 11.2 (1 H, br s, D_2O exchangeable) and 11.9 (1 H, br s, D_2O exchangeable) (Found: C, 57.2; H, 3.95; N, 18.4. $C_{11}H_{10}N_3O_3$ requires C, 57.1; H, 3.9; N, 18.2%.

General Procedure for the Preparation of Compounds **42** *and* **43**.—A solution of compound **40** or **41** (1 mmol) in dichloromethane (10 cm^3) at 0 °C was treated with *N*-methylhydrazine (1.5 mmol), and stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel, eluting with chloroform–methanol (20:1) of increasing polarity (to 10:1).

9-{[2-(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*} *adenine* **42**. This compound was obtained as a gum in 67% yield (0.36 mmol scale); ν_{max}(film)/cm^{-1} 3408, 3336, 3258, 3187, 2985, 2940, 2907, 1648, 1597, 1496, 1470, 1444 and 1411; δ_H[$(CD_3)_2SO$] 1.23 (9 H, m, 3 × CH_3), 2.70 (2 H, dd, *J* 17.0 and 20.6, PCH_2P), 3.7–4.15 (10 H, m, 3 × CH_2CH_3, PCH_2O, CH_2CH_2ON), 4.5 (2 H, m, CH_2ON), 7.36 (2 H, s, D_2O exchangeable NH_2), 8.15 (1 H, s, CH) and 8.39 (1 H, s, CH) (Found: C, 37.9; H, 5.5; N, 14.0. $C_{15}H_{27}N_5O_7P_2 \cdot 0.26CHCl_3$ requires C, 38.0; H, 5.7; N, 14.5%).

(R,S)-9-{2-*Acetoxymethyl*-2-[(*diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]*ethoxy*}*adenine* **43**. This compound was obtained as a gum in 86% yield (1 mmol scale); ν_{max}(KBr)/cm^{-1} 3334, 3260, 3184, 2982, 2940, 2905, 1740, 1644, 1595, 1468, 1440 and 1410; δ_H[$(CD_3)_2SO$] 1.33 (9 H, m, 3 × CH_3), 2.089 and 2.094 (3 H, s, CH_3CO), 2.60 (2 H, m, PCH_2P), 4.05–4.7 (13 H, m, 3 × CH_2CH_3, PCH_2O, CH_2OAc, CH_2ON, CH), 5.81 (2 H, D_2O exchangeable NH_2), 8.14 and 8.26 (1 H, 2 × s, CH) and 8.36 (1 H, s, CH) (Found: C, 40.9; H, 6.1; N, 13.1. $C_{18}H_{31}N_5O_9P_2 \cdot 0.5H_2O$ requires C, 40.6; H, 6.1; N, 13.15%).

General Procedure for the Preparation of Compounds **27**, **28**, **33**, **34**, **38** *and* **44**.—A solution of compound **25**, **26**, **31**, **32**, **37** or **43** in ethanol and hydrochloric acid (5 mol dm^{-3}) was heated at reflux for 1.5–4.5 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel.

1-{2-[(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]-2-*hydroxymethylethoxy*}*uracil* **27**. This compound was obtained as a glass in 90% yield [0.2 mmol scale, using hydrochloric acid (0.4 mmol) in ethanol (3 cm^3)] after 1.5 h and chromatography eluting with chloroform–methanol (20:1); ν_{max}(film)/cm^{-1} 3388, 3044, 2987, 2940, 2908, 2821, 1733, 1686, 1625, 1480, 1445 and 1420; δ_H($CDCl_3$) 1.37 (9 H, m, 3 × CH_3), 2.55 (2 H, m, PCH_2P), 3.5–4.6 (14 H, m, 3 × CH_2CH_3, PCH_2O, CH_2OH, CH_2ON, CH, plus D_2O exchangeable OH), 5.60 (1 H, s × d, *J* 8.2, 5-H), 7.62 and 7.83 (1 H, 2 × d, *J* 8.2, 6-H) and 8.88 (1 H, D_2O exchangeable NH) (Found: C, 38.9; H, 6.2; N, 5.9. $C_{15}H_{28}N_2O_{10}P_2 \cdot 0.5H_2O$ requires C, 38.55; H, 6.25; N, 6.0%).

(R,S)-1-{2-[(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]-2-*hydroxymethylethoxy*} *thymine* **28**. This compound was obtained as a glass in 68% yield [0.7 mmol scale using hydrochloric acid (1.5 mmol) in ethanol (5 cm^3)] after 2 h and chromatography eluting with chloroform–methanol (10:1); ν_{max}(film)/cm^{-1} 3410, 3180, 3040, 2985, 2935, 2910, 2815, 1715, 1685, 1460, 1445 and 1420; δ_H($CDCl_3$) 1.37, (9 H, m, 3 × CH_2CH_3), 1.93 (3 H, 2 × s, 5-CH_3), 2.55 (2 H, m, PCH_2P), 3.5–4.75 (14 H, m, 3 × CH_2CH_3, PCH_2O, CH_2OH, CH_2ON, CH_2ON, CH, plus D_2O exchangeable OH), 7.42 and 7.65 (1 H, 2 × s, 6-H) and 8.60 (1 H, br D_2O exchangeable NH) (Found: C, 38.2; H, 6.5; N, 4.9. $C_{16}H_{30}N_2O_{10}P_2 \cdot 1.5H_2O$ requires C, 38.5; H, 6.7; N, 5.6%).

1-{[2-(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*] *ethoxy*}*cytosine* **33**. The compound was obtained as a gum in 76% yield [0.7 mmol scale using hydrochloric acid (1.4 mmol) in ethanol (30 cm^3)] after 2.5 h and chromatography eluting with chloroform–methanol (10:1) of increasing polarity to (5:1); ν_{max}(KBr)/cm^{-1} 3339, 3167, 2983, 2933, 2905, 1644, 1513, 1486 and 1445; δ_H($CDCl_3$) 1.36 (9 H, m, 3 × CH_3), 2.50 (1 H, ddd, $J_{H,H}$ 15, $J_{H,P}$ 17.6 and $J_{H,P}$ 20.6, H_B of PCH_2P), 2.58 (1 H, ddd, $J_{H,H}$ 15, $J_{H,P}$ 17.2 and $J_{H,P}$ 20.5, H_A of PCH_2P), 3.85 (2 H, m, CH_2CH_2ON), 4.00 (2 H, d, *J* 6.6, PCH_2O), 4.20 (6 H, m, 3 × CH_2CH_3), 4.4 (2 H, m, CH_2ON), 5.73 (1 H, d, *J* 7.4, 5-H), 6.21 (2 H, br s, D_2O exchangeable NH_2) and 7.74 (1 H, d, *J* 7.4, 6-H) (Found: C, 38.25; H, 6.2; N, 9.6. $C_{14}H_{27}N_3O_8P_2 \cdot 0.5H_2O$ requires C, 38.5; H, 6.5; N, 9.6%).

(R,S)-1-{2-[(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]-2-(*hydroxymethyl*)*ethoxy*}*cytosine* **34**. This compound was obtained as a gum in 67% yield [0.8 mmol scale using hydrochloric acid (3 mmol) in ethanol (30 cm^3)] after 2 h and chromatography eluting with chloroform–methanol (10:1) of increasing polarity to (5:1); ν_{max}(KBr)/cm^{-1} 3338, 3195, 2983, 2920, 2906, 1645, 1514, 1487 and 1440; δ_H[$(CD_3)_2SO$] 1.22 (9 H, m, 3 × CH_3), 2.70 (2 H, m, PCH_2P), 3.52 (2 H, m, CH_2OH), 3.68 (1 H, m, CH), 3.9–4.3 (10 H, m, 3 × CH_2CH_3, PCH_2O, CH_2ON), 5.59 (1 H, d, *J* 7.6, 5-H), 7.16 (1 H, br s, D_2O exchangeable NH of NH_2), 7.85 and 7.87 (1 H, 2 × d, *J* 7.6, 6-H) (Found: M^+, 457.1376. $C_{15}H_{29}N_3O_9P_2$ requires *M*, 457.1379).

(R,S)-9{2-[(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphorylmethoxy*]-2-(*hydroxymethyl*)*ethoxy*}*guanine* **38**. This compound was obtained as a foam in 78% yield [0.8 mmol scale using hydrochloric acid (5 mmol) in ethanol (10 cm^3)] after 4.5 h and chromatography eluting with chloroform–methanol (4:1); ν_{max}(KBr)/cm^{-1} 3412, 3160, 2988, 1693, 1650, 1609, 1527, 1475 and 1445; δ_H[$(CD_3)_2SO$] 1.20 (9 H, m, 3 × CH_3), 2.75 (2 H, m, PCH_2P), 3.55 (2 H, m, CH_2OH), 3.75 (1 H, m, CH), 3.9–4.5 (10 H, m, 3 × CH_2CH_3, CH_2ON, PCH_2O), 5.90 (1 H, t, *J* 5.6, D_2O exchangeable OH), 6.71 (2 H, s, D_2O exchangeable NH_2), 7.98 and 8.00 (1 H, 2 × s, 8-H) and 10.77 (1 H, s, D_2O

exchangeable NH) (Found: C, 36.9; H, 5.5; N, 13.1. $C_{16}H_{29}N_5O_9P_2$·0.22$CHCl_3$ requires C, 36.7; H, 5.6; N, 13.4%).

(R,S)-9-{2-[(*Diethoxyphosphorylmethyl*)(*ethoxy*)*phosphoryl*-*methoxy*]-2-(*hydroxymethyl*)*ethoxy*}*adenine* **44**. This compound was obtained as a glass in 95% yield [0.9 mmol scale using hydrochloric acid (2 mmol) in ethanol (5 cm^3)] after 2 h and chromatography eluting with chloroform–methanol (10:1) of increasing polarity to (5:1); ν_{max}(KBr)/cm^{-1} 3400, 3214, 2985, 2928, 2910, 1653, 1645, 1636, 1600, 1475 and 1414; δ_H[$(CD_3)_2SO$] 1.23 (9 H, m, 3 × CH_3), 2.74 (2 H, m, CH_2), 3.5 (2 H, m, CH_2), 3.80 (1 H, m, CH), 4.05 (8 H, m, 4 × CH_2CH_3), 4.50 (2 H, m, CH_2ON), 4.9 (1 H, br s, D_2O exchangeable OH), 7.55 (2 H, s, D_2O exchangeable NH_2), 8.19 (1 H, s, CH) and 8.33 and 8.49 (1 H, 2 × s, CH) (Found: C, 35.9; H, 5.6; N, 13.3. $C_{16}H_{29}N_5O_8P_2$·HCl·H_2O requires C, 35.9; H, 6.0; N, 13.1%).

General Procedure for the Preparation of Compounds **3**–**12**.— A solution of compound **23**, **24**, **27**, **28**, **33**, **34**, **36**, **38**, **42** or **44** (1 mmol) in dichloromethane or DMF was treated with trimethylsilyl bromide (20 mmol) under nitrogen and the solution was stirred at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was evaporated to dryness three times with methanol (20 cm^3). The residue was chromatographed on reverse phase C_{18} silica gel, eluting with water.

1-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmethoxy*]-*ethoxy*}*uracil* **3**. This compound was obtained as a foam in 67% yield [0.5 mmol scale in dichloromethane (5 cm^3)]; λ_{max}-(H_2O)/nm 266 (ε 8930); ν_{max}(KBr)/cm^{-1} 3369, 3259, 3128, 3093, 2947, 2905, 2890, 2862, 2813, 2245, 1711, 1674, 1481, 1460, 1434 and 1411; δ_H[$(CD_3)_2SO$] 2.21 (2 H, dd, *J* 17.1 and 19.8, PCH_2P), 3.80 (4 H, m, PCH_2O, CH_2CH_2ON), 4.25 (2 H, m, CH_2ON), 5.45 (1 H, d, *J* 8.0, 5-H), 7.90 (3 H, br s, 3 × D_2O exchangeable OH), 7.97 (1 H, d, *J* 8.0, 6-H) and 11.47 (1 H, s, D_2O exchangeable NH) (Found: C, 25.9; H, 4.5; N, 7.6. $C_8H_{14}N_2O_9P_2$·1.5H_2O requires C, 25.9; H, 4.6; N, 7.55%).

(R,S)-1-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmeth*-*oxy*]-2-(*hydroxymethyl*)*ethoxy*}*uracil* **4**. This compound was obtained as a glass in 73% yield [0.3 mmol scale in dichloromethane (5 cm^3)]; λ_{max}(H_2O)/nm 266.5 (ε 8440) (hygroscopic); ν_{max}(KBr)/cm^{-1} 3425, 2961, 2919, 2339, 1717, 1685, 1457 and 1420; δ_H[$(CD_3)_2SO$] 2.23 (2 H, dd, $J_1 = J_2$ 19, PCH_2P), 3.52 (2 H, m, PCH_2O), 3.70 (1 H, m, CH), 3.88 (2 H, m, CH_2OH), 4.2 (2 H, m, CH_2ON), 5.25 (>4 H, br s, 4 × D_2O exchangeable OH plus H_2O), 5.46 (1 H, dd, *J* 2.0 and 8.25, 5-H), 8.03 (1 H, d, *J* 8.25, 6-H) and 11.47 (1 H, s, D_2O exchangeable NH) (Found: C, 27.9; H, 4.3; N, 7.1. $C_9H_{16}N_2O_{10}P_2$·0.5H_2O requires C, 28.2; H, 4.5; N, 7.3%).

1-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmethoxy*]-*ethoxy*}*thymine* **5**. This compound was obtained as a glass in 68% yield [0.7 mmol scale in dichloromethane (5 cm^3)], and crystallised from methanol, m.p. 195–196 °C; λ_{max}(H_2O)/nm 270 (ε 9311); ν_{max}(KBr)/cm^{-1} 3434, 3177, 3107, 3071, 2996, 2973, 2948, 2909, 2251, 1739, 1642, 1616, 1476 and 1411; δ_H[$(CD_3)_2SO$] 1.76 (3 H, d, *J* 1.2, 5-CH_3), 2.21 (2 H, dd, *J* 17.3 and 19.5, PCH_2P), 3.75 (4 H, m, PCH_2O, CH_2CH_2ON), 4.22 (2 H, m, CH_2ON), 6.40 (>3 H, br s, 3 × D_2O exchangeable OH plus H_2O), 7.86 (1 H, q, *J* 1.2, 6-H) and 11.45 (1 H, s, D_2O exchangeable NH) (Found: C, 30.0; H, 4.5; N, 7.7. $C_9H_{16}N_2O_9P_2$ requires C, 30.2; H, 4.5; N, 7.8%).

(R,S)-1-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosporylmeth*-*oxy*]-2-(*hydroxymethyl*)*ethoxy*}*thymine* **6**. This compound was obtained as a foam in 60% yield [0.3 mmol scale in dichloromethane (5 cm^3)]; λ_{max}(H_2O)/nm 271 (ε 8100); ν_{max}(KBr)/cm^{-1} 3418, 3160, 3052, 2956, 2890, 2818, 2298, 1711, 1678, 1465 and 1460; δ_H[$(CD_3)_2SO$] 1.76 (3 H, d, *J* 1.1, 5-CH_3), 2.23 (2 H, dd, $J_1 = J_2$ 18.2, PCH_2P), 3.53 (2 H, m, PCH_2O), 3.65 (1 H, m, CH), 3.86 (2 H, m, CH_2OH), 4.08 (1 H, dd, *J* 7.0 and 10.95, CH of CH_2ON), 4.28 (1 H, dd, *J* 3.0 and 10.95, CH of CH_2ON), 6.75 (>4 H, br s, 4 × D_2O exchangeable OH plus H_2O), 7.92 (1 H, q, *J* 1.1, 6-H) and 11.45 (1 H, s, D_2O exchangeable OH) (Found: C, 29.6; H, 5.1; N, 6.8. $C_{10}H_{18}N_2O_{10}P_2$·H_2O requires C, 29.6; H, 5.0; N, 6.9%).

1-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmethoxy*]-*ethoxy*}*cytosine* **7**. This compound was obtained as a foam in 91% yield [0.3 mmol scale in dichloromethane (5 cm^3)]; λ_{max}/nm 277 (ε 7220); ν_{max}(KBr)/cm^{-1} 3379, 3114, 3073, 2923, 2771, 1734, 1675, 1539 and 1460; δ_H[$(CD_3)_2SO$] 2.20 (2 H, dd, $J_1 = J_2$ 22, PCH_2P), 3.75 (4 H, m, PCH_2O, and CH_2CH_2ON), 4.80 (2 H, m, CH_2ON), 5.4 (>3 H, br s, 3 × D_2O exchangeable OH plus H_2O), 5.77 (1 H, d, *J* 7.7, 5-H), 7.80 (1 H, br s, D_2O exchangeable NH of NH_2), 8.12 (1 H, d, *J* 7.7, 6-H) and 8.50 (1 H, br s, D_2O exchangeable NH of NH_2) (Found: C, 23.75; H, 4.6; N, 10.25. $C_{18}H_{15}N_3O_8P_2$·0.5HBr·H_2O requires C, 23.9; H, 4.4; N, 10.5%).

(R,S)-1-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmeth*-*oxy*]-2-(*hydroxymethyl*)*ethoxy*}*cytosine* **8**. This compound was obtained as a very hygroscopic glass in 93% yield [0.4 mmol scale in dichloromethane (5 cm^3)]; λ_{max}(H_2O)/nm 274 (ε 6855); ν_{max}(KBr)/cm^{-1} 3390, 3126, 2954, 2783, 1740, 1676, 1534 and 1430; δ_H (hydrobromide) [$(CD_3)_2SO$] 2.24 (2 H, dd, $J_1 = J_2$ 18, PCH_2P), 3.45 (2 H, m, PCH_2O), 3.73 (1 H, m, CH), 3.87 (2 H, m, CH_2OH), 4.30 (2 H, m, CH_2ON), 5.90 (1 H, d, *J* 8, 5-H), 6.2 (5 H, br s, 4 × D_2O exchangeable OH plus HBr), 8.20 (1 H, s, D_2O exchangeable NH of NH_2), 8.38 (1 H, d, *J* 8, 6-H) and 9.35 (1 H, s, D_2O exchangeable NH of NH_2) (Found: C, 23.9; H, 3.6; N, 9.1. $C_9H_{17}N_3O_9P_2$·HBr requires C, 23.8; H, 4.0; N, 9.25).

9-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmethoxy*]-*ethoxy*}*guanine* **9**. This compound was obtained as a solid in 93% yield [0.6 mmol scale in dichloromethane (10 cm^3)], and crystallised from water, m.p. 263–264 °C; λ_{max}/nm 253 (ε 12 760), 267sh; ν_{max}(KBr)/cm^{-1} 3382, 3328, 3174, 3150, 2905, 2748, 2328, 1718, 1652, 1596, 1544, 1480, 1460 and 1413; δ_H[$(CD_3)_2SO$] 2.20 (2 H, dd, *J* 17.4 and 19.2, PCH_2P), 3.80 (4 H, m, CH_2CH_2ON plus PCH_2O), 4.38 (2 H, m, CH_2ON), 6.60 (2 H, br s, D_2O exchangeable NH_2), 7.97 (1 H, s, CH) and 10.6 (1 H, s, D_2O exchangeable NH) (Found: C, 28.4; H, 4.3; N, 18.6. $C_9H_{15}N_5O_8P_2$ requires C, 28.2; H, 3.95; N, 18.3%).

(R,S)-9-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmeth*-*oxy*]-2-(*hydroxymethyl*)*ethoxy*}*guanine* **10**.— This compound was obtained as a solid in 32% yield [0.2 mmol scale in DMF (5 cm^3)] m.p. >300 °C; λ_{max}(H_2O)/nm 253 (ε 12 300); ν_{max}(KBr)/cm^{-1} 3391, 3162, 2910, 2748, 1716, 1648 and 1596; δ_H[$(CD_3)_2SO$] 2.25 (2 H, dd, $J_1 = J_2$ 18, PCH_2P), 3.55 (2 H, m, PCH_2O), 3.71 (1 H, m, CH), 3.90 (2 H, m, CH_2OH), 4.35 (2 H, m, CH_2ON), 5.4 (>4 H, br s, 4 × D_2O exchangeable OH plus H_2O), 6.67 (2 H, br s, D_2O exchangeable NH_2) and 8.01 (1 H, s, CH), 10.65 (1 H, br s, D_2O exchangeable NH) (Found: C, 27.8; H, 4.0; N, 16.2. $C_{10}H_{17}N_5O_9P_2$·0.75H_2O requires C, 28.1; H, 4.4; N, 16.4%).

9-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmethoxy*]-*ethoxy*} *adenine* **11**. This compound was obtained as a solid in 61% yield [0.2 mmol scale in dichloromethane (5 cm^3)], m.p. 205–207 °C; λ_{max}(H_2O)/nm 259 (ε 13 100); ν_{max}(KBr)/cm^{-1} 3435, 3119, 2919, 2369, 1695, 1685, 1605, 1588, 1496, 1482, 1456 and 1415; δ_H[$(CD_3)_2SO$] 2.26 (2 H, dd, *J* 17.3 and 19.5, PCH_2P), 3.85 (4 H, m, PCH_2O, CH_2CH_2ON), 4.55 (2 H, m, CH_2ON), 6.6 (5 H, br s, 3 × D_2O exchangeable OH plus H_2O), 7.55 (2 H, br s, D_2O exchangeable NH_2) and 8.21 (1 H, s, CH) (Found: C, 27.8; H, 4.2; N, 17.9. $C_9H_{15}N_5O_7P_2$·H_2O requires C, 28.1; H, 4.45; N, 18.2%).

9-{2-[(*Hydroxy*)(*phosphonomethyl*)*phosphorylmethoxy*]-2-(*hydroxymethyl*)*ethoxy*}*adenine* **12**. This compound was obtained as a foam in 73% yield [0.7 mmol scale in DMF (5 cm^3)]; λ_{max}/nm 260 (ε 12 660); ν_{max}(KBr)/cm^{-1} 3350, 3090, 2955, 2910, 1697, 1612, 1468 and 1413; δ_H[$(CD_3)_2SO$] 2.26 (2 H, dd,

J 17.6 and 19.5, PCH_2P), 3.56 (2 H, m, PCH_2O), 3.78 (1 H, m, CH), 3.91 (2 H, m, CH_2OH), 4.47 (2 H, m, CH_2ON), 4.8 (>4 H, s, 4 × D_2O exchangeable OH plus H_2O), 7.58 (2 H, s, D_2O exchangeable NH_2) and 8.19 (1 H, s, CH), 8.52 (1 H, s, CH) (Found: C, 29.5; H, 4.4; N, 17.1. $C_{10}H_{17}N_5O_8P_2 \cdot 0.5H_2O$ requires C, 29.6; H, 4.5; N, 17.2%).

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