Preparation of carbocyclic analogues of 2′-deoxyribonucleotides possessing a phosphonate substituent at the 5′-position

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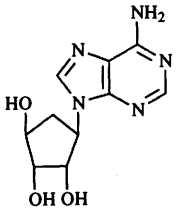
The epoxycyclopentanol 10 is converted into the methylphosphonate 15 in 30% overall yield. The diol 15 is converted into the protected carbocyclic nucleotide mimics 16, 18, 21 and 22 in 38–70% yield. The diol 15 is resolved using a lipase-catalysed esterification and the absolute configurations of the enantiomers are deduced by CD spectroscopy.

Introduction and background information

There is considerable current interest in the chemistry and biological activity of carbocyclic nucleosides and nucleotides.[1] Our recent work in this area has concentrated on the production of noraristeromycin **1**,[2] the phosphonate **2**, as well as the diphosphorylphosphonate **3**[3] which was found to be a potent inhibitor of HIV-reverse transcriptase.



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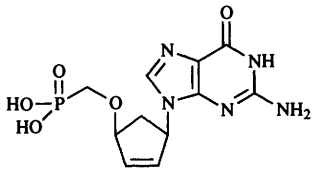

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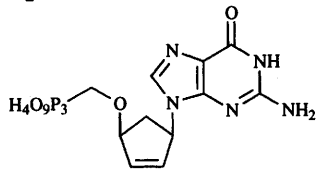

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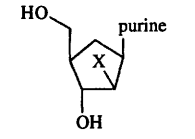
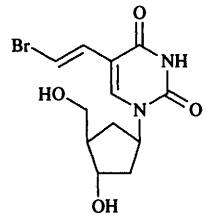
The preparation of carbocyclic deoxyribonucleosides **4** has been under scrutiny since the pioneering work of Shealy and O'Dell.[4] Fluoro compounds of type **5**,[5] and the bromovinyluridine derivative **6**[6] have been noted to be potent anti-herpes agents. The preparation of phosphonates of type **7** is of interest to us and we have published a communication describing the preparation of one member, **8**, of this series.[7] In this paper we describe the synthesis of a series of compounds of type **7** as well as a method for obtaining these compounds in optically active form with an established absolute configuration. The availability of optically active synthons allows target molecules to be prepared in homochiral form if the desirable biological activity resides in one enantiomer, as is often the case for molecules of the type **4**, **5** and **6**.



4 X = H
5 X = F



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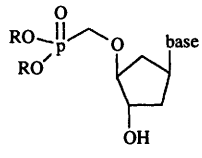

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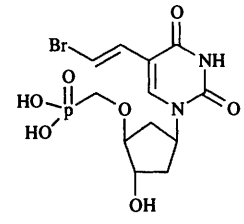

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Results and discussion

Cyclopent-3-enol **9** can be oxidized to the epoxy alcohol **10** (Scheme 1) using a literature procedure.[8] Boiling the epoxide **10** in a mixture of dimethyl sulfoxide and water containing potassium hydroxide gave the crude triol **11** which was isolated, purified and characterised as the triacetate **12**. Hydrolysis of this triester liberated the triol **11** which was converted into the silyl acetal **13** on treatment with di-*tert*-butylsilyl ditriflate and 2,6-dimethylpyridine (2,6-lutidine) in dimethylformamide.[9]

The phosphonate moiety was introduced using the requisite triflate $[(EtO)_2(P{=}O)CH_2OSO_2CF_3]$[10] whereafter removal of the silyl group from the bicyclic compound **14** was achieved using ammonium fluoride in methanol[11] to furnish the diol **15**.

The target compounds were readily prepared from the diol **15** under Mitsunobu reaction conditions. Thus, 6-chloropurine, the diol **15**, triphenylphosphine and diethyl azodicarboxylate were allowed to react in dioxane to give the purines **16** and **17** in the ratio ~6:1 and in 82% overall yield (Scheme 2). The isomers were distinguished by their UV absorbance spectra.[12] Note that displacement of the 3′-hydroxy group did not occur due to the steric hindrance offered by the phosphonate unit.

Similarly, 2-amino-6-chloropurine reacted with the diol **15** under Mitsunobu conditions to give the *N*-9 substituted purine **18** (isolated as the diacetate **19** and then deacylated to give **18**) and the isomer **20**. The ratio of purines **18**:**20** was ~12:1 and the overall yield was 41%. As with the 6-chloropurine derivatives, the isomers were distinguished by their UV absorbance spectra.[13]

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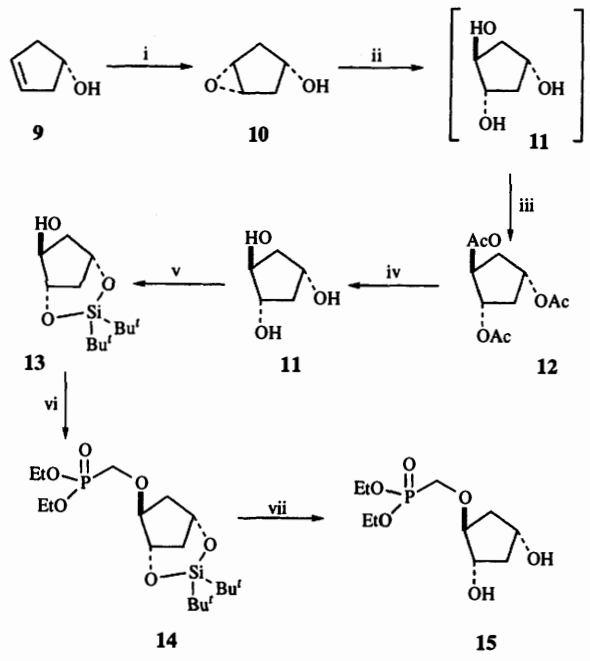


Scheme 1 *Reagents and conditions:* i, Bu^{t}OOH, VO(acac)$_2$;[8] ii, KOH, H_2O–DMSO, heat; iii, Ac_2O, pyridine, DMAP, RT, 56% (2 steps); iv, K_2CO_3–MeOH, RT, 72%; v, $Bu^t_2Si(OTf)_2$, 2,6-lutidine, DMF, 0 °C, 94%; vi, BuLi, $(EtO)_2(P{=}O)CH_2OSO_2CF_3$, THF, −25 °C, 93%; vii, NH_4F, MeOH, RT, 84%.

The diol **15** reacted cleanly with 3-benzoyl-5-bromovinyluracil to give the protected nucleotide mimic **21** (60%), whereas reaction of **15** with *N*-3-benzoylthymine[14] gave the desired compound **22** as the major product (49%) but also afforded the isomer **23** and the *N*-debenzoylated compound **24** in 15% and 14% yields, respectively. In this case, the isomers were distinguished by a 2D NMR ^1H-^{13}C correlation experiment.[15] For the *N*-alkylated product **22** a 3-bond coupling interaction was observed between C-6 and H-1′. This was not observed for the *O*-alkylated product **23**.

Resolution of the racemic form of the diol **15** was achieved using an enzyme-catalysed acylation process. Reaction of the diol with vinyl acetate catalysed by Lipase PS (Amano) for 30 h at 30 °C afforded equal amounts of the acetates (+)-**25** and (−)-**26** (total yield 70%) and recovered dextrorotatory starting material (23%). Acetate (+)-**25** was treated with potassium carbonate in methanol at 0 °C to give the diol (+)-**15** (77% ee) while acetate (−)-**26** was deacylated to give the enantiomeric diol (>95% ee). Enantiomeric excesses were determined using chiral shift ^1H NMR spectroscopy.

The absolute configuration of the diol (−)-**15** was established using circular dichroism (CD) spectroscopy after conversion of the diol into the corresponding dibenzoate (Scheme 4). Thus, (−)-**15** was subjected to a Mitsunobu reaction using benzoic acid as the nucleophile to give the monobenzoate (−)-**27**, whereupon benzoylation of the free hydroxy group afforded the dibenzoate (−)-**28**. A CD spectrum (see Fig. 1) was obtained for the dibenzoate (−)-**28**. Comparison of this CD spectrum with previously published data[16,17] allows the 1,3 diol (−)-**15** to be assigned the absolute stereochemistry illustrated in Scheme 4.

Experimental

General experimental

Analytical grade solvents were used for flash chromatography; the abbreviation LP refers to the light fraction of light petroleum distilling between 40 and 60 °C.

Anhydrous diethyl ether and tetrahydrofuran were obtained by distillation from sodium benzophenone ketyl. Anhydrous dichloromethane was obtained by distillation from calcium hydride. Anhydrous dimethylformamide 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.

Thin layer chromatography (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.

Melting points 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}.

The CD spectrum of (−)-**28** was measured with a JASCO J600 spectropolarimeter at a concentration of 0.43 mg ml^{-1} in methanol with a 0.1 cm pathlength cell.

IR spectra were recorded as thin films or KBr discs on a Perkin-Elmer 881 grating spectrometer; absorption maxima were recorded in cm^{-1}. UV absorptions were recorded using 1 cm solution cells on a Phillips PU 8720 UV–visible scanning spectrophotometer; absorption maxima are recorded in nm.

^1H NMR spectra were recorded on Brüker AM250 (250 MHz), AM300 (300 MHz) or AM400 (400 MHz) spectrometers; chemical shifts (δ_H) are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad.

^{13}C NMR spectra were recorded on Brüker AM250 (62.9 MHz), AM300 (75.5 MHz) or AM400 (100.6 MHz) spectrometers; chemical shifts (δ_C) are reported in ppm downfield from tetramethylsilane.

Mass spectra were run on a Kratos Profile HV-3 high resolution instrument.

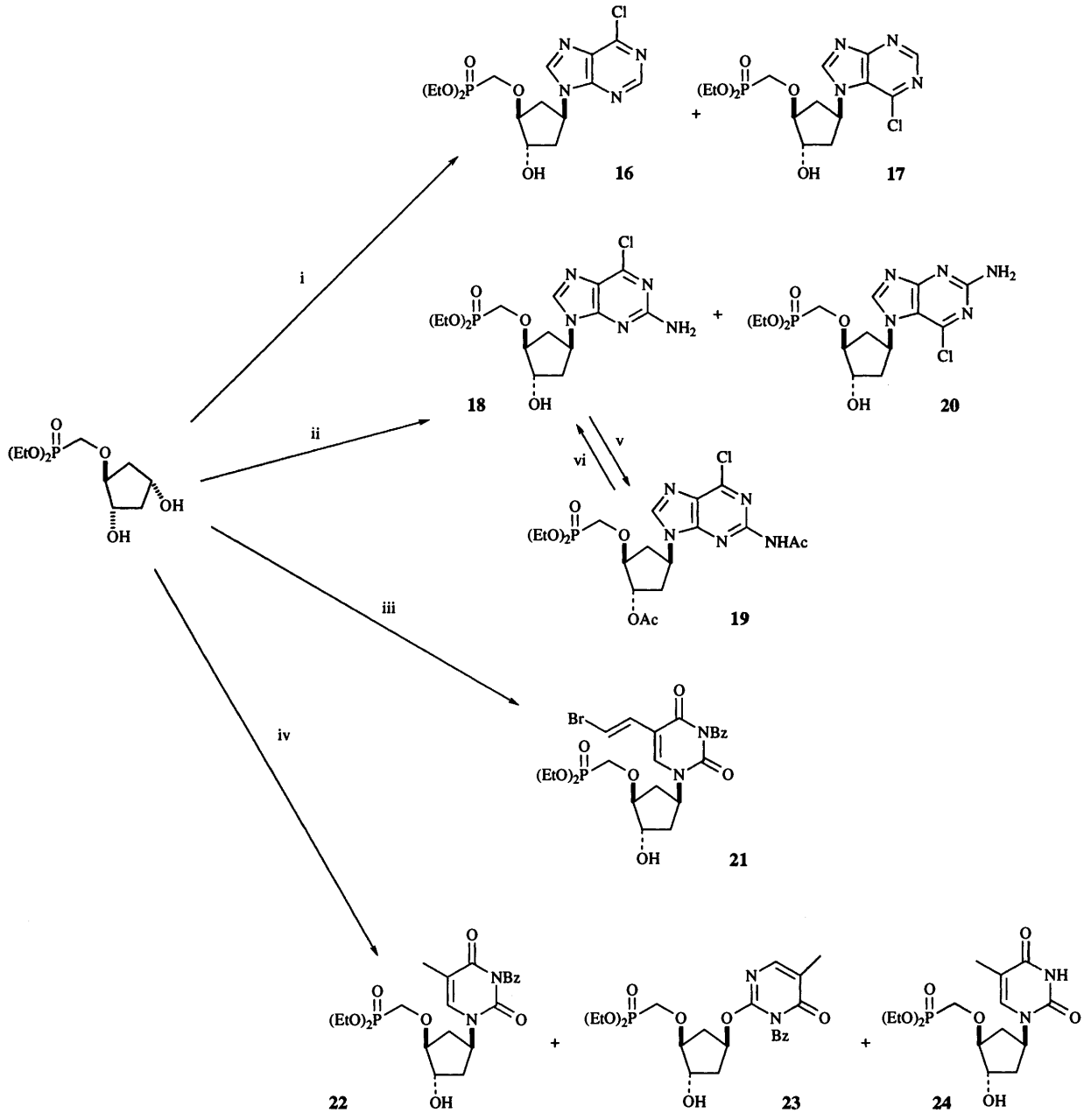
Enantiomeric excesses (ee's) were determined by ^1H NMR spectroscopy using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

3,4-Epoxycyclopentanol was obtained from Cookson Chemicals Ltd.

Experimental methods

(1β,2α,4α)-1,2,4-Triacetoxycyclopentane 12

To the epoxide **10** (1.00 g, 10.0 mmol) in water (73 cm^3) and DMSO (13 cm^3) was added potassium hydroxide (168 mg, 3.0 mmol). The mixture was refluxed for 3.5 h and then cooled to room temperature. The water was removed *in vacuo* and the DMSO solution azeotroped several times with toluene. Pyridine (20 cm^3) and DMAP (78 mg, 0.64 mmol) were then added to the DMSO solution. The mixture was cooled to 0 °C and acetic anhydride (6 cm^3, 64 mmol) added dropwise over 5 min. After 24 h the solvent was removed *in vacuo*. The residue was taken up in water (20 cm^3), and extracted with ethyl acetate (5 × 50 cm^3). The organic phase was washed with 2 M hydrochloric acid (2 × 20 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3) and brine (2 × 10 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to give the title product as a clear oil (1.37 g, 5.61 mmol, 56%); ν_{max}(film)/cm^{-1} 2992w (CH str.), 1745s (C=O), 1433m (CH def.), 1374s ($OCOCH_3$), 1231s (CO), 1074ms and 1043ms; δ_H(250 MHz; $CDCl_3$) 1.72 (1 H, ~dt, *J* 15.3, 4.0, 3-H), 2.00 (10 H, m, 5-H and 3 × $OCOCH_3$), 2.19 (1 H, dddd, *J* 14.6, 6.5, 4.5, 1.3, 5-H), 2.55 (1 H, dt, *J* 15.3, 7.5, 3-H), 5.01 (1 H, dt, *J* 7.4, 4.0, 1-H or 2-H), 5.17 [2 H, m, 4-H and 2-H (or 1-H)]; δ_C(63 MHz; $CDCl_3$) 20.83 (CH_3), 20.86 (CH_3), 20.97 (CH_3), 36.80 (CH_2), 36.87 (CH_2), 72.50 (CH), 76.72 (CH), 77.09 (CH), 169.95 (C), 170.02 (C), 170.35 (C); *m/z* 244 (M^+, 1%), 201 [(M − Ac)$^+$, 1.5], 185 [(M − OAc)$^+$, 25], 141 (53), 124 (72), 99 (89), 82 (100) and 54 (80) [Found (EI): M^+, 244.0953. $C_{11}H_{16}O_6$ requires 244.0947].



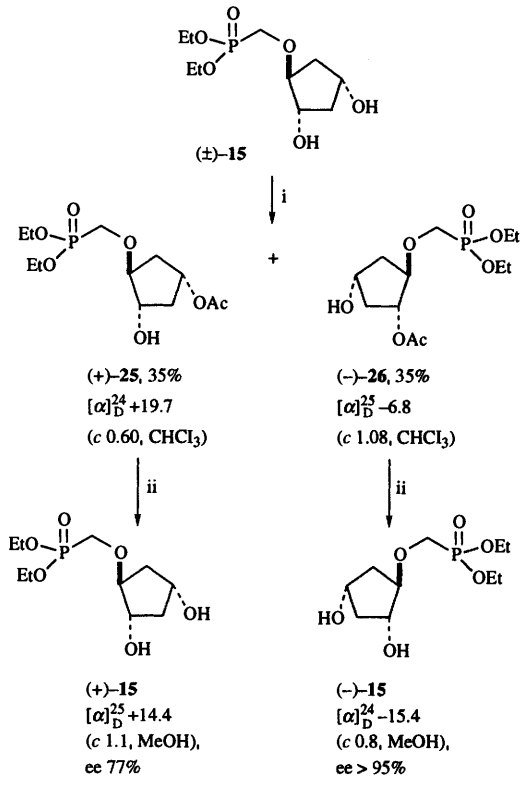
Scheme 2 *Reagents and conditions:* i, Ph_3P, 6-chloropurine, dioxane, DEAD, 70% and 12%; ii, Ph_3P, 2-amino-6-chloropurine, dioxane, DEAD, 38% and 3%; iii, Ph_3P, 3-benzoyl-5-bromovinyluracil, dioxane, DEAD, 60%; iv, Ph_3P, *N*-3-benzoylthymine, dioxane, DEAD, 49%, 15% and 14%.

(1β,2α,4α)-Cyclopentane-1,2,4-triol 11

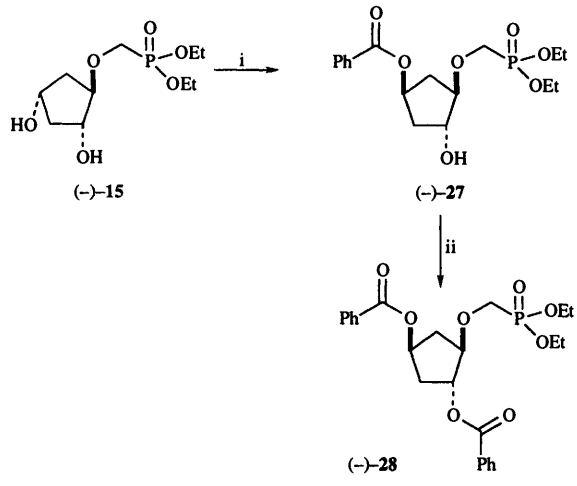
Potassium carbonate (224 mg, 1.62 mmol) was added to a cooled (0 °C) solution of the triacetate **12** (1.304 g, 5.34 mmol) in methanol (13 cm^3). The reaction mixture was allowed to warm to room temperature and stirred until reaction was complete (TLC evidence). Ether (25 cm^3) and hexane (25 cm^3) were added to the mixture which was then filtered through Celite. The solvents were removed *in vacuo* and the residue chromatograhed over silica (eluent 5:1; EtOAc–MeOH) to give the triol as a colourless oil (452 mg, 3.83 mmol, 72%); ν_{max}(film)/cm^{-1} 3361s, br (OH str.), 2936m (CH str.), 1352m (OH bend) and 1088ms (CO str.); δ_H(250 MHz; CD_3OD) 1.50 (1 H, dt, *J* 13.9, 5.5, 3-H), 1.89 (2 H, m, 2 × 5-H), 2.35 (1 H, dt, *J* 13.9, 7.0, 3-H), 3.85 (1 H, td, *J* 6.3, 4.4, 2-H), 4.05 (1 H, m, 1-H) and 4.28 (1 H, tt, *J* 6.9, 5.0, 4-H); δ_C(63 MHz; CD_3OD) 42.49 (CH_2), 42.62 (CH_2), 70.55 (CH), 78.64 (CH) and 78.96 (CH); *m/z* 118 (M^+, 1%), 100 [$(M - H_2O)^+$, 28], 82 [$(M - 2H_2O)^+$, 56], 73 (56) and 56 (100) [Found (EI): M^+ 118.0632. $C_5H_{10}O_3$ requires 118.0630].

(1α,5α,6β)-3,3-Di-*tert*-butyl-6-hydroxy-2,4-dioxa-3-silabicyclo-[3.2.1]octane 13

To the triol **11** (720 mg, 6.10 mmol) and 2,6-lutidine (1.94 g, 18.1 mmol) in dry DMF (88 cm^3) at 0 °C was added di-*tert*-butylsilyl ditriflate (2.45 cm^3, 6.72 mmol) in dry DMF (12 cm^3) over 1 h. After being stirred for an additional 30 min the reaction mixture was poured into ice cold water (530 cm^3). The solution was extracted with ether (4 × 150 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (95:5; $CHCl_3$–MeOH) of the residue gave the title product as a white crystalline solid (1.48 g, 5.74 mmol, 94%); mp 58–59 °C; R_F 0.52 (9:1; $CHCl_3$–MeOH); ν_{max}(film)/cm^{-1} 3441m, br (OH str.), 2940, 2862 both s (CH str.), 1478s, 1049s (CO) and 981s; δ_H(250 MHz; $CDCl_3$) 1.00 (9 H, s, Bu^t), 1.04 (9 H, s, Bu^t), 1.64 (1 H, ddd, *J* 15.4, 4.7, 2.6, 7-H), 1.78 (1 H, dt, *J* 13.8, 3.1, 8β-H), 2.05 (1 H, br, OH), 2.39 (1 H, br d, *J* 13.8, 8α-H), 2.64 (1 H, ddd, *J* 15.4, 6.8, 2.7, 7-H), 4.24 (1 H, br s, 1-H or 5-H), 4.52 (1 H, dt, *J* 6.8, 2.0, 6-H) and 4.61 (1 H, ~td, *J* 3.0, 1.3, 5-H or 1-H); δ_C(63 MHz; $CDCl_3$) 20.55 (C),



Scheme 3 *Reagents and conditions:* i, Lipase PS (Amano), vinyl acetate. 30 °C, 30 h; ii, K_2CO_3, MeOH, 0 °C, 3 h



Scheme 4 *Reagents and conditions:* i, Ph_3P, $PhCO_2H$, DEAD, THF, 72%; ii, PhCOCl, pyridine, DMAP, 39%

20.66 (C), 27.67 (3 × CH_3), 28.42 (3 × CH_3), 37.82 (CH_2), 44.64 (CH_2), 75.39 (CH), 77.12 (CH) and 81.04 (CH); *m/z* 258 (M^+, 0.2%), 201 [(M − Bu'), 33], 159 [(Bu'$_2$SiOH)$^+$, 100], 115 (38), 77 (74) and 57 (36) [Found (EI): M^+ 258.1649. $C_{13}H_{26}O_3Si$ requires 258.1651].

(1α,5α,6β)-3,3-Di-*tert*-butyl-6-(diethylphosphono)methoxy-2,4-dioxa-3-silabicyclo[3.2.1]octane 14

To the alcohol **13** (1.78 g, 6.90 mmol) in THF (22 cm^3) at −25 °C was added butyllithium (2.5 M solution in hexanes; 3.3 cm^3, 8.25 mmol) an internal reaction temperature <−20 °C being maintained. The reaction mixture was stirred at −25 °C for 30 min. To this solution was added diethylphosphonomethyl triflate (2.83 g, 9.43 mmol) in THF (14 cm^3), again an internal reaction temperature <−20 °C being maintained. The reaction mixture was stirred at −25 °C for an additional 30 min. Saturated aqueous sodium hydrogen carbonate (90 cm^3) was carefully added to the reaction mixture which was then warmed to

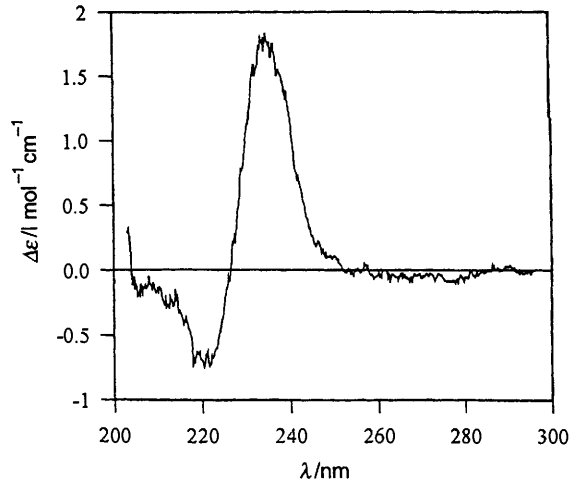


Fig. 1 CD spectrum of the dibenzoate (−)-**28**

room temperature, and extracted with ether (4 × 100 cm^3). The combined extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* and the residue was flash chromatographed over silica [eluent EtOAc–LP (4:1)] to yield the title product as a colourless oil (2.62 g, 6.42 mmol, 93%); ν_{max}(film)/cm^{-1} 2940ms (CH str.), 2862ms (CH str.), 1479m (CH def.), 1260m (P=O), 1109s (CO str.), 1055s (SiO), 1028s (PO-alkyl), 983s, 824ms, 765m and 641ms; δ_H(300 MHz; $CDCl_3$) 1.01 (9 H, s, Bu'), 1.04 (9 H, s, Bu'), 1.33 (6 H, t, *J* 7.1, 2 × CH_3CH_2O), 1.69 (1 H, ddd, *J* 13.8, 2.9, 2.5, 8β-H), 1.72 (1 H, ddd, *J* 15.4, 4.8, 2.6, 7β-H), 2.39 (1 H, br d, *J* 13.8, 8α-H), 2.59 (1 H, ddd, *J* 15.4, 6.8, 2.8, 7α-H), 3.81 (2 H, m, PCH_2O), 4.14 (5 H, m, 2 × CH_3CH_2O and 6-H), 4.41 (1 H, m, 5-H) and 4.59 (1 H, m, 1-H); δ_C(75 MHz; $CDCl_3$) 16.44 (CH_3, d, $^3J_{CP}$ 5.7, 2 × CH_3CH_2O), 20.53 (C), 20.65 (C), 27.63 (3 × CH_3, Bu'), 28.38 (3 × CH_3, Bu'), 38.17 (CH_2), 42.37 (CH_2), 62.41 (CH_2, d, $^2J_{CP}$ 6.7, CH_3CH_2O), 62.45 (CH_2, d, $^2J_{CP}$ 6.7, CH_3CH_2O), 64.06 (CH_2, d, $^1J_{CP}$ 168, PCH_2O), 74.91 (CH), 76.76 (CH) and 87.27 (CH, d, $^3J_{CP}$ 11.9, 6-C); *m/z* 408 (M^+, 0.2%), 351 [(M − Bu')$^+$, 100], 229 (98) and 57 (Bu'$^+$, 39) [Found (EI): M^+ 408.2109. $C_{18}H_{37}O_6PSi$ requires 408.2097].

(1α,3α,4β)-4-(Diethylphosphono)methoxycyclopentane-1,3-diol (±)-15

Ammonium fluoride (3.8 g, 103 mmol) was added to a stirred solution of the silyl ether **14** (2.62 g, 6.42 mmol) in methanol (170 cm^3) and the reaction mixture was stirred at room temperature for 24 h. Silica (40 g) was added to the mixture and the solvent removed *in vacuo*. The silica was packed onto the top of a column and eluted with LP–EtOAc (1:1) followed by EtOAc–MeOH (5:1) to give the title product as a colourless oil (1.44 g, 5.37 mmol, 84%); R_F 0.30 [EtOAc–MeOH (5:1)]; ν_{max}(film)/cm^{-1} 3348s (OH str.), 2984s (CH str.), 2938s (CH str.), 1239s (P=O) and 1094s (CO str.); δ_H(300 MHz; CD_3OD) 1.34 (6 H, t, *J* 7, 2 × CH_3CH_2O), 1.53 (1 H, dt, *J* 13.6, 6.0, 2-H), 1.94 (2 H, m, 2 × 5-H), 2.32 (1 H, dt, *J* 13.6, 6.8, 2-H), 3.90 (3 H, m, PCH_2O and 4-H), 4.02 (1 H, td, *J* 6.4, 4.0, 3-H), 4.16 (4 H, m, 2 × CH_3CH_2O) and 4.24 (1 H, quin, *J* 6.2, 1-H); δ_C(75 MHz; CD_3OD) 16.69 (CH_3, d, $^3J_{CP}$ 5.7, 2 × CH_3CH_2O), 39.99 (CH_2, 5-C), 42.60 (CH_2, 2-C), 63.99 (CH_2, d, $^1J_{CP}$ 167.7, PCH_2O), 64.12 (CH_2, d, $^2J_{CP}$ 6.7, CH_3CH_2O), 64.14 (CH_2, d, $^2J_{CP}$ 6.7, CH_3CH_2O), 70.28 (CH, 1-C), 76.67 (CH, 3-C) and 89.37 (CH, d, $^3J_{CP}$ 12.7, 4-C); *m/z* 269 [(M + H)$^+$, 0.4%], 152 {[(EtO)$_2$(P=O)CH$_3$]$^+$, 85}, 125 (100) and 97 (44) [Found (EI): (M + H)$^+$ 269.1160. $C_{10}H_{22}O_6P$ requires 269.1154].

General procedure for introducing the bases under Mitsunobu conditions

A solution of DEAD (117 μl, 0.744 mmol) in dioxane (1.1 cm^3) was added dropwise to a stirred suspension of the diol **15** (100

mg, 0.373 mmol), triphenylphosphine (196 mg, 0.748 mmol) and one of the nucleobases (0.746 mmol) in dioxane (3.6 cm^3) at room temperature. The reaction mixture was stirred until complete (TLC evidence, typically 24 h) after which it was evaporated *in vacuo*. The residue was flash chromatographed to yield the products.

9-[(1′β,3′α,4′β)-4′-(Diethylphosphono)methoxy-3′-hydroxycyclopentyl]-6-chloropurine 16 and the *N*-7 isomer 17

The above standard procedure (double quantity) was followed with the diol **15** (200 mg, 0.746 mmol) and 6-chloropurine (230 mg, 1.492 mmol). Flash chromatography eluting with EtOAc–MeOH (9:1) yielded the *N*-9 isomer **16** (205 mg, 0.507 mmol, 70%); R_F 0.36 [EtOAc–MeOH (5:1)]; λ_{max}(MeOH)/nm 266 (ε/1000 cm^3 mol^{-1} 8548); ν_{max}(film)/cm^{-1} 3372br, s (OH str.), 2986ms (CH str.), 1591s (C=N), 1559s (C=N), 1397s (CH_3 sym. def.), 1236s (P=O), 1025s (PO-alkyl), 955s and 636s; δ_H(400 MHz; CD_3OD) 1.34 (6 H, t, *J* 7, 2 × CH_3CH_2O), 2.19 (1 H, m, 5′-H), 2.42 (2 H, m, 2 × 2′-H), 2.81 (1 H, ddd, *J* 15, 9, 5.8, 5′-H), 4.00 (3 H, m, 4′-H and PCH_2O), 4.19 (4 H, m, 2 × CH_3CH_2O), 4.46 (1 H, m, 3′-H), 5.39 (1 H, dtd, *J* 9, 8.1, 5.5, 1′-H), 8.66 (1 H, s, 8-H) and 8.72 (1 H, s, 2-H); δ_C(100.6 MHz; CD_3OD) 15.39 (CH_3, d, $^3J_{CP}$ 5.4, 2 × CH_3CH_2O), 36.31 (CH_2, 5′-C), 39.12 (CH_2, 2′-C), 53.08 (CH, 1′-C), 62.58 (CH_2, d, $^1J_{CP}$ 168, PCH_2O), 62.82 (CH_2, d, $^2J_{CP}$ 6.7, 2 × CH_3CH_2O), 74.15 (CH, 3′-C), 87.56 (CH, d, $^3J_{CP}$ 12.6, 4′-C), 131.09 (C), 145.69 (CH), 149.75 (C), 151.35 (CH) and 151.84 (C); *m/z* 404 (M^+, 6%), 253 (100), 152 {$[(EtO)_2(P{=}O)CH_3]^+$, 86} and 125 (100) [Found (EI): M^+, 404.1019. $C_{15}H_{22}{}^{35}ClN_4O_5P$ requires 404.1016]. Further elution yielded the *N*-7 isomer **17** (35 mg, 0.087 mmol, 12%); R_F 0.25 [EtOAc–MeOH (5:1)]; λ_{max}(MeOH)/nm 270 (ε/1000 cm^3 mol^{-1} 10874); ν_{max}(film)/cm^{-1} 3374br, ms (OH str.), 2985ms (CH str.), 1595s (C=N), 1536s (C=N), 1385s (CH_3 sym. def.), 1260s (P=O), 1097s (C–O), 1032s (PO-alkyl), 976s and 754ms (C–Cl); δ_H(400 MHz; CD_3OD) 1.34 (6 H, m, 2 × CH_3CH_2O), 2.21 (1 H, m, 5′-H), 2.45 (2 H, m, 2 × 2′-H), 2.87 (1 H, ddd, *J* 15, 9, 6, 5′-H), 3.99 (2 H, m, PCH_2O), 4.00 (1 H, m, 4′-H), 4.17 (4 H, m, 2 × CH_3CH_2O), 4.45 (1 H, m, 3′-H), 5.75 (1 H, dtd, *J* 9, 7.8, 4.4, 1′-H), 8.77 (1 H, s, 2-H) and 8.87 (1 H, s, 8-H); δ_C(100.6 MHz; CD_3OD) 15.39 (CH_3, d, $^3J_{CP}$ 5.7, 2 × CH_3CH_2O), 37.32 (CH_2, 5′-C), 40.40 (CH_2, 2′-C), 55.85 (CH, 1′-C), 62.54 (CH_2, d, $^1J_{CP}$ 168, PCH_2O), 62.80 (CH_2, d, $^2J_{CP}$ 6.5, 2 × CH_3CH_2O), 74.12 (CH, 3′-C), 87.68 (CH, d, $^3J_{CP}$ 12, 4′-C), 143.12 (C), 148.24 (CH), 151.34 (C), 151.48 (CH) and 161.31 (C); *m/z* 404 (M^+, 2%), 253 (52), 204 (45), 155 [$(B + H)^+$, 61], 152 {$[(EtO)_2(P{=}O)CH_3]^+$, 60}, 125 (88) and 97 (100) [Found (EI): M^+, 404.0996. $C_{15}H_{22}{}^{35}ClN_4O_5P$ requires 404.1016].

9-[(1′β,3′α,4′β)-4′-(Diethylphosphono)methoxy-3′-hydroxycyclopentyl]-2-amino-6-chloropurine 18 and the *N*-7 isomer 20

The above standard procedure was followed with the diol **15** (100 mg, 0.373 mmol) and 2-amino-6-chloropurine (126 mg, 0.746 mmol). Flash chromatography eluting with [CH_2Cl_2–MeOH (95:5)] yielded the *N*-9 isomer **18** (60 mg, 0.143 mmol, 38%); R_F 0.25 [EtOAc–MeOH (5:1)]; λ_{max}(MeOH)/nm 310 (ε/1000 cm^3 mol^{-1} 10338); ν_{max}(film)/cm^{-1} 3333br, s (OH str.), 2929m (CH str.), 1611s (C=N), 1559s (C=N), 1232s (P=O), 1047s (CO) and 1022s (PO-alkyl); δ_H(400 MHz; CD_3OD) 1.34 (6 H, t, *J* 7, 2 × CH_3CH_2O), 2.11 (1 H, m, 5′-H), 2.33 (2 H, m, 2 × 2′-H), 2.72 (1 H, ddd, *J* 15, 9, 6, 5′-H), 3.95 (1 H, m, 4′-H), 3.97 (2 H, m, PCH_2O), 4.18 (4 H, m, 2 × CH_3CH_2O), 4.42 (1 H, m, 3′-H), 5.14 (1 H, dtd, *J* 9, 8.1, 5.5, 1′-H) and 8.17 (1 H, s, 8-H); δ_C(100.6 MHz; CD_3OD) 15.39 (CH_3, d, $^3J_{CP}$ 6, 2 × CH_3CH_2O), 36.04 (CH_2), 38.83 (CH_2), 52.16 (CH, 1′-C), 62.54 (CH_2, d, $^1J_{CP}$ 168, PCH_2O), 62.81 (CH_2, d, $^2J_{CP}$ 6, 2 × CH_3CH_2O), 74.20 (CH, 3′-C), 87.56 (CH, d, $^3J_{CP}$ 12.5, 4′-C), 123.69 (C), 141.84 (CH), 150.03 (C), 153.78 (C) and 160.04 (C); *m/z* 419 (M^+, 7%), 268 (81), 251 [$(M - B)^+$, 56], 170 [$(BH + H)^+$, 100] and 125 (65) [Found (EI): M^+, 419.1128. $C_{15}H_{23}{}^{35}ClN_5O_5P$ requires 419.1125]. Further elution yielded the unstable *N*-7 isomer **20** (5 mg, 0.012 mmol, 3%), R_F 0.12 [EtOAc–MeOH (5:1)]; λ_{max}(MeOH)/nm 320 (ε/1000 cm^3 mol^{-1} 5000); δ_H(300 MHz; CD_3OD) 1.34 (6 H, t, *J* 7, 2 × CH_3CH_2O), 2.13 (1 H, m, 5′-H), 2.37 (2 H, m, 2 × 2′-H), 2.82 (1 H, m, 5′-H), 3.98 (2 H, m, PCH_2O), 4.17 (4 H, m, 2 × CH_3CH_2O), 4.41 (1 H, m, 3′-H or 4′-H), 4.53 (1 H, m, 4′-H or 3′-H), 5.53 (1 H, m, 1′-H) and 8.46 (1 H, s, 8-H).

9-[(1′β,3′α,4′β)-4′-(Diethylphosphono)methoxy-3′-acetoxycyclopentyl]-2-acetylamino-6-chloropurine 19

A mixture of the diol **15**, 2-amino-6-chloropurine, and the *N*-9 isomer **18** was acetylated under standard conditions (acetic anhydride, pyridine, DMAP). Flash chromatography of the product eluting with [EtOAc–MeOH (95:5)] yielded the diacetate **19**; ν_{max}(film)/cm^{-1} 1735s (C=O), 1571s, 1372s, 1239s (P=O) and 1025s (PO-alkyl); δ_H(400 MHz; $CDCl_3$) 1.35 (3 H, t, *J* 7, CH_3CH_2O), 1.36 (3 H, t, *J* 7, CH_3CH_2O), 2.09 (3 H, s, CH_3COO), 2.18 (1 H, m, 5′-H), 2.49 (5 H, m, $NHCOCH_3$ and 2 × 2′-H), 2.74 (1 H, ddd, *J* 15.5, 10, 6, 5′-H), 3.95 (2 H, m, PCH_2O), 4.09 (1 H, m, 4′-H), 4.19 (4 H, m, 2 × CH_3CH_2O), 5.25 (1 H, dtd, *J* 9.5, 8.1, 5, 1′-H), 5.36 (1 H, m, 3′-H), 8.28 (1 H, s, 8-H) and 8.51 (1 H, s, br, NH); δ_C(100.6 MHz; $CDCl_3$) 16.51 (CH_3, d, $^3J_{CP}$ 5.5, CH_3CH_2O), 16.53 (CH_3, d, $^3J_{CP}$ 5.5, CH_3CH_2O), 21.04 (CH_3), 25.07 (CH_3), 37.37 (CH_2), 37.39 (CH_2), 52.72 (CH), 62.60 (CH_2, d, $^2J_{CP}$ 6.7, CH_3CH_2O), 62.66 (CH_2, d, $^2J_{CP}$ 6.9, CH_3CH_2O), 63.59 (CH_2, d, $^1J_{CP}$ 169, PCH_2O), 76.61 (CH), 84.55 (CH, d, $^3J_{CP}$ 11, 4′-C), 128.21 (C), 143.77 (CH), 151.18 (C), 151.89 (C), 152.62 (C) and 170.00 (2 × C=O); *m/z* 503 (M^+, 1%), 169 (42), 152 {$[(EtO)_2(P{=}O)CH_3]^+$, 58}, 125 (85), 81 (85) and 55 (100) [Found (EI): M^+, 503.1325. $C_{19}H_{27}{}^{35}ClN_5O_7P$ requires 503.1337].

1-[(1′β,3′α,4′β)-4′-(Diethylphosphono)methoxy-3′-hydroxycyclopentyl]-3-*N*-benzoylthymine 22, the *O*-2 isomer 23 and the debenzoylated product 24

The above standard procedure was followed using the diol **15** (100 mg, 0.373 mmol), and 3-*N*-benzoylthymine (171 mg, 0.746 mmol). Flash chromatography of the product eluting with [$CHCl_3$–MeOH (95:5)] yielded the *O*-2 isomer **23** (26 mg, 0.054 mmol, 15%), R_F 0.21 [$CHCl_3$–MeOH (95:5)]; ν_{max}(film)/cm^{-1} 3386br, m (OH str.), 2985m, (CH str.), 1744s (C=O), 1611ms (Ar), 1554ms (Ar), 1440s, 1242s (P=O), 1157s, (CO) and 1056s (PO-alkyl); δ_H(400 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7, CH_3CH_2O), 1.34 (3 H, t, *J* 7, CH_3CH_2O), 1.87 (1 H, m, 5′-H), 2.05 (1 H, dt, *J* 14.5, 7.5, 2′-H), 2.14 (3 H, s, Me), 2.27 (1 H, ddd, *J* 14.5, 7.5, 3.5, 2′-H), 2.67 (1 H, dt, *J* 14.5, 7.5, 5′-H), 3.78 (1 H, m, 4′-H), 3.91 (2 H, m, PCH_2O), 4.16 (4 H, m, 2 × CH_3CH_2O), 4.41 (1 H, td, *J* 7.5, 5.5, 3′-H), 5.30 (1 H, m, 1′-H), 7.54 (2 H, m, 2 × *m*-H), 7.66 (1 H, m, *p*-H), 8.17 (2 H, m, 2 × *o*-H) and 8.37 (1 H, s, 6-H); δ_C(100.6 MHz; $CDCl_3$) 12.12 (CH_3), 16.42 (CH_3, d, $^3J_{CP}$ 5, CH_3CH_2O), 16.47 (CH_3, d, $^3J_{CP}$ 5, CH_3CH_2O), 36.59 (CH_2, 5′-C), 38.14 (CH_2, 2′-C), 62.48 (CH_2, d, $^2J_{CP}$ 7, CH_3CH_2O), 63.14 (CH_2, d, $^2J_{CP}$ 7, CH_3CH_2O), 64.80 (CH_2, d, $^1J_{CP}$ 166, PCH_2O), 74.44 (CH, 1′-C), 75.55 (CH, 3′-C), 88.89 (CH, d, $^3J_{CP}$ 7, 4′-C), 115.59 (C, 5-C), 128.39 [C (Ph)], 128.74 [2 × CH (Ph)], 130.44 [2 × CH (Ph)], 134.23 [CH (Ph)], 161.73 (CH, 6-C), 163.15 [C, (C=O)Ph], 163.62 (C, 2-C) and 165.32 (C=O, 4-C); *m/z* 480 (M^+, 0.3%), 355 (11), 169 (24), 125 (22) and 105 [$(PhCO)^+$, 100] [Found (EI): M^+, 480.1671. $C_{22}H_{29}N_2O_8P$ requires 480.1662]. Further elution yielded the *N*-1 isomer **22** (88 mg, 0.183 mmol, 49%); R_F 0.16 [$CHCl_3$–MeOH (95:5)]; ν_{max}(film)/cm^{-1} 3392br, m (OH str.), 2987m (CH str.), 1745s (C=O), 1695s (C=O), 1656s (C=O), 1443ms, 1251s (P=O), 1026s (PO-alkyl) and 761ms (monosub. benzene ring); δ_H(400 MHz; $CDCl_3$) 1.35 (6 H, m, 2 × CH_3CH_2O), 1.74 (1 H, m, 5′-H), 1.97 (4 H, m, Me and 2′-H), 2.20 (1 H, ddd, *J* 14, 8.5, 2, 2′-H), 2.61 (1 H, ddd, *J* 15, 10, 6, 5′-H), 2.71 (1 H, br, OH), 3.84 (1 H, m, 4′-H), 3.87 (2 H, m, PCH_2O), 4.17 (4 H, m, 2 × CH_3CH_2O), 4.35 (1 H, m, 3′-H), 5.30 (1 H, dtd, *J* 10, 8.5, 5.5, 1′-H), 7.48 (3 H, m, 2 × *m*-H

and 6-H), 7.63 (1 H, m, *p*-H) and 7.90 (2 H, m, 2 × *o*-H); δ_H(100.6 MHz; $CDCl_3$) 12.54 (CH_3), 16.51 (CH_3, d, $^3J_{CP}$ 5.6, 2 × CH_3CH_2O), 35.89 (CH_2, 5'-C), 38.26 (CH_2, 2'-C), 52.76 (CH, 1'-C), 62.66 (CH_2, d, $^2J_{CP}$ 7, CH_3CH_2O), 62.76 (CH_2, d, $^2J_{CP}$ 8, CH_3CH_2O), 63.76 (CH_2, d, $^1J_{CP}$ 169, PCH_2O), 74.48 (CH, 3'-C), 87.40 (CH, d, $^3J_{CP}$ 11, 4'-C), 111.77 (C, 5-C), 129.12 [2 × CH (Ph)], 130.44 [2 × CH (Ph)], 131.70 [C (Ph)], 134.96 [CH (Ph)], 137.50 (CH, 6-C), 150.11 (C=O, 2-C), 162.80 (C=O, 4-C) and 169.32 [C, (C=O)Ph]; *m/z* 480 (M^+, 4%), 152 {$[(EtO)_2(P=O)CH_3]^+$, 36}, 125 (39) and 105 [$(PhCO)^+$, 100] [Found (EI): M^+, 480.1664. $C_{22}H_{29}N_2O_8P$ requires 480.1662]. Further elution yielded the debenzoylated isomer **24** (20 mg, 0.053 mmol, 14%); ν_{max}(film)/cm^{-1} 3380br, ms (OH str.), 2928s (CH str.), 1666s (C=O), 1578s (C=O), 1291ms (P=O), 1237ms (C–O), 1028s (PO-alkyl) and 970ms; δ_H(400 MHz; CD_3OD) 1.32 (6 H, t, *J* 7, 2 × CH_3CH_2O), 1.87 (1 H, dt, *J* 15, 3.5, 5'-H), 1.92 (3 H, d, *J* 0.9, Me), 2.11 (2 H, m, 2 × 2'-H), 2.58 (1 H, dt, *J* 15, 7, 5'-H), 3.82 (1 H, dt, *J* 7, 3.5, 4'-H), 3.92 (2 H, m, PCH_2O), 4.16 (4 H, m, 2 × CH_3CH_2O), 4.28 (1 H, td, *J* 5.5, 3.5, 3'-H), 5.40 (1 H, tt, *J* 6.5, 3.5, 1'-H), 7.57 (1 H, d, *J* 0.9, 6-H); δ_C(100.6 MHz; $CDCl_3$) 12.38 (CH_3), 16.44 (CH_3, d, $^3J_{CP}$ 6, 2 × CH_3CH_2O), 36.26 (CH_2), 38.71 (CH_2), 62.68 (CH_2, d, $^2J_{CP}$ 7, CH_3CH_2O), 62.98 (CH_2, d, $^2J_{CP}$ 7, CH_3CH_2O), 64.21 (CH_2, d, $^1J_{CP}$ 167, PCH_2O), 75.62 (CH), 76.06 (CH), 88.32 (CH, d, $^3J_{CP}$ 9, 4'-C), 117.64 (C), 150.95 (CH), 155.07 (C) and 164.46 (C); *m/z* 376 (M^+, 2%), 225 (22), 169 (47), 152 {$[(EtO)_2(P=O)CH_3]^+$, 79}, 125 (B^+, 100) and 97 (51) [Found (EI): M^+, 376.1394. $C_{15}H_{25}N_2O_7P$ requires 376.1399].

1-[(1'β,3'α,4'β)-4'-(Diethylphosphono)methoxy-3'-hydroxycyclopentyl]-3-*N*-benzoyl-5-(2-bromovinyl)uracil 21

To a stirred solution of triphenylphosphine (242.3 mg, 0.925 mmol) in anhydrous THF (4 cm^3) at −78 °C was added distilled dimethyl azodicarboxylate (135 mg, 0.925 mmol) dropwise over 10 min under an argon atmosphere. After 30 min, a solution of (1α,3α,4β)-4-(diethylphosphono)methoxycyclopentane-1,3-diol **15** (100 mg, 0.37 mmol) and 3-benzoyl-5-bromovinyluracil (238 mg, 0.74 mmol) in THF (4 cm^3) was added dropwise over 15 min to the stirred white slurry at −78 °C. The mixture was stirred for 20 min at −78 °C and then allowed to warm to ambient temperature at which it was kept for 3 h. Solvent was removed *in vacuo* at 30 °C, and the residue was chromatographed [EtOAc–MeOH (95:5)] to afford the title compound (129 mg, 0.226 mmol, 60%) as a thick oil; ν_{max}(film)/cm^{-1} 3360, 2992, 1750, 1702, 1665, 1448, 1237 and 1026; δ_H(300 MHz; CD_3OD) 1.37 (6 H, m, 2 × CH_3CH_2O), 1.90 (1 H, m, 5'-H), 2.15 (2 H, m, 2 × 2'-H), 2.62 (1 H, m, 5'-H), 3.90 (1 H, m, 4'-H), 3.99 (2 H, m, PCH_2O), 4.23 (4 H, m, 2 × CH_3CH_2O), 4.35 (1 H, m, 3'-H), 5.30 (1 H, m, 1'-H), 6.95 (1 H, d, *J* 13.5, HC=), 7.34 (1 H, d, *J* 13.5, HC=), 7.54 (2 H, m, 2 × *m*-H), 7.71 (1 H, m, *p*-H), 7.95 (1 H, s, 6-H) and 7.96 (2 H, m, 2 × *o*-H); δ_C(75.5 MHz; CD_3OD) 16.8 (CH_3CH_2O), 16.9 (CH_3CH_2O), 36.5 (CH_2, 5'-C), 39.4 (CH_2, 2'-C), 55.5 (CH, 1'-C), 63.0 (CH_2, d, $^1J_{CP}$ 168, PCH_2O), 64.0 (CH_3CH_2O), 64.1 (CH_3CH_2O), 75.0 (CH, 3'-C), 88.5 (CH, 4'-C), 109.5 (C=CHBr), 112.5 (C, 5-C), 130.3 [2 × CH(Ph)], 131.4 [C(Ph)], 131.5 [2 × CH(Ph)], 132.8 [CH(Ph)], 136.3 (*C*=CHBr), 142.5 (CH, 6-C), 150.4 (C=O, 2-C), 162.1 (C=O, 4-C) and 170.1 [C, (C=O)Ph]; δ_P (121.5 MHz; CD_3OD) 23.5 [Found (EI): $(M + H)^+$, 571.0850. $C_{23}H_{29}BrN_2O_8P$ requires 571.0845].

Enzyme resolution of (±)-(1α,3α,4β)-4-(diethylphosphono)-methoxycyclopentane-1,3-diol 15

Lipase PS Amano (170 mg) was added to a solution of the diol **15** (190 mg, 0.706 mmol) in vinyl acetate (15 cm^3) and the mixture was stirred in an orbital shaker (200 rev min^{-1}) at 30 °C for 30 h. The enzyme was then filtered off and the residue was washed with ethyl acetate. The combined filtrate and washings were concentrated *in vacuo* and the residue was flash chromatographed over silica [eluent MeOH–CH_2Cl_2 (5:95)] to yield (1*R*,3*S*,4*S*)-1-acetoxy-4-(diethylphosphono)methoxycyclopentan-3-ol (+)-**25** as a colourless oil (77 mg, 0.248 mmol, 35%); $[\alpha]_D^{24}$ +19.7 (*c* 0.60, $CHCl_3$); ν_{max}(film)/cm^{-1} 3399m, br (OH str.), 2985m (CH str.), 1738s (C=O), 1247s (P=O) and 1026s (PO-alkyl); δ_H(300 MHz; $CDCl_3$) 1.32 (3 H, t, *J* 7, CH_3CH_2O), 1.34 (3 H, t, *J* 7, CH_3CH_2O), 1.69 (1 H, m, 2-H), 2.02 (5 H, m, 2 × 5-H and CH_3CO), 2.46 (1 H, dt, *J* 14.5, 7.5, 2-H), 3.87 (2 H, m, PCH_2O), 3.92 (1 H, m, 4-H), 4.15 (5 H, m, 2 × CH_3CH_2O and 3-H) and 5.10 (1 H, tt, *J* 7.3, 3.7, 1-H); δ_C (75 MHz; $CDCl_3$) 16.43 (CH_3, d, $^3J_{CP}$ 7, 2 × CH_3CH_2O), 16.47 (CH_3CH_2O), 21.17 (CH_3CO), 36.71 (CH_2), 38.45 (CH_2), 62.46 (CH_2, d, $^2J_{CP}$ 6.8, CH_3CH_2O), 62.88 (CH_2, d, $^2J_{CP}$ 6.6, CH_3CH_2O), 64.71 (CH_2, d, $^1J_{CP}$ 167, PCH_2O), 72.13 (CH), 75.68 (CH), 88.87 (CH, d, $^3J_{CP}$ 8.1, 3-C) and 170.53 (C=O); *m/z* 310 (M^+, 0.2%), 152 {$[(EtO)_2(P=O)CH_3]^+$, 100}, 125 (79) and 97 (25) [Found (EI): M^+, 310.1187. $C_{12}H_{23}O_7P$ requires 310.1181]. Further elution afforded (1*S*,3*R*,4*R*)-3-acetoxy-4-(diethylphosphono)methoxycyclopentan-1-ol (−)-**26** as a colourless oil (76 mg, 0.245 mmol, 35%); $[\alpha]_D^{25}$ −6.8 (*c* 1.08, $CHCl_3$); ν_{max}(film)/cm^{-1} 3392s, br (OH str.), 2978s (CH str.), 1730s (C=O), 1233s (P=O) and 1025s (PO-alkyl); δ_H(300 MHz; $CDCl_3$) 1.32 (6 H, t, *J* 7, 2 × CH_3CH_2O), 1.69 (1 H, dtt, *J* 14.7, 3.6, 1.0, 2-H), 2.04 (5 H, m, 2 × 5-H and CH_3CO), 2.45 (1 H, dt, *J* 14.7, 7.0, 2-H), 3.84 (2 H, m, PCH_2O), 4.14 (5 H, m, 2 × CH_3CH_2O and 4-H), 4.41 (1 H, m, 1-H) and 5.04 (1 H, dt, *J* 7.0, 3.0, 3-H); δ_C(75 MHz; $CDCl_3$) 16.41 (CH_3, d, $^2J_{CP}$ 5.5, 2 × CH_3CH_2O), 21.17 (CH_3CO), 39.71 (CH_2), 40.51 (CH_2), 62.41 (CH_3CH_2O), 62.49 (CH_3CH_2O), 63.77 (CH_2, d, $^1J_{CP}$ 168, PCH_2O), 71.23 (CH), 78.01 (CH), 85.87 (CH, d, $^3J_{CP}$ 11.8, 4-C) and 170.25 (C=O); *m/z* 310 (M^+, 0.4%), 232 (39), 152 {$[(EtO)_2(P=O)CH_3]^+$, 100}, 125 (65) [Found (EI): M^+, 310.1175. $C_{12}H_{23}O_7P$ requires 310.1181]. Treatment of (+)-**25** (20 mg, 0.0645 mmol) with potassium carbonate (4 mg, 0.029 mmol) in methanol (1 cm^3) at 0 °C for 6 h afforded an oil which was purified by flash column chromatography [EtOAc–MeOH (5:1)] to yield the (1*R*,3*S*,4*S*)-diol (+)-**15** (15 mg, 0.056 mmol, 87%) as a colourless oil; $[\alpha]_D^{25}$ +14.4 (*c* 1.1, MeOH) (ee 77%). A similar treatment of (−)-**26** (20 mg, 0.0645 mmol) yielded the (1*S*,3*R*,4*R*)-diol (−)-**15** (17 mg, 0.0634 mmol, 98%); $[\alpha]_D^{24}$ −15.4 (*c* 0.8, MeOH) (ee >95%). Spectral data for both enantiomers were identical with those for the racemic compound.

(1*R*,3*R*,4*R*)-1-Benzoyloxy-4-(diethylphosphono)methoxycyclopentan-3-ol (−)-27

DEAD (12 μl, 0.076 mmol) was added to a solution of triphenylphosphine (20 mg, 0.076 mmol) in THF (1 cm^3) at 0 °C and the mixture was stirred at 0 °C for 40 min. A solution of the (−)-(1*R*,2*R*,4*S*)-diol (−)-**15** (17 mg, 0.0634 mmol) in THF (0.2 cm^3) was then added to the mixture, followed by a solution of benzoic acid (9.3 mg, 0.076 mmol) in THF (0.2 cm^3). The reaction mixture was then allowed to warm to room temperature and stirred until the reaction was complete (TLC evidence). The solvent was then removed *in vacuo*, and the residue flash chromatographed eluting with EtOAc to yield the title product as a colourless oil (17 mg, 0.0457 mmol, 72%); R_F 0.45 [EtOAc–MeOH (5:1)]; $[\alpha]_D^{28}$ −13.8 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3377mw (OH str.), 1714s (C=O), 1277s (P=O) and 1025s (CO str.); δ_H(400 MHz; $CDCl_3$) 1.32 (3 H, t, *J* 7, CH_3CH_2O), 1.33 (3 H, t, *J* 7, CH_3CH_2O), 1.87 (1 H, dddd, *J* 15, 7, 6.5, 1.5, 5-H), 2.07 (1 H, dt, *J* 15, 7.5, 2-H), 2.25 (1 H, dddd, *J* 15, 7, 3.5, 1.5, 2-H), 2.65 (1 H, dt, *J* 15, 7.5, 5-H), 3.82 (1 H, m, 4-H), 3.92 (2 H, m, PCH_2O), 4.02 (1 H, br, OH), 4.16 (4 H, m, 2 × CH_3CH_2O), 4.44 (1 H, td, *J* 7, 5.5, 3-H), 5.37 (1 H, tt, *J* 7, 3.5, 1-H), 7.42 (2 H, m, 2 × *m*-H), 7.55 (1 H, m, *p*-H) and 8.01 (2 H, m, 2 × *o*-H); δ_C(100.6 MHz; $CDCl_3$) 16.45 (CH_3, d, *J* 5.6, CH_3CH_2O), 36.83 (CH_2), 38.52 (CH_2), 62.51 (CH_2, d, $^2J_{CP}$ 6.7, CH_3CH_2O), 62.99 (CH_2, d, $^2J_{CP}$ 6.7, CH_3CH_2O), 64.85 (CH_2, d, $^1J_{CP}$ 166, PCH_2O), 72.56 (CH), 75.90 (CH), 89.01 (CH, d, $^3J_{CP}$ 7.7, 4-C), 128.30 (CH), 129.56 (CH), 130.36 (C), 132.92 (CH) and 166.12

(C=O); *m/z* 373 [(M + H)$^+$, 0.6%], 169 (27), 152 {[(EtO)$_2$(P=O)CH$_3$]$^+$, 100}, 125 (92) and 105 (79) [Found (EI): M$^+$, 372.1340. $C_{17}H_{25}O_7P$ requires 372.1338].

(1*R*,3*R*,4*R*)-1,3-Dibenzoyloxy-4-(diethylphosphono)-methoxycyclopentane (−)-28

Pyridine (0.3 cm^3) was added to the alcohol (−)-**27** (12 mg, 0.032 mmol) at 0 °C. A catalytic amount of DMAP was added to the mixture which was then stirred at 0 °C for 10 min. Benzoyl chloride (40 μl, 0.345 mmol) was added dropwise to the reaction mixture after which it was allowed to warm to room temperature and then stirred for 24 h. Ethyl acetate (15 cm^3) was added to the mixture and the organic phase was separated, washed with hydrochloric acid (0.25 M; 3 × 8 cm^3), water (2 cm^3) and brine (2 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed over silica [eluent EtOAc–LP (2:1), followed by EtOAc] to yield the title product as a colourless oil (6 mg, 0.0126 mmol, 39%); R_F 0.47 (EtOAc); $[\alpha]_D^{24}$ −40 (*c* 1.3, MeOH); ν_{max}(film)/cm^{-1} 3066mw (ArH str.), 2986s (CH str.), 1719s (C=O), 1602m (Ar), 1584m (Ar), 1452m (CH def.), 1273s (P=O), 1108s (C-O), 1030s (PO-alkyl) and 753 and 711 both s (mono-sub. benzene ring); δ_H(400 MHz; C_6D_6) 1.11 (3 H, t, *J* 7, C*H*$_3$CH$_2$O), 1.12 (3 H, t, *J* 7, C*H*$_3$CH$_2$O), 2.03 (1 H, dt, *J* 15, 3.5, 5β-H), 2.19 (1 H, ddd, *J* 15, 7, 3.5, 2α-H), 2.36 (1 H, dt, *J* 15, 7, 5α-H), 2.45 (1 H, dddd, *J* 15, 6.5, 5.5, 0.8, 2β-H), 3.96 (2 H, m, PCH$_2$O), 4.01 (1 H, m, 4-H), 4.08 (4 H, m, 2 × CH$_3$C*H*$_2$O), 5.56 (1 H, tdd, *J* 7.2, 5.5, 4, 1-H), 5.65 (1 H, ~dt, *J* 6.5, 3.2, 3-H), 7.18 (6 H, m, 4 × *m*-H and 2 × *p*-H), 8.14 (2 H, m, 2 × *o*-H) and 8.27 (2 H, m, 2 × *o*-H); δ_C(100.6 MHz; $CDCl_3$) 16.44 (CH$_3$, d, $^3J_{CP}$ 5.5, 2 × *C*H$_3$CH$_2$O), 36.95 (CH$_2$), 62.54 (CH$_2$, d, $^2J_{CP}$ 6, CH$_3$*C*H$_2$O), 62.60 (CH$_2$, d, $^2J_{CP}$ 6, CH$_3$*C*H$_2$O), 63.91 (CH$_2$, d, $^1J_{CP}$ 168, PCH$_2$O), 73.64 (CH), 77.87 (CH), 84.90 (CH, d, $^3J_{CP}$ 12, 4-C), 128.36 (CH), 128.48 (CH), 129.63 (CH), 129.67 (CH), 129.77 (C), 130.14 (C), 133.05 (CH), 133.30 (CH), 165.74 (C=O) and 166.26 (C=O); *m/z* 476 (M$^+$, 0.3%), 232 (69), 152 {[(EtO)$_2$(P=O)CH$_3$]$^+$, 59}, 105 (PhCO$^+$, 100) and 77 (Ph$^+$, 65) [Found (EI): M$^+$, 476.1591. $C_{24}H_{29}O_8P$ requires 476.1600].

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