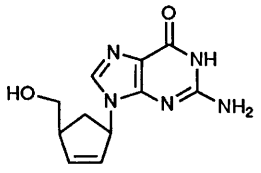
Total Synthesis of (−)-Carbovir

Martin F. Jones,* Peter L. Myers, Colin A. Robertson, Richard Storer and Christopher Williamson
Department of Medicinal Chemistry, Glaxo Group Research Limited, Greenford Road, Greenford, Middlesex, UB6 0HE

Optically pure (−)-carbovir has been prepared by two different routes involving stereospecific opening of chiral cyclopentene epoxides by substituted purines. Introduction of the 2′,3′ unsaturation was accomplished by mesylate elimination, either after introduction of the purine (Route 1), or earlier in the sequence, producing a novel vinyl epoxide (Route 2).

The emergence of carbovir **1**[1,2] as a potent and selective inhibitor of HIV replication has provided the first example of a carbocyclic nucleoside analogue with potential as a therapeutic agent for the treatment of AIDS.



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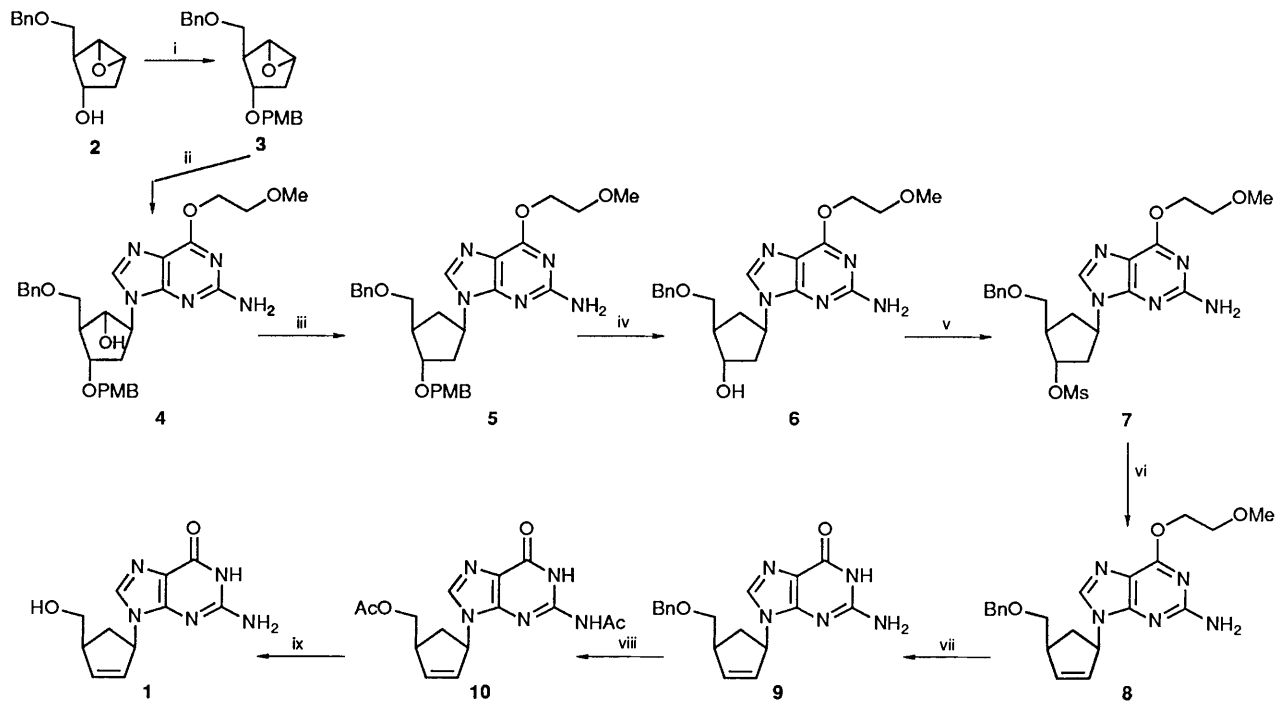
Results and Discussion

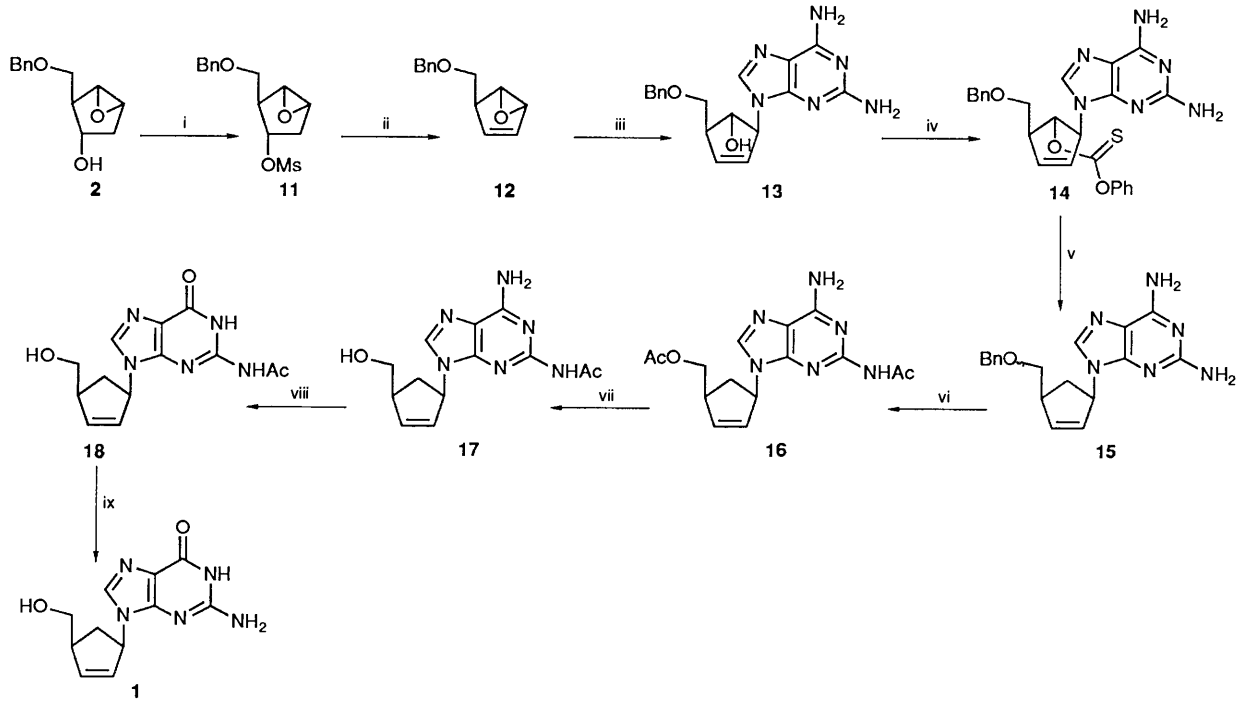
From our own[3] and others[4,5] experiences it was clear that, from a synthetic viewpoint, routes should target (−)-carbovir, and in the preceding paper[3b] we have described routes from the natural product (−)-aristeromycin. We report herein a conceptually different strategy: that of enantioselective total synthesis. Our strategy relied upon regioselective opening of chiral cyclopentene epoxides by appropriately substituted purine bases. Existing methodology[6] was adapted for use in the first route (Scheme 1), which involved base incorporation prior to installation of the 2′,3′ double bond by means of an E2-type mesylate elimination. For this purpose, differential protection of the secondary hydroxy group of the known chiral epoxide **2**[7] was required in advance of epoxide opening. Alkylation of **2** with *p*-methoxybenzyl chloride furnished ether **3** in good yield, and treatment of this compound with the lithium salt of 2-amino-6-methoxyethoxypurine in hot DMF selectively furnished the desired epoxide-opened product **4**. Not only was this process regioselective with respect to the epoxide, but alkylation of the purine occurred selectively at N-9, in accord with results reported by Kjellberg *et al.*[8] Radical deoxygenation of the 6′-hydroxy group[9] proceeded smoothly by treatment of the derived phenylthio carbonate with tributyltin hydride in hot toluene to deliver **5** in high yield. With the major features of the target now installed, the 3′-hydroxy group was unveiled by oxidative removal of the *p*-methoxybenzyl group,[10] and mesylation furnished **7** in excellent yield. Treatment of mesylate **7** with sodium methoxide in DMF resulted in a mixture of products. Although the desired elimination had been effected, some interchange of methoxide with the purine alkoxy substituent was noted, and the corresponding 6-methoxypurine derivative could be isolated in low yield. This problem was easily overcome by using the sodium salt of 2-methoxyethanol to effect the elimination, allowing us to obtain the alkene **8** in high yield. Regeneration of the guanine by cleavage of the 6-methoxyethyl ether proved troublesome. Treatment with hot 3 mol dm^{-3} hydrochloric acid led to extensive decomposition, and aluminium triiodide[11] proved the reagent of choice. The product **9**, however, was extensively contaminated by aluminium salts, and could not be satisfactorily purified. Thus, without further purification, **9** was used in the following stage. Acetolysis of the benzyl group of **9** was performed with boron trifluoride–diethyl ether in acetic anhydride, which resulted in concomitant acetylation of the amino group to give **10**. Finally, ammonolysis of the ester and amide acetyl groups furnished (−)-carbovir **1**, which was identical in all respects with an authentic sample prepared from the natural product aristeromycin.[3b]

An alternative strategy was offered by the possibility of introducing the double bond prior to epoxide opening by a purine base, and vinyl epoxide **12** presented itself as a suitable intermediate. By virtue of the allylic nature of the 5-position, we expected that this epoxide would be highly reactive, and would, moreover, open exclusively at the allylic position.

Our second route (Scheme 2) therefore firstly addressed the preparation of **12**. In view of the apparent ease of mesylate elimination, demonstrated in Route 1, crystalline mesylate **11** was prepared in high yield. Despite several attempts, using a variety of alkoxide and amine bases, mesylate elimination could not be effected. However, using tetrabutylammonium fluoride as base, in tetrahydrofuran, elimination took place to give the desired vinyl epoxide **12**. This compound proved somewhat unstable to chromatography and was therefore used without purification. Our choice of purine base for the epoxide opening was directed by the preference for a group at the 6-position potentially more labile than the methoxyethyl ether employed in Route 1. Work by Herdewijn[12] indicated that 2,6-diaminopurine could fulfil such an objective, and treatment of vinyl epoxide **12** with sodium hydride and 2,6-diaminopurine in the presence of 15-crown-5 gave epoxide-opened product **13**. As expected, the epoxide opening was completely regioselective for the allylic position, and with respect to the purine, alkylation was highly selective for N-9. After deoxygenation at the 6′-position, we were in a position to attempt the conversion of the 2,6-diaminopurine into a guanine base. It was envisaged that the 6-amino group would be readily removed by nitrous acid diazotisation and hydrolysis, but this would require protection of the 2-amino group. It was therefore fortunate that boron trifluoride–diethyl ether mediated acetolysis of the benzyl group of **15** resulted also in selective acetylation of the 2-amino functionality, the required protection. Initial experiments showed that the free amino group of the resultant acetamide **16** could be diazotised and hydrolysed to give the guanine equivalent, but the best overall yield for the sequence was obtained by conducting this reaction upon the *O*-deacetylated compound **17**. Thus, upon treatment of **19** with sodium nitrite in aqueous acetic acid, (−)-*N*-2-acetylcarbovir **18** was cleanly delivered, and final deprotection was performed by ammonolysis of the now more labile *N*-2-acetamide.



Scheme 1 *Reagents:* i, *p*-Methoxybenzyl chloride, NaH, TBAI; ii, 2-amino-6-methoxyethoxypurine, DMF, heat; iii (a), PhOCSCl, DMAP, (b) Bu_3SnH, AIBN, heat; iv, DDQ, CH_2Cl_2, H_2O; v, MsCl, DMAP; vi, $NaOCH_2CH_2OMe$, DMF; vii, AlI_3, MeCN, heat; viii, BF_3-Et_2O, Ac_2O; ix, NH_3, MeOH



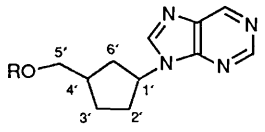
Scheme 2 *Reagents:* i, MsCl, Et_3N, DMAP; ii, Bu_4NF, THF; iii, 2,6-Diaminopurine, NaH, DMF, heat; iv, PhOCSCl, DMAP; v, Bu_3SnH, AIBN, heat; vi, BF_3; Et_2O, Ac_2O; vii, NH_3, MeOH; viii, $NaNO_2$, AcOH, H_2O; ix, NH_3, MeOH

Following completion of this work an alternative synthesis of (−)-carbovir has been reported by other workers.[13]

Experimental

All reactions were routinely carried out under an atmosphere of nitrogen. Organic extracts were dried over $MgSO_4$ unless otherwise stated, and evaporated using a rotary evaporator. Petroleum refers to the ˆ action boiling between 40 and 60 °C. Tetrahydrofuran was dried by passage through a column of activated alumina, and CH_2Cl_2 and DMF were stored over activated 4 Å sieves. Chemical shifts are reported in δ values relative to Me_4Si as an internal standard. *J* Values are in Hz. ^1H NMR spectra were recorded in the solvent indicated at 250 MHz on a Bruker AC250 spectrometer. IR spectra were recorded on a Nicolet 5 SXC FT instrument, UV spectra were recorded on a Perkin-Elmer Lambda 5 instrument, and optical rotations were determined using either a Perkin-Elmer 241 or an Optical Activity automatic polarimeter. $[\alpha]_D$ Values are in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a innigan

MAT 8400 double focussing spectrometer, and accurate mass determinations were made by Reading Scientific Services Ltd. using a VG Analytical 7070E instrument in EI mode on compounds estimated to be >95% pure by ^{1}H NMR spectroscopy and thin layer chromatography. NMR assignments of nucleoside analogues are labelled according to the scheme of Madhavan and Martin.[9]



(1S,2R,3S,5R)-2-*Benzyloxymethyl*-3-(4-*methoxybenzyloxy*)-6-*oxabicyclo*[3.1.0]*hexane* **3**.—A solution of **2** (30.40 g, 138 mmol) in tetrahydrofuran (60 ml) was added to a stirred suspension of sodium hydride (3.64 g, 152 mmol) in tetrahydrofuran (120 ml). After 1 h at room temperature 4-methoxybenzyl chloride (20.6 ml, 152 mmol) and tetrabutylammonium iodide (510 mg) were added, followed by DMF (30 ml). The mixture was heated under reflux for 1.5 h and allowed to cool. After evaporation of most of the solvent, the residue was diluted with diethyl ether (400 ml) and washed with water (3 × 150 ml) and brine (100 ml). The organic phase was dried and evaporated to provide an oil which was purified by column chromatography (petroleum–diethyl ether 1:2) yielding the *title compound* as a yellow oil (42.46 g, 90%), $[\alpha]_D^{22}$ +33.6 (*c* 1.49, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 2924, 2856, 1611 and 1511; $\delta_H(CDCl_3)$ 7.40–7.10 (7 H, m, ArH), 6.82 (2 H, d, *J* 8, ArH), 4.48 (2 H, s, PhCH_2), 4.40 (2 H, s, ArCH_2), 3.88 (1 H, d, *J* 7, 3-H), 3.80 (3 H, s, ArO*Me*), 3.52 (1 H, br s) and 3.45 (1 H, br s) (1-H and 5-H), 3.40 (2 H, m, CH_2O), 2.59 (1 H, t, *J* 7, 2-H), 2.13 (1 H, d, *J* 15, 4-H_a), 2.02 (1 H, dd, *J* 15 and 7, 4-H_b); *m/z* (EI) 340 (Found: M^+, 340.1672. $C_{21}H_{24}O_4$ requires *M*, 340.1674).

(1S,2R,3S,5S)-5-[2-*Amino*-6-(2-*methoxyethoxy*)-9H-*purin*-9-*yl*]-2-*benzyloxymethyl*-3-(4-*methoxybenzyloxy*)*cyclopentanol* **4**.—2-Amino-6-methoxyethoxypurine (7.15 g, 34 mmol) was added to a stirred suspension of lithium hydride (195 mg, 24 mmol) in dimethylformamide (90 ml) and the suspension was heated at 120 °C for 1 h. After the latter had cooled to room temperature, a solution of **3** (8.06 g, 24 mmol) in DMF (60 ml) was added to it, and the mixture was heated at 145 °C for 3.5 h. After the mixture had cooled, the solvent was removed and the residue was taken up in ethyl acetate (500 ml). This mixture was washed with water (3 × 200 ml) and brine (100 ml), dried and evaporated to afford a residue which was purified by column chromatography (ethyl acetate–ethanol, 9:1) to furnish the *title compound* as a cream coloured solid (6.97 g, 53%). An analytical sample was prepared by crystallisation from ethyl acetate, m.p. 118–120 °C; $[\alpha]_D^{22}$ −5.74 (*c* 1.61, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 3500–3000 br, 1610, 1587 and 1512; λ_{max}(EtOH)/nm 252 and 282; $\delta_H(CDCl_3)$ 7.52 (1 H, s, 8-H), 7.40–7.20 (7 H, m, ArH), 6.86 (2 H, bd, *J* 8, ArH), 6.38 (1 H, s, OH), 4.88 (2 H, br s, NH_2), 4.62 (3 H, m, 1′-H and OCH_2), 4.53 (2 H, s, PhCH_2O), 4.46 (2 H, br s, ArCH_2O), 4.25 (1 H, bt, *J* 7, 6′-H), 4.01 (1 H, m, 3′-H), 3.80 (5 H, m, CH_2OMe and ArO*Me*), 3.64 (2 H, m, 5′-$H_{a,b}$), 3.42 (3 H, s, CH_2O*Me*), 2.53 1 H, dd, *J* 13 and 8, 2′-H_a), 2.42 (1 H, m, 4′-H) and 2.28 (1 H, m, 2′-H_b) (Found: C, 63.1; H, 6.35; N, 12.7. $C_{29}H_{35}N_5O_6$ requires C, 63.27; H, 6.34; N, 12.74%).

(1S,2R,3S,5S)-5-[2-*Amino*-6-(2-*methoxyethoxy*)-9H-*purin*-9-*yl*]-2-*benzyloxymethyl*-3-(4-*methoxybenzyloxy*)*cyclopentyl Phenoxythiocarboxylate*.—4-Dimethylaminopyridine (2.85 g, 23.4 mmol) and *O*-phenyl chlorothioformate (2.05 ml, 14.8 mmol) were added to a stirred and cooled (0 °C) solution of **4** (8.04 g, 14.6 mmol) in dichloromethane (85 ml). The ice-bath was removed after 15 min and stirring was continued for a further 30 min. The solution was diluted with dichloromethane (80 ml), washed with water (70 ml), saturated aqueous sodium hydrogen carbonate (70 ml) and brine (50 ml), dried and evaporated. The residue was purified by column chromatography (chloroform–ethyl acetate, 1:1) to give the *title compound* as a colourless foam (9.01 g, 90%), $\delta_H(CDCl_3)$ 7.64 (1 H, s, 8-H), 7.40–7.20 (10 H, m, ArH), 7.00–6.85 (4 H, m, ArH), 6.17 (1 H, t, *J* 7, 6′-H), 5.20 (1 H, m, 1′-H), 4.81 (2 H, s, NH_2), 4.63 (2 H, t, *J* 5, OCH_2), 4.57 (2 H, s, PhCH_2O), 4.50 (2 H, s, ArCH_2O), 4.14 (1 H, m, 3′-H), 3.80 (7 H, m, ArO*Me*, 5′-$H_{a,b}$, CH_2OMe), 3.42 (3 H, s, CH_2O*Me*), 2.68 (2 H, m, 4′-H and 2′-H_a) and 2.40 (1 H, dd, *J* 13 and 7, 2′-H_b).

(1′R,3′S,4′R)-9-[4-*Benzyloxymethyl*-3-(4-*methoxybenzyloxy*)-*cyclopentyl*]-6-(2-*methoxyethoxy*)-9H-*purin*-2-*amine* **5**.—Tributyltin hydride (5.64 ml, 21 mmol) was added to a solution of the phenoxythiocarboxylate prepared above (9.01 g, 13 mmol) and azoisobutyronitrile (500 mg) in toluene (140 ml), and the solution was heated at 100 °C for 1 h. After cooling and evaporation, the residue was purified by column chromatography (ethyl acetate–ethanol, 9:1) to furnish the *title compound* (5.56 g, 79%) as a gum, $[\alpha]_D^{23}$ + 16.5 (*c* 1.09, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1610, 1584 and 1512; λ_{max}(EtOH)/nm 251 and 281; $\delta_H(CDCl_3)$ 7.64 (1 H, s, 8-H), 7.40–7.20 (7 H, m, ArH), 6.87 (2 H, br d, *J* 8, ArH), 4.95 (1 H, m, 1′-H), 4.80 (2 H, s, NH_2), 4.63 (2 H, t, *J* 4, OCH_2), 4.52 (2 H, s, PhCH_2O), 4.45 (2 H, s, ArCH_2O), 4.04 (1 H, m, 3′-H), 3.79 (5 H, m, CH_2OMe and ArO*Me*), 3.53 (2 H, m, 5′-$H_{a,b}$), 3.42 (3 H, s, CH_2O*Me*) and 2.60–1.80 (5 H, multiplets, 2′-$H_{a,b}$, 4′-H and 6′-$H_{a,b}$); *m/z* (EI) 533 (Found: M^+, 533.2639. $C_{29}H_{35}N_5O_5$ requires *M*, 533.2638).

(1S,2R,4R)-4-[2-*Amino*-6-(2-*methoxyethoxy*)-9H-*purin*-9-*yl*]-2-*benzyloxymethylcyclopentanol* **6**.—To a magnetically stirred solution of **5** (5.43 g, 10 mmol) in dichloromethane–water (19:1; 200 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 2.78 g, 12.2 mmol). The mixture was stirred vigorously overnight and then diluted with dichloromethane (200 ml) and repeatedly washed with saturated aqueous sodium hydrogen carbonate (3 × 200 ml). The combined aqueous washings were back extracted with dichloromethane (2 × 200 ml) and the combined extracts were evaporated. The residue was dissolved in hydrochloric acid (2 mol dm^{-3}; 120 ml) and washed with ethyl acetate (3 × 80 ml) before being basified to pH 9 by addition of solid sodium carbonate. After extraction with dichloromethane (4 × 120 ml) the combined organic extracts were washed with brine (100 ml), dried and evaporated to give a residue which was purified by column chromatography (chloroform–methanol, 9:1), to afford the crude product as a gum. This was triturated with diethyl ether to give the *title compound* (2.77 g, 66%) as a light brown powder, m.p. 113–115 °C; $[\alpha]_D^{22}$ − 17.8 (*c* 1.29 $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1609 and 1585; λ_{max}(EtOH)/nm 252 and 283; $\delta_H(CDCl_3)$ 7.64 (1 H, s, 8-H), 7.40–7.25 (5 H, m, *Ph*CH_2), 5.00 (1 H, m, 1′-H), 4.80 (2 H, s, NH_2), 4.63 (2 H, t, *J* 5, OCH_2), 4.57 (2 H, s, PhCH_2), 4.45 (1 H, m, 3′-H), 3.81 (2 H, t, *J* 5, CH_2OMe), 3.68 (1 H, dd, *J* 5 and 9, 5′-H_a), 3.54 (1 H, t, *J* 9, 5′-H_b), 3.42 (3 H, s, O*Me*), 2.50–2.20 (4 H, m) and 1.79 (1 H, m) (2′-$H_{a,b}$, 6′-$H_{a,b}$ and 4′-H) (Found: C, 60.6; H, 6.65; N, 16.85. $C_{21}H_{27}N_5O_4$ requires C, 60.99; H, 6.58; N, 16.94%).

(1S,2R,4R)-4-[2-*Amino*-6-(2-*methoxyethoxy*)-9H-*purin*-9-*yl*]-2-*benzyloxymethylcyclopentyl Methanesulphonate* **7**.—To a stirred and cooled (0 °C) solution of **6** (2.74 g, 6.64 mmol) and 4-dimethylaminopyridine (1.62 g, 13 mmol) in dichloromethane

(44 ml) was added methanesulphonyl chloride (0.616 ml, 7.97 mmol) dropwise. The solution was stirred at 0 °C for 15 min and at room temperature for 1 h. The mixture was diluted with dichloromethane (100 ml) washed with water (100 ml) and saturated aqueous sodium hydrogen carbonate (100 ml), dried and evaporated to give a gum which was purified by column chromatography (chloroform–methanol, 9:1) to afford the *title compound* as a foam (3.31 g, 100%), $\nu_{max}(CHBr_3)/cm^{-1}$ 1609 and 1585; $\lambda_{max}(EtOH)/nm$ 247 and 284; $\delta_H(CDCl_3)$ 7.62 (1 H, s, 8-H), 7.40–7.25 (5 H, m, *Ph*CH_2), 5.24 (1 H, m, 3′-H), 4.96 (1 H, m, 1′-H), 4.78 (2 H, s, NH_2), 4.61 (2 H, t, *J* 5, OCH_2), 4.58 (2 H, m, PhCH_2), 3.80 (2 H, t, *J* 5, CH_2OMe), 3.69 (1 H, m, 5′-H_a), 3.57 (1 H, m, 5′-H_b), 3.42 (3 H, s, OMe), 3.00 (3 H, s, SO_2Me), 2.70–2.45 (4 H, m) and 2.01 (1 H, m) (2′-$H_{a,b}$, 4′-H, 6′-$H_{a,b}$); *m/z* (+ve CI, CH_4) 396 (M − $HOSO_2Me)^+$, 210 and 97 $(HOSO_2Me + H)^+$

(1′R,4′S)-9-[4-*Benzyloxymethylcyclopent-2-enyl*]-6-(2-*methoxyethoxy*-9H-*purin*-2-*amine* **8**.—To a magnetically stirred suspension of sodium hydride (791 mg, 33 mmol) in dimethylformamide (57 ml) was added 2-methoxyethanol (2.72 ml, 34 mmol) dropwise. The mixture was stirred for 0.5 h and cooled to 0 °C. A solution of **7** (3.23 g, 6.6 mmol) in DMF (57 ml) was added, and stirring at 0 °C was continued for 2 h. The mixture was diluted with water (450 ml) and the crude product extracted into ethyl acetate (2 × 600 ml). The organic extract was washed with brine (200 ml), dried and evaporated to afford a residue which was purified by column chromatography (chloroform–methanol, 19:1) to give the *title compound* as a gum (2.41 g, 92%), $[\alpha]_D^{23}$ −93 (*c* 2.54, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 3500, 1609 and 1585; $\lambda_{max}(EtOH)/nm$ 251 and 281; $\delta_H(CDCl_3)$ 7.68 (1 H, s, 8-H), 7.40–7.20 (5 H, m, *Ph*CH_2), 6.16 (1 H, m, 2′-H), 5.85 (1 H, m, 3′-H), 5.57 (1 H, m, 1′-H), 4.86 (2 H, br s, NH_2), 4.65 (2 H, t, *J* 5, OCH_2), 4.52 (2 H, s, PhCH_2), 3.81 (2 H, t, *J* 5, CH_2OMe), 3.48 (2 H, m, 5′-$H_{a,b}$), 3.43 (3 H, s, OMe), 3.10 (1 H, m, 4′-H), 2.80 (1 H, dt, *J* 9, 9 and 15, 6′-H_a), 1.65 (1 H, dt, *J* 7, 7 and 15, 6′-H_b); *m/z* (+ve CI, CH_4) 396 (MH^+), 364 (MH − MeOH)$^+$, 338 (MH − $CH_3CH_2OMe)^+$, 210 and 152 (Found: M^+, 395.1963. $C_{21}H_{25}N_5O_3$ requires *M*, 395.1957).

(1″R,4″S)-N-[1,9-*Dihydro*-9-(4-*acetoxymethylcyclopent*-2-*enyl*)-6-*oxopurin*-2-*yl*]*acetamide* **10**.—A solution of aluminium triiodide in acetonitrile[9] (0.52 M; 18.0 ml, 9.36 mmol) was added to a stirred solution of **8** (2.39 g, 6 mmol) in acetonitrile (40 ml), and the mixture was heated under reflux for 2 h. After being cooled, the mixture was diluted with methanol (40 ml) and evaporated. The residue was subjected to column chromatography (chloroform–methanol, 9:1) to afford the major product as a gum (750 mg), $\lambda_{max}(EtOH)/nm$ 255; *m/z* (+ve CI, CH_4) 338 (MH^+), 152, 107 and 91. This was dissolved in acetic anhydride (25 ml) and the solution cooled to 0 °C. With stirring, boron trifluoride–diethyl ether (0.76 ml, 6.2 mmol) was added dropwise, and after 10 min at 0 °C, stirring was continued at room temperature for 1.5 h. The mixture was poured into saturated aqueous sodium hydrogencarbonate (200 ml) and the product extracted into ethyl acetate (3 × 150 ml). The combined organic extracts were washed with brine (100 ml) dried and evaporated, and the residue was purified by column chromatography (chloroform–methanol, 19:1) to afford the crude product as a foam. This was triturated with diethyl ether to yield the *title compound* (265 mg, 13%) as a tan powder, m.p. 144–146 °C; $[\alpha]_D^{23}$ +4.96 (*c* 1.25, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1715, 1681, 1610 and 1556; $\lambda_{max}(EtOH)/nm$ 260; $\delta_H(CDCl_3)$ 12.05 (1 H, br s, NH), 9.80 (1 H, br s, N*H*Ac) 7.70 (1 H, s, 8-H), 6.07 (1 H, m, 2′-H), 5.83 (1 H, m, 3′-H), 5.44 (1 H, m, 1′-H), 4.59 (1 H, dd, *J* 7 and 9, 5′-H_a), 4.22 (1 H, dd, *J* 7 and 9, 5′-H_b), 3.21 (1 H, m, 4′-H), 2.76 (1 H, dt, *J* 9, 9 and 15, 6′-H_a), 2.34 (3 H, s, NH*Ac*), 2.11 (3 H, s, OAc) and 1.81 (1 H, dt, *J* 6, 6 and 15, 6′-H_b) (Found: C, 54.2; H, 5.15; N, 20.9. $C_{15}H_{17}N_5O_4$ requires C, 54.38; H, 5.17; N, 21.14%).

(1′R,4′S)-2-*Amino*-9-(4-*hydroxymethylcyclopent*-2-*enyl*)-1,9-*dihydro*-6H-*purin*-6-*one*, (−)-*Carbovir* **1**.—A solution of **10** (157 mg, 0.47 mmol) in methanol (5 ml) was treated overnight at room temperature with saturated methanolic ammonia (30 ml). The solution was then evaporated and the residue was purified by column chromatography (chloroform–methanol, 4:1) to afford the crude product. Recrystallisation was from water to give the *title compound* as white crystals (75 mg, 64%), m.p. 272–274 °C (decomp.); $[\alpha]_D^{23}$ −68 (*c* 0.40, MeOH); ν_{max}(Nujol)/cm^{-1} 2924, 1724, 1627 and 1600; λ_{max}(pH 6 buffer)/nm 252; $\delta_H([^2H_6]DMSO)$ 10.58 1 H, br s, NH), 7.59 (1 H, s, 8-H), 6.45 (2 H, br s, NH_2), 6.11 (1 H, m, 2′-H), 5.85 (1 H, m, 3′-H), 5.33 (1 H, m, 1′-H), 4.74 (1 H, t, *J* 5, OH), 3.44 (2 H, t, *J* 7, 5′-$H_{a,b}$), 2.87 (1 H, m, 4′-H), 2.58 (1 H, dt, *J* 9, 9 and 14, 6′-H_a), 1.57 (1 H, dt, *J* 6, 6 and 14, 6′-H_b); (Found: C, 50.25; H, 5.5; N, 26.7. $C_{11}H_{13}N_5O_2$. $0.9H_2O$ requires C, 50.14; H, 5.66; N, 26.58%).

(1S,2R,3S,5R)-2-*Benzyloxymethyl*-6-*oxabicyclo*[3.1.0]*hexan*-3-*ylmethanesulphonate* **11**.—To a stirred and cooled (0 °C) solution of **2** (3.53 g, 16 mmol) in dichloromethane (70 ml) was added first 4-dimethylaminopyridine (53 mg) and then triethylamine (2.7 ml, 19 mmol). Methanesulphonyl chloride (1.37 ml, 17 mmol) was then added dropwise, and the solution was stirred at 0 °C for 45 min. The reaction was quenched by the addition of water (25 ml) and the layers were separated. The organic layer was washed with saturated aqueous sodium hydrogencarbonate (25 ml) and brine (10 ml), dried (Na_2SO_4) filtered and evaporated. The residue was triturated with diethyl ether to give the *title compound* as fawn crystals (3.87 g, 81%), m.p. 81–83 °C; $[\alpha]_D^{23}$ +51.9 (*c* 1.55, $CHCl_3$), $\nu_{max}(CHBr_3)/cm^{-1}$ 1357, 1330 and 1173; $\delta_H(CDCl_3)$ 7.40–7.20 (5 H, m, *Ph*CH_2), 5.11 (1 H, t, *J* 4, 3-H), 4.52 (2 H, m, CH_2Ph), 3.67–3.45 (4 H, m, 1-H, 5-H, CH_2OCH_2Ph), 3.00 (3 H, s, $MeSO_2$), 2.74 (1 H, t, *J* 5, 2-H) and 2.31 (2 H, d, 4-H) (Found: C, 56.3; H, 6.1. $C_{14}H_{18}O_5S$ requires C, 56.37; H, 6.08%).

(1S,2S,5R)-2-*Benzyloxymethyl*-6-*oxabicyclo*[3.1.0]*hex*-3-*ene* **12**.—Tetrabutylammonium fluoride solution (1 M in THF; 87 ml) was added to a stirred solution of **11** (2.61 g, 8.7 mmol) in tetrahydrofuran (30 ml) and the mixture was allowed to stand at room temperature for 3 days. It was then evaporated to about one third its volume, diluted with chloroform (250 ml), washed with water (4 × 100 ml) and brine (100 ml), dried and evaporated to give a brown oil (1.60 g) suitable for use in the next stage. A small sample was purified by column chromatography (petroleum–diethyl ether, 1:1) for characterisation purposes, giving the *title compound* as a light brown oil, $\nu_{max}(CHBr_3)/cm^{-1}$ 1485, 1450 and 1358; $\delta_H(CDCl_3)$ 7.40–7.30 (5 H, m, *Ph*CH_2), 6.23 (1 H, m, 4-H), 5.95 (1 H, m, 3-H), 4.55 (2 H, m, PhCH_2), 3.90 (1 H, m, 5-H), 3.80 (1 H, m, 1-H), 3.55 (1 H, dd, *J* 6 and 9, $PhCH_2OCH_a$), 3.30 (1 H, t, *J* 9, $PhCH_2OCH_b$) and 3.08 (1 H, m, 2-H); *m/z* (+ve CI, CH_4) 203 (MH^+), 185 and 92.

(1S,2S,5S)-5-*Benzyloxymethyl*-2-(2,6-*diamino*-9H-*purin*-9-*yl*)*cyclopent*-3-*enol* **13**.—To a magnetically stirred suspension of sodium hydride (864 mg, 36 mmol) in dry DMF (190 ml) was added 2,6-diaminopurine (8.20 g, 54 mmol), and the mixture was heated at 85 °C for 20 min and then cooled to room temperature. 15-Crown-5 (1 ml) was then added, followed by a solution of crude **12** (7.45 g, *ca.* 37 mmol) in DMF (40 ml). The mixture was heated at 100 °C for 3 h and cooled to room temperature. The solvent was removed and the residue dissolved in ethyl acetate (1000 ml) and phases were washed

thrice with water (500 ml). The combined aqueous phases were then extracted with a further portion of ethyl acetate (300 ml). The combined organic extracts were washed with brine (400 ml), dried and evaporated to give a residue, which was purified by column chromatography (chloroform–methanol, 9:1) to afford the *title compound* (6.49 g, 50%) as a fawn solid, m.p. 116–118 °C; $[\alpha]_D^{23}$ −41.5 (*c* 1.06, $CHCl_3$); $\nu_{max}(CHBr_3)$/ cm^{-1} 3404, 1625 and 1600; λ_{max}(EtOH)/nm 257 and 282; $\delta_H(CDCl_3)$, 7.39 (1 H, s, 8-H), 7.40–7.18 (5 H, m, *Ph*CH_2), 6.18 (2 H, br s, NH_2), 6.03 (1 H, m, 2′-H), 5.80 (1 H, m, 3′-H), 5.38 (2 H, br s, NH_2), 5.25 (1 H, m, 1′-H), 4.50 (2 H, s, PhCH_2), 4.31 (1 H, t, *J* 7, 6′-H), 3.60 (2 H, m, 5′-$H_{a,b}$) and 3.03 (1 H, m, 4′-H); *m*/*z* (+ve CI, CH_4) 353 (MH^+), 151, 107 and 91 (Found: C, 60.9; H, 5.7; N, 23.65. $C_{18}H_{20}N_6O_2$ requires: C, 61.34; H, 5.72; N, 23.85%).

(1S,2S,5S)-5-*Benzyloxymethyl*-2-(2,6-*diamino*-9H-*purin*-9-*yl*)*cyclopent*-3-*enylphenoxythiocarboxylate* **14**.—To a magnetically stirred solution of **13** (6.46 g, 18 mmol) in dichloromethane (190 ml) was added 4-dimethylaminopyridine (6.61 g, 54 mmol). The solution was cooled to −25 °C and *O*-phenyl chlorothioformate (6.29 g, 37 mmol) was added dropwise over 10 min. Stirring was continued at −20 °C for 1 h and then at − 15 °C for 0.75 h. After quenching of the reaction by addition of water (300 ml) the phases were separated and the organic layer was washed with saturated aqueous sodium hydrogencarbonate (300 ml), dried and evaporated. The residue was purified by column chromatography (chloroform–methanol, 19:1) to give the *title compound* (8.28 g, 92%) as a light brown powder, m.p. 152–153 °C; $[\alpha]_D^{23}$ −102 (*c* 0.76, $CHCl_3$), $\nu_{max}(CHBr_3)cm^{-1}$ 1624, 1602 and 1407; λ_{max}(EtOH)/nm 248 and 282; $\delta_H(CDCl_3)$ 7.68 (1 H, s, 8-H), 7.45–7.20 (8 H, m, ArH), 6.11 (1 H, m, 2′-H), 5.92 (1 H, t, *J* 4, 6′-H), 5.86 (1 H, m, 3′-H), 5.73 (1 H, m, 1′-H), 5.59 (2 H, br s, NH_2), 4.88 (2 H, br s, NH_2), 4.55 (2 H, s, CH_2Ph), 3.85–3.70 (2 H, m, 5′-$H_{a,b}$) and 3.26 (1 H, m, 4′-H).

(1′R,4′S)-9-(4-*Benzyloxymethylcyclopent*-2-*enyl*)-9H-*purine*-2,6-*diamine* **15**.—To a stirred solution of **14** (8.175 g, 16.7 mmol) in pyridine (150 ml) was added azoisobutyronitrile (250 mg) and a tributyltin hydride (8.98 ml, 33 mmol) and the solution was heated at 95 °C for 3 h. After evaporation of the mixture the residue was purified by column chromatography, eluting firstly with petroleum–ethyl acetate (1:1), and then with chloroform–methanol (19:1) to give the major product as a gum. This was crystallised from dichloromethane, to furnish the *title compound* as white crystals (2.17 g, 38%), m.p. 166–167 °C; $[\alpha]_D^{23}$ −85.7 (*c* 0.98, $CHCl_3$); $\nu_{max}(CHBr_3)/cm^{-1}$ 1623, 1600 and 1405; λ_{max}(EtOH)/nm 257 and 282; $\delta_H(CDCl_3)$ 7.60 (1 H, s, 8-H), 7.40–7.20 (5 H, m, *Ph*CH_2), 6.15 (1 H, m, 2′-H), 5.84 (1 H, m, 3′-H), 5.57 (3 H, m, 1′-H and NH_2), 4.80 (2 H, br s, NH_2), 4.52 (2 H, s, PhCH_2), 3.49 (2 H, m, 5′-$H_{a,b}$), 3.09 (1 H, m, 4′-H), 2.80 (1 H, dt, *J* 9, 9 and 14, 6′-H_a) and 1.68 (1 H, m, 6′-H_b); *m*/*z* (+ve CI, NH_3) 337 (MH^+), 151 (Found: M^+, 336.1690. $C_{18}H_{20}N_6O$ requires *M*, 336.1698).

(1″R,4″S)-N-[9-(4-*Acetoxymethylcyclopent*-2-*enyl*)-6-*amino*-9H-*purin*-2-*yl*]*acetamide* **16**.—Boron trifluoride–diethyl ether (1.89 ml, 15 mmol) was added to a stirred and cooled (0 °C) solution of **15** (1.30 g, 3.9 mmol) in acetic anhydride (40 ml). Stirring was continued at 0 °C for 10 min and then at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous sodium hydrogencarbonate (200 ml) and the product was extracted into ethyl acetate (3 × 200 ml). The combined organic extracts were washed with brine (100 ml), dried and evaporated to afford a residue which was purified by column chromatography (chloroform–methanol, 19:1) to give the *title compound* as a gum (699 mg, 55%). A small sample was crystallised by trituration with diethyl ether, m.p. 188–190 °C; $[\alpha]_D^{23}$ −117 (*c* 1.32, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 2924, 1726, 1661, 1635, 1613 and 1594; λ_{max}(EtOH)/nm 227 and 274; $\delta_H(CDCl_3)$ 10.08 (1 H, br s, *NH*Ac), 7.75 (1 H, s, 8-H), 6.80 (2 H, br s, NH_2), 6.17 (1 H, m, 22′-H), 5.98 (1 H, m, 3′-H), 5.61 (1 H, m, 1′-H), 4.15 (2 H, m, 5′-$H_{a,b}$), 3.20 (1 H, m, 4′-H), 2.87 (1 H, dt, *J* 8, 8 and 14, 6′-H_a), 2.64 (3 H, s, NH*Ac*), 2.07 (3 H, s, OAc) and 1.71 (1 H, m, 6′-H_b); *m*/*z* (+ve CI, NH_3) 331 (MH^+), 289 and 193 (Found: M^+, 330.1435. $C_{15}H_{18}N_6O_3$ requires *M*, 330.1440).

(1″R,4″S)-N-[6-*Amino*-9-(4-*hydroxymethylcyclopent*-2-*enyl*)-9H-*purin*-2-*yl*]*acetamide* **17**.—Saturated methanolic ammonia (15 ml) was added to a solution of **16** (480 mg, 1.45 mmol) in methanol (3 ml) and the mixture was kept at room temperature overnight. It was then evaporated to dryness and the residue subjected to column chromatography (chloroform–methanol, 93:7) to give a crude product which was triturated with diethyl ether to furnish the *title compound* as a white amorphous solid (252 mg, 60%), m.p. 114–117 °C; $[\alpha]_D^{23}$ −100 (*c* 1.09, MeOH); ν_{max}(Nujol)/cm^{-1} 3179, 1648, 1594 and 1471; λ_{max}(EtOH)/nm 227 and 273; $\delta_H([^2H_6]DMSO)$ 9.75 (1 H, br s, N*H*Ac), 7.94 (1 H, s, 8-H), 7.18 (2 H, br s, NH_2), 6.13 (1 H, m, 2′-H), 5.90 (1 H, m, 3′-H), 5.48 (1 H, m, 1′-H), 4.72 (1 H, br t, OH), 3.45 (2 H, m, 5′-$H_{a,b}$), 2.89 (1 H, m, 4′-H), 2.63 (1 H, m, 6′-H_a), 2.22 (3 H, s, NH*Ac*) and 1.62 (1 H, m, 6′-H_b); *m*/*z* (+ve CI, CH_4), 289 (MH^+), 193 and 151 (Found: M^+, 288.1334. $C_{13}H_{16}N_6O_2$ requires *M*, 288.1335).

(1″R,4″S)-N-[1,9-*Dihydro*-9-(4-*hydroxymethylcyclopent*-2-*enyl*)-6-*oxopurin*-2-*yl*]*acetamide* **18**.—Water (6 ml) and sodium nitrite (290 mg, 4.2 mmol) were added to a stirred solution of **17** (151 mg, 0.52 mmol) in glacial acetic acid (5 ml). After 30 min a further portion of sodium nitrite (290 mg, 4.2 mmol) was added, and stirring was continued overnight. Excess of nitrous acid was destroyed by addition of sulphamic acid until the solution showed a negative test on starch/iodide paper, and the mixture was then neutralised to pH 7 by addition of 2 M aqueous sodium hydroxide. The solvent was removed and the residue was purified by column chromatography (chloroform–methanol, 9:1) to yield the *title compound* as a white amorphous solid (147 mg, 97%), m.p. 140–142 °C; $[\alpha]_D^{23}$ −51 (*c* 1.7, MeOH), ν_{max}(Nujol)/cm^{-1} 3349, 3195, 2973, 1670, 1619 and 1553; λ_{max}(EtOH)/nm 260; $\delta_H([^2H_6]DMSO–^2H_2O)$ 7.90 (1 H, s, 8-H), 6.17 (1 H, m, 2′-H), 5.92 (1 H, m, 3′-H), 5.40 (1 H, m, 1′-H), 3.47 (2 H, m, 5′-$H_{a,b}$), 2.90 (1 H, m, 4′-H), 2.62 (1 H, dt, *J* 8, 8 and 14, 6′-H_a), 2.20 (3 H, s, NH*Ac*) and 1.62 (1 H, dt, *J* 11, 11 and 14, 6′-H_b); *m*/*z* (EI) 289 (Found: M^+, 289.1169. $C_{13}H_{15}N_5O_3$ requires *M*, 289.1175).

(1′R,4′S)-2-*Amino*-9-(4-*hydroxymethylcyclopent*-2-*enyl*)-1,9-*dihydropurin*-6-*one*, (−)-*Carbovir* **1**.—Saturated methanolic ammonia (30 ml) was added to a solution of **18** (100 mg, 0.34 mmol) in methanol (10 ml), and the solution was allowed to stand at room temperature overnight. It was then evaporated and the residue was purified by column chromatography (chloroform–methanol, 4:1). The crude product was crystallised from water, to furnish the *title compound* as white crystals (49 mg, 57%), m.p. 271–273 °C (decomp.); $[\alpha]_D^{23}$ −67.5 (*c* 0.40, MeOH); ν_{max}(Nujol)/cm^{-1} 3320, 3219, 2929, 1724 and 1627; λ_{max}(pH6 buffer)/nm 253; $\delta_H([^2H_6]DMSO)$ 10.58 (1 H, br s, NH), 7.59 (1 H, s, 8-H), 6.45 (2 H, br s, NH_2), 6.11 (1 H, m, 2′-H), 5.85 (1 H, m, 3′-H), 5.33 (1 H, m, 1′-H), 4.74 (1 H, t, *J* 5, OH), 3.44 (2 H, t, *J* 7, 5′-$H_{a,b}$), 2.87 (1 H, m, 4′-H), 2.58 (1 H, dt, *J* 9, 9 and 14, 6′-H_a) and 1.57 (1 H, dt, *J* 6, 6 and 14, 6′-H_b) (Found: C, 50.4; H, 5.6; N, 26.35. $C_{11}H_{13}N_5O_2$. $0.9H_2O$ requires C, 50.14; H, 5.66; N, 26.58%).

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References

1 (*a*) R. Vince, M. Hua, J. Brownell, S. Daluge, F. Lee, W. M. Shannon, G. C. Lavelle, J. Qualls, O. S. Weislow, R. Kiser, P. G. Canonico, R. H. Schultz, V. L. Narayanan, J. G. Mayo, R. H. Shoemaker and M. R. Boyd, *Biochem. Biophys. Res. Commun.*, 1988, **156**, 1046; (*b*) R. Vince and M. Hua, *J. Med. Chem.*, 1990, **33**, 17.

2 E. L. White, W. B. Parker, L. J. Macy, S. C. Shaddix, G. McCaleb, J. A. Secrist III, R. Vince and W. M. Shannon, *Biochem. Biophys. Res. Commun.*, 1989, **161**, 393.

3 (*a*) C. Williamson, M. F. Jones, C. L. Mo, P. L. Myers, I. L. Paternoster and R. Storer, Presentation at the International Symposium on Antiviral Chemotherapy, Porto Cervo, Sardinia, Italy, October 1–5, 1989; (*b*) preceding paper.

4 (*a*) A. D. Borthwick, S. Butt, K. Biggadike, A. M. Exall, S. M. Roberts, P. M. Youds, B. E. Kirk, B. R. Booth, J. M. Cameron, S. W. Cox, C. L. P. Marr and M. Shill, *J. Chem. Soc., Chem. Commun.*, 1988, 656; (*b*) J. Balzarini, H. Baumgartner, M. Bodenteich, E. DeClerq and H. Griengl, *J. Med. Chem.*, 1989, **32**, 1861.

5 R. Vince and J. Brownell, *Biochem. Biophys. Res. Commun.*, 1990, **168**, 912.

6 K. Biggadike, A. D. Borthwick, A. M. Exall, B. E. Kirk, S. M. Roberts and P. Youds, *J. Chem. Soc., Chem. Commun.*, 1987, 1083.

7 K. Biggadike, A. D. Borthwick, D. Evans, A. M. Exall, B. E. Kirk, S. M. Roberts, L. Stephenson and P. Youds, *J. Chem. Soc., Perkin Trans. 1*, 1988, 549.

8 J. Kjellberg, M. Liljenberg and N. G. Johansson, *Tetrahedron Lett.*, 1986, **27**, 877.

9 G. V. B. Madhavan and J. C. Martin, *J. Org. Chem.*, 1986, **51**, 1287.

10 Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885.

11 M. V. Bhatt and J. R. Babu, *Tetrahedron Lett.*, 1984, **25**, 3497.

12 P. Herdewijn, J. Balzarini, M. Baba, R. Pauwels, A. Van Aerschot, G. Janssen and E. DeClerq, *J. Med. Chem.*, 1988, **31**, 2040.

13 S. J. C. Taylor, A. G. Sutherland, C. Lee, R. Wisdom, S. Thomas, S. M. Roberts and C. Evans, *J. Chem. Soc., Chem. Commun.*, 1990, 1120.

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