Synthesis from (−)-Aristeromycin and X-Ray Structure of (−)-Carbovir[1]

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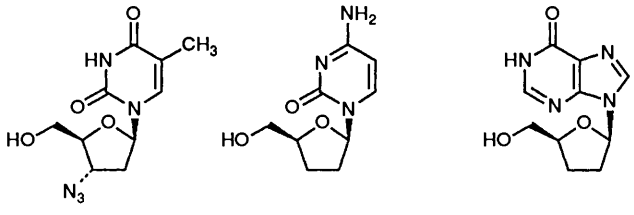
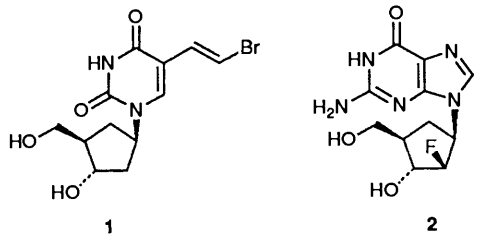
Efficient processes are described for the synthesis of (−)-carbovir **3** and its triphosphate derivative **28** from (−)-aristeromycin **4**. The X-ray structure of (−)-carbovir has been determined.

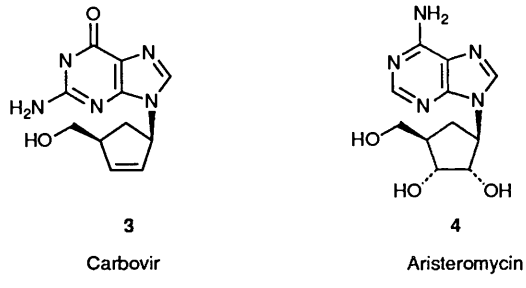
Since the emergence of 3′-azido-3′-deoxythymidine (AZT)[2] as an agent for the treatment of acquired immunodeficiency syndrome (AIDS), much attention has been focussed on 2′,3′-dideoxynucleosides in the search for superior compounds showing greater selectivity. A number of representatives of this structural class such as 2,′3′-dideoxycytidine (ddC)[3] and 2′,3′-dideoxyinosine (ddI)[4] have reached advanced stages of clinical investigation. It has been generally recognised that the potential of nucleoside analogues as therapeutic agents is limited not only by selectivity considerations but also by problems resulting from the lability of the glycosidic linkage. Various strategies have been employed in attempts to overcome the latter problem, prominent among which has been examination of the potential afforded by carbocyclic nucleoside analogues,[5] *i.e.* where the oxygen atom in the sugar-derived moiety has been replaced by a methylene linker.

A number of such compounds, *e.g.* carbocyclic 5-bromovinyl-2′-deoxyuridine **1**[6,7] and carbocyclic 2′-*ara*-fluoroguanosine **2**[8] have been shown to have potent antiherpetic activity. The discovery that carbovir **3**, synthesized in racemic form by Vince and co-workers,[9] showed potent and selective anti-HIV activity demonstrated for the first time the potential of carbocyclic nucleoside analogues as agents for the treatment of AIDS. In the cases of the antiherpetic compounds cited above, the antiviral activity has been shown[8,10] to reside principally in a single enantiomer; that corresponding to the absolute sterechemistry of the natural nucleosides. We expected that the mechanism of action of carbovir **3** would parallel that of other dideoxynucleoside analogues displaying anti-HIV activity and require intracellular phosphorylation to the triphosphate by host enzymes. We further reasoned that such enzymes would display enantioselectivity and that the anti-HIV activity shown by the racemate should reside largely in the 'natural' enantiomer. This has subsequently been shown[11] to be the case.

In consideration of synthetic approaches to carbovir, we therefore concerned ourselves exclusively with routes having the potential to prepare the required single enantiomeric form, subsequently referred to as (−)-carbovir. (−)-Aristeromycin **4** presented itself as a very attractive starting material. In our hands it was readily available as a secondary metabolite of *Streptomyces citricolor* and would afford (−)-carbovir **3** without the need to resort to an optical resolution. The required conversion of **4** into **3** involved two distinct transformations *viz*: an adenine to guanine base interconversion and introduction of the 2′,3′-double bond from the 2′,3′-diol. We report herein the synthesis of (−)-carbovir **3** using this approach and in an accompanying paper,[12] we describe an alternative synthetic strategy employing a conceptually different approach.

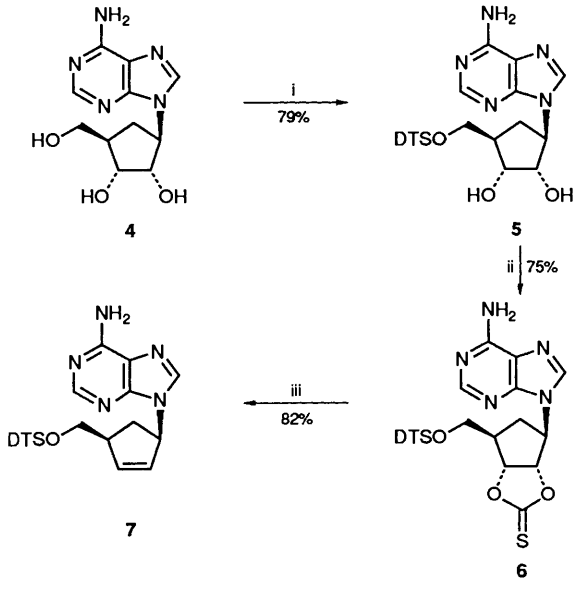




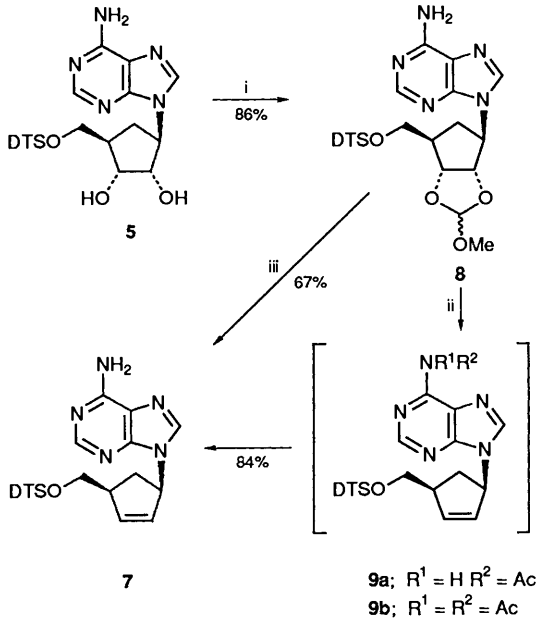


Results and Discussion

As expected,[13] reaction of (−)-aristeromycin **4** with dimethylthexylsilyl chloride[14] gave a high yield of the 5′-silyl ether **5** (Scheme 1). Treatment of **5** with 1,1′-thiocarbonyldiimidazole furnished the cyclic thionocarbonate **6** which on exposure to 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[15] (optimally 1.3 equiv.) in tetrahydrofuran at reflux under an inert atmosphere afforded the required cyclopentene **7**. In an alternative procedure (Scheme 2) the required double bond was introduced *via* the cyclic orthoester **8**, prepared in high yield by reaction of the diol **5** with trimethyl orthoformate in the presence of catalytic pyridinium toluene-*p*-sulphonate. Related ribonucleoside orthoesters have been shown[16] to undergo thermal



Scheme 1 *Reagents:* i, dimethylthexylsilyl chloride (DTSCl)/imidazole/DMF; ii, 1,1′-thiocarbonyldiimidazole/EtOAc/heat; iii, 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine/THF/heat/N_2



Scheme 2 *Reagents:* i, pyridinium tosylate/trimethyl orthoformate/Pr^i_2O/heat; ii, (*a*) Ac_2O/pyridine/heat (*b*) aqueous NaOH/heat; iii, benzoic acid/2-methoxyethyl acetate/heat/N_2

elimination with acetic anhydride at elevated temperatures. Such treatment of **8** in the presence of a catalytic quantity of pyridine resulted in the required elimination but with concomitant acylation of the 6-amino function in the purine base to afford a mixture of the mono- **9a** and di-acetyl **9b** derivatives. Hydrolysis of the mixture using aqueous sodium hydroxide furnished the required product **7**. It was subsequently shown that the conversion of **8** into **7** could be effected directly by treatment with benzoic acid in 2-methoxyethyl acetate at elevated temperature.

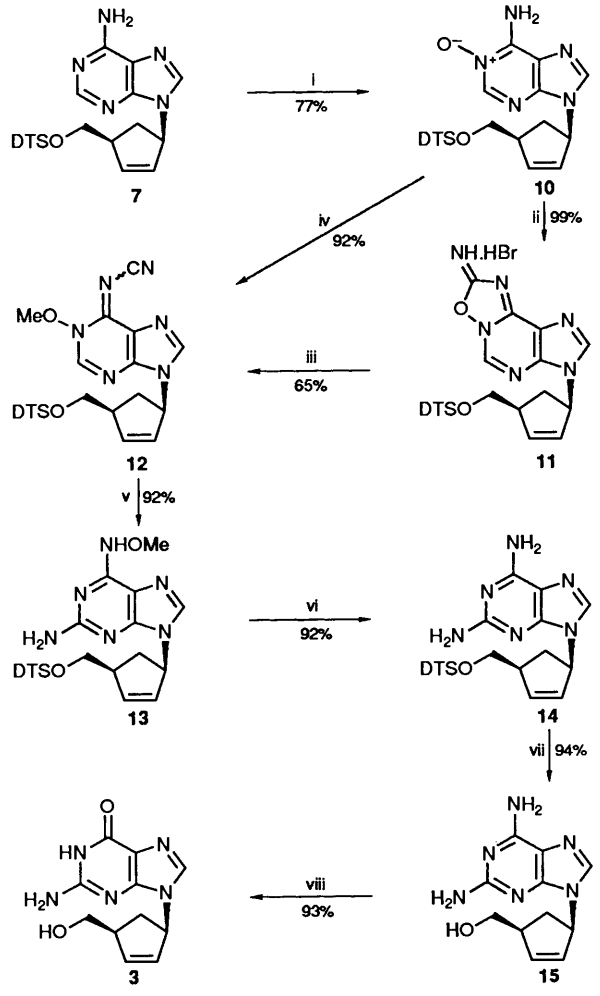
A chemical procedure for effecting adenine to guanine base transformation in nucleosides has been described by Ueda *et al.*[17] We successfully applied a modification of this method to aristeromycin[18] (*vide infra*) and it was subsequently employed in a synthesis[19] of compound **2** in optically pure form. The current work serves to exemplify further the generality of the procedure. Treatment of **7** with *m*-chloroperoxybenzoic acid in chloroform gave the required N^1-oxide **10**. Under these reaction conditions no epoxidation of the cyclopentene moiety was evident, but thorough washing with aqueous sodium hydrogencarbonate was necessary to remove *m*-chlorobenzoic acid and thus avoid salt formation with the product. Reaction of the *N*-oxide **10** with 1 equiv. of cyanogen bromide in methanol afforded the oxadiazole **11** which was isolated as the hydrobromide salt. Treatment of the salt **11** with triethylamine effected cleavage of the oxadiazole ring and methylation *in situ* of the resultant *N*-oxide gave **12**. In a more convenient one-pot procedure, a solution of *N*-oxide **10** in dimethylformamide underwent smooth conversion into **12** on sequential reaction with cyanogen bromide, triethylamine and iodomethane. The Dimroth rearrangement of **12** to afford the purine **13** was effected by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in aqueous ethanol at reflux.

The advantage of our adenine to guanine base conversion[18] over that described by Ueda[17] exploited the greater stability of the carbocyclic nucleoside to allow hydrolysis of the 6-methoxyamino function using aqueous hydrochloric acid at reflux. In the current work, however, treatment of **13** with 3M hydrochloric acid at room temperature effected only removal of the silyl protecting group and gross decomposition occurred at elevated temperatures. It was therefore necessary to employ an alternative strategy for completion of the synthesis which did not involve use of acidic conditions at elevated temperatures. Reductive cleavage[20] of the methoxyamino group was effected by treatment of **13** with freshly prepared aluminium amalgam to afford the 2,6-diaminopurine derivative **14**. Removal of the silyl group resulted from exposure of **14** to dilute hydrochloric acid in ethanol at ambient temperature to afford **15** in high yield. Hydrolysis of the diaminopurine **15** to (−)-carbovir **3** was accomplished in essentially quantitative yield by adenosine deaminase (EC.3.5.4.4) in aqueous solution maintained at pH 7.5 by the addition of phosphoric acid using an autotitrator (Scheme 3).

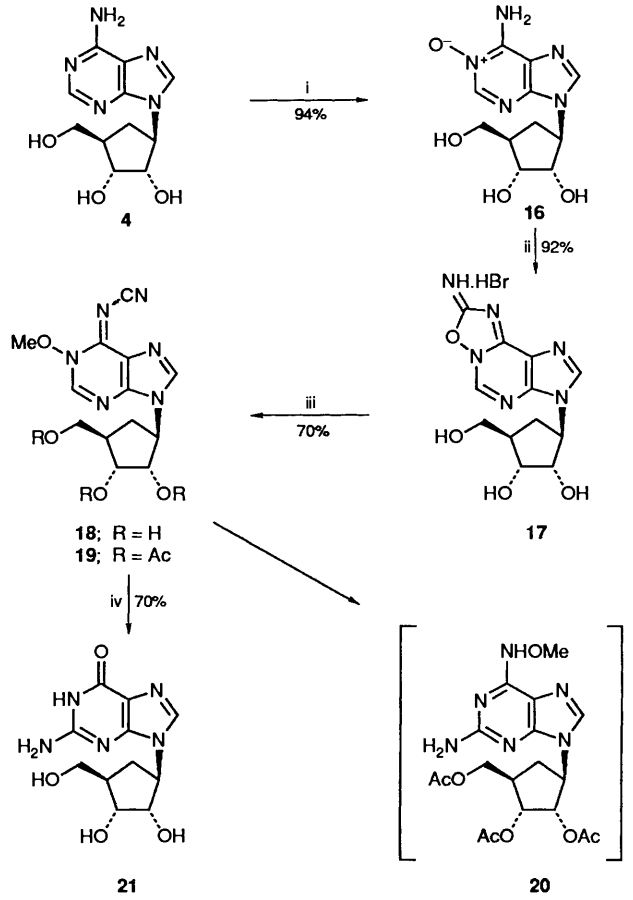
While the route described above allowed a highly efficient conversion of (−)-aristeromycin **4** into (−)-carbovir **3** we were keen to avoid a requirement for an aluminium amalgam reduction and to find a chemical approach which could provide us with alternatives to the use of adenosine deaminase. The preferred route proceeded *via* the intermediacy of (−)-carbocyclic guanosine **21**, effecting base interconversion prior to introduction of the 2′,3′ double bond.

Syntheses of (−)-carbocyclic guanosine **21** from (−)-aristeromycin **4** have been reported by workers at Takeda[21] and by ourselves[18] in the patent literature. Our procedure has the advantage of being shorter and more efficient. Thus (−)-aristeromycin **4** was treated with peracetic acid buffered with sodium acetate in aqueous acetone solution to give the *N*-oxide **16** (Scheme 4). Reaction of **16** with cyanogen bromide in methanol gave the oxadiazole **17**, which was isolated as the hydrobromide salt. Ring-opening of the oxadiazole mediated by triethylamine in dimethylformamide and *in situ* methylation of the resultant *N*-oxide using dimethyl sulphate afforded the *N*-methoxy derivative **18**. Isolation of **18** as the triol proved to be difficult but this problem was overcome by acetylation prior to purification. The Dimroth rearrangement of the triacetate **19** was effected by reaction with DBU in aqueous ethanol and afforded **20** which was hydrolysed *in situ* to (−)-carbocyclic guanosine **21** in good yield using 6M hydrochloric acid. The overall yield of this route from (−)-aristeromycin **4** was a respectable 43%.

Introduction of the 2′,3′ double bond paralleled the preferred method employed earlier in the synthesis of compound **7**. Treatment of (−)-carbocyclic guanosine **21** with dimethylthexylsilyl chloride afforded the silyl ether **22** which on



Scheme 3 *Reagents:* i, *m*-chloroperbenzoic acid/$CHCl_3$; ii, BrCN/MeOH; iii, (*a*) Et_3N/DMF, (*b*) MeI; iv, (*a*) BrCN/DMF, (*b*) Et_3N, (*c*) MeI; (v), DBU/aq EtOH/heat; vi, Al–Hg/aq. THF; vii, HCl/aq EtOH; viii, adenosine deaminase pH 7.5



Scheme 4 *Reagents:* i, peracetic acid; ii, cyanogen bromide/MeOH; iii, (*a*) Et_3N/DMF, (*b*) dimethyl sulphate, (*c*) Ac_2O/DMAP; iv, (*a*) DBU/aq EtOH/heat, (*b*) 6M HCl, (*c*) aq NaOH/heat

subsequent reaction with trimethyl orthoformate in the presence of toluene-*p*-sulphonic acid yielded the cyclic orthoester **23** as a mixture of isomers. The mixture, without purification, was subjected to treatment with acetic anhydride under reflux to afford **24**, the result of both elimination by degradation of the orthoester and acetylation of the 2-amino group in the guanine base. Stepwise deprotection of **24** using aqueous ammonia to effect *N*-deacetylation followed by treatment with hydrochloric acid to cleave the silyl ether and final neutralization using aqueous sodium hydroxide completed the alternative synthesis of (−)-carbovir **3** (Scheme 5).

The X-ray structure of (−)-carbovir was determined by single crystal analysis of a sample recrystallized from methanol. The asymmetric unit contained two crystallographically independent molecules (Figs. 1 and 2, Tables 1 and 2).

A number of dideoxynucleoside analogues which display significant anti-HIV activity have been shown[22] to adopt an unusual C-3′-*exo* ring conformation in the solid state. Clearly such a conformation is not available to (−)-carbovir **3** because of the planar nature of the C(1′)–C(4′) unit. Our data show that the compound exists in a C-6′-*endo* conformation, the equivalent of which is again rarely observed in natural nucleoside analogues.

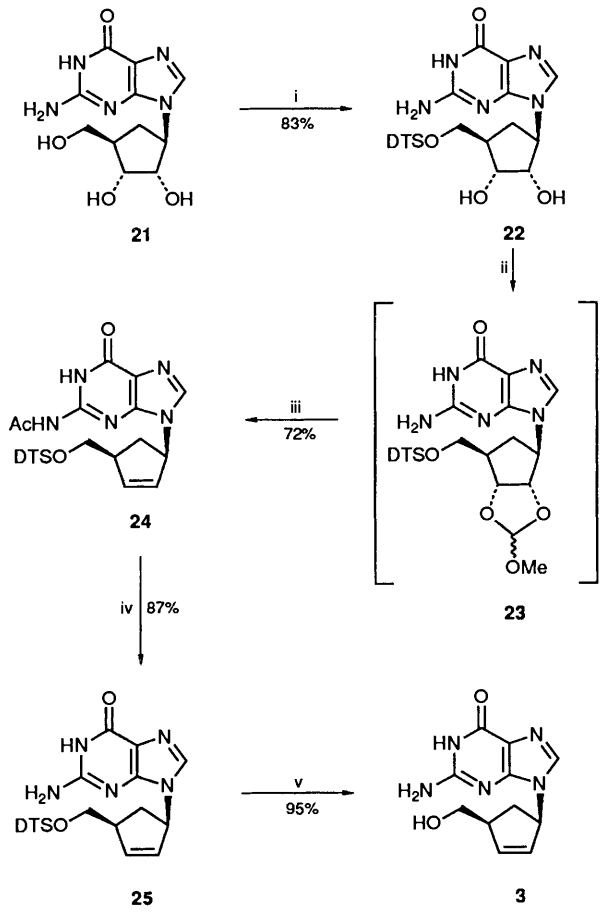
In order to examine the effect of (−)-carbovir triphosphate on HIV-reverse transcriptase, we prepared the required nucleotide derivative **28** (Scheme 6) using the method of Moffatt and Khorana.[23] Treatment of (−)-carbovir **3** with phosphorus oxychloride in trimethyl phosphate at 0 °C followed by appropriate work-up and chromatography on a charcoal column afforded the monophosphate **26** which was isolated as the ammonium salt. The morpholidate derivative **27** was obtained by reaction of monophosphate **26** with morpholine in the presence of 1,1′-dicyclohexylcarbodiimide in aqueous *tert*-butyl alcohol. Treatment of the morpholidate **27** with bis(tributylammonium) pyrophosphate in dimethyl sulphoxide afforded the required triphosphate **28** which was isolated as the ammonium salt. A minor product formed in the reaction was not isolated in pure form but was tentatively identified from its spectroscopic data as the monophosphate dimer **29**. The identity of this product was confirmed by synthesis from reaction of the morpholidate **27** with the monophosphate **26** in dimethyl sulphoxide.

Details of the anti-HIV activity of (−)-carbovir **3**[24] and inhibition of HIV-reverse transcriptase by (−)-carbovir triphosphate **28**[25] have been described elsewhere.

Following completion of this work an alternative synthesis of (−)-carbovir has been reported by other workers.[26]

Experimental

Reactions were carried out under nitrogen, and organic extract solutions were dried over magnesium sulphate, when so indicated in the text. Evaporation was performed at reduced pressure (Büchi rotary evaporators). Temperatures were recorded in °C. Solvents were of AnalaR or high quality drum grade. Dimethylformamide was dried over activated 4 Å molecular sieves. Industrial methylated spirits (IMS) is ethanol denatured with not more than 4% methanol. Charcoal was



Scheme 5 *Reagents:* i, DTSCl/imidazole/DMF; ii, pyridinium tosylate/trimethyl orthoformate/THF-IPE/heat; iii, Ac_2O/heat; iv, NH_3/MeOH; v, (*a*) HCl/Pr^{n}OH, (*b*) aq. NaOH

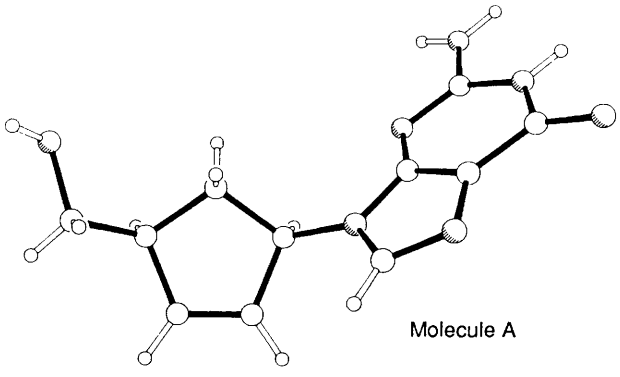


Fig. 1 X-Ray structure of (−)-carbovir (molecule A only).

supplied by Norit. ^{1}H NMR spectra were recorded in the solvent indicated at 200 or 250 MHz on a Varian SXL200 or Bruker AC250 spectrometer. ^{31}P NMR spectra were recorded on a Varian XR400 or JEOL GX500 spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane as an internal standard, coupling constants were measured in Hz. NMR assignments are labelled according to the scheme of Madhavan and Martin.[27] IR spectra were recorded on a Nicolet 5SXC or 20SXB FT instrument and UV spectra on a Perkin-Elmer Lambda 5 or Lambda 7 instrument. Molecular ion determination was performed on a Bio-Ion 20 plasma desorption time-of-flight mass spectrometer. Optical rotations were measured using a Perkin-Elmer model 241 or Optical Activity type AA-10 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a Reichert Kofler block and are uncorrected. Elemental analysis was performed on Carlo-Erba 1106 or Perkin-Elmer 240C instruments.

Table 1 Atomic coordinates ($\times 10^4$)

Atom	*x*	*y*	*z*
N(1)	7 015(8)	5 000	2 264(2)
C(2)	8 692(11)	4 920(6)	1 831(2)
N(2)	10 044(10)	6 052(6)	1 707(2)
N(3)	8 998(8)	3 845(5)	1 517(2)
C(4)	7 378(11)	2 834(6)	1 669(2)
C(5)	5 573(10)	2 809(6)	2 089(2)
C(6)	5 344(11)	3 979(6)	2 430(2)
O(6)	3 867(7)	4 149(5)	2 829(1)
N(7)	4 274(9)	1 593(5)	2 113(2)
C(8)	5 348(11)	898(6)	1 713(2)
N(9)	7 221(8)	1 599(5)	1 433(2)
C(1′)	8 654(12)	1 168(6)	945(2)
C(2′)	9 088(13)	−310(7)	910(2)
C(3′)	8 752(13)	−730(6)	382(2)
C(4′)	7 998(11)	373(6)	−30(2)
C(5′)	5 881(13)	30(7)	−502(2)
O(5′)	5 511(11)	1 198(6)	−865(2)
C(6′)	7 099(7)	1 484(5)	370(1)
N(11)	10 274(7)	10 418(5)	2 779(1)
C(12)	9 037(10)	11 117(6)	3 197(2)
N(12)	9 968(9)	12 366(6)	3 295(2)
N(13)	7 128(9)	10 621(5)	3 500(2)
C(14)	6 564(10)	9 351(6)	3 355(2)
C(15)	7 673(11)	8 561(6)	2 950(2)
C(16)	9 651(10)	9 133(6)	2 618(2)
O(16)	10 834(8)	8 603(5)	2 225(1)
N(17)	6 552(9)	7 288(5)	2 941(2)
C(18)	4 858(11)	7 324(6)	3 345(2)
N(19)	4 748(9)	8 520(5)	3 616(2)
C(11′)	3 085(10)	8 914(6)	4 080(2)
C(12′)	1 650(11)	7 794(6)	4 353(2)
C(13′)	1 682(11)	7 951(6)	4 906(2)
C(14′)	3 163(11)	9 227(6)	5 100(2)
C(15′)	4 964(13)	9 114(8)	5 644(2)
O(15′)	3 240(9)	9 261(6)	6 103(1)
C(16′)	4 769(12)	9 544(7)	4 586(2)

Adenosine deaminase [EC3.5.4.4] was supplied by Sigma (type A-1030) or Boehringer-Mannheim. The enzyme reaction was monitored with a Radiometer RT8822 recording titration system.

(1R,2S,3R,4R)-3-(6-*Aminopurin*-9-*yl*)-5-(*dimethylthexylsilyloxymethyl*)*cyclopentane*-1,2-*diol* **5**.*—Dimethylthexylsilyl chloride (200.1 g, 1.12 mol) was added to a suspension of aristeromycin **4** (300.2 g, 1.13 mol) and imidazole (300.2 g, 4.41 mol) in dimethylformamide (2.9 l) stirred at ambient temperatures. After 3 h, the mixture was poured into water (15 l), with vigorous stirring. The precipitate was filtered off, washed with water (5 l) and then dried in air at 50 °C overnight to give the *title compound* **5** (365.0 g, 79%); m.p. 182–183°; $[\alpha]_D^{22}$ −33 (*c* 1.04, MeOH) (Found: C, 55.9; H, 8.0; N, 17.3. $C_{19}H_{33}N_5O_3Si$ requires C, 56.0; H, 8.2; N, 17.2%); λ_{max}(MeOH)/nm 260.5; ν_{max}(Nujol)/cm^{-1} 3300, 3160 (OH, NH_2) and 1670 (C=N); δ_H(250 MHz, [$^2H_6$]DMSO) 8.13 (1 H, s, 2-H), 8.08 (1 H, s, 8-H), 7.20 (2 H, s, 6-NH_2), 4.99 (1 H, d, *J* 7, 2′-OH), 4.68 (2 H, m, 1′-H, 3′-OH), 4.36 (1 H, m, 2′-H), 3.84 (1 H, m, 3′-H), 3.64 (2 H, m, 5′-$H_{a,b}$), 2.20 (1 H, m, 6′-H_a), 2.08 (1 H, m, 4′-H), 1.78 (1 H, m, 6′-H_b), 1.60 (1 H, m, 2″-H), 0.8–0.9 (12 H, m, 1″-Me_2, 2″-Me_2) and 0.10 (6 H, s, $SiMe_2$).

* Thexyl has been used throughout for the radical 1,1,2-trimethylpropyl ($Me_2CHCMe_2^-$).

Table 2 Torsion angles for **3**

Mol. A		Mol. B	
C(2)–N(1)–C(6)–C(5)	0.0	C(12)–N(11)–C(16)–C(15)	−3.0
C(2)–N(1)–C(6)–O(6)	−179.5	C(12)–N(11)–C(16)–O(16)	178.1
C(6)–N(1)–C(2)–N(2)	175.8	C(16)–N(11)–C(12)–N(12)	179.4
C(6)–N(1)–C(2)–N(3)	−1.6	C(16)–N(11)–C(12)–N(13)	1.2
N(1)–C(2)–N(3)–C(4)	1.6	N(11)–C(12)–N(13)–C(14)	0.6
N(2)–C(2)–N(3)–C(4)	−175.8	N(12)–C(12)–N(13)–C(14)	−177.5
C(2)–N(3)–C(4)–C(5)	−0.1	C(12)–N(13)–C(14)–C(15)	−0.3
C(2)–N(3)–C(4)–N(9)	−179.6	C(12)–N(13)–C(14)–N(19)	176.3
N(3)–C(4)–C(5)–C(6)	−1.4	N(13)–C(14)–C(15)–C(16)	−1.8
N(3)–C(4)–C(5)–N(7)	179.6	N(13)–C(14)–C(15)–N(17)	178.8
N(3)–C(4)–N(9)–C(8)	−180.0	N(13)–C(14)–N(19)–C(18)	−178.5
N(3)–C(4)–N(9)–C(1′)	−4.2	N(13)–C(14)–N(19)–C(11′)	2.3
C(5)–C(4)–N(9)–C(8)	0.4	C(15)–C(14)–N(19)–C(18)	−1.2
C(5)–C(4)–N(9)–C(1′)	176.2	C(15)–C(14)–N(19)–C(11′)	179.6
N(9)–C(4)–C(5)–C(6)	178.2	N(19)–C(14)–C(15)–C(16)	−178.9
N(9)–C(4)–C(5)–N(7)	−0.8	N(19)–C(14)–C(15)–N(17)	1.7
C(4)–C(5)–C(6)–N(1)	1.4	C(14)–C(15)–C(16)–N(11)	3.1
C(4)–C(5)–C(6)–O(6)	−179.2	C(14)–C(15)–C(16)–O(16)	−178.1
C(4)–C(5)–N(7)–C(8)	0.9	C(14)–C(15)–M(17)–C(18)	−1.5
C(6)–C(5)–N(7)–C(8)	−177.9	C(16)–C(15)–N(17)–C(18)	179.2
N(7)–C(5)–C(6)–N(1)	−179.9	N(17)–C(15)–C(16)–N(11)	−177.6
N(7)–C(5)–C(6)–O(6)	−0.5	N(17)–C(15)–C(16)–O(16)	1.2
C(5)–N(7)–C(8)–N(9)	−0.6	C(15)–N(17)–C(18)–N(19)	0.7
N(7)–C(8)–N(9)–C(4)	0.1	N(17)–C(18)–N(19)–C(14)	0.3
N(7)–C(8)–N(9)–C(1′)	−175.5	N(17)–C(18)–N(19)–C(11′)	179.5
C(4)–N(9)–C(l′)–C(2′)	156.4	C(14)–N(19)–C(11′)–C(12′)	−170.4
C(4)–N(9)–C(1′)–C(6′)	−86.2	C(14)–N(19)–C(11′)–C(16′)	−52.9
C(8)–N(9)–C(1′)–C(2′)	−28.7	C(18)–N(19)–C(11′)–C(12′)	10.6
C(8)–N(9)–C(1′)–C(6′)	88.7	C(18)–N(19)–C(11′)–C(16′)	128.1
N(9)–C(1′)–C(2′)–C(3′)	141.2	N(19)–C(11′)–C(12′)–C(13′)	140.8
N(9)–C(1′)–C(6′)–C(4′)	−150.2	N(19)–C(11′)–C(16′)–C(14′)	−151.9
C(2′)–C(1′)–C(6′)–C(4′)	−26.3	C(12′)–C(11′)–C(16′)–C(14′)	−27.3
C(6′)–C(1′)–C(2′)–C(3′)	17.6	C(16′)–C(11′)–C(12′)–C(13′)	17.3
C(1′)–C(2′)–C(3′)–C(4′)	−0.8	C(11′)–C(12′)–C(13′)–C(14′)	0.1
C(2′)–C(3′)–C(4′)–C(5′)	−140.3	C(12′)–C(13′)–C(14′)–C(15′)	−139.9
C(2′)–C(3′)–C(4′)–C(6′)	−16.2	C(12′)–C(13′)–C(14′)–C(16′)	−17.5
C(3′)–C(4′)–C(5′)–O(5′)	−177.8	C(13′)–C(14′)–C(15′)–O(15′)	−83.0
C(3′)–C(4′)–C(6′)–C(1′)	25.7	C(13′)–C(14′)–C(16′)–C(11′)	27.0
C(5′)–C(4′)–C(6′)–C(1′)	151.0	C(15′)–C(14′)–C(16′)–C(11′)	150.9
C(6′)–C(4′)–C(5′)–O(5′)	64.6	C(16′)–C(14′)–C(15′)–O(15′)	161.2

(3aS,4R,6R,6aR)-4-(6-*Amino*-9H-*purin*-9-*yl*)-6-(*dimethylthexylsilyloxymethyl*)-3a,5,6,6a-*tetrahydrocyclopenta*-1,3-*dioxole*-2-*thione* **6**.—A suspension of **5** (354.2 g, 869 mmol) and 1,1′-thiocarbonyldiimidazole (203 g, 1.14 mol) in ethyl acetate (3.5 l) was stirred and heated at reflux for 1 h to give a turbid solution. This was cooled slightly, then treated with water (1.5 l). After a further 1.5 h, insoluble material was filtered off. Brine (500 ml) was added to the filtrate. The organic layer was separated, washed with water (2 × 500 ml) and brine (500 ml), concentrated, and then gradually diluted with diisopropyl ether (1.4 l). The resulting suspension was stirred at ambient temperature and then filtered. The collected solid was washed with diisopropyl ether (2 × 350 ml) and dried at 40 °C to give the *title compound* **6** (293.5 g, 75%); m.p. 197–198 °C; $[\alpha]_D^{22}$ −41 (*c* 1.11, MeOH) (Found: C, 53.6; H, 7.0; N, 15.6. $C_{20}H_{31}N_5O_3SSi$ requires C, 53.4; H, 6.95; N, 15.6%); λ_{max}(EtOH)/nm 240.2; ν_{max}($CHBr_3$)/cm^{-1} 3450, 3380 (NH_2) and 1630 (C=N); δ_H(250 MHz; [$^2H_6$]DMSO), 8.25 (1 H, s, 2-H), 8.13 (1 H, s, 8-H), 7.32 (2 H, br s, 6-NH_2), 5.82, 5.32 (1 H, 1 H, 2m, 2′-H and 3′-H), 5.29 (1 H, m, 1′-H), 3.6–3.8 (2 H, m, 5′-$H_{a,b}$), 2.57 (1 H, m, 4′-H), 2.26 (2 H, m, 6′-$H_{a,b}$), 1.60 (1 H, m, 2″-H), 0.84 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.12 (6 H, s, $SiMe_2$).

(1R,4S)-9-[4-(*Dimethylthexylsilyloxymethyl*)*cyclopent*-2-*enyl*]-9H-*purin*-6-*amine* **7**.—(*a*) A solution of **6** (290.6 g, 646 mmol) in tetrahydrofuran (2.25 l) was degassed with nitrogen for 50 min, treated with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (155 ml, 840 mmol) in tetrahydrofuran (250 ml) and then stirred and heated to reflux for 2 h. Solvent was removed by evaporation and the residual oil was diluted with diisopropyl ether (300 ml) to induce crystallisation. The suspension was further diluted with more diisopropyl ether (300 ml) and then filtered. The collected solid was washed with diisopropyl ether (3 × 100 ml) and then dried *in vacuo* at 40 °C to give the *title compound* **7** (165.1 g, 68%); m.p. 129–131°C; $[\alpha]_D^{22}$ −31 (*c* 1.20, MeOH) (Found: C, 61.0; H, 8.65; N, 18.7. $C_{19}H_{31}N_5OSi$ requires C, 61.1; H, 8.4; N, 18.75%); λ_{max}(EtOH)/nm 261.4; ν_{max}($CHBr_3$)/cm^{-1} 3450, 3330 (NH_2) and 1630 (C=N); δ_H(250 MHz; [$^2H_6$]DMSO), 8.14 (1 H, s, 2-H), 7.98 (1 H, s, 8-H), 7.22 (2 H, br s, 6-NH_2), 6.12 (1 H, m, 2′-H), 5.95 (1 H, m, 3′-H), 5.58 (1 H, m, 1′-H), 3.62 (2 H, d, *J* 7, 5′-$H_{a,b}$), 2.93 (1 H, m, 4′-H), 2.66 (1 H, dt, *J* 12, 7 and 7, 6′-H_a), 1.63 (1 H, dt, *J* 12, 6 and 6, 6′-H_b), 1.55 (1 H, m, 2″-H), 0.82 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.06 (6 H, s, $SiMe_2$).

(*b*) A suspension of **8** (5 g, 11 mmol) and pyridine (90 μl) in acetic anhydride (20 ml) was heated at reflux overnight, under nitrogen, to give a clear solution. Methanol (25 ml) was added, and the solution was chilled in ice before 17.5M aqueous sodium hydroxide (25 ml) was added dropwise to give a suspension of pH 8. This was adjusted to pH 7 with glacial acetic acid and then diluted with water (13 ml). The resulting suspension was stirred, ice-chilled and then filtered. The collected solid was washed with water (10 ml) and then dried at 40 °C to give the *title compound* **7** (3.5 g, 84%); m.p. 133–134 °C.

(*c*) A mixture of **8** (15.0 g, 33.3 mmol) and benzoic acid (4.0 g, 33.3 mmol) in 2-methoxyethyl acetate (100 ml) was heated at

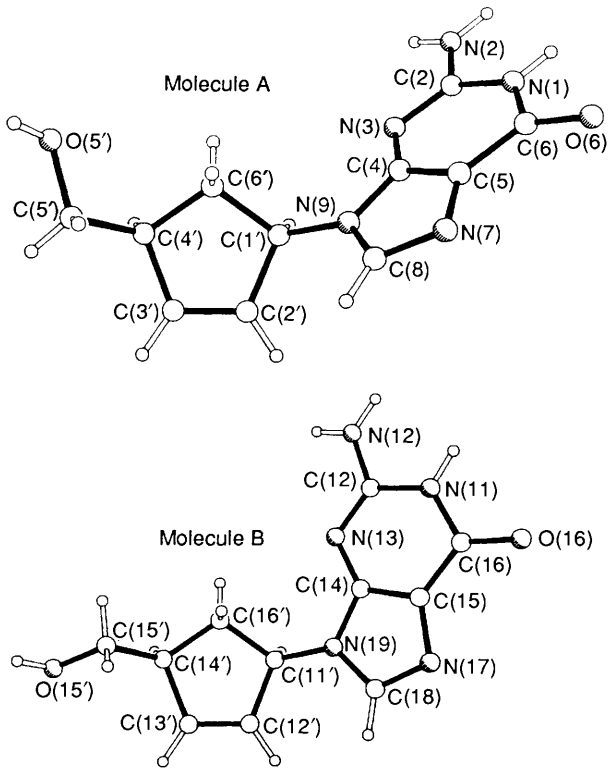
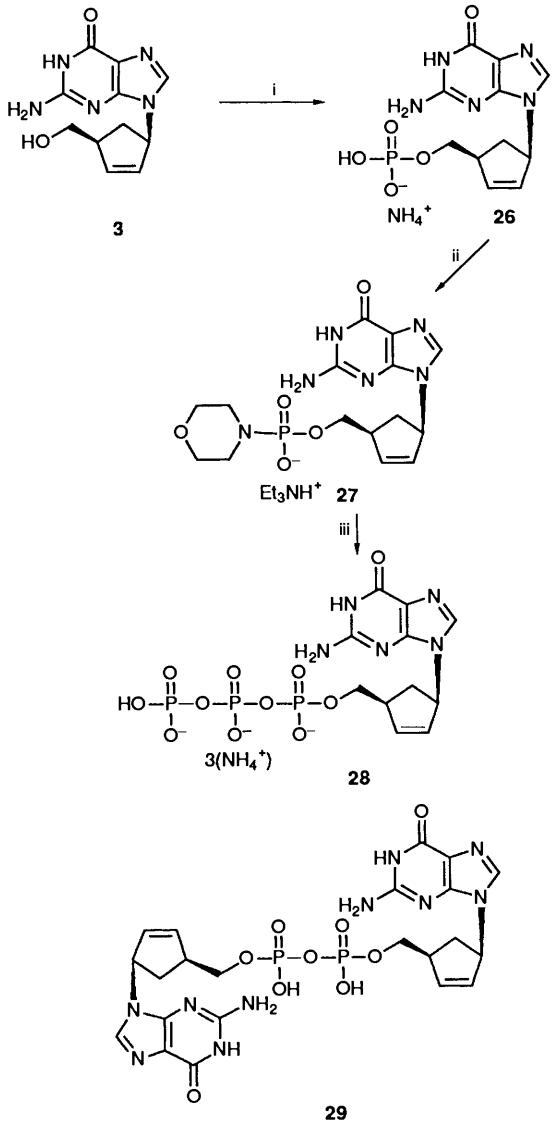


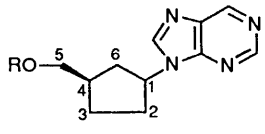
Fig. 2 X-Ray structure of (−)-carbovir (molecules A and B)

reflux under nitrogen for 14 h. Solvent was removed by evaporation and the residual oil was dissolved in diisopropyl ether (150 ml). This solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 ml) and brine (2 × 50 ml). The aqueous washes were back extracted with diisopropyl ether (25 ml). The combined organic solutions were evaporated several times with added water and diisopropyl ether, to ensure azeotropic removal of higher-boiling solvents and then finally concentrated to induce crystallisation. The collected solid was washed with diisopropyl ether (2 × 20 ml) and then dried *in vacuo* at 45 °C to give the title compound **7** (8.3 g, 67%); m.p. 133–135 °C.

(3aS,4R,6R,6aR)-9-[6-(*Dimethylthexylsilyloxymethyl*)-4,5,6,6a-*tetrahydro*-2-*methoxy*-3aH-*cyclopenta*-1,3-*dioxol*-4-*yl*]-9H-*purin*-6-*amine* **8**.—A suspension of **5** (25.0 g, 61.3 mmol) and pyridinium toluene-*p*-sulphonate (16.8 g, 67 mmol) in trimethyl orthoformate (62.5 ml, 570 mmol) and diisopropyl ether (190 ml) was heated at reflux for 10 min to give a clear solution. This was cooled and then washed with aqueous sodium hydrogen carbonate (2 × 250 ml) and brine (50 ml). The aqueous washings were back extracted with diisopropyl ether (100 ml). The combined organic solutions were concentrated, diluted with more diisopropyl ether (150 ml) to give a suspension and then filtered. The collected white solid was washed with diisopropyl ether (2 × 100 ml) and then dried *in vacuo* at 40 °C to give the isomer mixture (60:40) **8** (23.7 g, 86%); m.p. 100–115 °C; $[\alpha]_D^{22}$ −29 (*c* 1.25, MeOH) (Found: C, 56.0; H, 8.0; N, 15.5. $C_{21}H_{35}N_5O_4Si$ requires C, 56.1; H, 7.85; N, 15.6%); λ_{max}(EtOH)/nm 260.8; ν_{max}($CHBr_3$)/cm^{-1} 3500, 3400 (NH_2), 1620 (C=N) and 1060 (C–O); δ_H(200 MHz, [$^2H_6$] DMSO), 8.29, 8.25 (1 H, 2s, 2-H), 8.16 (1 H, s, 8-H), 7.22 (2 H, br s, 6-NH_2), 6.03, 5.95 (1 H, 2s, acetal CH), 5.17, 4.8–5.1, 4.64 (1 H, 1 H, 1 H, 3m, 1′-H, 2′-H and 3′-H), 3.72 (2 H, m, 5′-$H_{a,b}$), 3.36, 3.30 (3 H, 2s, acetal OMe), 2.1–2.5 (3 H, m, 4′-H and 6′-$H_{a,b}$), 1.62 (1 H, m, 2″-H), 0.88 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.12 (6 H, s, $SiMe_2$).



Scheme 6 *Reagents:* i, $POCl_3$/$PO(OMe)_3$, chromatography (aq. NH_3 eluent); ii, (*a*) H^+, (*b*) morpholine/DCC, chromatography (aq. Et_3NH^+·HCO_3^- eluent); iii, bis(tributylammonium pyrophosphate)/DMSO, chromatography (aq. NH_4^+·HCO_3^-)



(1R,4S)-6-*Amino*-9-[4-(*dimethylthexylsilyloxymethyl*)*cyclopent*-2-*enyl*]-9H-*purinium*-1-*olate* **10**.—*m*-Chloroperoxybenzoic acid (195.4 g, *ca.* 900 mmol) was added to a stirred, water-cooled solution of **7** (195.8 g, 520 mmol) in chloroform (2 l). After 3.5 h, the solution was washed with saturated aqueous sodium hydrogencarbonate (3 × 500 ml), water (500 ml) and brine (500 ml), dried ($MgSO_4$) and concentrated to induce crystallisation. This suspension was diluted with ethyl acetate (400 ml) and then filtered. The collected solid was washed with ethyl acetate (2 × 100 ml) and diisopropyl ether (2 × 100 ml) and then dried (217 g). The salt was redissolved in chloroform (2 l) and the solution was mixed with 5% aqueous sodium carbonate (500 ml) and stirred for 30 min. The mixture was then diluted with saturated brine (500 ml) and saturated aqueous sodium hydrogencarbonate (1 l). The organic layer was separated and then further washed with saturated aqueous

sodium hydrogencarbonate (2 × 1 l), water (2 × 1 l) and brine (2 × 1 l), dried ($MgSO_4$) and concentrated to induce crystallisation. The suspension was diluted with ethyl acetate (400 ml), chilled and then filtered. The collected solid was washed with ethyl acetate (2 × 100 ml) and diisopropyl ether (2 × 100 ml) and then dried *in vacuo* at 40 °C to give the *title compound* **10** (156.9 g, 77%); m.p. 253–255 °C; $[\alpha]_D^{22}$ −32 (*c* 1.03, MeOH) (Found: C, 58.4; H, 8.1; N, 18.1. $C_{19}H_{31}N_5O_2Si$ requires C, 58.6; H, 8.0; N, 18.0%); λ_{max}(EtOH)/nm 235.4, 263.8 and 300.0; $\nu_{max}(CHBr_3)/cm^{-1}$ 3450, 3330 (NH_2) and 1660 (C=N); δ_H(250 MHz, $CDCl_3$), 8.70 (1 H, s, 2-H), 7.99 (1 H, s, 8-H), 7.70 (2 H, br s, 6-NH_2), 6.23 (1 H, m, 2′-H), 5.95 (1 H, m, 3′-H), 5.70 (1 H, m, 1′-H), 3.6–3.8 (2 H, m, 5′-$H_{a,b}$), 3.04 (1 H, m, 4′-H), 2.88 (1 H, dt, *J* 13.8 and 8, 6′-H_a), 1.69 (1 H, dt, *J* 13, 6 and 6, 6′-H_b), 1.62 (1 H, m, 2″-H), 0.88 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.09 (6 H, s, $SiMe_2$).

(1R,4S)-7-[4-(*Dimethylthexylsilyloxymethyl*)*cyclopent*-2-*enyl*]-2-*imino*-1,2-*dihydro*[1,2,4]*oxadiazolo*[3,2-i]*purine Hydrobromide* **11**.—A solution of cyanogen bromide (44.4 g, 0.42 mol) in methanol (400 ml) was added over 25 min to a stirred ice-chilled suspension of **10** (155.3 g, 0.4 mol) in methanol (800 ml). After 30 min, the mixture was allowed to warm to ambient temperature and then after a further 2 h, solvent was evaporated. The residue was suspended in toluene and then re-evaporated to ensure removal of any cyanogen bromide. The resulting solid was stirred in diisopropyl ether (450 ml) and then filtered. The collected solid was washed with diisopropyl ether and then dried *in vacuo* at 40 °C to give the *title compound* **11** (196.9 g, 99.7%); m.p. 125 °C (decomp.); $[\alpha]_D^{22}$ −16 °C (*c* 1.01, MeOH) (satisfactory microanalysis was not obtained); λ_{max}(EtOH)/nm 250.2 and 294.6; $\nu_{max}(CHBr_3)/cm^{-1}$ 3100 (NH_2^+), 1710 and 1630 (C=N); δ_H(250 MHz; $CDCl_3$), 10.33 (1 H, s, 2-H), *ca.* 10.00 (2 H, br s, NH_2), 8.32 (1 H, s, 8-H), 6.24 (1 H, m, 2′-H), 6.04 (1 H, m, 3′-H), 5.91 (1 H, m, 1′-H), 3.6–3.8 (2 H, m, 5′-$H_{a,b}$), 3.03 (1 H, m, 4′-H), 2.88 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 1.68 (1 H, dt, *J* 13, 6 and 6, 6′-H_b), 1.58 (1 H, m, 2″-H), 0.82 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.09 (6 H, s, $SiMe_2$).

(1R,4S)-9-[4-(*Dimethylthexylsilyloxymethyl*)*cyclopent*-2-*enyl*]-6-*cyanoimino*-1,6-*dihydro*-1-*methoxy*-9H-*purine* **12**.—(*a*) A solution of the hydrobromide **11** (195.6 g, 390 mmol) in dimethylformamide (980 ml) was treated with triethylamine (164 ml, 1.18 mol) to give a suspension. This was ice-chilled and then treated with iodomethane (73 ml, 1.17 mol) added dropwise over 55 min; the mixture was then allowed to warm to ambient temperature. After 2 h, the resulting solution was concentrated and then slowly added to water (5 l) over 30 min to give a suspension. The collected damp solid was dissolved in ethyl acetate (2.5 l) and the resulting organic solution was separated from an aqueous layer. It was then washed with brine (2 × 500 ml), dried ($MgSO_4$) and evaporated to afford a solid. This was stirred in diisopropyl ether (400 ml) and then filtered off and washed with diisopropyl ether (2 × 200 ml) and dried *in vacuo* at 40 °C to give the *title compound* **12** (110.2 g, 65%).

(*b*) A chilled solution of cyanogen bromide (14.1 g, 133 mmol) in dimethylformamide (164 ml) was added dropwise over 10 min to a stirred, ice-chilled suspension of compound **10** (49.5 g, 127 mmol) in dimethylformamide (248 ml). The resulting solution was allowed to warm to ambient temperature. After 2.25 h, triethylamine (52 ml, 373 mmol) was added to give a suspension. This was chilled to 5 °C and then treated with iodomethane (22.6 ml, 363 mmol). The mixture was allowed to warm to ambient temperature to give a solution. After a further 1.5 h, volatile components were evaporated and the remaining solution was slowly added to water (1.4 l). The collected solid was washed with water (2 × 200 ml) and dried *in vacuo* to give the *title compound* **12** (50.2 g, 92%); m.p. 135–140 °C; $[\alpha]_D^{22}$ −16 (*c* 1.01, MeOH) (Found: C, 58.6; H, 7.4; N, 19.6. $C_{21}H_{32}N_6O_2Si$ requires C, 58.85; H, 7.5; N, 19.6%); λ_{max}(EtOH)/nm 287.0; $\nu_{max}(CHBr_3)/cm^{-1}$ 2190 (C=N) and 1630 (C=N); δ_H(250 MHz; $CDCl_3$) 8.20 (1 H, s, 2-H), 7.94 (1 H, s, 8-H), 6.23 (1 H, m, 2′-H), 5.83 (1 H, m, 3′-H), 5.64 (1 H, m, 1′-H), 4.19 (3 H, s, 1-OMe), 3.62 (2 H, m, 5′-$H_{a,b}$), 3.00 (1 H, m, 4′-H), 2.73 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 1.60 (2 H, m, 6′-H_b and 2″-H), 0.83 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.07 (6 H, s, $SiMe_2$).

(1R,4S)-9-[4-(*Dimethylthexylsilyloxymethyl*)*cyclopent*-2-*enyl*]-6-*methoxyamino*-9H-*purin*-2-*amine* **13**.—A suspension of the cyano imine **12** (109.4 g, 250 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (38 ml, 250 mmol) in water (110 ml) and ethanol (1.1 l) was stirred and heated to reflux to give a clear solution. After 80 min heating was stopped and solvents were evaporated. The residual oil was dissolved in ethyl acetate (1 l), and the solution was washed with water (4 × 250 ml) and brine (100 ml) and then concentrated before the gradual addition of diisopropyl ether (500 ml) to induce crystallisation. The resulting thick suspension was diluted with diisopropyl ether (500 ml) and ethyl acetate (100 ml) and then filtered. The collected white solid was washed with diisopropyl ether (2 × 100 ml) and then dried *in vacuo* at 40 °C to give the *title compound* **13** (88.3 g, 83%); m.p. 149–150 °C; $[\alpha]_D^{22}$ −51 (*c* 1.11, MeOH) (Found: C, 57.1; H, 8.2; N, 20.0. $C_{20}H_{34}N_6O_2Si$ requires C, 57.4; H, 8.2; N, 20.1%); λ_{max}(EtOH)/nm 281.6; $\nu_{max}(CHBr_3)/cm^{-1}$ 3500, 3400, 3330 (NH, NH_2) and 1605 and 1590 (C=N); δ_H(250 MHz; $CDCl_3$) 9.50 (1 H, br s, 6-NH), 7.64 (1 H, s, 8-H), 6.15 (1 H, m, 2′-H), 5.80 (1 H, m, 3′-H), 5.55 (1 H, m, 1′-H), 5.06 (2 H, br s, 2-NH_2), 3.92 (3 H, s, OMe), 3.58 (2 H, m, 5′-$H_{a,b}$), 2.96 (1 H, m, 4′-H), 2.74 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 1.58 (2 H, m, 6′-H_b and 2″-H), 0.84 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.07 (6 H, s, $SiMe_2$).

A second crop (10.1 g, 9%) was recovered from the liquors.

(1R,4S)-9-(4-*Dimethylthexylsilyloxymethylcyclopent*-2-*enyl*)-9H-*purine*-2,6-*diamine* **14**.—Aluminium amalgam, prepared from aluminium (145.4 g, 5.38 mol) sequentially washed with tetrahydrofuran, aqueous 1M potassium hydroxide, water (× 3), aqueous 0.56% mercuric chloride, water (× 3) and tetrahydrofuran, was added to a stirred solution of the methoxy amine **13** (97.2 g, 230 mmol) in tetrahydrofuran (2 l) and water (100 ml), causing some effervescence. After 26.5 h, solids were filtered off and washed with tetrahydrofuran (1 l). The combined filtrates were evaporated, and the residual solid was stirred with diisopropyl ether (600 ml) to give a suspension. The collected solid was washed with diisopropyl ether (2 × 100 ml) and then dried *in vacuo* at 40 °C to give the *title compound* **14** (60.2 g, 67%); m.p. 182–183 °C; $[\alpha]_D^{22}$ −108 (*c* 1.20 MeOH) (Found: C, 58.6; H, 8.3; N, 21.6. $C_{19}H_{32}N_6OSi$ requires C, 58.7; H, 8.3; N, 21.6%); λ_{max}(EtOH)/nm 256.6 and 282.6; $\nu_{max}(CHBr_3)/cm^{-1}$ 3510, 3400 (NH_2), 1625 and 1600 (C=N); δ_H(250 MHz; [$^2H_6$]DMSO), 7.55 (1 H, s, 8-H), 6.70 (2 H, br s, 2-NH_2), 6.08 (1 H, m, 2′-H), 5.92 (1 H, m, 3′-H), 5.80 (2 H, br s, 6-NH_2), 5.40 (1 H, m, 4′-H), 3.63 (2 H, m, 5′-$H_{a,b}$), 2.92 (1 H, m, 4′-H), 2.60 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 1.56 (2 H, m, 6′-H_b and 2″-H), 0.84 (12 H, m, 2″-Me_2 and 3″-Me_2) and 0.06 (6 H, s, $SiMe_2$).

A second crop (22.5 g, 25%) was obtained by further washing the aluminium solids with tetrahydrofuran–IMS (1:1) (3 × 1 l).

(1R,4S)-9-(4-*Hydroxymethylcyclopent*-2-*enyl*)-9H-*purine*-2,6-*diamine Hydrochloride* **15**.—3M Hydrochloric acid (210 ml) was added to a stirred solution of the silyl ether **14** (81.6 g, 210 mmol) in ethanol (800 ml), after which a precipitate gradually formed. After 2.25 h, solvent was evaporated and this was followed by a re-evaporation from toluene. The residual solid was stirred in ice-chilled ethanol (240 ml) and then filtered. The collected solid was washed with ethanol (2 × 40 ml) and

diisopropyl ether (2 × 80 ml), then dried *in vacuo* at 40 °C to give the hydrated *title compound* **15** (63.3 g, 94%); m.p. 240 °C (decomp); $[\alpha]_D^{22}$ −46 (*c* 0.86 MeOH) (Found: C, 41.8; H, 5.2; Cl, 20.0; N, 26.7. $C_{11}H_{14}N_6O{\cdot}0.2H_2O{\cdot}1.8HCl$ requires C, 41.9; H, 5.2; Cl, 20.2; N, 26.6%); λ_{max}(pH 6 buffer)/nm 255.0 and 281.8; ν_{max}(Nujol)/cm^{-1} 3310 (NH_2 and OH), 2720 (NH_3^+), 1695 and 1640 (C=N); δ_H(250 MHz, ^2H_2O in [$^2H_6$]DMSO), 8.04 (1 H, s, 8-H), 6.22 (1 H, m, 2′-H), 5.92 (1 H, m, 3′-H); 5.47 (1 H, m, 1′-H), 3.51 (2 H, d, *J* 6, 5′-$H_{a,b}$), 2.97 (1 H, m, 4′-H), 2.70 (1 H, dt, *J* 14, 8 and 8, 6′-H_a) and 1.67 (1 H, dt, *J* 14, 7 and 7, 6′-H_b).

(1R,2S,3R,4R)-6-*Amino*-9-(2,3-*dihydroxy*-4-*hydroxymethylcyclopentyl*)-9H-*purinium*-1-*olate* **16**.—Peracetic acid (36%; 250 ml, 940 mmol) was added over 10 min to a stirred mixture of aristeromycin **4** (200 g, 754 mmol) and sodium hydroxide (16 g, 400 mmol) in glacial acetic acid (30 ml), water (600 ml) and acetone (1.2 l) at *ca.* 15 °C. The mixture was stirred overnight and then diluted with acetone (4.8 l). The resulting suspension was stirred for 7 h before filtration. The collected solid was washed and then dried *in vacuo* at 55 °C to give the hydrated *title compound* **16** (199.5 g, 94%); m.p. 145–149 °C (decomp.), $[\alpha]_D^{22}$ −53 (*c* 1.22, MeOH) (Found: C, 45.2; H, 5.7; N, 23.5. $C_{11}H_{15}N_5O_4{\cdot}0.7H_2O$ requires C, 45.0; H, 5.6; N, 23.8%); λ_{max}(MeOH)/nm 234.5; ν_{max}(Nujol)/cm^{-1} 1660 (C=N) and 1030 (C–O); δ_H(250 MHz, [$^2H_6$]DMSO), 8.60 (1 H, s, 2-H), 8.39 (1 H, s, 8-H), 5.00 (1 H, d, *J* 6, 2′-OH), 4.70 (3 H, m, 1′-H, 3′-OH and 5′-OH), 4.31 (1 H, m, 2′-H), 3.83 (1 H, m, 3′-H), 3.48 (2 H, m, 5′-$H_{a,b}$), 2.25 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 2.04 (1 H, m, 4′-H) and 1.72 (1 H, m, 6′-H_b).

(1R,2S,3R,4R)-7-(2,3-*Dihydroxy*-4-*hydroxymethylcyclopentyl*)-2-*imino*-1,2-*dihydro*[1,2,4]*oxadiazolo*[3,2-i]*purine Hydrobromide* **17**.—Cyanogen bromide (84 g, 800 mmol) was added to a stirred suspension of **16** (200 g, 710 mmol) in methanol (4 l), chilled in ice–water. The suspension was allowed to warm to ambient temperature, to give a clear solution from which crystallisation subsequently occurred. Ethyl acetate (8 l) was added over 1.5 h, and stirring was continued for a further 1 h before filtration. The collected solid was washed with ethyl acetate (5 × 500 ml) and dried *in vacuo* at 50 °C, to give the hydrated *title compound* **17** (253.9 g, 92%); m.p. 160–163 °C (decomp.); $[\alpha]_D^{22}$ −44 (*c* 1.09, MeOH) (Found: C, 35.1; H, 4.0; Br, 19.5; N, 20.5. $C_{12}H_{14}N_6O_4{\cdot}HBr{\cdot}1.25H_2O$ requires C, 35.2; H, 4.3; Br, 19.5; N, 20.5%); λ_{max}(H_2O)/nm 228.6 and 284.0; ν_{max}(Nujol)/cm^{-1} 1720 (C=N) and 1300 (C–O); δ_H(250 MHz, [$^2H_6$]DMSO), 10.58 (2 H, br s, NH_2), 10.06 (1 H, s, 2-H), 8.98 (1 H, s, 8-H), 4.94 (1 H, q, *J* 10, 1′-H), 4.38 (1 H, dd, *J* 9, 5 and 5, 2′-H), 3.88 (1 H, m, 3′-H), 3.50 (2 H, m, 5′-$H_{a,b}$), 2.34 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 2.10 (1 H, m, 4′-H) and 1.73 (1 H, m, 6′-H_b).

(1R,2S,3R,4R)-9-(2,3-*Diacetoxy*-4-*acetoxymethylcyclopentyl*)-6-*cyanoimino*-1,6-*dihydro*-1-*methoxy*-9H-*purine* **19**.—Triethylamine (275 ml, 2.0 mol) was added to a stirred, chilled suspension of **17** (253.6 g, 655 mmol) in dimethylformamide (1 l). The mixture was stirred at *ca.* 12 °C for 20 min and then treated with dimethyl sulphate (186 ml, 2.0 mol) added carefully over 15 min, the temperature being kept < 25 °C by ice cooling. The resulting clear solution was treated with more triethylamine (92 ml, 660 mmol) and then more dimethyl sulphate (62 ml, 660 mmol). After 30 min, more triethylamine (90 ml, 645 mmol) was added. After a further 20 min, triethylamine (400 ml, 2.9 mol) and 4-dimethylaminopyridine (2.0 g, 16.4 mmol) were added and the mixture was cooled in ice; acetic anhydride (286 ml, 3.0 mol) was then added slowly. After a further 1 h, the mixture was cooled to 10 °C and diluted with iced water (500 ml), added over 5 min. Water (250 ml) was added after crystallisation began, followed by more water (3.25 l) to the resulting thick suspension. The mixture was stirred at *ca.* 10 °C for 1.5 h and then filtered. The collected solid was washed with water (3 × 300 ml) and dried *in vacuo* at 60 °C to give the hydrated *title compound* **19** (206.1 g, 70%); m.p. 204–207 °C; $[\alpha]_D^{22}$ −24 (*c* 1.13, DMSO) (Found: C, 49.9; H, 5.1; N, 18.1. $C_{19}H_{22}N_6O_7{\cdot}0.75H_2O$ requires C, 49.6; H, 5.15; N, 18.3%); λ_{max}(MeOH)/nm 221.7 and 286.7; ν_{max}(Nujol)/cm^{-1} 3100, 3050 (CH), 2160 (C=N), 1740, 1725 (OAc) and 1620 (C=N); δ_H(200 MHz), [$^2H_6$]DMSO), 8.92 (1 H, s, 2-H), 8.54 (1 H, s, 8-H), 5.62 (1 H, dd, *J* 8 and 6, 2′-H), 5.27 (1 H, dd, *J* 6 and 5, 3′-H), 5.10 (1 H, dt, *J* 11, 8 and 8, 1′-H), 4.1–4.4 (2 H, m, 5′-$H_{a,b}$), 4.13 (3 H, s, OMe), 2.4–2.7 (2 H, m, 4′-H and 6′-H_a), 2.08 (1 H, m, 6′-H_b), 2.09, 2.08 (3 H, 3 H, 2s, 2′-OAc and 3′-OAc) and 1.94 (3 H, s, 5′-OAc).

(1R,2S,3R,4R)-2-*Amino*-9-(2,3-*dihydroxy*-4-*hydroxymethylcyclopentyl*)-1,9-*dihydropurin*-6-*one* **21**.—A mixture of 1,8-diazabicyclo[5.4.0]undec-7-ene (69 ml, 461 mmol) and **19** (206 g, 461 mmol) in industrial methylated spirits (IMS) (1.4 l) and water (200 ml) was heated to reflux for 1.5 h to give a clear solution. Solvents were evaporated and the residual oil was dissolved in concentrated hydrochloric acid (280 ml) and water (280 ml). The solution was stirred overnight at *ca.* 90 °C and then concentrated. Acetone (100 ml) and water (300 ml) were added and the mixture was stirred whilst aqueous 3M sodium hydroxide (500 ml) was added. The mixture was warmed to 80 °C and then filtered to remove insoluble material. The filtrate was treated with further 3M aqueous sodium hydroxide (300 ml), added slowly, to induce crystallisation, to a final pH 7. The warm suspension was allowed to cool slowly and then chilled to −5 °C before filtration. The collected solid was washed with water (3 × 300 ml) and IMS (300 ml) and then dried *in vacuo* at 60 °C to give the hydrated *title compound* **21** (91.1 g, 70%); m.p. 297–298 °C (decomp.) [lit.,[2] 268–270 °C (decomp.)]; $[\alpha]_D^{22}$ −35 (*c* 1.22, DMSO); $[\alpha]_D^{22}$ −30.8 (*c* 0.98, DMF) [lit.,[2] $[\alpha]_D^{22}$ −31.4 (*c* 0.67, DMF)] (Found: C, 42.2; H, 5.95; N, 22.5. Calc. for: $C_{11}H_{15}N_5O_4{\cdot}1.75H_2O$: C, 42.2; H, 6.0; N, 22.4%), λ_{max}(H_2O)/nm 253.0; ν_{max}(Nujol)/cm^{-1} 3330 (NH, OH) 1728 (cyclic amide) and 1630 (C=N); δ_H(250 MHz, [$^2H_6$]DMSO), 10.54 (1 H, br s, NH), 7.79 (1 H, s, 8-H), 6.38 (2 H, br s, 2-NH_2), 4.90 (1 H, d, *J* 6, 2′-OH), 4.70 (1 H, t, *J* 5, 5′-OH), 4.59 (1 H, d, *J* 4, 3′-OH), 4.54 (1 H, m, 1′-H), 4.19 (1 H, m, 2′-H), 3.79 (1 H, m, 3′-H), 3.45 (2 H, m, 5′-$H_{a,b}$), 2.18 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 1.98 (1 H, m, 4′-H) and 1.48 (1 H, m, 6′-H_b).

(1R,2S,3R,4R)-2-*Amino*-9-[2,3-*dihydroxy*-4-(*dimethylthexylsilyloxymethyl*)*cyclopentyl*]-1,9-*dihydropurin*-6-*one* **22**.—Dimethylthexylsilyl chloride (13.4 ml, 68 mmol) was added dropwise to a stirred suspension of imidazole (9.25 g, 136 mmol) and **21** (19.2 g, 68 mmol) in dry dimethylformamide (192 ml) at *ca.* 12 °C. More dimethylthexylsilyl chloride and imidazole (totals 3.3 ml, 16.7 mmol and 2.3 g, 34 mmol) were added after 3 h and then after a further 40 min. The mixture was left at ambient temperature for 48 h and then diluted with methyl isobutyl ketone (50 ml). Water (384 ml) was added slowly over 1 h, to induce crystallisation. The resulting suspension was ice-chilled for 45 min and then filtered. The collected solid was washed with water (4 × 50 ml), methyl isobutyl ketone (2 × 50 ml) and diisopropyl ether (2 × 50 ml) and dried *in vacuo* at 60 °C to give the *title compound* **22** (24.0 g, 83%); m.p. 313–315 °C (decomp.); $[\alpha]_D^{22}$ −31 (*c* 0.46, DMSO) (Found: C, 53.65; H, 7.8; N, 16.2. $C_{19}H_{33}N_5O_4Si$ requires C, 53.9; H, 7.85; N, 16.5%); λ_{max}(MeOH)/nm 255.2; ν_{max}(Nujol)/cm^{-1} 3300, 3150, 2700 (NH, OH), 1705 (cyclic amide) and 1100 (C-O); δ_H(200 MHz, [$^2H_6$]DMSO) 10.50 (1 H, br s, NH), 7.73 (1 H, s, 8-H), 6.34 (2 H, br s, 2-NH_2), 4.94 (1 H, d, *J* 6, 2′-OH), 4.55 (2 H, m, 1′-H and 3′-OH), 4.20 (1 H, m, 2′-H), 3.80 (1 H, m, 3′-H), 3.62 (2 H, m, 5′-$H_{a,b}$), 2.22 (1 H, dt, *J* 12, 8 and 8, 6′-H_a), 2.07 (1 H, m, 4′-H), 1.61 (1 H, m, 2″-H), 1.48 (1 H, m, 6′-H_b), 0.86 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.12 (6 H, s, $SiMe_2$).

(1R,4S)-2-*Acetamido*-9-[4-(*dimethylthexylsilyloxymethyl*)-*cyclopent*-2-*enyl*]-1,9-*dihydropurin*-6-*one* **24**.—Pyridinium toluene-*p*-sulphonate (13.5 g, 54 mmol) and trimethyl orthoformate (240 ml, 2.2 mol) were added to a stirred suspension of **22** (116.3 g, 275 mmol) in tetrahydrofuran (600 ml) and diisopropyl ether (1.2 l). The mixture was heated to reflux for 1.5 h, cooled to *ca.* 15 °C and then diluted with water (600 ml). The organic layer was separated and washed with 8% aqueous sodium hydrogen carbonate (2 × 600 ml) and 30% aqueous sodium chloride (300 ml). The combined aqueous solutions were back-extracted with a mixture of tetrahydrofuran (50 ml), diisopropyl ether (100 ml) and ethyl acetate (150 ml). The organic solutions were combined and evaporated to afford a foam (158 g). This was dissolved in acetic anhydride (1.2 l) by heating at 90 °C for 30 min. The resulting solution was heated at 130 °C for 30 min at reflux, and then for 2.5 h as *ca.* 100 ml of distillate was collected. The resulting solution was cooled, and concentrated to give a thick suspension. This was cooled and diluted with diisopropyl ether (1.4 l). After overnight refrigeration, the suspension was filtered and the collected solid was washed with diisopropyl ether (3 × 100 ml) and dried *in vacuo* at 60 °C to give the hydrated *title compound* **24** (72.9 g, 72%); m.p. 218–222 °C; $[\alpha]_D^{22}$ −71 (*c* 1.14, MeOH) (Found: C, 57.05; H, 7.8; N, 15.9. $C_{21}H_{33}N_5O_3Si{\cdot}0.5H_2O$ requires C, 57.2; H, 7.8; N, 15.9%); λ_{max}(MeOH)/nm 260.7; ν_{max}($CHBr_3$)/cm^{-1} 3480 (NH), 1715, 1703, 1681 (cyclic and acyclic amides) and 1560 (acyclic amide); δ_H(200 MHz, [$^2H_6$]DMSO), 7.80 (1 H, s, 8-H), 6.14 (1 H, m, 2′-H), 5.97 (1 H, m, 3′-H), 5.43 (1 H, m, 1′-H), 3.60 (2 H, d, *J* 6, 5′-$H_{a,b}$), 2.93 (1 H, m, 4′-H), 2.63 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 2.17 (3 H, s, acetamide), 1.57 (2 H, m, 6′-H_b and 2″-H), 0.80 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.04 (6 H, s, $SiMe_2$).

(1R,4S)-2-*Amino*-9-[4-(*dimethylthexylsilyloxymethyl*)*cyclopent*-2-*enyl*]-1,9-*dihydropurin*-6-*one* **25**.—Aqueous ammonia (*d* 0.88) (120 ml) was added to a warm solution of **24** (72.7 g, 168 mmol) in methanol (725 ml) and water (120 ml) and the resulting solution was heated at *ca.* 65 °C for 1.25 h. Authentic product was used to seed the solution, which gave a suspension on cooling. After refrigeration, the solid was filtered off, washed with aqueous methanol (1:3) (3 × 100 ml) and dried *in vacuo* to give the *title compound* **25** (56.9 g, 87%); m.p. 282–284 °C; $[\alpha]_D^{22}$ −84 (*c* 1.10, MeOH) (Found: C, 58.7; H, 8.1; N, 18.0. $C_{19}H_{31}N_5O_2Si$ requires C, 58.6; H, 8.0; N, 18.0%); λ_{max}(MeOH)/nm 255.0; ν_{max}($CHBr_3$)/cm^{-1} 3308, 3140 (NH, NH_2) and 1690 (cyclic amide); δ_H(200 MHz, [$^2H_6$]DMSO); 10.52 (1 H, br s, NH), 7.52 (1 H, s, 8-H), 6.41 (2 H, br s, 2-NH_2), 6.10 (1 H, m, 2′-H), 5.92 (1 H, m, 3′-H), 5.37 (1 H, m, 1′-H), 3.61 (2 H, d, *J* 6, 5′-$H_{a,b}$), 2.92 (1 H, m, 4′-H), 2.51 (1 H, dt, *J* 13, 8 and 8, 6′-H_a), 1.62 (2 H, m, 6′-H_b and 2″-H), 0.83 (12 H, m, 1″-Me_2 and 2″-Me_2) and 0.07 (6 H, s, $SiMe_2$).

(1R,4S)-2-*Amino*-1,9-*dihydro*-9-[4-(*hydroxymethyl*)*cyclopent*-2-*enyl*]*purin*-6-*one* **3** *Hydrochloride*.—Concentrated hydrochloric acid (22 ml, 240 mmol) was added to a suspension of **25** (56.8 g, 146 mmol) in propan-1-ol (570 ml) and water (50 ml) to give a clear solution from which crystals began to form. After 6 h, the suspension was filtered and the collected solid was washed with propan-1-ol (100 ml) and diisopropyl ether (2 × 100 ml) and then dried to give the hydrated *title salt* **26** (40.2 g, 97%); m.p. 178–181 °C; $[\alpha]_D^{22}$ −76 (*c* 1.06, MeOH) (Found: C, 43.8; H, 5.5; Cl, 11.7; N, 22.8. $C_{11}H_{13}N_5O_2{\cdot}HCl{\cdot}1.1H_2O$ requires C, 43.5; H. 5.4; Cl, 11.7; N, 23.1%); λ_{max}(MeOH)/nm 255.4; ν_{max}(Nujol)/cm^{-1} 3430, 3300 (NH, OH), 2400 (NH_2^+ or NH_3^+), 1730, 1710 (cyclic amide), and 1625 and 1590 (C=N); δ_H(200 MHz, ^2H_2O) 8.79 (1 H, s, 8-H), 6.37 (1 H, m, 2′-H), 6.02 (1 H, m, 3′-H), 5.66 (1 H, m, 1′-H), 3.66 (2 H, m, 5′-$H_{a,b}$), 3.12 (1 H, m, 4′-H), 2.90 (1 H, dt, *J* 14, 8 and 8, 6′-H_a) and 1.77 (1 H, dt, *J* 14, 5 and 5, 6′-H_b).

(1R,4S)-2-*Amino*-1,9-*dihydro*-9-(4-*hydroxymethylcyclopent*-2-*enyl*)*purin*-6-*one*, (−)-*Carbovir*, **3**.—(*a*) A solution of the hydrochloride **15** (62.2 g, 195 mmol) in water (2.7 l) at 37 °C was adjusted to pH 7.50 and treated with adenosine deaminase (59,500 units) in 0.5M disodium phosphate buffer (pH 7.5; 300 ml). An auto-titrator was used to maintain pH 7.5 by the addition of 10% phosphoric acid. After 47.5 h, the resulting suspension was refrigerated overnight. The collected white solid was washed with water (2 × 50 ml), and then dried *in vacuo* at 40 °C to give hydrated (−)-*carbovir* **3** (47.9 g, 93%); m.p. 278–283 °C (decomp.); $[\alpha]_D^{22}$ −67 (*c* 1.0, MeOH) (Found: C, 50.4; H, 5.5; N, 27.1; H_2O, 5.2. $C_{11}H_{13}N_5O_2{\cdot}0.75H_2O$ requires C, 50.7; H, 5.6; N, 2.69; H_2O 5.2%); λ_{max}(MeOH)/nm 255; ν_{max}(Nujol)/cm^{-1} 3410, 3310, 3210 (NH_2, OH), 1724 (cyclic amide) and 1632 (C=N); δ_H(250 MHz, [$^2H_6$]DMSO), 10.56 (1 H, br s, 1-H), 7.60 (1 H, s, 8-H), 6.44 (2 H, br s, 2-NH_2), 6.11 (1 H, m, 2′-H), 5.88 (1 H, m, 3′-H), 5.33 (1 H, m, 1′-H), 4.73 (1 H, m, 5′-OH), 3.41 (2 H, m, 5′-$H_{a,b}$), 2.87 (1 H, m, 4′-H), 2.58 (1 H, dt, *J* 14, 9 and 9, 6′-H_a) and 1.58 (1 H, dt, *J* 14, 6 and 6, 6′-H_b).

(*b*) A solution of **26** (40.0 g, 141 mmol) in water (300 ml) and propan-1-ol (150 ml) was treated with charcoal (1 g), stirred for 20 min and then filtered. Solids were washed with water–propan-1-ol (2:1 v/v, 20 ml). The combined filtrates were stirred with more charcoal (3 g) and treated as above. Finally, the solution was treated with aqueous 1.5M sodium hydroxide (*ca.* 50 ml) to induce crystallisation. More 1.5M sodium hydroxide (*ca.* 45 ml) was added after 20 min to bring the solution to pH 6.4. The resulting suspension was concentrated, ice-chilled and filtered. The collected solid was washed with chilled water (2 × 100 ml), dried at 50 °C overnight and then re-equilibrated with air, to give the hydrated *title compound* **3** (35.6 g, 96%); m.p. 274–276 °C (decomp.), mixed m.p. with authentic material 278–281 °C (decomp.); $[\alpha]_D^{22}$ −68 (*c* 1.0, MeOH) (Found: C, 50.2; H, 5.4; N, 26.8. Calc. for $C_{11}H_{13}N_5O_2{\cdot}0.9H_2O$: C, 50.15; H, 5.7; N, 26.6%); λ_{max}(MeOH)/nm 255; ν_{max}(Nujol)/cm^{-1} 3400, 3310, 3200 (NH_2 and OH), 1725 (cyclic amide) and 1630 (C=N); δ_H(200 MHz, [$^2H_6$]DMSO), 10.6 (1 H, br s, NH), 7.62 (1 H, s, 8-H), 6.44 (2 H, br s, 2-NH_2), 6.12 (1 H, m, 2′-H), 5.88 (1 H, m, 3′-H), 5.36 (1 H, m, 1′-H), 4.72 (1 H, m, 5′-OH), 3.46 (2 H, m, 5′-$H_{a,b}$), 2.89 (1 H, m, 4′-H), 2.60 (1 H, dt, *J* 14, 9 and 9, 6′-H_a) and 1.60 (1 H, dt, *J* 14, 6 and 6, 6′-H_b).

X-Ray Experimental Data for (−)-*Carbovir*.—*Crystal data*. $C_{11}H_{13}N_5O_2$, M = 247.2. Crystallises from methanol as clear, colourless, hexagonal plates. Monoclinic, a = 4.8934(6), b = 10.056(2), c = 23.639(4) Å, β = 94.374(12)°, V = 1159.8(4) Å^3 (by least-squares refinement on diffractometer angles for 20 automatically centred reflections, λ = 1.541 84 Å). Space group $P2_1$ (No. 4), Z = 4, D_c = 1.42 g cm^{-3}. Dimensions of data crystal 0.16 × 0.18 × 0.02 mm, cut from a plate. F(000) = 520, μ(Cu-K_α) = 0.81 mm^{-1}.

Data collection and processing. Three-dimensional, room temperature (295 K) X-ray data collected on a Nicolet R3m/V diffractometer with monochromatised Cu-K_α X-radiation. $2\theta/\omega$ mode with scan range (ω) 1.12° plus K_α separation and a variable scan speed (1.72–9.77° min^{-1}). 3716 Reflections measured (1.0 < 2θ < 115°, min. *hkl* 0 −12 −26, max. *hkl* 6 12 26 1685 unique reflections [R(sigma) = 0.048, Friedel opposites merged]. 2271 Reflections with $I > 3.0\ \sigma(I)$ (point group symmetry) used for refinement. No absorption correction. 3 Control reflections monitored every 97 reflections showed no appreciable decay during 59.4 h of exposure of the crystal to X-rays.

Structure analysis and refinement. Direct methods resulted in the location of all the non-hydrogen atoms. Full matrix least-squares refinement with anisotropic thermal parameters for all non-hydrogen atoms. Evidence of hydrogen atoms seen on low angle diffraction map (sin θ < 50°). Hydrogen atoms placed

in idealized positions and then freely refined. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.000\,58|F_o|^2]^{-1}$ refinement converged at R 0.0441, R_w 0.0447, goodness-of-fit = 1.22. Max. shift/error in final cycle of refinement 0.013. The absolute configuration was not determined unequivocally due to insufficient anomalous scattering. The results presented are the most likely from the X-ray experiment and are consistent with the known chemistry. The two crystallographically independent molecules have identical conformations of the central ring, they differ only in the rotational arrangement of the attached groups. The final electron density difference synthesis showed no peaks >0.48 or <-0.47 eÅ^{-3}. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[28] Atomic co-ordinates for non-hydrogen atoms are listed in Table 1. A Table of conformational angles (Table 2) is also provided. A complete list of bond lengths and angles, hydrogen atom co-ordinates and thermal parameters has been deposited at the Cambridge Crystallographic Data Centre.*

(1R,4S)-2-*Amino*-1,9-*dihydro*-9-[4-(*hydroxymethyl*)*cyclopent*-2-*enyl*]*purin*-6-*one Phosphate* **26**.—(−)-Carbovir **3** (1.001 g, 4.05 mmol) was added over 10 min to a stirred, ice-chilled solution of phosphorus oxychloride (2.44 ml, 24.4 mmol) in trimethyl phosphate (40 ml). After 5 h at *ca.* 0 °C the resulting solution was poured into ice-chilled water (50 ml). The mixture was adjusted to pH 2.5 with aqueous 2M sodium hydroxide (*ca.* 25 ml) and washed with chloroform (3 × 100 ml). The aqueous solution was applied to a charcoal column (DARCO; 15 g), which was eluted with water (350 ml) and then ethanol-aqueous ammonia. Appropriate fractions was combined, concentrated and freeze-dried to give the *monophosphate* **26** as the ammonium salt, a white solid (1.185 g, 85%); $[\alpha]_D^{22}$ −68.2 (*c* 0.1 in H_2O); $\lambda_{max}(H_2O)$/nm 251.8; ν_{max}(Nujol)/cm^{-1} 2800–3600 (OH, NH) and 1690 (cyclic amide); δ_H(250 MHz, ^2H_2O), 7.86 (1 H, s, 8-H), 6.25 (1 H, m, 2′-H), 5.93 (1 H, m, 3′-H), 5.43 (1 H, m, 1′-H), 3.88 (2 H, t, *J* 6, 5′-$H_{a,b}$), 3.16 (1 H, m, 4′-H), 2.78 (1 H, dt, *J* 14, 9 and 9, 6′-H_a) and 1.68 (1 H, dt, *J* 14, 6 and 6, 6′-H_b).

(1R,4S)-2-*Amino*-1,9-*dihydro*-9-(4-*hydroxymethylcyclopent*-2-*enyl*)*purin*-6-*one Hydrogen Morpholinophosphinate* **27**.—The monophosphate ammonium salt **26** (500 mg, 1.45 mmol) in water was acidified to pH 2. The mixture was evaporated, and the residue was triturated with water (10 ml). The resulting solid was filtered off to give the free acid (348 mg, 73%). This was dissolved in water (14.3 ml) and *tert*-butyl alcohol (14.3 ml) at reflux and treated first with morphine (0.36 ml, 4.24 mmol) and then, over the following 2 h whilst reflux was maintained, a solution of 1,1′-dicyclohexylcarbodiimide (0.87 g, 4.24 mmol) in *tert*-butyl alcohol (20 ml). After a further 2 h at reflux, solvents were removed by evaporation, and the residue was treated with water (20 ml). Insoluble material was filtered off and the filtrate was washed with diethyl ether (3 × 30 ml). The aqueous layer was evaporated and the residue in water (5 ml) was applied to a column containing Dowex-1 1X2-200 (HCO_3^- form). Elution was performed with a linear gradient from water to 0.5M aqueous triethylammonium hydrogen carbonate. Appropriate fractions were combined and concentrated and then evaporated three times from methanol. The residue was dissolved in water and then freeze-dried to give the intermediate **27** as a triethylammonium *salt*, a light brown foam (510 mg, 99%); δ_H(250 MHz, ^2H_2O) 7.82 (1 H, s, 8-H), 6.27 (1 H, m, 2′-H), 6.00 (1 H, m, 3′-H), 5.38 (1 H, m, 1′-H), 3.79 (2 H, m, 5′-$H_{a,b}$), 3.57 (4 H, m, 3″-H_2 and 3‴-H_2), 3.21 (6 H, q, *J* 7, CH_2 of Et_3N), 3.08 (1 H, q, *J* 7, 4′-H), 2.92 (4 H, m, 2″-H_2 and 2‴-H_2), 2.76 (1 H, dt, *J* 14, 9 and 9, 6′-H_a), 1.70 (1 H, dt, *J* 14, 5 and 5, 6′-H_b) and 1.28 (9 H, t, *J* 7, CH_3 of Et_3N).

(1R,4S)-2-*Amino*-1,9-*dihydro*-9-[4-(*hydroxymethyl*)*cyclopent*-2-*enyl*]*purin*-6-*one Triphosphate* **28**.—The salt **27** (300 mg, 0.60 mmol), dried by evaporation with pyridine (2 × 15 ml) and then toluene (2 × 10 ml), was treated with a solution of bis(tributylammonium) pyrophosphate (*ca.* 2.68 mmol) in dry dimethyl sulphoxide (total 28 ml). The resulting solution was stirred at ambient temperature for 5 days and then quenched by the addition of water (40 ml). The solution was applied to a column containing 20 g of DEAE Sephadex A-25 (HCO_3^- form). Elution was performed with water (400 ml) and then a linear gradient from water (250 ml) to 0.4M aqueous ammonium hydrogen carbonate solution (250 ml), then neat 0.4M aqueous ammonium hydrogen carbonate (1 l). Fractions containing crude triphosphate were combined, concentrated, and freeze-dried (179 mg). The concentrate was dissolved in water (2 ml) and the solution re-applied to a column containing 20 g of DEAE Sephadex A-25 (HCO_3^- form). Elution was performed with a linear gradient from water to 0.4M aqueous ammonium hydrogen carbonate and finally neat 0.4M aqueous ammonium hydrogen carbonate. Appropriate fractions were combined, concentrated and freeze-dried to give the *triphosphate ammonium salt* **28** as a white solid (68 mg, 19%); δ_H(250 MHz, ^2H_2O), 7.93 (1 H, s, 8-H), 6.26 (1 H, m, 2′-H), 5.92 (1 H, m, 3′-H), 5.48 (1 H, m, 1′-H), 4.04 (2 H, m, 5′-$H_{a,b}$), 3.20 (1 H, m, 4′-H), 2.81 (1 H, dt, *J* 14, 9 and 9, 6′-H_a), 1.73 (1 H, dt, *J* 14, 6 and 6, 6′-H_b); δ_P(500 MHz, ^2H_2O) − 10.44 (1 P, d, *J* 18.8, Pδ), −10.58 (1 P, d, *J* 19.7, Pα), −22.82 (1 P, t, *J* 19.7, Pβ).

9,9′-*Oxybis*[*phosphinicooxymethylenecyclopent*-2-*en*-1,4-*diyl*]-bis(2-*amino*-1,9-*dihydropurin*-6-*one*) **29**.—A suspension of the anhydrous salt **27** (100 mg, 0.2 mmol) [repeated evaporation from pyridine (4 × 20 ml) and toluene (2 × 10 ml)] and anhydrous monophosphate ammonium salt **26** (69 mg, 0.2 mmol) [by repeated evaporation from pyridine (4 × 20 ml), then toluene (2 × 10 ml)] in dimethyl sulphoxide (3.3 ml) was stirred at ambient temperature for 12.5 days. The resulting solution was diluted with water (15 ml) and then applied to a column containing DEAE Sephadex A-25 (20 g; HCO_3^- form). Elution was performed with water (250 ml), a linear gradient from water to 0.4M aqueous ammonium hydrogen carbonate (total 400 ml) and then neat 0.4M aqueous ammonium hydrogen carbonate. Appropriate fractions were combined, concentrated then freeze-dried to give the dimer **29** (30.6 mg, 25%); δ_H(250 MHz, ^2H_2O), 8.10 (2 H, br s, 2 × 8-H), 6.27 (2 H, m, 2 × 2′-H), 5.93 (2 H, m, 2 × 3′-H), 5.50 (2 H, m, 2 × 1′-H), 4.11 (4 H, br s, 2 × 5′-$H_{a,b}$), 3.22 (2 H, br s, 2 × 4′-H), 2.81 (2 H, dt, *J* 14, 9 and 9, 2 × 6′-H_a), 1.66 (2 H, dt, *J* 14, 6 and 6, 2 × 6′-H_b); δ_P(400 MHz, ^2H_2O) −10.25 (s); *m/z* 637.8 ($C_{22}H_{26}N_{10}O_9P_2$ requires MH^+ 636.5).

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* For details of the CCDC scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1991, issue 1.

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