Conformationally locked carbocyclic nucleosides built on a bicyclo[3.1.0]hexane template with a fixed Southern conformation. Synthesis and antiviral activity

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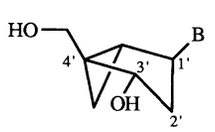
The construction of carbocyclic nucleosides with a fixed $_3$E ring pucker in the Southern hemisphere of the pseudorotational cycle is achieved from a common precursor carbocyclic amine, (1*S*,3*S*,4*R*,5*S*)-3-benzyloxy-4-benzyloxymethyl-1-aminobicyclo[3.1.0]hexane 20. This carbocyclic amine is efficiently assembled from optically pure 2-benzyloxymethylcyclopent-3-enol 11 in ten steps. The key cyclopropanation step is performed on (3*R*,4*S*)-1-cyano-4-benzyloxy-3-(benzyloxymethyl)cyclopentane 15, and proceeds regio- and stereo-selectively to give the critical cyanocarbocyclic intermediate 17 from which the amine 20 is subsequently obtained. Synthesis of the pyrimidine analogues 6–8 is accomplished *via* the intermediate acyclic acryloylureas 21 and 22. Preparation of purines 9 and 10 required prior *N*-formylation of the corresponding 4,6-dichloro-5-aminopyrimidine and 4,6-dichloro-2,5-diaminopyrimidine heterocyclic precursors for efficient coupling with amine 20. Except for (*S*)-2′-deoxy-*methanocarba*-A (9, the 2′-deoxyadenosine analogue), all Southern conformers appear to be devoid of antiviral activity.

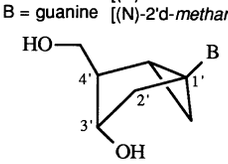
Introduction

Carbocyclic nucleosides built on a bicyclo[3.1.0]hexane template have a rigid pseudosugar ring that results in compounds with either a fixed Northern $_2$E (C2′-*exo*) or Southern $_3$E (C3′-*exo*) conformation, as defined in the pseudorotational cycle,[1] depending on the disposition of the base and the hydroxymethyl group. Syntheses of the Northern rigid conformers bearing all common bases (**1**–**5**) have been accomplished recently,[2]



$_2$E (C2′-*exo*, North)

1, B = thymine [(N)-*methanocarba*-T]
2, B = uracil [(N)-2′d-*methanocarba*-U]
3, B = cytosine [(N)-2′d-*methanocarba*-C]
4, B = adenine [(N)-2′d-*methanocarba*-A]
5, B = guanine [(N)-2′d-*methanocarba*-G]



$_3$E (C3′-*exo*, South)

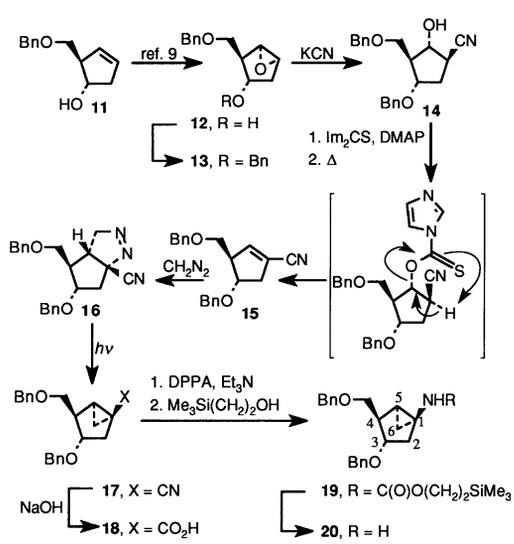
6, B = thymine [(S)-*methanocarba*-T]
7, B = uracil [(S)-2′d-*methanocarba*-U]
8, B = cytosine [(S)-2′d-*methanocarba*-C]
9, B = adenine [(S)-2′d-*methanocarba*-A]
10, B = guanine [(S)-2′d-*methanocarba*-G]

and among these, the thymidine [(N)-*methanocarba*-T, **1**],[2,3] 2′-deoxycytidine [(N)-2′-deoxy-*methanocarba*-C, **3**][4] and 2′-deoxyadenosine [(N)-2′-deoxy-*methanbocarba*-A, **4**][5] analogues have shown exceptional antiviral activities. Among the corresponding pseudorotational antipodes, only the Southern thymidine analogue **6** [(S)-*methanocarba*-T] has been reported,[6,7] and a recent comparison between **1** and **6** revealed that the latter was devoid of the strong antiherpetic activity characteristic of **1**.[2] In an effort to expand the scope of our investigation to the rest of the Southern conformers, we now describe their syntheses, which are based on a novel approach that was briefly communicated earlier for the thymidine analogue **6**.[7]

Results and discussion

Synthesis

One of the virtues of the method of synthesis of **6**[7] was that it was centred around the stable carbamate derivative **19** of the parent carbocyclic amine **20**, from which all the heterocyclic bases could be constructed (Scheme 1). The procedure to obtain

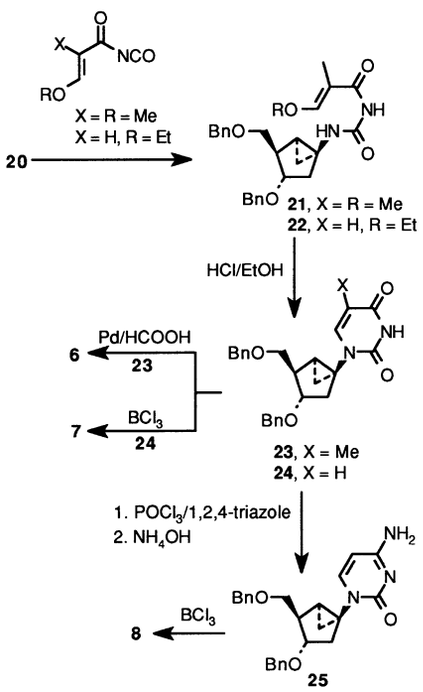


Scheme 1

19 in optically pure form was based on the availability of cyclopentene **11**, which represents an excellent homochiral starting material for accessing a variety of carbocyclic nucleosides.[8,9] This compound, and the ensuing epoxides **12** and **13**, were obtained as described.[9] Nucleophilic opening of the epoxide ring occurred with excellent regioselectivity to give the cyano intermediate **14**, from which the desired α,β-unsaturated nitrile **15** was obtained following the *syn*-β-elimination of the transitional thiocarbonylimidazolide. The 1,3-dipolar cycloaddition of diazomethane to **15** to give the *cis*-fused pyrazoline intermediate **16** occurred with the expected regioselectivity that is typical of diazomethane additions to electron deficient alkenes in which the carbon atom of diazomethane functions as the

negative end of the dipole. The stereofacial selectivity, on the other hand, appears to be controlled exclusively by the approach of the diazomethane from the less encumbered side of the double bond. With the stereochemistry of the cyano group secured, the desired bicyclo[3.1.0]hexane intermediate nitrile **17** was obtained after nitrogen extrusion from **16** by photolysis. In agreement with the pseudoboat conformation that is typical of bicyclo[3.1.0]hexane systems,[10] the proton NMR spectrum and coupling constants of **17** were fully consistent with an α-fused cyclopropane ring.[7] The nitrile function was converted to the protected carbocyclic amine derivative **19** following hydrolysis of **17** to the acid **18**, and continuing with a modified Curtius rearrangement of the corresponding acyl azide to the isocyanate.[11] The reactive isocyanate intermediate was trapped with 2-trimethylsilylethanol to give the stable carbamate **19**, and the required carbocyclic amine **20** was generated from it prior to the construction of the corresponding heterocyclic bases in each instance.

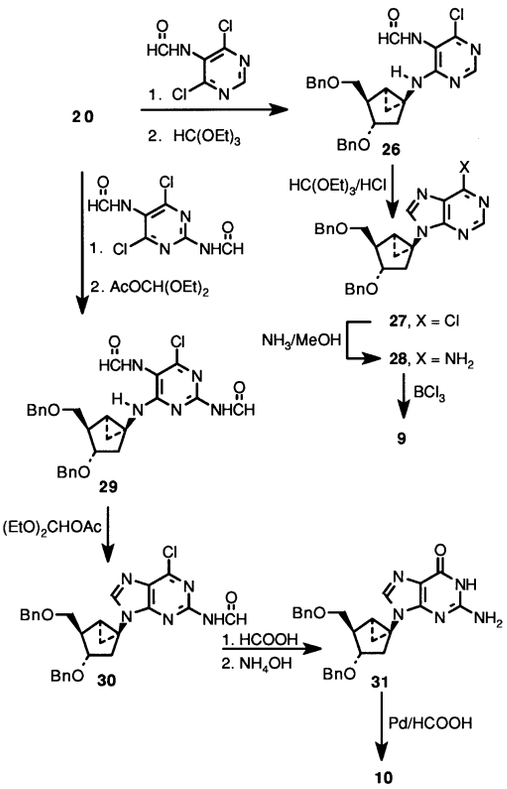
The pyrimidine bases of **23** and **24** were constructed by acid-catalysed cyclization of the intermediate acryloylureas **21** and **22** (Scheme 2), which were generated by reacting **20** with 3-



Scheme 2

methoxy-2-methylacryloyl isocyanate and 3-ethoxyacryloyl isocyanate, respectively.[12] Removal of the benzyl ethers by either catalytic transfer hydrogenation, or by treatment with BCl_3, afforded the pyrimidine targets (S)-*methanocarba*-T **6** and (S)-2′-deoxy-*methanocarba*-U **7**. Fashioning the carbocyclic cytidine **25** from the uridine analogue **24** was achieved *via* aqueous ammonia hydrolysis of the corresponding triazole intermediate, which was prepared according to published methodology.[13] Removal of the protective benzyl ethers from **25** gave the target (S)-2′-deoxy-*methanocarba*-C **8**.

The purine bases in **7** and **10** were also assembled from carbocyclic amine **20** according to Scheme 3. Noteworthy is the fact that displacement of chloride from either 5-amino-4,6-dichloropyrimidine or 2,5-diamino-4,6-dichloropyrimidine with **20** occurred very poorly or not at all. However, excellent results were obtained after conversion of the pyrimidines to their respective formyl or diformyl derivatives to give **26** and **29**. An improvement in the efficiency of coupling of these bases upon formylation has been reported, and their preparation was performed as described.[14] Closure of the imidazole ring of **26** was achieved by reaction with triethyl orthoformate and hydrochloric acid to afford the 6-chloropurine derivative **27**. Sub-



Scheme 3

sequent treatment of **27** with saturated methanolic ammonia, in a sealed tube, provided the adenine analogue **28**, and following the removal of the benzyl ethers with boron trichloride, the target (S)-2′-deoxy-*methanocarba*-A **9** was obtained. Ring closure of the imidazole ring in **29** was performed by heating in the presence of diethoxymethyl acetate at 140 °C to give compound **30**. Tandem hydrolyses of **30** with formic acid and ammonium hydroxide provided the guanine ring **31**, and removal of the benzyl ethers by catalytic transfer hydrogenation afforded the final (S)-2′-deoxy-*methanocarba*-G target **10**.

Antiviral activity

Table 1 reveals an almost complete lack of antiviral activity for all Southern conformers, save for (S)-2′-deoxy-*methanocarba*-A **9**, whose anti-HCMV potency is slightly better than that of its Northern pseudorotational antipode, (N)-2′-deoxy-*methanocarba*-A **4**.[5] Indeed, the EC_{50} value against HCMV for (S)-2′-deoxy-*methanocarba*-A **9** in the plaque reduction assay was 2.4 μg ml^{-1} (SI > 41.7, Table 1) *versus* an EC_{50} of 5.6 μg ml^{-1} (SI > 17.9) measured for (N)-2′-deoxy-*methanocarba*-A **4**.[5] This selective anti-HCMV activity of **9** is unusual and will be the subject of a future investigation. In general, the antiviral results reported here are preliminary and will be expanded to include other viruses. It is expected that as we gather more data, we will be able to draw important conclusions regarding the relationship between a fixed pseudosugar pucker and antiviral activity. These forthcoming results should be useful in the design of more potent and specific antiviral agents.

Experimental

All chemical reagents were commercially available. Melting points were determined on a Mel-Temp II apparatus, Laboratory Devices, USA, and are uncorrected. Column chromatography was performed on silica gel 60, 230–400 mesh (E. Merck) and analytical TLC was performed on Analtech Uniplates silica gel GF. Proton and ^{13}C NMR spectra were recorded on a Bruker AC-250 instrument at 250 and 62.9 MHz, respectively. *J* Values are given in Hz. Spectra were referenced to the solvent in which they were run (δ 7.24 for $CDCl_3$)

Table 1 Antiviral activity of Southern 2′-deoxy-*methanocarbocyclic* nucleosides

	Virus[a] (HFF cells)	EC_{50}[b] μg ml^{-1}	CC_{50}[c] μg ml^{-1}	SI[d]	Control[e] (EC_{50} μg ml^{-1})
6	HSV-1	>50[f]	>50	1	ACV (0.15)
6	HSV-2	>50[f]	>50	1	ACV (0.60)
6	HCMV	>20	70.5	<3.5	GCV (0.20)
7	HSV-1	>20	59.1	<3.0	ACV (0.20)
7	HSV-2	>20	59.1	<3.0	ACV (1.80)
7	HCMV	>100	>100	1	GCV (0.01)
8	HSV-1	>4.0	14.9	<3.7	ACV (0.20)
8	HSV-2	>4.0	14.9	<3.7	ACV (1.80)
8	HCMV	88.9	>100	>1.1	GCV (0.30)
9	HSV-1	>100	>100	1	ACV (0.20)
9	HSV-2	>100	>100	1	ACV (0.20)
9	HCMV	2.4[f]	>100	>41.7	GCV (0.20)
10	HSV-1	>20	75.0	<3.7	ACV (0.20)
10	HSV-2	>20	75.0	<3.7	ACV (1.80)
10	HCMV	>20	>20	1	GCV (0.01)

[a] HFF = human foreskin fibroblast; HSV-1 = herpes simplex type 1; HSV-2 = herpes simplex type 2; HCMV = human cytomegalovirus. [b] EC_{50} = inhibitory concentration required to reduce virus-induced cytopathogenicity or virus plaques by 50%. [c] CC_{50} = cyctotoxic concentration that produces 50% of cell death. [d] SI = selectivity index (CC_{50}/EC_{50}). [e] ACV = acyclovir control, GCV = gancyclovir control. [f] These values correspond to a plaque reduction assay.

unless stated otherwise. Specific rotations were measured in a Perkin-Elmer Model 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained on a VG 7070E mass spectrometer at an accelerating voltage of 6 kV and a resolution of 2000. Glycerol was used as the sample matrix and ionization was effected by a beam of xenon atoms. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Ether refers to diethyl ether and petrol refers to the fraction of light petroleum boiling in the range 35–60 °C.

(1*S*,2*R*,3*R*,4*R*)-1-Benzyloxy-2-benzyloxymethyl-4-cyano-3-hydroxycyclopentane 14

A magnetically stirred solution of epoxide **13**[9] (13.05 g, 42.04 mmol) in acetonitrile (150 cm^3) was treated with KCN (5.47 g, 84.09 mmol) and $LiClO_4$ (8.95 g, 84.09 mmol) under argon. The reaction was allowed to continue at 70 °C for 20 h, but TLC analysis (silica gel, hexanes–EtOAc, 2:1) still revealed about 30% of unreacted starting material. Additional KCN (2.70 g, 42.04 mmol) and $LiClO_4$ (4.5 g, 42.04 mmol) were added and stirring continued for two additional days to complete the reaction. After reaching room temperature conditions, water (200 cm^3) was added while stirring was continued, and the mixture was extracted with ether (3 × 200 cm^3). The organic phase was washed with brine (2 × 150 cm^3) until a neutral pH of the washings was obtained, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a residue which was purified by column chromatography (silica gel, hexanes–EtOAc, 4:1) to give compound **14** (11 g, 77.5%) as a light yellow syrup; $[\alpha]_D^{24}$ +36.7 (*c* 1.85 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3495, 2575, 2150 and 1600; δ_H($CDCl_3$, Me_4Si) 7.40–7.20 (10 H, m, ArH), 4.50 (2 H, s, $PhCH_2O$), 4.95 (2 H, AB q, *J* 11.8, $PhCH_2O$), 4.18 (1 H, t, *J* 8.0, 3-H), 3.80 (1 H, m, 1-H), 3.62 (1 H, dd, *J* 9.2, 5.1, C*H*HO), 3.50 (1 H, dd, *J* 9.2, 6.8, CH*H*O), 3.05 (1 H, m, 4-H), 2.70 (1 H, OH), 2.25 (2 H, m, 2-H and 5-H^a) and 2.05 (1 H, m, 5-H^b) (Found: C, 74.56; H, 6.80; N, 4.19. $C_{21}H_{23}NO_3$ requires C, 74.75; H, 6.87; N, 4.15%).

(3*R*,4*S*)-1-Cyano-4-benzyloxy-3-benzyloxymethylcyclopentene 15

A stirred solution of **14** (1.62 g, 4.8 mmol) in DMF (25 cm^3) was treated with 1,1′-thiocarbonyldiimidazole (1.0 g, 5.80 mmol) and DMAP (0.88 g, 7.2 mmol) under argon. The reaction was allowed to continue at room temperature for 3 h, after which time all the starting material had reacted. Upon heating at 70 °C for 30 min, the ensuing β-*syn* elimination proceeded to completion. The mixture was cooled to room temperature and EtOAc (200 cm^3) was added. Aqueous extraction of the organic layer (3 × 30 cm^3) was performed until a neutral pH of the washings was obtained. The organic layer was dried ($MgSO_4$) and evaporated to give an oily residue, which was purified by column chromatography (silica gel, 10% EtOAc–petrol) to give the vinyl cyanide deriative **15** (1.51 g, 98%) as a colourless syrup; $[\alpha]_D^{24}$ +85.4 (*c* 2.8 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2875, 2150 and 1600; δ_H($CDCl_3$, Me_4Si) 7.40–7.25 (10 H, m, ArH), 6.52 (1 H, dd, *J* 4.3, 2.1, 2-H), 4.55–4.45 (4 H, singlets, $PhCH_2O$ × 2), 4.12 (1 H, irregular quintet, 4-H), 3.45 (2 H, AB m, CH_2O), 3.15 (1 H, m, 3-H), 2.95–2.83 (1 H, ddt, *J* 16.7, 6.9, 2.1, 5-H^a), 2.70–2.58 (1 H, dm, *J* 16.7, 5-H^b) (Found: C, 78.88; H, 6.65; N, 4.32. $C_{21}H_{21}NO_2$ requires C, 78.97; H, 6.63; N, 4.39%).

(3a*R*,4*R*,5*S*,6a*R*)-4-Benzyloxymethyl-5-benzyloxy-6a-cyano-3,3a,4,5,6,6a-hexahydrocyclopentapyrazole 16

A stirred solution of the vinyl cyanide **15** (9.2 g, 28.81 mmol) in chloroform (50 cm^3) was cooled to 0 °C. A freshly prepared solution of diazomethane in ether (0.07 M; 850 cm^3) was slowly added, and stirring continued for three days at 0 °C until the reaction was complete. The solvent was removed under reduced pressure and the resulting colourless syrup of hexahydrocyclopentapyrazole **16** (10.04 g, 96.5%) was used directly in the subsequent photolytic reaction without further purification; δ_H($CDCl_3$, Me_4Si) 7.40–7.15 (10 H, m, ArH), 4.86 (1 H, d, *J* 6.4, 3-H), 4.50 (2 H, s, $PhCH_2O$), 4.40 (1 H, d, *J* 11.7, PhC*H*HO), 4.25 (1 H, d, *J* 11.7, PhCH*H*O), 3.90 (1 H, m, 5-H), 3.40 (2 H, AB d, *J* 5.5, CH_2O), 2.80–2.50 (3 H, m, 6-H, 3a-H), 2.15 (1 H, m, 4-H).

(1*S*,3*S*,4R,5*S*)-3-Benzyloxy-4-benzyloxymethyl-1-cyano-bicyclo[3.1.0]hexane 17

A solution of **16** (1.0 g, 2.76 mmol) in dry benzene–acetonitrile (1:1, 20 cm^3) containing benzophenone (0.25 g, 1.38 mmol) as photosensitizer was irradiated in a Pyrex flask inside a Rayonet Photochemical reactor model RPR-100 (4.5 W, 3500 Å) for 2 h. The solvent was removed under reduced pressure and the resulting yellow oil was purified by column chromatography (silica gel, 5% EtOAc–petrol) to give compound **17** (0.73 g, 79%) as a colourless oil; $[\alpha]_D^{24}$ +85.4 (*c* 2.8 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2875, 2150 and 1600; δ_H($CDCl_3$, Me_4Si) 7.40–7.20 (10 H, m, ArH), 4.51 and 4.37 (2 H, s, $PhCH_2O$), 3.90 (1 H, d, *J* 6.4, 3-H), 3.43 (1 H, dd, *J* 9.3, 5.9, C*H*HO), 3.33 (1 H, dd, *J* 9.3, 7.2, CH*H*O), 2.50 (1 H, t, *J* 6.5, 4-H), 2.30 (1 H, ddd, *J* 12.7, 6.5, 1.5, 2-H$^{\beta}$), 2.20 (1 H, d, *J* 12.7, 2-H$^{\alpha}$), 1.92 (1 H, dd, *J* 8.5, 5.0, 5-H), 1.45 (1 H, t, *J* 5.3, 7-H^{endo}), 1.25 (1 H, ddd, *J* 9.1, 5.3, 1.5, 7-H^{exo}) (Found: C, 76.74; H, 6.65; N, 4.10. $C_{22}H_{23}NO_2 \cdot 0.6H_2O$ requires C, 76.75; H, 7.08; N, 4.06%).

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-benzyloxymethylbicyclo[3.1.0]-hexane-1-carboxylic acid 18

A stirred solution of nitrile **17** (1.50 g, 4.49 mmol) in methanol (20 cm^3) was treated with NaOH (25% aqueous solution; 30 cm^3) and the reaction mixture was gently refluxed (oil bath, 90 °C) for 24 h. After cooling to room temperature and further cooling to 0 °C, the reaction mixture was acidified to pH 5 with 1 M HCl (*ca.* 153 cm^3). Extraction of the mixture with EtOAc (4 × 150 cm^3) was followed by a second extraction (2 × 50 cm^3) after the aqueous layer was saturated with NaCl. The combined organic extract was further washed with brine (2 × 10 cm^3) until a neutral pH of the washings was obtained. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting brownish syrup was dried under vacuum for 2 h to give compound **18** (1.58 g, 99.68%) as a viscous syrup. This compound was deemed pure enough to be used in the next step without further purification. An analytical sample of **18** (clear yellow syrup) was obtained after purification by flash chromatography (silica gel, 5% MeOH in EtOAc); $[\alpha]_D^{24}$ −70.3

(*c* 0.4 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400–3200, 2930, 1678 and 1601; δ_H($CDCl_3$, Me_4Si) 7.40–7.10 (10 H, m, ArH), 4.49 and 4.38 (2 H, br s, $PhCH_2O$), 3.91 (1 H, d, *J* 6.9, 3-H), 3.39 (1 H, dd, *J* 9.2, 6.1, C*H*HO), 3.25 (1 H, irregular t, *J ca* 8.7, CH*H*O), 2.48 (2 H, m, 2-H^{β}, 4-H), 2.05 (1 H, d, *J* 14.5, 2-H^{α}), 1.85 (1 H, dd, *J* 8.6, 5.5, 5-H), 1.60–1.40 (2 H, m, 6-H) (Found: C, 73.52; H, 6.76. $C_{22}H_{24}O_4 \cdot 0.4H_2O$ requires C, 73.47; H, 6.95%).

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-benzyloxymethyl-1-(2-trimethylsilylethoxyformamido)bicyclo[3.1.0]hexane 19

A stirred solution of **18** (3.9 g, 11.06 mmol) in freshly distilled toluene (80 cm^3) maintained at 0 °C under argon was treated with triethylamine (1.85 cm^3, 13.28 mmol) and diphenylphosphoryl azide (DPPA, 2.85 cm^3, 13.28 mmol). After the addition, the ice bath was removed and the reaction was allowed to continue at room temperature for 2 h. Then, the reaction mixture was heated (oil bath, 80 °C) for 2 h and 2-trimethylsilylethanol (3.2 cm^3, 22.13 mmol) was added. The reaction was allowed to continue at 80 °C for 2 h, and was later maintained overnight at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (400 cm^3). Extraction of the organic solution with brine (3 × 30 cm^3) was performed until a neutral pH of the washings was obtained. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting syrup was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give compound **19** as a yellow syrup (3.3 g, 64.4%); $[a]_D^{24}$ −4.7 (*c* 1.52 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3333, 2952 and 1715; δ_H($CDCl_3$, Me_4Si) 7.36–7.15 (10 H, m, ArH), 4.98 (1 H, br s, NH), 4.51 (2 H, s, $PhCH_2O$), 4.39 (2 H, AB q, *J* 12.0, $PhCH_2O$), 4.11 [2 H, q, *J* 9.2, 7.7, $C(O)OCH_2$], 3.90 (1 H, d, *J* 6.7, 3-H), 3.55 (2 H, m, CH_2O), 2.35 (2 H, m, 2-H^{β}, 4-H), 2.10 (1 H, d, *J* 13.9, 2-H^{α}), 1.35 (1 H, dd, *J* 8.9, 5.5, 5-H), 1.21 (1 H, t, *J* 4.8, 6-H^{endo}), 0.95 (2 H, m, $SiCH_2$), 0.84 (1 H, ddd, *J* 7.3, 5.3, <1, 6-H^{exo}), 0.00 [9 H, s, $(CH_3)_3Si$] (Found: C, 69.28; H, 7.96. $C_{27}H_{37}NO_4Si$ requires C, 69.34; H, 7.97%).

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-benzyloxymethyl-1-amino-bicyclo[3.1.0]hexane 20

A stirred solution of **19** (0.29 g, 0.62 mmol) in a mixture of CH_3CN–THF (10 cm^3, 4:1) was treated with tetrabutylammonium fluoride (1 M in THF; 5 cm^3) under a blanket of argon at room temperature. The temperature was then raised to 70 °C, and the reaction was finished after 4 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, 5 to 10% MeOH in $CHCl_3$) to give compound **20** (0.20 g, 99%) as a clear yellow syrup; δ_H($CDCl_3$, Me_4Si) 7.35–7.21 (10 H, m, ArH), 4.51 (2 H, AB q, *J* 12.1, $PhCH_2O$), 4.38 (2 H, AB q, *J* 12.4, $PhCH_2O$), 3.86 (1 H, d, *J* 6.7, 3-H), 3.44 (1 H, dd, *J* 9.3, 5.8, C*H*HO), 3.31 (1 H, irregular t, CH*H*O), 2.45 (2 H, br s, NH_2), 2.31 (1 H, irregular t, 4-H), 2.15 (1 H, d, *J* 13.8, 2-H^{α}), 2.01 (1 H, ddd, *J* 13.8, 6.7, 1.9, 2-H^{β}), 1.11 (1 H, dd, *J* 8.9, 3.9, 5-H), 1.04 (1 H, irregular t, *J ca*. 4.3, 6-H^{endo}), 0.80 (1 H, ddd, *J* 8.9, 4.5, 1.9, 6-H^{exo}). This amine was used immediately for the construction of all heterocyclic-containing carbocyclic nucleosides (*vide infra*).

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-benzyloxymethyl-1-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)bicyclo[3.1.0]-hexane 23

In a flame-dried flask, a solution of 3-methoxy-2-methylacryloyl chloride (1.44 g, 10.69 mmol) in toluene (40 cm^3) was refluxed with silver cyanate (2.24 g, 14.9 mmol) under argon for 40 min. The solution was rapidly decanted from the silver salt, and the solvent was evaporated under reduced pressure in a rotary evaporator. The residual oil was dissolved in CH_2Cl_2 (20 cm^3), and the solution was added dropwise over the course of 10 min directly to a cold (−60 °C) solution of amine **20** (1.73 g, 5.35 mmol) in CH_2Cl_2 (50 cm^3). The temperature was allowed to warm up to room temperature and the mixture was stired for 24 h to complete the coupling. The solvent was evaporated under reduced pressure and the residue was chromatographed (silica gel, hexanes–EtOAc, 2:1) to give the intermediate acryloyl urea **21** as a colourless syrup (2.13 g, 85.5%); δ_H($CDCl_3$, Me_4Si) 8.90 (1 H, s, imide NH), 7.90 (1 H, s, amide NH), 7.38–7.20 (11 H, m, C=C*H*OMe, ArH), 4.55 (2 H, AB q, *J* 12.2, $PhCH_2O$), 4.40 (2 H, AB q, *J* 12.0, $PhCH_2O$), 3.91 (1 H, d, *J* 6.3, 3-H), 3.82 (3 H, s, CH_3O), 3.52 (2 H, m, CH_2O), 2.36 (2 H, m, 4-H, 2-H^{β}), 2.20 (1 H, d, *J* 13.8, 2-H^{α}), 1.75 (3 H, d, *J* 0.6, CH_3), 1.40 (1 H, dd, *J* 9.3, 4.2, 5-H), 1.26 (1 H, t, *J* 4.9, 6-H^{endo}), 0.92 (1 H, m, 6-H^{exo}). Without any further purification, a stirred solution of **21** (2.12 g, 4.57 mmol) in ethanol (30 cm^3) was treated with 2 M HCl (6 cm^3) and gently refluxed for 30 h to complete the cyclization to the pyrimidine ring. The solvent was removed under reduced pressure at room temperature and the resulting residue was dissolved in EtOAc (300 cm^3) and washed successively with 5% $NaHCO_3$ (2 × 50 cm^3) and brine (2 × 150 cm^3) until a neutral pH of the washings was obtained. The organic solution was dried ($MgSO_4$) and evaporated to dryness to give **23** (1.95 g, 98%) as a white foam which was deemed pure enough to be used for the final deprotection reaction. An analytical sample of **23** (*ca*.. 30 mg) was obtained after chromatography (silica gel, hexanes–EtOAc, 2:1) giving a white solid, mp 70–72 °C; $[a]_D^{24}$ −19.0 (*c* 1.44 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3649, 3179, 3032, 2925, 1693 and 1608; δ_H($CDCl_3$, Me_4Si) 8.42 (1 H, s, NH), 7.40–7.20 (11 H, m, ArH, 6-H), 4.55 (2 H, AB q, *J* 12.2, $PhCH_2O$), 4.40 (2 H, s, $PhCH_2O$), 3.98 (1 H, br t, 3-H), 3.69 (2 H, m, CH_2O), 2.41 (1 H, t, *J* 5.7, 4-H), 2.31 (2 H, d, *J* 3.3, 2-H), 1.69 (3 H, s, CH_3), 1.62 (1 H, irregular t, *J ca*. 4, 5-H), 1.51 (1 H, t, *J* 5.3, 6-H^{endo}), 1.10 (1 H, dd, *J* 9.4, 5.5, 6-H^{exo}) (Found: C, 71.14; H, 6.57; N, 6.35. $C_{26}H_{28}N_2O_4 \cdot 0.25H_2O$ requires C, 71.45; H, 6.57; N, 6.41%).

(1*S*,3*S*,4*R*,5*S*)-3-Hydroxy-4-hydroxymethyl-1-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)bicyclo[3.1.0]hexane 6†

To a suspension of palladium black (0.95 g) in MeOH (50 cm^3) was added a solution of compound **23** (0.96 g, 2.21 mmol) and formic acid (2.5 cm^3). The reaction mixture was stirred at 40 °C for 2 h and filtered through a pad of Celite. The cake was washed thoroughly with methanol (3 × 15 cm^3) and the filtrate was evaporated under reduced pressure to give the title compound as a white foam. Chromatographic purification (silica gel, $CHCl_3$–MeOH, 9:1) produced **6** as a white solid (0.486 g, 87.72%); mp 206–207 °C (lit.,[6] 206–206.4 °C); $[a]_D^{25}$ −47.7 (*c* 0.58 in MeOH); ν_{max}(KBr)/cm^{-1} 3401, 3161, 2926, 1773, 1694 and 1578; δ_H(500 MHz, $[^2H]_6$DMSO, Me_4Si) 11.12 (1 H, s, NH), 7.45 (1 H, s, 6′-H), 4.70 (1 H, t, *J* 5.2, OH), 4.61 (1 H, d, *J* 2.1, OH), 4.02 (1 H, br d, *J* 5.4, 3-H), 3.51 (2 H, m, CH_2O), 2.12 (1 H, dd, *J* 13.1, 6.7, 2-H^{β}), 1.91 (1 H, d, *J* 13.1, 2-H^{α}), 1.88 (1 H, t, *J* 6.1, 4-H), 1.71 (3 H, s, CH_3), 1.56 (1 H, dd, *J* 9.3, 4.7, 5-H), 1.34 (1 H, t, *J* 4.9, 6-H^{endo}), 1.01 (1 H, m, 6-H^{exo}); δ_C(62.9 MHz, $[^2H]_6$DMSO) 11.94 (CH_3), 18.31 (6-C), 26.9 (5-C), 47.90 (2-C), 52.53 (4-C), 62.99 (CH_2OH), 73.03 (3-C), 108.53 (5′-C), 141.67 (6′-C), 151.02 (2′-C), 164.07 (4′-C); *m*/*z* (FAB) 253 (MH^+, 100%), 127 (B + 2 H, 15) (Found: C, 56.55; H, 6.26; N, 10.73. $C_{12}H_{16}N_2O_4 \cdot 0.10H_2O$ requires C, 56.72; H, 6.42; N, 11.03%).

(1*S*,3*S*,4*R*,5*S*)-3-Hydroxy-4-hydroxymethyl-1-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)bicyclo[3.1.0]hexane 7

In a similar manner as described for the synthesis of **23**, 3-ethoxyacryloyl chloride (0.333 g, 2.47 mmol) was reacted with silver cyanate (0.556 g, 3.71 mmol) in toluene (7 cm^3). The resulting acyl isocyanate was reacted with amine **20** (0.4 g, 12.4 mmol) to give intermediate **22** (0.50 g, 87%), which after purification by column chromatography (silica gel, hexanes–EtOAc, 3:1) was obtained as a light yellow syrup; δ_H($CDCl_3$, Me_4Si)

† In the Experimental section, the numbering system for compounds **6**–**10** follows from their IUPAC names. Hence, 1′–4′ given in the structures corresponds to 1–4 in the systematic names.

9.51 (1 H, s, imide NH), 8.90 (1 H, s, amide NH), 7.61 (1 H, d, *J* 12.2, COCH=C*H*OEt), 7.35–7.22 (10 H, m, ArH), 5.31 (1 H, d, *J* 12.2, COC*H*=CHOEt), 4.53 (2 H, AB q, *J* 11.9, PhCH_2O), 4.40 (2 H, AB q, *J* 12.1, PhCH_2O), 3.90 (3 H, m, 3-H, OCH_2CH$_3$), 3.60 (2 H, m, CH_2O), 2.41 (2 H, m, 4-H, 2-H$^{\beta}$), 2.21 (1 H, d, *J* 13.8, 2-H$^{\alpha}$), 1.41 (1 H, dd, *J* 9.0, 4.4, 5-H), 1.28 (1 H, t, *J* 4.9, 6-H^{endo}), 1.21 (3 H, t, *J* 7.0, OCH$_2$CH_3), 0.97 (1 H, m, 6-H^{exo}). Without further purification, a stirred solution of **22** (0.340 g, 0.73 mmol) in ethanol (15 cm^3) was treated with 2 M HCl (2.5 cm^3) and cyclization to the pyrimidine ring was performed in a similar manner as for **23**. After work-up and purification by column chromatography (silica gel, acetone–CH_2Cl_2, 5:1), compound **24** (0.2609 g, 85%) was obtained as a colourless syrup; $[\alpha]_D^{24}$ −22.7 (*c* 1 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3200, 2960, 1710 and 1600; δ_H($CDCl_3$, Me_4Si) 8.80 (1 H, br s, NH), 7.40–7.20 (11 H, m, 6′-H, ArH), 5.39 (1 H, dd, *J* 7.9, 2.2, 5′-H), 4.52 (2 H, AB q, *J* 11.4, PhCH_2O), 4.40 (2 H, AB q, *J* 12.4, PhCH_2O), 3.95 (1 H, d, *J* 6.3, 3-H), 3.71 (2 H, m, CH_2O), 2.42 (1 H, t, *J* 5.5, 4-H), 2.35–2.20 (2 H, m, 2-H), 1.65 (1 H, t, *J* 4.5, 5-H), 1.55 (1 H, t, *J* 5.3, 6-H^{endo}), 1.11 (1 H, m, 6-H^{exo}) (Found: C, 65.99; H, 5.88. $C_{25}H_{26}N_2O_4$·H_2O requires C, 66.06; H, 6.65%). A fraction of this syrup (0.080 g, 0.191 mmol) was dissolved in CH_2Cl_2 (4 cm^3), cooled to −78 °C, and treated under a blanket of argon with a solution of BCl_3 (1 M in CH_2Cl_2; 1.53 cm^3). The reaction mixture was stirred at −78 °C for 6 h, and then for 1 h at −30 °C. The mixture was cooled again to −78 °C then MeOH (6 cm^3) was added to it and the mixture was stirred at −78 °C for 1 h and then allowed to reach room temperature conditions. The solvent was removed under reduced pressure and the residue was evaporated thrice after the addition of 5 cm^3 portions of MeOH. The crude foam was dissolved in MeOH (1.2 cm^3) and treated with CH_2Cl_2 (2.5 cm^3) until cloudiness was observed. After the solution had been left to stand in the freezer, the precipitated solid was separated and washed with CH_2Cl_2 (1.5 cm^3) and petrol (3 cm^3) to give the target compound **7** (0.015 g, 33%) as a white powder; mp 212–214 °C; $[\alpha]_D^{25}$ −33.6 (*c* 0.25 in MeOH); δ_H(CD_3OD, Me_4Si) 7.68 (1 H, d, *J* 7.9, 6′H), 5.61 (1 H, d, *J* 7.9, 5′-H), 4.21 (1 H, d, *J* 6.9, 3-H), 3.70 (2 H, m, CH_2OH), 2.36 (1 H, ddd, *J* 13.4, 6.9, 2.2, 2-H$^{\beta}$), 2.06 (2 H, m, 2-H$^{\alpha}$, 4-H), 1.74 (1 H, ddd, *J* 9.7, 4.9, 1.1, 5-H), 1.45 (1 H, t, *J* 5.2, 6-H^{endo}), 1.15 (1 H, ddd, *J* 9.7, 5.4, 2.3, 6-H^{exo}); δ_C(CD_3OD) 19.18 (6-C), 28.96 (5-C), 41.19 (2-C), 54.00 (4-C), 65.09 (CH_2OH), 75.48 (3-C), 102.58 (5′-C), 147.80 (6′-C), 153.20 (2′-C), 165.40 (4′-C); *m*/*z* (FAB) (relative intensity) 239 (MH^+, 100), 113 (B + 2 H, 15) [Found (FAB): 239.1039. Calc. for MH^+, 239.1032].

(1*S*,3*S*,4*R*,5*S*)-3-Hydroxy-4-hydroxymethyl-1-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)bicyclo[3.1.0]hexane 8

A solution of **24** (0.190 g, 0.454 mmol), triethylamine (1.45 mm^3, 10.44 mmol) and 1*H*-1,2,4-triazole (0.705 g, 10.22 mmol) in acetonitrile (10 cm^3) was treated at room temperature with $POCl_3$ (104 mm^3, 1.11 mmol). The reaction mixture was stirred for 2 h at room temperature and then poured onto a mixture of CH_2Cl_2 (51 cm^3), triethylamine (5.1 cm^3) and saturated aqueous $NaHCO_3$ (15.5 cm^3). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a residue that was chromatographed through a short column (silica gel, ether) to give the triazole intermediate as a white foam; δ_H($CDCl_3$, Me_4Si) 9.21 (1 H, s, triazole), 8.09 (1 H, s, triazole), 7.98 (1 H, d, *J* 7.1, 6′-H), 7.35–7.22 (10 H, m, ArH), 6.70 (1 H, d, *J* 7.1, 5′-H), 4.55 (2 H, AB q, PhCH_2O), 4.41 (2 H, AB q, PhCH_2O), 4.01 (1 H, d, *J* 5.4, 3-H), 3.80 (2 H, m, CH_2O), 2.49 (1 H, t, *J* 5.5, 4-H), 2.40 (2 H, m, 2-H), 1.70 (2 H, m, 5-H, 6-H^{endo}), 1.20 (1 H, m, 6-H^{exo}). This material was dissolved in dioxane (6 cm^3) and stirred with concentrated aqueous ammonia (1.5 cm^3) for 24 h at 40 °C. After such time, analysis by TLC still showed unreacted starting material. Additional concentrated aqueous ammonia (1.6 cm^3) was added and stirring was continued for an additional 24 h to complete the reaction. The solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (15 cm^3) and water (15 cm^3). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 cm^3). The organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give compound **25** (0.064 g, 34%) as a colourless syrup; $[\alpha]_D^{24}$ −36.1 (*c* 1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3609–3445, 2924, 1771 and 1605; δ_H($CDCl_3$, Me_4Si) 7.35–7.20 (11 H, m, 6′-H, ArH), 5.48 (1 H, d, *J* 7.3, 5′-H), 4.51 (2 H, s, PhCH_2O), 4.40 (2 H, s, PhCH_2O), 3.94 (1 H, d, *J* 6.5, 3-H), 3.70 (2 H, m, CH_2O), 2.42 (1 H, irregular t, *J ca.* 6.2, 4-H), 2.31 (2 H, m, 2-H), 1.60 (1 H, dd, *J* 9.4, 4.7, 5-H), 1.48 (1 H, t, *J* 5.2, 6-H^{endo}), 1.01 (1 H, m, 6-H^{exo}). A fraction of this syrup (0.050 g, 0.119 mmol) was dissolved in CH_2Cl_2 (5 cm^3) and treated with BCl_3 (1 M in CH_2Cl_2; 0.96 cm^3) using the same protocol employed for the deprotection of **24**. The target compound **8** (0.025 g, 89%) was obtained as a white powder after crystallization from MeOH–CH_2Cl_2; mp 261–262 °C; $[\alpha]_D^{25}$ −30 (*c* 0.18, MeOH); δ_H($CDCl_3$, Me_4Si) 8.02 (1 H, d, *J* 7.7, 6′-H), 6.02 (1 H, d, *J* 7.7, 5′-H), 4.21 (1 H, d, *J* 6.9, 3-H), 3.71 (2 H, br d, *J* 5.51, CH_2OH), 2.40 (1 H, ddd, *J* 13.5, 7.0, 1.9, 2-H$^{\beta}$), 2.18–2.04 (2 H, m, 2-H$^{\beta}$, 4-H), 1.70 (1 H, ddd, *J* 9.7, 4.9, <1, 5-H), 1.52 (1 H, t, *J* 5.2, 6-H^{endo}), 1.21 (1 H, m, 6-H^{exo}); δ_C(CD_3OD) 19.36 (6-C), 28.92 (5-C), 40.91 (2-C), 51.16 (1-C), 54.10 (4-C), 64.87 (CH_2OH), 75.49 (3-C), 94.74 (5′-C), 168.88 (6′-C); *m*/*z* (FAB) (relative intensity) 238 (MH^+, 100), 112 (B + 2 H, 25) [Found: (FAB): 238.1221. Calc. for MH^+, 238.1192].

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-(benzyloxymethyl)-1-(6-chloropurin-9-yl)bicyclo[3.1.0]hexane 27

A stirred solution of carbocyclic amine **20** (0.025 g, 0.077 mmol), 4,6-dichloro-5-formamidopyrimidine[14] (0.015 g, 0.087 mmol) and triethylamine (183 mm^3, 1.314 mmol) in 1,4-dioxane (4 cm^3) was stirred under gentle reflux for 24 h. After cooling, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 3:1) to give compound **26** as a clear yellow syrup (0.034 g, 92%). This compound was immediately reacted with triethyl orthoformate (2 cm^3) and 12 M hydrochloric acid (43 mm^3) in DMF (0.7 cm^3), and the reaction mixture was stirred at room temperature for 2 days. The reaction was quenched with triethylamine (0.3 cm^3) and the solvent was evaporated. The residue was purified by column chromatography [silica gel, hexane–EtOAc, 4:1 (200 cm^3) and hexane–EtOAc, 3:1 (100 cm^3)] to give the chloro compound **27** (0.034 g, 47%) as a yellow syrup; $[\alpha]_D^{24}$ −31.5 (*c* 0.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2926, 1590 and 1557; δ_H($CDCl_3$, Me_4Si) 8.69 (1 H, s, 8′-H), 8.11 (1 H, s, 2′-H), 7.40–7.20 (10 H, m, ArH), 4.61 (2 H, s, PhCH_2O), 4.43 (2 H, s, PhCH_2O), 4.02 (1 H, br t, 3-H), 3.75 (2 H, m, CH_2O), 2.55 (1 H, t, *J* 6.2, 4-H), 2.49 (2 H, br d, *J* 3.2, 2-H), 1.85 (1 H, dd, *J* 9.2, 4.7, 5-H), 1.76 (1 H, t, *J* 5.2, 6-H^{endo}), 1.40 (1 H, dd, 9.2, 5.6, 6-H^{exo}) (Found: C, 67.19; H, 5.46. $C_{26}H_{25}ClN_4O_2$·0.1H_2O requires C, 67.40; H, 5.48).

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-(benzyloxymethyl)-1-(6-aminopurin-9-yl)bicyclo[3.1.0]hexane 28

A solution of **27** (0.034 g, 0.074 mmol) in saturated methanolic ammonia (5 cm^3) was heated in a sealed tube at 80 °C for 12 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 3% MeOH in EtOAc) to give **28** (0.031 g, 97%) as a white solid; mp 179–181 °C; $[\alpha]_D^{24}$ −35.7 (*c* 0.21 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3299, 2862 and 1601; δ_H($CDCl_3$, Me_4Si) 8.31 (1 H, s, 8′-H), 7.79 (1 H, s, 2′-H), 7.39–7.25 (10 H, m, ArH), 5.52 (2 H, br s, NH_2), 4.61 (2 H, s, PhCH_2O), 4.42 (2 H, s, PhCH_2O), 4.02 (1 H, br t, 3-H), 3.78 (2 H, m, CH_2O), 2.54 (1 H, t, *J* 6.4, 4-H), 2.49 (2 H, d, *J* 3.2, 2-H), 1.85–1.67 (2 H, m, 5-H, 6-H^{endo}), 1.38 (1 H, dd, *J* 9.4, 5.5, 6-H^{exo}) (Found: C, 70.55; H, 6.21. $C_{26}H_{27}N_5O_2$ requires C, 70.72; H, 6.16%).

(1*S*,3*S*,4*R*,5*S*)-3-Hydroxy-4-hydroxymethyl-1-(6-aminopurin-9-yl)bicyclo[3.1.0]hexane 9

A solution of **28** (0.026 g, 0.06 mmol) in CH_2Cl_2 (3 cm^3) was treated with BCl_3 (1 M in CH_2Cl_2; 500 mm^3) and deblocked in the same manner as **24** and **25**. The crude yellow solid was recrystallized from MeOH–CH_2Cl_2 to give the target compound **9** (0.014 g, 93%) as a white powder; mp 282–285 °C; $[\alpha]_D^{25}$ −30.0 (*c* 0.2 in MeOH); ν_{max}(KBr)/cm^{-1} 3650, 3620, 1627 and 1593; δ_H(D_2O, Me_4Si) 8.30 (1 H, s, 8′-H), 8.22 (1 H, s, 2′-H), 4.22 (1 H, d, *J* 6.8, 3-H), 3.72 (2 H, d, *J* 5.9, CH_2O), 2.41 (1 H, ddd, *J* 14.2, 7.0, 1.9, 2-H$^{\beta}$), 2.20 (1 H, d, *J* 14.2, 2-H$^{\alpha}$), 2.10 (1 H, t, *J* 5.9, 4-H), 1.90 (1 H, dd, *J* 9.5, 4.8, 5-H), 1.48–1.34 (2 H, m, 6-H); δ_C($CDCl_3$) 18.47 (6-C), 27.21 (5-C), 42.06 (2-C), 44.25 (1-C), 52.45 (4-C), 64.59 (CH_2OH), 75.30 (3-C), 145.05 (8′-C), 146.43 (2′-C); *m*/*z* (FAB) (relative intensity) 262 (MH^+, 100), 136 (B + 2 H, 25) (Found: C, 47.86; H, 5.39. $C_{12}H_{15}N_5O_2\cdot 2.25H_2O$ requires C, 47.75; H, 5.75%).

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-(benzyloxymethyl)-1-(2-formamido-6-chloropurin-9-yl)bicyclo[3.1.0]hexane 30

A solution of carbocyclic amine **20** (0.165 g, 0.510 mmol), 4,6-dichloro-2,5-diformamidopyrimidine[14] (0.132 g, 0.561 mmol) and *N*,*N*-diisopropylethylamine (0.358 cm^3, 2.053 mmol) in dry 1,4-dioxane (10 cm^3) was stirred at room temperature for 12 h and then refluxed for 30 min. The solvent was evaporated to dryness under reduced pressure and the residue was purified by column chromatography [silica gel, hexanes–EtOAc, 2:1 (100 cm^3) and hexanes–EtOAc, 1:1 (200 cm^3)] to give intermediate **29** (0.194 g, 73%) as a white solid, which was used without further purification in the following step. A solution of **29** (0.194 g, 0.372 mmol) in diethoxymethyl acetate (7 cm^3) was stirred at 140 °C under argon for 15 h. The mixture was cooled to room temperature and treated with MeOH (6 cm^3) and concentrated aqueous ammonia (0.5 cm^3) while stirring was continued. The solvent was evaporated to dryness and the residue was dissolved in EtOAc (50 cm^3) and extracted with water (2 × 30 cm^3) until neutral pH of the washings was obtained. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The resultant yellow solid was purified by flash chromatography (silica gel, hexanes–EtOAc mixtures, 19:1, 7:3 and 1:1) to give compound **30** (0.100 g, 53%) as a yellowish solid; mp 171–173 °C; $[\alpha]_D^{24}$ −26.7 (*c* 0.46 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3210, 3063, 2924, 1794 and 1598; δ_H($CDCl_3$, Me_4Si) 9.45 (1 H, d, *J* 10.5, *H*CONH), 7.98 (1 H, s, 8′-H), 7.91 (1 H, d, *J* 10.5, HCON*H*), 7.45–7.20 (10 H, m, ArH), 4.61 (2 H, s, PhCH_2O), 4.45 (2 H, s, PhCH_2O), 4.05 (1 H, br t, *J* 3.3, 3-H), 3.70 (2 H, m, CH_2O), 2.53 (1 H, t, *J* 6.1, 4-H), 2.43 (2 H, br d, *J* 4.3, 2-H), 1.81 (1 H, dd, *J* 9.6, 4.8, 5-H), 1.71 (1 H, t, *J* 5.2, 6-H^{endo}), 1.34 (1 H, dd, *J* 9.5, 5.7, 6-H^{exo}) (Found: C, 64.33; H, 5.27; N, 13.92. $C_{27}H_{26}ClN_5O_3$ requires C, 64.35; H, 5.20; N, 13.90%).

(1*S*,3*S*,4*R*,5*S*)-3-Benzyloxy-4-benzyloxymethyl-1-(2-amino-6-oxo-1,9-dihydro-6*H*-purin-9-yl)bicyclo[3.1.0]hexane 31

A solution of compound **30** (0.087 g, 0.172 mmol) in formic acid (4 cm^3) was refluxed for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was dissolved in MeOH (6 cm^3), treated with concentrated aqueous ammonia (5 drops) and stirred at 40 °C for 1 h. The solvent was evaporated and the resulting oil was purified by column chromatography [silica gel, EtOAc (50 cm^3), followed by 5% MeOH–EtOAc (100 cm^3), followed by 10% MeOH–$CHCl_3$ (50 cm^3)] to give compound **31** (0.074 g, 94%) as a white solid; mp 248–250 °C; $[\alpha]_D^{24}$ −21.7 (*c* 0.47 in Me_2SO); ν_{max}(KBr)/cm^{-1} 3588–3165, 2925, 1751 and 1600; δ_H($[^2H]_6$-DMSO, Me_4Si) 10.56 (1 H, br s, NH), 7.51 (1 H, s, 8′-H), 7.35–7.22 (10 H, m, ArH), 6.40 (2 H, br s, NH_2), 4.57 (2 H, s, PhCH_2O), 4.42 (2 H, AB q, *J* 12.2, PhCH_2O), 3.96 (1 H, m, 3-H), 3.68 (2 H, br d, *J* 6.8, CH_2O), 2.50–2.30 (3 H, m, 4-H, 2-H), 1.76 (1 H, dd, *J* 9.3, 4.6, 5-H), 1.37 (1 H, t, *J* 5.0, 6-H^{endo}), 1.23 (1 H, dd, *J* 9.3, 5.3, 6-H^{exo}) (Found: C, 67.72; H, 5.84; N, 15.20. $C_{26}H_{27}N_5O_3\cdot 0.1H_2O$ requires C, 67.98; H, 5.96; N, 15.24%).

(1*S*,3*S*,4*R*,5*S*)-3-Hydroxy-4-hydroxymethyl-1-(2-amino-6-oxo-1,9-dihydro-6*H*-purin-9-yl)bicyclo[3.1.0]hexane 10

A suspension of palladium black (25 mg) in MeOH (1 cm^3) was stirred at room temperature under argon, and a solution of compound **31** (0.035 g, 0.076 mmol) in MeOH–HCOOH (0.5 cm^3:1.5 cm^3) was added to it dropwise. After the addition, the reaction mixture was gently refluxed (40 °C) for 2 h. After cooling to room temperature, the mixture was filtered through a pad of Celite which was washed thoroughly with MeOH (3 × 10 cm^3). The solvent was evaporated under reduced pressure and the residue was dissolved in CCl_4 (10 cm^3) and evaporated again. This operation was repeated three times with CCl_4 after which compound **10** (0.018 g, 85.7%) was obtained as a white solid; mp 271–275 °C (decomp.); $[\alpha]_D^{25}$ −12.0 (*c* 0.15 in Me_2SO); δ_H($[^2H]_6$DMSO, Me_4Si) 10.60 (1 H, br s, NH, exchanges with D_2O), 7.62 (1 H, s, 8′-H), 6.42 (2 H, br s, NH_2, exchanges with D_2O), 4.90 (1 H, t, *J* 5.5, CH_2OH, exchanges with D_2O), 4.70 (1 H, d, *J* 2.8, CHO*H*, exchanges with D_2O), 4.10 (1 H, m, 3-H, becomes a d, *J* 6.1 after D_2O exchange), 3.60 (2 H, t, *J* 5.8, CH_2OH, becomes a d, *J* 6.l after D_2O exchange), 2.25 (1 H, dd, *J* 13.0, 6.3, 2-H$^{\beta}$), 2.10 (1 H, d, *J* 13.1, 2-H$^{\alpha}$), 1.95 (1 H, t, *J* 6.0, 4-H), 1.72 (1 H, dd, *J* 9.2, 4.5, 5-H), 1.49 (1 H, t, *J* 4.8, 6-H^{endo}), 1.15 (1 H, dd, *J* 8.4, 4.8, 6-H^{exo}); δ_C($[^2H]_6$DMSO) 17.30 (6-C), 25.76 (5-C), 41.57 (1-C), 42.27 (4-C), 52.27 (2-C), 63.27 (CH_2OH), 73.18 (3-C), 116.97 (5′-C), 137.70 (8′-C), 152.06 (4′-C), 153.39 (2′-C), 156.72 (6′-C); *m*/*z* (FAB) (relative intensity) 300 (M + Na^+, 50), 270 (MH^+, 51), 152 (B + 2 H, 19) [Found (FAB): 278.1247. Calc. for MH^+, 278.1253].

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