Synthesis of [1α,2β,3α-2,3-bis(benzyloxymethyl)cyclobutyl]imidazol-5-amines: important precursors to cyclobut-A derivatives[1]

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A comparative study has been carried out on two different reaction sequences starting either from Feist's acid or ketene diethyl ketal and diethyl fumarate to prepare protected derivatives of (1α,2β,3α)-2,3-dihydroxycyclobutylamine. Difficulties were experienced upon reaction of the *tert*-butyldimethylsilyl-protected amine **13a** with ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **6**, but the dibenzoyl derivative **13b** reacted smoothly to give the amidine **19** in high yield. The amidine is a useful intermediate for the synthesis of cyclobutane-based carbocyclic nucleosides. It can be readily converted by base treatment into the 4-cyanoimidazol-5-amine derivative **4b**; a precursor to the dibenzoyl derivative of racemic Cyclobut-A and a new 1-amino-6-iminopurine derivative **25**. Treatment of compound **19** with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the previously unknown 5-amino-4-(cyanoformimidoyl)imidazole derivative **20**. This has been used to synthesize new 1,2-dihydropurine and 1-methyl derivatives of Cyclobut-A in good yields.

Cyclobutane-based carbocyclic nucleosides have been found to have potent biological activity and have attracted a great deal of interest in recent years. The first such derivative to be synthesized was the guanine analogue SQ-32,829 **1**,[2,3] which shows promising antiviral activity against herpes simplex virus (HSV) and human cytomegalovirus (HCMV); the adenine analogue **2** has also been reported.[4] Cyclobut-A **3a** and cyclobut-G **3b** are carbocyclic analogues of the natural nucleoside oxetanocin. Cyclobut-G has been found to have anti-HIV (HIV = human immunodeficiency virus) activity comparable to that of AZT,[5] and both cyclobut-A and -G have become promising candidates for acquired immunodeficiency syndrome (AIDS) therapy,[6] and are also active against a range of herpes viruses.[7] The triphosphate derivative of diol **3b** selectively inhibits HSV-1 DNA polymerase. Not surprisingly, several total syntheses of these compounds have been reported,[8-14] but in all cases these syntheses rely upon the coupling of a preformed purine ring to the carbocyclic moiety. In the majority of cases this step requires forcing conditions and gives only moderate yields of the desired target molecule.

We were interested in developing a synthesis of the intermediates **4** and **5**, which could be converted into new purine base derivatives not readily available in the purine 'pool', and other heterocyclic bases which might have interesting biological properties. A similar strategy for purine synthesis has been used with some success by Shaw[15,16] starting from aminomalononitrile or amino(cyano)acetamide, but these methods appear to be little used as yields from aminomalonitrile are often variable, and amino(cyano)acetamide is not readily available. For some time now we have been exploring the use of ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **6**[17] as a precursor to purines and their derivatives,[18-20] as it is easily prepared in good yield from cheap diaminomaleodinitrile and reacts readily with a variety of aromatic and aliphatic amines to provide amidine and imidazole intermediates useful for the synthesis of purines and other nitrogen heterocycles.

In this paper we describe the synthesis of compound **4b** and a protected derivative of cyclobut-A from precursor **6** and show how compound **4b** can be used to prepare cyclobutane-based carbocyclic nucleosides.

Table 1 Conditions used for the cyclization of amidine **7**

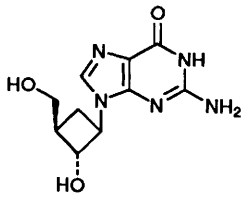
Base used (solvent)	Reaction time	Yield of **10** (%)
DBU (water)	20 min	75
$Ba(OH)_2$ (EtOH)	15 min	72
Na_2CO_3 (water)	12 h	74

Results and discussion

In a preliminary investigation the imidate **6** was converted into the amidine **7** in 71% yield by reaction with cyclobutylamine in ethanol at room temperature in the presence of a mild acid catalyst (anilinium chloride). Under similar conditions cyclopropylamine gave a 70% yield of compound **8**. Although reactions of compound **8** have not been studied further, its isolation in good yield demonstrates the potential of this method for the synthesis of cyclopropyl carbocyclic nucleosides, several of which are known to exhibit antiviral activity.[22]

Compounds **7** and **8** have been fully characterised by spectroscopic methods. It is notable that in the ^{1}H NMR spectra coupling (*J* 4.5 Hz) is observed between 5-H and the NH, and in the ^{13}C NMR spectra all the signals were sharp. This indicates that these amidines have the C=N located in conjugation with the C=C bond as shown. Conversely, (*Z*)-*N*^{1}-(2-amino-1,2-dicyanovinyl)-*N*^{2}-arylformamidines,[19] in which the C=N bond is in conjugation with the *N*-aryl ring, show a ^{1}H NMR coupling of 5.5 Hz and in the ^{13}C NMR spectra the carbon signals are broadened due to a dynamic equilibrium between **9** (*E*-1) and its rotomer **9** (*E*-2).

Amidine **7** cyclizes in the presence of various bases (see Table 1) to give the imidazole **10** in good yield. Careful monitoring of these reactions by TLC, including the reaction using a catalytic amount of DBU, failed to reveal any indication of the expected intermediate **11** indicating that elimination of HCN from cyanoimine **11** must be very rapid. An attempt to intercept intermediate **11** and form the 6-carbamoyl-1,2-dihydropurine **12** by carrying out the reaction between amidine **7** and DBU in acetone gave only a 36% yield of compound **12** as an orange solid after chromatography. As observed previously[20] with similar 1,2-dihydropurines, compound **12** exists



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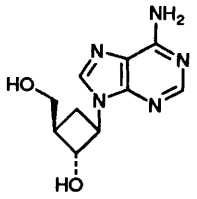

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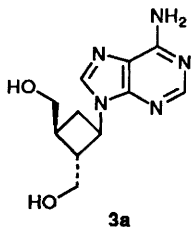
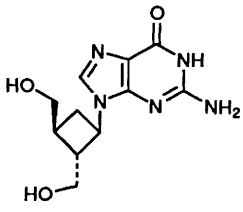
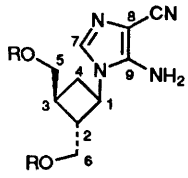


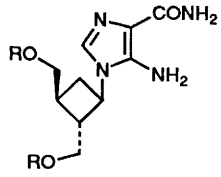
3a



3b



4a R = H
4b R = PhCO



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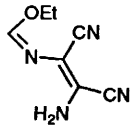

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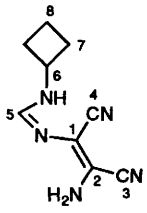

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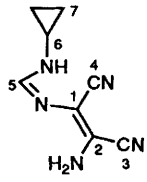

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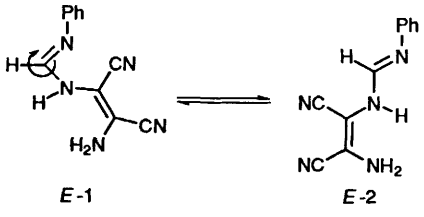

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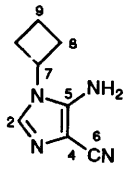
in solution as an equilibrium mixture of the tautomers **A** and **B**, resulting in significant broadening of the signals for the imidazole ring carbons in the ^{13}C NMR spectrum.



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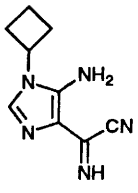

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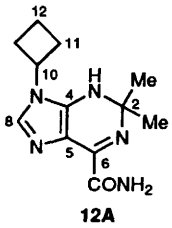
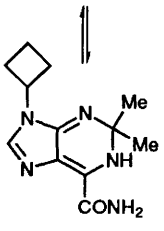
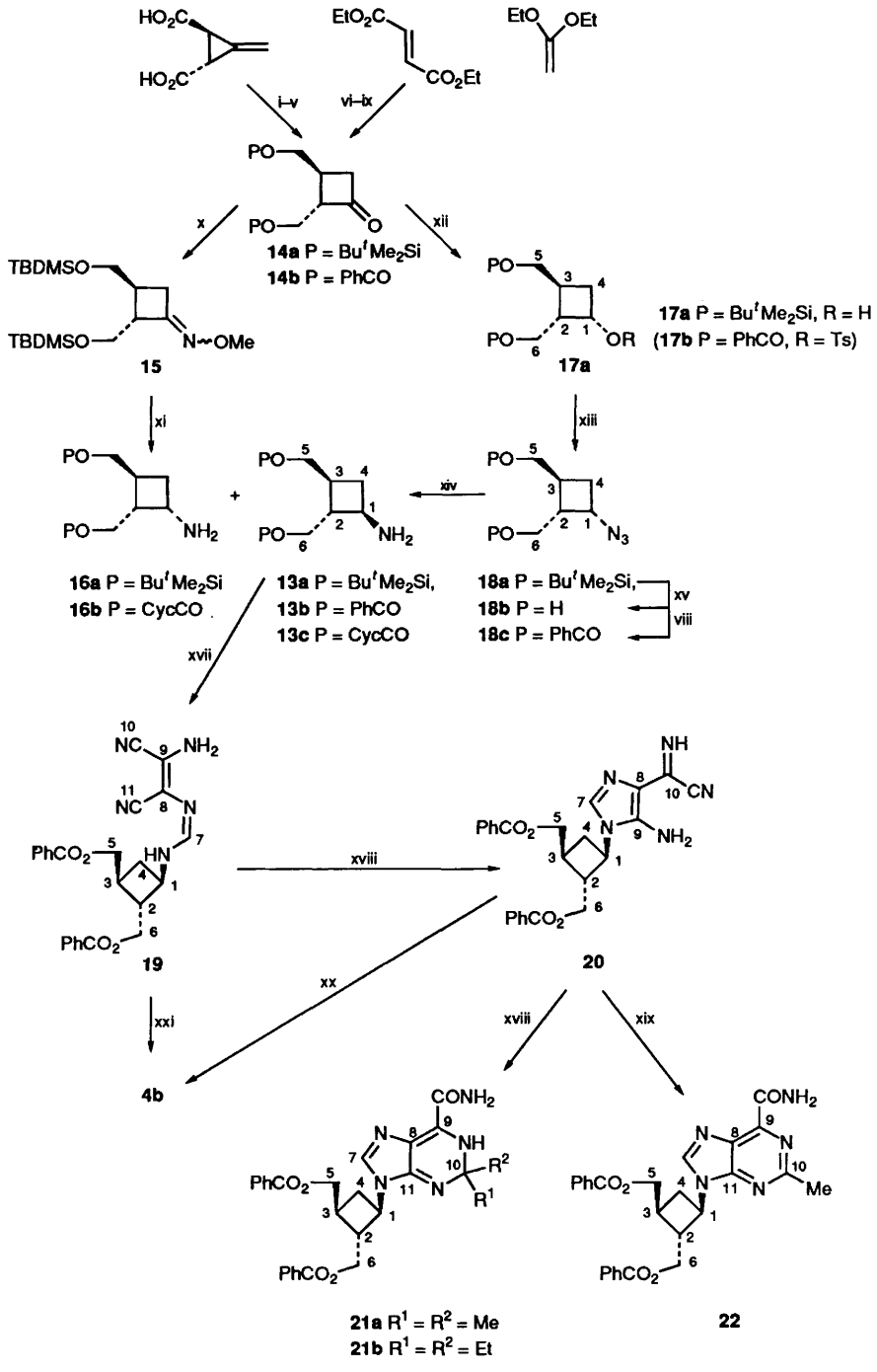


12A



12B

Encouraged by these preliminary findings the synthesis of cyclobut-A was explored. A key intermediate in the synthesis is the amine **13a** or some other protected derivative, such as **13b**, which is available from the corresponding cyclobutanone derivative **14a** or **14b**, respectively (see Scheme 1). A synthesis of amine **13a** *via* ketone **14a** starting from Feist's acid[21–23] has recently been described in the patent literature.[14] This method was attractive as Feist's acid can be resolved[24] and could, potentially, provide both enantiomers of the ketone **14** and, thence, the amine **13**. We have carried out the synthetic sequence as reported to obtain ketone **14a**, but experienced some difficulties in converting it into amine **13a** by using the published procedure. This involves conversion into the methyl oxime **15** and its reduction with sodium trifluoroacetoxyboranuide.[14] There are no problems with the methyl oxime step, but in our hands the reduction was not reproducible and in several attempts our best yield of compound **13a** was 42%, formed together with a 10% yield of the diastereoisomer **16a**. This contrasts with the reported yield of 62% of compound **13a** as the only product.[14] A rather better overall yield of compound **13a** was obtained by stereoselective reduction of ketone **14a** with LS-Selectride® in tetrahydrofuran (THF) at −78 °C to give the alcohol **17a** (87% yield), followed by formation of the mesyl ester and reaction with sodium azide in dimethylformamide (DMF) at 120 °C to give azide **18a** (91% yield). This upon hydrogenation afforded the desired amine **13a** in 98% yield, which was identical in all respects with that prepared *via* the oxime ether. Unfortunately, reaction of amine **13a** with the imidate **6** under mild acid catalysis was not a clean reaction and resulted in significant removal of the silyl protecting groups both from the starting material and the amidine product. In the absence of the acid catalyst, reaction was so slow that substantial decomposition occurred. Hence, it was necessary to change the protecting group to one which was less acid-sensitive, such as the benzoyl group. This was best achieved on the azide **18a** by deprotection using chlorotrimethylsilane in methanol, followed by treatment of the crude diol with benzoyl



Scheme 1 *Reagents and conditions:* i, MeOH, H^+; ii, LAH, −78 °C; iii, TBDMSCl, imidazole; iv, MCPBA, CH_2Cl_2 room temp.; v, LiI (cat.), CH_2Cl_2, 0 °C; vi, Bu^{t}OH, 84 °C; vii, LAH, 0 °C; viii, PhCOCl, py; ix, 0.5 mol dm^{-3} H_2SO_4, MeCN; x, $MeONH_3^+$ Cl^-, py; xi, $NaBH_3(OCOCF_3)$, THF; xii, LS-Selectride, THF; xiii, (a) $MeSO_2Cl$, Et_3N; then (b) NaN_3, DMF; xiv, H_2, Pd/C; xv, Me_3SiCl, MeOH; xvi, **6**, $PhNH_3^+$ Cl^- (cat.), EtOAc; xvii, DBU (cat.), $CHCl_3$; xviii, R^1R^2CO; xix, $MeCOCH_2COMe$; xx, DBU (excess), $CHCl_3$, room temp.

chloride in pyridine to give compound **18c** in 97% overall yield from silyl ether **18a**. Reduction of compound **18c** with 5% Pd/C in ethyl acetate gave amine **13b** in 75% isolated yield.

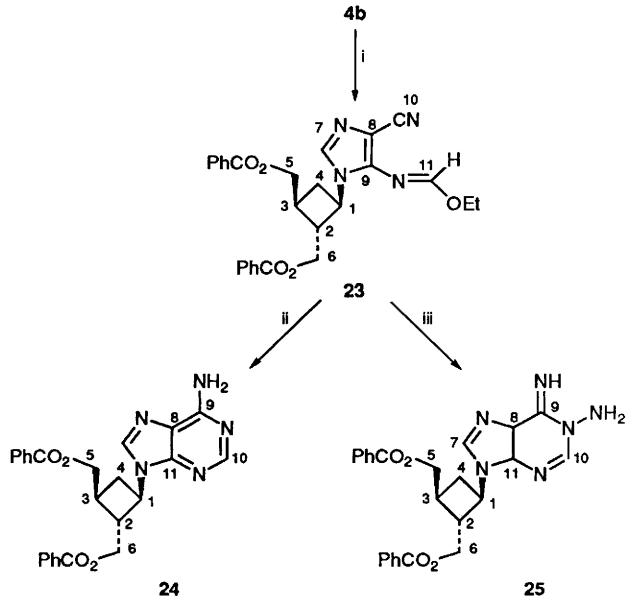
An alternative procedure, which offers some considerable advantages on a large scale, is from the ketone **14b**. This can be prepared in four steps starting from ketene diethyl acetal and diethyl fumarate as previously described.[6,7] Conversion of the ketone into its methyl oxime derivative (as a 2:1 mixture of geometrical isomers) as described previously (*vide supra*), followed by reduction with $NaBH_3(OCOCF_3)$ in THF, gave compound **13b** in 43% yield after chromatography. Although the final step gives only a moderate yield of the desired amine it is an improvement on the reported procedure from oxime **15**,[6,7] which uses catalytic hydrogenation (with PtO_2) resulting in a mixture of amine **13c** (20%) and its stereoisomer **16b** (28%) arising by reduction of the phenyl ring of the protecting groups. Probably the most effective synthesis of compound **13b** on a large scale is from ketene diethyl acetal to the cyclobutanone followed by the azide route as described above. This sequence avoids the problems often experienced in preparing Feist's acid on a large scale from ethyl acetoacetate,[21,22] if only the racemic amine is required.

As predicted, amine **13b** reacted smoothly with the imidate **6** to afford amidine **19** in 80% yield after flash chromatography.

Treatment of this with a catalytic amount of DBU in chloroform at 0 °C gave the 4-(cyanoformimidoyl)imidazol-5-amine derivative **20** in quantitative yield. This result contrasts with that found for the unsubstituted cyclobutyl derivative **7**, which gave only the 4-cyanoimidazol-5-amine under similar conditions. When either diester **19** or **20** was treated with an excess of DBU in chloroform the 4-cyanoimidazol-5-amine **4b** was obtained in 48% (from **19**) and 76% (from **20**) yield, respectively. Upon stirring of compound **20** in either acetone or pentan-3-one at room temperature over several hours the corresponding 6-carbamoyl-1,2-dihydropurines **21a** and **21b** were obtained in high yields (see Scheme 1), while similar treatment with pentane-2,4-dione gave the 6-carbamoyl-2-methylpurine derivative **22** in 57% isolated yield after flash chromatography. It has been noted previously within our group that pentane-2,4-dione does not behave in the same way as do simple aliphatic ketones, but the intermediate 1,2-dihydropurine readily eliminates acetone to give the methyl purine.[25]

When the 4-cyanoimidazol-5-amine was heated with triethyl orthoformate for several hours it gave a quantitative yield of the imidate **23**, which can be isolated (Scheme 2). Further treatment of this with a solution of anhydrous ethanolic ammonia gave the dibenzoyl derivative of Cyclobut-A (compound **24**) as the racemate in 65% yield. This compound has been prepared previously in 51% yield by a direct coupling of the tosyl derivative **17b** with adenine in the presence of potassium carbonate in DMF at 110 °C.[6] The same authors have demonstrated the deprotection to Cyclobut-A in 82% yield. Treatment of an ethanolic solution of the imidate **23** with hydrazine monohydrate afforded the new iminopurine **25** in 56% yield after chromatography (see Scheme 2). The biological activities of these types of compounds have, to our knowledge, not been explored. It is known, from work in our group and others,[26] that similar compounds can easily be converted into the corresponding 6-hydrazinopurines at room temperature in the presence of an excess of hydrazine hydrate.

We have not synthesized the 4-carbamoylimidazol-5-amine **5** (a precursor to Cyclobut-G) in this work, but our experience with similar compounds suggests that this is a trivial extension and can be carried out from compounds **18**, **19** or **4b** by heating them with aq. sodium hydroxide. Although the syntheses presented above were performed with racemic materials, our methodology clearly provides access to enantiomeric intermediates *via* Feist's acid route or by resolution at the amine stage.



Scheme 2 *Reagents and conditions:* i, $HC(OEt)_3$, heat; ii, NH_3, EtOH; iii, $N_2H_4{\cdot}H_2O$

Experimental

^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker XL300 instrument, and IR spectra on a Perkin-Elmer PE298 instrument. *J*-Values are given in Hz. Low-resolution mass spectra were carried out on a Kratos MS45 instrument and FAB spectra on a VG update AEI-M5902 instrument. The imidate **6** was prepared from diaminomaleodinitrile by a previously published procedure.[17,18] Dry column flash chromatography (DCFC) was carried out using Kieselgel 60H (Merck) and TLC using Merck Kieselgel $60F_{254}$ pre-coated aluminium-backed plates. Light petroleum refers to the fraction with distillation range 40–60 °C.

Preparation of (1α,2α,3β)-2,3-bis(*tert*-butyldimethylsiloxymethyl)cyclobutylamine 16a and (1β,2a,3β)-2,3-bis(*tert*-butyldimethylsiloxymethyl)cyclobutylamine 13a[14]

Trifluoroacetic acid (TFA) (9.6 cm^3, 125 mmol) was added dropwise over a period of 5 min to a stirred suspension of sodium boranuide (4.74 g, 125 mmol) in dry THF (125 cm^3) at room temperature under argon. The mixture was then stirred for a further 5 min before addition of a solution of the oxime ether **15** (10.23 g, 26.4 mmol) in dry THF (25 cm^3) dropwise over a period of 10 min. The mixture was stirred for 16 h at room temperature, diluted with dichloromethane (500 cm^3), washed with brine (2 × 200 cm^3), dried ($MgSO_4$), and concentrated to give a pale yellow oil, which was purified by chromatography [eluent (95:5–90:10) CH_2Cl_2–MeOH] to give compound **13a** as an oil (3.97 g, 42%) (Found: FAB $(M + H)^+$, 360 (100%). Calc. for $C_{18}H_{41}NO_2Si_2$: M, 359]; $\delta_H(CDCl_3)$ 0.05 (12 H, s, Me), 0.9 (18 H, s, Me), 1.3 (1 H, m, 3-H), 1.8 (2 H, m, 4-H_2), 2.2 (1 H, m, 2-H), 3.05 (1 H, m, 1-H), 3.5–3.6 (3 H, m, CH_2O), 3.7 (1 H, dd, *J* 4.5 and 10.5, CH_2O) and 4.0 (2 H, br s, NH_2); $\delta_C(CDCl_3)$ −5.3, 18.28, 18.32, 25.9, 32.5 (C-3), 32.6 (C-4), 47.5 (C-2), 52.0 (C-1), 64.2 and 65.9 (C-5 and -6). Compound **16a** was also obtained, also as an oil (0.96 g, 10%) [Found: FAB $(M + H)^+$, 360 (100%). Calc. for $C_{18}H_{41}NO_2Si_2$: M, 359]; $\delta_H(CDCl_3)$ 0.05 (12 H, s, Me), 0.85 (18 H, s, Me), 1.7 (1 H, m, 3-H), 2.1 (1 H, m, 2-H), 2.2 (1 H, m, 4-H^a), 2.35 (1 H, m, 4-H^b), 3.1 (1 H, m, 1-H) and 3.5–4.0 (6 H, m, CH_2O and NH_2); $\delta_C(CDCl_3)$ −5.2, 18.2, 18.4, 25.9, 26.0, 27.2 (C-4), 33.5 (C-3), 46.1 (C-2), 52.4 (C-1), 64.1 and 64.4 (C-5 and -6).

Preparation of (1α,2α,3β)-2,3-bis(*tert*-butyldimethylsiloxymethyl)cyclobutanol 17a

To a stirred solution of the ketone **14a** (15.15 g, 42.3 mmol) in dry THF (185 cm^3) at −78 °C under argon was added LS-Selectride (1 mol dm^{-3} in THF; 45 cm^3, 45.0 mmol) during 45 min. The mixture was stirred for a further 1 h at this temperature and was then warmed to room temperature over a period of 2 h before treatment with saturated aq. $NaHCO_3$ (50 cm^3) during 5 min. The resultant mixture was treated with 30% hydrogen peroxide (18 cm^3) at such a rate as to maintain the temperature at 25–30 °C. After the temperature had dropped to 20 °C the mixture was diluted with water (150 cm^3) and extracted with ethyl acetate (550 cm^3). The organic phase was washed with water (3 × 200 cm^3), dried ($MgSO_4$), and concentrated to give a yellow oil, which was purified by chromatography (eluent CH_2Cl_2) to give the alcohol **17a** as an oil (13.23 g, 87%) [Found: C, 60.3; H, 11.4; Si, 15.5%; FAB $(M + H)^+$, 361 (45%). Calc. for $C_{18}H_{40}O_3Si_2$: C, 60.0; H, 11.1;

Si, 15.6%; M, 360]. The spectral data for this compound were in agreement with those previously reported.[14]

Preparation of (1α,2α,3β)-2,3-bis(*tert*- butyldimethylsiloxymethyl)cyclobutyl methanesulfonate

To a stirred solution of the alcohol **17a** (9.02 g, 25 mmol) in dry dichloromethane (90 cm^3) and dry triethylamine (7.0 cm^3, 50 mmol) at 0 °C under argon was added freshly distilled methanesulfonyl chloride (4.20 g, 37 mmol). After 1 h, TLC showed complete reaction, and 10% aq. sodium carbonate (2 × 50 cm^3) was added before extraction with diethyl ether (200 cm^3). After the extract had been washed successively with 10% aq. sodium carbonate, water and brine, removal of the solvent gave the mesyl ester as a pale yellow oil (10.93 g, 100%). This was sufficiently pure for use in the next stage.

Preparation of (1α,2β,3α)-1-azido-2,3-bis(*tert*-butyldimethylsiloxymethyl)cyclobutane 18a

A mixture of the above mesyl ester (3.00 g, 6.85 mmol) and sodium azide (4.45 g, 68.5 mmol) in dry DMF (30 cm^3) under argon was heated to 120 °C for 2 h. After cooling, the mixture was diluted with water (70 cm^3) and extracted with diethyl ether (300 cm^3) to afford azide **18a** as a pale yellow oil (2.39 g, 91%). A pure sample (oil) was obtained by DCFC [(40:1) hexane–ethyl acetate] {Found: C, 56.4; H, 10.4; N, 10.7; Si, 14.2%; FAB $[(M + H) - N_2]^+$, 358 (7%). $C_{18}H_{39}N_3O_2Si_2$ requires C, 56.1; H, 10.1; N, 10.9; Si, 14.55%; M, 385}; ν_{max}(neat film)/cm^{-1} 2110s (N_3); δ_H($CDCl_3$) 0.05 (12 H, m, Me), 0.9 (18 H, s, Me), 1.75 (1 H, m, 3-H), 2.0 (1 H, m, 4-H^a), 2.15 (1 H, m, 4-H^b), 2.3 (1 H, m, 2-H) and 3.5–3.7 (5 H, m, 5- and 6-H_2 and 1-H); δ_C($CDCl_3$) −5.3, 18.3, 25.9, 27.6 (C-4), 31.9 (C-3), 46.9 (C-2), 53.2 (C-1), 62.6 (C-5) and 64.7 (C-6).

Preparation of (1α,2β,3α)-1-azido-2,3-bis(hydroxymethyl)cyclobutane 18b

To a stirred solution of the silyl ether **18a** (9.48 g, 24.6 mmol) in dry methanol (150 cm^3) was added chlorotrimethylsilane (7.70 cm^3, 60.8 mmol), and the mixture was stirred at room temperature for 2 h before removal of the solvent and co-evaporation with methanol (3 × 100 cm^3) to give crude diol **18b** (3.86 g, 100%) as a pale yellow oil [Found: CI $(M + H)^+$, 158 (4%) and $(M - N_2 - OH)^+$ (100%). $C_6H_{11}N_3O_2$ requires M, 157]; ν_{max}(neat film)/cm^{-1} 3100–3600br s (OH) and 2120s (N_3); δ_H(D_2O) 1.75 (1 H, m, 4-H^a), 2.0 (1 H, m, 4-H^b), 2.35 (2 H, m, 2- and 3-H) and 3.6–3.75 (5 H, m, 5- and 6-H_2 and 1-H); δ_C($CDCl_3$) 28.2 (C-4), 35.0 (C-3), 49.9 (C-2), 53.5 (C-1), 63.1 (C-5) and 65.3 (C-6).

Preparation of (1α,2β,3α)-1-azido-2,3-bis(benzoyloxymethyl)cyclobutane 18c

Benzoyl chloride (6.0 cm^3, 17.1 mmol) was added to a stirred solution of diol **18b** (2.68 g, 17.1 mmol) in dry pyridine (27 cm^3) at 0 °C and the mixture was then kept at room temperature for 2.5 h before addition of water (13 cm^3) dropwise to the mixture and stirring of the mixture for 15 h. Extraction with diethyl ether (300 cm^3) and washing of the extract successively with 10% HCl (2 × 100 cm^3) and 10% aq. Na_2CO_3 (2 × 100 cm^3), then drying ($MgSO_4$) gave, after removal of the solvent, diester **18c** (6.07 g, 97%) as a pale yellow oil [Found: FAB $(M + H)^+$, 366 (100%). $C_{20}H_{19}N_3O_4$ requires M, 365]; ν_{max}(neat film)/cm^{-1} 2120s (N_3) and 1730s (C=O); δ_H($CDCl_3$) 1.95 (1 H, m, 3-H), 2.35–2.5 (2 H, m, 4-H_2), 2.7 (1 H, m, 2-H), 3.7 (1 H, m, 1-H), 4.3–4.5 (4 H, m, 5- and 6-H_2), 7.4 (4 H, m, ArH), 7.55 (2 H, m, ArH) and 8.0 (4 H, m, ArH); δ_C($CDCl_3$) 28.6 (C-3), 30.1 (C-4), 45.0 (C-2), 54.0 (C-1), 64.5 (C-5), 66.1 (C-6), 128.33, 128.36, 129.48, 129.50, 129.7, 133.0 (aromatics) and 166.3 (C=O).

Preparation of (1α,2β,3α)-2,3-bis(benzoyloxymethyl)cyclobutylamine 13b

A solution of azide **18c** (4.43 g, 12.1 mmol) in ethyl acetate (35 cm^3) containing 5% palladium on charcoal (470 mg) was stirred for 15 h under hydrogen. The mixture was filtered through Celite and concentrated to give a crude product, which was purified by DCFC (100% CH_2Cl_2–10% MeOH in CH_2Cl_2) to give *title amine* **13b** (3.10 g, 75%) as a solid, mp 119–121 °C [Found: C, 70.8; H, 6.2; N, 4.0%; FAB $(M + H)^+$, 340 (100%). $C_{20}H_{21}NO_4$ requires C, 70.8; H, 6.2; N, 4.1%; M, 339]; ν_{max}(neat film)/cm^{-1} 3400–3600br w (N–H) and 1720s (C=O); δ_H($CDCl_3$) 1.5 (1 H, m, 3-H), 2.2 (2 H, m, 4-H_2), 2.45 (1 H, m, 2-H), 3.2 (1 H, m, 1-H), 4.3–4.4 (4 H, m, 5- and 6-H_2), 7.4 (4 H, m, ArH), 7.5 (2 H, m, ArH) and 8.0 (4 H, m, ArH); δ_C($CDCl_3$) 30.2 (C-3), 33.3 (C-4), 47.8 (C-2), 49.8 (C-1), 65.4 (C-5), 67.3 (C-6), 128.4, 129.9, 130.0, 132.88 and 132.90 (aromatics) and 166.4 and 166.5 (C=O).

Reaction of ethyl (*Z*)-*N*-(2-Amino-1,2-dicyanovinyl) formamidate 6

(a) With cyclobutylamine. Cyclobutylamine (0.48 g, 0.34 cm^3, 6.8 mmol) was added dropwise to a stirred suspension of the imidate **6** (1.00 g, 6.8 mmol) in ethanol (2.5 cm^3) containing a catalytic amount of anilinium chloride (10 mg). After 10 min the imidate had completely dissolved to give a deep yellow solution and after 1 h TLC indicated complete reaction. Removal of the solvent under reduced pressure gave a dark residue, which upon trituration with cold hexane gave a light brown solid. Recrystallisation from chloroform–light petroleum gave the pure (Z)-N-(2-*amino*-1,2-*dicyanovinyl*)-N′-*cyclobutylformamidine* **7** as a solid (0.856 g, 71%), mp 110–112 °C [Found: C, 56.8; H, 6.1%; EI (M^+), 189 (31.4%). $C_9H_{11}N_5$ requires C, 57.1; H, 5.8%; M, 189]; ν_{max}(Nujol)/cm^{-1} 3460s, 3320s (N–H) and 2240m and 2200m (C≡N); δ_H[$(CD_3)_2SO$] 1.60–2.00 (4 H, m, 2 × 7-H_2), 2.35 (2 H, m, 8-H_2), 4.55 (1 H, m, 6-H), 6.15 (< 2 H, br s, NH_2), 7.6 (1 H, d, *J* 4.5, 5-H) and 8.1 (< 1 H, br s, NH); δ_C[$(CD_3)_2SO$] 18.9 (C-8), 34.0 (C-7), 49.3 (C-6), 110.3 (C-1), 119.0 (C-2), 120.2 and 120.9 (C-7 and -8) and 153.2 (C-4).

(b) With cyclopropylamine. Under similar conditions to those described above, cyclopropylamine (2.0 g, 35.1 mmol), the imidate **6** (2.0 g, 12.2 mmol) and anilinium chloride (0.02 g) in ethanol (4 cm^3) gave an impure product as a dark solid, which was purified by dissolution in chloroform and passage of the solution through a short, dry flash column. A second chromatographic separation ($CHCl_3$ eluent) gave (Z)-N-(2-*amino*-1,2-*dicyanovinyl*)-N′-*cyclopropylformamidine* **8** as a solid (1.5 g, 70%), mp 59–60 °C [Found: C, 55.1; H, 4.8; N, 39.7%; FAB $(M + H)^+$, 176 (100%). $C_8H_9N_5$ requires C, 54.9; H, 5.1; N, 40.0%; M, 175]; ν_{max}(Nujol)/cm^{-1} 3410s and 3380s (N–H) and 2220s and 2200s (C≡N); δ_H[$(CD_3)_2SO$] 0.61 (2 H, br m, 2 × 7-H^a), 0.80 (2 H, m, 2 × 7-H^b), 3.05 (1 H, br s, 6-H), 6.13 (2 H, br s, NH_2), 7.71 (1 H, s, 5-H) and 7.9 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 10.1 (C-7), 27.8 (C-6), 110.7 (C-1), 119.1 and 120.3 (C-4 and -3), 121.1 (C-2) and 155.4 (C-5).

(c) With (1α,2β,3α)-2,3-bis(benzoyloxymethyl)cyclobutyl amine 13b. A mixture of the amine **13b** (2.20 g, 3.9 mmol), the imidate **6** (0.645 g, 3.9 mmol) and anilinium chloride (6 mg) in dry ethyl acetate (4 cm^3) was stirred at room temperature for 2 d, when TLC indicated complete reaction. The mixture was concentrated, and subjected to DCFC ($CHCl_3$ eluent) to give (Z)-N-(2-*amino*-1,2-*dicyanovinyl*)-N′-[(1α,2β,3α)-2,3-*bis*(*benzoyloxymethyl*)*cyclobutyl*]*formamidine* **19** as an off-white foam (1.445 g, 80%) mp > 50 °C (decomp.) [Found: FAB $(M + H)^+$, 458.1805 (100%). $C_{25}H_{24}N_5O_4$ requires *m/z*, 458.1828]; ν_{max}-(Nujol)/cm^{-1} 3341 br s (N–H) and 2221s and 2199s (C≡N); δ_H[$(CD_3)_2SO$] 1.86 (1 H, m, 3-H), 2.39–2.60 (3 H, m, 2- and 4-H), 4.40–4.55 (5 H, m, 1-H, 5- and 6-H_2), 6.12 (< 2 H, br s,

NH_2), 7.55–7.69 (5 H, m, ArH and 7-H), 7.70–7.79 (2 H, m, ArH), 7.98–8.14 (4 H, m, ArH) and 8.24 (1 H, m, NH); δ_C[$(CD_3)_2SO$] 33.5 (C-4), 34.9 (C-3), 48.8 (C-2), 50.2 (C-1), 69.8 (C-5), 70.8 (C-6), 110.4 (C-8), 121.16 (C-9), 121.2 (C-10), 121.23 (C-11), 132.7, 132.8, 133.2, 133.3, 133.75, 133.78, 137.36 and 137.43 (aromatics), 153.6 (C-7) and 169.8 and 169.6 (C=O).

Preparation of 5-amino-1-[(1α,2β,3α)-2,3-bis(benzoyloxymethyl)cyclobutyl]-4-(cyanoformimidoyl)-imidazole 20

DBU (90 mm^3, 0.6 mmol) was added to a stirred solution of compound **19** (2.55 g, 5.58 mmol) in dry chloroform (20 cm^3) under argon at 0 °C. After 7 h, TLC analysis indicated complete reaction and the mixture was diluted with chloroform (100 cm^3), washed with water (2 × 100 cm^3), and dried ($MgSO_4$). Removal of most of the solvent followed by DCFC ($CHCl_3$ eluent) gave compound **20** (2.55 g, 100%) as a pale green solid, mp 88–88 °C (decomp.) [Found: FAB (M + H)$^+$, 458 (100%). $C_{25}H_{23}N_5O_4$ requires M, 457]; ν_{max}(Nujol)/cm^{-1} 3307m and 3290m (N–H); δ_H[$(CD_3)_2SO$] 2.29 (1 H, m, 3-H), 2.57 (1 H, m, 4-H^a), 2.77 (1 H, m, 4-H^b), 3.22 (1 H, m, 2-H), 4.40–4.70 (5 H, m, 5- and 6-H_2 and 1-H), 6.85 (< 2 H, br s, NH_2), 7.52 (2 H, t, *J* 7.5, ArH), 7.61 (2 H, t, *J* 7.5, ArH), 7.67–7.78 (3 H, m, ArH and 7-H), 7.92 (2 H, d, *J* 7.5, ArH), 8.09 (2 H, d, *J* 7.5, ArH) and 11.0 (< 1 H, br s, NH); δ_C[$(CD_3)_2SO$] 34.2 (C-4), 34.3 (C-3), 49.6 (C-2), 50.6 (C-1), 69.2 (C-5), 70.9 (C-6), 117.6 (C-8), 120.4 (C-11), 132.60, 132.8, 133.6 and 133.7 (aromatics), 134.1 (C-7), 137.3 and 137.4 (aromatics), 147.1 (C-9), 148.1 (C-10) and 169.6 and 169.8 (C=O).

Prepration of 5-amino-1-[(1α,2β,3α)-2,3-bis(benzoyloxymethyl)cyclobutyl]imidazole-4-carbonitrile 4b

(a) From compound 19. DBU (140 mm^3, 0.94 mmol) was added to a stirred solution of dinitrile **19** (0.20 g, 0.44 mmol) in dry chloroform (1 cm^3) under argon and after 24 h at room temperature TLC indicated complete reaction. Concentration, and DCFC on the residue, gave *title compound* **4b** (90 mg, 48%) as an off-white foam, mp 64–66 °C [Found: C, 66.7; H, 5.4; N, 12.7%; FAB (M + H)$^+$ 431 (100%). $C_{25}H_{23}N_5O_4$ requires C, 67.0; H, 5.1; N, 13.0%; M, 430]; ν_{max}(Nujol)/cm^{-1} 3331m (N–H) and 2207m (C≡N); δ_H[$(CD_3)_2SO$] 2.18 (1 H, m, 3-H), 2.55 (1 H, m, 4-H^a), 2.74 (1 H, m, 4-H^b), 3.20 (1 H, m, 2-H), 4.40–4.70 (5 H, m, 5- and 6-H_2 and 1-H), 6.32 (< 2 H, br s, NH_2), 7.60 (4 H, m, ArH), 7.74 (3 H, m, ArH and 7-H), 7.95 (2 H, d, *J* 7.5, ArH) and 8.07 (2 H, d, *J* 7.5, ArH); δ_C†[$(CD_3)_2SO$] 34.2 (C-3), 34.4 (C-4), 49.5 (C-2), 51.0 (C-1), 69.1 (C-5), 71.0 (C-6), 94.6 (C-8), 121.5 (C-10), 132.7, 132.9, 133.3, 133.6 and 133.7 (aromatics), 134.7 (C-7), 137.45 and 137.47 (aromatics), 151.4 (C-9) and 169.7 and 169.8 (C=O).

(b) From compound 20. Under similar conditions a mixture of DBU (0.80 cm^3) and compound **20** (0.84 g, 1.84 mmol) in chloroform (7 cm^3) gave compound **4b** (604 mg, 76%).

Preparation of 5-amino-1-cyclobutylimidazole-4-carbonitrile 10

To a stirred, fine suspension of the amidine **7** (98 mg, 0.52 mmol) in water (7 cm^3) was added DBU (20 mm^3). The mixture became homogeneous after 10 min and after a further 20 min a solid precipitated. This was filtered off, and washed with diethyl ether, to give compound **10** (63 mg, 75%) as a pale brown solid, mp > 160 °C (decomp.) [Found: EI (M^+), 162 (36%). $C_8H_{10}N_4$ requires M, 162]; ν_{max}(Nujol)/cm^{-1} 2360m, 2300m and 2160s (N–H) and 2220s (C≡N); δ_H[$(CD_3)_2SO$] 1.85 (2 H, m, 2 × 8-H^a), 2.3–2.5 (4 H, m, 2 × 8-H^b and 9-H_2), 4.55 (1 H, m, 7-H), 6.2 (< 2 H, br s, NH_2) and 7.55 (1 H, s, 2-H); δ_C[$(CD_3)_2SO$] 19.8 (C-9), 34.9 (C-7), 95.6 (C-4), 122.7 (C-6), 135.6 (C-2) and 152.2 (C-5).

The same compound could also be obtained in 74% yield by stirring of a suspension of the amidine **7** in saturated aq. sodium carbonate for 15 h.

Preparation of 9-cyclobutyl-2,2-dimethyl-2,3-dihydropurine-6-carboxamide 12

A mixture of the amidine **7** (200 mg, 1.1 mmol), DBU (6 mm^3) and acetone (10 cm^3) was stirred at room temperature for 3 d and was then chromatographed by DCFC (acetone eluent) to give title compound **12** (100 mg, 36%) as an orange solid, mp 119–120 °C. This compound decomposed rapidly in air and a satisfactory elemental analysis could not be obtained [Found: EI (M + H)$^+$, 248 (99.9%). $C_{12}H_{17}N_5O$ requires M, 247); ν_{max}(Nujol)/cm^{-1} 3000–3600br s (N–H) and 1650s (C=O); δ_H[$(CD_3)_2SO$] 1.4 (6 H, s, 2 × Me), 1.8 (2 H, m, 12-H_2), 2.4–2.6 (4 H, m, 2 × 11-H_2), 4.6 (1 H, m, 10-H), 6.3 (< 1 H, br s, NH), 7.5 (1 H, s, 8-H), 7.5–7.8 (< 1 H, br s, NH) and 8.3 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 18.4 (C-12), 32.4 (Me), 33.5 (C-11), 50.9 (C-10), 75.9 (C-2), 121.3 (C-5) and 167.6 (C=O) (the carbon atoms C-4, C-6 and C-8 could not be distinguished from the noise due to broadening caused by tautomerism in solution).

Reactions of 20

(a) With acetone. A solution of compound **20** (380 mg, 0.83 mmol) in dry acetone (3 cm^3) was stirred at room temperature for 3 days before removal of the solvent to give an orange solid, which was purified by DCFC (eluent 0–10% EtOH–$CHCl_3$) to give 9-[(1α,2β,3α)-2,3-*bis*(*benzoyloxymethyl*)*cyclobutyl*]-2,2-*dimethyl*-1,2-*dihydropurine*-6-*carboxamide* **21a** (394 mg, 92%), mp 60–63 °C (decomp.) [Found: FAB (M + H)$^+$, 516.2241 (100%). $C_{28}H_{29}N_5O_5$ requires (M + H), 516.2247]; ν_{max}(Nujol)/cm^{-1} 3376m and 3319m (N–H), 1716 (C=O ester) and 1689 (C=O amide); δ_H‡[$(CD_3)_2SO$] 1.37 (3 H, s, Me), 1.42 (3 H, s, Me), 2.30–2.60 (3 H, m, 3-H and 4-H_2), 3.21 (1 H, m, 2-H), 4.38–4.62 (5 H, m, 5- and 6-H_2 and 1-H), 6.29 (< 1 H, br s, NH), 7.48–7.80 (7 H, m, ArH and 7-H), 7.85–8.15 (5 H, m, ArH and NH) and 8.28 (< 1 H, br s, NH); δ_C‡[$(CD_3)_2SO$] 32.9* (C-3), 34.3 (Me), 48.9* (C-2), 50.8* (C-1), 71.1 (C-6), 76.0 (C-10), 132.6, 132.8, 133.18, 133.22, 133.67, 133.74, 137.3 and 137.4 (aromatics) and 169.6 and 169.8 (C=O) (* signals broadened due to tautomerism—not all peaks were observed for this reason).

(b) With pentan-3-one. Under similar conditions compound **20** (408 mg, 0.89 mmol) in pentan-3-one (3 cm^3) gave 9-[(1α,2β,3α)-2,3-*bis*(*benzoyloxymethyl*)*cyclobutyl*]-2,2-*diethyl*-1,2-*dihydropurine*-6-*carboxamide* **21b** (428 mg, 88%) as an orange solid, mp 49–51 °C (decomp.) [Found: FAB (M + H)$^+$, 544.2546 (80%). $C_{30}H_{33}N_5O_5$ requires (M + H), 544.2560]; ν_{max}(Nujol)/cm^{-1} 3376m and 3319m (N–H), 1716 (C=O ester) and 1689 (C=O amide); δ_H‡[$(CD_3)_2SO$] 0.81 (3 H, t, *J* 7, Me), 0.88 (3 H, t, *J* 7, Me), 1.37 (3 H, s, Me), 1.48–1.76 (4 H, m, 2 × CH_2), 2.40–2.50 (3 H, m, 3-H and 4-H_2), 3.28 (1 H, m, 2-H), 4.38–4.61 (5 H, m, 5- and 6-H_2 and 1-H), 5.88 (< 1 H, br s, NH), 7.48–8.11 (12 H, m, ArH, 7-H and NH) and 8.25 (< 1 H, br s, NH); δ_C‡[$(CD_3)_2SO$] 11.6 (Me), 32.5* (C-3), 34.1* (CH_2), 36.1* (C-4), 48.91 (C-2), 51.0* (C-1), 69.4 (C-5), 71.1 (C-6), 82.0 (C-10), 121.3* (C-8), 132.6, 132.8, 133.2, 133.7 and 133.75 (aromatics), 136.7* (C-11), 137.3 and 137.4 (aromatics), 149.8* (C-7), 160.4* (C-9), 166.6* (C-12) and 169.7 and 169.8 (C=O) (* signals broadened due to tautomerism).

† Locants follow the numbering scheme shown in structure **4b**.

‡ Numbering refers to the scheme shown in structures **21**, **22** (Scheme 1).

(c) With pentane-2,4-dione. A solution of compound **20** (0.400 g, 0.88 mmol) in pentane-2,4-dione (2 cm^3) was stirred at room temperature for 7 days, before removal of the solvent and chromatography [eluent (25:1) CH_2Cl_2–EtOH] to give 9-[(1α,2β,3α)-2,3-*bis*(*benzoyloxymethyl*)*cyclobutyl*]-2-*methylpurine*-6-*carboxamide* **22** (0.25 g, 57%) as a solid, mp 105–108 °C [Found: C, 62.9; H, 5.3; N, 13.2%; FAB $(M + H)^+$, 500 (55%). $C_{27}H_{25}N_5O_5 \cdot H_2O$ requires C, 62.7; H, 5.3; N, 13.5%; M, 499]; ν_{max}(Nujol)/cm^{-1} 3392 br m (N–H), 1715s (C=O of ester) and 1690s (C=O of amide) δ_H‡($CDCl_3$) 2.60–2.82 (6 H, m, 3-H, 4-H_2 and Me), 3.43 (1 H, m, 2-H), 4.49–4.65 (4 H, m, 5- and 6-H_2), 4.94 (1 H, app. q, *J* 9, 1-H), 6.07 (1 H, br s, NH), 7.35 (2 H, t, *J* 8, ArH), 7.42–7.62 (4 H, m, ArH), 7.80 (2 H, d, *J* 8, ArH), 8.05 (2 H, d, *J* 8, ArH), 8.21 (1 H, s, 7-H) and 8.51 (1 H, br s, NH); δ_C‡($CDCl_3$) 25.7 (Me), 29.1 (C-4), 31.0 (C-3), 45.7 (C-2), 48.8 (C-1), 64.6 (C-5), 66.2 (C-6), 128.2, 128.4, 129.15, 129.2, 129.2, 129.4 and 129.6 (aromatics), 130.0 (C-8), 133.09 and 133.13 (aromatics), 144.8 (C-7) 145.5 (C-9), 154.3 (C-11), 162.0 (C-10), 165.1 (C-12) and 166.1 and 166.3 (C=O).

Preparation of ethyl *N*-{1-[(1α,2β,3α)-2,3-bis(benzoyloxymethyl)cyclobutyl]-4-cyanoimidazol-5-yl}formimidate 23

A solution of amine **4b** (238 mg, 0.55 mmol) in triethyl orthoformate (5 cm^3) was heated at 70–80 °C for 12 h under argon. Evaporation of the solvent gave crude compound **23** (269 mg, 100%)—this product, which was pure by TLC, was used in subsequent reactions without further purification [Found: FAB $(M + H)^+$, 487 (100%). $C_{27}H_{26}N_4O_5$ requires M, 486]; δ_H§($CDCl_3$) 1.27 (3 H, t, *J* 7, Me), 2.33 (1 H, m, 3-H), 2.57 (1 H, m, 4-H^a or -H^b), 2.66 (1 H, m, 4-H^b or -H^a), 2.97 (1 H, m, 2-H), 4.23 (2 H, dq, *J* 7, 2.5, CH_2), 4.36–4.63 (5 H, m, 5- and 6-H_2 and 1-H), 7.39–7.62 (7 H, m, ArH and 7-H), 7.90 (2 H, d, *J* 8, ArH), 8.02 (2 H, d, *J* 8, ArH) and 8.20 (1 H, s, 11-H); δ_C§($CDCl_3$) 13.7 (Me), 29.6 (C-4), 30.7 (C-3), 46.7 (C-2), 47.7 (C-1), 63.7 (CH_2), 64.2 (C-5), 65.8 (C-6), 99.1 (C-8), 115.8 (C-10), 128.4, 128.44, 129.25, 129.27, 129.33 and 129.47 (aromatics), 133.1 (C-7), 133.2, 133.3 (aromatics), 144.6 (C-9), 159.7 (C-11) and 166.0 and 166.2 (C=O).

Reaction of compound 23

(a) With ammonia. A solution of crude compound **23** (269 mg, 0.55 mmol) in anhydrous ethanol saturated with ammonia (5 cm^3) was stirred at room temperature for 15 h before removal of the solvent and chromatography [eluent (25:1) $CHCl_3$–EtOH] to give 9-[(1α,2β,3α)-2,3-*bis*(*benzoyloxymethyl*)*cyclobutyl*]*adenine* **24** (165 mg, 65%) as a solid, mp 138–140 °C (lit.,[7] 150–152 °C) [Found: C, 65.3; H, 5.2; N, 15.3%; FAB $(M + H)^+$, 458 (100%). Calc. for $C_{25}H_{23}N_5O_4$: C, 65.6; H, 5.0; N, 15.3%; M, 457]; ν_{max}(Nujol)/cm^{-1} 3330m and 3154m (N–H) and 1717s (C=O); δ_C§($CDCl_3$) 29.1 (C-4), 31.0 (C-3), 45.2 (C-2), 48.9 (C-1), 64.6 (C-5), 65.9 (C-6), 120.0 (C-8), 128.2, 128.3, 129.3, 129.4, 129.5, 129.7 and 133.0 (aromatics), 139.1 (C-7), 150.1 (C-11), 152.6 (C-10), 155.7 (C-9) and 166.2 and 166.4 (C=O). The ^1H NMR spectrum compared well with that reported[7] except that the signals in the range δ 7.35–8.2 integrated for 11 protons rather than the 10 protons quoted by the previous authors.

(b) With hydrazine. A solution of crude compound **23** (0.554 g, 1.14 mmol) and hydrazine monohydrate (0.25 g, 5 mmol) in ethanol (6 cm^3) gave, after 1 h at room temperature, 1-*amino*-9-[(1α,2β,3α)-2,3-*bis*(*benzoyloxymethyl*)*cyclobutyl*]-6-*imino*-1,6-*dihydropurine* **25** as an off-white solid (304 mg, 56%), mp 108–110 °C (decomp.), which was purified by DCFC [eluent (0–50%) EtOH–$CHCl_3$] [Found: C, 59.2; H, 5.1; N, 15.8%; FAB $(M + H)^+$, 473 (100%). $C_{25}H_{24}N_6O_4 \cdot 2H_2O$ requires C, 59.2; H, 5.15; N, 16.5%; M, 472]; ν_{max}(Nujol)/cm^{-1} 3100–3600br m (N–H + H_2O) and 1716s (C=O); δ_H§($CDCl_3$) 2.50–2.72 (3 H, m, 3-H and 4-H_2), 3.34 (1 H, m, 2-H), 4.42–4.58 (4 H, m, 5- and 6-H_2), 4.67 (1 H, app. q, *J* 9, 1-H), 4.73 (2 H, br s, NH_2), 7.34–7.62 (6 H, m, ArH), 7.65 (1 H, s, 7- or 10-H), 7.74 (1 H, s, 10- or 7-H), 7.85 (2 H, d, *J* 8, ArH) and 8.07 (2 H, d, *J* 8, ArH); δ_C§($CDCl_3$) 29.3 (C-4), 31.0 (C-3), 45.8 (C-2), 48.8 (C-1), 64.6 (C-5), 65.8 (C-6), 123.2 (C-8), 128.3, 128.4, 129.3, 129.5, 129.7, 133.0 and 133.1 (aromatics), 137.2 (C-2), 142.1 (C-11), 147.6 (C-10), 155.7 (C-9) and 166.1 and 166.3 (C=O).

§ Locants refer to the numbering scheme shown in structures **23**–**25** (Scheme 2).

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