Synthesis of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-adenine and -guanine

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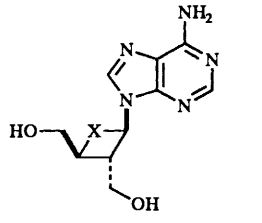
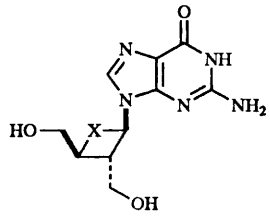
2,2-Dichloro-3-(benzyloxymethyl)cyclobutanone **15**, which was prepared in 50% yield by the cycloaddition of dichloroketene to allyl benzyl ether **14**, was converted in four steps and in ~40% overall yield into *trans*-3-(benzyloxymethyl)cyclobutanol **11b**. The latter alcohol **11b** was coupled under Mitsunobu conditions with 6-(4-chlorophenylsulfanyl)-9*H*-purine **21b** and 6-(4-chlorophenylsulfanyl)-2-(phenylacetamido)-9*H*-purine **21c** to give the 9-cyclobutylpurine derivatives **22** and **24**, respectively, in 88 and 60% yield. The former product **22** was converted in three steps and in 39% overall yield into 9-[*cis*-3-(hydroxymethyl)cyclobutyl]adenine **6**, and the latter product was converted in four steps and in 42% overall yield into 9-[*cis*-3-(hydroxymethyl)cyclobutyl]guanine **7**. X-Ray crystallographic data relating to compounds **22** and **24** are also reported.

Introduction

Oxetanocin A **1a** is a naturally occurring nucleoside antibiotic[1] that exhibits both antiviral and antitumour activity. Oxetanocin G **2a** has also been found[2] to exhibit antiviral activity. The observed biological activity of the latter nucleoside analogues **1a** and **2a** stimulated organic chemists to undertake[3–5] the synthesis of the corresponding carbocyclic analogues **1b** and **2b**, respectively. The enantiomerically pure guanine derivative **2b** was found[6] to have very high *in vitro* activity against herpes simplex virus types 1 and 2, varicella zoster virus and murine cytomegalovirus. Acyclovir[7] **3** and penciclovir[8] 4 are other guanine derivatives with non-sugar substituents in the 9-position that are also powerful antiviral agents. The search for anti-Human Immunodeficiency Virus (anti-HIV) agents has led to the development of 2',3'-dideoxynucleosides,[9] such as 2',3'-dideoxyinosine (ddI) **5**, as drugs for the treatment of Acquired Immunodeficiency Syndrome (AIDS). We now report the synthesis of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-adenine and -guanine (**6** and **7**, respectively) which may be regarded as the symmetrical isomers of the corresponding 2',3',4'-trideoxyribonucleosides (**8**; B = adenin-9-yl and guanin-9-yl, respectively).



1a; X = O
b; X = CH_2



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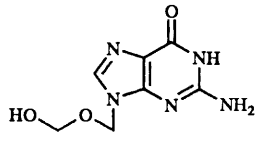

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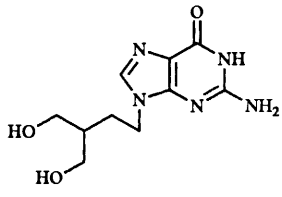

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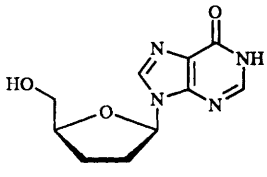

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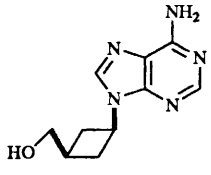

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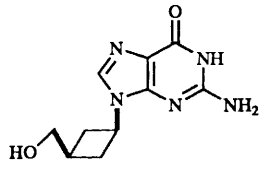

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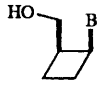

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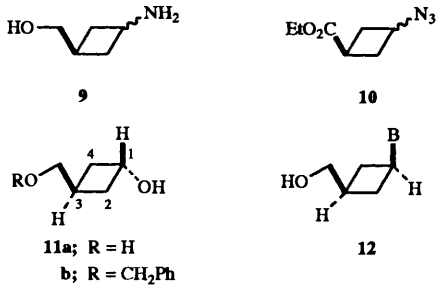
Results and discussion

We are aware of only one previous report[10] relating to the synthesis of the carbocyclic nucleoside analogues **6** and **7**. The approach followed involved the reaction between a diastereoisomeric mixture of *cis*- and *trans*-3-(hydroxymethyl)cyclobutylamines **9** and appropriate 5-amino-4,6-dichloropyrimidine derivatives. This coupling reaction was followed by a number of steps including ring closure with triethyl orthoformate and separation of the *cis*- and *trans*-diastereoisomers. The latter approach has two inherent disadvantages. First, the use of a diastereoisomeric mixture **9** as a starting material leads to a mixture of *cis*- and *trans*-isomers (*i.e.*, compound **6** and its *trans*-isomer, and compound **7** and its *trans*-isomer) that need to be separated and also characterized. Secondly, the required heterocyclic ring system needs to be constructed after the initial coupling reaction. This may not always be possible. It should be added that the cyclobutane derivative **9** is not particularly readily accessible. The latter material **9** is prepared by the action of lithium aluminium hydride on ethyl 3-azidocyclobutanecarboxylate **10**, which is itself prepared[11] in seven steps and in poor overall yield from epibromohydrin.

Our approach to the synthesis of the carbocyclic nucleoside analogues **6** and **7** has been to undertake the preparation of a derivative of *trans*-(3-hydroxymethyl)cyclobutanol **11a** in



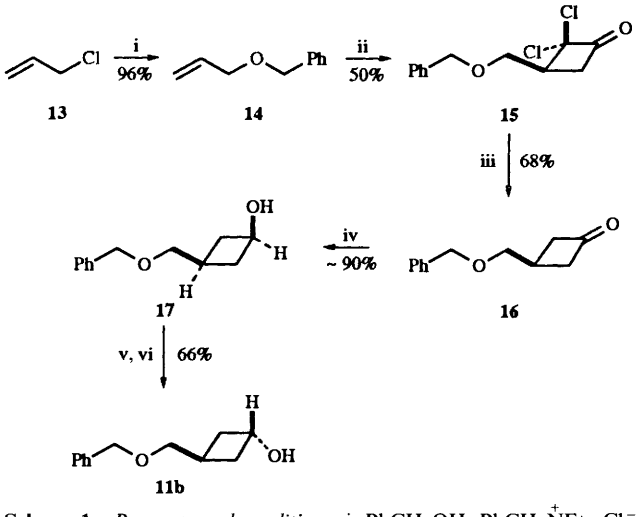
9 **10**

11a; R = H
b; R = CH_2Ph

12

which the primary hydroxy function is suitably protected. It was anticipated that it would be possible to activate the secondary hydroxy function [*e.g.*, by treatment with toluene-4-sulfonyl chloride in pyridine solution or with triphenylphosphine and diethyl azodicarboxylate (DEAD)[12] in tetrahydrofuran (THF) solution], and then effect substitution at C-1 by attack with an appropriate purine, pyrimidine or indeed other heterocyclic derivative. Such substitution would be expected[12] to proceed with inversion of configuration at C-1, thereby leading to the desired *cis*-stereochemistry. This approach should, in principle, make a wide range of carbocyclic nucleoside derivatives of general structure **12** available. It was decided that benzyl would be a suitable protecting group for the primary hydroxy function. We therefore undertook the synthesis of *trans*-(3-benzyloxymethyl)cyclobutanol **11b**.

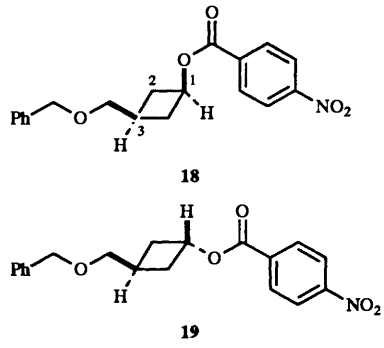
The six-step synthesis of the latter cyclobutanol derivative **11b**, starting from allyl chloride **13**, is outlined in Scheme 1.



13 **14** **15** **16** **17** **11b**

Scheme 1 *Reagents and conditions:* i, $PhCH_2OH$, $PhCH_2\overset{+}{N}Et_3$ Cl^-, conc. aq. NaOH, room temp.; ii, $Cl_3C{\cdot}COCl$, $POCl_3$, Zn–Cu couple, Et_2O, reflux; iii, Zn dust, AcOH, reflux; iv, L-Selectride, THF, −78 °C; v, 4-$(O_2N)C_6H_4CO_2H$, Ph_3P, DEAD, THF, room temp.; vi, NaOH, aq. 1,4-dioxane, room temp.

Allyl benzyl ether[13,14] **14** was prepared in 96% isolated yield by treatment of benzyl alcohol with a large excess of allyl chloride and conc. aq. sodium hydroxide, in the presence of benzyltriethylammonium chloride (BTEACl) under phase-transfer conditions.[14] Addition of dichloroketene (generated[15] from trichloroacetyl chloride, phosphoryl trichloride and zinc–copper couple) to the latter compound **14** in diethyl ether solution gave the dichlorocyclobutanone **15** as a distillable liquid in 50% isolated yield. This reaction has not yet been optimized and attempts to scale it up have led so far to diminished yields.† It was clear from the ^{13}C NMR spectrum of the products that the cycloaddition reaction was at least highly regioselective. When the dichloro compound **15** was heated, under reflux, with zinc dust in glacial acetic acid,[16] 3-(benzyloxymethyl)cyclobutanone **16** was obtained and isolated as a liquid in 68% yield. The ^{13}C NMR spectrum of the cyclobutanone derivative **16** displayed only three resonance signals (at δ_C 50.1, 72.9 and 73.2 ppm) assignable to methylene carbon atoms. The signals at δ_C 72.9 and 73.2 ppm may be assigned to the resonances of the two carbon atoms adjacent to the ether oxygen atom and the remaining signal at δ_C 50.1 may be assigned to the resonance of both of the cyclobutane methylene carbon atoms. The symmetrical structure of the ketone **16**, which was further characterized as its crystalline 4-phenylsemicarbazone, was thereby established.



18 **19**

Reduction of the ketone **16** with lithium tri-*sec*-butylboranuide[17] (L-Selectride) in THF solution gave a ~20:1 mixture of the diastereoisomeric alcohols **17** and **11b** in ~95% combined yield. It was assumed and later confirmed (see below) that hydride delivery had occurred on the less hindered side of the substrate **16** and that the *cis*-compound **17** was the major product. Treatment of the mixture obtained with 4-nitrobenzoyl chloride and pyridine in dichloromethane solution and crystallization of the products gave the *cis*-(4-nitrobenzoate) ester **18** as needles in 75% isolated yield; when the same mixture of alcohols was treated with 4-nitrobenzoic acid, triphenylphosphine and DEAD[12] in THF solution (Scheme 1, reaction v), the diastereoisomeric *trans*-(4-nitrobenzoate) ester **19** was obtained as the major product and isolated as a crystalline solid in 71% yield. Inconclusive results were obtained in an attempt to characterize the esters **18** and **19** on the basis of nuclear Overhauser effect (NOE) measurements. However, in the ^1H NMR spectra of the diastereoisomers **18** and **19**, the 3-H protons resonated at δ 2.30 and 2.66, respectively. This difference can perhaps be accounted for by the deshielding effect of the *cis*-(4-nitrobenzoyloxy) group on 3-H in the *trans*-diastereoisomer **19**. Saponification of the latter compound **19** (Scheme 1, reaction vi) gave the required *trans*-(3-benzyloxymethyl)cyclobutanol **11b** in 94% yield.

We recently reported[18] that when 2-amino-6-(4-chlorophenylsulfanyl)-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine **20a** was heated, under reflux, with an excess each of boron trifluoride–diethyl ether and phenol in dichloromethane solution, the corresponding aglycone **21a** was obtained in 89% isolated yield. The latter compound **21a**, which may be regarded as a masked form of guanine, was required[18] as an intermediate in a synthesis of acyclovir. The 6-(4-chlorophenylsulfanyl)

† **Note added in proof:** Since the submission of this paper, Mr Matthieu Giraud has found that if the cycloaddition is carried out in the presence of 1,2-dimethoxyethane (instead of phosphoryl trichloride) according to the procedure of Johnston *et al.* (B. D. Johnston, E. Czyzewska and A. C. Oehlschlayer, *J. Org. Chem.*, 1987, **52**, 3693) then compound **15** may reproducibly be obtained in 75% isolated yield.

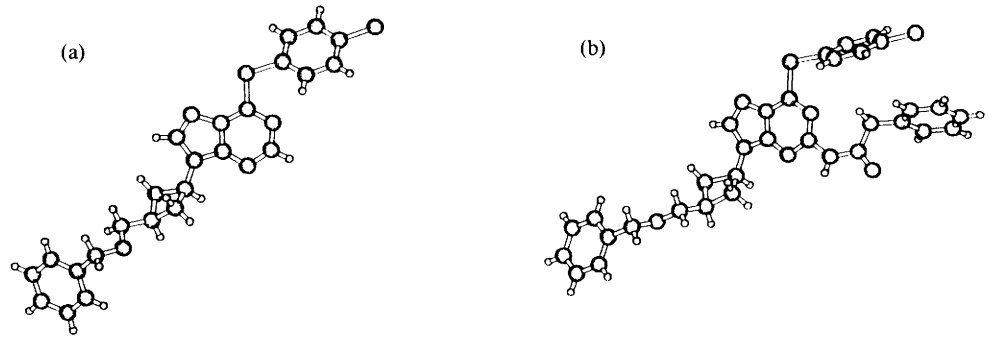
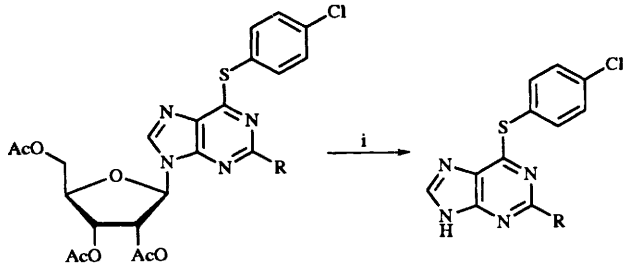


Fig. 1 Computer-drawn plots of the molecular structures of (*a*) 9-[*cis*-3-(benzyloxymethyl)cyclobutyl]-6-(4-chlorophenylsulfanyl)-9*H*-purine **22** and (*b*) 9-[*cis*-3-(benzyloxymethyl)cyclobutyl]-6-(4-chlorophenylsulfanyl)-2-(phenylacetamido)-9*H*-purine **24**



20 **21**

a, R = NH_2; **b**, R = H; **c**, R = $NHCOCH_2Ph$

Scheme 2 *Reagents and conditions:* i, $Et_2O{\rightarrow}BF_3$, PhOH, CH_2Cl_2

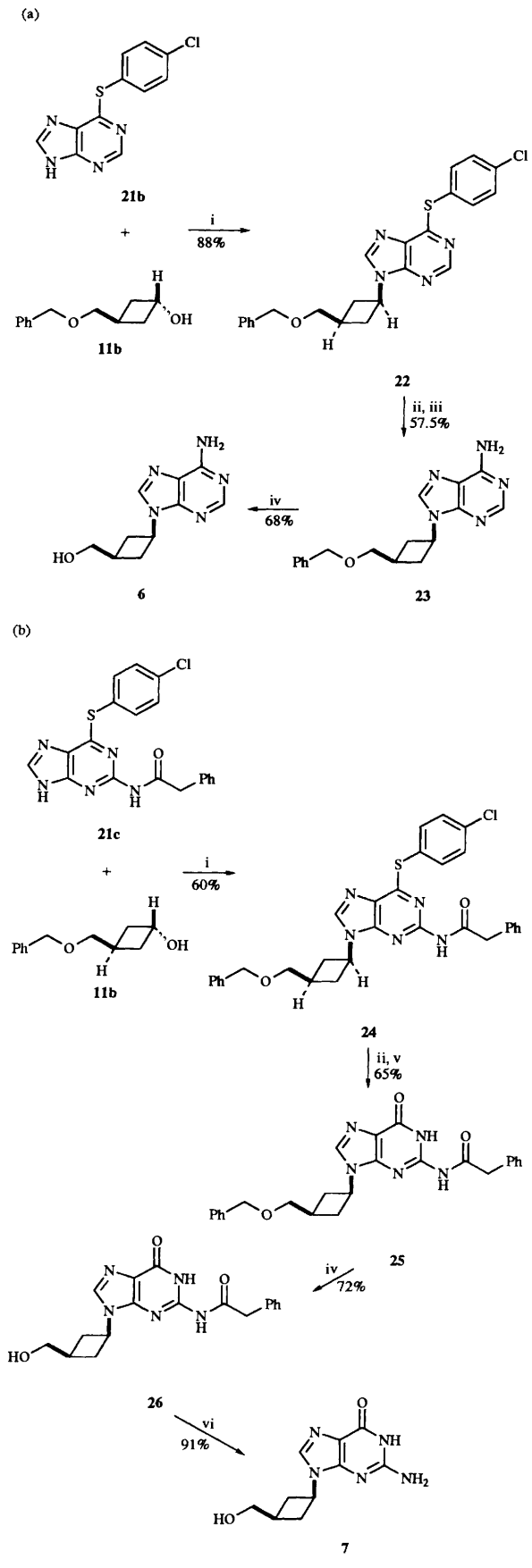
group was introduced for two reasons. First, it was hoped that, on steric grounds, subsequent alkylation would then take place with a very high degree of regioselectivity on N-9 rather than on N-7. Secondly, it was anticipated that, following alkylation, nucleophilic displacement of the 4-chlorophenylsulfanyl group, leading to the introduction of the desired substituent at C-6, would be possible. The latter process could, if necessary, be facilitated by oxidation of the sulfide function[18,19] to the corresponding sulfoxide or sulfone prior to displacement. We now report that 6-(4-chlorophenylsulfanyl)-9*H*-purine **21b**, which may be regarded as a masked form of adenine, was obtained as a crystalline solid in 73% yield by heating of 6-(4-chlorophenylsulfanyl)-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine[19] **20b** with boron trifluoride–diethyl ether and phenol, under reflux, in dichloromethane solution (Scheme 2). The latter nucleoside derivative **20b** was itself prepared[19] from inosine in three steps and in ~87% overall yield. Following our previous studies,[18] we felt that 6-(4-chlorophenylsulfanyl)-2-(phenylacetamido)-9*H*-purine **21c** would be a more useful masked form of guanine than the corresponding 2-aminopurine derivative **21a**. When compound **20a** was allowed to react with phenylacetyl chloride in the presence of 2,6-dimethylpyridine (2,6-lutidine) in acetonitrile solution, and the product was then treated with boron trifluoride–diethyl ether and phenol in dichloromethane solution (Scheme 2), the 2-(phenylacetamido)-purine derivative **21c** was obtained and isolated as a crystalline solid in 58% overall yield.

The synthesis of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-adenine **6** [Scheme 3(a)] was undertaken first. The Mitsunobu reaction[12] was used to couple 6-(4-chlorophenylsulfanyl)-9*H*-purine **21b** with the cyclobutanol derivative **11b**. Only one product, compound **22**, was obtained; it was isolated as a crystalline solid in 88% yield and its structure was confirmed by an X-ray crystal structure analysis [Fig. 1(*a*)]. If it is assumed that the Mitsunobu reaction proceeds with inversion of configuration,[12] then the structures assigned to the diastereoisomeric cyclobutanols **11b** and **17** are also confirmed. The product **22** was allowed to react with a ~two-fold excess of 3-chloroperbenzoic acid (MCPBA) in dichloromethane solution[19] and the resulting putative sulfone was further treated with ammonia in 1,4-dioxane solution. The adenine derivative **23** was obtained in 57.5% isolated overall yield for the two steps. Finally, the benzyl protecting group was removed by treatment with boron trichloride[20] in dichloromethane solution, and the desired product **6** was obtained as a crystalline solid in 68% isolated yield. The latter compound **6** proved to be reasonably active against HIV (EC_{50} = 0.8 μmol dm^{-3}) and was also relatively non-cytotoxic (TC_{50} > 1000 μmol dm^{-3}).

The synthesis of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]guanine **7** [Scheme 3(b)] was then undertaken. The Mitsunobu reaction[12] was again used to couple the appropriate purine derivative **21c** with *trans*-3-(benzyloxymethyl)cyclobutanol **11b**. Again only one product, compound **24**, was obtained; it was isolated as a crystalline solid in 60% yield and its structure was confirmed by an X-ray crystal structure analysis [Fig. 1(*b*)]. The fact that the yield of this coupling reaction was lower than that obtained above [Scheme 3(a), reaction i] is not significant as no attempt had been made to optimize either reaction. The desired transformation at C-6 was brought about by first oxidizing the sulfide to the putative sulfone[19] and then effecting nucleophilic substitution with the conjugate base of butane-2,3-dione monoxime.‡ The protected guanine derivative **25** was thereby obtained and isolated from the products as a crystalline solid in 65% overall yield. The benzyl protecting group was then removed in the same way as in the above preparation of the corresponding adenine derivative **6** [Scheme 3(a)] to give 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-2-*N*-(phenylacetyl)guanine **26** in 72% isolated yield. Following treatment of the latter compound **26** with alcoholic methylamine,[24] fully unblocked 9-[*cis*-3-(hydroxymethyl)cyclobutyl]guanine **7** was obtained and isolated as a crystalline solid in 91% yield. The latter compound **7** proved to be less active against HIV (EC_{50} = 8 μmol dm^{-3}) than the corresponding adenine derivative **6**, but it was also relatively non-cytotoxic (TC_{50} > 1000 μmol dm^{-3}).

In conclusion, we believe that the approach described in this article could form the basis of a more general synthesis of carbocyclic nucleoside analogues containing four-membered rings. Clearly, the *trans*-diastereoisomers corresponding to compounds **6** and **7** could be prepared in the same way, starting

‡ The conjugate base of butane-2,3-dione monoxime was first found to be an effective unblocking agent for aryl-protected internucleotide linkages[21] in the phosphotriester approach to oligonucleotide synthesis; however, like the conjugate base of (*E*)-2-nitrobenzaldoxime[22] it can also behave[23] as a masked hydroxide ion-equivalent in heterocyclic nucleophilic substitution reactions.



Scheme 3 *Reagents and conditions:* i, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 0 °C to room temp.; ii, $3\text{-}ClC_6H_4CO_3H$, CH_2Cl_2, room temp.; iii, NH_3, 1,4-dioxane, room temp.; iv, BCl_3, CH_2Cl_2, −78 °C; v, $MeC(=NOH)C(=O)Me$, $(Me_2N)_2C{=}NH$, MeCN, 0 °C; vi, $MeNH_2$, EtOH, MeOH, room temp.

from *cis*-3-(benzyloxymethyl)cyclobutanol **17**. Furthermore, uracil (or thymine) and cytosine derivatives corresponding to compounds **6** and **7** could be prepared from appropriate pyrimidine intermediates and the *trans*-alcohol **11b**. Finally, the ketones **15** and **16** could be modified (*e.g.*, by alkylation) before reduction and coupling with appropriate purine and pyrimidine derivatives. Studies along these lines are currently in progress in this laboratory.

Experimental

Mps were measured with a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra were measured at 360 MHz with a Bruker AM 360 spectrometer; ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Tetramethylsilane was used as an internal standard, and *J*-values are given in Hz. UV spectra were measured with a Perkin-Elmer Lambda-3 spectrophotometer; IR spectra were measured with a Perkin-Elmer model 983G spectrometer. Merck silica gel 60 F_{254} TLC plates were developed in solvent systems A [light petroleum (distillation range 40–60 °C)–ethyl acetate (4:1 v/v)], B [light petroleum (40–60 °C)–ethyl acetate (1:1 v/v)], C [chloroform–methanol (19:1 v/v)] and D [chloroform–methanol (9:1 v/v)]. Merck silica gel H was used for short-column chromatography. Acetonitrile, THF, pyridine and 2,6-lutidine were dried by heating, under reflux, over calcium hydride, and were then distilled. N^1,N^1,N^3,N^3-Tetramethylguanidine was dried by distillation over calcium hydride under reduced pressure; diethyl ether and dichloromethane were dried over sodium wire and phosphorus pentaoxide, respectively, and were then distilled. X-Ray crystallographic data on compounds **22** and **24** were collected by the EPSRC National Crystallographic Service. The structures were solved by direct methods and refined by least-square techniques, to *R*-factors of 0.0644 for compound **22** (1806 reflections) and 0.0486 for compound **24** (2250 reflections). Full details for X-ray crystallographic work are available from the Cambridge Crystallographic Data Centre.§

3-(Benzyloxy)prop-1-ene 14

A solution of sodium hydroxide (222.2 g, 5.56 mol) in water (445 cm^3) was stirred mechanically with benzyl alcohol (95.6 cm^3, 0.924 mol), allyl chloride (603.4 cm^3, 7.4 mol) and TBEACl (10.5 g, 46 mmol) at room temperature for 12 h. The organic layer was separated, washed in turn with water (500 cm^3), 1.0 mol dm^{-3} hydrochloric acid (2 × 200 cm^3), saturated aq. sodium hydrogen carbonate (2 × 500 cm^3) and again water (500 cm^3), and was then dried ($MgSO_4$). The resulting dark brown solution was concentrated (water-pump pressure; room temp.) and the residue was distilled to give 3-(benzyloxy)prop-1-ene **14** (131.5 g, 96%) as a liquid, bp 62–64 °C/0.8 mmHg (lit.,[13] 204–205 °C); $\delta_H[(CD_3)_2SO]$ 4.00 (2 H, m), 4.48 (2 H, s), 5.17 (1 H, d, *J* 10.4), 5.27 (1 H, d, *J* 17.3), 5.94 (1 H, m) and 7.33 (5 H, m); $\delta_C[(CD_3)_2SO]$ 70.3, 71.2, 116.3, 127.3, 127.4, 128.2, 135.1 and 138.3.

3-(Benzyloxymethyl)-2,2-dichlorocyclobutanone 15

(**a**) A solution of trichloroacetyl chloride (5.0 cm^3, 44.8 mmol) and freshly distilled phosphoryl trichloride (4.1 cm^3, 44.0 mmol) in dry diethyl ether (40 cm^3) was added dropwise over a period of 1 h to a well stirred solution of 3-(benzyloxy)prop-1-ene **14** (6.0 g, 40.5 mmol) in dry diethyl ether (60 cm^3) in the presence of zinc–copper couple (3.1 g). The reaction mixture was then heated, under reflux, for 18 h. The cooled products

§ For details see 'Instructions for Authors' (1995), *J. Chem. Soc., Perkin Trans. 1*, 1995, issue 1.

were filtered and concentrated to ~20 cm^3. Light petroleum (distillation temp. 30–40 °C; ~40 cm^3) was then added and the supernatant solution was decanted from the residue. The latter solution was washed in turn with water (100 cm^3) and brine (50 cm^3); it was then dried ($MgSO_4$), concentrated under reduced pressure, and the residue was distilled to give 3-(*benzyloxymethyl*)-2,2-*dichlorocyclobutanone* **15** (5.3 g, 50%) (Found: M^+, 258.0252. $^{12}C_{12}{}^1H_{12}{}^{35}Cl_2{}^{16}O_2$ requires M, 258.0214); bp 58 °C/3.0 mmHg as a pale yellow viscous liquid; ν_{max}(film)/cm^{-1} 1811; δ_H($CDCl_3$) 3.1–3.25 (2 H, m), 3.42 (1 H, m), 3.69 (1 H, m), 3.84 (1 H, m), 4.57 (2 H, s) and 7.34 (5 H, m); δ_C($CDCl_3$) 45.5, 45.8, 69.4, 73.9, 87.9, 128.1, 128.2, 128.9, 137.9 and 192.7.

(b) A larger-scale preparation, starting from trichloroacetyl chloride (24.88 cm^3, 0.22 mol), phosphoryl trichloride (20.78 cm^3, 0.22 mol), 3-(benzyloxy)prop-1-ene (30.0 g, 0.20 mol) and zinc–copper couple (15.9 g), was carried out in the same way. Following work-up and distillation of the products, 3-(benzyloxymethyl)-2,2-dichlorocyclobutan-1-one **15** (18.3 g, 35%) was obtained.

3-(Benzyloxymethyl)cyclobutanone 16

Zinc dust (12.1 g, 0.185 mol) was added to a solution of 3-(benzyloxymethyl)-2,2-dichlorocyclobutanone **15** (8.0 g, 30.9 mmol) in glacial acetic acid (52 cm^3) at room temperature. The reactants were heated, under reflux, for 4 h. Dry diethyl ether (50 cm^3) was added to the cooled products, which were then filtered. The residue was washed with diethyl ether (50 cm^3). The combined filtrate and washings were concentrated under reduced pressure. The residue was dissolved in dichloromethane (100 cm^3) and the solution was washed successively with saturated aq. sodium hydrogen carbonate (2 × 50 cm^3) and water (50 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was distilled to give 3-(benzyloxymethyl)cyclobutanone **16** (4.02 g, 68%) as a mobile liquid, bp 115 °C/1.0 mmHg; ν_{max}(film)/cm^{-1} 1782; δ_H($CDCl_3$) 2.70 (1 H, m), 2.88 (2 H, m), 3.12 (2 H, m), 3.59 (2 H, d, *J* 6.4), 4.56 (2 H, s) and 7.34 (5 H, m); δ_C($CDCl_3$) 23.7, 50.1, 72.9, 73.2, 127.7, 127.8, 128.5, 138.1 and 207.5.

A solution of 3-(benzyloxymethyl)cyclobutanone **16** (2.0 g, 10.5 mmol) and 4-phenylsemicarbazide (2.06 g, 13.6 mmol) in absolute ethanol (15 cm^3) was heated, under reflux, for 2 h. The cooled products were concentrated under reduced pressure and the residue was fractionated by short-column chromatography on silica gel to give the 4-*phenylsemicarbazone of* 3-(*benzyloxymethyl*)*cyclobutanone* (2.59 g, 76%) (Found in material crystallized from absolute ethanol and dried *in vacuo* over P_2O_5: C, 70.5; H, 6.7; N, 13.0. $C_{19}H_{21}N_3O_2$ requires C, 70.6; H, 6.55; N, 13.0%), mp 124 °C.

***cis*-3-(Benzyloxymethyl)cyclobutanol 17**

A solution of lithium tri-*sec*-butylboranuide in THF (L-Selectride, 1.0 mol dm^{-3}; 75.8 cm^3, 75.8 mmol) was added, under argon and dropwise over a period of 40 min, to a stirred solution of 3-(benzyloxymethyl)cyclobutanone **16** (12.0 g, 63 mmol) in dry THF (100 cm^3) at −78 °C (acetone–solid CO_2-bath). The products were then allowed to warm up to room temperature and saturated aq. sodium hydrogen carbonate (80 cm^3) was added over a period of 5 min. The resulting solution was then cooled (ice–water-bath) and 30% aq. hydrogen peroxide (30 cm^3) was added dropwise at such a rate so as to maintain the temperature at 25–30 °C. Water (200 cm^3) and ethyl acetate (500 cm^3) were then added. The organic layer was separated, washed with water (3 × 250 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure to give the title alcohol **17** as a liquid (11.5 g, ~95%) (Found: M^+, 192.1161. $^{12}C_{12}{}^1H_{16}{}^{16}O_2$ requires M, 192.1150); δ_H($CDCl_3$: D_2O exchange) 1.69 (2 H, m), 2.09 (1 H, m), 2.45 (2 H, m), 3.44 (2 H, d, *J* 5.7), 4.13 (1 H, m), 4.52 (2 H, s) and 7.25–7.40 (5 H, m); δ_C($CDCl_3$) 25.9, 36.6, 64.2, 73.0, 127.6, 127.65, 128.4 and 138.4. This material appeared from its ^{13}C NMR spectrum to be contaminated with ~5% of its *trans*-isomer **11b** (see below).

***cis*-3-(Benzyloxymethyl)cyclobutyl 4-nitrobenzoate 18**

4-Nitrobenzoyl chloride (0.558 g, 3.0 mmol) was added to a stirred solution of *cis*-3-(benzyloxymethyl)cyclobutanol **17** (0.34 g, 1.8 mmol) and pyridine (0.28 cm^3, 3.5 mmol) in dry dichloromethane (10 cm^3) at room temperature. After 2 h, dichloromethane (50 cm^3) was added and contaminants were extracted with saturated aq. sodium hydrogen carbonate (3 × 50 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure and the residue was crystallized from ethyl acetate–light petroleum (40–60 °C) to give cis-3-(*benzyloxymethyl*)*cyclobutyl* 4-*nitrobenzoate* **18** (0.45 g, 75%) (Found: C, 66.7; H, 5.6; N, 4.0. $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.6; N, 4.1%) as needles, mp 73 °C; R_f 0.64 (system A); δ_H($CDCl_3$) 2.05 (2 H, m), 2.30 (1 H, m), 2.62 (2 H, m), 3.50 (2 H, d, *J* 5.9), 4.54 (2 H, s), 5.18 (1 H, m), 7.25–7.4 (5 H, m), 8.19 (2 H, m) and 8.27 (2 H, m); δ_C($CDCl_3$) 27.2, 33.3, 67.4, 73.1, 73.7, 123.5, 127.6, 127.7, 128.5, 130.8, 135.7, 138.5, 150.5 and 164.1.

***trans*-3-(Benzyloxymethyl)cyclobutyl 4-nitrobenzoate 19**

A solution of DEAD (18.9 cm^3, 0.12 mol) in dry THF (50 cm^3) was added dropwise over a period of 20 min to a stirred solution of *cis*-3-(benzyloxymethyl)cyclobutanol **17** (11.0 g, 57.2 mmol), 4-nitrobenzoic acid (19.13 g, 0.114 mol) and triphenylphosphine (31.52 g, 0.12 mol) in dry THF (100 cm^3) at 0 °C (ice–water-bath). The reactants were then allowed to warm up to room temperature. After 8 h, the products were evaporated under reduced pressure and the residue was fractionated by short column chromatography on silica gel: appropriate fractions eluted with light petroleum (40–60 °C)–ethyl acetate (96:4 v/v) were combined, and concentrated under reduced pressure. Crystallization of the resulting solid residue from ethyl acetate–light petroleum (40–60 °C) gave trans-3-(*benzyloxymethyl*)*cyclobutyl* 4-*nitrobenzoate* **19** (14.0 g, 71%) (Found: C, 66.8; H, 5.5; N, 4.2%); mp 71 °C; R_f 0.73 (system A); δ_H($CDCl_3$) 2.40 (4 H, m), 2.66 (1 H, m), 3.54 (2 H, d, *J* 6.6), 4.57 (2 H, s), 5.36 (1 H, m), 7.25–7.4 (5 H, m), 8.21 (2 H, m) and 8.28 (2 H, m); δ_C($CDCl_3$) 28.5, 32.3, 70.1, 73.2, 73.3, 123.5, 127.7, 128.4, 130.7, 135.7, 138.4, 150.5 and 164.1.

***trans*-3-(Benzyloxymethyl)cyclobutanol 11b**

Aq. sodium hydroxide (0.4 mol dm^{-3}; 29.3 cm^3, 11.7 mmol) was added to a solution of *trans*-3-(benzyloxymethyl)cyclobutyl 4-nitrobenzoate **19** (2.0 g, 5.86 mmol) in 1,4-dioxane (45 cm^3) at room temperature. After 30 min, acetic acid (0.50 cm^3, 8.7 mmol) was added and the products were concentrated to small volume under reduced pressure. The residue was partitioned between ethyl acetate (25 cm^3) and saturated aq. sodium hydrogen carbonate (2 × 25 cm^3). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure to give trans-(3-*benzyloxymethyl*)*cyclobutanol* **11b** as a liquid (1.06 g, 94%) (Found: M^+, 192.1134. $^{12}C_{12}{}^1H_{16}{}^{16}O_2$ requires M, 192.1150); δ_H($CDCl_3$) 2.04 (2 H, m), 2.17 (2 H, m), 2.39 (1 H, br), 2.46 (1 H, m), 3.44 (2 H, d, *J* 7.0), 4.34 (1 H, m), 4.51 (2 H, s) and 7.25–7.4 (5 H, m); δ_C($CDCl_3$) 26.8, 35.2, 66.1, 73.0, 73.9, 127.56, 127.60, 128.4 and 138.4.

6-(4-Chlorophenylsulfanyl)-9*H*-purine 21b

Phenol (1.58 g, 16.8 mmol) and boron trifluoride–diethyl ether (8.4 cm^3, 68.3 mmol) were added to a stirred solution of 6-(4-chlorophenylsulfanyl)-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine[19] **20b** (4.35 g, 8.35 mmol) in dry dichloromethane (100 cm^3) at room temp. The reactants were then heated, under

reflux, for 1 h. The cooled products were evaporated under reduced pressure and the residue was triturated with aq. sodium hydrogen carbonate. The resulting pale yellow solid was crystallized from methanol to give 6-(4-*chlorophenylsulfanyl*)-9H-*purine* **21b** as a solid (1.61 g, 73%) (Found: C, 50.4; H, 3.0; N, 21.2. $C_{11}H_7ClN_4S$ requires C, 50.3; H, 2.7; N, 21.3%), mp 263 °C; R_f 0.28 (system C); $\delta_H[(CD_3)_2SO]$ 7.57 (2 H, m), 7.67 (2 H, m), 8.54 (1 H, s), 8.58 (1 H, s), and 13.65 (1 H, br); $\delta_C[(CD_3)_2SO]$ includes the following signals: 126.0, 129.3, 134.5, 137.1, 143.8 and 151.5.

6-(4-Chlorophenylsulfanyl)-2-(phenylacetamido)-9*H*-purine 21c

Phenylacetyl chloride (2.8 cm^3, 21.2 mmol) was added dropwise over a period of 10 min to a stirred mixture of 2-amino-6-(4-chlorophenylsulfanyl)-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purine[18] **20a** (6.0 g, 11.2 mmol) and 2,6-lutidine (3.25 cm^3, 27.9 mmol) in dry acetonitrile (200 cm^3). The reactants were then stirred at room temperature. After 2 h, the products were concentrated under reduced pressure, redissolved in chloroform (200 cm^3), and the solution was extracted successively with water (100 cm^3) and saturated aq. sodium hydrogen carbonate (2 × 100 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was fractionated by short-column chromatography on silica gel to give the putative 2-phenylacetamido derivative **20c** as a glass (6.2 g); R_f 0.43 (system C).

Phenol (1.58 g, 16.8 mmol) and redistilled boron trifluoride–diethyl ether (8.28 cm^3, 67.3 mmol) were added to a stirred solution of the latter phenylacetamido derivative **20c** (5.5 g) in dry dichloromethane (200 cm^3) at room temperature. After 8 h, the products were concentrated under reduced pressure and saturated aq. sodium hydrogen carbonate (300 cm^3) was added cautiously. The solid precipitate obtained was collected by filtration, washed successively with cold water (100 cm^3) and ice-cold ethyl acetate (100 cm^3), and was then crystallized from methanol to give 6-(4-*chlorophenylsulfanyl*)-2-(*phenylacetamido*)-9H-*purine* **21c** (2.3 g, 58%) (Found: C, 57.15; H, 3.5; N, 17.4. $C_{19}H_{14}ClN_5OS{\cdot}0.2H_2O$ requires C, 57.1; H, 3.6; N, 17.5%); mp 273 °C; R_f 0.32 (system C); $\delta_H[(CD_3)_2SO]$ 3.66 (2 H, s), 7.15–7.3 (5 H, m), 7.47 (2 H, m), 7.70 (2 H, m), 8.35 (1 H, s), 10.44 (1 H, s) and 13.41 (1 H, br); $\delta_C[(CD_3)_2SO]$ 42.7, 126.2, 126.3, 128.0, 129.2, 129.3, 134.3, 135.6, 136.5, 151.9 and 169.8.

9-[*cis*-3-(Benzyloxymethyl)cyclobutyl]-6-(4-chlorophenylsulfanyl)-9*H*-purine 22

A solution of DEAD (1.4 cm^3, 8.9 mmol) in dry THF (3 cm^3) was added dropwise over a period of 10 min to a stirred solution of *trans*-3-(benzyloxymethyl)cyclobutanol **11b** (0.70 g, 3.6 mmol), 6-(4-chlorophenylsulfanyl)-9*H*-purine **21b** (1.05 g, 4.0 mmol) and triphenylphosphine (2.31 g, 8.8 mmol) in dry THF (40 cm^3) at 0 °C (ice–water-bath). The reactants were then stirred at room temperature. After 12 h, the products were concentrated under reduced pressure and the residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with light petroleum (40–60 °C)–ethyl acetate (3:1 v/v), were combined, and evaporated under reduced pressure. The residue was crystallized from ethyl acetate–light petroleum (40–60 °C) to give 9-[cis-3-(*benzyloxymethyl*)*cyclobutyl*]-6-(4-*chlorophenylsulfanyl*)-9H-*purine* **22** (1.41 g, 88%) (Found: C, 63.3; H, 5.0; N, 12.8. $C_{23}H_{21}ClN_4OS$ requries C, 63.2; H, 4.8; N, 12.8%); mp 106 °C; R_f 0.54 (system B); $\delta_H(CDCl_3)$ 2.53 (3 H, m), 2.73 (2 H, m), 3.56 (2 H, d, *J* 4.2), 4.58 (2 H, s), 4.99 (1 H, m), 7.34 (5 H, m), 7.45 (2 H, m), 7.59 (2 H, m), 8.17 (1 H, s) and 8.60 (1 H, s); $\delta_C(CDCl_3)$ 28.6, 32.9, 45.2, 72.5, 73.1, 125.8, 127.6, 127.7, 128.4, 129.5, 131.0, 135.8, 136.7, 138.2, 141.8, 148.9, 151.9 and 159.7.

9-[*cis*-3-(Benzyloxymethyl)cyclobutyl]adenine 23

MCPBA (~55%; 0.97 g, ~3.1 mmol) was added to a stirred solution of 9-[*cis*-3-(benzyloxymethyl)cyclobutyl]-6-(4-chlorophenylsulfanyl)-9*H*-purine **22** (0.70 g, 1.6 mmol) in dichloromethane (20 cm^3) at room temperature. After 1 h, more dichloromethane (20 cm^3) was added and the products were washed with ice-cold aq. sodium hydrogen sulfite (pH 7.5; 2 × 25 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure and the residue was redissolved in dry 1,4-dioxane (3 cm^3). A saturated solution of ammonia in dry 1,4-dioxane (25 cm^3) was added to the stirred solution at 10–15 °C. The stirred reactants were then allowed to warm up to room temperature. After 20 h, the products were concentrated under reduced pressure, and the residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform–methanol (97:3 v/v), were combined, and evaporated under reduced pressure to give a glass (0.305 g). Crystallization of this material from ethyl acetate–light petroleum (40–60 °C) gave 9-[cis-3-(*benzyloxymethyl*)*cyclobutyl*]*adenine* **23** (0.285 g, 57.5%) (Found: C, 66.0; H, 5.95; N, 23.0. $C_{17}H_{19}N_5O$ requires C, 66.0; H, 6.2; N, 22.6%) as crystals, mp 109 °C; R_f 0.54 (system D); $\delta_H[(CD_3)_2SO]$ 2.41 (3 H, m), 2.56 (2 H, m), 3.55 (2 H, d, *J* 5.3), 4.50 (2 H, s), 4.89 (1 H, m), 7.22 (2 H, br s), 7.2–7.4 (5 H, m), 8.12 (1 H, s) and 8.28 (1 H, s); $\delta_C[(CD_3)_2SO]$ 27.9, 33.1, 44.7, 72.0, 73.5, 119.1, 127.4, 127.5, 128.3, 138.6, 139.4, 149.4. 152.3 and 156.0.

9-[*cis*-3-(Hydroxymethyl)cyclobutyl]adenine 6

Boron trichloride (1.0 mol dm^{-3} solution in dichloromethane; 2.9 cm^3, 2.9 mmol) was added dropwise over a period of *ca.* 5 min to a stirred solution of 9-[*cis*-3-benzyloxymethyl)-cyclobutyl]adenine **23** (0.30 g, 0.97 mmol) in dichloromethane (3 cm^3) at −78 °C (solid CO_2–acetone-bath). After the reactants had been stirred for a further period of 7 h at −78 °C, a low temperature was maintained while methanolic ammonia (~8 mol dm^{-3}; 3 cm^3) was added dropwise over a period of *ca.* 5 min. The products were then concentrated under reduced pressure and the residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform–methanol (92:8 v/v), were combined and evaporated under reduced pressure. The residue was crystallized from ethyl acetate to give 9-[*cis*-3-(hydroxymethyl)cyclobutyl]adenine **6** as crystals (0.146 g, 68%) (Found: C, 55.05; H, 5.8; N, 32.2. Calc. for $C_{10}H_{13}N_5O$: C, 54.8; H, 6.0; N, 31.9%), mp 135 °C (lit.,[10] 145–146 °C); R_f 0.24 (system D); λ_{max}(95% EtOH) /nm 260 (ε 15 300); λ_{min}/nm 228.5 (ε 2800); $\delta_H[(CD_3)_2SO]$ 2.33 (3 H, m,), 2.50 (2 H, m), 3.50 (2 H, m), 4.66 (1 H, t, *J* 5.4), 4.86 (1 H, m), 7.22 (2 H, br s), 8.13 (1 H, s) and 8.28 (1 H, s); $\delta_C[(CD_3)_2SO]$ 30.2, 32.3, 44.3, 64.3, 118.9, 139.2, 149.3, 152.2 and 155.9.

9-[*cis*-3-(Benzyloxymethyl)cyclobutyl]-6-(4-chlorophenylsulfanyl)-2-(phenylacetamido)-9*H*-purine 24

A solution of DEAD (0.89 cm^3, 5.7 mmol) in dry THF (3 cm^3) was added dropwise over a period of 10 min to a well stirred solution of *trans*-3-(benzyloxymethyl)cyclobutanol **11b** (0.45 g, 2.3 mmol), 6-(4-chlorophenylsulfanyl)-2-(phenylacetamido)-9*H*-purine **21c** (1.02 g, 2.6 mmol) and triphenylphosphine (1.48 g, 5.6 mmol) in dry THF (40 cm^3) at 0 °C (ice–water-bath). After 24 h, the products were concentrated under reduced pressure and the residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with light petroleum (40–60 °C)–ethyl acetate (3:2 v/v), were combined, and evaporated under reduced pressure. The residue was crystallized from ethyl acetate–petroleum (40–60 °C) to give 9-[cis-3-(*benzyloxymethyl*)*cyclobutyl*]-6-(4-*chlorophenylsulfanyl*)-2-(*phenylacetamido*)-9H-*purine* **24** (0.80 g, 60%)

(Found: C, 65.25; H, 5.0; N, 12.1. $C_{31}H_{28}ClN_5O_2S$ requires C, 65.3; H, 4.95; N, 12.3%), mp 118 °C; R_f 0.37 (system B); $\delta_H(CDCl_3)$ 2.49 (3 H, m), 2.68 (2 H, m), 3.54 (2 H, d, *J* 4.0), 3.86 (2 H, s), 4.55 (2 H, s), 4.88 (1 H, m), 7.16 (2 H, m), 7.26–7.39 (10 H, m), 7.51 (2 H, m), 7.81 (1 H, s) and 8.04 (1 H, s); $\delta_C(CDCl_3)$ 28.6, 33.0, 43.5, 45.2, 72.6, 73.2, 125.4, 127.1, 127.7, 127.8, 128.5, 128.7, 129.5, 129.6, 134.4, 136.2, 137.2, 138.2, 141.4, 149.9, 151.7, 161.0 and 171.3.

9-[*cis*-3-(Benzyloxymethyl)cyclobutyl]-2-*N*-(phenylacetyl)-guanine 25

MCPBA (~55%; 0.79 g, 2.5 mmol) was added to a stirred solution of 9-[*cis*-3-(benzyloxymethyl)cyclobutyl]-6-(4-chlorophenylsulfanyl)-2-(phenylacetamido)-9*H*-purine **24** (0.75 g, 1.32 mmol) in dichloromethane (20 cm^3) at room temperature. After 1 h, more dichloromethane (30 cm^3) was added, and the products were washed first with aq. sodium hydrogen sulfite (50 cm^3) and then with saturated aq. sodium hydrogen carbonate (2 × 25 cm^3). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure. Toluene (2 × 25 cm^3) was added, and removed by evaporation under reduced pressure. The residue was dissolved in dry acetonitrile (10 cm^3), and butane-2,3-dione monoxime (0.14 g, 1.4 mmol) and N^1,N^1, N^3,N^3-tetramethylguanidine (0.175 cm^3, 1.4 mmol) were added to the stirred, cooled (ice–water-bath) solution. After 5 min, a solution of trifluoroacetic acid (0.05 cm^3, 0.65 mmol) in acetonitrile (1 cm^3) was added and the products were concentrated under reduced pressure. The residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform–methanol (96:4 v/v) were combined, and evaporated under reduced pressure. The residue was crystallized from propan-2-ol to give 9-[cis-3-(*benzyloxymethyl*)*cyclobutyl*]-2-N-(*phenylacetyl*)*guanine* **25** as crystals (0.382 g, 65%) (Found: C, 67.4; H, 5.7; N, 15.8. $C_{25}H_{25}N_5O_3$ requires C, 67.7; H, 5.7; N, 15.8%); mp 218 °C; R_f 0.54 (system D); $\delta_H(CDCl_3)$ 2.28–2.46 (3 H, m), 2.55 (2 H, m), 3.46 (2 H, d, *J* 4.8), 3.85 (2 H, s), 4.51 (2 H, s), 4.63 (1 H, m), 7.25–7.42 (10 H, m) and 7.77 (1 H, s); $\delta_C(CDCl_3)$ 28.5, 33.1, 44.1, 44.9, 72.7, 73.2, 121.3, 127.6, 127.8, 128.0, 128.5, 129.3, 129.5, 132.6, 137.5, 138.2, 146.7, 148.0, 155.8 and 172.6.

9-[*cis*-3-(Hydroxymethyl)cyclobutyl]-2-*N*-(phenylacetyl)-guanine 26

Boron trichloride (1.0 mol dm^{-3} solution in dichloromethane; 2.4 cm^3, 2.4 mmol) was added dropwise over a period of *ca.* 5 min to a stirred solution of 9-[*cis*-3-(benzyloxymethyl)-cyclobutyl]-2-*N*-(phenylacetyl)guanine **25** (0.35 g, 0.79 mmol) in dichloromethane (5 cm^3) at −78 °C (solid CO_2–acetone-bath). The reactants were then stirred at −78 °C for a further period of 7 h. The products were worked up as in the above preparation of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]adenine **6** and fractionated by short-column chromatography on silica gel: the appropriate fractions, eluted with chloroform–methanol (92:8 v/v), were combined, and evaporated under reduced pressure. The residue was crystallized from aq. ethanol to give 9-[cis-3-(*hydroxymethyl*)*cyclobutyl*]-2-N-(*phenylacetyl*)*guanine* **26** as crystals (0.202 g, 72%) (Found: C, 61.0; H, 5.4; N, 19.4. $C_{18}H_{19}N_5O_3$ requires C, 61.2; H, 5.4; N, 19.8%), mp 243 °C; R_f 0.36 (system D); $\delta_H[(CD_3)_2SO]$ 2.26 (2 H, m), 2.50 (3 H, m), 3.48 (2 H, m), 3.81 (2 H, s), 4.63 (1 H, t, *J* 5.3), 4.72 (1 H, m), 7.25–7.35 (5 H, m), 8.19 (1 H, s) and 11.89 (2 H, br); $\delta_C[(CD_3)_2SO]$ 30.3, 32.6, 42.5, 44.4, 64.2, 120.3, 127.0, 128.4, 129.4, 134.3, 138.0, 147.4, 148.2, 154.9 and 174.0.

9-[*cis*-3-(Hydroxymethyl)cyclobutyl]guanine 7

A solution of methylamine in ethanol (8.0 mol dm^{-3}; 1.16 cm^3, 9.3 mmol) was added to a stirred solution of 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-2-*N*-(phenylacetyl)guanine **26** (0.11 g, 0.31 mmol) in methanol (1.0 cm^3) at 0 °C (ice–water-bath). The reaction solution was stirred at room temperature for 1 h and the product mixture was then evaporated under reduced pressure. The residue was washed with dichloromethane (2 × 3 cm^3) and crystallized from absolute ethanol to give 9-[*cis*-3-(hydroxymethyl)cyclobutyl]guanine **7** as crystals (0.067 g, 91%) (Found: C, 48.0; H, 5.8; N, 27.6. Calc. for $C_{10}H_{13}N_5O_2 \cdot 0.9H_2O$: C, 47.8; H, 5.9; N, 27.85%), mp 280 °C (lit.,[10] 288–290 °C); R_f 0.61 [chloroform–methanol (7:3 v/v)]; λ_{max}(95% EtOH)/nm 253.5 (ε 13 900); λ_{min}/nm) 225 (ε 3 900); $\delta_H[(CD_3)_2SO]$ 2.20 (3 H, m), 2.42 (2 H, m), 3.46 (2 H, t, *J* 5.0), 4.63 (2 H, m), 6.40 (2 H, br s), 7.87 (1 H, s) and 10.54 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 30.1, 32.5, 43.7, 64.2, 116.6, 135.5, 150.8, 153.2 and 156.8.

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References

1 N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii and T. Takita, *J. Antibiot.*, 1986, **39**, 1623; H. Nakamura, S. Hasegawa, N. Shimada, A. Fujii, T. Takita and Y. Iitaka, *J. Antibiot.*, 1986, **39**, 1626.
2 N. Shimada, S. Hasegawa, S. Saito, T. Nishikiori, A. Fujii and T. Takita, *J. Antibiot.*, 1987, **40**, 1788.
3 M. Honjo, T. Maruyama, Y. Sato and T. Horii, *Chem. Pharm. Bull.*, 1989, **37**, 1413.
4 Y. Ichikawa, A. Narita, A. Shiozawa, Y. Hayaski and K. Narasaka, *J. Chem. Soc., Chem. Commun.*, 1989, 1919.
5 G. A. Jacobs, J. A. Tino and R. Zahler, *Tetrahedron Lett.*, 1989, **30**, 6955.
6 G. S. Bisacchi, A. Braitman, C. W. Cianci, J. M. Clark, A. K. Field, M. E. Hagen, D. R. Hockstein, M. F. Malley, T. Mitt, W. A. Slusarchyk, J. E. Sundsen, B. J. Terry, A. V. Tuomari, E. R. Weaver, M. G. Young and R. Zahler, *J. Med. Chem.*, 1991, **34**, 1415.
7 G. B. Elion, P. A. Furman, J. A. Fyfe, P. de Miranda, L. M. Beauchamp and H. J. Schaeffer, *Proc. Natl. Acad. Sci. USA*, 1977, **74**, 5716.
8 M. R. Harnden and R. L. Jarvest, *Tetrahedron Lett.*, 1985, **26**, 4265.
9 M. Nasr, C. Litterst and J. McGowan, *Antiviral Res.*, 1990, **14**, 1257.
10 T. Maruyama, Y. Sato, T. Horii, H. Shiota, K. Niatta, T. Shirasaka, H. Mitsuya and M. Honjo, *Chem. Pharm. Bull.*, 1990, **38**, 2719.
11 M. Avram, C. D. Nenitzescu and M. Maxim, *Chem. Ber.*, 1957, **90**, 1424.
12 O. Mitsunobu, *Synthesis*, 1981, 1.
13 R. H. Baker, K. H. Cornell and M. J. Cron, *J. Am. Chem. Soc.*, 1948, **70**, 1490.
14 H. H. Freedman and R. A. Dubois, *Tetrahedron Lett.*, 1975, 3251.
15 L. R. Krepski and A. Hassner, *J. Org. Chem.*, 1978, **43**, 2879.
16 P. W. Jeffs, G. Molina, M. W. Cass and N. A. Cortese, *J. Org. Chem.*, 1982, **47**, 3871.
17 H. C. Brown and S. Krisnamurthy, *J. Am. Chem. Soc.*, 1972, **94**, 7159.
18 I. M. Buck, A. Eleuteri and C. B. Reese, *Tetrahedron*, 1994, **50**, 9195.
19 I. M. Buck and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2937.
20 W. Gerrard and M. F. Lappert, *Chem. Rev.*, 1958, **58**, 1081.
21 C. B. Reese and L. Zard, *Nucleic Acids Res.*, 1981, **9**, 4611.
22 C. B. Reese and P. A. Skone, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1263.
23 K. A. Cruickshank, Ph.D. Thesis, London University, 1982, p. 43.
24 C. B. Reese and R. Saffhill, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2937.

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