New Cyclobutyl Analogs of Adenosine and Guanosine. Part 1. Synthesis of the 9-[3,3-Bis(hydroxymethyl)cyclobutyl]purine Nucleoside Analogs

Hassane Boumchita [a], Michel Legraverend* [a],
Christiane Huel [b], and Emile Bisagni [a]

[a] URA 1387 CNRS, [b] U. 219 INSERM, Institut Curie-Biologie, Bât. 110-112, Centre Universitaire, 91405 Orsay, France

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The synthesis of 1-amino-3,3-bis(benzyloxymethyl)cyclobutane has been performed from 3,3-bis(benzyloxymethyl)cyclobutanone, *via* the corresponding oxime which was reduced with lithium aluminum hydride. The amine thus obtained led to two new cyclobutyl analogs of adenosine and guanosine which were devoid of antiviral activity against HSV-1, HCMV and HIV in cell culture.

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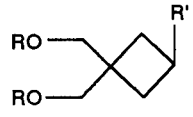
Most nucleoside analogs which are active antiviral agents against HSV (Herpes Simplex Virus) and HIV (Human Immunodeficiency Virus) share at least one important structural feature, namely the presence of a primary alcohol function that mimics the 5'hydroxyl group of naturally occuring nucleosides [1]. These molecules can then be phosphorylated by certain kinases and thereby inhibit the viral polymerase(s). These properties are often the basis of the biochemical mechanism of action of nucleoside analogs. From this point of view we thought that the rigid cyclobutane ring system deserved attention because it might "freeze" some conformation of the primary hydroxy group in a conformation which would be optimal for enzyme(s) interaction(s). This idea is supported by the recent discovery of oxetanocin A (**1**), a natural oxetane-containing nucleoside, which has been shown to exhibit anti-HSV [2] and anti-HIV [3] activities. Oxetanocin G (**2**) is also a very potent and selective inhibitor of human cytomegalovirus (HCMV) *in vitro* [4]. The carbocyclic analog **3** of oxetanocin A has been synthesized recently [5] but no biological activity was reported.

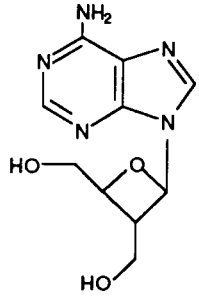
As anti-HIV activity has been reported for carbocyclic nucleoside analogs [6] such as **4**, **5a** and carbovir (**5b**), we thought that the structures **6** and **7** deserved to be tested as antiviral agents.



6 : R=H
R'=adenine

7 : R=H
R'=guanine

8 : R=benzyl
R'=NH_2



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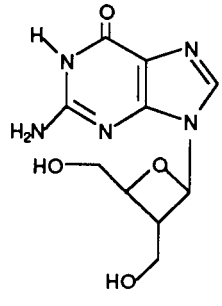

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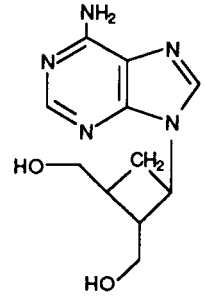

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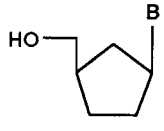
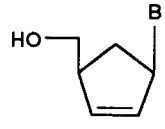


4 : B= adenine



5 a : B= adenine
5 b : B= guanine

We report in the present paper the synthesis of the purine nucleoside analogs **6** and **7** as well as the synthesis of the cyclobutylamine precursor **8**.

Results and Discussion.

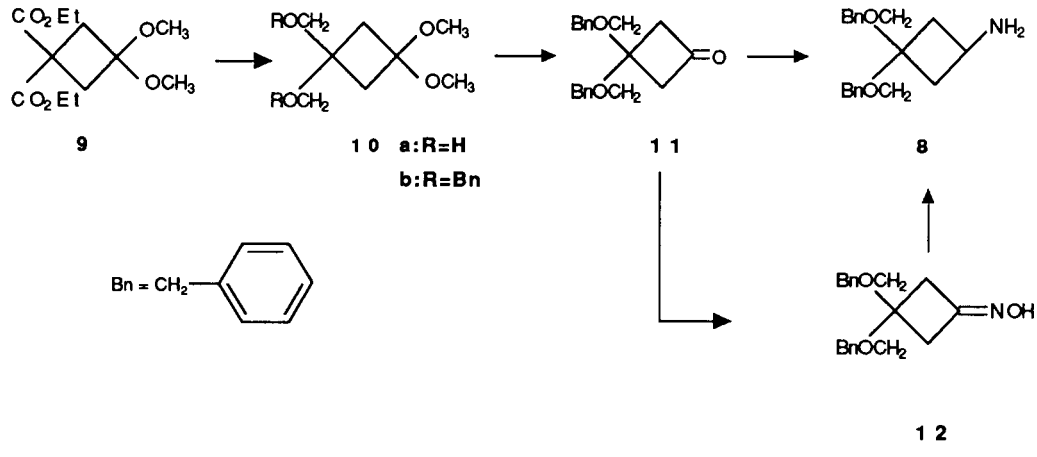
The synthesis of the cyclobutylamine precursor **8** was achieved starting from the known diethyl-3,3-dimethoxycyclobutane-1,1-dicarboxylate (**9**) (Scheme 1) which is readily available [7] in large (hundreds of grams) scale.

Simultaneous reduction of the two ester functions with lithium aluminum hydride in tetrahydrofuran led to the diol **10a**. The dimethyl ketal portion of the dibenzylether **10b** was then deprotected by treatment with formic acid to give the ketone **11** in high yield. Attempts to transform **11** into the corresponding amine **8** in one step with sodium cyanoborohydride in the presence of ammonium acetate [8] furnished only a low yield (< 10%) of the amine **8** and the corresponding alcohol as the main product. Therefore, we looked for a better strategy which involved the transformation of the ketone **11** into the oxime **12** with hydroxylamine hydrochloride [9], followed by reduction of **12** with lithium aluminum hydride in refluxing diethyl ether. Amine **8** was thus obtained in an overall yield of 50% from the ketone **11**.

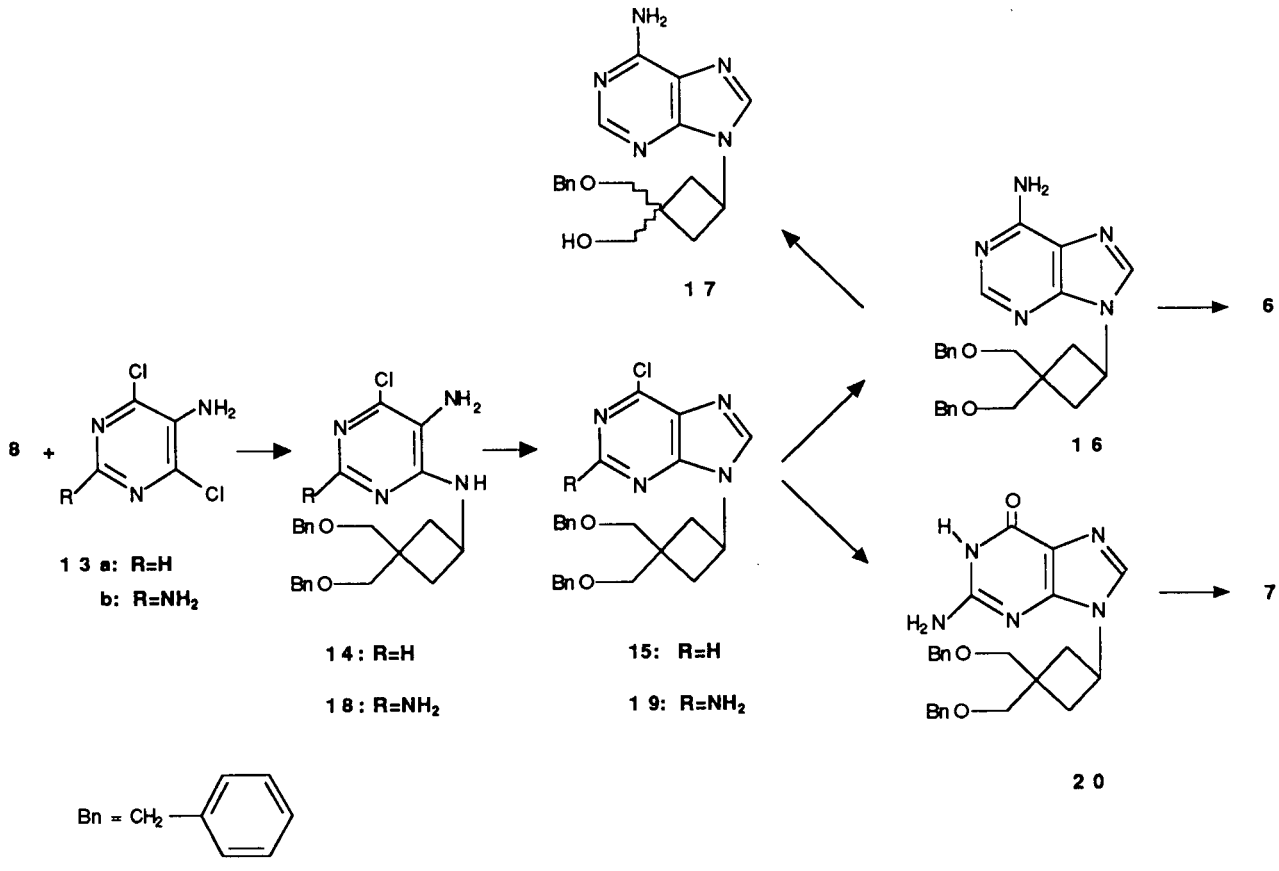
The 9-substituted adenine and guanine precursors, **16** and **20** respectively, were elaborated by a known [10] three-step sequence (Scheme II). Reaction of amine **8** with 5-amino-4,6-dichloropyrimidine (**13a**) in ethanol in the presence of triethylamine under reflux for 48 hours, led to **14** in 74% yield. Acid catalyzed cyclisation of **14** with triethyl orthoformate in dimethylacetamide furnished the purine derivative **15** in 90% yield, which in turn was reacted with liquid ammonia (room temperature, 24 hours) in a stainless steel bomb to give **16** in 90% yield. The removal of the benzyl groups from **16** to give the unprotected compound **6** was expected to proceed smoothly by catalytic hydrogenolysis over palladium on charcoal. However, under these conditions a monobenzylated compound **17** was obtained even after treatment with 10% palladium on charcoal for 24 hours. Nuclear Overhauser effect measurements were carried out to identify the position of the benzyl group but results were not significant. Straightforward deprotection of **16** by boron trichloride in dichloromethane at -78° gave the adeninyl derivative **6** in 80% yield. Similarly, synthesis of the guanine precursor **20** was carried out starting with the condensation of amine **8** and 2,5-diamino-4,6-dichloropyrimidine (**13b**) which was achieved in 64% yield. This pyrimidine synthon **13b** can be obtained according to the method of Temple [11] *et al.* but we used a shorter route to this synthon which will be reported in a separate paper [12]. Cyclisation of the intermediate **18** gave **19** in 90% yield (using the same conditions as for **15**). Chlorine hydrolysis in **19** was performed in 1*N* hydrochloric acid under reflux for 6 hours and gave **20** in 87% yield. It should be noticed here that lengthening the reaction time of the chlorine hydrolysis (up to 24 hours) led to the formation of the debenzylated product **7** as well as the guanine derivative **20**. The boron trichloride cleavage of the benzyl groups proceeded smoothly and led to the guanine derivative **7** in 76% yield.

In summary, an efficient synthesis of new hydroxymethylcyclobutyl derivatives of adenine and guanine has been described which starts with the easily prepared amine **8**. These new analogs of adenosine and guanosine where the furanose moiety is replaced by a 3,3'-bis(hydroxymethyl)cyclobutyl group are members of a new family of carbocyclic nucleoside analogs. One should notice here that analogs **6** and **7** do not exhibit any optical activity because of the presence of a plane of symmetry in these molecules. The biological activities of compounds **6** and **7**

Scheme I



Scheme II



were studied against HSV-1, HCMV and HIV-1 in cell culture according to protocols already described. Neither **6** nor **7** exhibited any antiviral activity against the three viruses tested.

EXPERIMENTAL

The melting points were taken on a Kofler hot stage apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian XL100 and a Bruker AM400 WB instrument (^{1}H nmr, 100 MHz and 400 MHz respectively) and chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane. Elemental analyses were performed by the "Service de Microanalyses", CNRS, ICSN, 91190 Gif sur Yvette, France. Preparative chromatography was carried out in glass columns packed with 230-400 mesh silica gel (Kieselgel 60, Merck) under low pressure (1-10 bars).

3,3-Dimethoxycyclobutane-1,1-dimethanol (**10a**).

A solution of **9** (15 g, 57.7 mmoles) in tetrahydrofuran (70 ml) was added dropwise at 0° to a suspension of lithium aluminum hydride (2.6 g, 68.7 mmoles) in tetrahydrofuran (70 ml). The mixture was stirred for 2 hours at 0° and for 20 hours at room temperature under exclusion of moisture. The mixture was cooled to 0° and a 15% sodium hydroxide solution (10 ml) was added slowly. The solid was filtered and washed with tetrahydrofuran. The filtrate and washing solutions were combined, dried (magnesium sulfate) and evaporated to dryness. The residual oil was distilled to give 8.2 g (81%) of **10a**, bp 116-118° (0.07 mm); ^{1}H nmr (deuteriochloroform): δ 3.68 (d, 4H, CH_2O, J = 5 Hz), 3.19 (2t, 2H, 2 x OH), 3.12 (s, 6H, 2 x CH_3), 1.94 (s, 4H, 2 x CH_2).

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.33; H, 9.15. Found: C, 54.46; H, 8.88.

3,3-Dimethoxy-1,1-bis(benzyloxymethyl)cyclobutane (**10b**).

A solution of **10a** (7.5 g, 42.7 mmoles) in dry tetrahydrofuran (40 ml) was added dropwise at room temperature to sodium hydride (60% dispersion in oil, 3.75 g, 93.7 mmoles) in tetrahydrofuran (80 ml) under nitrogen. The mixture was stirred for 2 hours and benzyl bromide (15.3 g, 89.7 mmoles) in tetrahydrofuran (30 ml) was added with tetrabutylammonium hydrogen sulfate (0.21 g, 0.6 mmole). Stirring was continued for 18 hours at room temperature under nitrogen and ethanol (5 ml) was added. The solvent was evaporated, the residue was then dissolved in dichloromethane (100 ml) and washed with water (100 ml). The dichloromethane solution was dried (magnesium sulfate) and evaporated under reduced pressure to give an oil which distilled at 183-188° (0.07 mm) to yield 15 g (98%) of **10b** which was sufficiently pure to be used in the next step; ^{1}H nmr (deuteriochloroform): δ 7.34 (s, 10H, 2 Ph*H*), 4.55 (s, 4H, 2 C*H*$_2$-Ph), 3.57 (s, 4H, 2 CH_2), 3.13 (s, 6H, 2CH_3), 2.04 (s, 4H, 2CH_2).

3,3-Bis(benzyloxymethyl)cyclobutanone (**11**).

A solution of **10b** (1 g, 3.2 mmoles) in 98% formic acid (20 ml) was stirred overnight at room temperature and afterwards evaporated to dryness. Co-evaporation with toluene (3 x 20 ml) removed any residual formic acid. Purification by column chromatography (elution with 2% *n*-hexane in dichloromethane) afforded a quantitative yield of **11** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 7.33 (s, 10H, 2 Ph*H*), 4.57 (s, 4H, 2C*H*$_2$-Ph), 3.63 (s, 4H, 2 OC*H*$_2$), 2.94 (s, 4H, 2 CH$_2$).

Anal. Calcd. for $C_{20}H_{22}O_3$ (310.38): C, 77.39; H, 7.14. Found: C, 77.22; H, 7.10.

3,3-Bis(benzyloxymethyl)cyclobutanone Oxime (**12**).

A solution of cyclobutanone **11** (0.56 g, 1.8 mmoles) in pyridine-ethanol (1:1, 10 ml) and hydroxylamine hydrochloride (1.2 g, 18 mmoles) was stirred for 15 minutes at room temperature. This mixture was poured into brine (100 ml) which was extracted with ethyl acetate (3 x 50 ml). The organic phase was washed with 1*N* hydrochloric acid (2 x 20 ml), brine (2 x 20 ml), dried (magnesium sulfate) and evaporated under diminished pressure. The yield of crude product **12**, which was sufficiently pure for the next step, was 0.29 g (50%). An analytical sample was obtained as an oil after chromatography (dichloromethane); ^{1}H nmr (deuteriochloroform): δ 7.32 (s, 10H, 2 Ph*H*), 4.54 (s, 4H, 2 C*H*$_2$-Ph), 3.54 (s, 4H, 2 C*H*$_2$O), 2.75 (s, 2H, CH$_2$), 2.74 (s, 2H, CH$_2$).

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.59; H, 6.92; N, 4.14.

1-Amino-3,3-bis(benzyloxymethyl)cyclobutane (**8**).

A solution of oxime **12** (3 g, 9.2 mmoles) in anhydrous diethyl ether (50 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.51 g, 13.4 mmoles) in diethyl ether (100 ml) at room temperature and heated at reflux for 4 hours. After cooling, the excess hydride was destroyed by slow addition of ethyl acetate followed by a 10% aqueous solution of sodium bicarbonate (50 ml). After five minutes stirring, the two phases were separated and the aqueous phase was extracted with diethyl ether (3 x 250 ml). The organic phase was dried over magnesium sulfate and evaporated. The residue was purified by chromatography (dichloromethane:ethanol, 95:5) to give 1.32 g (46%) of a hygroscopic solid which became oily on contact with air; mp 76-80°; ^{1}H nmr (deuteriochloroform): δ 7.32 (s, 5H, Ph*H*), 7.31 (s, 5H, Ph*H*), 4.54 (s, 2H, C*H*$_2$Ph), 4.52 (s, 2H, C*H*$_2$Ph), 3.44 (m, 3H, C*H*$_2$O, H1), 3.43 (s, 2H, CH$_2$O), 3.35 (s, 2H, NH$_2$), 2.18-2.31 (m, 2H, H2 + H4), 1.68-1.83 (m, 2H, H2 + H4); ms: (m/e) 312 (MH$^+$).

Anal. Calcd. for $C_{20}H_{25}NO_2 \cdot 1.4H_2O$: C, 71.38; H, 8.26; N, 4.16. Found: C, 71.45; H, 7.92; N, 3.82.

5-Amino-6-chloro-4-[[3,3-bis(benzyloxymethyl)cyclobut-1-yl]-amino]pyrimidine (**14**).

A mixture of **8** (1.25 g, 4 mmoles), 5-amino-4,6-dichloropyrimidine (**13a**) (0.78 g, 4.8 mmoles), triethylamine (5.6 ml) and 50 ml of ethanol was boiled under reflux for 48 hours under nitrogen. The solution was evaporated to dryness and the residue dissolved in dichloromethane (50 ml). The solution was washed with water (2 x 20 ml) and dried (magnesium sulfate). The product was purified by column chromatography. Elution with dichloromethane first gave compound **13a**, followed by the title compound **14** which was eluted with dichloromethane-ethanol (95:5) and recovered as an oil. The yield of **14** was 1.04 g (74%), which was of sufficient purity for use in the next step; ^{1}H nmr (deuteriochloroform): δ 8.00 (s, 1H, H2), 7.36 (s, 5H, Ph*H*), 7.34 (s, 5H, Ph-*H*), 5.60 (d, 1H, NH, J = 7.1 Hz), 4.56 (s, 2H, C*H*$_2$-Ph), 4.54 (s, 2H, C*H*$_2$-Ph), 4.24 (d, 1H, H1', J = 5.5 Hz), 3.49 (s, 4H, 2 C*H*$_2$O), 3.36 (broad s, 2H, NH$_2$), 2.40 (m, 2H, H2', H4'), 2.00 (m, 2H, H2', H4').

6-Chloro-9-[3,3-bis(benzyloxymethyl)cyclobut-1-yl]-9*H*-purine (**15**).

Freshly distilled triethyl orthoformate (10 ml) and concentrated hydrochloric acid (0.5 ml) were added to a cooled (0°) solution of **14** (1.3 g, 2.28 mmoles) in distilled dimethylacetamide (10 ml). The solution was stirred overnight at room temperature in a stoppered fask and afterwards evaporated to dryness under reduced pressure (0.1 mm). Several portions of water were added to the residue which was then evaporated to dryness. The oily residue was purified by chromatography (dichloromethane) to give 1.15 g (90%) of an oil; ^{1}H nmr (deuteriochloroform): δ 8.70 (s, 1H, H8), 8.36 (s, 1H, H2), 7.35-7.36 (2s, 10H, 2 Ph*H*), 5.17 (q, 1H, H1'), 4.60 (s, 4H, 2 C*H*$_2$-Ph), 3.57 (s, 2H, CH$_2$O) 3.54 (s, 2H, CH$_2$O), 2.68 (m, 4H, CH$_2$).

Anal. Calcd. for $C_{25}H_{25}N_4O_2Cl$: C, 66.89; H, 5.61; N, 12.48. Found: C, 66.75; H, 5.23; N, 12.15.

9-[3,3-Bis(benzyloxymethyl)cyclobut-1-yl]adenine (**16**).

A solution of **15** (0.8 g, 1.78 mmoles) in methanol (10 ml) and liquid ammonia (250 ml) was stirred in a stainless steel bomb for 24 hours. The solution was evaporated to dryness, and the residue was afterwards dissolved in dichloromethane (50 ml), washed with water (2 x 15 ml) and dried (magnesium sulfate). Purification by chromatography (dichloromethane) gave 0.68 g (90%) of **16** as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 8.33 (s, 1H, H8), 8.04 (s, 1H, H2), 7.35 (s, 10H, 2 Ph*H*), 5.65 (s, 2H, NH$_2$), 5.10 (q, 1H, H1'), 4.60 (s, 2H, C*H*$_2$-Ph), 4.59 (s, 2H, C*H*$_2$ Ph), 3.58 (s, 2H, CH$_2$O), 3.55 (s, 2H, CH$_2$O), 2.63 (m, 4H, 2CH$_2$).

Anal. Calcd. for $C_{25}H_{27}N_5O_2$: C, 69.90; H, 6.34; N, 16.30. Found: C, 69.90; H, 6.44; N, 16.17.

9-[3,3-Bis(hydroxymethyl)cyclobut-1-yl]adenine (**6**).

A solution of **16** (200 mg, 0.46 mmole) in dichloromethane (5 ml) and 1*M* solution of boron trichloride in dichloromethane (5 ml) at -78° was stirred under nitrogen for 6 hours. A solution of methanol-dichloromethane (1:1) (10 ml) was then added and the mixture was stirred for 30 minutes at room temperature before it was evaporated to dryness. The residue was dissolved in ethanol (10 ml), neutralized with 1*N* sodium hydroxide and evaporated to dryness. The residue was adsorbed onto silica gel and subjected to column chromatography. Elution with dichloromethane-ethanol (9:1) gave the title compound **6**, 80 mg (80%) as an oil which crystallized on drying, mp 220°; ^{1}H nmr DMSO-d$_6$): δ 8.32 (s, 1H, H8), 8.15 (s, 1H, H2), 4.82 (t, 1H, OH, J = 5.3 Hz), 4.76 (t, 1H, OH, J = 5.3 Hz), 3.54 (d, 2H, C*H*$_2$OH, J = 5.4 Hz), 3.48 (d, 2H, C*H*$_2$OH, J = 5.4 Hz), 2.36 (m, 2H, H2', H4'), 1.32 (m, 2H, H2', H4').

Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07. Found: C, 52.82; H, 6.21.

9-[3-Benzyloxymethyl-3-hydroxymethylcyclobut-1-yl]adenine (**17**).

A solution of **16** (0.2 g, 0.46 mmole) in ethanol (50 ml) was stirred at 40° for 24 hours in the presence of 50 mg of 10% palladium on carbon. The suspension was filtered through a pad of Celite and the ethanol was removed under reduced pressure. Column chromatography on silica gel eluting with dichloromethane-ethanol 98:2, gave **17** after crystallization from ethanol

in 65% yield, mp 173°; ^{1}H nmr (DMSO-d_6): δ 8.30 (s, 1H, H2); 8.16 (s, 1H, H8), 7.44 (s, 5H, Ph-*H*), 7.18 (s, 2H, NH_2), 5.1 (m, 1H, H1', 4.82 (br, 1H, OH), 4.62 (s, 2H, C*H*$_2$-Ph), 3.59 (s, 2H, C*H*$_2$O), 3.53 (s, 2H, C*H*$_2$O), 2.45 (m, 4H, 2 x CH_2).

Anal. Calcd. for $C_{18}H_{21}N_5O_2$: C, 63.71; H, 6.78. Found: C, 63.39; H, 6.70.

2,5-Diamino-6-chloro-4-[[3,3-bis(benzyloxymethyl)cyclobut-1-yl]-amino]pyrimidine (**18**).

A mixture of **8** (1 g, 3.21 mmoles), 2,5-diamino-4,6-dichloropyrimidine (**13b**) (0.62 g, 3.46 mmoles), triethylamine (10 ml) and butan-1-ol (50 ml) was boiled under reflux for 48 hours under nitrogen. The solution was evaporated to dryness and worked up similar to the procedure for compound **14**. Elution with dichloromethane-ethanol (98:2) gave 917 mg (61%) of **18** as an oil which was sufficiently pure for the next step; ^{1}H nmr (deuteriochloroform): δ 7.34 (d, 10H, 2 Ph*H*), 5.54 (d, 1H, NH), 5.08 (m, 1H, H1'), 4.55 (m, 8H, 2 C*H*$_2$Ph, 2NH_2), 3.50 (s, 2H, C*H*$_2$O), 3.46 (s, 2H, C*H*$_2$O), 2.40 (m, 2H, H2', H4'), 1.93 (m, 2H, H2', H4').

2-Amino-6-chloro-9-[3,3-bis(benzyloxymethyl)cyclobut-1-yl]-9*H*-purine (**19**).

A solution of **18** (700 mg, 1.54 mmoles) in distilled *N,N*-dimethylacetamide (10 ml) was cooled to 0° while freshly distilled triethyl orthoformate (10 ml) and concentrated hydrochloric acid (0.5 ml) were added. The mixture was stirred overnight at room temperature and evaporated to dryness. The residue was stirred in 50% acetic acid in water (20 ml) for 4 hours before evaporation to dryness and several coevaporations with methanol (20 ml each). The syrup was stirred in 10% ammonia in methanol (20 ml) for 4 hours and evaporated to dryness. Purification was performed by column chromatography with dichloromethane-ethanol (98:2) as the eluant to yield 640 mg (89%) of a colorless oil; ^{1}H nmr (deuteriochloroform): δ 7.99 (s, 1H, H8), 7.34 (2s, 10H, 2 Ph*H*), 4.85-5.02 (m, 3H, H1', NH_2), 4.59 (s, 4H, 2 C*H*$_2$Ph), 3.55 (s, 2H, C*H*$_2$O), 3.51 (s, 2H, C*H*$_2$O), 2.65-2.51 (m, 4H, H2', H4').

Anal. Calcd. for $C_{25}H_{26}N_5O_2Cl$: C, 64.79; H, 5.61. Found: C, 64.58; H, 5.58.

9-[3,3-Bis(benzyloxymethyl)cyclobut-1-yl]guanine (**20**).

A solution of **18** (350 mg, 0.75 mmole) in 1*N* hydrochloric acid (10 ml) was refluxed for 6 hours. Evaporation to dryness and coevaporation with ethanol gave a residue, which was dissolved in water (5 ml) and neutralized with 6*N* sodium hydroxide. After evaporation of the reaction mixture, the residue was adsorbed on silica gel and chromatographed on a silica gel column eluting successively with dichloromethane, followed by dichloromethane-ethanol 98:2 and 95:5. The pure fractions were combined and the title compound **20** crystallized from ethanol to yield 264 mg (87%), mp 244°; ^{1}H nmr (DMSO-d_6): δ 10.6 (s, 1H, NH), 7.84 (s, 1H, H8), 7.32 (2s, 10H, Ph*H*), 6.35 (broad s, 2H, NH_2), 4.79 (q, 1H, H1'), 4.54 (2s, 4H, 2 C*H*$_2$-Ph), 3.54 (broad s, 4H, 2 C*H*$_2$O), 2.48-2.32 (m, 4H, H2', H4').

Anal. Calcd. for $C_{25}H_{27}N_5O_3$: C, 67.41; H, 6.06; N, 15.73. Found: C, 67.19; H, 6.08; N, 15.91.

9-[3,3-bis(hydroxymethyl)cyclobut-1-yl)guanine (**7**).

A solution of **20** (100 mg, 0.22 mmole), in dichloromethane (10 ml) was stirred in the presence of a 1*M* boron trichloride solution in dichloromethane (6 ml) for 5 hours at -78° under dry nitrogen. A solution of methanol-dichloromethane (1:1, 10 ml) was added dropwise and the mixture was allowed to warm to room temperature. The reaction mixture was stirred for 30 minutes at room temperature, and afterwards evaporated to dryness. The residue was redissolved in ethanol-water 8:2, neutralized with 1*N* sodium hydroxide, and evaporated to dryness. The solid was adsorbed on silica gel and chromatographed on a silica gel column eluting with dichloromethane-ethanol 85:15 to yield 45 mg (76%) mp >260° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 10.59 (broad s, 1H, NH), 7.90 (s, 1H, H8), 6.48 (broad s, 2H, NH_2), 4.83-4.66 (m, 3H, H1', 20H), 3.54 (2d, 4H, 2 C*H*$_2$O, J = 6 Hz), 2.36 (s, 2H, H2', H4'), 2.27 (s, 2H, H2', H4'); ms: (m/e) 266 (MH^+).

Anal. Calcd. for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.66; N, 26.41. Found: C, 50.02; H, 5.45; N, 26.58.

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