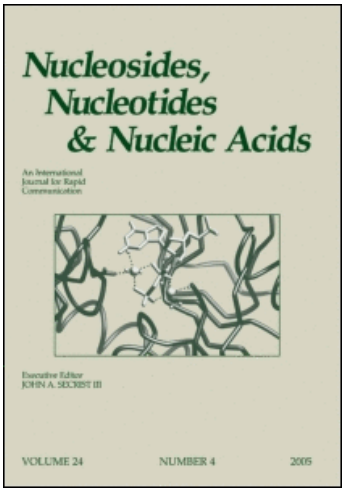

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SYNTHESIS OF METHYLENECYCLOBUTYL- AND CYCLOBUTENYL ADENINE, POTENT ANTIVIRAL CARBOCYCLIC ANALOGUES OF OXETANOCIN A

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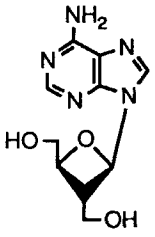
Abstract

9-Cyclobutyladenines bearing both methylene and hydroxymethyl groups, **3** and **4**, were prepared by dehydration of carbocyclic oxetanocin A (**1a**). Introduction of a double bond into cyclobutane ring was achieved by allylic oxidation of N^6-benzoyl-9-[3-methylenecyclobutyl]adenine (**12**), which after several steps, afforded 9-[3-(hydroxy-methyl)-2-cyclobutenyl)adenine (**5**).

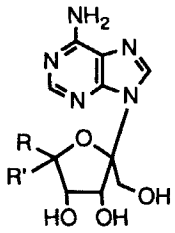
INTRODUCTION

Oxetanocin A, isolated from *B. megaterium* by Shimada *et al*, was found to exhibit antiviral activity against HIV type 1 *in vitro*.[1] Synthesis of carbocyclic analogues of oxetanocin (A;**1a**, G;**1b**) and evaluation of their antiviral activity has been reported from several groups, including ours.[2] As regards anti-HIV activity, it appears that the presence of a 2'-hydroxymethyl group is not necessarily required for antiviral action because both carbocyclic oxetanocin A (**1a**) and 9-[*cis*-3-(hydroxymethyl)cyclobutyl]-adenine (**2**) protect ATH8 cells against the infectivity and cytopathic effect of HIV-1.[2d,g] Toxicity at high concentration limits further development of these compounds for clinical use against AIDS patients; this derivatives improved in toxicity are needed. It is already known that the nucleoside antibiotic decoyinine shows similar biological activity to that of psicofuranine.[3] Moreover, the isolation and biological activity of neplanocin A has been reported.[3,4] This background prompted us to introduce a double bond into the carbocyclic moiety of **1a** and **2**. In this paper, we report the synthesis of decoyinine type analogues (**3**, **4**) and a neplanocin type analogue (**5**).

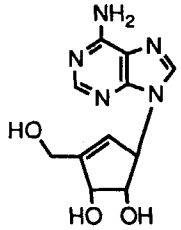
This paper is dedicated to the late Professor Tohru Ueda who passed away on September 19, 1990.



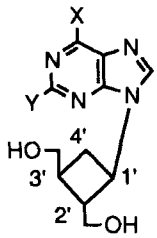
Oxetanocin A



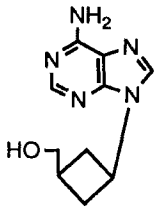
Psicofuranine;
R = CH_2OH, R'= H
Decoyinine; R, R' = CH_2



Neplanocin A



1a; X=NH_2, Y=H
1b; X=OH, Y=NH_2



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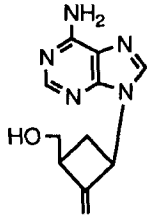

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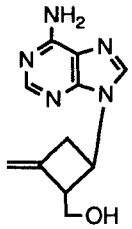
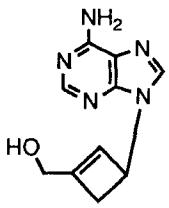


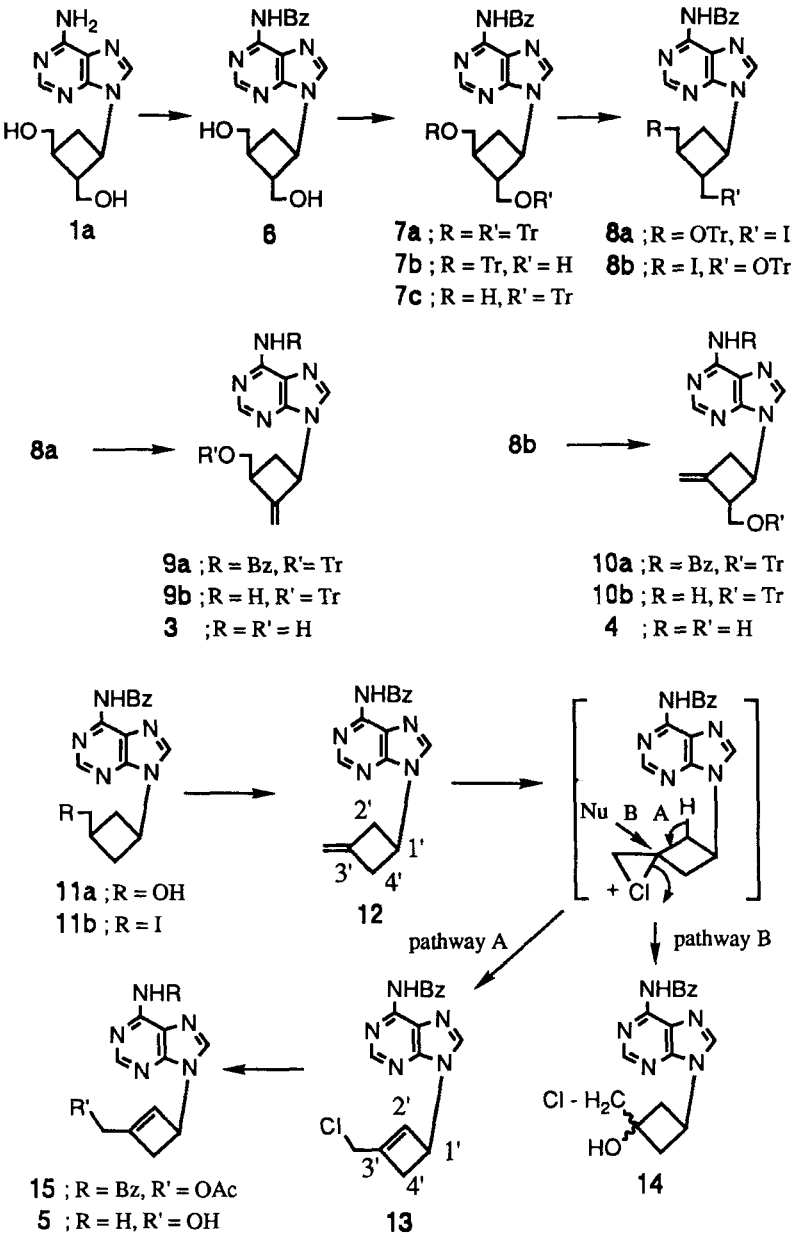
4



5

DEHYDRATION OF 1a

Synthesis of **3** was achieved by the dehydration of the racemic carbocyclic oxetanocin A ((±)-**1a**) using a modification of the method of McCarthy *et al.*[5] Perbenzoylation of (±)-**1a** with benzoyl chloride in pyridine and alkaline hydrolysis of the product using 2M NaOH for 1 h at 0° gave N^6-benzoyl carbocyclic oxetanocin A (**6**). Partial protection of the 2'- or 3'-hydroxymethyl group was carried out by the reaction of **6** with an equimolar amount of trityl chloride. Three major products, N^6-benzoyl-9-[*trans*-*trans*-2,3-bis(trityloxy-methyl)cyclobutyl]adenine (**7a**), N^6-benzoyl-9-[*trans*-2-(hydroxymethyl)-trans-3-(trityloxymethyl)cyclobutyl]adenine (**7b**), and N^6-benzoyl-9-[*trans*-3-(hydroxymethyl)-trans-2-(trityloxymethyl)cyclobutyl]adenine (**7c**), were isolated from the reaction mixture after separation by silica gel column chromatography in 19, 22, and 28% yields, respectively. Starting material (**6**) was recovered in 20% yield. Ditritylated compound (**7a**) was converted to **6** by detritylation, and utilized again. The structures of **7b** and **7c** were determined by ^1H NMR spectroscopy as follows. In the case of **7b**, irradiation at H2' (2.77 ppm) changed the signal of 2'-CH_2OH (3.82ppm) from triplet to doublet and a similar operation at 3.82 ppm changed the signal of the 2'-$CH_2\underline{OH}$ (4.31ppm), indicating the presence of a hydroxymethyl group attached to the 2'-carbon. Using the same technique, the presence of 3'-CH_2OH in **7c** was also confirmed. 3'-*O*-Protected product (**7b**) was treated with methyltriphenoxyphosphonium iodide[6] to afford iodomethylcyclobutane (**8a**) in good yield. An elimination reaction which removes hydrogen iodide from **8a** was achieved by its potassium *t*-butoxide to give methylenecyclobutane (**9a**) in 91% yield. The structure of



Chart

9a was confirmed by ^{1}H NMR spectrum in which signals attributable to olefin protons appeared at 5.16 and 4.95 ppm. Methanolysis of the N^6-benzoyl group in the presence of sodium methoxide followed by acid hydrolysis of the 5'-*O*-trityl group gave 9-[*cis*-3-(hydroxymethyl)-2-methylenecyclobutyl]adenine (**3**) as white crystals. The 3'-methylene isomer (**4**) was synthesized from **8b** in a manner similar to that described for **3**.

SYNTHESIS OF 5

Arita *et al* reported allylic oxidation of methylenecyclopentanes with *t*-butylhypochlorite to form chloromethylcyclopentenes in the course of a synthesis of neplanocin A and its analogues.[7] We adopted this method for cyclobutene ring formation. N^6-Benzoyl-9-(3-methylenecyclobutyl)adenine (**12**) was prepared from **11a** in a manner similar to that described for **3**. **12**, thus obtained, was allowed to react with *t*-butylhypochlorite in methyl formate at -78° for 10 min. Two major products were obtained after separation by column chromatography on silica gel 60. The first fraction was collected and evaporated to dryness to obtain N^6-benzoyl-9-[3-(chloromethyl)-2-cyclobutenyl]-adenine (**13**) as a gum in 31.5% yield. The structure of **13** was confirmed by ^{1}H NMR spectroscopy (6.36 ppm, olefin proton attached to C-2), MS spectrum (*m/z* : 339, 341 (M^+)), and UV spectrum. On evaporation of the second fraction, a by-product (**14**) was obtained as pale yellowish crystals in 22% yield. The formula was elucidated as $C_{17}H_{16}ClN_5O_2$ by elemental analysis, and a partial structure of the carbocyclic moiety from its ^{1}H NMR spectrum included a cyclobutane attached to chloromethyl group. In addition, the UV spectrum was almost superimposable on that of **12**, so that the base moiety was not altered in this reaction. In view of the above result, the structure was determined to be N^6-benzoyl-9-[3-(chloromethyl)-3-hydroxycyclobutyl]adenine. Although the mechanism is not clear at present, it seems that initial approach of Cl^+ to the exocyclic double bond results in the formation of a three-membered ring cation as an intermediate. Subsequent elimination of the 2'-proton will cause allylic oxidation to form **13** (pathway A). The strain energy of the cyclobutene is so large that reaction pathway A will not proceed as smoothly as in the cyclopentane system. This gives rise to nucleophilic attack of the solvent on the intermediate cation to form a chlorohydrin adduct (**14**) (pathway B). Nucleophilic substitution of **13** with sodium acetate in the presence of sodium iodide gave an acetate **15**, and removal of the protecting group with sodium methoxide afforded **5** as white crystals in 21% yield.[8]

Preliminary antiviral evaluation revealed that **4** had moderate activity against herpes simplex virus type-1 (HSV-1) but **3** was inactive against that virus.[9]

^{1}H NMR SPECTROSCOPY OF 12 AND 13

It is noteworthy that the chemical shifts of two protons attached to C-4' are different in **12** and **13**. Both H4' proton resonances of **12** appear at ca. 3.4 ppm. In **13**, the down-side H4' proton appears at almost the same position as that of **12**, but the up-side H4' proton appears at about 0.5 ppm upfield (2.77 ppm). Those phenomena would be explained by the steric hindrance between the H2' protons of the carbocyclic ring and the purine base. Because it is coplanar with the cyclobutene ring, the proton attached to

C-2' (olefin proton) of **13** would not cause steric hindrance. As a result, **13** takes a *syn* conformation causing the purine ring anisotropic shift to the up-side H4' proton. On the other hand, the two up-side protons attached to C-2' and C-4' of **12** would prevent the approach of purine, so that it takes an *anti* conformation.

EXPERIMENTAL

Melting points (m.p.) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low resolution mass spectra were obtained on a Shimadzu-LKB 9000B mass spectrometer in the direct-inlet mode. High resolution mass spectra were obtained on a JMS AX-500 spectrometer in the direct-inlet mode. ^{1}H NMR spectra were recorded on either JEOL FX-90Q (90 MHz) or JEOL GX-400 (400 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography and silica gel 60 (Merck 7734, 60 - 200 mesh) was employed for column chromatography.

***N*^{6}-Benzoyl-9-[*trans-trans*-2,3-bis(hydroxymethyl)cyclobutyl]adenine (6).** Benzoyl chloride (2 ml, 17.2 mmol) was added to a solution of (±)-**1a** (613 mg, 2.46 mmol) in pyridine (25 ml) and the mixture was stirred for 3 h at room temperature, then ice-cooled. The usual workup of the resulting solution gave the fully benzoylated product of **1a** as a syrup, which was treated with 2M NaOH in pyridine (10 ml) - MeOH (10 ml) for 1 h at 0° . The solution was neutralized with AcOH. After removal of the solvent, the residue was evaporated azeotropically twice with toluene (25 ml) and dissolved in a small amount of EtOH. The alcoholic solution was chromatographed on a column of silica gel 60 (ϕ 3.0 X 20 cm) with a gradient of 0 - 20% EtOH in $CHCl_3$ (600 ml) to afford a gum (554 mg, 64%). UV: λ max(MeOH) 281nm.

Tritylation of 6. Trityl chloride (986 mg, 1 eq.) and **6** (1.25 g, 3.54 mmol) were dissolved in pyridine (5 ml) and the mixture was stirred for 1 h at room temperature. After addition of water (3 ml), the solution was evaporated to give a pale brownish gum, which was dissolved in benzene (200 ml). The organic solution was washed twice with water (100 ml), dried over $MgSO_4$, and concentrated to a small volume. The solution was chromatographed on a column of silica gel 60 (ϕ 3.6 X 50 cm) with a gradient of 0 - 4.8% EtOH in $CHCl_3$ (2 l). The first fraction was collected and evaporated to dryness to give *N*^{6}-benzoyl-9-[*trans-trans*-2,3-bis(trityloxymethyl)cyclobutyl]adenine (**7a**) (557 mg, 18.8%) as a solid. UV: λ max(MeOH) 281nm.

From the second fraction, *N*^{6}-benzoyl-9-[*trans*-2-(hydroxymethyl)-trans-3-(trityloxymethyl)cyclobutyl]adenine (**7b**) (463 mg, 22.0%) was obtained as a foam. Anal. Calcd. for $C_{37}H_{33}N_5O_3$. C; 74.60, H; 5.58, N; 11.76. Found: C; 74.94, H; 5.61, N; 11.50. UV: λ max(MeOH) 281nm. ^{1}H NMR ($CDCl_3$) δ : 9.07 (1H, br s, *N*^{6}-H), 8.77 (1H, s, H8), 8.03 (1H, s, H2), 7.2 - 8.05 (ca 20H, 3'-$CH_2OC(C_6H_5)_3$, C_6H_5CO-), 4.62 (1H, q, J=8.6 Hz, H1'), 4.31 (1H, t, J= 6.1 Hz, 2'-CH_2OH), 3.82 (2H, t, J= 6.1 Hz, 2'-

CH_2OH), 3.32 (1H, dd, J=4.88 Hz, J=9.28 Hz, 3'-$CH_2OC(C_6H_5)_3$), 3.21 (1H, dd, J=6.35 Hz, J=9.76 Hz, 3'-$CH_2OC(C_6H_5)_3$), 2.77 (1H, m, H2'), 2.65 (1H, m, H4'a), 2.38 (1H, q, J=9.93 Hz, H4'b), 2.27 (1H, m, H3').

The third fraction was evaporated to afford N^6-benzoyl-9-[*trans*-3-(hydroxymethyl)-*trans*-2-(trityloxymethyl)cyclobutyl]adenine (**7c**) (589 mg, 28.0%) as a foam. UV: λ max(MeOH) 281 nm. ^{1}H NMR ($CDCl_3$) δ : 9.06 (1H, br s, N^6-H), 8.77 (1H, s, H8), 7.97 (1H, s, H2), 7.2 - 8.05 (ca 20H, 2'-$CH_2OC(C_6H_5)_3$, C_6H_5CO-), 4.71 (1H, q, J=8.6 Hz, H1'), 3.74 (2H, m, 3'-CH_2OH), 3.43 (1H, dd, J=5.13 Hz, J=10.0 Hz, 2'-$CH_2OC(C_6H_5)_3$), 3.32 (1H, dd, J=6.60 Hz, J=10.0 Hz, 2'-$CH_2OC(C(C_6H_5)_3)$, 2.74 (1H, dd, J=5.0 Hz, J=6.5 Hz, 3'-CH_2OH), 2.62 (1H, m, H4'a), 2.50 (1H, m, H4'b), 2.33 (1H, m, H3').

N^6-Benzoyl-9-[*trans*-2-(iodomethyl)-*trans*-3-(trityloxymethyl)cyclobutyl]-adenine (8a). Methyltriphenoxyphosphonium iodide (530 mg, 1.2 mmol) was added to a solution of **7b** (450 mg, 0.76 mmol) in DMF (20 ml) and the mixture was stirred for 1 h at room temperature. After dilution with benzene (150 ml), the organic layer was washed successively with water (200 ml), 5% $Na_2S_2O_3$ (100 ml) and water (200 ml). The solution was dried over $MgSO_4$, concentrated to a small volume, then chromatographed on a column of silica gel 60 (ϕ 2.2 X 20 cm) with a gradient of 0 - 50% AcOEt in benzene (760 ml) to afford a gum (452 mg, 85%). UV: λ max(MeOH) 281 nm. ^{1}H NMR ($CDCl_3$) δ : 9.07 (1H, br s, N^6-H), 8.76 (1H, s, H8), 8.05 (1H, s, H2), 7.2 - 8.05 (ca 20H, 3'-$CH_2OC(C_6H_5)_3$), C_6H_5CO-), 4.62 (1H, q, J = 8.2Hz, H1'), 3.0 - 3.5 (5H, m, H2', 2'-CH_2I, 3'-$CH_2OC(C_6H_5)_3$), 2.55 (2H, m, H4'), 2.18 (1H, m, H3').

N^6-Benzoyl-9-[*trans*-3-(iodomethyl)-*trans*-2-(trityloxymethyl)cyclobutyl]-adenine (8b). Methyltriphenoxyphosphonium iodide (670 mg) was added to a solution of (**7c**) (575 mg, 0.97 mmol) in DMF (25 ml) and the solution was stirred for 1 h at room temperature. The resulting solution was subjected to the standard workup to give a foam (568 mg, 83%). UV: λ max (MeOH) 281nm.

N^6-Benzoyl-9-[2-methylene-*cis*-3-(trityloxymethyl)cyclobutyl]adenine (9a). Potassium *t*-butoxide (637 mg, 5.7 mmol) was added to a solution of **8a** (444 mg, 0.63 mmol) in pyridine (10 ml) - *t*-butanol (20 ml) and the mixture was stirred for 1 h at room temperature. The solution was neutralized with acetic acid, and evaporated to dryness. The residual syrup was dissolved in benzene (10 ml), and after washing with water, evaporated azeotropically with toluene (20 ml) twice. The solution was chromatographed on a column of silica gel 60 (ϕ 2.5 X 20 cm) with a gradient of 0 - 67% AcOEt in benzene (450 ml) to afford a foam (332 mg, 91%). UV: λ max (MeOH) 281nm. ^{1}H NMR ($CDCl_3$) δ : 9.11 (1H, br s, N^6-H), 8.79 (1H, s, H8), 8.13 (1H, s, H2), 7.2 - 8.1 (ca 20H, 3'-$CH_2OC(C_6H_5)_3$, C_6H_5CO-), 5.72 (1H, t, J=8.4Hz, H1'), 5.16, 4.95 (each 1H, s, = CH_2), 3.40 (2H, m, 3'-$CH_2OC(C_6H_5)_3$, 3.31 (1H, m, H3'), 2.81 (1H, m, H4'a), 2.35 (1H, m, H4'b).

N^6-Benzoyl-9-[3-methylene-*cis*-2-(trityloxymethyl)cyclobutyl]adenine (10a). Potassium *t*-butoxide (784 mg) was added to a solution of **8b** (547 mg, 0.78 mmol) in pyridine (10 ml) - *t*-butanol (25 ml) and the mixture was stirred for 1 h at room temperature. The solution was treated in the same manner as described above to give a foam (416 mg, 93%). UV: λ max(MeOH) 281nm.

Removal of Protecting Group.

9-[2-Methylene-*cis*-3-(trityloxymethyl)cyclobutyl]adenine (9b). Compound **9a** (126 mg, 0.22 mmol) was treated with 0.02M NaOMe in MeOH (5 ml) for 6 h at 60° , then cooled. The solution was neutralized with 1M HCl (0.1 ml) and, after evaporation of the solvent, the residue was dissolved in $CHCl_3$ (20 ml). The organic layer was washed with water (10 ml), dried over $MgSO_4$, and evaporated to dryness. The resulting syrup was crystallized from a small amount of MeOH to give white crystals (90.2 mg, 87%). mp 213 - 215° . Anal. Calcd. for $C_{30}H_{27}N_5O$. C; 76.08, H; 5.75, N; 14.79. Found: C; 76.25, H; 5.77, N; 14.50. UV: λ max(MeOH) 260nm.

9-[3-Methylene-*trans*-2-(trityloxymethyl)cyclobutyl]adenine (10b). Compound **10a** (396 mg, 0.69 mmol) was treated with 0.02M NaOMe in MeOH (12 ml) for 4 h at 60° and the solution was subjected to the standard processing. Crystallization of the product from MeOH gave white crystals (291 mg, 90%). mp 196 - 198° . UV: λ max(MeOH) 260.5 nm.

9-[2-Methylene-*cis*-3-(hydroxymethyl)cyclobutyl]adenine (3). 1M HCl (1 ml) was introduced to a solution of **9b** (190 mg, 0.4 mmol) in MeOH (10 ml), then stirred for 1.5 h at 60° . After cooling, Amberlite IR 400 (OAc^-, 3 ml) was added to the mixture to capture HCl. The resin was removed by filtration and the filtrate was evaporated to leave a residue, which was partitioned between $CHCl_3$ (5 ml) and water (10 ml). The aqueous layer was washed with $CHCl_3$ and concentrated to a small volume to afford white crystals (68 mg, 73%). mp 133 - 135° . Anal. Calcd. for $C_{11}H_{13}N_5O$. C; 57.13, H; 5.67, N; 30.28. Found: C; 56.70, H; 5.57, N; 30.47. UV: λ max(0.1N HCl) 259.5nm (ε 13600), λ max(H_2O) 261nm (ε 13800), λ max(0.1N NaOH) 261nm (ε 13900). MS: *m/z* 231 (M^+), 214 (M^+- OH), 200 (M^+-CH_2OH). HR MS Calcd. for $C_{11}H_{13}N_5O$: *m/z* 231.1120. Found: *m/z* 231.1127. ^1H NMR (10% D_2O in DMSO-d_6) δ : 8.24 (1H, s, H8), 8.17 (1H, s, H2), 5.51 (1H, t, J = 8.5Hz, H1'), 5.08, 4.77 (each 1H, s, $=CH_2$), 3.68 (2H, d, J = 5.5 Hz, 3'-CH_2OH), 3.04 (1H, m, H3'), 2.63 (1H, q, J=9.8 Hz, H4'a), 2.42 (1H, q, J = 9.2 Hz, H4'b).

9-[3-Methylene-*trans*-2-(hydroxymethyl)cyclobutyl]adenine (4). 1M HCl (1.5 ml) was added to a solution of **10b** (280 mg, 0.59 mmol) in MeOH (20 ml) and the solution was stirred for 1 h at 60° . The mixture was treated in the same manner as described above to give white crystals (108 mg, 79%). mp 176 - 178° . Anal. Calcd. for $C_{11}H_{13}N_5O$. C; 57.13, H; 5.67, N; 30.28. Found: C; 56.94, H; 5.64, N; 29.99. UV: λ max(0.1N HCl) 259.5nm (ε 14800), λ max(H_2O) 261nm (ε 15100), λ max(0.1N NaOH) 261nm (ε 15000). ^1H NMR (DMSO-d_6) δ : 8.25 (1H, s, H8), 8.14 (1H, s, H2),

7.15 (2H, br s, $-NH_2$), 5.02 and 4.97 (each 1H, m, $=CH_2$), 4.77 (2H, m, H1', 2'-CH_2OH), 3.76 (1H, m, H2'), 3.67 (2H, m, 2'-CH_2OH), 3.37 (1H, m, H4'a), 3.09 (1H, q, J = 9.2 Hz, H4'b).

N^6-Benzoyl-9-[3-(iodomethyl)cyclobutyl]adenine (11b). Methyltriphenoxyphosphonium iodide (4.13g, 9.13 mmol) was added to a solution of (**11a**) (1.99g, 6.15 mmol) and the solution was stirred for 1 h at room temperature. The solution was treated in the same manner as described for **8a** to afford white crystals (2.33 g, 87%). mp 178 - 181° . Anal. Calcd. for $C_{17}H_{16}IN_5O$. C; 47.13, H; 3.72, N; 16.16. Found: C; 47.03, H; 3.64, N; 16.10. UV: λ max(MeOH) 280 nm. ^1H NMR ($CDCl_3$) δ : 9.09 (1H, br s, N^6-H), 8.80 (1H, s, H8), 8.09 (1H, s, H2), 8.07, 7.58 (2H and 3H, m, C_6H_5CO-), 5.20 (1H, m, H1'), 3.49 (2H, d, J = 6.4 Hz, $-CH_2I$), 2.3 - 3.1 (ca 5H, m, H2', H3', H4').

N^6-Benzoyl-9-[3-methylenecyclobutyl]adenine (12). To a solution of **11b** (2.33 g, 5.38 mmol) in pyridine (70 ml) - *t*-butanol (90 ml) was added potassium *t*-butoxide (5.3 g, 47 mmol). After stirring for 1 h at room temperature, the solution was subjected to the standard workup and crystallized from benzene to give pale yellowish crystals (1.58 g, 96%). mp 172 - 175° . Anal. Calcd. for $C_{17}H_{15}N_5O$. C; 66.87, H; 4.95, N; 22.94. Found: C; 66.76, H; 4.87, N; 22.59. UV: λ max(MeOH) 284 nm. ^1H NMR ($CDCl_3$) δ : 9.06 (1H, br s, N^6-H), 8.81 (1H, s, H8), 8.14 (1H, s, H2), 8.03, 7.58 (2H and 3H, m, C_6H_5CO-), 5.17 (1H, m, H1'), 5.08 (2H, quintet, J =1.6 Hz, $=CH_2$), 3.42 (ca 4H, m, H2', H4').

Allylic Oxidation of 12. A solution of **12** (800 mg, 2.62 mmol) in methyl formate (80 ml) was cooled to -78° under N_2 atmosphere and *t*-butylhypochlorite (1.8 ml, 15 mmol) was added to the solution, then stirred for 10 min. Ice-water was introduced to the reaction mixture and the solution was extracted three times with benzene (100 ml), dried over $MgSO_4$, and concentrated to a small volume. The solution was chromatographed on a column of silica gel 60 (ϕ 3.7 X 30 cm) with a gradient of 0-1.6% EtOH in $CHCl_3$ (3.2 l). The first fraction was collected to give N^6-benzoyl-9-[3-(chloromethyl)-2-cyclobutenyl]adenine (**13**) (280 mg, 31.5%) as a pale yellowish sryup. UV: λ max(MeOH) 280nm. MS *m/z* 339,341 (M^+). ^1H NMR ($CDCl_3$) δ : 8.81 (1H, s, H8), 8.08 (1H, s, H2), 8.05, 7.46 (2H and 3H, m, C_6H_5CO-), 6.36 (1H, m, H2'), 5.59 (1H, m, H1'), 4.18 (2H, br s, $-CH_2Cl$), 3.36 (1H, m, J = 13.1 Hz, J=4.8 Hz, H4'a), 2.77 (1H, m, H4'b).

Evaporation of the second fraction followed by crystallization from EtOH afforded N^6-benzoyl-9-[3-(chloromethyl)-3-hydroxycyclobutyl]adenine (**14**) (206.2 mg, 22.0%) as pale yellowish crystals. mp 227 - 230° . Anal. Calcd. for $C_{17}H_{16}ClN_5O_2$. C; 57.07, H; 4.51, N; 19.57. Found: C; 56.82, H; 4.53, N; 19.29. UV: λ max(MeOH) 281nm. ^1H NMR ($CDCl_3$) δ : 8.72 (1H, s, H8), 8.63 (1H, s, H2), 8.05, 7.60 (2H and 3H, m, C_6H_5CO-), 5.80 (1H, s, 3'-OH), 4.87 (1H, q, J=9 Hz, H1'), 3.65 (2H, s, $-CH_2Cl$), 2.82 (2H, t, J=9 Hz, H2'a, H4'a), 2.70 (2H, t, J=9 Hz, H2'b, H4'b). MS *m/z* 341,343 (M^+-16).

N^6-Benzoyl-9-[3-(acetyloxymethyl)-2-cyclobutenyl]adenine (15). Anhydrous sodium acetate (200 mg, 2.44 mmol) and sodium iodide (190 mg, 1.27 mmol) was added to a solution of **13** (280 mg, 0.82 mmol) in DMF (15 ml) and the mixture was stirred for 5 h at 50° , then cooled. The solution was poured into satd. NaCl solution and the aqueous solution was extracted four times with AcOEt (200 ml). The combined organic layer was dried over $MgSO_4$, concentrated to a small volume, and chromatographed on a column of silica gel 60 (ϕ 2.6 X 30 cm) with a gradient of 0-2% EtOH in $CHCl_3$ (1.6 l) to afford a foam (192.3 mg, 67%). UV: λ max(MeOH) 281nm. ^{1}H NMR ($CDCl_3$) δ : 9.02 (1H, br s, N^6-H), 8.82 (1H, s, H8), 8.08 (1H, s, H2), 7.45 - 8.1 (5H, m, C_6H_5CO-), 6.26 (1H, m, H2'), 5.60 (1H, m, H1'), 4.74 (2H, br s, -CH_2O-), 3.36 (1H, m, J= 13.4 Hz, H4'a), 2.72 (1H, m, H4'b), 2.15 (3H, s, 3'-$OCOCH_3$).

9-[3-(Hydroxymethyl)cyclobutenyl]adenine (5). A solution of **15** (192.3 mg, mmol) in 0.02M NaOMe in MeOH (15 ml) was kept for 5 h at 50° , then cooled. The solution was treated in the same manner as described for **3** to give white crystals (24.9 mg, 21%). mp 250° (dec.). UV: λ max (MeOH) 261nm. MS:*m/z* 217 (M^+), 200 (M^+-OH), 186 (M^+- CH_2OH). HR-MS Calcd. for $C_{10}H_{11}N_5O$: *m/z* 217.0964. Found: *m/z* 217.0962. ^{1}H NMR (10% DMSO-d_6) δ : 8.13 (1H, s, H8), 8.10 (1H, s, H2), 7.20 (2H, br s, 6-NH_2), 6.17 (1H, s, H2'), 5.28 (1H, m, H1'), 5.01 (1H, m, 3'-CH_2OH), 4.05 (2H, m, 3'-CH_2OH), 3.07 (1H, J = 13.2 Hz, H4'a), 2.63 (1H, d, J = 13.2 Hz, H4'b).

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