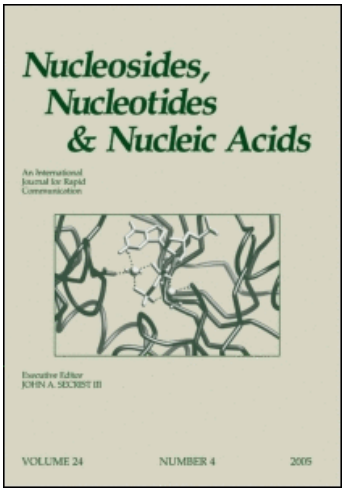

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Synthesis and Biological Evaluation of 9-(f-2, c-3-Bishydroxymethyl-r-cyclopropylmethyl)-9H-adenine (A Lower Methylene Homolog of Carbocyclic Oxetanocin) and Related Compounds

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SYNTHESIS AND BIOLOGICAL EVALUATION OF 9-(*t*-2, *c*-3-BISHYDROXYMETHYL-*r*-1-CYCLOPROPYLMETHYL)-9*H*-ADENINE (A LOWER METHYLENE HOMOLOG OF CARBOCYCLIC OXETANOCIN) AND RELATED COMPOUNDS.[1)]

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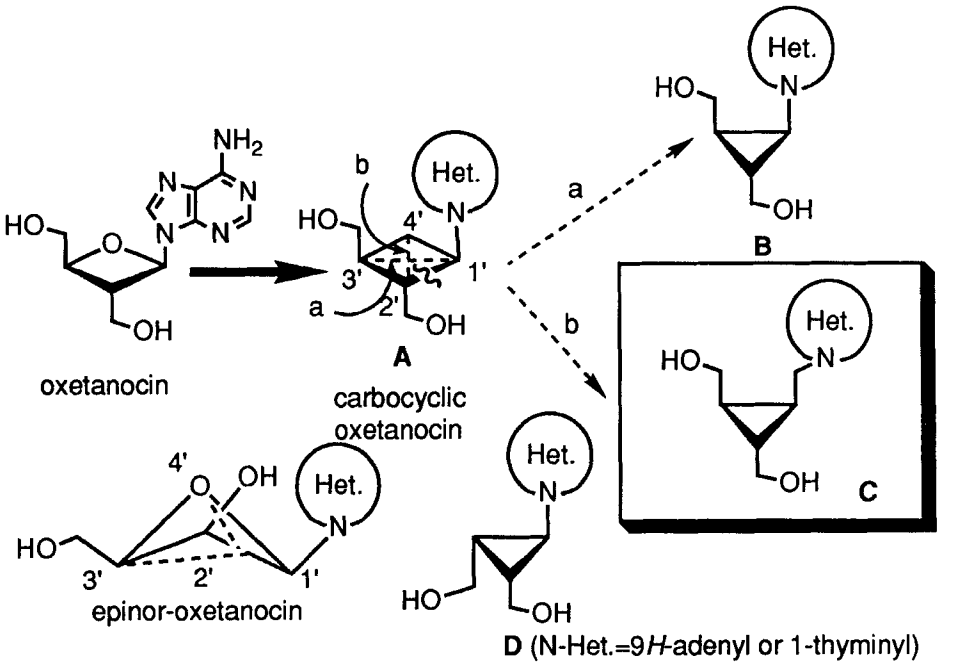
ABSTRACT: Adenine (**7** and **16**), thymine (**9a** and **18a**), and 5-fluorouracil (**9b** and **18b**) involving *t*-2, *c*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl- and *t*-2, *t*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl residues were synthesized, starting from *trans*-1,4-dibenzyloxy-2-butene and its *cis* isomer, respectively. These compounds were evaluated for anti HSV-1 activity.

Since oxetanocin [2,3,4)] isolated from a strain of *Bacillus megaterium* was found to possess significant biological activity, syntheses and biological evaluations of its analogues have been extensively studied. [5-12)] As a result, the carbocyclic analogue (**A**) was found to show, just as with oxetanocin itself, significant antiviral activity.[12)] Previously, we reported the highly stereoselective synthesis of carbocyclic analogue (**A**) of oxetanocin from 2-azabicyclo[2.2.0]-hex-5-en-3-one (a so-called photopyridone) by means of a regioselective amidobond cleavage reaction followed by an alkaline-mediated inversion reaction as the key steps.[13)] In order to clarify the structure-activity relationship between oxetanocin and its related compounds, we have synthesized 9-(*t*-2, *c*-3-bishydroxymethyl-*r*-1-cyclopropyl)-9*H*-adenine and related compounds (**B**) which correspond to lower methylene homologues of carbocyclic oxetanocin (cf. division of the cyclobutane ring along **a** in Scheme 1), and found that the *cis* isomers (**D**) show antiviral activity against BLV(bovine leukemia virus).[14)]

This paper is dedicated to the memory of the late Professor Tohru Ueda.

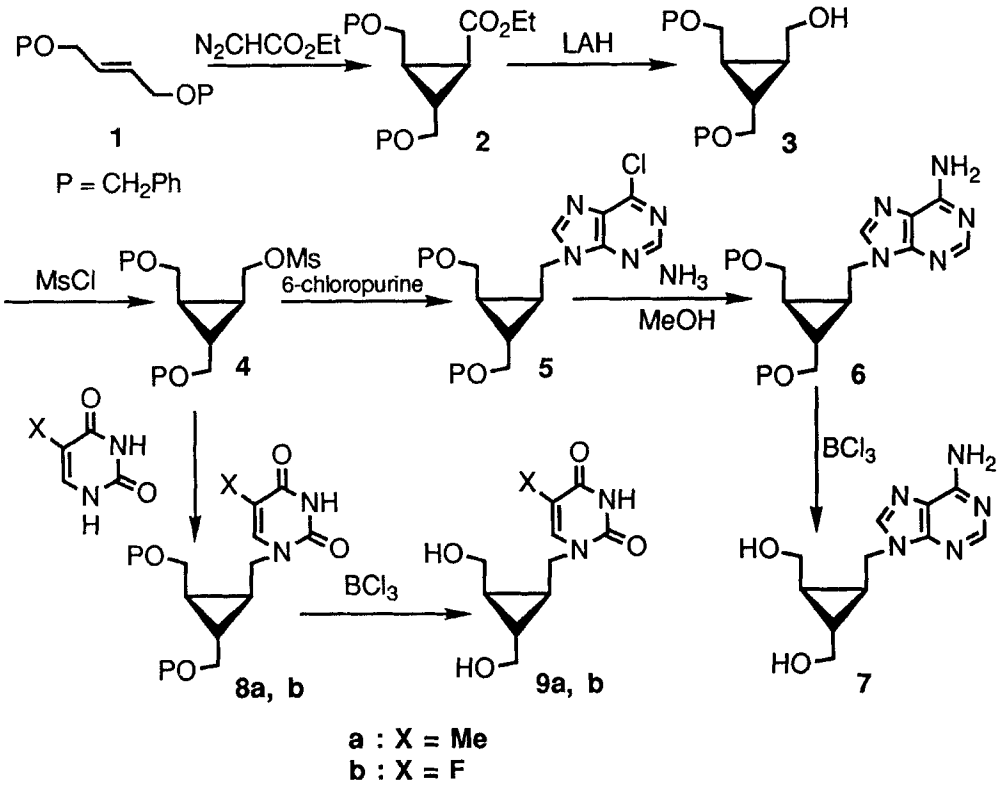


Scheme 1

The activity might be due to the fact that these isomers (**D**) have three heteroatoms in nearly the same space as epinor-oxetanocin[15] which exhibits significant antiviral activity (Noted that, taking a plane of $C_{3'}$, $C_{4'}$ and the midpoint of $C_{1'}$-$C_{2'}$ in epinor-oxetanocin, two oxygen atoms occupy the same side of the plane and an opposite side of the adenine ring).

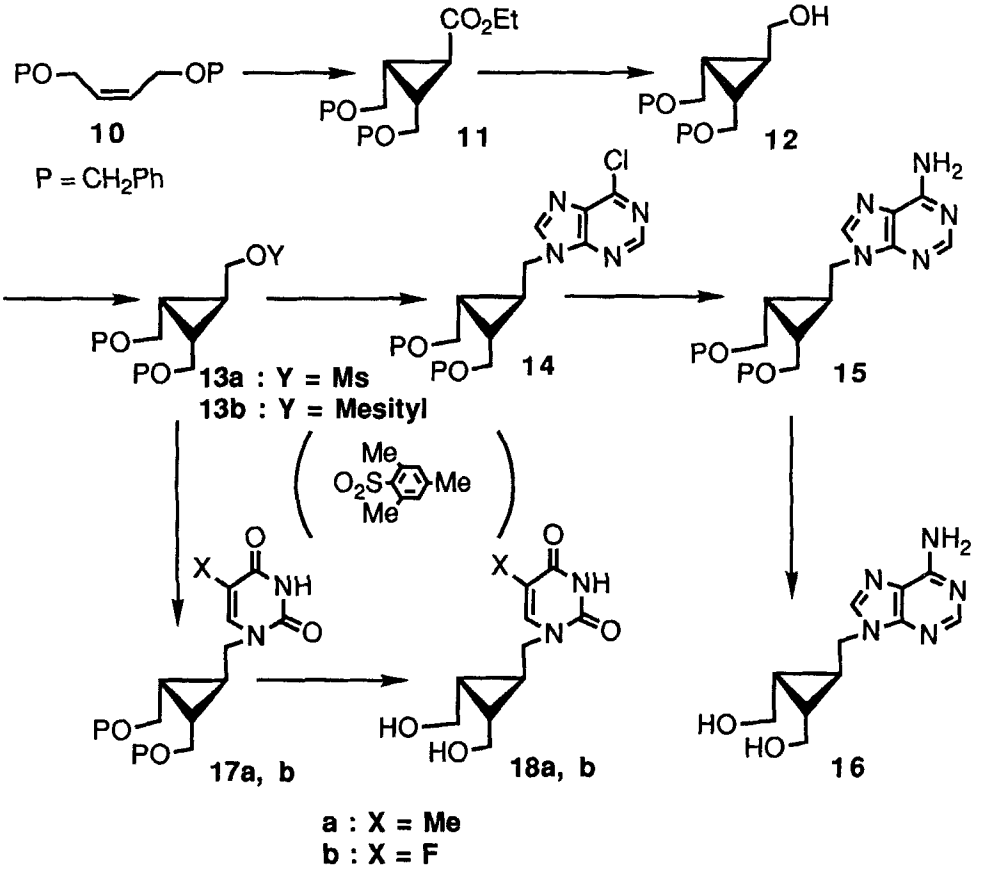
In connection with our continuing interest in the synthesis and biological activity of oxetanocin analogues, we now wish to report the synthesis and biological evaluation of 9-(*t*-2, *c*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl)-9*H*-adenine and related compounds (**C**)[16] which correspond to the ones formed by division along **b** followed by cleavage of the $C_{1'}$-$C_{2'}$ bond (Scheme 1) from carbocyclic oxetanocin.

We initially chose *trans*-1,4-dibenzyloxy-2-butene (**1**) as a starting material in order to construct a cyclopropylmethyl moiety. When **1** was allowed to react with ethyl diazoacetate in the presence of copper without solvent at 110 °C, a cyclopropane derivative **2** was obtained as a sole product in 34% yield.[14] The usual reduction of **2** with lithium aluminum hydride (LAH) in THF afforded



Scheme 2

an alcohol **3** in 58% yield. Mesylation of **3** with methanesulfonyl chloride in the presence of triethylamine afforded the *O*-mesyl derivative **4**. Since compound **4** was not stable enough to be purified by silica gel column chromatography, the crude **4** was directly treated with 6-chloropurine in the presence of sodium hydride in *N*,*N*-dimethylformamide (DMF). However, the reaction gave a complex mixture and the desired compound **5** was not detected. When the reaction was carried out in the presence of potassium carbonate and 18-crown-6 in (DMF) at 110 °C, **5** was obtained in 36% yield. Ammonolysis of **5** with a solution of ammonia in methanol gave an adenine derivative **6**, together with a 6-methoxypurine derivative as a by-product. According to our previous report,[14] deprotection of the benzyl group of **6** by boron trichloride was carried out. However, the monobenzyl derivative was obtained as a sole product, instead of the desired compound. The desired cyclopropylmethyl adenine



Scheme 3

derivative **7** was obtained from the monobenzyl derivative, however, by catalytic hydrogenolysis with $Pd(OH)_2/C$.

Using a similar way, introduction of thymine and 5-fluorouracil into **4** was carried out to give **8a, b**. Deprotection of **8a, b** with boron trichloride afforded the cyclopropylmethyl derivatives (**9a,b**).

In a similar manner, adenine (**16**), thymine (**18a**), and 5-fluorouracil (**18b**) involving *t*-2, *t*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl residue were obtained from *cis*-1,4-dibenzyloxy-2-butene (**10**) as a starting material. Though condensation of **13a** with 6-chloropurine afforded **14** in a low yield (14%), the yield was improved appreciably (47%) by the utilization of the mesitylene-sulfonyl group instead of the methanesulfonyl group as a leaving group.

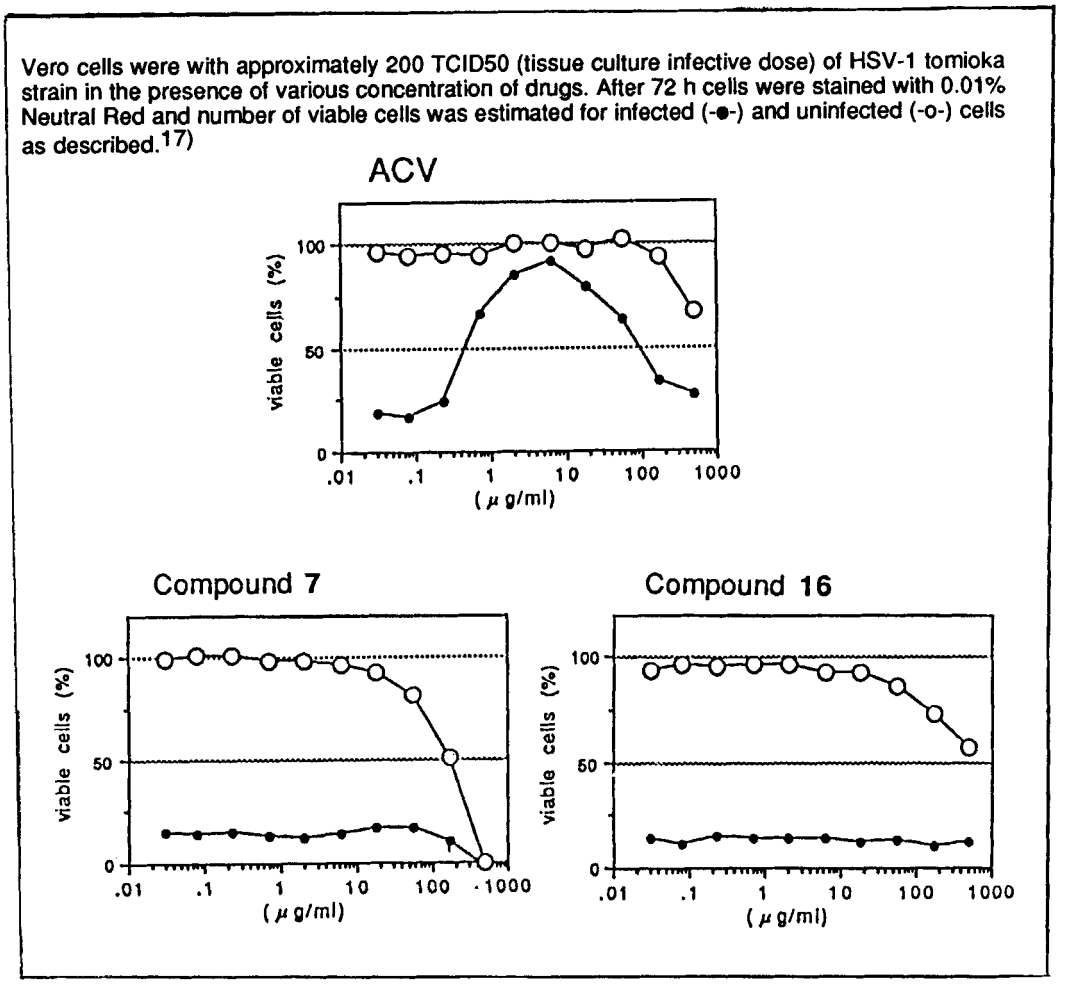


Fig. 1 Antiherpes Virus Activitiy of Nucleic Acid Bases (**7**, **9a**, **b**, **16**, and **18a**, **b**) Involving Cyclopropylmethyl moiety.

All compounds (**7**, **9a**, **b**, **16**, and **18a**, **b**) thus obtained were tested for anti HSV-1 activity. None of them exhibited any inhibitory activity up to 100 μg/ml concentrations. However, some cytotoxity was observed in compound **7**. The results for biological evaluation of **7** and **16** are shown in Fig 1, together with anti HSV-1 activity of ACV (Acyclovir). Evaluation for anti HIV activity of these compounds is in progress.

EXPERIMENTAL

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer and proton nuclear magnetic resonance (^{1}H-NMR) spectra on a JEOL JNM-PMX 60 SI or JEOL JNM-FX 500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a JEOL JMS-01SG-2 or JEOL JMS-DX 303 spectrometer. Column chromatography was performed on silica gel (Wakogel C-200) and TLC on Merck Kieselgel 60F_{254}.

General Procedure for the Preparation of Alcohols (3 and 12)

A solution of **2** or **11** (310 mg, 0.88 mmol) in anhydrous THF (5 ml) was added dropwise to a suspension of $LiAlH_4$ (38 mg, 1 mmol) in anhydrous THF (10 ml) with stirring at room temperature. After being refluxed for 4 h, water was added portionwise to the reaction mixture until evolution of hydrogen gas ceased. The resulting precipitate was dissolved by addition of 10% H_2SO_4. The clear solution was condensed under reduced pressure to give a residue, to which water was added. The mixture was extracted with Et_2O. The ethereal layer was dried (Na_2SO_4) and the solvent was removed. The residue was chromatographed over a silica gel (31 g) column with hexane-AcOEt (2:1) to give **3** (162 mg, 58%) or **12** (170 mg, 61%) as a colorless oil. Physical data for *t*-2,*c*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethanol (**3**): High resolution MS *m/z* Calcd for $C_{20}H_{25}O_3$ (M^++H): 313.1804. Found: 313.1784. IR ($CHCl_3$): 3500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (1H, m, C_1-H), 1.30 (2H, m, C_2-, C_3-H), 1.60 (1H, br s, CH_2OH), 3.20, 3.24 (each 1H, d, *J*=10 Hz, CH_2OH), 3.32, 3.41(each 1H, dd, *J*=10, 7 Hz, CH_2OBn), 3.92, 3.96 (each 1H, dd, *J*= 10, 6 Hz, CH_2OBn), 4.50 (2H, s, CH_2Ph), 4.51, 4.56 (each 1H, d, *J*=12 Hz, CH_2Ph), 7.30 (10H, m, 2xPh). Physical data for *t*-2,*t*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethanol (**12**): High resolution MS *m/z* Calcd for $C_{20}H_{25}O_3$ (M^++H): 313.1804. Found: 313.1836. IR ($CHCl_3$): 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, m, C_1-, C_2-, C_3-H), 2.98 (1H, br s, CH_2OH), 3.46, 3.49 (each 1H, dd, *J*=7, 3 Hz, CH_2OH), 3.66, 3.69 (each 2H, dd, *J*=5, 2 Hz, 2xCH_2OBn), 4.50, (4H, s, 2xCH_2Ph), 7.35 (10H, m, 2xPh).

General Procedure for the Condensation of Methanesulfonates (4 and 13a) with 6-Chloropurine

Methanesulfonyl chloride (MsCl)(138 mg, 1.2 mmol) was added portionwise to a solution of **3** or **12** (312 mg, 1 mmol) and Et_3N (121 mg, 1.2 mmol) in dry CH_2Cl_2 (10 ml) with stirring under ice-cooling. After being stirred for 1 h, the solvent was removed under reduced pressure to give a residue, which was

dissolved in dry DMF (10 ml). A solution of 6-chloropurine (308 mg, 2 mmol), K_2CO_3 (276 mg, 2 mmol), and 18-crown-6 (264 mg, 1 mmol) in dry DMF (10 mg) was added to the solution with stirring. The mixture was warmed at 60 °C with stirring for 11 h. The solvent was removed under reduced pressure. The residue was chromatographed over a silica gel (50 g) column with hexane-AcOEt (1:1) to give **5** (160 mg, 36%) or **14** (62 mg, 14%) as a colorless oil. Physical data for 6-Chloro-9-(*t*-2, *c*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)purine (**5**) : High resolution MS *m/z* Calcd for $C_{18}H_{18}ClN_4O_2$ (M^+-Bn): 357.1118. Found: 357.1114. ^{1}H-NMR ($CDCl_3$) δ: 1.31-1.53 (3H, m, C_1-, C_2-, C_3-H), 3.30-3.93 (4H, m, 2xCH_2OBn), 4.33 (2H, m, CH_2N-), 4.43, 4.47 (each 2H, s, 2xCH_2Ph), 7.30 (10H, s, 2xPh), 8.47, 8.70 (each 1H, s, C_2-, C_8-H). Physical data for 6-Chloro-9-(*t*-2, *t*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)purine (**14**) High resolution MS *m/z* Calcd for $C_{18}H_{18}ClN_4O_2$ (M^+-Bn): 357.1118. Found: 357.1090. ^{1}H-NMR ($CDCl_3$) δ: 1.07-1.57 (3H, m, C_1-, C_2-, C_3-H), 3.47 (4H, m, 2xCH_2OBn), 4.20 (2H, d, *J*=7 Hz, CH_2N-), 4.43 (4H, s, 2xCH_2Ph), 7.23 (10H, s, 2xPh), 8.47, 8.70 (each 1H, s, C_2-, C_8-H).

***t*-2, *t*-3-Bisbenzyloxymethyl-*r*-1-cyclopropylmethanol *O*-Mesitylenesulfonate (13b)**

To a solution of **12** (100 mg, 0.32 mmol) in dry CH_2Cl_2 (5 ml) were added successively Et_3N (48 mg, 0.48 mmol) and mesitylenesulfonyl chloride (105 mg, 0.48 mmol) with stirring at room temperature. After being stirred for 5 days, the solvent was evaporated off under reduced pressure to give a residue, which was subjected to silica gel (10 g) column chromatography. Elution with hexane-AcOEt (4:1) gave **13b** (108 mg, 68%) as a coloress oil. Physical data for **13b**: High resolution MS *m/z* Calcd for $C_{29}H_{34}O_5S$(M^+): 494.427. Found: 494.427.^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, m, C_1-, C_2-, C_3-H), 2.27 (3H, s, Me), 2.60 (6H, s, 2xMe), 3.40 (4H, dd, *J*=5, 2 Hz, CH_2OBn), 3.87 (2H, dd, *J*=5, 2 Hz, CH_2OSO_2-), 4.40 (4H, s, 2xCH_2Ph), 6.83 (2H, s, aromatic-H), 7.20 (10H, s, 2xPh).

Preparation of 14 from 13b

To a solution of **13b** (320 mg, 0.65 mmol) in DMF (10 ml) were added successively 6-chloropurine (300 mg, 1.94 mmol), K_2CO_3 (449 mg, 3.25 mmol), and 18-crown-6 (512 mg, 1.94 mmol) with stirring at 60 °C. The solvent was evaporated off under reduced pressure to give a residue, which was subjected to silica gel (32 g) column chromatography. Elution with hexane-AcOEt (1:1) gave **14** (137 mg, 47%) as a colorless oil.

General Procedure for the Ammonolysis of 5 and 14

Ammonia gas was passed over a solution of **5** or **14** (1.12 mmol) in abs. MeOH (20 ml) under ice-salt cooling for 1 h. The mixture was heated in a sealed tube at 90 °C for 12 h, and condensed under reduced pressure to give an oily residue.The residue was chromatographed over a silica gel (50 g) column with $CHCl_3$-MeOH (25:1) to give **6** (395 mg, 82%) as a colorless oil or **15** (370 mg, 77%) as colorless columns (mp 139-140 °C from EtOAc). Physical data for 9-(*t*-2, *c*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)-9*H*-adenine (**6**): High resolution MS *m/z* Calcd for $C_{18}H_{20}N_5O_2$ (M^+-Bn): 338.1621. Found: 338.1617. IR ($CHCl_3$): 3550, 3500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (1H, quint., *J*=7 Hz, $C_{1'}$-H), 1.34-1.44 (2H, m, $C_{2'}$-, $C_{3'}$-H), 3.33 (1H, dd, *J*=10, 7 Hz, 3'-CH*H*OBn), 3.44 (2H, m, 2'-CH_2OBn), 3.83 (1H, dd, *J*=10, 5 Hz, 3'-C*H*HOBn), 4.22, 4.27 (each 1H, dd, *J*=10, 5 Hz, CH_2N-), 4.45 (2H, s, CH_2Ph), 4.44, 4.55 (each 1H, d, *J*=13 Hz, CH_2Ph), 5.70 (2H, br s, NH_2), 7.30 (10H, m, 2xPh), 8.14, 8.38 (each 1H, s, C_2-, C_8-H). Physical data for 9-(*t*-2, *t*-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)-9*H*-adenine (**15**): *Anal.* Calcd for $C_{25}H_{27}N_5O_2$: C, 69.80; H, 6.34; N, 16.30. Found: C, 69.55; H, 6.31; N, 16.27. IR ($CHCl_3$): 3450, 1640 cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 1.54-1.64 (3H, m, $C_{1'}$-, $C_{2'}$- $C_{3'}$-H), 3.56 (2H, dd, *J*=10, 8 Hz, 2xC*H*HOBn), 3.73 (2H, dd, *J*= 10, 7 Hz, 2xCH*H*OBn), 4.28 (2H, d, *J*=7 Hz, CH_2N-), 4.48 (4H, s, 2xCH_2Ph), 5.95 (2H, br s, NH_2), 7.30 (10H, m, 2xPh), 8.08, 8.34 (each 1H, s, $C_{2'}$-, C_8-H).

General Procedure for the Deprotection of 6 and 15

A 1M solution of BCl_3 in CH_2Cl_2 (6.5 g, 4.4 mmol) was added dropwise to a solution of **6** or **15** (280 mg, 0.65 mmol) in dry CH_2Cl_2 (30 ml) at -78 °C under a N_2 atmosphere with stirring. After being stirred for 2 h, a mixture of dry CH_2Cl_2 (10 ml) and abs. MeOH (10 ml) was added to the reaction mixture. The reaction temperature was raised gradually to room temperature. The solvent was removed under reduced pressure to give a residue, which was dissolved again in abs. MeOH (10 ml). The solvent was evaporated again under reduced pressure. This treatment was repeated four times. The resulting residue was chromatographed over a silica gel (28 g) column with $CHCl_3$-MeOH (8:1) to give a crystalline substance (135 mg, 61%), whose ^{1}H-NMR spectrum revealed that the compound was a mixture of 2-benzyloxymethyl- and 3-benzyloxymethyl derivatives. A mixture of monobenzyl derivative (60 mg, 0.176 mmol), 20% $Pd(OH)_2$/C (30 mg), and $CHCl_3$ (0.3 ml) in abs. MeOH (10 ml) was shaken in a hydrogen atmosphere at room temperature for 5 h. Since the starting material still remained, 20% $Pd(OH)_2$/C (20 mg) and $CHCl_3$ (0.3 ml) were added again

to the reaction mixture. Shaking was continued for further 5 h. The resulting reaction mixture was filtered through celite. The filtrate was condensed under reduced pressure to give a residue, which was subjected to silica gel (12 g) column chromatography. Elution with $CHCl_3$-MeOH (5:1) gave **7** (43 mg, quant.) or **16** (43 mg, quant.) as a crystalline substance. Due to their instability, both **7** and **16** were not purified by recrystallization. Physical data for 9-(*t*-2, *c*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl)-9*H*-adenine (**7**): High resolution MS *m/z* Calcd for $C_{11}H_{15}N_5O_2$ (M^+): 249.1226. Found: 249.1266. UV (MeOH) λmax nm: 260, ^{1}H-NMR (CD_3OD) δ: 0.96-1.40 (3H, m, $C_{1'}$-, $C_{2'}$-, $C_{3'}$-H), 3.38 (1H, dd, *J*=12, 8 Hz, CH*H*OH), 3.51 (1H, dd, *J*=12, 6 Hz, C*H*HOH), 3.60 (1H, dd, *J*=12, 10 Hz, C*H*HOH), 3.94 (1H, dd, *J*=12, 6 Hz, CH*H*OH), 4.34 (2H, d, *J*=8 Hz, CH_2N-), 8.20, 8.32 (2H, each s, purine-H). Physical data for 9-(*t*-2, *t*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl)-9*H*-adenine (**16**): High resolution MS *m/z* Calcd for $C_{11}H_{15}N_5O_2$ (M^+): 249.1226. Found: 249.1231. UV (MeOH) λmax nm: 260, ^{1}H-NMR (CD_3OD) δ: 0.94-1.40 (3H, m, $C_{1'}$-, $C_{2'}$-, $C_{3'}$-H), 3.52 (2H, ddd, *J*=12, 7, 2 Hz, 2xCH*H*OH), 3.66 (2H, ddd, *J*=12, 7, 2 Hz, 2xC*H*HOH), 4.18 (2H, d, *J*=7 Hz, CH_2N-), 8.26, 8.20 (2H, each s, purine-H).

General Procedure for Condensation of 4 and 13a with Thymine and 5-Fluorouracil.

Methanesulfonyl chloride (529 mg, 4.46 mmol) was added dropwise to a solution of alcohol (**3** or **12**, 964 mg, 3.09 mmol), and Et_3N (469 mg, 4.64 mmol) with stirring under ice-cooling. The mixture was stirred for 1 h, and condensed under reduced pressure. The residue was dissolved in dry DMF (20 ml). A solution of thymine or 5-fluorouracil (7.19 mmol), K_2CO_3 (992 mg, 7.19 mmol), and 18-crown-6 (816 mg, 3.09 mmol) in dry DMF (10 ml) was added to the above solution with stirring. The mixture was warmed with stirring at 60 °C for 20 h. The solvent was removed under reduced pressure to give a residue, which was subjected to silica gel (120 g) column chromatography. Elution with hexane-AcOEt (1:1) gave **8a** (700 mg, 52%), **8b** (283 mg, 21%) and **17a** (377 mg, 28%), **17b** (377 mg, 28%) as a colorless oil. Physical data for 1-(*t*-2, *c*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)thymine (**8a**): High resolution MS *m/z* Calcd for $C_{18}H_{21}N_2O_4$ (M^+-Bn): 329.1501. Found: 329.1480. IR ($CHCl_3$): 3400, 1715, 1680, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17-1.40 (3H, m, C_1-, C_2-, C_3-H), 1.73 (3H, d, *J*=1 Hz, C_5-Me), 3.40-4.20 (6H, m, 2xCH_2OBn, CH_2N-), 4.47, 4.49 (each 2H, s, 2xCH_2Ph), 7.33 (11H, s, 2xPh, C_6-H), 8.67 (1H, br s, N*H*). Physical data for 1-(*t*-2, *c*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)-5-fluorouracil (**8b**): High resolution MS *m/z* Calcd for $C_{17}H_{18}FN_2O_3$ (M^+-OBn):

317.1304. Found: 317.1302. IR ($CHCl_3$): 3400, 1700, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07-1.37 (3H, m, $C_{1'}$-, $C_{2'}$-, $C_{3'}$-H), 3.10-3.77 (6H, m, 2xCH_2OBn, CH_2N-), 4.47, (4H, s, 2xCH_2Ph), 7.20 (10H, s, 2xPh,), 7.67 (1H, d, *J*=6 Hz, C_6-H), 9.37 (1H, br s, N*H*). Physical data for 1-(*t*-2, *t*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)thymine (**17a**): High resolution MS *m/z* Calcd for $C_{18}H_{21}N_2O_4$ (M^+-Bn): 329.1501. Found: 329.1480. IR ($CHCl_3$): 3300, 1700, 1680, cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93-1.47 (3H, m, $C_{1'}$-, $C_{2'}$-, $C_{3'}$-H), 1.77 (3H, s, C_5-H), 3.40-3.67 (6H, m, 2xCH_2OBn, CH_2N-), 4.43 (4H, s, 2xCH_2Ph), 7.23 (11H, s, 2xPh, C_6-H), 9.40 (1H, br s, N*H*). Physical data for 1-(*t*-2, *t*-3-bisbenzyloxymethyl-*r*-1-cyclopropylmethyl)-5-fluorouracil (**17b**): High resolution MS *m/z* Calcd for $C_{17}H_{18}FN_2O_3$ (M^+-OBn): 317.1290. Found: 317.1302. IR ($CHCl_3$): 3300, 1700, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93-1.47 (3H, m, $C_{1'}$-, $C_{2'}$-, $C_{3'}$-H), 3.27-3.67 (6H, m, 2xCH_2Ph), 7.23 (10H, s, 2xPh), 9.63 (1H, br s, N*H*).

General Procedure for Deprotection of 8a, b and 17a, b.

A 1M solution (11.9 g, 17.9 mmol) of BCl_3 in CH_2Cl_2 was added dropwise to a solution of **8a, b** or **17a, b** (150 mg, 0.36 mmol) in dry CH_2Cl_2 (10 ml) in a N_2 atmosphere with stirring at -78 °C. After being stirred for 2.5 h at -78 °C, a mixture of dry CH_2Cl_2 (10 mmol) and abs. MeOH (10 ml) was added to the reaction mixture. The reaction temperature was raised gradually to room temperature. The solvent was removed under reduced pressure to give a residue, which was dissolved in abs. MeOH (10 ml). The solvent was evaporated again under reduced pressure. This manipulation was repeated four times. The residue thus obtained was subjected to silica gel (15 g) column chromatography. Elution with $CHCl_3$-MeOH (8:1) gave **9a** (36 mg, 42%), **9b** (52 mg, 61%) and **18a** (52 mg, 61%), **18b** (46 mg, 54%) as colorless oil. Physical data for 1-(*t*-2, *c*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl)thymine (**9a**): High resolution MS *m/z* Calcd for $C_{11}H_{16}N_2O_4$ (M^+): 240.1110. Found: 240.1124. UV (MeOH) λmax nm: 270. ^{1}H-NMR (CD_3OD) δ: 1.05 (1H, m, $C_{1'}$-H), 1.21 (2H, m, $C_{2'}$-, $C_{3'}$-H), 1.88 (3H, s, C_5-Me), 3.37 (1H, dd, *J*=11, 8 Hz, C*H*HOH), 3.55 (2H, dd, *J*=12, 7 Hz, CH_2N-), 3.78 (1H, dd, *J*=14, 7 Hz, CH*H*OH), 3.86 (1H, dd, *J*=11, 5 Hz, C*H*HOH), 3.96 (1H, dd, *J*=14, 7 Hz, CH*H*OH), 7.60 (1H, s, C_6-H). Physical data for 1-(*t*-2, *c*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl)-5-fluoro-uracil (**9b**): High resolution MS *m/z* Calcd for $C_{10}H_{13}FN_2O_4$ (M^+): 244.0859. Found: 244.0874. UV (MeOH) λmax nm: 272. ^{1}H-NMR (CD_3OD) δ: 1.04-1.22 (3H, m, $C_{1'}$-, $C_{2'}$-, $C_{3'}$-H), 3.36 (1H, dd, *J*=12, 8 Hz, C*H*HOH), 3.48 (1H, dd, *J*=12, 9 Hz, CH*H*OH), 3.54 (1H, dd, *J*=14, 7 Hz, C*H*HOH-), 3.80 (1H, dd, *J*=14, 7 Hz, C*H*HN-), 3.88 (1H, dd,

J=14, 7 Hz, CH*H*N-), 3.89 (1H, dd, *J*=12, 5 Hz, C*H*HOH), 8.02 (1H, d, *J*=7 Hz, C_6-H). Physical data for 1-(*t*-2, *t*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl)-thymine (**18a**): High resolution MS *m/z* Calcd for $C_{11}H_{16}N_2O_4$ (M^+): 240.1110. Found: 240.1122. UV (MeOH) λmax nm: 271. ^{1}H-NMR (CD_3OD) δ: 0.94-1.42 (3H, m, $C_{1'}$-, $C_{2'}$-, $C_{3'}$-H), 1.89 (3H, s, C_5-Me), 3.33 (2H, t, *J*=11 Hz, CH_2N-), 3.52 (2H, ddd, *J*=11, 5, 2 Hz, 2xCH*H*OH), 3.68 (2H, ddd, *J*=11, 5, 2 Hz, C*H*HOH), 7.51 (1H, s, C_6-H). Physical data for 1-(*t*-2, *t*-3-bishydroxymethyl-*r*-1-cyclopropylmethyl)-5-fluoro-uracil (**18b**): High resolution MS *m/z* Calcd for $C_{10}H_{13}FN_2O_4$ (M^+): 244.0859. Found: 244.0874. UV (MeOH) λmax nm: 272. ^{1}H-NMR (CD_3OD) δ: 1.13 (1H, m, $C_{1'}$-H), 1.31 (2H, m, $C_{2'}$-, $C_{3'}$-H), 3.44 (2H, d, *J*=7 Hz, CH_2N-), 3.54 (2H, dd, *J*=12, 7 Hz, 2xC*H*HOH), 3.66 (2H, t, *J*=7 Hz, 2xCH*H*OH), 7.92 (1H, d, *J*=6 Hz, C_6-H).

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REFERENCES AND NOTES

1. Part 24 in the series "Synthesis of Nucleosides and Related Compounds". For Part 23, see N. Katagiri, M. Nomura, H. Sato, C. Kaneko, K. Yusa, and T. Tsuruo, *J. Med. Chem.*, submitted.
2. Isolation and structure determination: N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujita, and T. Takita, *J. Antibiot.*, **39**, 1623 (1986); H. Nakamura, S. Hasegawa, N. Shimada, A. Fujii, T. Takita, and I. Yoichi, *ibid.*, **39**, 1626 (1986).
3. Synthesis: a) S. Niitsuma, Y. Ichikawa, K. Kato, and T. Takita, *Tetrahedron Lett.*, **28**, 3967 (1987); *idem*, *ibid.*, **28**, 4713 (1987); b) D. W. Norbeck and J. B. Krammer, *J. Am. Chem. Soc.*, **110**, 7217 (1988). S. Nishiyama, S. Yamamura, K. Kato, and T. Takita, *Tetrahedron Lett.*, **29**, 4739, 4743 (1988). R. Hambalek and G. Just, *ibid.*, **31**, 5445 (1990). F. X. Wilson, G. W. J. Fleet, K. Vogt, Y. Wang, D. R. Witty, S. Choi, R. Storer, P. L. Myers, and C. J. Wallis, *ibid.*, **31**, 6931 (1990).
4. Biological activities: H. Hoshino, N. Shimizu, N. Shimada, T. Takita, and T. Takeuchi, *J. Antibiot.*, **40**, 1077 (1987). See also, N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii, and T. Takita, *ibid.*, **39**, 1623 (1986).

5. F. X. Wilson, G. W. J. Fleet, D. R. Witty, K. Vogt, Y. Wang, R. Storer, P. L. Myers, and C. J. Wallis, *Tetrahedron: Asymmetry*, **1**, 525 (1990).
6. Y. Wang, G. W. J. Feet, R. Storer, P. L. Myers, C. J. Wallis, O. Doherty, D. J. Watkin, K. Vogt, D. R. Witty, F. X. Wilson, and J. M. Peach, *Tetrahedron: Asymmetry*, **1**, 527 (1990).
7. M. Honjo, T. Maruyama, Y. Sato, and T. Horii, *Chem. Pharm. Bull.*, **37**, 1413 (1989).
8. Y. Ichikawa, A. Narita, A. Shiozawa, Y. Hayashi, and K. Narasaka, *J. Chem. Soc., Chem. Commun.*, **1989**, 1919.
9. W. A. Slusarchyk, M. G. Young, G. S. Bisacchi, D. R. Hockstein, and R. Zahler, *Tetrahedron Lett.*, **30**, 6453 (1989).
10. G. A. Jacobs, J. A. Tino, and R. Zahler, *Tetrahedron Lett.*, **30**, 6955 (1989).
11. C.-N. Hsiao and S. M. Hannick, *Tetrahedron Lett.*, **31**, 6609 (1990).
12. D. W. Norbeck, E. Kern, S. Hayashi, W. Rosenbrook, H. Sham, T. Herrin, J. J. Plattnen, J. Erickson, J. Clement, R. Swanson, N. Shipkowitz, D. Hardy, K. Marsh, G. Arnett, W. Shannon, S. Broder, and H. Mitsuya, *J. Med. Chem.*, **33**, 1285 (1990).
13. N. Katagiri, H. Sato, and C. Kaneko, *Chem. Pharm. Bull.*, **38**, 288 (1990).
14. N. Katagiri, H. Sato, and C. Kaneko, *Chem. Pharm. Bull.*, **38**, 3184 (1990).
15. S. Nishiyama, T. Ohgiya, S. Yamamura, K. Kato, M. Nagai, and T. Takita, *Tetrahedron Lett.*, **31**, 705 (1990).
16. 9-(Cyclopropylmethyl)-9*H*-adenines were for the first time prepared by Ashton and his coworkers. However, 9-(2,3-bishydroxymethyl-cyclopropylmethyl)-9*H*-adenine is not hitherto synthesized. W. T. Ashton, L. C. Meurer, C. L. Cantone, A. K. Field, J. Hannah, J. D. Karkas, R. Liou, G. F. Patel, H. C. Perry, A. F. Wagnen, E. Walton, and R. L. Tolman, *J. Med. Chem.*, **31**, 2304 (1988).
17. M. Langlosis, J. P. Allard, F. Nugier, and M. Aymard, *J. Biol. Stand.*, **14**, 201 (1986).

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