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Studies on Griseolic Acid Derivatives. VII.[1] Synthesis and Phosphodiesterase Inhibitory Activity of the $C^{4'}$–$C^{5'}$ Hydrogenated Products of Griseolic Acid and Their Base-Exchanged Derivatives

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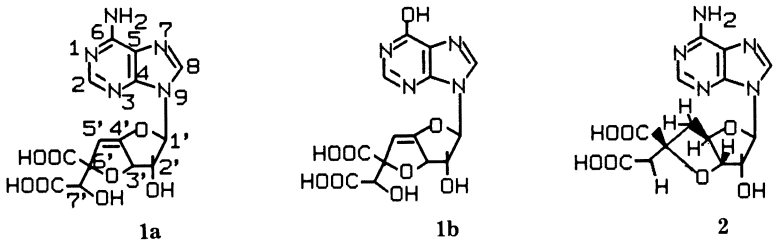
Addition reactions of the $C^{4'}$–$C^{5'}$ double bond of griseolic acid were investigated. $C^{4'}$–$C^{5'}$ Dihydrogriseolic acid was obtained by reduction of the adduct having halogen at the 4′-position. The ring juncture of the two five-membered rings of the $C^{4'}$–$C^{5'}$ dihydro derivatives was of all-"*cis*" configuration. Acetolysis of the protected dihydrogriseolic acid gave the corresponding 1′-acetoxy sugar derivative. Reaction of this sugar derivative with silylated bases gave guanine and uracil derivatives of the dihydrogriseolic acid. The cyclic nucleotide phosphodiesterase (PDE)-inhibitory activity of the $C^{4'}$–$C^{5'}$ *cis* dihydrogriseolic acid derivative was weaker than that of griseolic acid. The uracil derivative of $C^{4'}$–$C^{5'}$ *cis* dihydrogriseolic acid completely lost the inhibitory activity against both adenosine 3′,5′-cyclic monophosphate (cAMP) and guanosine 3′,5′-cyclic monophosphate (cGMP) PDE, whereas the guanine derivative showed reduced inhibitory activity against cAMP PDE, but retained its activity against cGMP PDE. It was also apparent that the $C^{4'}$–$C^{5'}$ *trans* dihydro derivative which was obtained as a minor product from the same culture broth of griseolic acid had almost the same inhibitory activity as griseolic acid.

Keywords——griseolic acid; base-exchanged derivative; adenosine 3′,5′-cyclic monophosphate; guanosine 3′,5′-cyclic monophosphate; inhibitory activity; cAMP phosphodiesterase; cGMP phosphodiesterase

Introduction

Griseolic acid (**1**) is a new type of nucleoside which was isolated from the culture broth of *Streptomyces griseoaurantiacus* SANK 63479.[2] Its structure was subsequently determined as **1** by X-ray crystallographic analysis.[3]

We have reported synthetic procedures for griseolic acid derivatives having different substituents at the N^1-, C^6-, $C^{2'}$- or $C^{7'}$-position and their phosphodiesterase (PDE)-inhibitory activities.[1,4,5] These studies revealed that the modification at the C^6 or N^1 position caused marked changes of the PDE-inhibitory activity, whereas substitution of the $C^{2'}$ or $C^{7'}$ position with various functional groups had little effect on the PDE-inhibitory activity. Furthermore, it became clear that 4′α,5′-dihydro-7′-deoxygriseolic acid (**2**, *trans* $C^{4'}$–$C^{5'}$ dihydro derivative) which was isolated as a minor product from the same culture broth as griseolic acid showed almost the same PDE-inhibitory activity as that of griseolic acid.[6] Model building studies of griseolic acid (**1**) and the *trans* $C^{4'}$–$C^{5'}$ dihydro derivative (**2**) showed that the three-dimensional structures of the base moiety and the fused five-membered sugar moiety of these two compounds were very similar to each other and also to that of adenosine 3′,5′-cyclic monophosphate (cAMP). On the other hand, the *cis* $C^{4'}$–$C^{5'}$ dihydro derivative had a



1a 1b 2

Fig. 1

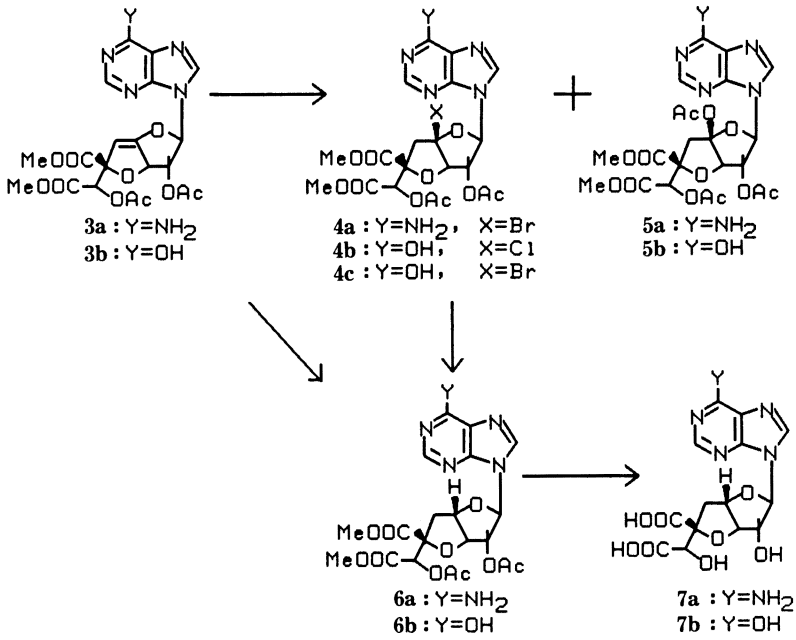


Fig. 2

completely different three-dimensional structure. Thus, we were very interested in the PDE-inhibitory activity of dihydro derivatives of griseolic acid at the $C^{4'}$–$C^{5'}$ double bond. This paper describes the synthesis of *cis* $C^{4'}$–$C^{5'}$ dihydro griseolic acid and its base-exchanged guanine and uracil derivatives. The PDE-inhibitory activities of these compounds were determined, and the role of the $C^{4'}$–$C^{5'}$ double bond of griseolic acid in the PDE-inhibitory activity is discussed.

Results and Discussion

Synthesis

Synthesis of 4′β,5′-Dihydrogriseolic Acid Derivative (Fig. 2)——It has been reported that the addition reaction to the vinyl ether bond can be carried out in the presence of an acidic catalyst such as mineral acid, *p*-toluenesulfonic acid, phosphoryl chloride or acid ion exchange resin.[7] As griseolic acid has a vinyl ether moiety in its molecule, it was expected that griseolic acid would also undergo an addition reaction. When **3a** was heated at room temperature for 3 d in acetic acid containing 4% hydrogen halide, a complex decomposed mixture of sugar and base moiety was obtained. However, when this reaction was carried out under restricted conditions, the desired reaction proceeded. For example, **3a** gave **4a** in 37%

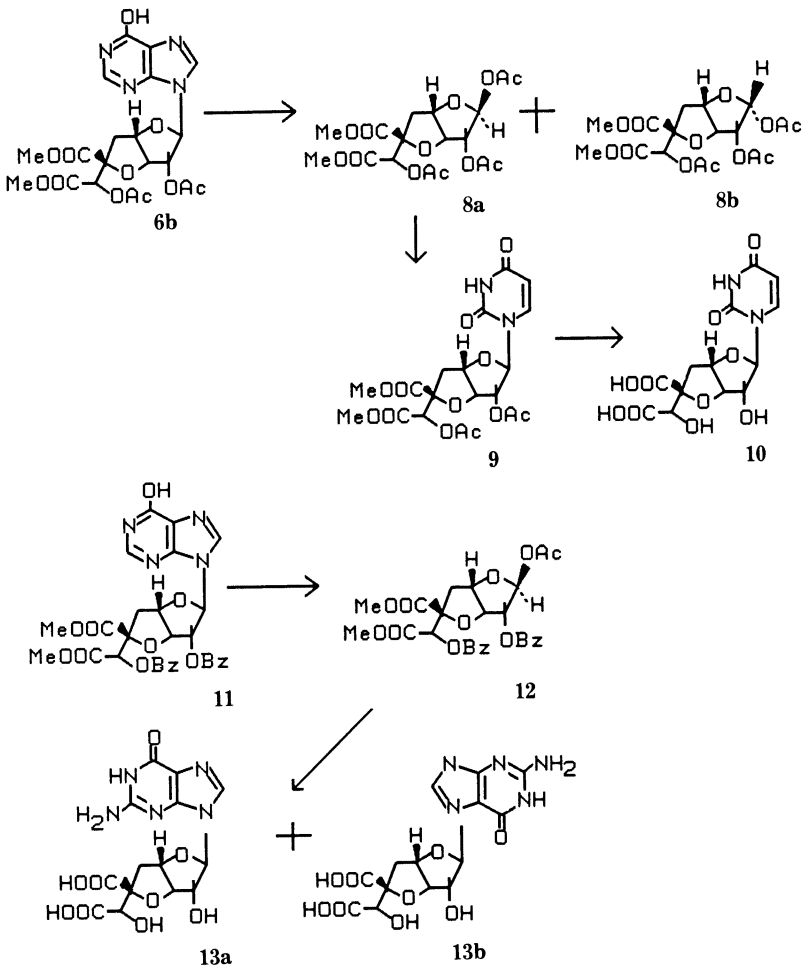


Fig. 3

yield when it was heated at 50 °C for 15 min in acetic acid containing 4% hydrogen bromide. The adduct of acetic acid to the $C^{4'}$–$C^{5'}$ double bond (**5a**) was also obtained by this reaction in the yield of 7.6%. In the case of reaction of **3b** at 80 °C for 2 h in acetic acid containing 4% hydrogen chloride, **4b** was obtained in 46.5% yield. In addition **5b** was also obtained in the yield of 6%.

Reduction of the halides (**4a**—**4c**) with zinc in an aqueous acetic acid or tri-*n*-butyltinhydride[8] gave a 4′*β*,5′-dihydrogriseolic acid derivative (**6a** or **6b**). Deprotection of **6a** and **6b** with aqueous alkaline solution gave **7a** and **7b**. The structures of these compounds were identified from the nuclear magnetic resonance (NMR) spectrum, elemental analysis and mass spectrum (MS). The ring juncture of the sugar moiety of **7a** and **7b** will be discussed later. Compound **6a** was also obtained by medium-pressure catalytic reduction of **3a** using platinum oxide in acetic acid at room temperature in poor yield. In addition, reduction of **3a** with palladium on carbon in dilute hydrochloric acid at atmospheric pressure gave **6a** quantitatively. None of the *trans* dihydro derivative was detected in the reaction mixtures of these reduction reactions. This suggests that reduction of the $C^{4'}$–$C^{5'}$ double bond occurred from the same side as the adenine ring.

Synthesis of Base-Exchanged Derivatives of 4′*β*,5′-Dihydrogriseolic Acid (Fig. 3)—Attemps to exchange the base moiety of protected griseolic acid by using various acidic cat-

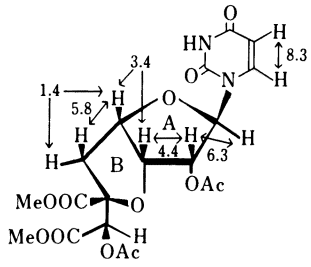


Fig. 4

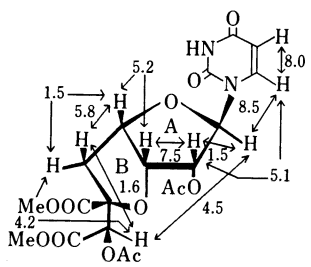


Fig. 5

alysts were unsuccessful. In addition, acetolysis[9] which usually yields the 1′-acetoxy sugar residue of a protected nucleoside, gave a complex mixture in the case of acylated griseolic acid. The reason for this seems to be addition reactions to the $C^{4'}$–$C^{5'}$ double bond of griseolic acid. Accordingly, in the cases of **6a** and **6b**, a good result of acetolysis was expected. While in the case of **6a**, acetolysis did not proceed smoothly, **6b** gave the desired 1′-acetoxy sugar derivatives. That is, the 1β-acetoxy derivative (**8a**) and its α anomer (**8b**) were obtained in the ratio of 9 : 1 in good yield when **6b** was allowed to stand at room temperature for 14 h in a mixture of acetic acid and acetic anhydride in the presence of concentrated sulfuric acid. It is considered that the formation of an acyloxonium ion by the 2′-acetoxy group of **6b** caused the production of **8a** as a main product. The sugar derivative (**8a**) was reacted with bis(trimethylsilyl)uracil at room temperature in the presence of tin tetrachloride to yield the uracil derivative (**10**),[10–13] after deprotection with a 1 N aqueous solution of sodium hydroxide. The stereostructure was investigated in detail by decoupling and nuclear Overhauser effect (NOE) experiments in the NMR spectrum. These analyses are described in the next section.

The sugar derivative **12** was also obtained by the same method as **8a** from compound **11**. When **12** was reacted with bis(trimethylsilyl)acetylguanine in the presence of trimethylsilyl triflate under the same reaction conditions as used for **9**, 9-guanino (**13a**) and 7-guanino (**13b**) derivatives were obtained after hydrolyzing the protecting groups of the products. The structures of these compounds were identified from the NMR and ultraviolet (UV) spectra, elemental analysis and fast atom bombardment (FAB) MS.

Determination of Stereostructure of Compound 9——The stereostructure of compound **9** was investigated in detail with ^{1}H-NMR by means of decoupling and NOE experiments.[14] The chemical shift of each proton of compound **9** and the decoupling data are shown in Fig. 4. The NOE data are shown in Fig. 5. Irradiation at 1′-H gave a 1.5% increase in the intensity of the 2′-H signal and irradiation at 4′-H gave a 5.2% increase in the intensity of the 3′-H signal. From these results, the configurations of 1′-H and 2′-H, 2′-H and 3′-H, 3′-H and 4′-H were determined as *trans*, *cis*, *cis*. In addition, irradiation at 1′-H unexpectedly caused a 4.5% increase in the intensity of the 7′-H signal. This fact suggests that 1′-H and 7′-H are located in close proximity. It became clear from a model building study that the uracil ring of compound **9** takes the β-configuration and the ring juncture of A and B is *cis*, and thus 1′-H, the A-ring, the B-ring, the 7′-carbon and 7′-H form a highly folded structure like a cage. On the other hand, the A-ring and B-ring of griseolic acid (**1**) and the *trans* dihydro derivative (**2**) form a planar structure. These conclusions are supported by the fact that 1′-H and 2′-H of **1** and **2** do not couple with each other, whereas the coupling constant of 1′-H and 2′-H of compound **9** was 6.3 Hz, which suggests that the dihedral angle of the two protons is about 135°. This relatively large coupling constant between 1′-H and 2′-H was also observed in compounds **4a**—**c**, **5a**—**b**, **6a**—**b**, **7a**—**b**, and **13a**—**b**, which were supposed to have *cis* configuration between the A-ring and B-ring.

TABLE I. PDE-Inhibitory Activity of Griseolic Acid Derivatives

Compound No.		1a	1b	2	7a	7b	10	13a	13b
IC_{50} (μM)	cAMP	0.16	0.32	0.14	12.6	188	558	50.0	73.0
	cGMP	0.63	0.13	0.63	53.8	3.41	339	1.5	65.5
	cAMP/cGMP	0.25	2.46	0.22	0.23	55.13	1.65	33.3	1.11

PDE-Inhibitory Activity (Table I)

The test was carried out essentially according to Pichard and Cheung.[15] The details were reported previously.[4,5]

Naturally occurring 4′α,5′-dihydro-7′-deoxygriseolic acid (*trans* dihydrogenated form, **2** in Fig. 1) had the same PDE-inhibitory activity as that of griseolic acid, whereas the *cis* dihydro derivative (**7a**) showed only about 1/80 (cAMP PDE) and 1/85 (guanosine 3′,5′-cyclic monophosphate (cGMP) PDE) of the activity. The *cis* dihydro hypoxanthine derivative (**7b**) showed about 1/1180 (cAMP PDE) and 1/26 (cGMP PDE) of the activity of 6-deamino-6-hydroxygriseolic acid (**1b**). These results revealed that *trans* dihydrogenation of griseolic acid caused little change of the three-dimensional relationship between the base moiety and the dicarboxylic acid residue. On the other hand, *cis* dihydrogenation caused a great change of this relationship. That is, the *cis* dihydrogenated derivatives have a highly folded stereostructure and can not bind tightly with the PDE binding site. This tendency was even more marked when the base moiety of the *cis* dihydrogenated derivative was changed to uracil. Thus, compound **10** had no inhibitory activity against cAMP or cGMP PDE. In contrast, the *cis* dihydrogenated guanin-9-yl derivative (**13a**) retained inhibitory activity against cGMP PDE, but showed 1/312 times weaker activity against cAMP PDE than that of griseolic acid.

From these results, it became apparent that uracil could not substitute for either adenine or guanine in the binding site of PDE. In contrast, hydroxanthine seems to be able to substitute for guanine but not adenine.

Conclusion

It has been reported that the structure of griseolic acid is an extended one, as determined by X-ray crystallographic analysis,[3] and it also became clear from model building studies that griseolic acid (**1**) and the *trans* dihydrogenated natural product (**2**) had almost the same three-dimensional structure. In contrast, the *cis* dihydrogenated derivatives, which were first synthesized in this work, had completely different stereostructures from the natural compounds (**1** and **2**). The stereostructure of this type of compound was defined as a highly folded one by NMR analysis. It also became apparent that the PDE-inhibitory potency showed a good correlation with the three-dimensional structure of the griseolic acid derivatives. That is, the PDE-inhibitory activities of griseolic acid (**1**) and the *trans* dihydrogenated derivative (**2**) were almost the same. In contrast, *cis* dihydrogenated derivatives showed extremely low inhibitory activity against cAMP PDE. However, it is very interesting that *cis* dihydrogenated guanin-9-yl derivatives retained the same inhibitory activity against cGMP PDE as that of griseolic acid.

Consequently, it is expected that guanine derivative of griseolic acid which has the intact double bond would show strong inhibitory activity against cGMP PDE. Synthetic studies of guanine derivative along this line are in progress in this laboratory.

Experimental

General——Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. ^{1}H-

NMR spectra were obtained with a Varian EM-390 spectrometer (90 MHz) and with a JEOL GX-400 spectrometer (400 MHz), and the chemical shifts are expressed in ppm from tetramethylsilane as an internal standard: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet; br, broad. UV spectra were obtained using a Hitachi 200-20 spectrophotometer. Thin-layer chromatographies (TLC) were carried out on Merck silica gel F_{254} pre-coated TLC plates, layer thickness 0.25 mm, and spots were visualized by UV irradiation or by spraying with 30% aqueous sulfuric acid followed by heating. Ordinary chromatography was performed by the rapid chromatography method[16] using Merck silica gel (Kieselgel 60 Art. 9385).

Dimethyl $O^{2'}$,$O^{7'}$-Diacetylgriseolate (3a)——In a round-bottomed flask, 10 g (24.55 mmol) of dimethyl griseolate[1] was dissolved in 150 ml of pyridine, and 33 ml (0.32 mmol) of acetic anhydride was added under ice-cooling. The mixture was allowed to stand at room temperature for 2 h. At the end of this time, 15 ml of water was added under ice-cooling and the solvent was evaporated off under reduced pressure. The residue was dissolved in 400 ml of methylene chloride and the resulting solution was washed with 400 ml of a 1 N aqueous solution of hydrochloric acid, 400 ml of water and 400 ml of a saturated aqueous solution of sodium bicarbonate in that order. The solution was extracted twice with methylene chloride. The methylene chloride extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated off under reduced pressure to give 6.70 g (55.6%) of **3a** as crystals. *Anal.* Calcd for $C_{20}H_{21}N_5O_{10}\cdot 5/2H_2O$: C, 44.78; H, 4.85; N, 13.05. Found: C, 44.86; H, 4.84; N, 12.95. UV $\lambda_{max}^{methanol}$ nm (ε): 257 (17100). NMR (DMSO-d_6) δ: 5.17 (1H, d, J=3.0 Hz, 5'-H), 5.66 (1H, d, J=6.0 Hz, 2'-H), 5.73 (1H, s, 7'-H), 6.31 (1H, dd, J=3.0, 6.0 Hz, 3'-H), 6.89 (1H, s, 1'-H), 8.23 (1H, s), 8.36 (1H, s), 7.41 (2H, br s, NH_2), 3.78 (3H, s, CH_3), 3.69 (3H, s, CH_3), 2.19 (6H, s, CH_3CO).

Dimethyl $O^{2'}$,$O^{7'}$-Diacetyl-6-deamino-6-hydroxygriseolate (3b)——Sodium nitrite (2.55 g, 36.96 mmol) was added to a solution of 1.82 g (3.70 mmol) of **3a** in a 80% (v/v) aqueous solution of acetic acid (100 ml) under ice-cooling, and the mixture was allowed to stand for 16 h in a tightly stoppered vessel. TLC at this stage showed that the starting material remained in the reaction mixture. A further 1 g of sodium nitrite was added and the mixture was allowed to stand for 3 h. The residue obtained by evaporation of the solvent under reduced pressure was dissolved in acetone. Toluene was added to the mixture and then distilled off. This process was repeated three times. The residue was dissolved in a mixture of water and chloroform. The organic layer was washed with an aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a pale brown glass-like substance. This substance was purified by silica gel column chromatography and dissolved in a small quantity of acetone. An appropriate amount of benzene was added to the solution and the mixture was allowed to stand. The resulting white crystals were collected by filtration to give 1.28 g (70.4%) of **3b** as fine white crystals. *Anal.* Calcd for $C_{20}H_{20}N_4O_{11}$: C, 48.78; H, 4.09; N, 11.38. Found: C, 48.91; H, 3.91; N, 11.35. UV $\lambda_{max}^{50\%\,(v/v)\,aqueous\,methanol}$ nm (ε): 243 (12700), 248 sh (12500), 270 sh (4300). NMR (DMSO-d_6) δ: 5.22 (1H, d, J=3.0 Hz, 5'-H), 5.62 (1H, d, J=6.0 Hz, 2'-H), 5.73 (1H, s, 7'-H), 6.13 (1H, dd, J=3.0, 6.0 Hz, 3'-H), 6.88 (1H, s, 1'-H), 8.18 (1H, s), 8.34 (1H, s), 3.80 (3H, s, CH_3), 3.69 (3H, s, CH_3), 2.19 (6H, s, CH_3CO).

Addition of HBr to 3a

Synthesis of 4a and 5a——Compound **3a** (2.45 g, 4.99 mmol) was suspended in anhydrous acetic acid containing 4% (w/v) hydrobromic acid (50 ml). The mixture was heated with stirring at 50 °C for 20 min under protection from moisture. The solvent was then distilled off. Acetone and toluene were added to the residue and then distilled off; this was done three times. The residue was dissolved in a mixture of 50 ml of ethyl acetate and 30 ml of an aqueous solution of sodium bicarbonate. The organic phase was separated and washed, in turn, with 30 ml of a 5% (w/v) aqueous solution of sodium bicarbonate, 30 ml of water and 30 ml of a saturated aqueous solution of sodium chloride. It was dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The caramel-like residue was purified by silica gel column chromatography eluted with a mixture of 3% (v/v) methanol and methylene chloride. From the fractions following **5a** (210 mg, 7.6%), 1.06 g (37.1%) of **4a** was obtained.

4a: *Anal.* Calcd for $C_{20}H_{22}BrN_5O_{10}\cdot 1/2H_2O$: C, 41.32; H, 3.99; Br, 13.74; N. 12.05. Found: C, 41.22; H, 3.77; Br, 13.89; N, 11.85. UV $\lambda_{max}^{methanol}$ nm (ε): 258 (15300). NMR (DMSO-d_6) δ: 2.98 (1H, d, J=15.0 Hz, 5'-H), 3.45 (1H, d, J=15.0 Hz, 5'-H), 5.38 (1H, d, J=3.9 Hz, 3'-H), 5.57 (1H, s, 7'-H), 6.40 (1H, dd, J=3.9, 6.0 Hz, 2'-H), 6.58 (1H, d, J=6.0 Hz, 1'-H), 8.27 (1H, s), 8.51 (1H, s), 3.73 (3H, s, CH_3), 3.81 (3H, s, CH_3), 2.07 (3H, s, CH_3CO), 2.25 (3H, s, CH_3CO).

5a: *Anal.* Calcd for $C_{22}H_{25}N_5O_{12}$: C, 47.91; H, 4.54; N, 12.70. Found: C, 47.66; H, 4.47; N, 12.47. UV $\lambda_{max}^{methanol}$ nm (ε): 259 (16600). NMR (DMSO-d_6) δ: 2.83 (1H, d, J=15.0 Hz, 5'-H), 3.20 (1H, d, J=15.0 Hz, 5'-H), 5.07 (1H, d, J=4.2 Hz, 3'-H), 5.62 (1H, s, 7'-H), 6.18 (1H, dd, J=4.2, 6.6 Hz, 2'-H), 6.52 (1H, d, J=6.6 Hz, 1'-H), 8.29 (1H, s), 8.46 (1H, s), 3.83 (3H, s, CH_3), 3.89 (3H, s, CH_3), 2.10 (3H, s, CH_3CO), 2.17 (3H, s, CH_3CO), 2.37 (3H, s, CH_3).

Addition of HCl to 3b

Synthesis of 4b and 5b——Compound **3b** (4 g, 8.12 mmol) was placed in a two-necked flask fitted with a cooler and the flask was purged with nitrogen gas. Next, 4% (w/v) hydrogen chloride in acetic acid (40 ml) was added and the mixture was heated at 80 °C for 2 h. At the end of this time, the solvent was distilled off under reduced pressure. The residue was dissolved in a mixture of toluene and methylene chloride and distillation was effected three times after adding toluene and methylene chloride prior to each distillation. The residue was extracted with methylene chloride

and washed three times with a saturated aqueous solution of sodium bicarbonate. The extract was dried over anhydrous magnesium sulfate and then evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography eluted with 4% (v/v) methanol in methylene chloride, affording 2.0 g (46.5%) of **4b** and 270 mg (6%) of **5b**.

4b: *Anal.* Calcd for $C_{20}H_{21}ClN_4O_{11}$: C, 45.42; H, 4.00; Cl, 6.70; N, 10.59. Found: C, 45.12; H, 4.23; Cl, 6.67; N, 10.55. UV $\lambda_{max}^{50\%\,(v/v)\,aqueous\,methanol}$ nm (ε): 248 (9500). NMR (a 1 : 1 by volume mixture of D_2O and DMSO-d_6) δ: 3.32 (1H, d, J=15.0 Hz, 5′-H), 3.75 (1H, d, J=15.0 Hz, 5′-H), 5.28 (1H, d, J=4.5 Hz, 3′-H), 6.00 (1H, s, 7′-H), 6.28 (1H, dd, J=4.5, 5.9 Hz, 2′-H), 6.55 (1H, d, J=5.9 Hz, 1′-H), 8.18 (1H, s), 8.47 (1H, s), 4.12 (3H, s, CH_3), 4.25 (3H, s, CH_3), 2.47 (3H, s, CH_3CO), 2.65 (3H, s, CH_3CO).

5b: *Anal.* Calcd for $C_{22}H_{24}N_4O_{13}$: C, 47.83; H, 4.35; N, 10.14. Found: C, 48.08; H, 4.58; N, 9.85. UV $\lambda_{max}^{50\%\,(v/v)\,aqueous\,methanol}$ nm (ε): 248.5 (10200). NMR ($CDCl_3$) δ: 2.75 (1H, d, J=15.6 Hz, 5′-H), 3.21 (1H, d, J=15.6 Hz, 5′-H), 5.11 (1H, d, J=4.9 Hz, 3′-H), 5.77 (1H, s, 7′-H), 6.03 (1H, dd, J=4.9, 7.3 Hz, 2′-H), 6.49 (1H, d, J=7.3 Hz, 1′-H), 8.07 (1H, s), 8.16 (1H, s), 3.80 (3H, s, CH_3), 3.86 (3H, s, CH_3), 2.07 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO), 2.34 (3H, s, CH_3CO).

Addition of HBr to 3b

Synthesis of 4c——Compound **3b** (500 mg, 1.02 mmol) was added to 4% (w/v) hydrobromic acid in acetic acid (5 ml) and the mixture was dissolved by ultrasonic vibration for 30 min. The solution was allowed to stand for 64 h at room temperature and the solvent was distilled off under reduced pressure. Distillation was done three times, each time first adding acetone and toluene to the residue. Ethyl acetate (30 ml) was added to the residue and the mixture was subjected to ultrasonic vibration. Insolubles were separated by filtration and dissolved in 30 ml of ethyl acetate and a 5% (w/v) aqueous solution of sodium bicarbonate. The organic phase was washed with 20 ml of a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography to give 60 mg (10.3%) of **4c** in the form of a white powder.

4c: *Anal.* Calcd for $C_{20}H_{21}BrN_4O_{11}\cdot 1/2H_2O$: C, 41.25; H, 3.78; Br, 13.72; N, 9.62. Found: C, 41.14; H, 4.08; Br, 13.57; N, 9.40. UV $\lambda_{max}^{methanol}$ nm (ε): 244 (14200), 249 sh (13800), 270 sh (6000). NMR (DMSO-d_6) δ: 2.98 (1H, d, J=15.6 Hz, 5′-H), 3.47 (1H, d, J=15.6 Hz, 5′-H), 5.35 (1H, d, J=4.2 Hz, 3′-H), 5.57 (1H, s, 7′-H), 6.32 (1H, dd, J=4.2, 6.6 Hz, 2′-H), 6.53 (1H, d, J=6.6 Hz, 1′-H), 8.17 (1H, s), 8.47 (1H, s), 4.13 (3H, s, CH_3), 4.24 (3H, s, CH_3), 2.48 (3H, s, CH_3CO), 2.64 (3H, s, CH_3CO).

Dimethyl $O^{2'}$,$O^{7'}$-Diacetyl-4′β,5′-dihydrogriseolate (6a)——Compound **4a** (572 mg, 1.00 mmol) was dissolved in 10 ml of acetone. Next, 80% (v/v) aqueous acetic acid (10 ml) and 690 mg (10.55 atom) of zinc powder was added and the mixture was stirred at room temperature for 4.3 h. At the end of this time, the solvent was distilled off and the residue was dissolved in a mixture of 10 ml of water and 20 ml of ethyl acetate. The solution was adjusted to pH 1 by the addition of 1 N hydrochloric acid and the insolubles were filtered off. The organic phase was washed successively with 20 ml of a saturated aqueous solution of sodium chloride and 20 ml of a 5% aqueous solution of sodium bicarbonate, and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography eluted with a mixture of 3% (v/v) aqueous methanol and methylene chloride to give 129 mg (26.2%) of **6a** in the form of a colorless caramel-like substance. *Anal.* Calcd for $C_{20}H_{23}N_5O_{10}$: C, 48.68; H, 4.67; N, 14.19. Found: C, 48.53; H, 4.67; N, 13.96. UV $\lambda_{max}^{methanol}$ nm (ε): 258 (13700). NMR (DMSO-d_6) δ: 2.1—2.4 (2H, m, 5′-H), 4.90—5.10 (1H, m, 3′-H), 5.63 (1H, s, 7′-H), 5.18—5.30 (1H, m, 4′-H), 5.97 (1H, dd, J=3.3, 6.6 Hz, 2′-H), 6.40 (1H, d, J=6.6 Hz, 1′-H), 8.23 (1H, s), 8.53 (1H, s), 3.71 (3H, s, CH_3), 3.73 (3H, s, CH_3), 2.05 (3H, s, CH_3CO), 2.28 (3H, s, CH_3CO), 7.33 (2H, br s, NH_2).

Dimethyl $O^{2'}$,$O^{7'}$-Diacetyl-6-deamino-4′β,5′-dihydro-6-hydroxygriseolate (6b)——(i) Compound **4b** (500 mg, 0.95 mmol), 10 mg (0.06 mmol) of 2,2′-azobisisobutyronitrile, 20 ml of benzene and 3.1 ml of tributyltin hydride were added to a reaction vessel in that order, and the mixture was refluxed with stirring under a nitrogen atmosphere for 2 h. The solvent was then distilled off and the residue was purified by silica gel column chromatography eluted with 3% (v/v) methanol in methylene chloride to give 350 mg (74.9%) of **6b**.

(ii) Compound **3b** (600 mg, 1.22 mmol) was subjected to Parr catalytic reduction at room temperature and at 50 psig for 6 h using 70 ml of acetic acid and 600 mg (2.84 atom) of platinum oxide. At the end of this period, the vessel was purged with nitrogen and then the reaction mixture was filtered. Water was added to the filtrate, which was extracted three times, each time with 50 ml of methylene chloride. The organic phase was collected and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluted with 70% (v/v) benzene in acetone to give 60 mg (10.5%) of **6b**.

(iii) Compound **3b** (600 mg, 1.22 mmol) was subjected to reduction at room temperature for 6 h using 30 ml of 0.5 N hydrochloric acid and 600 mg of palladium on carbon. At the end of this period, the vessel was purged with nitrogen and then the reaction mixture was filtered and neutralized by adding sodium hydrogen carbonate. Water was added to the filtrate, which was extracted three times, each time with 50 ml of methylene chloride. The organic phase was collected and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography eluted with 70% (v/v) benzene in acetone to give 450 mg (74.7%) of **6b**. *Anal.* Calcd for $C_{20}H_{22}N_4O_{11}$: C, 48.59; H, 4.49; N, 11.33. Found: C, 48.36; H, 4.72; N, 11.07.

UV $\lambda_{max}^{50\%\,(v/v)\,aqueous\,methanol}$ nm (ε): 248.7 (10400). NMR ($CDCl_3$ in the presence of D_2O) δ: 2.4—3.0 (2H, m, 5′-H), 5.1—5.4 (2H, m, 3′ and 4′-H), 5.88 (1H, s, 7′-H), 5.94 (1H, dd, J=4.5, 7.5 Hz, 2′-H), 6.30 (1H, d, J=7.5 Hz, 1′-H), 7.97 (1H, s), 8.23 (1H, s), 3.80 (3H, s, CH_3), 3.82 (3H, s, CH_3), 2.088 (3H, s, CH_3CO), 2.26 (3H, s, CH_3CO).

4′β,5′-Dihydrogriseolic Acid (7a)——Compound **6a** (80 mg, 0.16 mmol) was added to a 0.2 N aqueous solution of sodium hydroxide (5 ml) and dissolved by ultrasonic vibration for about 10 min. The solution was allowed to stand for 2 h and then its pH was adjusted to a value of 2.3 by the addition of 1 N hydrochloric acid. The reaction mixture was then purified by chromatography through an Rp-8 prepacked column (Merck) eluted with 10% (v/v) aqueous acetonitrile to give 57 mg (92.2%) of **7a** in the form of a white powder. *Anal.* Calcd for $C_{14}H_{15}N_5O_8 \cdot H_2O$: C, 42.11; H, 4.29; N, 17.54. Found: C, 41.98; H, 3.99; N, 17.38. UV $\lambda_{max}^{H_2O}$ nm (ε): 258 (13600); 0.1 N NaOH; 260 (13000); 0.1 N HCl: 256.5 (12000). NMR (DMSO-d_6) δ: 2.3—2.8 (2H, m, 5′-H), 4.47 (1H, s, 7′-H), 4.6—5.2 (3H, m, 2′,3′,4′-H), 6.13 (1H, d, J=6.9 Hz, 1′-H), 8.22 (1H, s), 8.37 (1H, s).

6-Deamino-4′β,5′-dihydro-6-hydroxygriseolic Acid (7b)——Compound **6b** (350 mg, 0.71 mmol) was dissolved under ice-cooling in 20 ml of 1 N aqueous sodium hydroxide and the solution was allowed to stand at room temperature for 2 h. At the end of this time, the reaction mixture was adjusted to pH 1 with hydrochloric acid under ice-cooling. This mixture was subjected to Rp-18 reverse-phase column chromatography eluted with a mixture of 3% (v/v) acetonitrile, 0.3% (v/v) acetic acid and water to give 140 mg (51.7%) of **7b**. *Anal.* Calcd for $C_{14}H_{14}N_4O_9 \cdot 7/6H_2O$: C, 42.00; H, 4.00; N, 14.00. Found: C, 41.79; H, 3.84; N, 14.06. UV $\lambda_{max}^{H_2O}$ nm (ε): 248.5 (11800); 0.1 N NaOH: 253 (12900); 0.1 N HCl: 248.5 (11500). NMR (DMSO-d_6) δ: 2.46 (1H, dd, J=7.5, 14.3 Hz, 5′-H), 2.58 (1H, dd, J=2.3, 14.3 Hz, 5′-H), 4.32 (1H, s, 7′-H), 4.63 (1H, dd, J=4.3, 7.8 Hz, 2′-H), 4.72—4.83 (1H, m, 3′-H), 4.99—5.02 (1H, m, 4′-H), 6.00 (1H, d, J=7.8 Hz, 1′-H), 8.06 (1H, s), 8.28 (1H, s), 12.40 (1H, br s, OH).

Dimethyl 1′β-Acetoxy-$O^{2'}$,$O^{7'}$-diacetyl-1′-deadenino-4′β,5′-dihydrogriseolate (8a)——Concentrated sulfuric acid (2 ml, 0.04 mmol) was added to a solution of 500 mg (1.01 mmol) of compound **6b** in 100 ml of a 4 : 1 (v/v) mixture of acetic acid and acetic anhydride, and the mixture was allowed to stand at room temperature for 14 h in a nitrogen atmosphere. Sodium acetate (15 g) was added to the reaction mixture and the solvent was evaporated off under reduced pressure. The residue was dissolved in a saturated aqueous solution of sodium bicarbonate and the solution was extracted three times with methylene chloride. The methylene chloride extracts were combined and dried over anhydrous magnesium sulfate. The solvent was then evaporated off under reduced pressure. The residue was purified by silica gel column chromatography eluted with a 2 : 1 (v/v) mixture of cyclohexane and ethyl acetate. Evaporation of the solvent from the second fraction gave 292 mg (69.0%) of **8a**. *Anal.* Calcd for $C_{17}H_{22}O_{12}$: C, 48.81; H, 5.30. Found: C, 49.05; H, 5.50. NMR ($CDCl_3$) δ: 2.65 (1H, dd, J=3.0, 14.7 Hz, 5′α-H), 2.45 (1H, dd, J=6.6, 14.7 Hz, 5′β-H), 4.97 (1H, ddd, J=4.6, 3.0, 6.6 Hz, 4′-H), 5.02 (1H, dd, J=4.6, 5.1 Hz, 3′-H), 5.72 (1H, s, 7′-H), 5.16 (1H, dd, J=2.7, 5.1 Hz, 2′-H), 6.29 (1H, d, J=2.7 Hz, 1′-H), 2.08 (3H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 2.25 (3H, s, CH_3CO), 3.75 (3H, s, CH_3), 3.79 (3H, s, CH_3). MS m/z: 474 (M+43). FAB-MS m/z: 431 (M^+).

Dimethyl 1′α-Acetoxy-$O^{2'}$,$O^{7'}$-diacetyl-1′-deadenino-4′β,5′-dihydrogriseolate (8b)——The first fraction separated from the column chromatography described in connection with the synthesis of **8a** was concentrated by evaporation under reduced pressure to give 33 mg (7.8%) of **8b**. *Anal.* Calcd for $C_{17}H_{22}O_{12}$: C, 48.81; H, 5.30. Found: C, 49.08; H, 5.33. NMR ($CDCl_3$) δ: 2.99 (1H, dd, J=3.0, 15.3 Hz, 5′α-H), 2.67 (1H, dd, J=7.5, 15.3 Hz, 5′β-H), 4.99 (1H, ddd, J=5.0, 3.0, 7.5 Hz, 4′-H), 4.96 (1H, dd, J=5.0, 5.3 Hz, 3′-H), 5.61 (1H, s, 7′-H), 5.06 (1H, dd, J=4.8, 5.3 Hz, 2′-H), 6.38 (1H, d, J=4.8 Hz, 1′-H), 2.09 (3H, s, CH_3CO), 2.16 (3H, s, CH_3CO), 2.19 (3H, s, CH_3CO), 3.76 (3H, s, CH_3), 3.78 (3H, s, CH_3). MS m/z: 474 (M+43). FAB-MS m/z: 431 (M^+).

1′-Deadenino-4′β,5′-dihydro-1′β-(uracil-1-yl)griseolic Acid (10)——In a two-necked flask, 70 mg, (0.17 mmol) of **8a**, 0.4 ml of bistrimethylsilyluracil, and 20 ml of 1,2-dichloroethane were placed under an atmosphere of nitrogen. The mixture was ice-cooled, mixed with 0.13 mg (0.5 μmmol) of tin tetrachloride and stirred overnight. The solvent was evaporated off under reduced pressure and the residue was dissolved into a mixture of methylene chloride and a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride three times. The methylene chloride extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography eluted with methylene chloride containing 3% methanol to give 65.5 mg (83.2%) of dimethyl $O^{2'}$,$O^{7'}$-diacetyl-1′-deadenino-4′β,5′-dihydro-1′β-(uracil-1-yl)griseolate (**9**). **9**: *Anal.* Calcd for $C_{19}H_{22}N_2O_{12}$: C, 48.51; H, 4.68; N, 5.96. Found: C, 48.39; H, 4.76; N, 5.71. UV $\lambda_{max}^{methanol}$ nm (ε): 257.5 (9900). NMR ($CDCl_3$) δ: 5.98 (1H, d, J=6.8 Hz, 1′-H), 5.48 (1H, dd, J=6.8, 4.4 Hz, 2′-H), 4.98 (1H, t, J=4.4 Hz, 3′-H), 5.12—5.15 (1H, m, 4′-H), 2.77 (1H, dd, J=1.5, 15.1 Hz, 5′-H), 2.49 (1H, dd, J=6.3, 15.1 Hz, 5′-H), 5.79 (1H, s, 7′-H), 7.20 (1H, d, J=8.3 Hz, 6-H), 5.76 (1H, d, J=8.3 Hz, 5-H), 3.79 (3H, s, CH_3), 3.80 (3H, s, CH_3), 2.11 (3H, s, CH_3CO), 2.24 (3H, s, CH_3CO), 8.77 (1H, s, NH). $[\alpha]_D^{25}$ −66 (c=0.1, CH_2Cl_2).

Compound **9** (40 mg, 0.09 mmol) was dissolved in 5 ml of 1 N sodium hydroxide under ice-cooling. The mixture was allowed to stand at room temperature for 4 h, adjusted to a pH value of 1 with 1 N hydrochloric acid and subjected to chromatography by using a reverse-phase prepacked RP-18 column (Merck) eluted with water containing 5% acetonitrile to afford 25.5 mg (83.7%) of **10**. **10**: *Anal.* Calcd for $C_{13}H_{14}N_2O_{10} \cdot 2H_2O$: C, 39.59; H, 4.56; N, 7.11. Found: C, 39.58; H, 4.33; N, 7.17. UV $\lambda_{max}^{H_2O}$ nm (ε): 260.2 (9200). NMR (DMSO-d_6) δ: 5.90 (1H, d, J=6.9 Hz, 1′-H), 4.25 (1H, m, 2′-H), 4.52 (1H, t, J=4.8 Hz, 3′-H), 4.90—4.95 (1H, m, 4′-H), 2.54 (1H, dd, J=2.7, 14.4 Hz, 5′-H), 2.39 (1H, dd, J=7.5, 14.4 Hz, 5′-H), 4.28 (1H, s, 7′-H), 7.69 (1H, d, J=7.5 Hz, 6-H), 5.65 (1H, d, J=

7.5 Hz, 5-H), 11.30 (1H, s, NH).

Dimethyl 1′β-Acetoxy-$O^{2'}$,$O^{7'}$-dibenzoyl-1′-deadenino-4′β,5′-dihydrogriseolate (12)——Concentrated sulfuric acid (2 ml, 0.04 mmol) was added under ice-cooling to a solution of 400 mg (0.65 mmol) of compound **11** (synthesized as described in the synthesis of **6b**), dissolved in 80 ml of a 4 : 1 (v/v) mixture of acetic acid and acetic anhydride, and the mixture was allowed to stand at room temperature for 14 h. The reaction mixture was then mixed with 15 g of sodium acetate and concentrated by evaporation under reduced pressure. The residue was dissolved in a mixture of methylene chloride and a saturated aqueous sodium bicarbonate solution and extracted three times with methylene chloride. The methylene chloride extracts were combined and dried over anhydrous magnesium sulfate and the solvent was evaporated off under reduced pressure. The residue was purified by silica gel column chromatography, eluted with a 2 : 1 (v/v) mixture of cyclohexane and ethyl acetate to give 243 mg (69.3%) of **12**.

11: *Anal.* Calcd for $C_{30}H_{26}N_4O_{11}$: C, 58.25; H, 4.24; N, 9.06. Found: C, 58.02; H, 4.44; N, 8.99. NMR (DMSO-d_6) δ: 2.45—2.59 (1H, m, 5′-H), 2.66—2.92 (1H, m, 5′-H), 5.06—5.25 (2H, m, 3′-H), 5.31—5.53 (1H, m, 4′-H), 5.87 (1H, s, 7′-H), 6.18 (1H, dd, J=6.0, 7.0 Hz, 2′-H), 6.56 (1H, d, J=6.0 Hz, 1′-H), 8.10 (1H, s), 8.45 (1H, s), 3.66 (3H, s, CH_3), 3.80 (3H, s, CH_3), 7.28—8.22 (10H, m, benzoyl).

12: *Anal.* Calcd for $C_{27}H_{26}O_{12}$: C, 59.78; H, 4.80; N, 0.00. Found: C, 59.59; H, 4.80; N, 0.01. NMR ($CDCl_3$) δ: 2.54 (1H, dd, J=6.1, 15.2 Hz, 5′-H), 2.98 (1H, dd, J=1.7, 15.2 Hz, 5′-H), 5.14 (1H, dd, J=4.0, 5.1 Hz, 3′-H), 5.49 (1H, dd, J=2.2, 5.1 Hz, 2′-H), 5.88 (1H, s, 7′-H), 5.06—5.10 (1H, m, 4′-H), 6.52 (1H, d, J=2.2 Hz, 1′-H), 3.58 (3H, s, CH_3), 3.81 (3H, s, CH_3), 2.12 (3H, s, CH_3CO), 7.15—8.16 (10H, m, benzoyl). MS m/z: 585 (M+43).

2-Amino-6-deamino-2-dehydro-6-hydroxy-4′β,5′-dihydrogriseolic Acid (13a)——Compound **12** (200 mg, 0.37 mmol) and 200 mg (0.59 mmol) of bistrimethylsilyl-N^2-acetylguanine was placed in a two-necked flask under an atmosphere of nitrogen and dissolved in 40 ml of 1,2-dichloroethane. Trimethylsilyl trifluoromethanesulfonate (0.4 ml, 0.002 mmol) was added under ice-cooling and the reaction mixture was allowed to stand at room temperature for 4 d, then worked up in the same manner as described in the synthesis of compound **12**. It was purified by silica gel column chromatography eluted with methylene chloride containing 3% (v/v) of methanol to give 54.8 mg (22.0%) of dimethyl 6-deamino-6-hydroxy-2-acetylamino-2-dehydro-4′β,5′-dihydro-$O^{2'}$,$O^{7'}$-dibenzoylgriseolate (isolated from the second fraction. *Anal.* Calcd for $C_{32}H_{29}N_5O_{12}\cdot 1/2H_2O$: C, 56.14; H, 4.50; N, 10.23. Found: C, 56.28; H, 4.53; N, 9.93. UV $\lambda_{max}^{methanol}$ nm (ε): 257 sh (13600), 265 (14100), 273 sh (12800), 282 sh (11500). NMR (DMSO-d_6) δ: 2.59—2.96 (2H, m, 5′-H), 5.12—5.32 (1H, m, 4′-H), 5.32—5.63 (1H, m, 3′-H), 5.83 (1H, s, 7′-H), 6.11 (1H, dd, J=4.5, 3.9 Hz, 2′-H), 6.47 (1H, d, J=4.5 Hz, 1′-H), 8.32 (1H, s, 8-H), 3.67 (3H, s, CH_3), 3.78 (3H, s, CH_3), 2.18 (3H, s, CH_3CO), 7.3—8.3 (10H, m, benzoyl), 11.73 (1H, s, NH), 12.33 (1H, s, NH).

Dimethyl 6-deamino-6-hydroxy-2-acetylamino-2-dehydro-4′β,5′-dihydro-$O^{2'}$,$O^{7'}$-dibenzoylgriseolate (40 mg, 0.06 mmol) was dissolved in 5 ml of a 1 N aqueous solution of sodium hydroxide under ice-cooling and the mixture was allowed to stand at room temperature for 4 h. The mixture was then adjusted to pH 1 with a 1 N aqueous solution of hydrochloric acid and subjected to column chromatography using an RP-18 reverse-phase prepacked column eluted with water containing 5% (v/v) acetonitrile to afford 22.0 mg (84.6%) of 2-acetylamino-6-deamino-2-dehydro-6-hydroxy-4′β,5′-dihydrogriseolic acid. *Anal.* Calcd for $C_{16}H_{17}N_5O_{10}\cdot 3H_2O$: C, 38.95; H, 4.66; N, 14.20. Found: C, 38.97; H, 4.82; N, 14.39. NMR (D_2O) δ: 2.58 (1H, dd, J=6.5, 15.4 Hz, 5′-H), 2.76 (1H, dd, J=15.4, 1.5 Hz, 5′-H), 4.60—4.75 (3H, m, 2′, 4′, or 7′-H), 5.10—5.16 (1H, m, 3′-H), 5.97 (1H, d, J=6.8 Hz, 1′-H), 8.20 (1H, s), 2.10 (3H, s, CH_3).

2-Acetylamino-6-deamino-2-dehydro-6-hydroxy-4′β,5′-dihydrogriseolic acid (21 mg, 0.05 mmol) was placed in a round-bottomed flask under a nitrogen atmosphere. Methanol containing 20% (v/v) ammonia (10 ml) was added, and the mixture was then allowed to stand at room temperature for 1 d in a tightly stoppered vessel. The solvent was evaporated off under reduced pressure and the residue was mixed with water. The mixture was then adjusted to pH 1 with a 1 N aqueous solution of hydrochloric acid. This solution was subjected to column chromatography using an RP-18 reverse-phase prepacked column. Elution with water containing 3% (v/v) acetonitrile gave 16 mg (84.3%) of **13a**. It was reported that the UV spectra of guanin-7-yl and guanin-9-yl nucleosides were extremely different.[17] The structures of compounds **13a** and **13b** were determined by comparing their UV data with reported values. *Anal.* Calcd for $C_{14}H_{15}N_5O_9\cdot 2H_2O$: C, 38.80; H, 4.42; N, 16.16. Found: C, 38.52; H, 4.44; N, 16.37. UV $\lambda_{max}^{H_2O}$ nm (ε): 252 (12800), 273 sh (8900); 0.1 N NaOH: 258 (10900), 265 (11000); 0.1 N HCl: 257 (11000), 280 sh (7700). NMR (D_2O) δ: 2.49 (1H, dd, J=6.3, 15.5 Hz, 5′-H), 2.64 (1H, dd, J=15.5, 1.5 Hz, 5′-H), 4.54—4.77 (3H, m, 2′, 4′ or 7′-H), 5.01—5.05 (1H, m, 3′-H), 5.89 (1H, d, J=7.3 Hz, 1′-H), 8.00 (1H, s).

1′-Deadenino-1′β-(guanin-7-yl)-4′β,5′-dihydrogriseolic Acid (13b)——In the reaction described for the synthesis of **13a**, 102.0 mg (41.0%) of dimethyl 1′-deadenino-1′β-(N^2-acetylguanin-7-yl)-4′β,5′-dihydro-$O^{2'}$,$O^{7'}$-dibenzoylgriseolate was isolated from the first fraction of silica gel column chromatography. *Anal.* Calcd for $C_{32}H_{29}N_5O_{12}\cdot 2H_2O\cdot 1/2$benzene: C, 56.00; H, 4.83; N, 9.33. Found: C, 55.71; H, 5.03; N, 9.09. UV $\lambda_{max}^{CH_3OH}$ nm (ε): 232 (28300), 260 sh (17300), 282 sh (13000), 253 (17700), 275 (13300). NMR (DMSO-d_6) δ: 6.52 (1H, d, J=6.0 Hz, 1′-H), 6.13 (1H, dd, J=6.0, 3.3 Hz, 2′-H), 5.01—5.20 (1H, m, 3′-H), 5.38—5.62 (1H, m, 4′-H), 2.62—2.88 (2H, m, 5′-H), 5.87 (1H, s, 7′-H), 8.50 (1H, s, 8-H), 3.66 (3H, s, CH_3), 3.79 (3H, s, CH_3), 2.19 (3H, s, CH_3CO), 7.2—8.2 (13H, m, benzoyl+1/2benzene), 11.53 (1H, s, NH), 12.19 (1H, s, NH).

In the same manner as described for the synthesis of **13a**, 28.0 mg (53.8%) of 1′β-(N^2-acetylguanin-7-yl)-1′-

deadenino-4′β,5′-dihydrogriseolic acid was obtained from 80 mg (0.12 mmol) of the compound obtained above. *Anal.* Calcd for $C_{16}H_{17}N_5O_{10}\cdot 3H_2O$: C, 38.95; H, 4.66; N, 14.20. Found: C, 38.62; H, 4.51; N, 14.39. NMR (D_2O) δ: 6.02 (1H, d, J=6.6 Hz, 1′-H), 4.65—4.79 (3H, m, 2′-, 4′- and 7′-H), 5.11—5.16 (1H, m, 3′-H), 2.47 (1H, dd, J=6.4, 15.1 Hz, 5′-H), 2.67 (1H, dd, J=15.1, 1.6 Hz, 5′-H), 8.22 (1H, s, 8-H), 2.11 (3H, s, CH_3).

Using 24 mg (0.05 mmol) of the compound obtained above, a similar reaction to that used in the synthesis of **13a** was carried out at room temperature for 2 d. Worked-up gave 16 mg (73.7%) of **13b**. *Anal.* Calcd for $C_{14}H_{15}N_5O_9\cdot 3H_2O$: C, 37.26; H, 4.69; N, 15.51. Found: C, 36.98; H, 4.88; N, 15.72. UV $\lambda_{max}^{H_2O}$ nm (ε): 246 sh (6400), 285 (7800); 0.1 N NaOH: 282 (6800); 0.1 N HCl: 250 (7800), 264 (7100). NMR (D_2O) δ: 5.92 (1H, d, J=7.3 Hz, 1′-H), 4.4—4.66 (3H, m, 2′-, 4′- and 7′-H), 4.99—5.01 (1H, m, 3′-H), 2.36 (1H, dd, J=15.8, 6.5 Hz, 5′-H), 2.48 (1H,dd, J=15.8, 1.6 Hz, 5′-H), 8.05 (1H, s, 8-H).

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References and Notes

1) Part VI: *Chem. Pharm. Bull.*, **36**, 1309 (1988).
2) F. Nakagawa, T. Okazaki, A. Naito, Y. Iijima, and M. Yamazaki, *J. Antibiot.*, **38**, 823 (1985).
3) S. Takahashi, F. Nakagawa, K. Kawazoe, Y. Furukawa, S. Sato, C. Tamura, and T. Naito, *J. Antibiot.*, **38**, 830 (1985).
4) Y. Murofushi, M. Kimura, Y. Iijima, M. Yamazaki, and M. Kaneko, *Chem. Pharm. Bull.*, **35**, 1036 (1987).
5) Y. Murofushi, M. Kimura, Y. Iijima, M. Yamazaki, and M. Kaneko, *Chem. Pharm. Bull.*, **35**, 4442 (1987).
6) F. Nakagawa, Y. Tsujita, and M. Yamazaki, Japan Kokai., No. 60-246396 [*Chem. Abstr.*, **104**, 67509*g* (1986)].
7) S. Goldschmidt, R. Endres, and R. Dirsch, *Chem. Ber.*, **58**, 572 (1925); W. E. Rarham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948); H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, **1950**, 3646; M. Anbar and D. Ginsbury, *Chem. Ber.*, **54**, 925 (1954); P. Mastagli, P. Lambert, and G. Francois, *Bull. Soc. Chim. Fr.*, **1957**, 764; H. J. E. Loewenthal, *Tetrahedron*, **6**, 303 (1959); K. L. Erickson and K. Kim., *J. Org. Chem.*, **36**, 2915 (1971); G. L. Grady and S. K. Chokshi, *Synthesis*, **1972**, 483; H. Arita, N. Ueda, and Y. Matsushima, *Bull. Chem. Soc. Jpn.*, **45**, 567 (1972).
8) W. Reppe, *Ann. Chem.*, **601**, 91 (1956).
9) M. Saneyoshi and E. Satoh, *Chem. Pharm. Bull.*, **27**, 2518 (1979); M. Saneyoshi, J. Tohyama, and C. Nakayama, *ibid.*, **30**, 2223 (1982).
10) Condensation using a halogeno sugar in the presence of $SnCl_4$: K. A. Watanabe, D. H. Hollenberg, and J. J. Fox, *J. Carbohydr. Nucleosides Nucleotides*, **1**, 1 (1974); E. K. Ryu and T. J. Bardos, *J. Heterocycl. Chem.*, **16**, 1049 (1979); V. Nelson, H. S. El. Khadem, B. K. Whitten, and D. Sesselman, *J. Med. Chem.*, **26**, 1071 (1983); HD. Winkeler and F. Seela, *J. Org. Chem.*, **48**, 3119 (1983); K. A. Watanabe and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 109 (1969).
11) Condensation using an acetoxy sugar with a purine base in the presence of $SnCl_4$: Y. Furukawa and M. Honjo, *Chem. Pharm. Bull.*, **16**, 1076 (1968); C. Nakayama and M. Saneyoshi, *Nucleosides & Nucleotides*, **1**, 139 (1982).
12) Condensation using an acetoxy sugar with a pyrimidine base in the presence of $SnCl_4$: U. Niedballa and H. Vorbrueggen, *J. Org. Chem.*, **39**, 3654 (1974); A. Szemzo, A. Szabolcs, J. Sagi, and L. Oetvoes, *J. Carbohydr. Nucleosides Nucleotides*, **7**, 365 (1980).
13) Reviews of condensation: R. R. Schmidt, G. R. Loesch, and P. Fischer, *Chem. Ber.*, **113**, 2891 (1980); H. Vorbrueggen and G. Hoefle, *ibid.*, **114**, 1256 (1981); H. Vorbrueggen, K. Krolikiewicz, and B. Bennua, *ibid.*, **114**, 1234 (1981); H. Vorbrueggen and B. Bennua, *ibid.*, **114**, 1279 (1981).
14) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect-Chemical Applications," Academic Press, New York and London, 1971, pp. 190—200.
15) A. L. Pichard and W. Y. Cheung, *J. Biol. Chem.*, **251**, 5726 (1976).
16) E. J. Prishe, J. Smejkal, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **41**, 1836 (1976).
17) T. Azuma, and K. Isono, *Chem. Pharm. Bull.*, **25**, 3348 (1977).