# Synthesis and Optical Properties of 2′-Deoxy-8,2′-methanoguanosine

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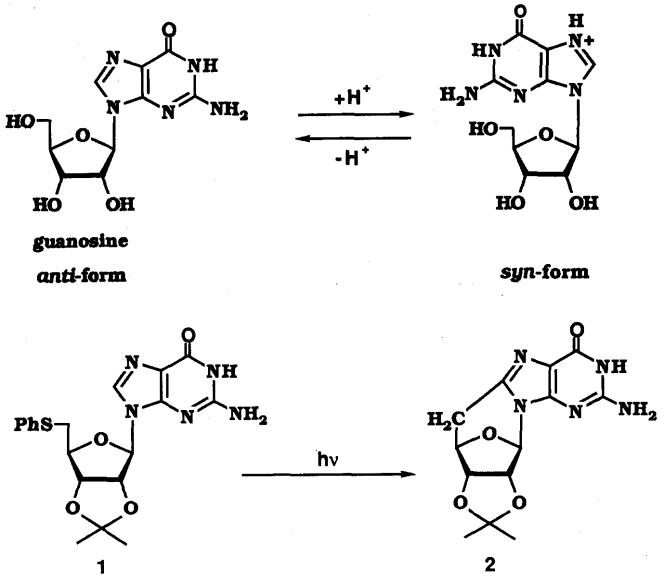
**The synthesis of a new carbon-bridged cyclopurine nucleoside, 2′-deoxy-8,2′-methanoguanosine (25), which is fixed in a high-anti torsional angle region, was accomplished. 2-Acetamido-6-ethoxy-8-methanesulfonyl-9-(3,5-di-*O*-acetyl-2-*O*-tosyl-1-β-D-ribofuranosyl)purine (18) was cyclized with carbanions of malonic esters, followed by sequential deblocking and decarboxylation to afford 25. The ultraviolet spectra of 25 in neutral solution revealed two separated bands corresponding to their $B_{1u}$ and $B_{2u}$ transitions, which was rather similar to the case of its $O^6$-ethyl derivative (22), but quite different from the previously reported 8,2′-methanoguanosine (26), a ribosyl counterpart of 25. The circular dichroism spectra of these cyclonucleosides are also discussed.**

**Keywords** 2′-deoxy-8,2′-methanoguanosine; nucleoside; carbon-bridged cyclonucleoside; CD spectrum; UV spectrum; carbanion; malonic ester; conformation

It has been shown that circular dichroism (CD) spectra provide important information about the conformation of molecules. In nucleosides and nucleotides, they reflect the anomeric configuration as well as the orientation of the nucleobase chromophores. In neutral aqueous solution of guanosine, a negative CD band appears around the 250 nm ($B_{1u}$ transition) region, whereas in acidic media, a positive band just like a mirror image is seen. As the guanine base in guanosine is known to be protonated at the N-7 position in acidic medium, Guschlbauer and Courtois postulated a conformational change between the *anti*-conformer and the *syn*-conformer of guanosine in protonation.[1] In order to clarify this phenomenon further, we synthesized a conformationally-fixed guanosine in the *anti* form, 5′-deoxy-8,5′-cycloguanosine (**2**), by a photo-induced radical cyclization reaction of 5′-deoxy-5′-phenylthioguanosine derivative (**1**).[2] The CD spectrum of **2** in neutral aqueous solution showed a negative CD band in the 250 nm ($B_{1u}$ transition) region, and its magnitude was about 2.5 times larger than that of guanosine itself. However, in acidic solution, **2** had a positive band at around 250 nm and a negative band at 285 nm ($B_{2u}$ transition), whose magnitudes were also larger than that of guanosine.[2a,b] Since this carbon-bridged cycloguanosine (**2**) does not rotate around the glycosyl linkage, we concluded that the CD spectral differences of guanosine in neutral and acidic solutions were not due to *anti–syn* equilibrium but to electronic structural changes of the chromophore caused by protonation. In order to investigate the CD phenomena *versus syn–anti* conformation further, we needed cycloguanosines in which the glycosyl linkages were fixed in different torsional angles.




Recently, we reported the synthesis of 8,2′-methanoguanosine from a 2′-ketoguanosine derivative.[3] This process, however, gave a mixture of the α- and β-anomers as a result of anomerization of the 2′-keto nucleoside. On the other hand, we also reported a new method for the synthesis of 2′-deoxy-8,2′-methanoadenosine which involved intramolecular cyclization of a 2′-*O*-tosyladenosine 8-malonate derivative.[4] The latter process represents a useful alternative approach to the synthesis of carbon-bridged cyclopurine nucleosides.

In this paper, we describe the synthesis of 2′-deoxy-8,2′-methanoguanosine (**25**) by the reaction of doubly activated guanosine derivative with carbanions of malonic esters which serve as a one-carbon synthon of a bridge-head position of **25**. The optical properties of **25** and other compounds are also described. A preliminary account of this work has appeared previously.[5]

It seems necessary to protect the $N^1$ or $O^6$-dissociable proton when a carbon substituent is to be introduced into the 8-position of guanosine by a nucleophilic substitution reaction. Recently, alkyl protection of the $O^6$-position of guanosine has been reported[6] using the Mitsunobu reaction. Treatment of $N^2$,2′,3′,5′-*O*-tetraacetylguanosine (**3**) with triphenylphosphine, diethyl azodicarboxylate, and ethanol in dioxane afforded the 6-ethoxy derivative (**4**) in good yield. However, in the large scale preparation of **4**, removal of the co-product, triphenylphosphine oxide, became difficult. In order to avoid such complications, the reaction mixture was treated with methanolic ammonia at room temerature to remove the acetyl groups in the sugar moiety, and 2-acetamido-6-ethoxypurine riboside (**5**) was directly crystallized from methanol in 71% yield. Bromination of **5** at the 8-position was next examined. Treatment of **5** with *N*-bromosuccinimide (NBS) in *N*,*N*-

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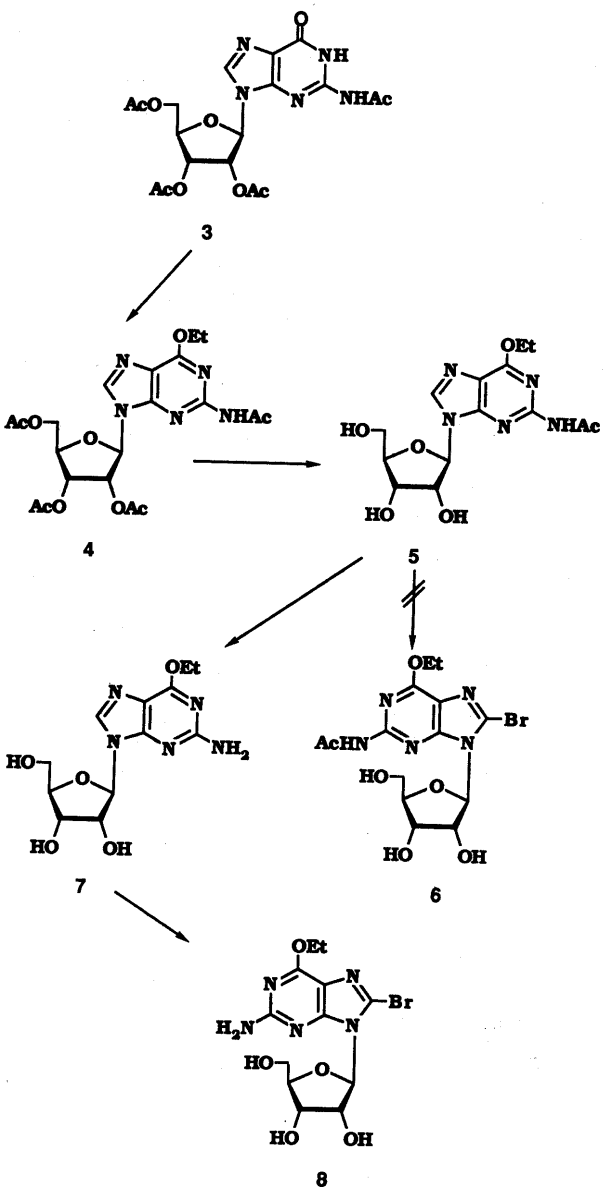
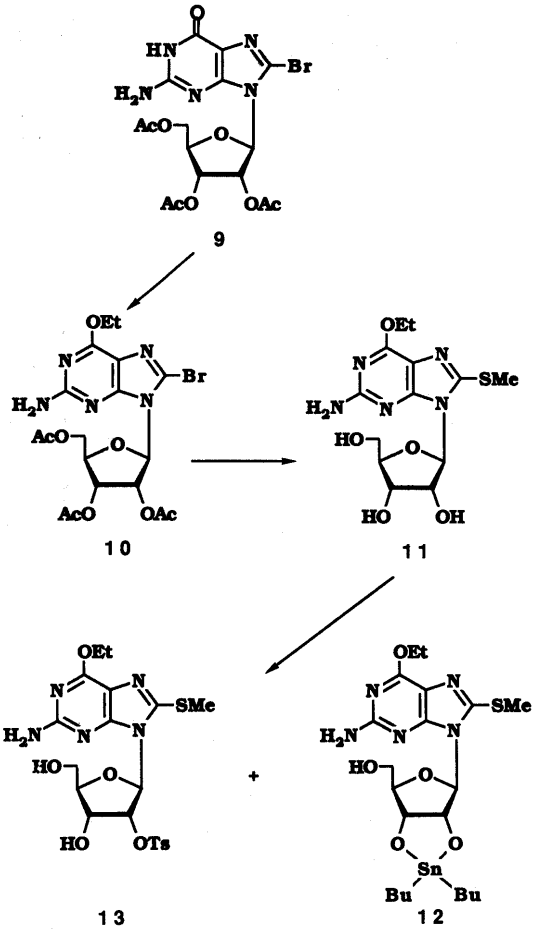
dimethylformamide (DMF) at room temperature gave the desired 8-bromo derivative (**6**) only in a trace amount. However, compound **7**, obtained by removal of the acetyl group at the $N^2$-position of **5** with methanolic ammonia at 65 °C in a sealed tube, was smoothly brominated with NBS to afford 2-amino-8-bromo-6-ethoxypurine riboside (**8**) in 68% yield from **5**. Treatment of **8** with sodium methanethiolate in DMF gave the 8-methylthio derivative (**11**) in a good yield. Since this sequence of reactions to obtain **11** was rather lengthy, we devised a more convenient method.




In the protection of the $O^6$-position of guanosine by the Mitsunobu reaction, Pfleiderer *et al.* reported that the 2-amino group of guanosine has to be acylated.[6] The acidity of the $N^1$-proton may be important in this reaction. In 8-bromoguanosine, the acidity of the $N^1$-proton should be sufficiently strong. On treatment of tri-*O*-acetyl-8-bromoguanosine (**9**) with triphenylphosphine, diethyl azodicarboxylate and ethanol in dioxane, the desired 8-bromo-6-ethoxy derivative (**10**) was readily obtained, and this, without isolation, was then reacted with sodium methanethiolate in DMF to furnish **11** in 82% yield from **9**.




An initial attempt at the tosylation of the 2′-hydroxyl group of **11** by treatment with dibutyltin oxide in methanol followed by tosyl chloride and triethylamine,[7] gave the desired tosylate **13** in 22% yield, along with the 2′,3′-cyclic-stannylene derivative (**12**) in 13% yield, due to the low solubility of **12** in methanol. In order to increase the solubility in methanol, the 2-amino group of **11** was acetylated. Compound **11** was fully acetylated first with acetic anhydride and a catalytic amount of 4-dimethylaminopyridine (DMAP) in pyridine at reflux temperature giving **14**. This was followed by selective removal of the acetyl groups in the sugar moiety with methanolic ammonia to afford **15** in 85% yield. Tosylation of **15** proceeded well to give **16** in 88% yield. Re-acetylation of the sugar hydroxyl groups of **16** to increase the solubility to tetrahydrofuran (THF) and to avoid undesired glycosyl bond cleavage[7] was carried out with acetic anhydride and DMAP in acetonitrile.[8] The resultant fully protected nucleoside (**17**) was oxidized with *m*-chloroperoxybenzoic acid in dichloromethane to furnish the 8-methylsulfone (**18**), the key material for the reaction with carbanions, in 94% yield from **16**.

Compound **18** was treated with sodio diethyl malonate in THF at reflux temperature for 4 h. The desired cyclized nucleoside (**19**) was obtained in 81% yield as a foam after purification by silica gel column chromatography. In contrast, treatment of **18** with sodio dimethyl malonate under similar conditions gave the cyclized monoester product (**20**) in 88% yield. Assignment of the cyclized structures of **19** and **20** rests on their proton nuclear magnetic resonance

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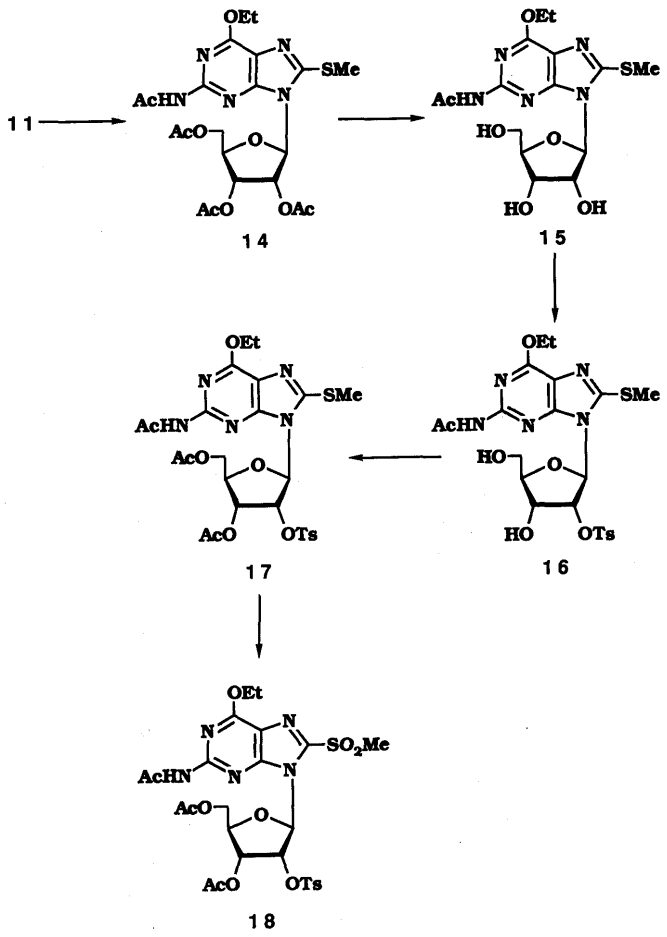
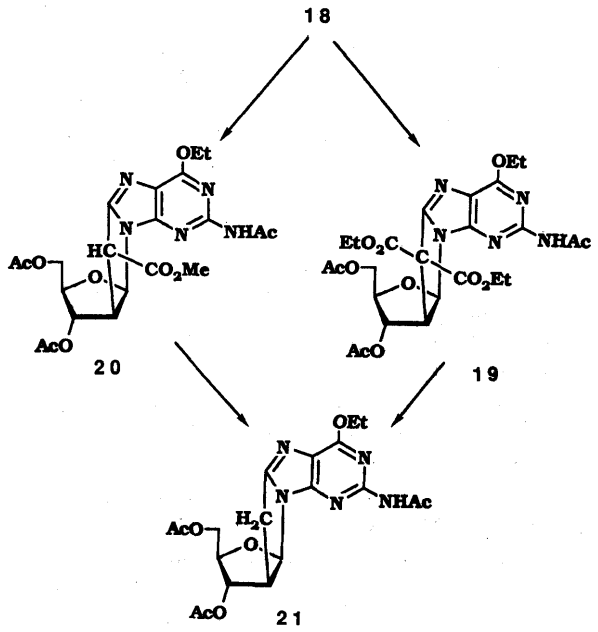
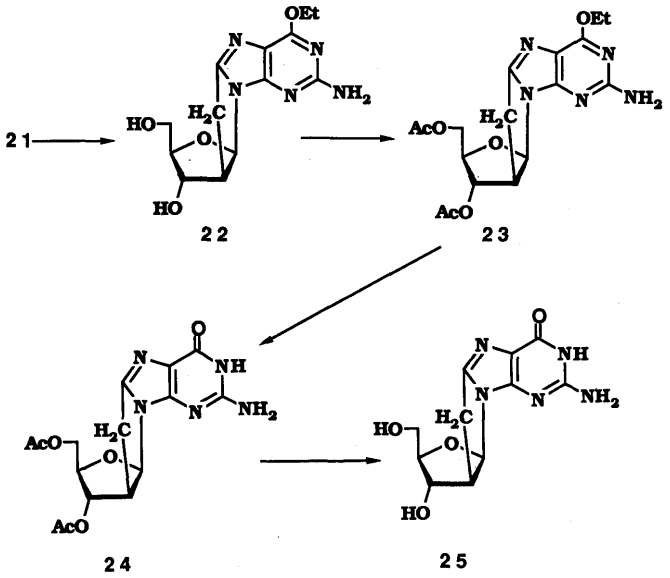



($^1$H-NMR) spectra which showed absence of the tosyl protons and characteristic upfield shifts of the 2′-proton signal from $\delta$6.16 (in **18**) to 4.29 (in **19**) or 4.04 (in **20**). These data, together with the mass spectroscopic data ($M^+$ for **19**, *m/z* 577, 5.4% and $M^+$ for **20**, *m/z* 491, 100%), confirmed the structures of **19** and **20**. These carbon-bridged cyclonucleosides **19** or **20** were then heated in aqueous pyridine at reflux temperature to afford the decarboxylated methano derivative (**21**) in 78% yield after 3 d from **19** or in 94% yield after 1 d from **20**.




Deblocking of **21** in both sugar and base moieties can lead to the target 2-deoxy-8,2′-methanoguanosine (**25**). Initially, de-*O*-ethylation of **21** with trimethylsilyl iodide (prepared from trimethylsilyl chloride and sodium iodide in acetonitrile) was attempted.[9] In this case, however, only an intractable mixture was obtained. After deacetylation of **21** to give **22** with methanolic ammonia at 100 °C in a sealed tube, the sugar hydroxyls of **22** were selectively acetylated to give **23**. Treatment of **23** with trimethylsilyl iodide in acetonitrile afforded di-*O*-acetyl-2′-deoxy-8,2′-methanoguanosine (**24**) in 71% yield. Compound **24** was deacetylated by treatment with methanolic ammonia to furnish 2′-deoxy-8,2′-methanoguanosine (**25**) in a crystalline form. The structure of **25** was confirmed on the basis of the following data. The mass spectrum (MS) of **25** revealed a molecular ion peak at 279 (*m/z* 14%) and the correct elemental analysis ($C_{11}H_{13}N_5O_4$) as a hydrate was obtained. In its $^1$H-NMR spectrum, two sets of double doublets at $\delta$2.86 and 3.13 were assigned as bridge methylene protons at C-2″ whose coupling constants with H-2′ were 3.8 Hz (for H-2″a) and 9.8 Hz (for H-2″b). From these data, it is clear that the correlation between H-2′ and H-2″a is an eclipsed conformation. The sugar puckering in **25** is assumed to be of the 4′-*endo*-3′-*exo* form based on the coupling constants of other sugar protons (see the experimental section) and the guanine base is fixed in a high-*anti* torsional angle.




The CD and ultraviolet (UV) spectra of 2′-deoxy-8,2′-methanoguanosine (**25**) and its $O^6$-ethyl derivative (**22**) are shown in Fig. 1. The spectra of 8,2′-methanoguanosine (**26**)[3] are also included for comparison. As has been discussed previously[10] the sign and magnitude of the CD spectra are a function of the glycosyl torsion angle of the nucleosides. The CD and UV spectra of **22** closely resemble to those of the ribosyl counterpart,[3] having two negative CD bands corresponding to their $B_{1u}$ and $B_{2u}$ transitions. However, the CD spectra of **25** exhibited a somewhat different pattern than expected from that of the ribosyl counterpart (**26**), and the overall shape (sign of the respective bands) was rather similar to that of **2**,[2a,b] although

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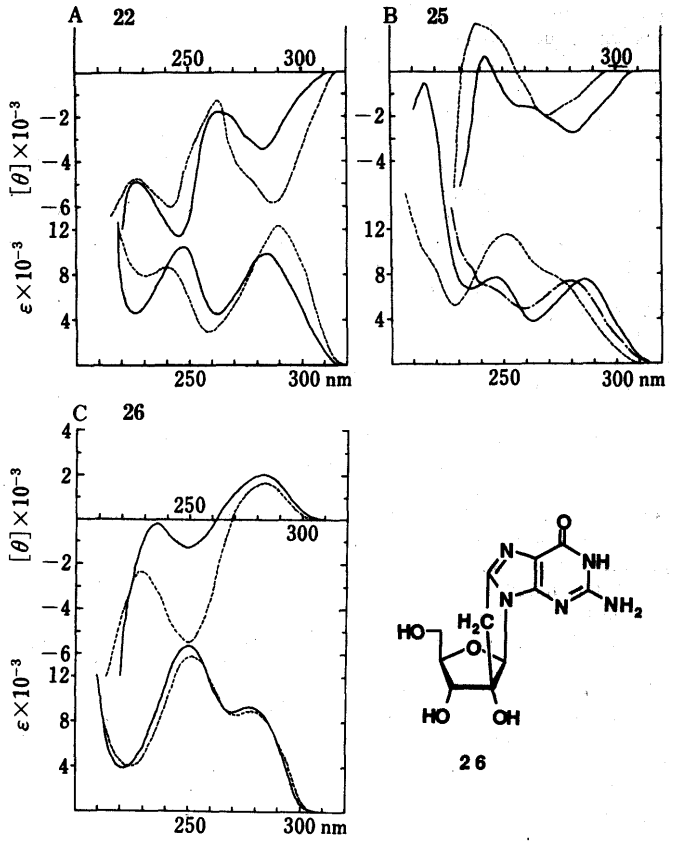


Fig. 1. CD and UV Spectra of 2-Amino-6-ethoxy-8,2′-methano-9-(2-deoxy-β-D-arabinofuranosyl)-9*H*-purine (**22**, A), 2′-Deoxy-8,2′-methanoguanosine (**25**, B) and 8,2′-Methanoguanosine (**26**, C)

——, in $H_2O$; ------, in 0.5 N HCl; —·—, in 0.5 N NaOH.

the amplitudes were smaller than those in both the neutral and acidic form. It should be noted that the UV spectrum of **25** in neutral solution was rather different from those of **26** and other guanosine derivatives, in separating the $B_{1u}$ and $B_{2u}$ absorption peaks. At present, it is difficult to explain the difference in the UV (and CD) spectra between **25** and **26** which was caused simply by the presence or absence of the 2′-hydroxyl group. There may be some distortion of the planarity of the guanine chromophore due to the two condensed 5-membered rings which might be affected by the absence or presence of the 2′-hydroxyl group and might also change the glycosyl torsion angle. In compound **26**, extra intramolecular hydrogen bond formation or solvation would be possible on the 2′-hydroxyl group which is not expected in **25**. Also of note is the difference in $pK_{a1}$ values: whereas **26** showed a $pK_{a1}$ of 2.07 for the N-7 protonation, the $pK_{a1}$ of **25** was found to be 3.02. This difference (1 $pK_a$ unit) is more than that expected from the presence or absence of the 2′-hydroxyl group. The distortion of the guanine chromophore of **25** may be a consequence of this increased basicity. The non-negligible UV difference between **25** and **26** should reflect the diffrences in the CD spectra. Such differences of CD spectra due to a slight change of structure have also been observed in a series of carbon-bridged cycloadenosines.[10] In the case of 8,2′-methanoadenosine and its 2′-deoxy counterpart, the difference concerned the amplitude.[10] Precise determinations of the molecular structure and glycosyl torsion angles of methanoguanosines in the solid state (or in solution) and theoretical treatment of the CD spectra are needed to resolve these problems.

## Experimental

Melting points were determined in a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The $^1$H-NMR spectra were recorded using a JEOL FT100FT or FX-270FT spectrometer with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million ($\delta$), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). All exchangeable protons were confirmed by addition of $D_2O$. UV absorption spectra were recorded with a Shimadzu UV-240 spectrophotometer. MS were measured on a JEOL D-300 spectrometer. CD spectra were recorded using a JASCO J-500A spectropolarimeter at room temperature. Thin layer chromatography (TLC) was performed on Merck Kieselgel F254 precoated plates. The silica gel employed for column chromatography was Merck Kieselgel 60 (70—230 mesh).

**2-Acetamido-6-ethoxy-9-(β-D-ribofuranosyl)-9*H*-purine (5)** A solution of diethyl azodicarboxylate (98%, 8.8 ml, 53 mmol) in dioxane (20 ml) was added dropwise over 40 min to a mixture of $N^2$,2′,3′,5′-*O*-tetraacetylguanosine (**3**, 14.9 g, 33 mmol) and triphenylphosphine (13 g, 50 mmol) in dioxane (100 ml) containing EtOH (7.8 ml, 133 mmol) with stirring at 0 °C. The reaction mixture was further stirred for 30 min at room temperature, and then evaporated to dryness *in vacuo*. The residue was treated with methanolic ammonia (100 ml, saturated at 0 °C) overnight at room temperature. Evaporation of the mixture gave a thick oil which was crystallized from MeOH to afford **5** (8.3 g, 71%), mp 195—198 °C. MS *m/z*: 353 ($M^+$, 16%), 221 ($B^+$, 50%). $^1$H-NMR (DMSO-$d_6$): 1.41 (3H, t, $OCH_2\underline{CH_3}$), 2.23 (3H, s, Ac), 3.64 (2H, m, H-5′, 5″), 3.94 (1H, m, H-4′), 4.18 (1H, m, H-3′), 4.47—4.68 (3H, m, H-2′, $O\underline{CH_2}CH_3$), 4.96 (1H, t, 5′-OH), 5.16 and 5.46 (each 1H, d, 2′- or 3′-OH), 5.89 (1H, d, H-1′, $J_{1',2'}$ = 5.9 Hz), 8.43 (1H, s, H-8), 10.36 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{19}N_5O_6$: C, 47.59; H, 5.42; N, 19.82. Found: C, 47.74; H, 5.59; N, 19.84.

**2-Amino-6-ethoxy-9-(β-D-ribofuranosyl)-9*H*-purine (7)**[12] A mixture of **5** (3.09 g, 8.7 mmol) in mthanolic ammonia (50 ml, saturated at 0 °C) was heated at 65 °C in a sealed tube. After 1 d, the mixture was evaporated *in vacuo* and the residue was crystallized from water to give **7** (2.75 g, 97.5%), mp 201—202 °C. MS *m/z*: 311 ($M^+$, 10%), 281 ($M^+-30$, 2%), 222 ($M^+-89$, 10%), 179 ($B^+$, 100%). $^1$H-NMR (DMSO-$d_6$): 1.36 (3H, t, $OCH_2\underline{CH_3}$), 3.59 (2H, m, H-5′,5″), 3.89 (1H, m, H-4′), 4.11 (1H, m, H-3′), 4.35—4.56 (3H, m, H-2′, $O\underline{CH_2}CH_3$), 5.04 (1H, t, 5′-OH), 5.11 and 5.38 (each, 1H, d, 2′- or 3′-OH), 5.78 (1H, d, H-1′, $J_{1',2'}$ = 5.9 Hz), 6.38 (2H, br s, $NH_2$), 8.08 (1H, s, H-8). UV $\lambda_{max}^{H_2O}$ nm (ε): 280.5 (8400), 249 (8500), 211 (20000); $\lambda_{min}$: 262 (4520), 227 (3600). $\lambda_{max}^{0.5\,N\,NaOH}$: 280.5 (8880), 249 (8440); $\lambda_{min}$: 262 (5030), 234 (6100). $\lambda_{max}^{0.5\,N\,HCl}$: 290.5 (8620), 244 (6140); $\lambda_{min}$: 262 (2840). CD ($H_2O$) [θ] (nm): 280 (−460), 248 (−3580), 236 (0), 225 (+2560). *Anal.* Calcd for $C_{12}H_{17}N_5O_5$: C, 46.30; H, 5.51; N, 22.50. Found: C, 46.29; H, 5.80; N, 22.43.

**2-Amino-8-bromo-6-ethoxy-9-(β-D-ribofuranosyl)-9*H*-purine (8)** A mixture of NBS (2.32 g, 13 mmol) and **7** (2.6 g, 8.7 mmol) in dry DMF (20 ml) was stirred for 2 h at room temperature, and then evaporated to dryness. The resulting oil was crystallized from aqueous MeOH to give **8** (2.25 g, 68.4%), mp 121—124 °C. MS *m/z*: 391, 389 ($M^+$, 6%), 302, 300 ($M^+-89$, 11%), 259, 257 ($B^+$, 100%). $^1$H-NMR (DMSO-$d_6$): 1.35 (3H, t, $OCH_2\underline{CH_3}$), 3.65 (2H, m, H-5′,5″), 3.86 (1H, m, H-4′), 4.18 (1H, m, H-3′), 4.44 (2H, q, $O\underline{CH_2}CH_3$), 4.99—5.20 (3H, m, OH, H-2′, after addition of $D_2O$, the peaks became triplet at $\delta$ 5.03 ppm, $J_{1',2'} = J_{2',3'}$ = 6.4 Hz), 5.37 (1H, d, 2′- or 3′-OH), 5.74 (1H, d, H-1′), 6.48 (2H, br s, 2-$NH_2$). *Anal.* Calcd for $C_{12}H_{16}BrN_5O_5$: C, 36.94; H, 4.13; N, 17.95. Found: C, 37.25; H, 4.28; N, 17.69.

**2′,3′,5′-Tri-*O*-acetyl-8-bromoguanosine (9)** Acetic anhydride (21.6 ml, 229 mmol) was added to a solution of 8-bromoguanosine[11] (20.7 g, 57.2 mmol), DMAP (150 mg) and $Et_3N$ (31.9 ml, 229 mmol) in dry acetonitrile (200 ml). The mixture was stirred for 1.5 h at room temperature, and then quenched by addition of MeOH (30 ml). The mixture was evaporated and the oily residue was crystallized from $H_2O$ to give **9** (23.5 g, 84.1%), mp 215—217 °C, lit.[13] mp 214—217 °C.

**2-Amino-6-ethoxy-8-methylthio-9-(β-D-ribofuranosyl)-9*H*-purine (11)** a) A solution of diethyl azodicarboxylate (5.53 ml, 35 mmol) in dioxane (30 ml) was added dropwise over 30 min to a suspension of **9** (11.42 g, 23.4 mmol), triphenylphosphine (9.2 g, 35 mmol), and EtOH (2.04 ml, 35 mmol) in dioxane (250 ml) with stirring at room temperature. After further stirring for 30 min, the reaction mixture was evaporated to dryness

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*in vacuo*. The residue (**10**) was dissolved in DMF (100 ml) and 15% aqueous NaSMe solution (43.4 ml) was added to the above solution. The mixture was heated at 70 °C for 1 d, then neutralized with 1 N HCl with bubbling $N_2$, and evaporated to dryness. Silica gel was added to the MeOH solution of the residue which was evaporated to dryness. The resulting silica gel was placed on top of a silica gel column (3.5 × 38 cm) which was washed with 4% EtOH in $CHCl_3$ to remove triphenylphosphine oxide and then eluted with 30% EtOH in $CHCl_3$ to afford **11** (6.83 g, 81.7%, crystallized from $H_2O$), mp 120—124 °C then solidified and melted at 190—192 °C. MS *m/z*: 357 ($M^+$, 17%), 268 ($M^+-89$, 12%), 225 ($B^+$, 100%). $^1$H-NMR (DMSO-$d_6$): 1.36 (3H, t, $OCH_2\underline{CH_3}$), 2.63 (3H, s, $SCH_3$), 3.59 (2H, m, H-5′, 5″), 3.87 (1H, m, H-4′), 4.14 (1H, m, H-3′), 4.44 (2H, q, $O\underline{CH_2}CH_3$), 4.86—5.20 (3H, m, OH, H-2′, after addition of $D_2O$, they became triplet at 4.94 ppm, $J_{1',2'}=J_{2',3'}=6.8$ Hz), 5.37 (1H, d, OH), 5.66 (1H, d, H-1′), 6.27 (2H, br s, $NH_2$). *Anal.* Calcd for $C_{13}H_{19}N_5O_5S$: C, 43.69; H, 5.36; N, 19.60. Found: C, 43.49; H, 5.39; N, 19.48.

b) A mixture of **7** (5.75 g, 18.5 mmol) and NBS (4.91 g) in DMF (35 ml) was stirred for 2 h at room temperature (to give **8**), and then 15% aqueous NaSMe solution (23.4 ml) was added to the mixture which was further stirred at room temperature. After 1 d, the reaction mixture was neutralized with 1 N HCl with bubbling $N_2$, and evaporated to dryness. The residue was crystallized from $H_2O$ to give 5.03 g (76.2%) of **11**.

**Tosylation of Compound 11** A mixture of **11** (4.5 g, 12.6 mmol) and dibutyltin oxide (3.44 g, 13.8 mmol) in MeOH (600 ml) was heated under reflux for 4 h. Tosyl chloride (35.2 g, 185 mmol) was then added portionwise to the above mixture containing triethylamine (24.1 ml, 173 mmol) with stirring at 0 °C. The mixture was stirred for a further 3 h at room temperature. The precipitate was collected by filtration to give **12** (965 mg, 13%), mp 255—257 °C (dec.). *Anal.* Calcd for $C_{21}H_{35}N_5O_5SSn$: C, 42.87; H, 6.00; N, 11.91. Found: C, 42.78; H, 5.97; N, 11.77. The filtrate was evaporated to dryness and the residue was purified over a silica gel column (4.5 × 31 cm) which was washed with hexane/$Et_2O$ (1 : 1) and $CHCl_3$ and then eluted with 4% EtOH in $CHCl_3$ to give **13** (1.46 g, 22%, crystallized from $H_2O$).

**2-Acetamido-6-ethoxy-8-methylthio-9-(β-D-ribofuranosyl)-9*H*-purine (15)** A mixture of **11** (10 g, 28 mmol), DMAP (30 mg) and $Ac_2O$ (13.2 ml, 140 mmol) in dry pyridine (70 ml) was heated under reflux for 24 h. It was then evaporated to dryness *in vacuo*, and subsequently coevaporated several times with benzene. The residue (**14**) was treated with methanolic ammonia (150 ml, saturated at 0 °C) for 8 h at room temperature, and then evaporated to dryness. The residue dissolved in MeOH was mixed with silica gel and the whole sample was evaporated to dryness. The residue was placed on a silica gel column (3.5 × 20 cm) which was washed with 8% EtOH in $CHCl_3$, and then eluted with 16% EtOH in $CHCl_3$. From the latter fractions, compound **15** (9.5 g, 85%, crystallized from EtOH, mp 206—208 °C) was obtained. MS *m/z*: 399 ($M^+$, 18%), 310 ($M^+-89$, 13%), 267 ($B^+$, 96%). $^1$H-NMR (DMSO-$d_6$): 1.40 (3H, t, $OCH_2\underline{CH_3}$), 2.20 (3H, s, NH$\underline{Ac}$), 2.69 (3H, s, SMe), 3.42—3.65 (2H, m, H-5′,5″), 3.82 (1H, m, H-4′), 4.22 (1H, m, H-3′), 4.54 (2H, q, $O\underline{CH_2}CH_3$), 5.07 (1H, t, H-2′, $J_{1',2'}=J_{2',3'}=6.4$ Hz), 5.67 (1H, d, H-1′), 10.31 (1H, br s, NH). *Anal.* Calcd for $C_{15}H_{21}N_5O_6S$: C, 45.11; H, 5.30; N, 17.53. Found: C, 44.99; H, 5.26; N, 17.61.

**2-Acetamido-6-ethoxy-8-methylthio-9-(2-*O*-tosyl-1-β-D-ribofuranosyl)-9*H*-purine (16)** A suspension of **15** (5.8 g, 14.5 mmol) and dibutyltin oxide (3.98 g, 16 mmol) in MeOH (600 ml) was heated under reflux for 2 h (at this time, a clear solution was obtained), and the mixture was then cooled in an ice bath. Triethylamine (29 ml, 208 mmol) and tosyl chloride (40.1 g, 210 mmol) were added to the mixture, which was stirred for 3 h at room temperature followed by evaporation *in vacuo*. The residue was partitioned between $CHCl_3$ and $H_2O$ and the organic phase was washed several times with $H_2O$, dried ($Na_2SO_4$), and evaporated to dryness. The residue was chromatographed over a silica gel column (9.4 × 40 cm) with $CHCl_3$–2% EtOH in $CHCl_3$ (about 3000 ml), and then with 8% EtOH in $CHCl_3$. The fractions containing **16** were evaporated to dryness to give 7.07 g (88%, foam). $^1$H-NMR (DMSO-$d_6$): 1.43 (3H, t, $OCH_2\underline{CH_3}$), 2.23 (6H, s, NH$\underline{Ac}$, TsMe), 2.68 (3H, s, SMe), 3.69—4.42 (4H, m, H-3′,4′,5′,5″), 4.53 (2H, q, $O\underline{CH_2}CH_3$), 5.73—5.91 (4H, m, H-1′,2′,3′- and 5′-OH), 6.94 (2H, d, Ph), 7.40 (2H, d, Ph), 10.32 (1H, br s, NH). *Anal.* Calcd for $C_{22}H_{27}N_5O_8S_2$: C, 47.73; H, 4.92; N, 12.65. Found: C, 47.49; H, 4.96; N, 12.56

**2-Acetamido-6-ethoxy-8-methanesulfonyl-9-(3,5-di-*O*-acetyl-2-*O*-tosyl-1-β-D-ribofuranosyl)-9*H*-purine (18)** Triethylamine (3.2 ml, 23 mmol) was added to a solution of **16** (4.21 g, 7.6 mmol) and DMAP (10 mg) in dry acetonitrile (50 ml) containing $Ac_2O$ (2.2 ml). The mixture was stirred for 1 h at room temperature, and MeOH (10 ml) was then added to the mixture to decompose excess $Ac_2O$. The mixture was evaporated to dryness and the residue was partitioned between EtOAc (100 ml) and $H_2O$ (20 ml × 2). The separated organic phase was dried ($Na_2SO_4$) and evaporated to dryness. A solution of the oily residue in $CH_2Cl_2$ (20 ml) was treated with *m*-chloroperoxybenzoic acid (4.7 g, 27 mmol) for 3 h at room temperature. After purification on a silica gel column (3.5 × 35 cm), which was washed with a mixture of benzene and EtOAc (1 : 1, 1000 ml), and then eluted with a mixture of benzene and EtOAc (1 : 5), compound **18** was obtained from the latter fractions in 94% yield (4.78 g, as a foam). MS *m/z*: 669 ($M^+$, 2.4%). $^1$H-NMR ($CDCl_3$): 1.53 (3H, t, $OCH_2\underline{CH_3}$), 2.00 (3H, s, Ac), 2.12 (3H, s, Ac), 2.36 (3H, s, Ac), 2.48 (3H, s, TsMe), 3.46 (3H, s, $SO_2\underline{Me}$), 4.34—4.55 (3H, m, H-4′,5′,5″), 4.65 (2H, q, $O\underline{CH_2}CH_3$), 5.71—5.81 (1H, m, H-3′), 6.16 (1H, dd, H-2′, $J_{1',2'}=4.9$, $J_{2',3'}=5.9$ Hz), 6.72 (1H, d, H-1′), 7.12 (2H, d, Ph), 7.59 (2H, d, Ph), 8.16 (1H, br s, NH). *Anal.* Calcd for $C_{26}H_{31}N_5O_{12}S_2$: C, 46.63; H, 4.67; N, 10.46. Found: C, 46.61; H, 4.74; N, 10.71.

**2-Acetamido-6-ethoxy-8,2′-diethoxycarbonylmethano-9-(3,5-di-*O*-acetyl-2-deoxy-β-D-arabinofuranosyl)-9*H*-purine (19)** A mixture of diethyl malonate (6.1 ml, 40 mmol) and dry THF (15 ml) was treated with NaH (494 mg, 12.4 mmol, 60% in mineral oil). After the evolution of $H_2$ gas had ceased, **18** (2.04 g, 3.05 mmol) in THF (20 ml) was added, and the mixture was heated under reflux for 4 h. The resultant suspension was neutralized with AcOH and filtered through a celite pad. The filtrate was concentrated and purified on a silica gel column (4.5 × 20 cm) which was washed with $CHCl_3$ (400 ml) to remove excess diethyl malonate. Compound **19** (1.43 g, 81.3%, foam) was eluted with 2% EtOH in $CHCl_3$. MS *m/z*: 577 ($M^+$, 5.4%), 505 ($M^+-CO_2Et+H$, 34%), 459 (505 − EtOH, 24%). $^1$H-NMR ($CDCl_3$): 1.35 (6H, t, $OCH_2\underline{CH_3}$), 1.49 (3H, t, $OCH_2\underline{CH_3}$), 1.86 (3H, s, Ac), 2.15 (3H, s, Ac), 2.58 (3H, s, Ac), 4.04 (2H, m, H-5′, 5″), 4.29 (1H, dd, H-2′, $J_{1',2'}=6.8$, $J_{2',3'}=1.0$ Hz), 4.45 (1H, m, H-4′), 4.59 (6H, q, $O\underline{CH_2}CH_3$), 5.14 (1H, t, H-3′, $J_{3',4'}=2.9$ Hz), 6.50 (1H, d, H-1′), 7.94 (1H, br s, NH).

**2-Acetamido-6-ethoxy-8,2′-methoxycarbonylmethano-9-(3,5-di-*O*-acetyl-2-deoxy-β-D-arabinofuranosyl)-9*H*-purine (20)** A mixture of dimethyl malonate (14.3 ml, 125 mmol) and THF (20 ml) was treated with NaH (1.14 g, 28.5 mmol, 60% in mineral oil). After the evolution of $H_2$ gas had ceased, **18** (4.78 g, 7.14 mmol) in dry THF (30 ml) was added, and the mixture was heated under reflux for 4 h. The suspension was neutralized with AcOH and filtered through a celite pad. The filtrate was evaporated to dryness and purified on a silica gel column (3.5 × 25 cm) which was washed with $CHCl_3$ (1000 ml) to remove an excess dimethyl malonate, and then eluted with 4% EtOH in $CHCl_3$ to give **20** (3.09 g, 88.1%, foam). MS *m/z*: 491 ($M^+$, 100%), 459 ($M^+$ − MeOH, 25%), 449 ($M^+-42$, 32%), 433 ($M^+-CO_2Me$, 13%), 417 ($M^+$ − MeOH − 42, 58%). $^1$H-NMR ($CDCl_3$): 1.49 (3H, t, $OCH_2\underline{CH_3}$), 1.86 (3H, s, Ac), 2.15 (3H, s, Ac), 2.58 (3H, s, NHAc), 3.85 (3H, s, $CO_2\underline{Me}$), 4.04 (3H, m, H-2′,5′,5″), 4.45—4.69 (4H, m, H-2″,4′, $O\underline{CH_2}CH_3$), 5.13 (1H, t, H-3′, $J_{2',3'}=J_{3',4'}=2.9$ Hz), 6.50 (1H, d, H-1′, $J_{1',2'}=6.8$ Hz), 7.91 (1H, br s, NH).

**2-Acetamido-6-ethoxy-8,2′-methano-9-(3,5-di-*O*-acetyl-2-deoxy-β-D-arabinofuranosyl)-9*H*-purine (21)** a) A solution of **20** (3.05 g, 6.2 mmol) in 85% aqueous pyridine (50 ml) was heated under reflux for 1 d. The mixture was evaporated and then coevaporated several times with benzene to leave a residue which was re-acetylated with $Ac_2O$ (1.8 ml), $Et_3N$ (2.6 ml) and DMAP (14 mg) in $CH_3CN$ (35 ml) for 1 h at room temperature. After the usual work-up, the residue was purified on a silica gel column (3.5 × 21 cm) which was eluted with 4% EtOH in $CHCl_3$ to give **21** (2.35 g, 94%, foam). MS *m/z*: 391 ($M^+$, 100%). $^1$H-NMR ($CDCl_3$): 1.49 (3H, t, $OCH_2\underline{CH_3}$), 1.88 (3H, s, Ac), 2.15 (3H, s, Ac), 2.58 (3H, s, Ac), 3.18 (1H, dd, H-2″a, $J_{2''a,2'}=2$, $J_{2''a,2''b}=17$ Hz), 3.43 (1H, dd, H-2″b, $J_{2''b,2'}=5.4$ Hz), 3.58—3.75 (1H, m, H-2′), 4.03 (2H, d, H-5′,5″, $J=4.4$ Hz), 4.44—4.51 (1H, m, H-4′), 4.57 (2H, q, $O\underline{CH_2}CH_3$), 5.14 (1H, t, H-3′, $J_{2',3'}=J_{3',4'}=2.4$ Hz), 6.42 (1H, d, H-1′, $J_{1',2'}=6.4$ Hz), 7.92 (1H, br s, NH).

b) A solution of **19** (1.4 g, 2.4 mmol) in 85% aqueous pyridine (40 ml) was heated under reflux for 3 d. After a similar work-up had been carried out as described in a), compound **21** was obtained as a foam in 78% yield (820 mg).

**2-Amino-6-ethoxy-8,2′-methano-9-(2-deoxy-β-D-arabinofuranosyl)-9*H*-purine (22)** A solution of **21** (1.33 g, 3 mmol) in methanolic ammonia (30 ml, saturated at 0 °C) was heated at 100 °C for 36 h in a sealed glass tube. After evaporation of the solvent, the residue was crystallized from EtOH to give **22** (912 mg, 96.8%), mp 142—144 °C. MS *m/z*: 307 ($M^+$, 100%). $^1$H-NMR (DMSO-$d_6$, 270 MHz): 1.33 (3H, t, $OCH_2\underline{CH_3}$), 2.82 (1H, dd, H-2″a, $J_{2''a,2'}=3.9$, $J_{2''a,2''b}=17.1$ Hz), 3.07 (1H, dd, H-2″b, $J_{2''b,2'}=9.8$ Hz), 3.08—3.25 (2H, m, H-5′,5″), 3.31—3.45 (1H, m, H-2′),

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3.91 (1H, m, H-4′), 4.03 (1H, m, H-3′), 4.41 (2H, q, $O\underline{CH_2}CH_3$), 4.72 (1H, t, 5′-OH), 5.42 (1H, d, 3′-OH), 6.14 (1H, d, H-1′, $J_{1',2'}=6.4$ Hz), 6.28 (2H, br s, $NH_2$). UV $\lambda_{max}^{H_2O}$ nm (ε): 284 (9900), 247 (10470), 210 (23900); $\lambda_{min}$: 263 (4460), 226 (4510). $\lambda_{max}^{0.5\,N\,NaOH}$: 284 (10300), 247 (10770); $\lambda_{min}$: 262 (5040), 232 (6930). $\lambda_{max}^{0.5\,N\,HCl}$: 289 (12370), 240 (8730); $\lambda_{min}$: 258 (2870), 229 (7940). CD ($H_2O$) [θ] (nm): 283 (−3430), 263 (−1780), 246 (−7320), 226 (−4890). CD (0.5 N HCl) [θ] (nm): 289 (−5810), 260 (−1690), 242 (−6040), 228 (−4760). *Anal.* Calcd for $C_{13}H_{17}N_5O_4 \cdot H_2O$: C, 47.99; H, 5.88; N, 21.53. Found: C, 47.43; H, 5.51; N, 21.35.

**2-Amino-6-ethoxy-8,2′-methano-9-(3,5-di-*O*-acetyl-2-deoxy-β-D-arabino-furanosyl)-9*H*-purine (23)** Triethylamine (1.4 ml, 10 mmol) was added to a suspension of **22** (1 g, 3.25 mmol), DMAP (5 mg), and $Ac_2O$ (1 ml, 10.6 mmol) in $CH_3CN$ (20 ml). The mixture was stirred for 1 h at room temperature and MeOH (1 ml) was added to the mixture. The whole sample was evaporated to dryness and the residue was purified on a silica gel column (3 × 20 cm) which was eluted with 8% EtOH in $CHCl_3$ to give **23** (1.21 g, 95.3%, foam). MS *m/z*: 391 ($M^+$, 100%). $^1$H-NMR (DMSO-$d_6$, 270 MHz): 1.33 (3H, t, $OCH_2\underline{CH_3}$, $J=7.1$ Hz), 1.82 (3H, s, Ac), 2.09 (3H, s, Ac), 3.10 (1H, dd, H-2″a, $J_{2''a,2'}=5.5$ Hz, $J_{2''a,2''b}=18.1$ Hz), 3.20 (1H, dd, H-2″b, $J_{2''b,2'}=9.9$ Hz), 3.45 (1H, m, H-2′), 3.69 (1H, m, H-4′), 3.79 (1H, dd, H-5′a, $J_{5'a,4'}=5.5$, $J_{5'a,5'b}=12.1$ Hz), 3.90 (1H, dd, H-5′b, $J_{5'b,4'}=4.4$ Hz), 4.42 (3H, m, H-3′ and $O\underline{CH_2}CH_3$), 6.28 (1H, d, H-1′, $J_{1',2'}=6.6$ Hz), 6.35 (2H, br s, 2-$NH_2$).

**3′,5′-Di-*O*-acetyl-2′-deoxy-8,2′-methanoguanosine (24)** A solution of compound **23** (430 mg, 1.1 mmol) in $CH_3CN$ (10 ml) was added to a mixture of dry NaI (970 mg, 6.5 mmol) and trimethylsilyl chloride (0.83 ml, 6.5 mmol) in $CH_3CN$ (20 ml) at 0 °C. After stirring for 2 h at room temperature, triethylamine (0.9 ml, 6.5 mmol) was added to the reaction mixture and the whole sample was evaporated to dryness. The residue was suspended in $CH_3CN$ (20 ml), and treated with $Ac_2O$ (0.32 ml, 3.4 mmol), triethylamine (0.46 ml, 3.3 mmol), and DMAP (5 mg) for 1 h at room temperature. The solvent was removed under reduced pressure to leave a solid which was suspended in MeOH and mixed with silica gel. The mixture was evaporated to dryness and the residue was placed on a silica gel column (3.5 × 20 cm) which was washed with 0—15% EtOH in $CHCl_3$ (1000 ml) and then eluted with 30% EtOH in $CHCl_3$ to give **24** (282 mg, 70.5%, crystallized from $H_2O$), mp > 300 °C. MS *m/z*: 363 ($M^+$, 11%). $^1$H-NMR (DMSO-$d_6$, 270 MHz): 1.85 (3H, s, Ac), 2.08 (3H, s, Ac), 3.12 (1H, dd, H-2″a, $J_{2''a,2'}=4.4$, $J_{2''a,2''b}=17.6$ Hz), 3.23 (1H, dd, H-2″b, $J_{2''b,2'}=9.3$ Hz), 3.46 (1H, m, H-2′), 3.62 (1H, m, H-4′), 3.79 (1H, dd, H-5′a, $J_{5'a,4'}=4.9$, $J_{5'a,5'b}=12.1$ Hz), 3.87 (1H, dd, H-5′b, $J_{5'b,4'}=4.9$ Hz), 4.39 (1H, m, H-3′), 6.13 (2H, br s, 2-$NH_2$), 6.32 (1H, d, H-1′, $J_{1',2'}=6.6$ Hz), 10.71 (1H, br s, NH). UV $\lambda_{max}^{H_2O}$ nm (ε): 285 (7100), 246 (7600), 215 (24800); $\lambda_{min}$ 263 (3500), 234.5 (6450). $\lambda_{max}^{0.5\,N\,NaOH}$: 279 (7150); $\lambda_{min}$: 259 (4800). $\lambda_{max}^{0.5\,N\,HCl}$: 275 (7350), 265 (sh, 8850), 252 (10550); $\lambda_{min}$: 229 (5650). CD ($H_2O$) [θ] (nm): 275 (−2480), 264 (−2120), 248 (−4020), 241 (−2780), 215 (−105900). CD (0.5 N HCl) [θ] (nm): 253 (−3300), 239 (−2290), 215 (−57200). *Anal.* Calcd for $C_{15}H_{17}N_5O_6$: C, 49.59; H, 4.72; N, 19.28. Found: C, 49.43; H, 4.79; N, 18.99.

**2′-Deoxy-8,2′-methanoguanosine (25)** Compound **24** (206 mg, 0.57 mmol) was treated in methanolic ammonia (30 ml, saturated at 0 °C) for 24 h at room temperature and the solvent was removed under reduced pressure. The residue was crystallized from aqueous EtOH to afford **25** (135 mg, 85%), mp > 300 °C. MS *m/z*: 279 ($M^+$, 14%). $^1$H-NMR (DMSO-$d_6$, 270 MHz at 80 °C): 2.86 (1H, dd, H-2″a, $J_{2''a,2''b}=17.6$, $J_{2''a,2'}=3.8$ Hz), 3.13 (1H, dd, H-2″b, $J_{2''b,2'}=9.8$ Hz), 3.14 (1H, m, H-5′a, $J_{5'a,4'}=6.1$, $J_{5'a,5'b}=11.5$ Hz), 3.21 (1H, m, H-5′b, $J_{5'b,4'}=5.0$ Hz), 3.35 (1H, 8 lines, H-2′, $J_{2',3'}=3.3$ Hz), 3.92 (1H, m, H-4′), 4.05 (1H, dd, H-3′, $J_{3',4'}=3.3$ Hz), 4.40 (1H, t, 5′-OH), 5.16 (1H, d, 3′-OH), 5.92 (2H, br s, $NH_2$), 6.19 (1H, d, H-1′, $J_{1',2'}=6.6$ Hz), 10.47 (1H, br s, NH). UV $\lambda_{max}^{H_2O}$ nm (ε): 285 (7450), 246 (7650), 215 (24900); $\lambda_{min}$: 263 (3700), 235 (6540). $\lambda_{max}^{0.5\,N\,NaOH}$: 279 (7400); $\lambda_{min}$: 259 (4850). $\lambda_{max}^{0.5\,N\,HCl}$: 275 (7550), 263 (sh, 9100), 251 (5200); $\lambda_{min}$: 228 (5200). CD ($H_2O$) [θ] (nm): 282 (−2720), 260 (−1660), 246 (0), 242 (+680), 239 (0), 215 (−81500). CD (0.5 N HCl) [θ] (nm): 269 (−2040), 256 (0), 238 (+2070), 232 (0), 215 (−41500). *Anal.* Calcd for $C_{11}H_{13}N_5O_4 \cdot H_2O$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.95; H, 4.92; N, 23.34.

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