Novel synthesis of purine acyclonucleosides possessing a chiral 9-hydroxyalkyl group by sugar modification of 9-D-ribitylpurines

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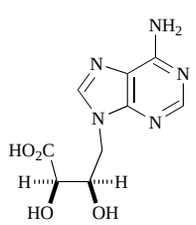
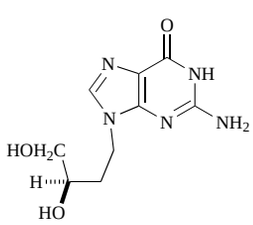
A novel approach to the synthesis of purine acyclonucleosides having chiral carbons in the N^9-hydroxyalkyl chain was achieved by using 9-(2,3-*O*-isopropylidene-D-ribityl)purines 1, which are readily prepared from commercially available purine nucleosides. 9-[(2*S*,3*R*)-2,3,4-Trihydroxybutyl]purines 4a and 4b, 9-[(2*S*,3*S*)-2,3,4-trihydroxybutyl]purines 6a and 6b, L-eritadenine 8, and its analogue 11 are conveniently synthesized *via* key intermediates, (2*S*,3*S*)-2,3-isopropylidenedioxy-4-(purin-9-yl)butanals 2 prepared by $NaIO_4$ oxidation of diols 1.

Introduction

During the search for effective, selective and nontoxic antiviral agents, a potent antiviral agent, 9-[(2-hydroxyethoxy)methyl]-guanine (acyclovir) has been developed for the treatment of herpes virus type 1 infections.[1] The discovery of acyclovir has stimulated extensive research in the synthesis of new acyclonucleosides in which the carbohydrate moieties are acyclic chains mimicking the sugar portion of naturally occurring nucleosides. Several purine acyclonucleosides having chiral carbons in the N^9-hydroxyalkyl chain, such as D-eritadenine[2,3] and buciclovir[4] have been shown to possess antiviral activity. Most



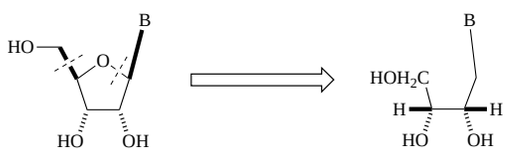
D-eritadenine



buciclovir

synthetic methods for the preparation of such acyclonucleosides involve the condensation of a base moiety with an appropriate side-chain moiety.[5] These methods, however, incur some difficulties in stereoselective synthesis of the side-chain moiety and/or regioselective condensation of the base moiety with the side-chain moiety. Synthetic methods starting from commercially available nucleosides such as adenosine and guanosine have been unprecedented except for an example of oxidative cleavage of the 2′,3′-*cis*-diol portion of ribonucleosides with $NaIO_4$.[6]

A few years ago we reported a convenient formation of acyclonucleosides, 9-D-ribitylpurines **1**, by the reductive cleavage of the C-1′–O-4′ bond of purine nucleosides with diisobutylaluminium hydride (DIBAL).[7] The 9-D-ribitylpurines **1** were utilized for the development of a novel methodology to prepare acyclonucleosides having chiral carbons in the side chain from commercially available purine nucleosides. Our strategy involves two disconnections of the C-1′–O-4′ and C-4′–C-5′ bonds of purine nucleosides as depicted in Scheme 1. In this paper, we describe the asymmetric construction of 9-(2,3,4-trihydroxybutyl)purines **4** and **6** and eritadenine



Scheme 1 B = adenin-9-yl or guanin-9-yl

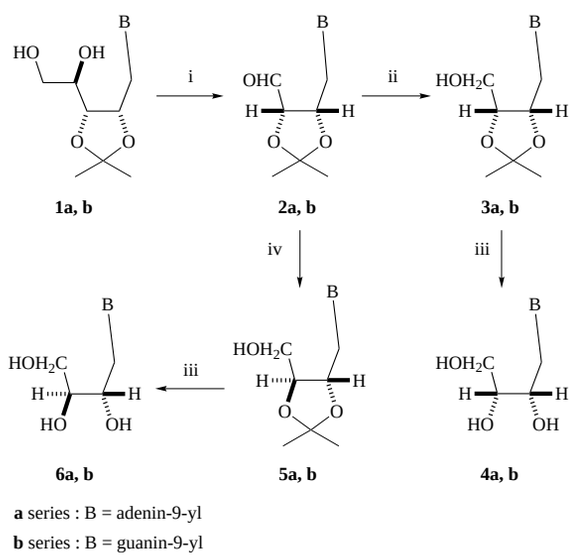
analogues **8** and **11** as potential antiviral agents by taking advantage of two of the chiral carbons of substrates **1**.[8]

Results and discussion

First, (2*S*,3*S*)-4-(adenin-9-yl)-2,3-isopropylidenedioxybutanal **2a** was synthesized as a chiral key intermediate for the preparation of acycloadenosines. Oxidation of diol **1a**[7] with $NaIO_4$ afforded aldehyde **2a** in 92% yield. The structure of compound **2a** was determined by ^1H NMR spectral analyses. Thus, the ^1H NMR {$(CD_3)_2SO$, [$^2H_6$]DMSO} spectrum of compound **2a** exhibited complicated signals at room temperature. Upon raising the probe temperature to 100 °C these signals came to merge into one set of signals for the aldehyde structure. The aldehyde **2a** would exist in the form of both a polymer and a hydrate at ambient temperature; Schmid *et al.* have reported that D-glyceraldehyde acetonide tended to polymerize and easily form a hydrate in the presence of water.[9] Reduction of compound **2a** with $NaBH_4$ afforded the primary alcohol **3a** in 78% yield. The stereochemistry of alcohol **3a** was confirmed by its conversion into the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetate (MTPA ester).[10] ^{19}F NMR analyses of the ester showed no formation of any detectable epimeric isomer. This fact evidently indicates that the formation of compounds **2a** and **3a** proceeds with complete retention of steric configuration. The alcohol **3a** smoothly underwent removal of the isopropylidene protection with 80% aq. AcOH to afford 9-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]adenine **4a**,[11,12] quantitatively. On the other hand, an epimer **5a** was synthesized by inversion at the 2-position of the aldehyde **2a** and by the subsequent reduction. Lee and co-workers have reported that an alcoholic solvent was favourable for the easy epimerization of 2,3-*erythro*-aldose acetonide to 2,3-*threo*-aldose acetonide.[13] Therefore, treatment of compound **2a** with NaOMe in MeOH followed by reduction with $NaBH_4$ gave a mixture of alcohols **5a**

and **3a** (**5a**:**3a** = 94:6). Both epimers could be separated by silica gel column chromatography to give isomer **5a** in 66% yield. Enantiomeric purity of product **5a** was confirmed by the conversion to its MTPA ester and its ^{19}F NMR analysis. Deprotection of compound **5a** afforded 9-[(2*S*,3*S*)-2,3,4-trihydroxybutyl]adenine **6a**[12] in 60% yield (Scheme 2).

This methodology was applied to the synthesis of acycloguanosines. When oxidation of 9-(2,3-*O*-isopropylidene-D-ribityl)-guanine **1b** and subsequent reduction were conducted under analogous reaction conditions, a diastereomeric mixture of compound **3b** (*erythro*) and its (3′*S*)-isomer **5b** (*threo*) was formed in the ratio 83:17. The $NaIO_4$ oxidation of diol **1b** in a sodium acetate buffer (pH 4) gave the aldehyde **2b** as a hydrate in 87% yield and subsequent reduction of aldehyde **2b** led to the quantitative formation of a chiral alcohol **3b** without epimerization. Deprotection of compound **3b** with 80% aq. AcOH afforded 9-[(2*S*,3*R*)-2,3,4-trihydroxybutyl]guanine **4b** in 93% yield (Scheme 2). The preparation of a (3′*S*)-epimer **6b** was

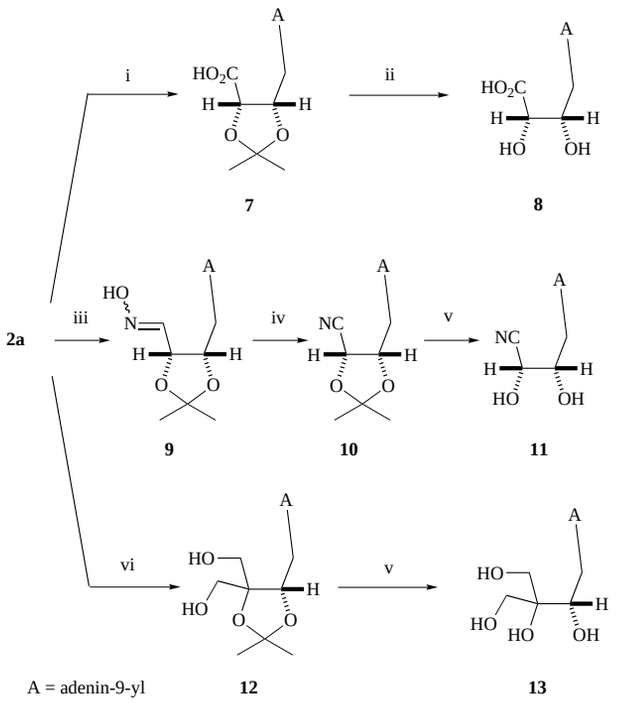


Scheme 2 *Reagents and conditions:* i, for **2a**, aq. $NaIO_4$; for **2b**, $NaIO_4$, AcOH–AcONa buffer (pH 4); ii, aq. $NaBH_4$, pH 7–8; iii, 80% AcOH; iv, for **5a**, NaOMe, MeOH, then aq. $NaBH_4$; for compound **5b**, K_2CO_3, MeOH; then aq. $NaBH_4$

conducted using a modified method of that described for compound **6a**. Thus, treatment of compound **2b** with K_2CO_3 in MeOH gave the (2*R*)-epimer of aldehyde **2b** as a diastereomeric mixture with **2b** (*threo*:*erythro* = >95:<5) in 75% yield, and subsequent $NaBH_4$ reduction gave the corresponding alcohol **5b**. Deprotection of compound **5b** afforded the desired 9-[(2*S*,3*S*)-2,3,4-trihydroxybutyl]guanine **6b** as the sole isomer in 88% yield.

It is noteworthy that the stereochemistry at the 3′-position of acyclonucleosides **4** and **6** could be easily controlled by the use of the aldehyde **2** as a chiral pool.

The aldehyde **2a** was utilized as a novel approach to the synthesis of L-eritadenine **8**, which is the enantiomer of naturally occurring D-eritadenine.[3] Votruba and Holy have reported that L-eritadenine, which is the most effective, next to D-eritadenine, of the four stereoisomeric eritadenines, inhibits *S*-adenosyl-L-homocysteine hydrolase.[3a] Our first attempted preparation of L-eritadenine **8**, oxidation of compound **2a** with $KMnO_4$ in aq. alkaline solution, resulted in the formation of an epimeric mixture of the corresponding carboxylic acid **7** (*erythro*) and its (2*R*)-isomer (*threo*) in 63% yield (*erythro*:*threo* = 32:68). The epimerization of D-eritadenine methyl ester under basic conditions has been described in the literature.[14] Therefore, the Pt/C-catalyzed oxidation of compound **2a** with O_2 was carried out under neutral conditions to afford acid **7** in 46% yield without any detectable epimer. Deprotection of compound **7** with 10% aq. AcOH gave L-eritadenine **8** quantitatively, whose optical activity, $[\alpha]_D^{26}$ −14.3 (*c* 0.07, 1 M HCl),† was identical with that reported by Holy *et al.* (Scheme 3).[3b]



Scheme 3 *Reagents and conditions:* i, Pt/C, O_2, water; ii, 10% AcOH; iii, $NH_2OH{\cdot}HCl$, NaOMe, MeOH; iv, $SOCl_2$, DMF; v, CF_3CO_2H; vi, HCHO, 2 M NaOH, water; then $NaBH_4$

Furthermore, the synthesis of the nitrile **11**, which is structurally analogous to L-eritadenine **8**, was attempted. The reaction of compound **2a** with 1.5 mol equiv. of hydroxylamine afforded the oxime **9** in 71% yield as a mixture of geometrical isomers (*E*:*Z* = 38:62). Dehydration of oxime **9** by using 5 mol equiv. of thionyl dichloride in dimethylformamide (DMF) gave the nitrile **10** in 79% yield as a single diastereomer. The steric configuration of compound **10** (*erythro*-isomer) was confirmed by comparison of its ^1H NMR spectrum with those of compounds **2a**, **3** and **5** and by nuclear Overhauser effect (NOE) experiments on compounds **10** and **5a**. Thus, the difference in chemical shifts of the two methyl singlets of the isopropylidene group in nitrile **10** (0.23 ppm) is close to those in *erythro*-compounds **2a**, **3a** and **3b** (0.22, 0.21, and 0.19 ppm, respectively), but larger than those in *threo*-compounds **5a** and **5b** (0.06 and 0.04 ppm, respectively).[13b] Irradiation of 2-H of compound **10** showed an NOE enhancement (8.6%) at 3-H, whereas in a similar NOE experiment on *threo*-compound **5a** an enhancement was hardly observed (see Experimental section). These facts supported the idea that the conversion of **2a** into **10** proceeded with retention of enantiomeric configuration; otherwise, the inversion at both the 2- and 3-position would occur completely. Deprotection of compound **10** with CF_3CO_2H (TFA) afforded the desired dihydroxy nitrile **11** in 57% yield.

Another synthetic application of compound **2a** as a chiral intermediate was examined for the synthesis of tetraol **13** which has the sole chiral centre in the alkyl chain. Crossed aldol condensation of aldehyde **2a** and formaldehyde in basic media followed by $NaBH_4$ reduction afforded isopropylidene-protected tetraol **12** in 89% yield in a one-pot procedure. The optical rotation of product **12** was $[\alpha]_D^{28}$ −38.5 (*c* 0.27, MeOH). The desired tetraol **13** was obtained by treatment of compound **12** with TFA in 83% yield.

† $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Among acyclic analogues of adenosine, compounds **4a**, **6a** and **13** were virtually inactive against influenza A, respiratory syncytial virus, human immunodeficiency virus, herpes simplex virus type 1, and human cytomegalovirus with EC_{50} values of >40 μg ml^{-1}. Biological evaluations of adenosine analogues **8** and **11** and guanosine analogues **4b** and **6b** are in progress.

This methodology using 2′,3′-*O*-isopropylidene-protected 9-D-ribitylpurines as chiral starting materials was shown to be widely applicable to the synthesis of biologically interesting acyclonucleosides. In particular, the aldehydes **2a** and **2b** are useful intermediates for the preparation of purine acyclonucleosides mimicking ribonucleosides.

Experimental

Mps (uncorrected) were determined with a Yanagimoto melting point apparatus. Elemental analyses were performed by the microanalytical laboratory of our university. Optical rotations were measured on a JASCO DIP-370 polarimeter. UV absorption spectra were recorded on a Shimadzu 260 spectrophotometer. IR spectra were measured using a Perkin-Elmer 1640 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM GX-270 (270 MHz) or a JNM EX-400 (400 MHz) spectrometer. Chemical shifts (δ_H) are expressed in ppm relative to tetramethylsilane in $CDCl_3$ as solvent or internally referenced to the residual protonated solvent resonances (δ_H 2.49) in [$^2H_6$]DMSO as solvent. *J*-Values are given in Hz. ^{13}C and ^{19}F NMR spectra were recorded on a JEOL JNM EX-400 spectrometer (100 MHz and 376 MHz, respectively). Solvent peak ($CDCl_3$ δ_C 77.0; [$^2H_6$]DMSO: δ_C 39.5) was used as an internal standard for ^{13}C NMR, and TFA (δ_F −76.5) was used as an external standard for ^{19}F NMR. Mass spectra and high-resolution mass spectra were taken on JEOL JMS-D 300 or a JMS-SX 102A machine. Fast-atom bombardment (FAB) mass spectra were measured with *m*-nitrobenzyl alcohol (NBA) as matrix.

TLC analyses were carried out on precoated Silicagel 60 F_{254} plates (Merck, Art 5715). The silica gel used for column chromatography was Wakogel C-300 or Fujigel BW-200. Reversed-phase chromatography was accomplished by Sep-Pak® (C_{18}) cartridge (Waters).

(2*S*,3*S*)-4-(Adenin-9-yl)-2,3-isopropylidenedioxybutanal 2a

To a stirred aqueous solution of 9-(2,3-*O*-isopropylidene-D-ribityl)adenine **1a** (853 mg, 2.76 mmol in 25 ml) was added $NaIO_4$ (885 mg, 4.14 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. The mixture was quenched with ethylene glycol (153.8 μl, 2.76 mmol) and was further stirred at 0 °C for 1 h. After the solvent had been evaporated off *in vacuo*, anhydrous MeOH was added to the residue. The precipitate was filtered off over a Celite pad and then the filtrate was concentrated to dryness. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 30:1) to give *title aldehyde* **2a** (700 mg, 92%) as an amorphous substance, λ_{max}(water)/nm 260; ν_{max}(KBr)/cm^{-1} 3345, 3213, 2988, 2938, 1615, 1479, 1380, 1331, 1298, 1222, 1162, 1076, 891, 797 and 648; δ_H(400 MHz; [$^2H_6$]DMSO; 100 °C) 1.32 and 1.54 (each 3 H, s, isopropylidene), 4.20 (1 H, dd, *J* 14.2 and 9.3, 4-H), 4.44 (1 H, dd, *J* 14.2 and 3.4, 4-H), 4.74 (1 H, dd, *J* 7.3 and 2.0, 2-H), 4.90 (1 H, ddd, *J* 9.3, 7.3 and 3.4, 3-H), 6.78 (2 H, br s, adenine 6-NH_2), 8.02 (1 H, s, adenine, 2- or 8-H), 8.16 (1 H, s, adenine 8- or 2-H) and 9.74 (1 H, d, *J* 2.0, CHO); *m*/*z* (EI) 277 (M^+, 17%), 190 (100) and 136 (79) [Found (EI): M^+, 277.1185. $C_{12}H_{15}N_5O_3$ requires *M*, 277.1175].

(2*S*,3*S*)-4-(Guanin-9-yl)-2,3-isopropylidenedioxybutanal 2b

To a stirred suspension of 9-(2,3-*O*-isopropylidene-D-ribityl)-guanine **1b** (162.7 mg, 0.5 mmol) in AcOH–AcONa buffer (pH 4) (~100 ml) was added $NaIO_4$ (160.4 mg, 0.75 mmol) at 0 °C and the mixture was stirred at room temp. for 1.5 h before being quenched with ethylene glycol (13.9 μl, 0.25 mmol), further stirred at 0 °C for 1 h and concentrated *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 9:1) to give solid *aldehyde* **2b** as a monohydrate (134.8 mg, 87%), mp 257 °C (decomp.) (Found: C, 46.2; H, 5.45; N, 22.4. $C_{12}H_{17}N_5O_5$ requires C, 46.30; H, 5.50; N, 22.50%); λ_{max}(water)/nm 252; ν_{max}(KBr)/cm^{-1} 3346, 3160, 2989, 2942, 2784, 1693, 1657, 1621, 1575, 1542, 1486, 1384, 1222, 1166, 1076, 1044, 889, 847, 780, 726, 637 and 580; δ_H(400 MHz; [$^2H_6$]DMSO) 1.21 and 1.43 (each 3 H, s, isopropylidene), 3.96 (1 H, t, *J* 6.8, 2-H), 4.00 (1 H, dd, *J* 14.2 and 10.7, 4-H), 4.26 (1 H, dd, *J* 14.2 and 2.4, 4-H), 4.40 (1 H, ddd, *J* 10.7, 6.8 and 2.4, 3-H), 4.88 (1 H, td, *J* 6.8 and 5.9, 1-H), 6.16 (1 H, d, *J* 6.8, 1-OH), 6.23 (1 H, d, *J* 5.9, 1-OH), 6.41 (2 H, br s, guanine 2-NH_2), 7.59 (1 H, s, guanine 8-H) and 10.48 (1 H, s, guanine N^1-H); δ_C([$^2H_6$]DMSO) 25.36, 27.78, 43.45, 74.25, 79.59, 88.04, 108.21, 116.33, 138.09, 151.13, 153.34 and 156.69; *m*/*z* (FAB, NBA) 312 (M^+ + H, 88%).

9-[(2′*S*,3′*R*)-4′-Hydroxy-2′,3′-isopropylidenedioxybutyl]-adenine 3a

To aq. aldehyde **2a** (27.7 mg, 0.1 mmol in 5 ml) was added $NaBH_4$ (18.9 mg, 0.5 mmol) at 0 °C and then the pH of the reaction mixture was adjusted to 7–8 with 10% aq. AcOH. After being stirred at 0 °C for 1.5 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 18:1) to give *compound* **3a** (21.7 mg, 78%) as a solid, which was recrystallized from EtOH–Et_2O, mp 192–194 °C (lit.,[12] 182–184 °C) (Found: C, 51.45; H, 6.2; N, 24.75. $C_{12}H_{17}N_5O_3 \cdot 1/10H_2O$ requires C, 51.27; H, 6.17; N, 24.92%); the existence of water in this product was confirmed by ^{1}H NMR analysis; λ_{max}(MeOH)/nm 260; ν_{max}(KBr)/cm^{-1} 3436, 3298, 3225, 2986, 2943, 2881, 1676, 1605, 1575, 1477, 1418, 1384, 1306, 1242, 1061, 909, 844, 779 and 721; δ_H(270 MHz; [$^2H_6$]DMSO) 1.20 and 1.41 (each 3 H, s, isopropylidene), 3.62 (2 H, t, *J* 5.4, 4′-H_2), 4.19 (1 H, dd, *J* 13.7 and 10.3, 1′-H), 4.24 (1 H, dd, *J* 6.4 and 5.4, 3′-H), 4.36 (1 H, dd, *J* 13.7 and 2.4, 1′-H), 4.56 (1 H, ddd, *J* 10.3, 6.4 and 2.4, 2′-H), 5.03 (1 H, t, *J* 5.4, 4′-OH), 7.19 (2 H, s, 6-NH_2), 8.07 (1 H, s, 2- or 8-H) and 8.12 (1 H, s, 8- or 2-H); δ_C([$^2H_6$]DMSO) 25.35, 27.83, 43.47, 58.96, 74.54, 76.81, 108.12, 118.54, 141.15, 149.52, 152.28 and 155.90; *m*/*z* (EI) 279 (M^+, 22%), 264 (46), 204 (97) and 136 (100).

9-[(2′*S*,3′*R*)-4′-Hydroxy-2′,3′-isopropylidenedioxybutyl]-guanine 3b

Compound **2b** (15.6 mg, 0.05 mmol) was treated in a manner similar to that described for the preparation of compound **3a**. After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 9:1) to give *title compound* **3b** (14.6 mg, 99%) as a solid, λ_{max}(MeOH)/nm 254; ν_{max}(KBr)/cm^{-1} 3397, 3135, 2986, 2939, 2772, 1691, 1655, 1479, 1379, 1219, 1167, 1072, 1050, 842, 781, 694 and 634; δ_H(400 MHz; [$^2H_6$]DMSO) 1.22 and 1.41 (each 3 H, s, isopropylidene), 3.57 (2 H, m, 4′-H_2), 4.01 (1 H, dd, *J* 14.2 and 10.3, 1′-H), 4.17 (1 H, dd, *J* 14.2 and 2.9, 1′-H), 4.20 (1 H, q, *J* 6.4, 3′-H), 4.48 (1 H, ddd, *J* 10.3, 6.4 and 2.9, 2′-H), 4.98 (1 H, t, *J* 4.9, 4′-OH), 6.43 (2 H, br s, 2-NH_2), 7.64 (1 H, s, 8-H) and 10.50 (1 H, s, N_1-H); δ_C([$^2H_6$]DMSO) 25.31, 27.80, 43.08, 59.00, 74.58, 76.75, 108.04, 116.35, 137.76, 151.17, 153.43 and 156.71; *m*/*z* (EI) 295 (M^+, 87%), 280 (63), 220 (75), 165 (100) and 152 (98) [Found (EI): M^+, 295.1289. $C_{12}H_{17}N_5O_4$ requires *M*, 295.1280].

Preparation of (+)-MTPA ester of alcohol 3a

To a solution of (*R*)-(+)-α-(trifluoromethyl)phenylacetic acid (19.7 mg, 0.084 mmol) and DMF (6.5 μl, 0.084 mmol) in hexane (3.5 ml) was added oxalyl dichloride (36.6 μl, 0.42 mmol) at room temp. After being stirred for 1 h, the mixture was filtered and the filtrate was evaporated *in vacuo*. To the residue was

added a mixture of alcohol **3a** (19.6 mg, 0.07 mmol), Et_3N (29.3 μl, 0.21 mmol) and 4-(dimethylamino)pyridine (DMAP) (6.0 mg, 0.049 mmol) in CH_2Cl_2 (0.7 ml), and further pyridine (0.1 ml) after 23 h. This operation was repeated until the disappearance of starting alcohol **3a** was observed by TLC analysis ($CHCl_3$–MeOH, 5:1). As a result MTPA (78.7 mg, 0.336 mmol), DMF (26.0 μl, 0.377 mmol), hexane (14 ml), oxalyl dichloride (166.4 μl, 1.907 mmol), Et_3N (118.5 μl, 0.85 mmol) and DMAP (24.0 mg, 0.196 mmol) were used for the esterification. Several drops of MeOH were added to the mixture, which was then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 100:1–50:1) to give the (+)-MTPA ester of alcohol **3a** (26.1 mg, 75%) as a solid, λ_{max}(MeOH)/nm 260; ν_{max}(KBr)/cm^{-1} 3449, 3334, 3316, 3142, 2951, 2856, 1761, 1665, 1605, 1579, 1477, 1380, 1271, 1243, 1168, 1127, 1086, 1022, 989, 920, 724 and 652; δ_H(400 MHz; $CDCl_3$) 1.27 and 1.50 (each 3 H, s, isopropylidene), 3.60 (3 H, s, OCH_3), 3.85 (1 H, dd, *J* 14.2 and 9.8, 1′-H), 4.32 (1 H, dd, *J* 14.2 and 2.4, 1′-H), 4.44–4.52 (3 H, m, 2′-, 3′- and 4′-H), 4.58 (1 H, m, 4′-H), 5.89 (2 H, s, 6-NH_2), 7.33–7.58 (5 H, m, Ph), 7.71 (1 H, s, 2- or 8-H) and 8.33 (1 H, s, 8- or 2-H); δ_F($CDCl_3$) −72.14; *m/z* (EI) 495 (M^+, 14%), 480 (24), 204 (100) and 189 (40) [Found (EI): M^+, 495.1738. $C_{22}H_{24}F_3N_5O_5$ requires *M*, 495.1729].

9-[(2′*S*,3′*R*)-2′,3′,4′-Trihydroxybutyl]adenine 4a

A solution of partially protected triol **3a** (42 mg, 0.15 mmol) in 80% aq. AcOH was stirred at 60 °C for 5 h and then the solvent was evaporated off *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19:1) to give *title triol* **4a** (35 mg, 98%) as a solid, mp 232–233 °C (lit.,[11] 218–219 °C; lit.,[12] >260 °C) (Found: C, 44.5; H, 5.4; N, 29.05. $C_9H_{13}N_5O_3 \cdot 1/8H_2O$ requires C, 44.76; H, 5.53; N, 29.00%); the existence of water in this product was confirmed by ^1H NMR analysis; λ_{max}(MeOH)/nm 260; ν_{max}(KBr)/cm^{-1} 3396, 3331, 3263, 2925, 1659, 1608, 1577, 1487, 1419, 1334, 1306, 1248, 1209, 1080, 1054, 887, 796, 767, 724, 683, 651 and 598; δ_H(400 MHz; [$^2H_6$]DMSO) 3.29 (1 H, m, 3′-H), 3.38 (1 H, dt, *J* 10.8 and 5.4, 4′-H), 3.57 (1 H, ddd, *J* 10.8, 5.4 and 3.9, 4′-H), 3.70 (1-H, m, 2′-H), 4.04 (1 H, dd, *J* 14.2 and 8.3, 1′-H), 4.40 (1 H, dd, *J* 14.2 and 2.9, 1′-H), 4.45 (1 H, t, *J* 5.4, 4′-OH), 4.97 (1 H, d, *J* 5.4, 3′-OH), 5.07 (1 H, d, *J* 6.4, 2′-OH), 7.16 (2 H, br s, 6-NH_2), 8.00 (1 H, s, 2- or 8-H) and 8.11 (1 H, s, 8- or 2-H); δ_C([$^2H_6$]DMSO) 46.47, 63.00, 69.68, 73.30, 118.58, 141.80, 148.65, 152.10 and 155.90; *m/z* (EI) 239 (M^+, 11%), 221 (23), 190 (36), 178 (94), 148 (96) and 135 (100).

9-[(2′*S*,3′*R*)-2′,3′,4′-Trihydroxybutyl]guanine 4b

A solution of partially protected triol **3b** (10 mg, 33.9 μmol) in 80% aq. AcOH (~2 ml) was stirred at 70 °C for 4.5 h and then the solvent was evaporated off *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19:1) to give title triol **4b** (8 mg, 93%) as a solid, λ_{max}(MeOH)/nm 253; ν_{max}(KBr)/cm^{-1} 3455, 3425, 3388, 3194, 2927, 2855, 2649, 1690, 1638, 1611, 1476, 1396, 1359, 1194, 1170, 1111, 1077, 1042, 914, 867, 784, 740 and 699; δ_H(400 MHz; [$^2H_6$]DMSO) 3.27 (1 H, m, 3′-H), 3.36 (1 H, dt, *J* 11.2 and 5.9, 4′-H), 3.55–3.62 (2 H, m, 2′- and 4′-H), 3.83 (1 H, dd, *J* 14.2 and 8.3, 1′-H), 4.22 (1 H, dd, *J* 14.2 and 2.4, 1′-H), 4.43 (1 H, t, *J* 5.9, 4′-OH), 4.87 (1 H, d, *J* 4.9, 3′-OH), 5.03 (1 H, d, *J* 5.9, 2′-OH), 6.42 (2 H, br s, 2-NH_2), 7.56 (1 H, s, 8-H) and 10.49 (1 H, s, N^1-H); δ_C([$^2H_6$]-DMSO) 46.18, 62.98, 69.73, 73.26, 116.27, 138.44, 151.19, 153.31 and 156.74; *m/z* (FAB, NBA) 256 (M^+ + H, 15%) [Found (FAB): (M^+ + H), 256.1039. $C_9H_{14}N_5O_4$ requires *m/z* 256.1046].

9-[(2′*S*,3′*S*)-4′-Hydroxy-2′,3′-isopropylidenedioxybutyl]adenine 5a

To a stirred solution of aldehyde **2a** (27.7 mg, 0.1 mmol) in anhydrous MeOH (2.0 ml) at room temp. was added NaOMe (30.7 μl of a 4.88 M solution in MeOH, 0.15 mmol) dropwise. After being stirred at room temp. for 11 h, the resulting solution was quenched with AcOH (1.0 ml of a 5×10^{-2} M solution in MeOH, 0.05 mmol) and concentrated *in vacuo*. The residue was roughly purified by column chromatography on silica gel ($CHCl_3$–MeOH, 18:1) to give the (2*R*)-epimer of aldehyde **2a** (18.3 mg, 0.066 mmol).

To an aqueous solution of the (2*R*)-epimer of aldehyde **2a** (18.3 mg, 0.066 mmol in 3 ml) was added $NaBH_4$ (10.1 mg, 0.33 mmol) at 0 °C. After being stirred at 0 °C for 0.5 h and then being stirred at room temp. for 1 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 17:1) to give *title compound* **5a** (18.5 mg, 66% for 2 steps from aldehyde **2a**) as a solid, which was recrystallized from EtOH–Et_2O, mp 167–169 °C (lit.,[12] 158–159 °C) [Found: C, 51.75; H, 6.2; N, 24.5. $C_{12}H_{17}N_5O_3 \cdot 1/10(C_2H_5)_2O$ requires C, 51.94; H, 6.33; N, 24.43%]; the existence of diethyl ether in this product was confirmed by ^1H NMR analysis; λ_{max}(MeOH)/nm 259; δ_H(400 MHz; [$^2H_6$]DMSO) 1.21 and 1.27 (each 3 H, s, isopropylidene), 3.42–3.49 (2 H, m, 4′-H_2), 3.76 (1 H, dt, *J* 7.8 and 4.9, 3′-H), 4.19 (1 H, ddd, *J* 7.8, 6.4 and 4.4, 2′-H), 4.30 (1 H, dd, *J* 14.7 and 6.4, 1′-H^a), 4.39 (1 H, dd, *J* 14.7 and 4.4, 1′-H^b), 4.89 (1 H, t, *J* 5.4, 4′-OH), 7.20 (2 H, br s, 6-NH_2), 8.06 (1 H, s, 2- or 8-H) and 8.13 (1 H, s, 8- or 2-H); NOE, irradiate 2′-H, observe 4′-H (1.7%), 3′-H (1.8%) and 1′-H^b (2.1%); irradiate 3′-H, observe 4′-H (1.8%), 2′-H (1.4%), 1′-H^a (1.5%) and 1′-H^b (1.0%); δ_C([$^2H_6$]DMSO) 26.85, 27.03, 44.62, 61.12, 75.89, 78.87, 108.74, 118.32, 141.31, 149.63, 152.50 and 155.92; *m/z* (FAB, NBA) 280 (M + H, 84%).

9-[(2′*S*,3′*S*)-4′-Hydroxy-2′,3′-isopropylidenedioxybutyl]guanine 5b

To a suspension of aldehyde **2b** (78 mg, 0.25 mmol) in anhydrous MeOH (20 ml) at room temp. was added K_2CO_3 (69 mg, 0.5 mmol). After being stirred at room temp. for 20 h, the resulting solution was neutralized with 10% aq. AcOH and concentrated *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19:1) to give the (2*R*)-epimer of aldehyde **2b** (58 mg, 75%) as a hydrate; λ_{max}(water)/nm 252; ν_{max}(KBr)/cm^{-1} 3423, 3218, 3137, 2989, 2940, 2758, 1689, 1638, 1604, 1543, 1478, 1377, 1217, 1161, 1076, 904, 852, 782, 690 and 638; δ_H(400 MHz; [$^2H_6$]DMSO) 1.26 and 1.28 (each 3 H, s, isopropylidene), 3.56 (1 H, dd, *J* 7.3 and 5.9, 2′-H), 4.03 (1 H, dd, *J* 14.2 and 7.3, 4′-H), 4.18 (1 H, td, *J* 7.3 and 3.4, 3′-H), 4.26 (1 H, dd, *J* 14.2 and 3.4, 4′-H), 4.74 (1 H, td, *J* 6.3 and 5.9, 1′-H), 6.03 (1 H, d, *J* 6.3, 1′-OH), 6.09 (1 H, d, *J* 6.3, 1′-OH), 6.41 (2 H, br s, guanine 2-NH_2), 7.65 (1 H, s, guanine 8-H), 10.28 (1 H, br s, guanine N^1-H); *m/z* (FAB, NBA) 312 (M^+ + H, 26%) [Found (FAB): (M^+ + H), 312.1302. $C_{12}H_{18}N_5O_5$ requires *m/z*, 312.1308].

To a suspension of the (2*R*)-epimer of aldehyde **2b** (31 mg, 0.1 mmol) in water (10 ml) was added $NaBH_4$ (19 mg, 0.5 mmol) at 0 °C. After being stirred at 0 °C for 10 min and at room temp. for 70 min, the mixture was neutralized with 10% aq. AcOH and concentrated *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19:1–9:1) to give *title compound* **5b** (26 mg, 88%) as a solid, λ_{max}(MeOH)/nm 253; ν_{max}(KBr)/cm^{-1} 3422, 3132, 2988, 2937, 2761, 1690, 1655, 1638, 1608, 1543, 1479, 1378, 1216, 1162, 1075, 1063, 845, 782, 690 and 637; δ_H(400 MHz; [$^2H_6$]DMSO) 1.25 and 1.29 (each 3 H, s, isopropylidene CH_3), 3.39–3.45 (2 H, m, 4′-H_2), 3.77 (1 H, dt, *J* 7.8 and 4.9, 3′-H), 4.06–4.20 (3 H, m, 1′-H_2 and 2′-H), 4.83 (1 H, t, *J* 5.4, 4′-OH), 6.41 (2 H, br s, 2-NH_2), 7.63 (1 H, s, 8-H) and 10.52 (1 H, s, N^1-H); δ_C([$^2H_6$]DMSO) 26.88, 26.99, 44.40, 61.08, 75.66, 79.11, 108.67, 116.16, 137.78, 151.26, 153.54 and 156.75; *m/z* (EI) 295 (M^+, 26%), 280 (33), 219 (86), 164 (55) and 151 (100) [Found (EI): M^+, 295.1299. $C_{12}H_{17}N_5O_4$ requires *M*, 295.1280].

Preparation of (+)-MTPA ester of alcohol 5a

The (+)-MTPA ester of alcohol **5a** was obtained by the procedure described for the preparation of (+)-MTPA ester of diastereomer **3a**, in 73% yield, λ_{max}(MeOH)/nm 260; ν_{max}(neat)/cm^{-1} 3319, 3152, 2927, 2855, 1752, 1646, 1602, 1471, 1455, 1419, 1378, 1243, 1172, 1109, 1022, 917, 848, 799, 764, 720 and 648; δ_H(400 MHz; $CDCl_3$) 1.20 and 1.26 (each 3 H, s, isopropylidene), 3.56 (3 H, s, OCH_3), 3.80 (1 H, ddd, *J* 8.3, 4.4 and 3.9, 2′-H), 4.17 (1 H, dt, *J* 8.3 and 3.9, 3′-H), 4.37 (2 H, t, *J* 3.9, 4′-H), 4.48 (1 H, dd, *J* 12.2 and 4.4, 1′-H), 4.57 (1 H, dd, *J* 12.2 and 3.9, 1′-H), 5.79 (2 H, br s, 6-NH_2), 7.39–7.54 (5 H, m, Ph), 7.88 (1 H, s, 2- or 8-H) and 8.29 (1 H, s, 8- or 2-H); δ_F($CDCl_3$) −72.21; *m*/*z* (FAB, NBA) 496 (M^+ + H, 32%) [Found (FAB): (M^+ + H), 496.1790. $C_{22}H_{25}F_3N_5O_5$ requires *m*/*z*, 496.1808].

9-[(2′*S*,3′*S*)-2′,3′,4′-Trihydroxybutyl]adenine 6a

A solution of partially protected triol **5a** (27.9 mg, 0.1 mmol) in 80% aq. AcOH (2.5 ml) was stirred at 70 °C for 19 h and then the solvent was evaporated off *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19 : 1) and the resulting product was triturated with MeOH–Et_2O to give *title triol* **6a** (14.4 mg, 60%) as a solid, mp 233–236 °C (decomp.) (lit.,[12] 215 °C) (Found: C, 45.0; H, 5.6; N, 27.95. $C_9H_{13}N_5O_5$·1/3CH_3OH requires C, 44.85; H, 5.78; N, 28.03%); the existence of methanol in this product was confirmed by ^{1}H NMR analysis; λ_{max}(MeOH)/nm 260; δ_H(400 MHz; [$^2H_6$]-DMSO) 3.37–3.42 (2 H, m, 3′- and 4′-H), 3.47 (1 H, ddd, *J* 10.3, 5.4 and 4.4, 4′-H), 3.88 (1 H, m, 2′-H), 4.10 (1 H, dd, *J* 14.2 and 9.3, 1′-H), 4.23 (1 H, dd, *J* 14.2 and 4.4, 1′-H), 4.49 (1 H, t, *J* 4.4, 4′-OH), 4.73 (1 H, d, *J* 4.9, 3′-OH), 4.78 (1 H, d, *J* 6.8, 2′-OH), 7.15 (2 H, br s, 6-NH_2), 8.02 (1 H, s, 2- or 8-H) and 8.12 (1 H, s, 8- or 2-H); δ_C([$^2H_6$]DMSO) 46.29, 62.14, 68.78, 71.85, 118.63, 141.53, 148.58, 152.10 and 155.83; *m*/*z* (FAB, NBA) 240 (M^+ + H, 12%).

9-[(2′*S*,3′*S*)-2′,3′,4′-Trihydroxybutyl]guanine 6b

A solution of partially protected triol **5b** (17 mg, 57.6 μmol) in 80% aq. AcOH (~5 ml) was stirred at 70 °C for 9 h and then solvent was evaporated off *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19 : 1) to give *title triol* **6b** (13 mg, 88%) as a solid, λ_{max}(MeOH/nm 254; ν_{max}(KBr)/cm^{-1} 3423, 3144, 2961, 2767, 1693, 1657, 1620, 1544, 1478, 1404, 1378, 1314, 1195, 1171, 1117, 1074, 810, 780, 691, 635, 595 and 560; δ_H(400 MHz; [$^2H_6$]DMSO) 3.29–3.40 (2 H, m, 3′- and 4′-H), 3.45 (1 H, dt, *J* 10.3 and 5.9, 4′-H), 3.79 (1 H, dddd, *J* 8.8, 6.8, 4.9 and 2.4, 2′-H), 3.92 (1 H, dd, *J* 14.2 and 8.8, 1′-H), 4.00 (1 H, dd, *J* 14.2 and 4.9, 1′-H), 4.47 (1 H, t, *J* 5.9, 4′-OH), 4.67 (1 H, d, *J* 5.4, 3′-OH), 4.71 (1 H, d, *J* 6.8, 2′-OH), 6.40 (2 H, br s, 2-NH_2), 7.58 (1 H, s, 8-H) and 10.47 (1 H, s, N^1-H); δ_C([$^2H_6$]DMSO) 45.90, 62.12, 68.72, 71.76, 116.40, 138.18, 151.22, 153.40 and 156.82; *m*/*z* (FAB, NBA) 256 (M^+ + H, 10%) [Found (FAB) (M^+ + H), 256.1039. $C_9H_{14}N_5O_4$ requires *m*/*z*, 256.1046].

(2*S*,3*S*)-4-(Adenin-9-yl)-2,3-isopropylidenedioxybutanoic acid 7

A mixture of aldehyde **2a** (127 mg, 0.46 mmol) and 3% Pt/C (149 mg, 0.023 mmol of Pt) in water (5 ml) was stirred under oxygen (balloon) at 45 °C. The pH of the reaction mixture was adjusted to ~7.5 with aq. $NaHCO_3$ twice during the reaction. After being stirred at 45 °C for 49 h, the mixture was filtered through a Celite pad and concentrated *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19 : 1) to give acid **7** (62 mg, 46%) as a solid, λ_{max}(MeOH)/nm 260; ν_{max}(KBr)/cm^{-1} 3424, 3187, 2990, 2937, 1637, 1607, 1479, 1422, 1379, 1331, 1305, 1249, 1217, 1081, 1052, 891, 850, 797, 725 and 650; δ_H(400 MHz; [$^2H_6$]DMSO) 1.17 and 1.40 (each 3 H, s, isopropylidene), 4.02 (1 H, dd, *J* 14.2 and 9.8, 4-H), 4.33 (1 H, dd, *J* 14.2 and 2.9, 4-H), 4.41 (1 H, d, *J* 6.8, 2-H), 4.51 (1 H, ddd, *J* 9.8, 6.8 and 2.9, 3-H), 7.12 (2 H, br s, adenine 6-NH_2), 8.08 (1 H, s, adenine 2- or 8-H) and 8.09 (1 H, s, adenine 8- or 2-H); δ_C([$^2H_6$]DMSO) 25.62, 27.76, 44.88, 74.41, 77.89, 108.19, 118.54, 141.58, 149.70, 152.15, 155.85 and 169.29; *m*/*z* (FAB, Gly) 294 (M^+ + H, 11%) [Found (FAB): (M^+ + H), 294.189. $C_{12}H_{16}N_5O_4$ requires *m*/*z* 294.1202].

L-Eritadenine [(2*S*,3*S*)-4-(adenin-9-yl)-2,3-dihydroxybutanoic acid] 8

A solution of compound **7** (49 mg, 0.167 mmol) in 10% aq. AcOH (6 ml) was stirred at 65 °C for 4 h, and then the solvent was evaporated off *in vacuo* to give diol **8** (42 mg, 99%) as a solid, $[\alpha]_D^{26}$ −14.3 (*c* 0.07, 1 M HCl) {lit.,[3b] $[\alpha]_D^{20}$ −14.8 (*c* 0.5, 1 M HCl)}; λ_{max}(MeOH)/nm 260; δ_H(400 MHz; [$^2H_6$]DMSO) 3.27 (1 H, d, *J* 8.3, 2-H), 3.63 (1 H, td, *J* 8.3 and 2.4, 3-H), 4.03 (1 H, dd, *J* 13.7 and 8.3, 4-H), 4.38 (1 H, dd, *J* 13.7 and 2.4, 4-H), 7.12 (2 H, br s, adenine 6-NH_2), 8.03 (1 H, s, adenine 2- or 8-H) and 8.10 (1 H, s, adenine 8- or 2-H); δ_C(100 MHz; [$^2H_6$]DMSO) 46.63, 70.54, 71.25, 118.43, 141.66, 149.69, 152.15, 155.83 and 175.18; *m*/*z* (FAB, Gly) 254 (M^+ + H, 10%) [Found (FAB): (M^+ + H), 54.0879. $C_9H_{12}N_5O_4$ requires *m*/*z* 254.0889].

(2*R*,3*S*)-4-(Adenin-9-yl)-2,3-isopropylidenedioxybutanal oximes 9 (*E*/*Z*)

To a stirred solution of hydroxylamine hydrochloride (125 mg, 1.8 mmol) in anhydrous MeOH (30 ml) was added NaOMe (369 μl of 4.88 M solution in MeOH, 1.8 mmol) at room temp. The mixture was stirred at room temp. for 3 h and was then filtered through a Celite pad to remove resulting NaCl. The mixture of the filtrate and aldehyde **2a** (333 mg, 1.2 mmol) was stirred at room temp. for 6 h and was then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 30 : 1–10 : 1) to give *geometrical mixture* **9** (249 mg, 71%; *E*/*Z* = 38 : 62) as a solid, which was recrystallized from EtOH, mp 234–237 °C (decomp.) (Found: C, 49.1; H, 5.45; N, 28.55. $C_{12}H_{16}N_6O_3$ requires C, 49.31; H, 5.52; N, 28.75%); λ_{max}(MeOH)/nm 260; ν_{max}(KBr)/cm^{-1} 3328, 3199, 2989, 2937, 2884, 1690, 1647, 1611, 1579, 1480, 1422, 1382, 1340, 1306, 1248, 1219, 1164, 1072, 981, 953, 911, 876, 797, 727 and 650; δ_H(400 MHz; [$^2H_6$]DMSO); for (*Z*)-isomer: 1.25 and 1.48 (each 3 H, s, isopropylidene), 4.03 (1 H, dd, *J* 13.87 and 9.8, 4-H), 4.16 (1 H, dd, *J* 13.7 and 2.9, 4-H), 4.80 (1 H, ddd, *J* 9.8, 6.8 and 2.9, 3-H), 5.27 (1 H, dd, *J* 6.8 and 4.4, 2-H), 6.97 (1 H, d, *J* 4.4, 1-H), 7.18 (2 H, br s, adenine 6-NH_2), 8.03 (1 H, s, adenine 2- or 8-H), 8.11 (1 H, s, adenine 8- or 2-H) and 11.65 (1 H, s, N-OH); for (*E*)-isomer: 1.26 and 1.47 (each 3 H, s, isopropylidene), 4.21 (2 H, m, 4-H_2), 4.72 (1 H, q, *J* 6.8, 3-H), 4.79 (1 H, m, 2-H), 7.20 (2 H, br s, adenine 6-NH_2), 7.46 (1 H, d, *J* 7.8, 1-H), 8.05 (1 H, s, adenine 2- or 8-H), 8.12 (1 H, s, adenine 8- or 2-H) and 11.28 (1 H, s, N-OH); *m*/*z* (EI) 292 (M^+, 51%), 277 (25), 234 (29), 217 (41), 148 (97) and 135 (100).

(2*R*,3*S*)-4-(Adenin-9-yl)-2,3-isopropylidenedioxybutanenitrile 10

To a solution of oxime **9** (102 mg, 0.35 mmol) in DMF (0.7 ml) was added thionyl dichloride (127.7 μl, 1.75 mmol) at 0 °C. After being stirred at 0 °C for 2.5 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 20 : 1–10 : 1) to give *nitrile* **10** (76 mg, 79%) as a solid, λ_{max}(MeOH)/nm 260; ν_{max}(neat)/cm^{-1} 3345, 3151, 2991, 2940, 1658, 1602, 1490, 1422, 1379, 1331, 1312, 1236, 1153, 1073, 730 and 646; δ_H(400 MHz; [$^2H_6$]DMSO) 1.27 and 1.50 (each 3 H, s, isopropylidene), 4.45 (1 H, dd, *J* 14.2 and 9.3, 4-H), 4.61 (1 H, dd, *J* 14.2 and 3.4, 4-H), 4.80 (1 H, ddd, *J* 9.3, 4.9 and 3.4, 3-H), 5.41 (1 H, d, *J* 4.9, 2-H), 7.24 (2 H, s, adenine 6-NH_2), 8.14 (1 H, s, adenine 2- or 8-H) and 8.15 (1 H, s, adenine 8- or 2-H); δ_H(400 MHz; $CDCl_3$) 1.34 and 1.64 (each 3 H, s, isopropylidene), 4.48 (1 H, dd, *J* 14.2 and 7.8, 4-H), 4.68 (1 H, ddd, *J* 7.8, 5.4 and 3.9, 3-H), 4.73 (1 H, dd, *J* 14.2 and 3.9, 4-H), 4.94 (1 H, d, *J* 5.4, 2-H), 5.87 (2 H, br s, adenine 6-NH_2), 7.94 (1 H, s, adenine 2- or 8-H) and 8.36 (1 H, s, adenine 8- or 2-H); NOE ($CDCl_3$), irradiate 2-H, observe 3-H

(8.6%); δ_C($CDCl_3$) 25.78, 27.07, 44.23, 66.32, 74.88, 113.47, 115.79 (CN), 119.54, 141.03, 149.93, 153.21 and 155.58; *m*/*z* (EI) 274 (M^+, 35%), 259 (25), 216 (76), 149 (100) and 135 (68) [Found (EI): M^+, 274.1169. $C_{12}H_{14}N_6O_2$ requires *M*, 274.1178].

(2*R*,3*S*)-4-(Adenin-9-yl)-2,3-dihydroxybutanenitrile 11

A solution of compound **10** (43 mg, 0.157 mmol) in TFA (2 ml) was stirred at room temp. for 45 h, and then solvent was removed *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 4:1) to give *diol* **11** (21 mg, 57%) as a solid, λ_{max}(MeOH)/nm 260; ν_{max}(KBr)/cm^{-1} 3423, 3178, 2931, 2244 (CN), 1702, 1653, 1609, 1478, 1422, 1303, 1252, 1074, 794, 727, 650 and 591; δ_H(400 MHz; [$^2H_6$]DMSO) 3.99 (1 H, m, 3-H), 4.05 (1 H, dd, *J* 13.7 and 8.8, 4-H), 4.37 (1 H, dd, *J* 13.7 and 2.4, 4-H), 4.45 (1 H, t, *J* 6.4, 2-H), 6.04 (1 H, d, *J* 6.4, 3-OH), 6.82 (1 H, d, *J* 6.4, 2-OH), 7.21 (2 H, s, adenine 6-NH_2), 8.03 (1 H, s, adenine 2- or 8-H) and 8.13 (1 H, s, adenine 8- or 2-H); δ_C([$^2H_6$]DMSO) 45.68, 63.49, 69.82, 118.60, 119.84, 141.58, 149.54, 152.28 and 155.92; *m*/*z* (FAB, NBA) 235 (M^+ + H, 8%) [Found (FAB) (M^+ + H), 235.0949. $C_9H_{11}N_6O_2$ requires *m*/*z*, 234.0943].

9-[(2′*S*)-4′-Hydroxy-3′-hydroxymethyl-2′,3′-isopropylidenedioxybutyl]adenine 12

To a suspension of aldehyde **2a** (27.7 mg, 0.1 mmol) and formaldehyde (45.0 μl of 37 wt.% solution in water, 0.6 mmol) was added 2 M NaOH (0.1 ml, 0.2 mmol) at room temp. and the mixture was stirred at this temp. for 24 h. The mixture was treated with $NaBH_4$ (15.1 mg, 0.4 mmol) at 0 °C and was stirred at 0 °C for 2 h, neutralized by the addition of 10% aq. AcOH, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 15:1) to give *compound* **12** (27.6 mg, 89%) as a solid, mp 192–194 °C (decomp.) (Found: C, 48.8; H, 6.05; N, 22.0. $C_{13}H_{19}N_5O_4 \cdot 1/2H_2O$ requires C, 49.05; H, 6.33; N, 22.00%); the existence of water in this product was confirmed by ^{1}H NMR analysis; $[a]_D^{28}$ −38.5 (*c* 0.27 in MeOH); λ_{max}(MeOH)/nm 260; ν_{max}(KBr)/cm^{-1} 3421, 3338, 3222, 2990, 2937, 2875, 1648, 1604, 1578, 1479, 1421, 1382, 1324, 1246, 1216, 1054, 932, 842, 722 and 646; δ_H(400 MHz; [$^2H_6$]DMSO) 1.21 and 1.38 (each 3 H, s, isopropylidene), 3.45–3.51 (2 H, m, 4′-H and 3′-C*H*HOH), 3.53–3.58 (2 H, m, 4′-H and 3′-C*H*HOH), 4.36 (1 H, dd, *J* 12.7 and 9.8, 1′-H), 4.41 (1 H, d, *J* 9.8, 2′-H), 4.50 (1 H, d, *J* 12.7, 1′-H), 4.83 (2 H, m, 4′-OH and 3′-CH_2O*H*), 7.18 (2 H, s, 6-NH_2), 8.07 (1 H, s, 2- or 8-H) and 8.13 (1 H, s, 8- or 2-H); δ_C([$^2H_6$]DMSO) 26.66, 28.44, 42.98, 60.70, 62.31, 77.16, 83.81, 107.75, 118.47, 140.85, 149.47, 152.37 and 155.90; *m*/*z* (EI) 309 (M^+, 12%), 294 (18), 251 (36), 234 (46), 203 (32) and 136 (100).

9-[(2′*S*)-2′,3′,4′-Trihydroxy-3′-(hydroxymethyl)butyl]adenine 13

A solution of compound **12** (21.2 mg, 0.069 mmol) in TFA (1 ml) was stirred at room temp. for 2 h, and then solvent was removed *in vacuo*. The residue was purified by reversed-phase chromatography (water–MeCN, 19:1) to give tetraol **13** (15.3 mg, 83%) as a solid, λ_{max}(MeOH)/nm 261; ν_{max}(KBr)/cm^{-1} 3403, 3323, 3193, 2940, 2887, 1683, 1656, 1620, 1580, 1478, 1423, 1340, 1309, 1253, 1054, 723, 652 and 609; δ_H(400 MHz; [$^2H_6$]DMSO) 3.42–3.55 (4 H, m, 4′-H and 3′-CH_2OH), 3.84 (1 H, m, 2′-H), 4.10 (1 H, dd, *J* 14.2 and 10.3, 1′-H), 4.29 (1 H, br s, 3′-OH), 4.45 (1 H, dd, *J* 14.2 and 2.0, 1′-H), 4.48 (2 H, br, 4′-OH and 3′-CH_2O*H*), 4.84 (1 H, br 2′-OH), 7.17 (2 H, br s, 6-NH_2), 8.02 (1 H, s, 2- or 8-H) and 8.12 (1 H, s, 8- or 2-H); δ_C([$^2H_6$]DMSO) 45.28, 62.10, 62.82, 70.90, 74.96, 118.61, 141.79, 149.56, 151.77 and 155.61; *m*/*z* (FAB, NBA) 270 (M^+ + H, 4%) [Found (FAB): (M^+ + H), 270.1210. $C_{10}H_{16}N_5O_4$ requires *m*/*z*, 270.1202].

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