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Ribofuranose-ring Cleavage of Purine Nucleosides with Diisobutylaluminum Hydride: Convenient Method for the Preparation of Purine Acyclonucleosides

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Abstract: The reaction of 2',3'-O-isopropylidene protected purine nucleosides with diisobutylaluminum hydride (DIBAL-H) caused the reductive cleavage of the C-1'-O-4' bond to give the corresponding 9-D-ribitylpurines. The ring cleavage of inosine 1a, thioinosine 1f, and their derivatives having an alkyl group at the O^{6} - or S^{6} -position 1c, e, and g proceeded smoothly to afford the corresponding ribityl derivatives $2a, f, c, e, and g, whereas N^{6}$ -methylated adenosine derivatives 1k and 1 remarkably resisted the DIBAL-H reduction. 5'-Deoxy and 5'-chloro-5'-deoxy derivatives 1b, d, i, and j also underwent reductive cleavage at the sugar moiety under similar conditions. An acyclic analog of guanosine 6, which is of biological interest, was prepared from a guanosine derivative 5 in a similar way. The present methodology for the synthesis of purine acyclonuculeosides was also applied to the preparation of an acyclic analog 17 of neplanocin A. © 1997 Elsevier Science Ltd.

INTRODUCTION

In the search for effective, selective, and nontoxic antiviral agents, a variety of strategies have been devised to design nucleoside analogs.¹ Among them, acyclonucleosides such as acyclovir² and ganciclovir³ have been developed for the treatment of certain herpes virus infections. Most synthetic methods for the preparation of such acyclonucleosides involve the condensation of a nucleobase moiety with an appropriate side chain moiety.⁴ Synthetic methods starting from commercially available nucleosides such as adenosine and guanosine have been unprecedented except for an example of the oxidative cleavage of 2', 3' -*cis*-diol portion of ribonuculeosides with NaIO₄.^{4b, 5} In the course of our study on the synthesis of 1,6-dihydropurine nucleosides using various reducing agents, we found that the reaction of purine nucleosides with diisobutylaluminum hydride (DIBAL-H) caused a selective cleavage of the C-1'-O-4' bond in the ribose ring to give the corresponding 9-D-ribitylpurines.^{6a} Although numerous examples of the reductive cleavage of acetals,⁷ aminals,⁸ and ethers⁹ by DIBAL-H have been reported, no applications of DIBAL-H for such cleavage of the C-1'-O-4' bond of nucleosides have been reported.¹⁰ In this paper, further synthetic examples of 9-D-ribitylpurines and the scope and limitations of this methodology are described.

RESULTS AND DISCUSSION

The reaction of 2', 3'-O-isopropylideneinosine $(1a)^{11}$ with 5 equiv of DIBAL-H in anhydrous THF under argon atmosphere for 24 h gave 9-(2,3-O-isopropylidene-D-ribityl)hypoxanthine (2a) in 67% isolated yield.

The structure of 2a was fully supported by spectral data and elemental analyses. Further proof of the structure of 2a rests upon its easy conversion into 9-(2,3;4,5-bis-O-isopropylidene-D-ribityl)hypoxanthine (3).



 Table 1. Solvent Effect on the DIBAL-H Reduction of 2', 3'-O-Isopropylideneinosine (1a).^a

	Yield	l (%) ^b
Solvent	Product 2a	Recovery 1a
THF	68	24
Et ₂ O	35	8
CH ₂ Cl ₂	3	14
Toluene	1	13

^aThese reactions were carried out using 5 equiv of DIBAL-H in the stated medium under argon atmosphere at 25 °C for 24 h. ^bDetermined by TLC scanner (Shimadzu CS-9000).

Table 2. Stoichiometric Study on the DIBAL-H Reduction of 2', 3'-O-Isopropylideneinosine (1a).^a

DIBAL-H	Yield	1 (%) ^b
(equiv)	Product 2a	Recovery 1a
3	24	65
4	43	51
5	68	24
7	69	22
10	69	8

^aThese reactions were carried out using stated equiv of DIBAL-H in THF under argon atmosphere at 25 °C for 24 h. ^bDetermined by TLC scanner (Shimadzu CS-9000).

The DIBAL-H reduction of **1a** was investigated in several anhydrous solvents (Table 1). In general, the DIBAL-H reductions are conducted in a solvent possessing no oxygen atom, *e.g.*, CH_2Cl_2 ,¹² because, if an oxygen-containing solvent such as THF is used, oxygenophilicity of the aluminum atom facilitates the coordination of this reagent with the oxygen atom of the solvent rather than with that of a substrate, thus decreasing the reductive activity of the reagent.^{9b} In the present reductive cleavage, however, THF and Et₂O were favored over CH_2Cl_2 and toluene as solvents. The TLC analyses of the reaction mixture in CH_2Cl_2 or

toluene indicated a weak UV absorption spots due to the product remained by the over-reduction.¹³ Of the four solvents in our trials, THF was found to be most effective, and it led to a smoother and cleaner conversion of **1a** into **2a** than Et_2O . The coordination of DIBAL-H with THF oxygen could prevent the over-reduction of **1a** to result in the selective cleavage of the furanose ring. Stoichiometric study on the reduction of **1a** with DIBAL-H in THF was also carried out (Table 2). The results show that the use of excess DIBAL-H (>5 equiv) is necessary for the satisfactory conversion.

Table 3. DIBAL-H Reductions of 6-Substituted Purine Nucleosides and Purine 5'-Deoxynucleosides.^a



Starting Compd.		Yield (%) ^b		
No.	X	Y	Product 2	Recovery 1
a	ОН	OH	67 (68) ^c	23 (24) ^c
b	OH	Cl	82	9
с	OCH ₃	OH	64	ND^d
d	OCH ₃	Br	57	ND^d
e	OCH(CH ₃) ₂	OH	65	ND^d
f	SH	OH	61	6
g	SCH ₃	OH	41	8
h	NH ₂	OH	40 (44) ^c	43 (47) ^c
			5]°	40 ^e
			59 ^r	24 ^r
i	NH ₂	Н	29	71
j	NH ₂	Cl	26	58
k	NHCH ₃	OH	14 (14) ^c	75 (81) ^c
1	$N(CH_3)_2$	OH	2 (trace) ^c	54 (55) ^c
m ^g	CH ₃	OH	38	ND^d
n	Ph	ОН	28	29

"These reactions were carried out using 5 equiv of DIBAL-H in THF under argon atmosphere at 25 °C for 24 h, unless otherwise noted. ^hIsolated yield. ^cThe yields in parenthesis were determined by TLC scanner (Shimadzu CS-9000). ^dNot determined. ^cIn the presence of 2 equiv of HMPA, 5 equiv of DIBAL-H was used. ^cIn the presence of 3 equiv of HMPA, 7 equiv of DIBAL-H was used. ^eThe reaction was performed for 18 h.

We utilized the best reaction conditions obtained for 1a to reduce a variety of 6-substituted purine nucleosides and purine 5'-deoxynucleosides; the results are summarized in Table 3. O^6 -Methyl and O^6 -isopropyl substituted inosine derivatives $1c^{14}$ and $1e^{14}$ were cleaved smoothly to give the corresponding 9-D-ribitylhypoxanthine derivatives 2c and 2e in 64% and 65% yields, respectively. Similarly, 5'-modified purine nucleosides, 5'-chloro-5'-deoxyinosine and 5'-bromo-5'-deoxy- O^6 -methylinosine derivatives $1b^{15}$ and $1d^{16}$ were cleaved to ribityl derivatives 2b and 2d, respectively, in good to moderate yields. Their reactivities were almost similar to those for 1a. Analogous treatment of 6-thioinosine and its S^6 -methyl derivatives $1f^{17}$ and $1g^{18}$ also gave the corresponding ribityl derivatives 2f and 2g in moderate yields, respectively.

On the other hand, the yields of reduction products from adenosine derivatives were generally low; 2', 3' - O-isopropylideneadenosine, 5'-deoxy-, and 5'-chloro-5'-deoxy-2', 3' - O-isopropylideneadenosine $(1h-j)^{19, 20}$ gave the corresponding 9-D-ribityladenines 2h-j in 40%, 29%, and 26% yields,

respectively. Furthernore, the reaction of N^6 -methyl- and N^6, N^6 dimethyladenosines $1k^{21}$ and $1l^{22}$ resulted in marked decrease of the yields (14% and 2%) of the reduction products 2k and 2l, respectively. For a practical purpose, 2l was alternatively synthesized in 64% overall yield (four steps) from 2a via 6-chloropurine riboside 4 (see, experimental section). In order to improve the yield of 2h, the DIBAL-H reduction of 1h was examined in the presence of hexamethylphosphoric triamide (HMPA). Tsuda *et al.* reported²³ that a remarkable change in the reducing reactivity of DIBAL-H was



brought about by addition of HMPA. The presence of 2 equiv of HMPA in the reaction mixture of 1h raised the yield of 2h up to 51%. When 3 equiv of HMPA and 7 equiv of DIBAL-H were used, 2h was obtained in 59% yield with the recovered 1h (24%). The presence of an appropriate amount of HMPA led to some improvement in the yield of 2h.

The reduction of 6-methylpurine riboside and 6-phenylpurine riboside $1 m^{24}$ and 1 n,²⁵ both of which have no heteroatom at the 6-position in the base moiety, gave ribityl products 2m and 2n in 38% and 28% yields, respectively, together with intractable materials.



Biopterin²⁶ and riboflavin²⁷ are biologically interesting and naturally occurring compounds. Biosyntheses of these compounds are accompanied with two cleavages at the imidazole and ribose rings of guanosine 5'-triphosphate.²⁸ Therefore, the present reductive cleavage of the ribofuranose moiety of 2',3'-O-isopropylideneguanosine (5) can be considered as a kind of bio-mimetic chemical reaction. Treatment of 5 with 6 equiv of DIBAL-H gave a ribityl derivative 6 in 38% yield. This compound 6 is also expected to be an excellent intermediate for the preparation of antiviral acycloguanosine. An example of the cleavage of imidazole ring was found when adenosine 1-oxide 7^{29} was subjected to our reaction. We could isolate, besides a main product 8, a base-ring opening product 9 in 3% yield.



Contrary to the purine nucleosides, 7-deaza-inosine and adenosine derivatives 10^{30} and 11^{31} were hardly cleaved with DIBAL-H to result in the recovery of the starting materials. These results indicate that electron density and/or structure of the purine base exerts a great influence on the reductive cleavage of the ribose moiety. The coordination of DIBAL-H with a substrate as depicted in the figure A seems to be important for the selective cleavage.



In the case of the DIBAL-H reduction of unprotected adenosine (12), the significant decrease of the yield of the obtained ribityl derivative 13^{32a} was observed (6% yield and 93% recovery of 12). On the contrary, 2'-deoxyadenosine (14) gave a ribityl derivative 15^{33} in 39% yield together with recovery of 14 (55%) in analogy with the result for the protected adenosine 1h. It seems likely that the 2' free hydroxyl group of 12 suppresses the reductive cleavage of the C-1'-O-4'.



TrO

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was allowed to react with DIBAL-H, the base moiety was reduced in preference to the sugar moiety to afford the corresponding 5,6-dihydrouridine derivative 16^{35} in 48% yield instead of the expected 9-D-ribityl derivative. So far, the synthesis of 5,6-dihydrouridines has been performed by a catalytic hydrogenation of uridine derivatives over rhodium on alumina.^{35, 36} The expected cleavage of 2',3'-*O*-isopropylidenecytidine gave a complex mixture, from which a 1-D-ribitylcytosine derivative could not be isolated. Therefore, the present reductive cleavage seems to be inapplicable to the synthesis of pyrimidine acyclonucleosides.

We have applied the present convenient method to the synthesis of an acyclic analog 17 of neplanocin A,^{6b} that has been shown to have significant antiviral activity due to the inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase, to which great attention has been recently paid as a target enzyme.³⁷ Thus, *tert*-butyldimethylsilyl (TBDMS) protection at the 5'-position of 2h gave a silylated derivative 18 in 78% yield. Oxidation of 18 with chromic acid afforded the 4'-keto derivative 19³⁸ in 52% yield. Wittig reaction of 19 with Ph₃PCH₃Br/BuLi and subsequent deprotection of the resulting 4'-methylene derivative 20³⁸ with 80% acetic acid resulted in the formation of the desired acycloneplanocin A 17.



Reagents and conditions: i) tert-butyldimethylsilyl chloride (5 equiv), imidazole (10 equiv), in DMF, r. t., 5 min, 78%; ii) CrO₃ (4 equiv), pyridine (8 equiv), Ac₂O (4 equiv), in CH₂Cl₂, r. t., 6 h, 52%; iii) Ph₃PCH₃Br (10 equiv), BuLi (8.3 equiv), in THF, 0 $^{\circ}$ C, overnight, 69%; iv) 80% AcOH, 60 $^{\circ}$ C, 6 h, 79%.

Although 17 indicated faint inhibitory activity toward AdoHcy hydrolase (rabbit erythrocyte) with IC_{50} values of 350 μ M, 17 was virtually inactive against herpes simplex virus type 1 (HSV-1), influenza virus, and human cytomegarovirus (HCMV) with EC₅₀ values of >50 μ g/mL.

In conclusion, the treatment of a variety of 2', 3'-O-isopropylidene protected purine nucleosides with DIBAL-H in THF caused the selective cleavage of the C-1'- O-4' bond in the ribose moiety to give 9-D-ribitylpurine derivatives. The reactivity in the reduction was fairly affected by the purine base moiety. This methodology was shown to be useful for the synthesis of 9-D-ribitylpurines³² and applicable to the synthesis of biologically important purine acyclonucleosides, although could not be utilized for synthesizing pyrimidine acyclonucleosides.

EXPERIMENTAL

Anhydrous THF and diethyl ether were obtained by distillation from sodium benzophenone ketyl. Anhydrous dichloromethane was obtained by distillation from calcium hydride. Anhydrous toluene (thiophene free) was obtained by distillation from sodium after pre-treatment with sulfuric acid. Thin-layer chromatographic (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 Waters Sep-Pak[®] (C₁₈) cartridge.

Melting points (uncorrected) were determined on a Yanagimoto melting point apparatus. UV absorption spectra were recorded on a Shimadzu UV-260 spectrophotometer. IR spectra were measured using a Perkin Elmer 1640 FT-IR spectrometer. ¹H 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 CDCl₃ as a solvent or internally referenced to the residual protonated solvent resonances (2.49 ppm) in DMSO-*d*₆ as a solvent. ¹³C NMR spectra were recorded on a JEOL JNM EX-400 (100 MHz) spectrometer. Mass spectra and high-resolution mass spectra were taken on a JEOL JMS-D 300 or a JMS-SX 102A machine. Elemental analyses were performed by the Microanalytical Laboratory of our University.

General Procedure for the DIBAL-H Reduction of Nucleosides.

To a stirred suspension of nucleoside (0.2 mmol) in anhydrous THF (15 mL) at room temperature was added DIBAL-H (1.0 mL of 1.0 M solution in toluene, 1.0 mmol) dropwise under argon atmosphere. After being stirred at 25 $^{\circ}$ C for 24 h, the reaction mixture was treated and purified by the following methods A-C unless otherwise noted.

Method A. The resulting solution was quenched with saturated aqueous potassium sodium tartrate solution (10 mL) at 0 $^{\circ}$ C and stirred at room temperature overnight. The THF layer was separated and the aqueous layer was extracted with BuOH (50 mL × 3). The combined THF and BuOH layers were dried over Na₂SO₄ and evaporated *in vacuo*. The residue was purified by reversed phase chromatography (H₂O/MeCN, 49:1–9:1).

Method B. The resulting solution was quenched with saturated aqueous potassium sodium tartrate solution (10 mL) at 0 $^{\circ}$ C and stirred at room temperature overnight. The THF layer was separated and the aqueous layer was extracted with BuOH (40 mL × 3). The combined THF and BuOH layers were dried over Na₂SO₄ and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 50:1–12:1).

Method C. The resulting solution was quenched with 10% aqueous AcOH at 0 $^{\circ}$ C, and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 50:1–12:1).

9-(2,3-O-Isopropylidene-D-ribityl)hypoxanthine (2a). Obtained from 1a (61.7 mg, 0.2 mmol) according to the method A in 67% yield (41.6 mg) as a colorless solid, which was recrystallized from EtOH-MeOH. mp 246-248 °C; UV (MeOH) λ_{max} 249 nm; IR (KBr) ν_{max} 3422, 3058, 2988, 2938, 2888,

1688, 1589, 1545, 1418, 1378, 1218, 1075, 897, 847, 790, 646, 613 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; DMSOd₆) 1.19 and 1.42 (each 3H, s, isopropylidene), 3.41 (1H, dt, J = 11.7 and 5.4 Hz, 5'-H), 3.61-3.64 (2H, m, 4'-H and 5'-H), 4.10 (1H, dd, J = 9.3 and 5.9 Hz, 3'-H), 4.21 (1H, dd, J = 13.7 and 10.7 Hz, 1'-H), 4.49 (1H, ddd, J = 10.7, 5.9 and 2.4 Hz, 2'-H), 4.53 (1H, dd, J = 13.7 and 2.4 Hz, 1'-H), 4.64 (1H, t, J = 5.4 Hz, 5'-OH), 5.12 (1H, d, J = 5.4 Hz, 4'-OH), 8.02 (2H, s, 2-H and 8-H), 12.26 (1H, s, N₁-H); ⁻¹³C NMR $\delta_{\rm C}$ (100 MHz; DMSO-d₆) 25.58, 27.98, 44.27, 63.84, 69.33, 75.05, 75.88, 108.56, 123.79, 140.93, 145.39, 148.48, 156.67; MS (EI) *m*/z 310 (M⁺, 18%), 295 (32), 150 (100), 137 (90). Anal. Calcd for C₁₃H₁₈O₅N₄: C, 50.31; H, 5.85; N, 18.06. Found: C, 50.08; H, 5.76; N, 17.88.

9-(**5**-Chloro-**5**-deoxy-**2**, 3-*O*-isopropylidene-D-ribityl)hypoxanthine (2b). Obtained from **1b** (65.3 mg, 0.2 mmol) according to the method B in 82% yield (53.6 mg) as a colorless solid, which was recrystallized from EtOH-CHCl₃. mp 205–206 °C (dec.); UV (MeOH) λ_{max} 249 nm; IR (KBr) v_{max} 3448, 3428, 2990, 2928, 2863, 1688, 1583, 1212, 1074. 891, 791, 691 cm⁻¹; ¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_6) 1.21 and 1.42 (each 3H, s, isopropylidene), 3.68 (1H, dd, J = 11.7 and 5.4 Hz, 5'-H), 3.80 (1H, dd, J = 11.7 and 2.5 Hz, 5'-H), 3.88–3.91 (1H, m, 4'-H), 4.14 (1H, dd, J = 9.3 and 6.3 Hz, 3'-H), 4.25 (1H, dd, J = 14.2 and 10.7 Hz, 1'-H), 4.52 (1H, dd, J = 14.2 and 2.9 Hz, 1'-H), 4.55 (1H, ddd, J = 10.7, 6.3 and 2.9 Hz, 2'-H), 5.72 (1H, d, J = 5.9 Hz, 4'-OH), 8.02 (2H, s, 2-H and 8-H), 12.26 (1H, s, N₁-H); MS (EI) *m/z* 328 (M*, 21%), 330 (7), 313 (37), 292 (36), 221 (54), 150 (100), 137 (87). Anal. Calcd for C₁₃H₁₇O₄N₄Cl: C, 47.49; H, 5.21; N, 17.04. Found: C, 47.30; H, 5.16; N, 17.02.

9-(2,3-O-Isopropylidene-D-ribityl)-6-methoxypurine (2c). Obtained from **1c** (483 mg, 1.5 mmol) according to the method C in 64% yield (313 mg) as a colorless solid, which was recrystallized from EtOH-Et₂O. mp 99–102 °C; UV (MeOH) λ_{max} 249 nm; IR (KBr) v_{max} 3423, 2991, 2938, 1604, 1579, 1481, 1351, 1319, 1229, 1065, 897, 648 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; CDCl₃) 1.30 and 1.50 (each 3H, s, isopropylidene), 3.76 (1H, dd, J = 10.7 and 5.4 Hz, 5'-H), 3.81 (1H, m, 4'-H), 3.91 (1H, dd, J = 10.7 and 2.4 Hz, 5'-H), 4.19 (3H, s, 6-OCH₃), 4.22 (1H, dd, J = 8.8 and 5.9 Hz, 3'-H), 4.30 (1H, dd, J = 14.2 and 9.3 Hz, 1'-H), 4.57 (1H, ddd, J = 9.3, 5.9 and 2.4 Hz, 2'-H), 4.91 (1H, dd, J = 14.2 and 2.4 Hz, 1'-H), 8.11 (1H, s, 2-H or 8-H), 8.54 (1H, s, 2-H or 8-H); MS (EI) m/z 324 (M⁺, 7%), 235 (100), 151 (91); HRMS (EI) Calcd. for C₁₄H₂₀O₅N₄ (M⁺): 324.1434. Found: 324.1454. Anal. Calcd for C₁₄H₂₀O₅N₄· 1/10(C₂H₅)₂O·1/4H₂O: C, 51.43; H, 6.45; N, 16.66. Found: C, 51.36; H, 6.40; N, 16.60. The existence of ether and water in this product was confirmed by ¹H NMR analysis.

9-(5-Bromo-5-deoxy-2, 3-*O***-isopropylidene-D-ribityl)-6-methoxypurine (2d).** Obtained from **1d** (101 mg, 0.262 mmol), according to the method B except for the use of CHCl₃ for extraction (instead of BuOH) and the eluent for the column chromatography (toluene/EtOAc, 1:2), in 57% yield (58 mg) as a colorless amorphous. UV (MeOH) λ_{max} 248 nm; IR (KBr) v_{max} 3424, 3260, 2988, 2939, 1602, 1580, 1482, 1406, 1383, 1349, 1317, 1229, 1166, 1068, 973, 888, 784, 736, 646 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; CDCl₃) 1.30 and 1.49 (each 3H, s, isopropylidene), 3.62 (1H, dd, J = 10.8 and 6.4 Hz, 5'-H), 3.80 (1H, dd, J = 10.8 and 6.4 Hz, 5'-H), 3.80 (1H, dd, J = 10.8 and 2.4 Hz, 5'-H), 3.81–3.83 (1H, m, 4'-H), 4.17 (1H, dd, J = 9.3, 6.4 and 2.9 Hz, 2'-H), 4.91 (1H, dd, J = 14.7 and 2.9 Hz, 1'-H), 8.09 (1H, s, 2-H or 8-H), 8.55 (1H, s, 2-H or 8-H); MS (FAB, Gly) *m/z* 387 (M⁺+H, 28%), 389 (27). HRMS (FAB) Calcd for $C_{14}H_{20}O_4N_4Br$ (M⁺+H): 387.0668. Found (FAB): 387.0675.

6-Isopropoxy-9-(2,3-*O***-isopropylidene-D-ribityl)purine (2e).** Obtained from 1e (526 mg, 1.5 mmol) according to the method C in 65% yield (342 mg) as a colorless solid, which was recrystallized from EtOH-Et₂O. mp 160-162 °C; UV (MeOH) λ_{max} 249 nm; IR (KBr) v_{max} 3420, 3137, 2981, 2932, 2879, 1600, 1578, 1460, 1413, 1385, 1318, 1228, 1168, 1103, 1069, 1052, 890, 846, 796, 730, 646 cm⁻¹; ¹H NMR δ_{H} (270 MHz; DMSO- d_{6}) 1.18 and 1.42 (each 3H, s, isopropylidene), 1.38 (6H, d, J = 6.4 Hz, 6-OCH(CH_{J_2}), 3.52 (1H, dt, J = 11.7 and 5.9 Hz, 5'-H), 3.59–3.70 (2H, m, 4'-H and 5'-H), 4.12 (1H, dd, J = 9.3 and 5.9 Hz, 3'-H), 4.30 (1H, dd, J = 13.2 and 10.3 Hz, 1'-H), 4.55 (1H, ddd, J = 10.3, 5.9 and 2.4 Hz,

2'-H), 4.61 (1H, dd, J = 13.2 and 2.4 Hz, 1'-H), 4.64 (1H, t, J = 5.9 Hz, 5'-OH), 5.14 (1H, d, J = 5.9 Hz, 4'-OH), 5.59 (1H, m, J = 6.4 Hz, 6-OCH(CH₃)₂), 8.29 (1H, s, 2-H or 8-H), 8.47 (1H, s, 2-H or 8-H); MS (EI) *m*/z 352 (M⁺, 3%), 263 (67), 137 (100). Anal. Calcd for C₁₆H₂₄O₅N₄: C, 54.53; H, 6.87; N, 15.90. Found: C, 54.42; H, 6.93; N, 15.81.

9-(2,3-*O*-**Isopropylidene-D-ribityl**)-**6-thiopurine (2f).** Obtained from **1f** (32 mg, 0.1 mmol) according to the method C in 61% yield (20 mg) as a colorless solid, which was recrystallized from EtOH-Et₂O. mp 266 °C (dec.); UV (MeOH) λ_{max} 226, 322 nm; IR (KBr) v_{max} 3424, 3054, 2987, 2936, 2883, 2734, 1597, 1561, 1544, 1407, 1378, 1339, 1199, 1074, 964, 883, 846, 785, 730, 654 cm⁻¹; ¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_6) 1.19 and 1.42 (each 3H, s, isopropylidene), 3.41 (1H, dt, J = 11.7, and 5.9 Hz, 5'-H), 3.60-3.64 (2H, m, 4'-H and 5'-H), 4.11 (1H, dd, J = 8.8 and 5.9 Hz, 3'-H), 4.25 (1H, dd, J = 13.7 and 10.7 Hz, 1'-H), 4.48-4.56 (2H, m, 1'-H and 2'-H), 4.64 (1H, t, J = 5.9 Hz, 5'-OH), 5.13 (1H, d, J = 5.9 Hz, 4'-OH), 8.18 (1H, s, 2-H or 8-H), 8.22 (1H, s, 2-H or 8-H), 13.69 (1H, s, N₁-H); MS (FAB, Gly) *m/z* 327 (M⁺+H, 6%). HRMS (FAB, Gly) Calcd for C₁₃H₁₉O₄N₄S (M⁺+H): 327.1127. Found: 327.1135; *Anal.* Calcd for C₁₃H₁₈O₄N₄S·1/10(C₂H₅)₂O·9/10H₂O: C, 45.98; H, 5.99; N, 16.00. Found: C, 46.10; H, 5.74; N, 15.77. The existence of ether and water in this product was confirmed by ¹H NMR analysis.

9-(2,3-0-Isopropylidene-D-ribityl)-6-methylthiopurine (2g). Obtained from **1g** (91 mg, 0.27 mmol) according to the method C in 41% yield (37.4 mg) as a colorless solid, which was recrystallized from EtOH-Et₂O. mp 112.5-114.5 °C; UV (MeOH) λ_{max} 218, 282, 289 nm; IR (KBr) v_{max} 3424, 2987, 2934, 1655, 1629, 1571, 1438, 1400, 1384, 1332, 1255, 1213, 1166, 1070, 944, 869, 782, 740, 646, 591 cm⁻¹; ¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_6) 1.18 and 1.42 (each 3H, s, isopropylidene), 2.66 (3H, s, 6-SCH₃), 3.41 (1H, dt, J = 11.2 and 5.4 Hz, 5'-H), 3.60-3.66 (2H, m, 4'-H and 5'-H), 4.12 (1H, dd, J = 9.3 and 5.9 Hz, 3'-H), 4.33 (1H, dd, J = 13.7 and 10.7 Hz, 1'-H), 4.56 (1H, dd, J = '0.7, 5.9 and 2.4 Hz, 2'-H), 4.64 (1H, dd, J = 13.7 and 2.4 Hz, 1'-H), 4.65 (1H, t, J = 5.4 Hz, 5'-OH), 5.16 (1H, d, J = 5.4 Hz, 4'-OH), 8.40 (1H, s, 2-H or 8-H), 8.72 (1H, s, 2-H or 8-H); MS (EI) m/z 340 (M⁺, 26%), 325(18), 251 (47), 167 (48), 66 (100). HRMS (EI) Calcd for C₁₄H₂₀O₄N₄S (M⁺): 340.1205. Found: 340.1187. Anal. Calcd for C₁₄H₂₀O₄N₄S·1/2H₂O: C, 48.12; H, 6.06; N, 16.04. Found: C, 48.01; H, 5.85; N, 15.90. The existence of water in this product was confirmed by ¹H NMR analysis.

9-(2,3-O-Isopropylidene-D-ribityl)adenine (2h). Obtained from **1h** (61.5 mg, 0.2 mmol) according to the method B in 40% yield (24.5 mg) as a colorless solid, which was recrystallized from MeOH–Et₂O. mp 154–156 °C; UV (MeOH) λ_{max} 260 nm; IR (KBr) v_{max} 3356, 3213, 2989, 2935, 1648, 1602, 1479, 1419, 1382, 1331, 1304, 1247, 1218, 1168, 1070, 901, 797, 725, 649 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_6) 1.19 and 1.42 (each 3H, s, isopropylidene), 3.41 (1H, m, 5'-H), 3.60–3.64 (2H, m, 4'-H and 5'-H), 4.10 (1H, dd, J = 9.3 and 5.9 Hz, 3'-H), 4.20 (1H, dd, J = 14.2 and 11.2 Hz, 1'-H), 4.54 (2H, m, 1'-H and 2'-H), 4.64 (1H, t, J = 5.9 Hz, 5'-OH), 5.14 (1H, d, J = 5.9 Hz, 4'-OH), 7.18 (2H, brs, 6-NH₂), 8.06 (1H, s, 2-H or 8-H), 8.12 (1H, s, 2-H or 8-H); MS (EI) m/z 309 (M⁺, 7%), 294 (24), 220 (100), 136 (84). HRMS (EI) Calcd. for C₁₃H₁₉O₄N₅ (M⁺): 309.1437. Found: 309.1417. Anal. Calcd for C₁₃H₁₉O₄N₅ · 1/2H₂O: C, 49.05; H, 6.33; N, 22.00. Found: C, 49.11; H, 6.35; N, 21.95. The existence of water in this product was confirmed by ⁻¹H NMR analysis.

9-(5-Deoxy-2, 3-*O***-isopropylidene-D**-ribityl)adenine (2i). Obtained from 1i (29.1 mg, 0.1 mmol) according to the method B except for the use of CHCl₃ for extraction in 29% yield (8.6 mg) as a colorless amorphous. UV (MeOH) λ_{max} 260 nm; IR (neat) v_{max} 3328, 3187, 2985, 2930, 1641, 1599, 1477, 1416, 1373, 1329, 1305, 1243, 1218, 1116, 1069, 894, 721, 648 cm⁻¹; ⁻¹H NMR δ_{H} (270 MHz; CDCl₃) 1.33 and 1.52 (each 3H, s, isopropylidene), 1.38 (3H, d, J = 5.9 Hz, 5'-H), 3.91–4.04 (2H, m, 3'-H and 4'-H), 4.24 (1H, dd, J = 9.3 and 14.2 Hz, 1'-H), 4.53 (1H, ddd, J = 9.3, 5.9 and 2.4 Hz, 2'-H), 4.80 (1H, dd, J = 14.2 and 2.4 Hz, 1'-H), 5.86 (2H, brs, 6-NH₂), 7.96 (1H, s, 2-H or 8-H), 8.35 (1H, s, 2-H or 8-H); MS (EI) *m/z* 293 (M⁺, 24%), 278 (36), 218 (81), 191 (40), 149 (56), 136 (100). HRMS (EI) Calcd for C₁₃H₁₉O₃N₅ (M⁺): 293.1488. Found: 293.1492.

9-(5-Chloro-5-deoxy-2, 3-*O***-isopropylidene-D-ribityl**)**adenine (2j).** Obtained from 1j (65.2 mg, 0.2 mmol) according to the method B in 26% yield (16.9 mg) as a colorless solid, which was recrystallized from EtOH–Et₂O. mp 195–198 °C; UV (MeOH) λ_{max} 260 nm; IR (KBr) v_{max} 3423, 3213, 2996, 2934, 2866, 1705, 1654, 1600, 1476, 1376, 1248, 1220, 1071, 1020, 882, 694 cm⁻¹; ¹H NMR δ_{H} (400 MHz; DMSO- d_{6}) 1.20 and 1.42 (each 3H, s, isopropylidene), 3.69 (1H, dd, J = 11.2 and 5.4 Hz, 5'-H), 3.82 (1H, dd, J = 11.2 and 2.4 Hz, 5'-H), 3.90 (1H, m, 4'-H), 4.14 (1H, dd, J = 9.8 and 6.4 Hz, 3'-H), 4.24 (1H, dd, J = 14.2 and 11.2 Hz, 1'-H), 4.53 (1H, dd, J = 14.2 and 2.4 Hz, 1'-H), 4.60 (1H, m, 2'-H), 5.74 (1H, d, J = 5.9 Hz, 4'-OH), 7.19 (2H, s, 6-NH₂), 8.06 (1H, s, 2-H or 8-H), 8.12 (1H, s, 2-H or 8-H); MS (FAB, NBA) *m/z* 328 (M⁺+H, 100%), 330 (35). HRMS (FAB) Calcd for C₁₃H₁₉O₃N₅Cl (M⁺+H): 328.1176. Found (FAB): 328.1187. *Anal.* Calcd for C₁₃H₁₈O₃N₅Cl·2/3C₂H₅OH·1/3H₂O: C, 47.23; H, 6.27; N, 19.22. Found: C, 47.52; H, 6.10; N, 18.94. The existence of ethanol and water in this product was confirmed by ¹H NMR analysis.

*N*⁶-Methyl-9-(2, 3-*O*-isopropylidene-D-ribityl)adenine (2k). Obtained from 1k (64.3 g, 0.2 mmol) according to the method B in 14% yield (9.3 mg) as a colorless solid, which was recrystallized from EtOH. mp 219–220 °C; UV (MeOH) λ_{max} 266 nm; IR (KBr) v_{max} 3424, 2990, 2940, 2878, 1628, 1495, 1380, 1329, 1296, 1235, 1073, 897, 845, 791, 732, 648 cm⁻¹; ¹H NMR δ_H (400 MHz; DMSO-*d*₆) 1.19 and 1.42 (each 3H, s, isopropylidene), 2.95 (3H, brs, 6-NHCH₃), 3.42 (1H, m, 5'-H), 3.61–3.64 (2H, m, 4'-H and 5'-H), 4.10 (1H, dd, *J* = 9.3 and 5.9 Hz, 3'-H), 4.21 (1H, dd, *J* = 14.2 and 11.2 Hz, 1'-H), 4.52–4.56 (2H, m, 1'-H and 2'-H), 4.62 (1H, t, *J* = 5.4 Hz, 5'-OH), 5.11 (1H, d, *J* = 5.9 Hz, 4'-OH), 7.62 (1H, brs, 6-NHCH₃), 8.05 (1H, s, 2-H or 8-H), 8.20 (1H, s, 2-H or 8-H); MS (EI) *m/z* 323 (M⁺, 20%), 234 (100), 149 (66). *Anal.* Calcd for C₁₄H₂₁O₄N₅: C, 52.00; H, 6.55; N, 21.66. Found: C, 51.75; H, 6.51; N, 21.39.

*N*⁶, *N*⁶-**Dimethyl-9**-(**2**, **3**-*O*-**isopropylidene-D**-**ribityl**) adenine (**2**I). Obtained from **11** (838 mg, 2.5 mmol) according to the method C in 2% yield (14 mg) as a colorless solid, which was recrystallized from EtOH–Et₂O. mp 158 °C; UV (MeOH) λ_{max} 275 nm; IR (KBr) v_{max} 3423, 2929, 2866, 1600, 1561, 1423, 1342, 1296, 1217, 1075, 1042, 891, 791, 648 cm⁻¹; ¹H NMR δ_{H} (400 MHz; DMSO-*d*₆) 1.18 and 1.42 (each 3H, s, isopropylidene), 3.38–3.44 (7H, m, 5'-H and 6-N(*CH*₃)₂), 3.60–3.65 (2H, m, 4'-H and 5'-H), 4.10 (1H, dd, *J* = 9.3 and 5.9 Hz, 3'-H), 4.21 (1H, dd, *J* = 14.7 and 11.2 Hz, 1'-H), 4.50–4.57 (2H, m, 1'-H and 2'-H), 4.64 (1H, t, *J* = 5.4 Hz, 5'-OH), 5.13 (1H, d, *J* = 5.9 Hz, 4'-OH), 8.08 (1H, s, 2-H or 8-H), 8.19 (1H, s, 2-H or 8-H); MS (EI) *m/z* 337 (M⁺, 39%), 262 (78), 248 (100), 164 (50), 134 (78). HRMS (EI) Calcd. for C₁₅H₂₃O₄N₅ (M⁺): 337.1750. Found: 337.1739. *Anal.* Calcd for C₁₅H₂₃O₄N₅: C, 53.40; H, 6.87; N, 20.76. Found: C, 53.26; H, 6.88; N, 20.75.

9-(2,3-*O*-**Isopropylidene-D-ribityl)-6-methylpurine (2m).** Obtained from **1m** (245 mg, 0.8 mmol) according to the method C except for the reaction time (18 h instead of 24 h) in 38% yield (94 mg) as a colorless amorphous. UV (MeOH) λ_{max} 261 nm; IR (neat) v_{max} 3322, 2987, 2933, 1729, 1603, 1506, 1405, 1374, 1336, 1216, 1071, 892, 755, 647 cm⁻¹; ¹H NMR $\delta_{\rm H}$ (400 MHz; CDCl₃) 1.30 and 1.51 (each 3H, s, isopropylidene), 2.88 (3H, s, 6-CH₃), 3.73–3.83 (2H, m, 4'-H and 5'-H), 3.91 (1H, dd, J = 10.3 and 2.4 Hz, 5'-H), 4.22 (1H, dd, J = 9.3 and 6.4 Hz, 3'-H), 4.33 (1H, dd, J = 14.7 and 9.3 Hz, 1'-H), 4.59 (1H, ddd, J = 9.3, 6.4 and 2.9 Hz, 2'-H), 4.93 (1H, dd, J = 14.7 and 2.9 Hz, 1'-H), 8.20 (1H, s, 2-H or 8-H); MS (FAB, Gly) *m/z* 309 (M⁺+H, 100%), 135(20). HRMS (FAB) Calcd for C₁₄H₂₁O₄N₄ (M⁺+H): 309.1563. Found: 309.1554.

9-(2,3-O-Isopropylidene-D-ribityl)-6-phenylpurine (2n). Obtained from **1n** (73.7 mg, 0.2 mmol) according to the method B except for the use of EtOAc for extraction in 28% yield (20.6 mg) as a colorless amorphous. UV (MeOH) λ_{max} 289 nm; IR (neat) v_{max} 3358, 3063, 2988, 2932, 1725, 1582, 1505, 1456, 1439, 1402, 1381, 1328, 1219, 1072, 931, 891, 757, 696, 646 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; CDCl₃) 1.30 and 1.52 (each 3H, s, isopropylidene), 3.78 (1H, dd, J = 10.7 and 5.4 Hz, 5'-H), 3.87 (1H, m, 4'-H), 3.93 (1H, d, J = 10.7 Hz, 5'-H), 4.24 (1H, dd, J = 9.3 and 5.9 Hz, 3'-H), 4.30 (1H, dd, J = 14.2 and 9.8 Hz,

1'-H), 4.60 (1H, ddd, J = 9.8, 5.9 and 2.0 Hz, 2'-H), 4.97 (1H, dd, J = 14.2 and 2.0 Hz, 1'-H), 7.50–7.58, 8.74–8.76 (5H, m, 6-Ph), 8.29 (1H, s, 2-H or 8-H), 9.00 (1H, s, 2-H or 8-H); MS (EI) m/z 370 (M⁺, 19%), 355 (33), 281 (96), 197 (100), 149 (50). HRMS (EI) Calcd for $C_{19}H_{22}O_4N_4$ (M⁺): 370.1641. Found: 370.1658.

The DIBAL-H Reduction of 1h in the Presence of HMPA To a suspension of 1h (61.5 mg, 0.2 mmol) in anhydrous THF (15 mL) under argon atmosphere was added HMPA (70 μ L, 0.4 mmol) at room temperature and the mixture was stirred for 30 min. To the mixture was added DIBAL-H (1.0 mL, 1.0 mmol) dropwise. After being stirred at 25 °C for 24 h, the resulting solution was treated according to the method B to give 2h (31.6 mg, 51%). The reaction of 1h (61.5 mg, 0.2 mmol) with DIBAL-H (1.4 mL, 1.4 mmol) in THF (15 mL) in the presence of HMPA (104 μ L, 0.6 mmol) was conducted in the same manner as described above to give 2h (36.8 mg, 59%).

Alternative Synthesis of 21 (from 2a). To a solution of 2a (193.9 mg, 0.625 mmol) in pyridine was added acetic anhydride (0.3 mL, 3.12 mmol) at room temperature. After being stirred for 30 h, the resulting solution was quenched with EtOH, and then evaporated in vacuo. The mixture of the residue, DMF (116 μ L, 1.50 mmol) and thionyl chloride (119 μ L, 1.62 mmol) in CH₂Cl₂ (15 mL) was heated under reflux for 6 h. The resulting solution was quenched with an aqueous solution of NaHCO₃ (341 mg, 4.06 mmol) at 0 °C and was extracted with CHCl₃. The organic layers were dried over Na₂SO₄ and evaporated in vacuo. The residue was treated with NH₃/MeOH (saturated at 0 °C, 13 mL) for 11 h at -20 °C to room temperature and then MeOH was evaporated in vacuo. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 25:1) to give 6-chloro derivative 4. ¹H NMR δ_{H} (400 MHz; CDCl₃) 1.30 and 1.51 (each 3H, s, isopropylidene), 3.76-3.86 (2H, m, 4'-H and 5'-H), 3.94 (1H, ddd, J = 10.8, 4.9 and 2.9 Hz, 5'-H), 4.22(1H, dd, J = 8.8 and 5.9 Hz, 3'-H), 4.32 (1H, dd, J = 14.2 and 9.8 Hz, 1'-H), 4.58 (1H, ddd, J = 9.8, 5.9 Hz, 1'-H)and 2.4 Hz, 2'-H), 4.99 (1H, dd, J = 14.2 and 2.4 Hz, 1'-H), 8.29 (1H, s, 2-H or 8-H), 8.76 (1H, s, 2-H or 8-H); MS (FAB, NBA) m/z 329 (M*+H, 5%). HRMS (FAB) Calcd for C₁₃H₁₈O₄N₄Cl (M*+H): 329.1017. Found (FAB): 329.1004. To a solution of 4 in DMF was added dimethylamine hydrochloride (275.4 mg, 3.38 mmol) and triethylamine (565 μ L, 4.05 mmol). The mixture was stirred at room temperature for 28 h and concentrated in vacuo. The residue was partitioned between CHCl₃ and H₂O. The organic layer was dried over Na₂SO₄ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 30:1) to give 21 (134.9 mg, 64% from 2a) as a colorless solid, which was recrystallized from EtOH-Et₂O. Spectral data were described above (see, synthesis of **21** by the reaction of **11** with DIBAL-H).

9-(2,3;4,5-bis-O-Isopropylidene-D-ribityl)hypoxanthine (3). To a solution of *p*-TsOH·H₂O (209 mg, 1.1 mmol) in acetone (5 mL) were added **2a** (310 mg, 1 mmol) and ethyl orthoformate (665 μ L, 4 mmol) at room temperature. After being stirred overnight, the mixture was neutralized with 2.8% aqueous ammonia and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 50:1) to give **3** (237 mg, 68%) as a colorless solid, which was recrystallized from EtOH. mp 294–296 °C; UV (MeOH) λ_{max} 249 nm; IR (KBr) v_{max} 3450, 3053, 2988, 2879, 1704, 1688, 1583, 1378, 1343, 1254, 1215, 1161, 1069, 849, 792, 692, 646, 611 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO-*d*₆) 1.22, 1.28, 1.36 and 1.40 (each 3H, s, isopropylidene), 3.82 (1H, dd, *J* = 8.3 and 5.9 Hz, 5'-H), 4.10–4.14 (2H, m, 3'-H and 5'-H), 4.21 (1H, dt, *J* = 9.3 and 5.9 Hz, 4'-H), 4.28 (1H, dd, *J* = 14.2 and 9.8 Hz, 1'-H), 4.41 (1H, dd, *J* = 14.2 and 2.9 Hz, 1'-H), 4.59 (1H, ddd, *J* = 9.8, 5.9 and 2.9 Hz, 2'-H), 8.04 (2H, s, 2-H and 8-H), 12.27 (1H, s, N₁-H); MS (EI) *m/z* 350 (M⁴, 9%), 335 (89), 192 (65), 150 (77), 137 (68). *Anal.* Calcd for C₁₆H₂₂O₅N₄: C, 54.85; H, 6.33; N, 15.99. Found: C, 54.72; H, 6.36; N, 15.99.

9-(2,3-*O***-Isopropylidene-D-ribityl)guanine (6).** To a stirred suspension of **5** (1.617 g, 5.0 mmol) in anhydrous THF (300 mL) at room temperature was added DIBAL-H (30 mL, 30 mmol) dropwise under argon atmosphere. After being stirred at room temperature for 50 h, the resulting mixture was quenched with saturated aqueous potassium sodium tartrate solution at 0 °C and stirred at room temperature for 24 h. The mixture was concentrated *in vacuo* and the residue was triturated with a small amount of H_2O . The residue was

separated by filtration and washed with Et₂O to give **6** (621 mg, 38%) as a pale yellow solid, which was recrystallized from H₂O. mp 295 °C (dec.); UV (MeOH) λ_{max} 253, 267 (sh) nm; IR (KBr) ν_{max} 3424, 3181, 2937, 1689, 1655, 1608, 1578, 1379, 1221, 1168, 1073, 892, 847, 781, 734, 673 cm⁻¹; ¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_6) 1.20 and 1.40 (each 3H, s, isopropylidene), 3.39 (1H, dt, J = 11.2 and 5.4 Hz, 5'-H), 3.58–3.61 (2H, m, 4'-H and 5'-H), 3.99–4.06 (2H, m, 1'-H and 3'-H), 4.32 (1H, dd, J = 14.2 and 2.9 Hz, 1'-H), 4.47 (1H, ddd, J = 10.7, 5.9 and 2.9 Hz, 2'-H), 4.60 (1H, t, J = 5.4 Hz, 5'-OH), 5.05 (1H, d, J = 5.4 Hz, 4'-OH), 6.42 (2H, brs, 2-NH₂), 7.62 (1H, s, 8-H), 10.49 (1H, s, N₁-H); MS (FAB, NBA) *m/z* 326 (M⁺+H, 12%). HRMS (FAB) Calcd for C₁₃H₂₀O₅N₅ (M⁺+H): 326.1464. Found: 326.1453. *Anal.* Calcd for C₁₃H₁₉O₅N₅·1/2H₂O: C, 46.70; H, 6.03; N, 20.95. Found: C, 46.68; H, 5.76; N, 20.94. The existence of water in this product was confirmed by ¹H NMR analysis.

The DIBAL-H Reduction of 2', 3'-O-Isopropylideneadenosine 1-Oxide (7). Compound 7 (323 mg, 1.0 mmol) was treated according to the method C except for the reaction time (25 h instead of 24 h) and the eluent for the column chromatography (CHCl₃/MeOH/AcOH, 400:30:1) to give 8 (92 mg, 28%), 9 (9 mg, 3%), 2h (16 mg, 5%) and trace amount of 1h with recovery of the starting material 7 (106 mg, 33%).

9-(2,3-*O*-**Isopropylidene-D-ribityl)adenine 1-Oxide (8)**; mp 256.5–258.5 °C (recrystallized from EtOH); UV (MeOH) λ_{max} 234, 262, 300 nm; IR (KBr) v_{max} 3423, 3282, 2988, 2937, 1671, 1509, 1379, 1220, 1139, 1079, 1053, 904, 828, 702, 644 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_6) 1.20 and 1.43 (each 3H, s, isopropylidene), 3.41 (1H, dt, J = 11.7 and 5.9 Hz, 5'-H), 3.60–3.64 (2H, m, 4'-H and 5'-H), 4.11 (1H, dd, J = 9.3 and 5.9 Hz, 3'-H), 4.23 (1H, dd, J = 14.2 and 11.2 Hz, 1'-H), 4.52 (1H, ddd, J = 11.2, 5.9 and 2.4 Hz, 2'-H), 4.53 (1H, dd, J = 14.2 and 2.4 Hz, 1'-H), 4.63 (1H, t, J = 5.9 Hz, 5'-OH), 5.13 (1H, d, J = 5.9 Hz, 4'-OH), 7.3–9.3 (2H, br, 6-NH₂), 8.23 (1H, s, 2-H or 8-H), 8.60 (1H, s, 2-H or 8-H); MS (EI) *m/z* 325 (M⁺, 100%), 310 (22), 220 (41), 151 (40). HRMS (EI) Calcd for C₁₃H₁₉O₅N₅ (M⁺): 325.1386. Found: 325.1398. Anal. Calcd for C₁₃H₁₉O₅N₅ · 1/2H₂O: C, 46.70; H, 6.03; N, 20.95. Found: C, 46.80; H, 5.79; N, 20.74. The existence of water in this product was confirmed by ¹H NMR analysis.

6-Amino-4-(2,3-*O***-isopropylidene-D-ribofuranosylamino)-5-(***N***-methylamino)pyrimidine 1-Oxide (9)**; ¹H NMR δ_H (400 MHz; DMSO-*d*₆) 1.31 and 1.51 (each 3H, s, isopropylidene), 2.67 (3H, d, *J* = 5.9 Hz, 5-NCH₃), 3.52 (2H, m, 5'-H), 4.12 (1H, m, 4'-H), 4.86 (1H, dd, *J* = 5.9 and 2.4 Hz, 3'-H), 4.93 (1H, q, *J* = 5.9 Hz, 5-NH), 5.07 (1H, dd, *J* = 5.9 and 3.4 Hz, 2'-H), 5.44 (2H, s, 6-NH₂), 5.65 (1H, d, *J* = 3.4 Hz, 1'-H), 7.64 (1H, s, 2-H), 9.08 (1H, brs, 4-NH); ¹³C NMR δ_C (100 MHz; DMSO-*d*₆) 25.18, 26.99, 35.55, 61.28, 80.89, 83.72, 85.42, 88.51, 113.26, 118.10, 130.14, 138.20, 149.14; MS (FAB, Gly) *m/z* 328 (M*+H, 93%), 312 (55), 185 (100). HRMS (FAB, Gly) Calcd for $C_{13}H_{22}O_5N_5$ (M*+H): 328.1621. Found: 328.1631.

9-D-Ribityladenine (13). Obtained from **12** (53.4 mg, 0.2 mmol) according to the method A in 6% yield (3.3 mg) as a colorless solid, which was identical with the product described below.

Alternative Synthesis of 13 (from 2h). To a suspension of 2h (15.5 mg, 0.05 mmol) in THF (0.5 mL) was added trifluoroacetic acid (1.0 mL) at room temperature. After being stirred for 1.5 h, the resulting solution was evaporated *in vacuo*. The residue was purified by reversed phase chromatography (H₂O/MeCN, 19:1) to give 13 quantitatively (13.5 mg) as a colorless solid, which was recrystallized from EtOH. mp 218–219 °C (lit. ^{32a} mp 209–210 °C); UV (MeOH) λ_{max} 259 nm; IR (KBr) v_{max} 3392, 3322, 3166, 2950, 2896, 1680, 1619, 1424, 1331, 1304, 1250, 1100, 1013, 684, 644 cm⁻¹; ¹H NMR δ_{H} (270 MHz; DMSO- d_{6}) 3.32–3.45 (2H, m, 3'-H and 5'-H), 3.49–3.63 (2H, m, 4'-H and 5'-H), 3.91 (1H, m, 2'-H), 4.08 (1H, dd, J = 14.2 and 8.3 Hz, 1'-H), 4.38 (1H, dd, J = 14.2 and 2.4 Hz, 1'-H), 4.41 (1H, t, J = 5.4 Hz, 5'-OH), 4.72 (1H, d, J = 4.9 Hz, 4'-OH), 5.01–5.05 (2H, m, 2'-OH and 3'-OH), 7.16 (2H, s, 6-NH₂), 8.01 (1H, s, 2-H or 8-H), 8.11 (1H, s, 2-H or 8-H); MS (EI) *m/z* 269 (M⁺, 3%), 208 (30), 178 (97), 148 (79), 135 (100). HRMS (EI) Calcd. for C₁₀H₁₅O₄N₅ (M⁺): 269.1124. Found: 269.1115. *Anal.* Calcd for C₁₀H₁₅O₄N₅ ·57/H₂O: C, 42.57; H, 5.87; N, 24.83. Found: C, 42.78; H, 5.52; N, 24.57. The existence of water in this product was confirmed by ¹H NMR analysis.

1-(Adenin-9-yl)-1,2-dideoxy-D-*erythro*-pentitol (15). Obtained from 14 (251 mg, 1.0 mmol) according to the method A in 39% yield (100 mg) as a colorless solid. mp 210–212 °C (lit. ³³ mp 185 °C); UV (MeOH) λ_{max} 260 nm; IR (KBr) v_{max} 3394, 3329, 3173, 2938, 2900, 2740, 1667, 1617, 1577, 1491, 1424, 1310, 1229, 1069, 1014, 926, 846, 724, 642, 574 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_{6}) 1.72 (1H, m, 2-H), 2.13 (1H, m, 2-H), 3.24–3.35 (3H, m, 3-H, 4-H and 5-H), 3.48 (1H, ddd, 10.3, 5.9 and 4.4 Hz, 5-H), 4.18 (1H, dt, J = 13.7 and 7.8 Hz, 1-H), 4.27 (1H, ddd, J = 13.7, 8.3 and 4.9 Hz, 1-H), 4.33 (1H, t, J = 5.9 Hz, 5-OH), 4.52 (1H, d, J = 4.9 Hz, 4-OH), 4.75 (1H, d, J = 5.9 Hz, 3-OH), 7.14 (2H, s, 6-NH₂ of adenine), 8.08 (1H, s, 2-H or 8-H of adenine), 8.12 (1H, s, 2-H or 8-H of adenine); ⁻¹³C NMR $\delta_{\rm C}$ (100 MHz; DMSO- d_{6}) 33.12, 40.29, 63.15, 68.41, 74.80, 118.74, 140.96, 149.45, 152.21, 155.87; MS (FAB. NBA) m/z 254 (M*+H, 10%). HRMS (FAB) Calcd for C₁₀H₁₆O₃N₅ (M*+H): 254.1253. Found: 254.1257. Anal. Calcd for C₁₀H₁₅O₃N₅ · 1/3H₂O: C, 46.32; H, 6.09; N, 27.01. Found: C, 46.33; H, 5,95; N, 26.89. The existence of water in this product was confirmed by ¹H NMR analysis.

5,6-Dihydro-2',3'-*O*-isopropylidene-5'-*O*-trityluridine (16). Obtained from 2',3'-*O*-isopropylidene-5'-*O*-trityluridine (1.580 g, 3 mmol) according to the method C in 48% yield (759 mg) as a colorless solid, which was recrystallized from EtOH–H₂O. mp 113–115 °C (dec.); UV (MeOH) λ_{max} 221 nm; IR (KBr) v_{max} 3449, 3421, 3087, 3060, 2987, 2935, 2873, 1703, 1489, 1449, 1376, 1280, 1211, 1081, 864, 765, 706, 633, 598 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO- d_6) 1.25 and 1.44 (each 3H. s, isopropylidene), 2.41–2.58 (2H. m, 5-H), 3.11 (1H. dd, J = 10.3 and 3.4 Hz, 5'-H), 3.17 (1H. dd, J = 10.3 and 5.9 Hz, 5'-H), 3.34–3.41 (2H. m, 6-H), 3.95 (1H. ddd, J = 5.9, 5.4 and 3.4 Hz, 4'-H), 4.60 (1H. dd, J = 6.4 and 5.4 Hz, 3'-H), 4.83 (1H, J = 6.4 and 2.4 Hz, 2'-H), 5.79 (1H. d, J = 2.4 Hz, 1'-H), 7.24–7.39 (15H. m, C(C_6H_5)₃), 10.34 (1H, s, N₃-H); MS (EI) *m/z* 513 (M*–15, 3%), 243 (100). *Anal.* Calcd for $C_{31}H_{32}O_6N_2$: C. 70.44; H, 6.10; N, 5.30. Found: C, 70.44; H, 6.12; N, 5.25.

9-(**5**-*O*-*tert*-**Butyldimethylsilyl-2**, **3**-*O*-isopropylidene-D-ribityl)adenine (18). A solution of **2h** (286 mg, 0.925 mmol), *tert*-butyldimethylsilyl chloride (697 mg, 4.63 mmol), and imidazole (630 mg, 9.25 mmol) in DMF was stirred at room temperature for 5 min. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 40:1), to give **18** (306 mg, 78%) as a colorless solid. mp 235 °C; UV (MeOH) λ_{max} 261 nm; IR (KBr) v_{max} 3442, 2931, 1639, 1475, 1384, 1254, 1070, 837, 782 cm⁻¹; ⁻¹H NMR $\delta_{\rm H}$ (400 MHz; DMSO-*d*₆) 0.06 (6H, s, Si-(*CH*₃)₂), 0.89 (9H, s, Si-*tert*-butyl), 1.19 and 1.42 (each 3H, s, isopropylidene), 3.63–3.70 (2H, m, 4'-H and 5'-H), 3.77 (1H, m, 5'-H), 4.15 (1H, dd, *J* = 9.3 and 6.4 Hz, 3'-H), 4.21 (1H, dd, *J* = 14.2 and 10.7 Hz, 1'-H), 4.52–4.57 (2H, m, 1'-H and 2'-H), 5.12 (1H, d, *J* = 5.4 Hz, 4'-OH), 7.15 (2H, brs, 6-NH₂), 8.05 (1H, s, 2-H or 8-H), 8.11 (1H, s, 2-H or 8-H); MS (EI) *m/z* 423 (M⁺, 4%), 408 (20), 366 (100). *Anal.* Calcd for C₁₉H₃₃O₄N₅Si: C. 53.88; H, 7.85; N, 16.54. Found: C, 53.91; H, 7.95; N, 16.65.

5-Adenin-9-yl-1-*O-tert***-butyldimethylsilyl-5-deoxy-3,4-***O***-isopropylidene-L***-erythro***-2-pentulose (19).** To a stirred mixture of pyridine ($32.4 \ \mu$ L, 0.4 mmol) in anhydrous CH₂Cl₂ (0.5 mL) was added chromic acid (20 mg, 0.2 mmol) at room temperature and the mixture was stirred for 1 h. To the mixture were added a solution of **18** (21 mg, 0.05 mmol) in anhydrous CH₂Cl₂ (2 mL) and acetic anhydride (18.9 μ L, 0.2 mmol) at room temperature. After being stirred for 6 h, the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluent, EtOAc), to give **19** (11 mg, 52%) as a colorless solid. ¹H NMR $\delta_{\rm H}$ (400 MHz; CDCl₃) 0.14 (6H, s, Si-(CH₃)₂), 0.94 (9H, s, Si-*tent*-butyl), 1.34 and 1.63 (each 3H, s, isopropylidene), 3.89 (1H, dd, J = 14.2 and 9.8 Hz, 5-H), 4.43 (1H, d, J = 19.0 Hz, 1-H), 4.54 (1H, d, J = 19.0 Hz, 1-H), 4.56 (1H, dd, J = 14.2 and 2.4 Hz, 5-H), 4.82 (1H, ddd, J = 9.8, 7.8 and 2.4 Hz, 4-H), 4.96 (1H, d, J = 7.8 Hz, 3-H), 5.60 (2H, brs, 6-NH₂ of adenine), 7.86 (1H, s, 2-H or 8-H of adenine); MS (EI) *m/z* 421 (M⁺, 2%), 406 (5), 306 (61), 171 (100), 136 (70). HRMS (EI) Calcd for C₁₉H₃₁O₄N₅Si (M⁺): 421.2145. Found: 421.2123.

1-Adenin-9-yl-5-O-tert-butyldimethylsilyl-1,4-dideoxy-4-methylene-2,3-O-isopropylidene-D-erythro-pentitol (20). To a suspension of methyltriphenylphosphonium bromide (864 mg, 2.420 mmol) in anhydrous THF under argon atmosphere at 0 $^{\circ}$ C was added butyl lithium (1.2 mL of a 1.66 M solution in hexane, 2.02 mmol) dropwise and the mixture was stirred for 30 min. To the mixture was added a solution of **19** (102 mg, 0.242 mmol) in anhydrous THF at 0 $^{\circ}$ C. The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 50:1), to give **20** (70 mg, 69%) as a colorless solid. UV (MeOH) λ_{max} 259 nm; IR (KBr) v_{max} 3279, 3130, 2955, 2932, 2860, 1676, 1605, 1476, 1377, 1308, 1251, 1080, 1016, 928, 839, 778, 698 cm⁻¹; ⁻¹H NMR δ_{H} (400 MHz; CDCl₃) 0.12 (6H, s, Si-(CH₃)₂), 0.92 (9H, s, Si-*tert*-butyl), 1.37 and 1.60 (each 3H, s, isopropylidene), 3.89 (1H, dd, J = 14.2 and 10.7 Hz, 1-H_a), 4.24 (1H, d, J = 13.2 Hz, 5-H_a), 4.29 (1H, d, J = 13.2 Hz, 5-H_b), 4.30 (1H, dd, J = 14.2 and 2.5 Hz, 1-H_b), 4.60 (1H, ddd, J = 10.7, 6.4 and 2.5 Hz, 2-H), 4.85 (1H, d, J = 6.4 Hz, 3-H), 5.34 (1H, s, 4-methylene), 5.44 (1H, s, 4-methylene), 5.67 (2H, brs, 6-NH₂ of adenine), 7.90 (1H, s, 2-H or 8-H of adenine), 8.32 (1H, s, 2-H or 8-H of adenine); NOE, irradiate 2-H, observe 3-H (11.3%) and 1-H_b (4.3%); irradiate 3-H, observe 2-H (10.5%) and 5-H_a (2.6%); MS (EI) *m/z* 419 (M⁺, 25%), 404 (35), 362 (100), 169 (76). HRMS (EI) Calcd for C₂₀H₃₃O₃N₅Si (M⁺): 419.2352. Found: 419.2368.

1-Adenin-9-yl-1, 4-dideoxy-4-methylene-D-*erythro*-pentitol (17). A solution of 20 (70 mg, 0.167 mmol) in 80% aqueous AcOH was stirred at 60 °C for 6 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (CHCl₃/MeOH, 10:1), to give 17 (35 mg, 79%) as a colorless solid. UV (MeOH) λ_{max} 260 nm; ¹H NMR δ_{H} (400 MHz; DMSO- d_{6}) 3.81 (1H, m, 2-H), 3.96–4.05 (4H, m, 1-H, 3-H and 5-H×2), 4.32 (1H, dd, J = 14.2 and 2.4 Hz, 1-H), 4.79 (1H, t, J = 5.4 Hz, 5-OH), 5.04 (1H, d, J = 6.4 Hz, 2-OH), 5.11 (1H, s, 4-methylene), 5.12 (1H, s, 4-methylene), 5.25 (1H, d, J = 4.9 Hz, 3-OH), 7.14 (2H, brs, 6-NH₂ of adenine), 8.00 (1H, s, 2-H or 8-H of adenine), 8.11 (1H, s, 2-H or 8-H of adenine); ¹³C NMR δ_{C} (100 MHz; DMSO- d_{6}) 45.86, 61.28, 70.59, 73.96, 110.13, 118.60, 141.77, 149.63, 150.05, 152.12, 155.85; MS (EI) *m/z* 265 (M⁺, 12%), 178 (98), 135 (100). HRMS (EI) Calcd for C₁₁H₁₅O₃N₅ (M⁺): 265.1175. Found: 265.1149.

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- 38. Compound **19** and **20** could be isolated as a single diastereomer. The NOE experiment of **20** supported its configuration; see experimental section.

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