Pergamon

Tetrahedron, Vol. 53, No. 49, pp. 16683-16698, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10098-9

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

Kosaku Hirota,[a]* Yasunari Monguchi,[a] Yukio Kitade,[b] and Hironao Sajiki[a]

[a]Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502, Japan
[b]Department of Biomolecular Science, Faculty of Engineering, Gifu University, Yanagido, Gifu 501-11, Japan

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 **l** 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.

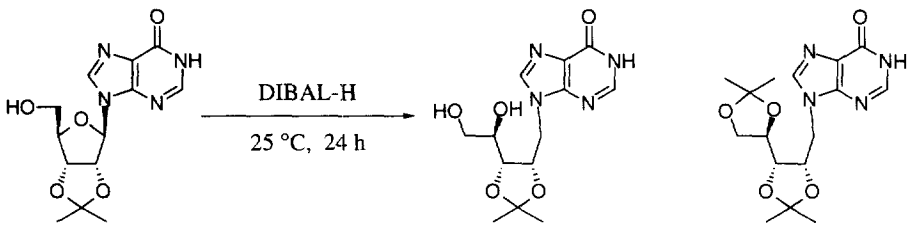
INTRODUCTION

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 acyclovir[2] and ganciclovir[3] 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 $NaIO_4$.[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 ethers[9] 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**).



1a **2a** **3**

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

	Yield (%)[b]	
Solvent	Product **2a**	Recovery **1a**
THF	68	24
Et_2O	35	8
CH_2Cl_2	3	14
Toluene	1	13

[a]These reactions were carried out using 5 equiv of DIBAL-H in the stated medium under argon atmosphere at 25 °C for 24 h. [b]Determined by TLC scanner (Shimadzu CS-9000).

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

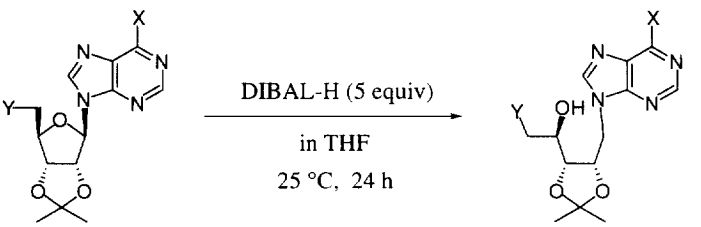
DIBAL-H	Yield (%)[b]	
(equiv)	Product **2a**	Recovery **1a**
3	24	65
4	43	51
5	68	24
7	69	22
10	69	8

[a]These reactions were carried out using stated equiv of DIBAL-H in THF under argon atmosphere at 25 °C for 24 h. [b]Determined 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 Et_2O 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]



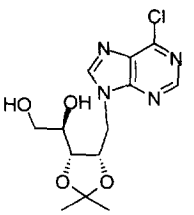
1a–n **2a–n**

Starting Compd.			Yield (%)[b]	
No.	X	Y	Product **2**	Recovery **1**
a	OH	OH	67 (68)[c]	23 (24)[c]
b	OH	Cl	82	9
c	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]
			51[e]	40[e]
			59[f]	24[f]
i	NH_2	H	29	71
j	NH_2	Cl	26	58
k	$NHCH_3$	OH	14 (14)[c]	75 (81)[c]
l	$N(CH_3)_2$	OH	2 (trace)[c]	54 (55)[c]
m[g]	CH_3	OH	38	ND[d]
n	Ph	OH	28	29

[a]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. [b]Isolated yield. [c]The yields in parenthesis were determined by TLC scanner (Shimadzu CS-9000). [d]Not determined. [e]In the presence of 2 equiv of HMPA, 5 equiv of DIBAL-H was used. [f]In the presence of 3 equiv of HMPA, 7 equiv of DIBAL-H was used. [g]The reaction was performed for 18 h.

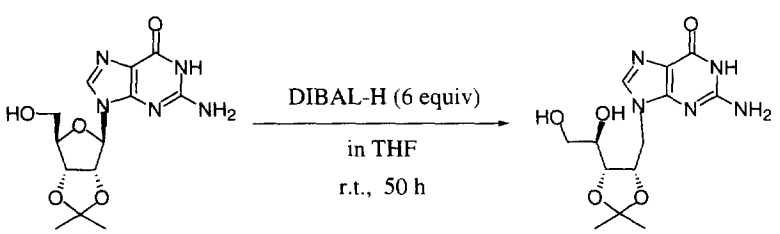
We utilized the best reaction conditions obtained for **1a** to reduce a variety of 6-substituted purine nucleosides and purine 5'-deoxynucleosides; the results are summarized in Table 3. O^6-Methyl and O^6-isopropyl substituted inosine derivatives **1c**[14] and **1e**[14] were cleaved smoothly to give 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. Furthermore, 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.* reported[23] 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**.



4

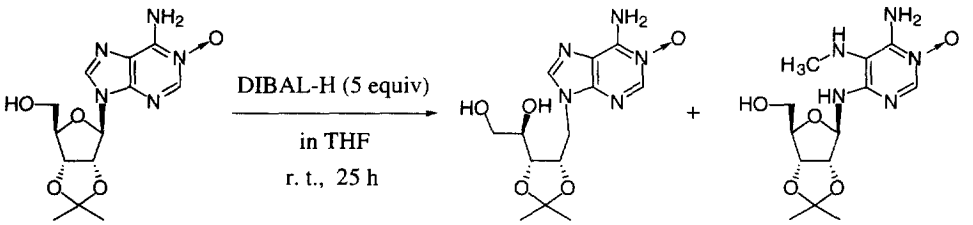
The reduction of 6-methylpurine riboside and 6-phenylpurine riboside **1m**[24] and **1n**,[25] both of which have no heteroatom at the 6-position in the base moiety, gave ribityl products **2m** and **2n** in 38% and 28% yields, respectively, together with intractable materials.



5 **6**

Biopterin[26] and riboflavin[27] 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

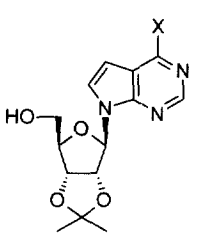
ring was found when adenosine 1-oxide **7**[29] was subjected to our reaction. We could isolate, besides a main product **8**, a base-ring opening product **9** in 3% yield.



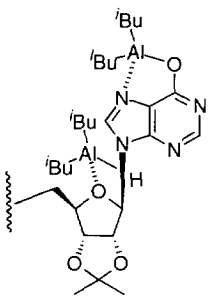
7 **8** (28%) **9** (3%)

+ **1h** (trace) + **2h** (5%) + **7** (33%, recovery)

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.

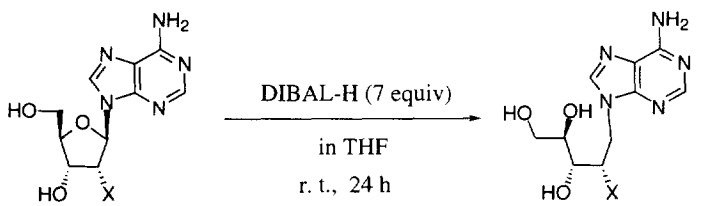


10 : X = OH
11 : X = NH_2



A

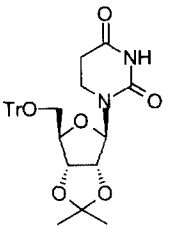
In the case of the DIBAL-H reduction of unprotected adenosine (**12**), the significant decrease of the yield of the obtained ribityl derivative **13**[32a] was observed (6% yield and 93% recovery of **12**). On the contrary, 2'-deoxyadenosine (**14**) gave a ribityl derivative **15**[33] in 39% yield 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'.



12 : X = OH
14 : X = H

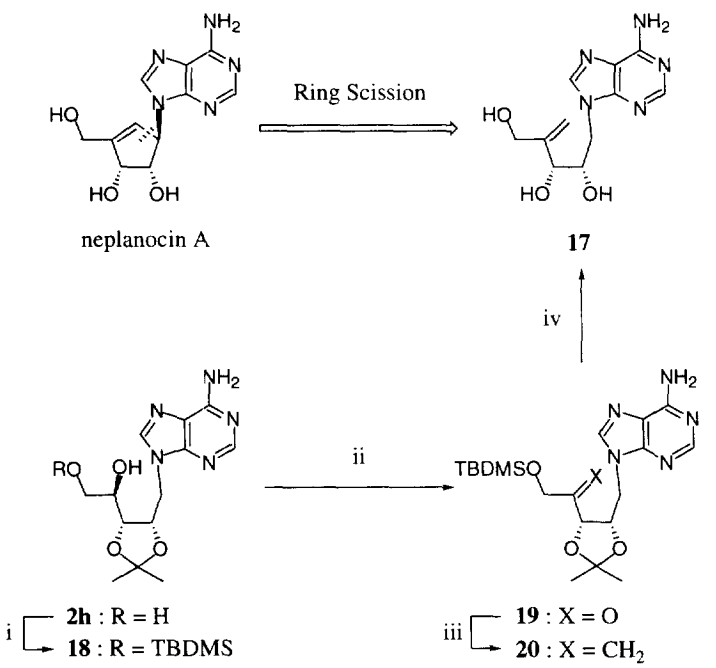
13 : X = OH
15 : X = H

When a pyrimidine nucleoside, 2',3'-*O*-isopropylidene-5'-*O*-trityluridine,[34] 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.



16

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 **19**[38] in 52% yield. Wittig reaction of **19** with Ph_3PCH_3Br/BuLi and subsequent deprotection of the resulting 4'-methylene derivative **20**[38] 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) CrO_3 (4 equiv), pyridine (8 equiv), Ac_2O (4 equiv), in CH_2Cl_2, r. t., 6 h, 52%; iii) Ph_3PCH_3Br (10 equiv), BuLi (8.3 equiv), in THF, 0 °C, overnight, 69%; iv) 80% AcOH, 60 °C, 6 h, 79%.

Although **17** indicated faint inhibitory activity toward AdoHcy hydrolase (rabbit erythrocyte) with IC_{50} values of 350 μM, **17** was virtually inactive against herpes simplex virus type 1 (HSV-1), influenza virus, and human cytomegarovirus (HCMV) with EC_{50} values of >50 μg/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-ribitylpurines[32] 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® (C_{18}) 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. ^{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 a solvent or internally referenced to the residual protonated solvent resonances (2.49 ppm) in DMSO-d_6 as a solvent. ^{13}C 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 ℃ 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 ℃ 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 Na_2SO_4 and evaporated *in vacuo*. The residue was purified by reversed phase chromatography (H_2O/MeCN, 49:1–9:1).

Method B. The resulting solution was quenched with saturated aqueous potassium sodium tartrate solution (10 mL) at 0 ℃ 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 Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50:1–12:1).

Method C. The resulting solution was quenched with 10% aqueous AcOH at 0 ℃, and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$/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 δ_H (400 MHz; DMSO-d_6) 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, N_1-H); ^{13}C NMR δ_C (100 MHz; DMSO-d_6) 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 $C_{13}H_{18}O_5N_4$: 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-$CHCl_3$. mp 205–206 °C (dec.); UV (MeOH) λ_{max} 249 nm; IR (KBr) ν_{max} 3448, 3428, 2990, 2928, 2863, 1688, 1583, 1212, 1074. 891, 791, 691 cm^{-1}; ^1H NMR δ_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, N_1-H); MS (EI) *m/z* 328 (M^+, 21%), 330 (7), 313 (37), 292 (36), 221 (54), 150 (100), 137 (87). *Anal.* Calcd for $C_{13}H_{17}O_4N_4Cl$: 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–Et_2O. mp 99–102 °C; UV (MeOH) λ_{max} 249 nm; IR (KBr) ν_{max} 3423, 2991, 2938, 1604, 1579, 1481, 1351, 1319, 1229, 1065, 897, 648 cm^{-1}; ^1H NMR δ_H (400 MHz; $CDCl_3$) 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-OCH_3), 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 $C_{14}H_{20}O_5N_4$ (M^+): 324.1434. Found: 324.1454. *Anal.* Calcd for $C_{14}H_{20}O_5N_4 \cdot 1/10(C_2H_5)_2O \cdot 1/4H_2O$: 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 $CHCl_3$ 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) ν_{max} 3424, 3260, 2988, 2939, 1602, 1580, 1482, 1406, 1383, 1349, 1317, 1229, 1166, 1068, 973, 888, 784, 736, 646 cm^{-1}; ^1H NMR δ_H (400 MHz; $CDCl_3$) 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 2.4 Hz, 5'-H), 3.81–3.83 (1H, m, 4'-H), 4.17 (1H, dd, J = 9.3 and 6.4 Hz, 3'-H), 4.20 (3H, s, 6-OCH_3), 4.31 (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), 4.91 (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–Et_2O. mp 160–162 °C; UV (MeOH) λ_{max} 249 nm; IR (KBr) ν_{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-$OCH(CH_3)_2$), 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-OC*H*$(CH_3)_2$), 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 $C_{16}H_{24}O_5N_4$: 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–Et_2O. mp 266 °C (dec.); UV (MeOH) λ_{max} 226, 322 nm; IR (KBr) ν_{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 δ_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, N_1-H); MS (FAB, Gly) *m/z* 327 (M^++H, 6%). HRMS (FAB, Gly) Calcd for $C_{13}H_{19}O_4N_4S$ (M^++H): 327.1127. Found: 327.1135; *Anal.* Calcd for $C_{13}H_{18}O_4N_4S \cdot 1/10(C_2H_5)_2O \cdot 9/10H_2O$: 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-*O*-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–Et_2O. mp 112.5–114.5 °C; UV (MeOH) λ_{max} 218, 282, 289 nm; IR (KBr) ν_{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 δ_H (400 MHz; DMSO-d_6) 1.18 and 1.42 (each 3H, s, isopropylidene), 2.66 (3H, s, 6-SCH_3), 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, ddd, J = 10.7, 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 $C_{14}H_{20}O_4N_4S$ (M^+): 340.1205. Found: 340.1187. *Anal.* Calcd for $C_{14}H_{20}O_4N_4S \cdot 1/2H_2O$: 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–Et_2O. mp 154–156 °C; UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{max} 3356, 3213, 2989, 2935, 1648, 1602, 1479, 1419, 1382, 1331, 1304, 1247, 1218, 1168, 1070, 901, 797, 725, 649 cm^{-1}; ^1H NMR δ_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-NH_2), 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 $C_{13}H_{19}O_4N_5$ (M^+): 309.1437. Found: 309.1417. *Anal.* Calcd for $C_{13}H_{19}O_4N_5 \cdot 1/2H_2O$: 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 $CHCl_3$ for extraction in 29% yield (8.6 mg) as a colorless amorphous. UV (MeOH) λ_{max} 260 nm; IR (neat) ν_{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; $CDCl_3$) 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-NH_2), 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 $C_{13}H_{19}O_3N_5$ (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–Et_2O. mp 195–198 °C; UV (MeOH) λ_{max} 260 nm; IR (KBr) ν_{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-NH_2), 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 $C_{13}H_{19}O_3N_5Cl$ (M^++H): 328.1176. Found (FAB): 328.1187. *Anal.* Calcd for $C_{13}H_{18}O_3N_5Cl \cdot 2/3C_2H_5OH \cdot 1/3H_2O$: 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) ν_{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-NHCH_3), 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-N*H*CH_3), 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 $C_{14}H_{21}O_4N_5$: 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 (2l). Obtained from **1l** (838 mg, 2.5 mmol) according to the method C in 2% yield (14 mg) as a colorless solid, which was recrystallized from EtOH–Et_2O. mp 158 °C; UV (MeOH) λ_{max} 275 nm; IR (KBr) ν_{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 $C_{15}H_{23}O_4N_5$ (M^+): 337.1750. Found: 337.1739. *Anal.* Calcd for $C_{15}H_{23}O_4N_5$: 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) ν_{max} 3322, 2987, 2933, 1729, 1603, 1506, 1405, 1374, 1336, 1216, 1071, 892, 755, 647 cm^{-1}; ^1H NMR δ_H (400 MHz; $CDCl_3$) 1.30 and 1.51 (each 3H, s, isopropylidene), 2.88 (3H, s, 6-CH_3), 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), 8.84 (1H, s, 2-H or 8-H); MS (FAB, Gly) *m/z* 309 (M^++H, 100%), 135(20). HRMS (FAB) Calcd for $C_{14}H_{21}O_4N_4$ (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) ν_{max} 3358, 3063, 2988, 2932, 1725, 1582, 1505, 1456, 1439, 1402, 1381, 1328, 1219, 1072, 931, 891, 757, 696, 646 cm^{-1}; ^1H NMR δ_H (400 MHz; $CDCl_3$) 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 μL, 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 ℃ 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 μL, 0.6 mmol) was conducted in the same manner as described above to give **2h** (36.8 mg, 59%).

Alternative Synthesis of 2l (*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 μL, 1.50 mmol) and thionyl chloride (119 μL, 1.62 mmol) in CH_2Cl_2 (15 mL) was heated under reflux for 6 h. The resulting solution was quenched with an aqueous solution of $NaHCO_3$ (341 mg, 4.06 mmol) at 0 °C and was extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was treated with NH_3/MeOH (saturated at 0 ℃, 13 mL) for 11 h at –20 ℃ to room temperature and then MeOH was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 25 :1) to give 6-chloro derivative **4**. ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 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 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 $C_{13}H_{18}O_4N_4Cl$ (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 μL, 4.05 mmol). The mixture was stirred at room temperature for 28 h and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 30:1) to give **2l** (134.9 mg, 64% from **2a**) as a colorless solid, which was recrystallized from EtOH–Et_2O. Spectral data were described above (see, synthesis of **2l** by the reaction of **1l** with DIBAL-H).

9-(2,3;4,5-bis-*O*-Isopropylidene-D-ribityl)hypoxanthine (3). To a solution of *p*-TsOH·H_2O (209 mg, 1.1 mmol) in acetone (5 mL) were added **2a** (310 mg, 1 mmol) and ethyl orthoformate (665 μL, 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 ($CHCl_3$/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) ν_{max} 3450, 3053, 2988, 2879, 1704, 1688, 1583, 1378, 1343, 1254, 1215, 1161, 1069, 849, 792, 692, 646, 611 cm^{-1}; ^{1}H NMR δ_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, N_1-H); MS (EI) *m/z* 350 (M^+, 9%), 335 (89), 192 (65), 150 (77), 137 (68). *Anal.* Calcd for $C_{16}H_{22}O_5N_4$: 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 ℃ 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 Et_2O to give **6** (621 mg, 38%) as a pale yellow solid, which was recrystallized from H_2O. mp 295 ℃ (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 δ_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-NH_2), 7.62 (1H, s, 8-H), 10.49 (1H, s, N_1-H); MS (FAB, NBA) *m/z* 326 (M^++H, 12%). HRMS (FAB) Calcd for $C_{13}H_{20}O_5N_5$ (M^++H): 326.1464. Found: 326.1453. *Anal.* Calcd for $C_{13}H_{19}O_5N_5 \cdot 1/2H_2O$: 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 ($CHCl_3$/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) ν_{max} 3423, 3282, 2988, 2937, 1671, 1509, 1379, 1220, 1139, 1079, 1053, 904, 828, 702, 644 cm^{-1}; ^1H NMR δ_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-NH_2), 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 $C_{13}H_{19}O_5N_5$ (M^+): 325.1386. Found:, 325.1398. Anal. Calcd for $C_{13}H_{19}O_5N_5 \cdot 1/2H_2O$: 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-NCH_3), 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-NH_2), 5.65 (1H, d, J = 3.4 Hz, 1'-H), 7.64 (1H, s, 2-H), 9.08 (1H, brs, 4-NH); ^{13}C 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 (H_2O/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) ν_{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-NH_2), 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 $C_{10}H_{15}O_4N_5$ (M^+): 269.1124. Found: 269.1115. *Anal.* Calcd for $C_{10}H_{15}O_4N_5 \cdot 5/7H_2O$: 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) ν_{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 δ_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-NH_2 of adenine), 8.08 (1H, s, 2-H or 8-H of adenine), 8.12 (1H, s, 2-H or 8-H of adenine); ^{13}C NMR δ_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 $C_{10}H_{16}O_3N_5$ (M^++H): 254.1253. Found: 254.1257. *Anal.* Calcd for $C_{10}H_{15}O_3N_5 \cdot 1/3H_2O$: 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–H_2O. mp 113–115 °C (dec.); UV (MeOH) λ_{max} 221 nm; IR (KBr) ν_{max} 3449, 3421, 3087, 3060, 2987, 2935, 2873, 1703, 1489, 1449, 1376, 1280, 1211, 1081, 864, 765, 706, 633, 598 cm^{-1}; ^1H NMR δ_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, N_3-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 ($CHCl_3$/MeOH, 40:1), to give **18** (306 mg, 78%) as a colorless solid. mp 235 °C; UV (MeOH) λ_{max} 261 nm; IR (KBr) ν_{max} 3442, 2931, 1639, 1475, 1384, 1254, 1070, 837, 782 cm^{-1}; ^1H NMR δ_H (400 MHz; DMSO-d_6) 0.06 (6H, s, Si-(CH_3)$_2$), 0.89 (9H, s, Si-*tert*-butyl), 1.19 and1.42 (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-NH_2), 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 $C_{19}H_{33}O_4N_5Si$: 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 μL, 0.4 mmol) in anhydrous CH_2Cl_2 (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 CH_2Cl_2 (2 mL) and acetic anhydride (18.9 μL, 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 δ_H (400 MHz; $CDCl_3$) 0.14 (6H, s, Si-(CH_3)$_2$), 0.94 (9H, s, Si-*tert*-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-NH_2 of adenine), 7.86 (1H, s, 2-H or 8-H of adenine), 8.33 (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 $C_{19}H_{31}O_4N_5Si$ (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 °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 °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 ($CHCl_3$/MeOH, 50:1), to give **20** (70 mg, 69%) as a colorless solid. UV (MeOH) λ_{max} 259 nm; IR (KBr) ν_{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; $CDCl_3$) 0.12 (6H, s, Si-(CH_3)$_2$), 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-NH_2 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 $C_{20}H_{33}O_3N_5Si$ (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 ($CHCl_3$/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-NH_2 of adenine), 8.00 (1H, s, 2-H or 8-H of adenine), 8.11 (1H, s, 2-H or 8-H of adenine); ^{13}C 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 $C_{11}H_{15}O_3N_5$ (M^+): 265.1175. Found: 265.1149.

REFERENCES AND NOTES

1. a) *Antiviral Drug Development: A Multidisciplinary Approach*; De Clercq, E.; Walker, R. T., Eds.; Plenum Press: New York, 1988. b) *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press Inc.: Greenwich, Connecticut, 1996; Vol. 2.
2. a) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; De Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. USA* **1977**, *74*, 5716–5720. b) Schaeffer, H. J.; Beauchamp, L.; De Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* (London) **1978**, *272*, 583–585.
3. a) Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. *J. Med. Chem.* **1983**, *26*, 759–761. b) Ogilvie, K. K.; Cheriyan, U. O.; Radatus, B. K.; Smith, K. O.; Galloway, K. S.; Kennell, W. L. *Can. J. Chem.* **1982**, *60*, 3005–3010. c) Ashton, W. T.; Karkas, J. D.; Field, A. K.; Tolman, R. L. *Biochem. Biophys. Res. Commun.* **1982**, *108*, 1716–1721. d) Smith, K. O.; Galloway, K. S.; Kennell, W. L.; Ogilvie, K. K.; Radatus, B. K. *Antimicrob. Ag. Chemoth.* **1982**, *22*, 55–61.
4. a) Chu, C. K.; Cutler, S. J. *J. Heterocycl. Chem.* **1986**, *23*, 289–319. b) El Ashry, E. S. H.; El Kilany, Y. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1997; Vol. 67, pp 391–438. c) El Ashry, E. S. H.; El Kilany, Y. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1997; Vol. 68, pp 1–88.
5. a) Nemec, J; Rhoades, J. M. *Nucleosides, Nucleotides* **1983**, *2*, 99–112. b) Lerner, L. M. *Carbohydr. Res.* **1984**, *127*, 141–145. c) Birnbaum, G. I.; Stolarski, R.; Kazimierczuk, Z; Shugar, D. *Can. J. Chem.* **1985**, *63*, 1215–1221. d) Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1985**, *26*, 1305–1306. e) Mikhailov, S. N.; Florentiev, V. L.; Pfleiderer, W. *Synthesis*, **1985**, 399–400. f) McGee, D. P. C.; Martin, J. C. *Can. J. Chem.* **1986**, *64*, 1885–1889. g) Beaton, G.; Jones, S.; Walker, R. T. *Tetrahedron* **1988**, *44*, 6419–6428.

6. We preliminarily reported as communications: a) Kitade, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett.* **1993**, *34*, 4835–4836. b) Kitade, Y.; Monguchi, Y.; Hirota, K.; Maki, Y. *ibid.* **1993**, *34*, 6579–6580.
7. a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581–4584. b) Ishihara, K.; Mori, A.; Arai, I.; Yamamoto, H. *ibid.* **1986**, *27*, 983–986. c) Mori, A.; Ishihara, K; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755–764. d) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593–1596. e) Mikami, T.; Asano, H.; Mitsunobu, O. *ibid.* **1987**, 2033–2036. f) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *ibid.* **1988**, 927–930. g) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 6613–6616. h) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595–4612.
8. Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186–4194.
9. a) Pino, P.; Lorenzi, G. P. *J. Org. Chem.* **1966**, *31*, 329–331. b) Winterfeldt, E. *Synthesis* **1975**, 617–630. c) Hilscher, J. C. German Patent 2,409,991, 1975; *Chem. Abstr.* **1976**, *84*, 567.
10. a) Kawana has reported that the reaction of pyrrole ribonucleoside with MeMgI caused the methylative cleavage of its furanose ring to give a diastereomeric open-chain product as a sole example: Kawana, M. *Chem. Lett.* **1981**, 1541–1542. b) Meyers *et al.* have reported that the treatment of aryl oxazolines with DIBAL-H caused the selective cleavage of C-2–O-1 bond without C-2–N-3 bond cleavage: Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. *J. Org. Chem.* **1983**, *48*, 4053–4058.
11. All starting compounds in this paper were prepared *via* isopropylidene protection step which was carried out by Tomasz's or its slightly modified method: Tomasz, J. In *Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques*; Townsend, L. B.; Tipson, R. S., Eds.; John Wiley & Sons, Inc.: New York, 1978; Part 2, pp 765–769.
12. Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597–3600.
13. In the reaction mixture of **1h** with DIBAL-H (5 equiv) in CH_2Cl_2, the formation of a small amount of 2'-*O*-isopropyl- and 3'-*O*-isopropyladenosine was observed by means of ^1H NMR and HRMS measurements but they could not be sufficiently purified. Further, the reduction or decomposition of the purine ring was detected by ^1H NMR and UV data in the case of the reduction of adenosine analogs, *e.g.*, N^6,N^6-dimethyladenosine derivative **1l**, in THF.
14. O^6-Substituted inosine derivatives **1c** and **1e** were obtained by the treatment of 2',3'-*O*-isopropylidene protected 6-chloropurine riboside with alkoxides (NaOMe and NaOPr^i) in 96% and 58% yields, respectively.
15. Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1972**, *37*, 2289–2299.
16. Obtained by 5'-bromination of **1c** using PPh_3 (2.5 equiv) and CBr_4 (2.5 equiv) in CH_2Cl_2.
17. Hampton, A. *J. Am. Chem. Soc.* **1961**, *83*, 3640–3645.
18. Fleming, W. C.; Lee, W. W.; Henry, D. W. *J. Med. Chem.* **1973**, *16*, 570–571.
19. a) Gani, D.; Johnson, A. W.; Lappert, M. F. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 3065–3069. b) Dechlorination of 5'-chloro-5'-deoxyadenosine was carried out according to the following report: Wang, Y.; Hogenkamp, H. P. C. *Cabohydr. Res.* **1977**, *59*, 449–457.
20. Tang, K.-C.; Mariuzza, R.; Coward, J. K. *J. Med. Chem.* **1981**, *24*, 1277–1284.
21. Maki, Y.; Kameyama, K.; Suzuki, M.; Sako, M.; Hirota, K. *J. Chem. Research (S)* **1984**, 388–389.
22. Kato, T.; Zemlicka, J. *J. Org. Chem.* **1980**, *45*, 4006–4010.
23. Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540.
24. a) Woenckhaus, C. W. *Chem. Ber.* **1964**, *97*, 2439–2446. b) 6-Methylpurine riboside **1m** was prepared *via* a palladium-catalyzed cross-coupling reaction of 6-chloropurine derivative using Me_3Al: Hirota, K.; Kitade, Y.; Kanbe, Y.; Maki, Y. *J. Org. Chem.* **1992**, *57*, 5268–5270.
25. 6-Phenylpurine riboside **1n** was prepared *via* a palladium-catalyzed cross-coupling reaction of 6-chloropurine derivative using $PhSuBu_3$: Gundersen, L.-L. *Tetrahedron Lett.* **1994**, *35*, 3155–3158.
26. a) Kaufman, S. *Proc. Natl. Acad. Sci. USA* **1963**, *50*, 1085–1093. b) Patterson, E. L.; Broquist, H. P.; Albrecht, A. M.; Von Saltza, M. H.; Stokstad, E. L. R. *J. Am. Chem. Soc.* **1955**, *77*, 3167–3168.

27. a) Wood, A. W.; Sayer, J. M.; Newmark, H. L.; Yagi, H.; Michaud, D. P.; Jerina, D. M.; Conney, A. H. *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 5122–5126. b) Nakayama, O.; Yagi, M.; Kiyoto, S.; Okuhara, M.; Kohsaka, M. *J. Antibiot.* **1990**, *43*, 1615–1616.
28. a) Burg, A. W.; Brown, G. M. *J. Biol. Chem.* **1968**, *243*, 2349–2358. b) Plowman, J.; Cone, J. E.; Guroff, G. *ibid.* **1974**, *249*, 5559–5564. c) Mitsuda, H.; Nakajima, K.; Yamada, Y. *ibid.* **1978**, *253*, 2238–2243.
29. MacCoss, M.; Ryu, E. K.; White, R. S.; Last, R. L. *J. Org. Chem.* **1980**, *45*, 788–794.
30. Torrence, P. F.; De Clercq, E.; Waters, J. A.; Witkop, B. *Biochemistry* **1974**, *13*, 4400–4408.
31. Anzai, K..; Matsui, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3228–3232.
32. In general, 9-D-ribityladenine **13** and 9-D-ribitylguanine have been synthesized by the multistep method: a) Davoll, J.; Evans, D. D. *J. Chem. Soc.* **1960**, 5041–5049. b) Ross, D. L.; Skinner, C. G.; Shive, W. *J. Org. Chem.* **1961**, *26*, 3582–3583.
33. Holy, A. *Collct. Czech. Chem. Commun.* **1982**, *47*, 2786–2805.
34. Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3478–3487.
35. Skaric, V.; Gaspert, B.; Hohnjec, M., *J. Chem. Soc. (C)* **1970**, 2444–2447.
36. Hanze, A. R. *J. Am. Chem. Soc.* **1967**, *89*, 6720–6725.
37. a) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521–1530. b) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R.. T. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press Inc.: Greenwich, Connecticut, 1996: Vol 2, pp 41–88.
38. Compound **19** and **20** could be isolated as a single diastereomer. The NOE experiment of **20** supported its configuration; see experimental section.

(*Received in Japan* 13 *August* 1997; *accepted* 19 *September* 1997)