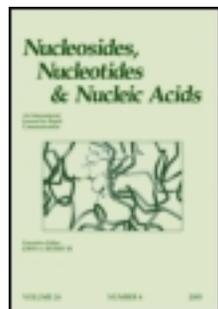


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Synthesis of 2',3'- Dideoxypurinenucleosides via the Palladium Catalyzed Reduction of 9- (2,5-Di-O-acetyl-3-bromo-3-deoxy- β -d- xylofuranosyl)purine Derivatives

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SYNTHESIS OF 2',3'-DIDEOXYPURINENUCLEOSIDES VIA THE PALLADIUM CATALYZED REDUCTION OF 9-(2,5-DI-O-ACETYL-3-BROMO-3-DEOXY- β -D-XYLOFURANOSYL)PURINE DERIVATIVES[†]

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Abstract: Practical method to produce 2',3'-dideoxypurinenucleosides from 9-(2,5-di-O-acetyl-3-bromo-3-deoxy- β -D-xylofuranosyl)purines (**1**) was developed. High ratio of 2',3'-dideoxynucleoside to 3'-deoxyribonucleoside was obtained by selecting the reaction conditions (solvent, pH and/or base), or changing 2'-acyloxy leaving group. The reaction mechanism was studied by deuteration experiments of **1a** and 1-(3,5-di-O-acetyl-2-bromo-2-deoxy- β -D-ribofuranosyl)thymine (**12**).

Introduction

Attention has been focused upon the transformation of the sugar moiety of nucleosides in order to develop virucides. 3'-Azido-3'-deoxythymidine (AZT),¹ 2',3'-dideoxyinosine (ddI),² 2',3'-dideoxycytidine (ddC)³ and 1-(2,3-dideoxy- β -D-glycero-pent-2-enofuranosyl)thymine (d4T)⁴ are the drugs approved for the treatment of HIV⁵ (Human immunodeficiency virus) infection in the USA. Since natural purineribonucleosides are manufactured by large scale fermentation, direct commercial synthesis of 2',3'-dideoxypurinenucleosides from purineribonucleosides is foreseeable. Several methods of 2',3'-dideoxypurinenucleoside synthesis have been reported,⁶ but they are limited to a particular nucleoside and therefore have no advantage from an industrial perspective.

The reductive elimination of β -substituted alkyl halides into alkenes has been studied by Kochi (Cr^{II}),⁷ Jain (Cr^{II}),⁸ Classon (Zn-Cu)⁹ and Amino (viologen).¹⁰ This process is hampered by the fact that isomerization of the olefins or protolytic reduction¹¹ of the

[†]Dedicated to Dr. Yoshihisa Mizuno on the occasion of his 75th birthday.

carbon-halogen bond competes with the desired reductive elimination. Furthermore, the 2',3'-unsaturated purinenucleoside derivatives obtained by the reductive elimination were so unstable that a considerable amount of heterocyclic bases were produced during the hydrogenation into dideoxynucleosides. The direct hydrogenation of bromo acetates into dideoxynucleosides with palladium catalyst has also been reported, but the protolytic reduction of the carbon-halogen bond predominated.¹²

In order to improve the selectivity and the yield of the reaction, we made enormous efforts and found that palladium catalyzed reduction gave satisfactory results for the synthesis of 2',3'-dideoxypurinenucleosides.

Results and Discussion

9-(2,5-Di-*O*-acetyl-3-bromo-3-deoxy- β -D-xylofuranosyl)adenine (**1a**)¹³ was selected as a suitable substrate for the synthesis of 2',3'-dideoxyadenosine (ddA, **2a**). Combination of solvent and base remarkably affected the yield of **2a** and the ratio of **2a** to 3'-deoxyadenosine (**3a**). In fact, high yield (83%) and selectivity (**2a/3a**=10.4) were obtained when the reaction was performed in acetonitrile/water controlled at pH 9.5 by adding 25% sodium hydroxide in the presence of 2.2 equiv. of sodium acetate, with only a small amount of **3a** being produced (Run 1). Addition of sodium acetate plays an important role to stabilize pH during the reaction. Comparable result was obtained with 1.1 equiv. of sodium carbonate and 2.2 equiv. of sodium acetate (Run 4). It is postulated that the production of **3a** might be suppressed under the developed conditions and consequently **2a** was produced predominantly. Very interestingly, it was found that the yield and selectivity are strongly affected by the reaction pH. The yield of **2a** decreased by more than 10 % and the selectivity also decreased in the reaction at pH 9 or 10 (Runs 2 and 3). Desired nucleoside **2a** was not selectively produced when triethylamine was used as base in anhydrous condition (Run 7). All attempts to improve the yield and selectivity by changing catalyst, pressure, temperature, and additives were unsuccessful.

The bromo acetates **4**¹⁴ and **5**¹⁵ which have a different substituent at 5'-position were obtained by published methods. Among these substrates **1a** gave the highest yield of **2a** and the selectivity (Runs 1, 8 and 9). Slightly higher selectivity was obtained by changing 2'-substituent of **1a** from acetate into benzoate (**6**) or pentanoate (**7**) (Runs 10 and 11). We have reported selective 2'-*O*-deacetylation of **1a** and discussed the reduction of **8** and **9**.¹⁶ The palladium catalyzed reduction of bromohydrin **8** gave **3a** but the reaction was very slow (Run 12). On the contrary, the reduction of bromo mesylate **9** proceeded rapidly and gave **2a** selectively (Run 13). These results suggest that the ester group at 2'-position is essential for reductive β -elimination¹⁷ and the reaction is accelerated by introducing good leaving group at 2'-position.

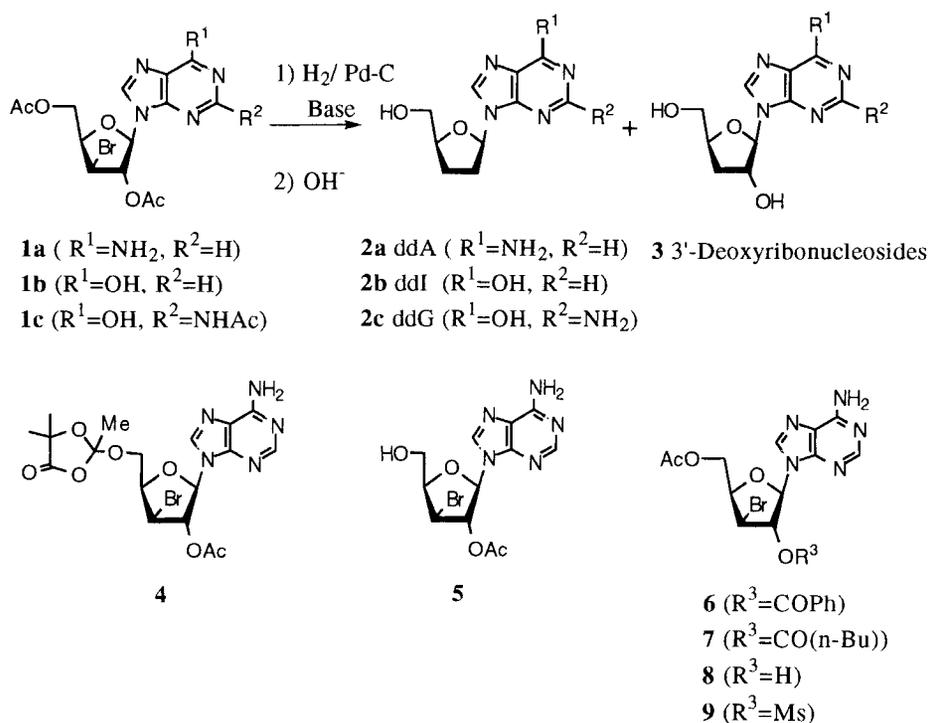


FIG. 1. Synthesis of 2',3'-dideoxynucleosides by palladium catalyzed reduction

2',3'-Dideoxyinosine (ddI, **2b**) and 2',3'-dideoxyguanosine (ddG, **2c**)¹⁸ were also obtained in satisfactory yield from 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)hypoxanthine (**1b**) and 2-*N*-acetyl-9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)guanine (**1c**), respectively. However, the most appropriate reduction conditions of **1b** and **1c** giving high selectivity of 2',3'-dideoxynucleoside are different from those of **1a**. When the reactions were performed in acetonitrile/water at pH 9.5 which is the optimum conditions to obtain **2a**, the selectivity of **2b** and **2c** were much lower than that of **2a** (Runs 14 and 15). On the contrary, high selectivity was observed in anhydrous conditions. The highest selectivity of **2b** was obtained with 5 equiv. of 4-*N,N*-dimethylaminopyridine (DMAP) in acetonitrile at 5 °C (Run 16). Similar result was obtained with 4 equiv. of triethylamine and 1 equiv. of DMAP (Run 17). The ratio of **2c** to **3c** under various conditions resembles that of **2b** to **3b**, and **2c** was obtained in 65% yield when the reaction was carried out with 5 equiv. of triethylamine in acetonitrile at 5 °C (Run 19).

TABLE 1. Synthesis of 2',3'-dideoxynucleosides by palladium catalyzed reduction

Run	starting nucleoside	solvent	conditions ^a		%yield & selectivity		
			base (equiv.)	time (h)	2	3	2/3
1	1a	MeCN-H ₂ O	NaOH(pH 9.5) AcONa(2.2)	9	83	8	10.4
2	1a	MeCN-H ₂ O	NaOH(pH 9) AcONa(2.2)	12	71	13	5.5
3	1a	MeCN-H ₂ O	NaOH(pH 10) AcONa(2.2)	6	60	15	4.0
4	1a	MeCN-H ₂ O	Na ₂ CO ₃ (1.1) AcONa(2.2)	8	80	9	8.9
5	1a	MeCN-H ₂ O	Na ₂ CO ₃ (1.1)	5	69	16	4.3
6	1a	MeCN-H ₂ O	NaHCO ₃ (1.1)	10	31	37	0.8
7	1a	MeCN	Et ₃ N(1.2)	1	54	27	2.0
8	4	MeCN	NaOH(pH 9.5) AcONa(2.2)	3	51	28	1.8
9	5	MeCN	NaOH(pH 9.5) AcONa(2.2)	6	67	18	3.7
10	6	MeCN-H ₂ O	NaOH(pH 9.5) AcONa(2.2)	13	80	5	16.0
11	7	MeCN-H ₂ O	NaOH(pH 9.5) AcONa(2.2)	11	78	7	11.0
12	8	MeCN-H ₂ O	Na ₂ CO ₃ (1.1)	24	0	82	0
13	9	MeCN-H ₂ O	Na ₂ CO ₃ (1.1)	2	85	0.8	106
14	1b	MeCN-H ₂ O	NaOH(pH 9.5) AcONa(2.2)	9	55	22	2.5
15	1c	MeCN-H ₂ O	NaOH(pH 9.5) AcONa(2.2)	10	47	19	2.5
16	1b	MeCN	DMAP(5)	12 ^b	75	6	12.5
17	1b	MeCN	Et ₃ N (4) DMAP(5)	14 ^b	80	8	10.0
18	1b	MeCN	Et ₃ N(5)	10 ^b	67	14	4.8
19	1c	MeCN	Et ₃ N (5)	12 ^b	65	14	4.6

^a Reactions were performed at room temperature with 10% palladium on carbon (5 mol%) under hydrogen atmosphere (1 atm).

^b Reactions were performed at 5 °C.

The deuteration experiments of **1a** were carried out in order to confirm the production mechanism of 2',3'-dideoxynucleoside (**2**) and 3'-deoxyribonucleoside (**3**) and to examine the relationship between the selectivity (**2/3**) and the reaction conditions. Catalytic reduction of **1a** in acetonitrile with 5 equiv. of triethylamine under an atmosphere of deuterium at 1 atm, followed by deprotection gave a mixture of deuterated ddA (**10**) (50%) and 3'-deoxyadenosine (**11**) (25%). These products were isolated and purified by column chromatography using synthetic adsorption resin (SP-207, Mitsubishi Kasei Co.). Two dimensional ^1H NMR (400 MHz) and decoupling analyses were performed to clarify the structures. Chemical shifts and coupling constants of the protons at the C-1' to C-4' carbons and the deuterated positions in **10** and **11** were assigned. The NMR coupling constants were consistent with the data obtained by the Karplus equation of the torsion angle, which was calculated using SYBYL, and supported the structures. The isolated **10** was found to be 2'(α),3'(α)-dideuterated compound. The same product **10** was obtained by reducing **16** with deuterium, followed by deprotection. The isolated **11** was a mixture of 3'(α)- and 3'(β)-deuterated isomers (α -D/ β -D=79/21) (FIG. 2). The structure of **10** supports the notion that the reaction occurs *via* reductive β -elimination, followed by *cis* hydrogenation of olefin.¹² On the contrary, **11** is not produced *via* β -elimination of HBr at the 2',3'- or 3',4'-positions, followed by hydrogenation. It is interesting to note that the comparable isomeric ratio (α -D/ β -D=88/12) was observed by radical reduction of ribo/arabino 2'-*O*-phenoxythiocarbonyladenine derivatives.¹⁹

To further investigate the reaction mechanism in detail, the reaction of a pyrimidine derivative with different configuration was performed. Nucleoside **12**, which was produced from 5-methyluridine by the action of acetyl bromide, had 2'-bromo and 3'-acetoxy substituents in the *syn* configuration, because the reaction proceeded *via* the 2-(*O*)-2'-cyclic intermediate by neighboring group participation.²⁰ Molecular structures of **1a** and **12** were confirmed by X-ray crystallography (Fig. 3). The catalytic reduction of **12** with deuterium, followed by deprotection and isolation gave deuterated thymidine (**14**) (46%) and 2',3'-dideoxy-5-methyluridine (**13**) (40%). Obtained **13** was found to be 2'(α),3'(α)-dideuterated compound and **14** was a mixture of 2'(α)- and 2'(β)-deuterated isomers (α -D/ β -D=83/17). The isomeric ratio of **14** was determined by transforming **14** into 3',5'-*O*-(1,1,3,3-tetraisopropylidisiloxy-1,3-diyl) derivative (**15**).²¹ As well the case of **10**, the hydrogenation of **17** with deuterium followed by deprotection gave **13**.

These similar results about the deuterated position and the ratio in both cases provide corroborative evidence for the reaction mechanism suggested above. The selectivity to produce deoxyribo derivative against dideoxy derivative is higher in the case of **12** than that of **1a**. The *syn* configuration of 2'-bromo and 3'-acetoxy substituents

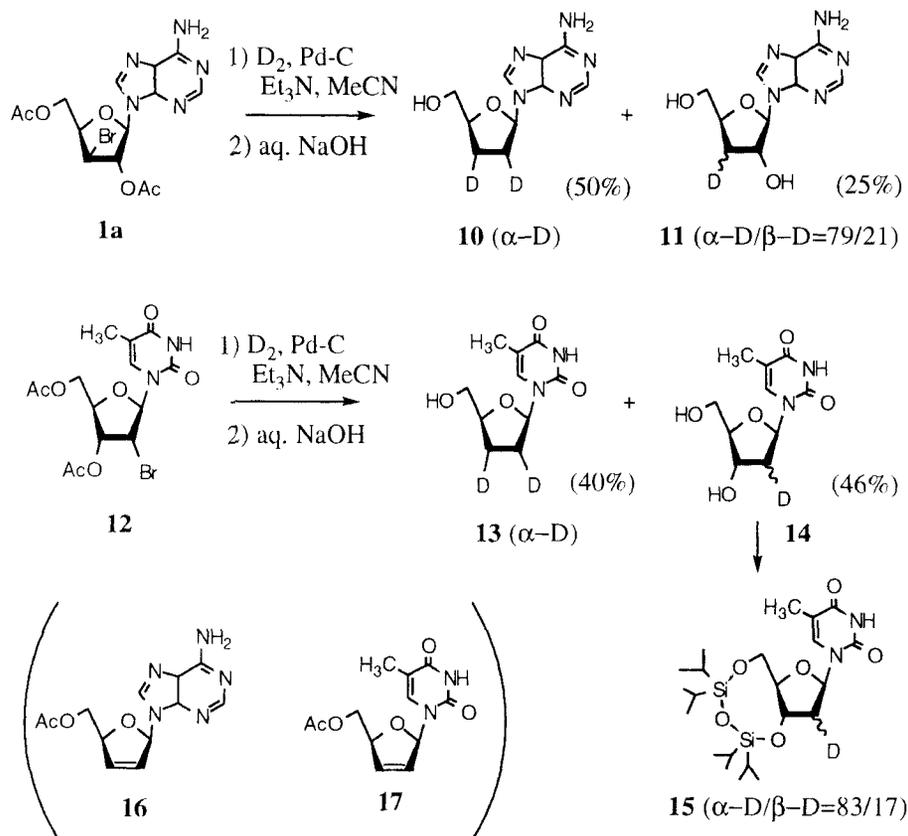


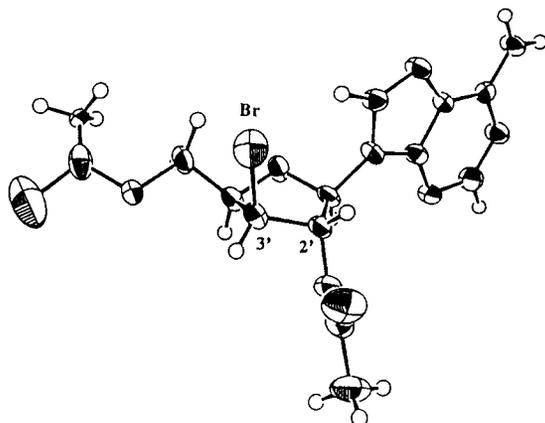
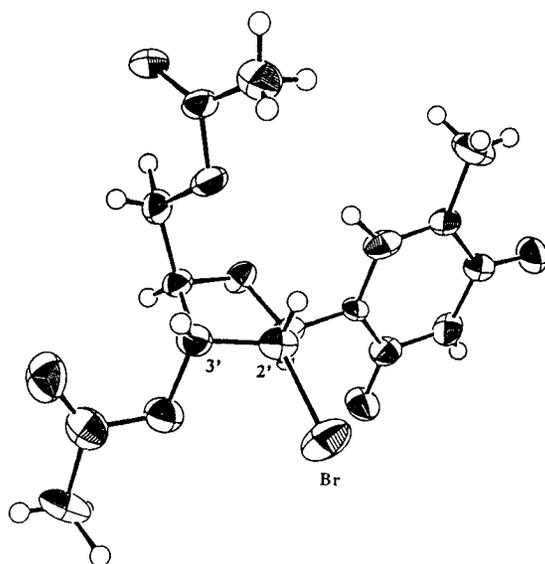
FIG. 2. Palladium catalyzed reduction with deuterium

seems to suppress the reductive β -elimination and promote the elimination of bromide,²⁰ so that thymidine must be obtained selectively by optimizing the reduction condition.²²

In summary, a synthetic method for 2',3'-dideoxypurineribonucleosides from ribonucleosides by selective reduction of 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy- β -D-xylofuranosyl)purines (**1**) was developed. This method allowed the production of ddA, ddI and ddG from natural purineribonucleosides on an industrial scale.

Experimental Section

Adenosine, inosine, guanosine and 5-methyluridine are produced at Ajinomoto. Melting points were measured with a Yamato melting point apparatus and are uncorrected. UV spectra were recorded on a Hitachi U-3200 spectrometer. ¹H NMR spectra were obtained on a Varian XL-300 or JEOL JNM-GX 400 spectrometers and are reported as

9-(2,5-Di-*O*-acetyl-3-bromo-3-deoxy- β -D-xylofuranosyl)adenine (**1a**)1-(3,5-Di-*O*-acetyl-2-bromo-2-deoxy- β -D-ribofuranosyl)thymine (**12**)FIG. 3. ORTEP drawing of **1a** and **12**

ppm values downfield from Me₄Si (Me₂SO-*d*₆) or 3-(trimethylsilyl)propanesulfonic acid sodium salt (D₂O). Mass spectra (MS) were obtained with a JEOL D-300 instrument with fast atom bombardment (FAB) ionization. HPLC was carried out on a 15 cm YMC A-312 column with a Hitachi 655 system equipped with a Shimadzu C-R4A integrator and Hitachi variable wavelength UV monitor set at 260 nm.

Synthesis of 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (1a) from adenosine. To a suspension of 20.0 g (74.6 mmol) of adenosine in acetic acid (100 mL) was added 11.7 mL (1.3 equiv.) of trimethyl orthoacetate and the resulting mixture was stirred at 50 °C for 3 h. After concentrating the reaction solution under reduced pressure, 100 mL of acetonitrile was added and the reaction mixture was cooled to 10 °C, to which 22 mL of acetyl bromide (4 equiv.) was added slowly over 1 h. The reaction mixture was stirred for another 2 h at 15 °C, and the mixture was neutralized with an aqueous sodium carbonate and organic layer was separated. Aqueous layer was extracted with acetonitrile (50 mL) and the combined organic layers were dried over Na₂SO₄, concentrated, and chromatographed on silica gel (CHCl₃/MeOH, 5/1) to give **1a** (27.2 g, 65.6 mmol, 88%). By recrystallization from acetonitrile an analytical sample was obtained: mp 163-164 °C; λ_{max}(H₂O) 259 nm (ε 1.40×10⁴), λ_{min}(H₂O) 227 nm (ε 2.51×10³); ¹H NMR (Me₂SO-*d*₆) δ 2.06 (s, 3H, Ac), 2.11 (s, 3H, Ac), 4.38 (m, 2H, H-5'ab), 4.56 (m, 1H, H-4'), 4.92 (dd, 1H, *J*=2.5, 4.7 Hz, H-3'), 5.90 (dd, 1H, *J*=2.5, 3.1 Hz, H-2'), 6.17 (d, 1H, *J*=3.1 Hz, H-1'), 7.37 (s, 2H, NH₂), 8.16 (s, 1H, H-8), 8.30 (s, 1H, H-2); MS *m/z* 414, 416 (1:1, MH⁺). Anal. Calcd for C₁₄H₁₆BrN₅O₅: C, 40.60; H, 3.89; N, 16.91. Found: C, 40.45; H, 3.88; N, 16.88.

Synthesis of 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)hypoxanthine (1b) from inosine. To a suspension of 20.0 g (74.6 mmol) of inosine in acetic acid (100 mL) was added 11.7 mL (1.3 equiv.) of trimethyl orthoacetate. The mixture was stirred at 50 °C for 5 h. After concentrating the reaction solution under reduced pressure, 20 mL of acetic acid was added and the mixture was concentrated again under reduced pressure. To the concentrate, acetonitrile (100 mL) was added, and the reaction mixture was cooled to 5 °C, to which 22 mL of acetyl bromide (4 equiv.) was added slowly over 2 h. After stirring the reaction mixture for another 4 h at 10 °C, the mixture was neutralized with an aqueous sodium carbonate and organic layer was separated. Aqueous layer was extracted with acetonitrile (50 mL) and the combined organic layers were dried over Na₂SO₄, concentrated, and purified by silica gel column chromatography (CHCl₃/MeOH, 5/1) to give **1b** (24.8 g, 59.7 mmol, 80%). By recrystallization from acetonitrile an analytical sample was obtained: mp 171-172 °C; λ_{max}(H₂O) 249 nm (ε 1.32×10⁴), λ_{min}(H₂O) 222 nm (ε 3.12×10³); ¹H NMR (Me₂SO-

d_6) δ 2.06 (s, 3H, CH₃), 2.11 (s, 3H, CH₃), 4.36 (m, 2H, H-5'ab), 4.57 (dt, 1H, $J=4.4, 7.9$ Hz, H-4'), 4.92 (dd, 1H, $J=2.4, 4.4$ Hz, H-3'), 5.82 (dd, 1H, $J=2.4, 2.9$ Hz, H-2'), 6.16 (d, 1H, $J=2.9$ Hz, H-1'), 8.10 (s, 1H, H-8), 8.26 (s, 1H, H-2); MS m/z 415, 417 (1:1, MH⁺). Anal. Calcd for C₁₄H₁₅BrN₄O₆: C, 40.50; H, 3.64; N, 13.49. Found: C, 40.39; H, 3.63; N, 13.50.

Synthesis of 2-N-acetyl-9-(2,5-di-O-acetyl-3-bromo-3-deoxy- β -D-xylofuranosyl)guanine (1c) from guanosine. Trimethyl orthoacetate (11.0 mL, 1.3 equiv.) was added to a suspension of 20.0 g (70.3 mmol) of guanosine in acetic acid (100 mL) and the resulting mixture was stirred at 50 °C for 5 h. After concentrating the reaction solution under reduced pressure, 20 mL of acetic acid was added and concentrated again under reduced pressure. Acetonitrile (100 mL) was added and the reaction mixture was cooled to 5 °C, to which 27.5 mL of acetyl bromide (5 equiv.) was added slowly over 2 h. The reaction mixture was stirred for another 2 h at 10 °C and 2 h at 20 °C, and the solution was neutralized with an aqueous sodium carbonate and organic layer was separated. Aqueous layer was extracted with acetonitrile (50 mL) and the combined organic layers were dried over Na₂SO₄, concentrated, and purified by silica gel column chromatography (CHCl₃/MeOH, 5/1) to give **1c** (24.9 g, 52.7 mmol, 75%). By recrystallization from acetonitrile an analytical sample was obtained: mp 115-120 °C; $\lambda_{\max}(\text{H}_2\text{O})$ 259 nm (ϵ 1.58x10⁴), $\lambda_{\min}(\text{H}_2\text{O})$ 227 nm (ϵ 3.94x10³); ¹H NMR (Me₂SO- d_6) δ 2.06 (s, 3H, CH₃), 2.11 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 4.34 (m, 2H, H-5'ab), 4.52 (dt, 1H, $J=4.7, 9.3$ Hz, H-4'), 4.93 (dd, 1H, $J=2.2, 4.4$ Hz, H-3'), 5.73 (dd, 1H, $J=2.7, 2.7$ Hz, H-2'), 6.00 (d, 1H, $J=3.0$ Hz, H-1'), 6.54 (br s, 2H, 2-NH₂), 8.19 (s, 1H, H-8); MS m/z 472, 474 (1:1, MH⁺). Anal. Calcd for C₁₆H₁₈BrN₅O₇: C, 40.69; H, 3.84; N, 14.83. Found: C, 40.09; H, 3.80; N, 14.52.

2',3'-Dideoxyadenosine (ddA, 2a)

(Na₂CO₃/AcONa system). To a solution of **1a** (1.0 g, 2.4 mmol) in acetonitrile (50 mL) were added aqueous sodium carbonate (281 mg, 2.7 mmol in 10 mL of water), sodium acetate (433 mg, 5.3 mmol), and 10% palladium on carbon (120 mg on a dry basis, 0.11 mmol). The mixture was stirred for 8 h at room temperature under hydrogen atmosphere at 1 atm. After disappearance of the starting material, the catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 10% NaOH (adjusted to pH 12) for 1 h at room temperature and neutralized by 5% HCl. The mixture was chromatographed on synthetic adsorption resin (SP-207, Mitsubishi Kasei Co., eluent 30% MeOH), to give **2a** (439 mg, 1.9 mmol, 78%). By recrystallization from water, an analytical sample was obtained: mp 187-188 °C; $\lambda_{\max}(\text{H}_2\text{O})$ 261 nm (ϵ 1.55x10⁴); $\lambda_{\min}(\text{H}_2\text{O})$ 227 nm (ϵ 2.33x10³); ¹H NMR (D₂O) δ

2.04 (dddd, 1H, $J=7.8, 8.3, 8.3, 13.5$ Hz, H-3' β), 2.24 (dddd, 1H, $J=4.4, 8.3, 11.3, 13.5$ Hz, H-3' α), 2.52 (dddd, 1H, $J=3.9, 7.8, 8.3, 13.5$ Hz, H-2' β), 2.60 (dddd, 1H, $J=4.4, 8.3, 11.3, 13.5$ Hz, H-2' α), 3.67 (dd, 1H, $J=4.4, 12.5$ Hz, H-5'a), 3.84 (dd, 1H, $J=3.2, 12.5$ Hz, H-5'b), 4.36 (ddt, 1H, $J=4.4, 8.3, 4.4$ Hz, H-4'), 6.27 (dd, 1H, $J=3.9, 4.4$ Hz, H-1'), 8.13 (s, 1H, H-8), 8.28 (s, 1H, H-2); MS m/z 236 (MH⁺). Anal. Calcd for C₁₀H₁₃N₅O₂: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.05; H, 5.57; N, 29.78.

A small amount of 3'-deoxyadenosine (**3a**) was obtained as a by-product (54 mg, 0.22 mmol, 9.0%): mp 227-228 °C; $\lambda_{\max}(\text{H}_2\text{O})$ 260 nm (ϵ 1.51x10⁴); $\lambda_{\min}(\text{H}_2\text{O})$ 227 nm (ϵ 2.21x10³); ¹H NMR (Me₂SO-*d*₆) δ 1.92 (ddd, 1H, $J=5.6, 8.5, 13.5$ Hz, H-3' β), 2.26 (ddd, 1H, $J=3.9, 6.4, 13.5$ Hz, H-3' α), 3.52 (m, 1H, H-5'a), 3.70 (m, 1H, H-5'b), 4.36 (ddt, 1H, $J=6.4, 8.5, 4.0$ Hz, H-4'), 4.58 (ddd, 1H, $J=2.2, 3.9, 5.6$ Hz, H-2'), 5.18 (t, 1H, $J=5.6$ Hz, 5'-OH), 5.67 (d, 1H, $J=4.3$ Hz, 2'-OH), 5.87 (d, 1H, $J=2.2$ Hz, H-1'), 7.27 (s, 2H, NH₂), 8.14 (s, 1H, H-8), 8.34 (s, 1H, H-2); MS m/z 252 (MH⁺). Anal. Calcd for C₁₀H₁₃N₅O₂: C, 47.81; H, 5.22; N, 27.87. Found: C, 47.79; H, 5.20; N, 28.04.

(pH control system). To a solution of **1a** (1.0 g, 2.4 mmol) in acetonitrile (50 mL) was added 10% palladium on carbon (120 mg on a dry basis, 0.12 mmol). The mixture was stirred for 10 h at pH 9.5 by adding 25% aqueous sodium hydroxide under hydrogen atmosphere at 1 atm. After disappearance of the starting material, the catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 10% NaOH (adjusted to pH 12) for 1 h at room temperature and neutralized by 5% HCl. The mixture was chromatographed on synthetic adsorption resin (SP-207, Mitsubishi Kasei Co., eluent 30% MeOH) to give **2a** (451 mg, 1.9 mmol, 80%). A small amount of **3a** was obtained as a by-product (48 mg, 0.19 mmol, 8.0%).

2',3'-Dideoxyinosine (ddI, 2b). To a solution of **1b** (1.0 g, 2.4 mmol) in acetonitrile (50 mL) were added 4-dimethylaminopyridine (1.47 g, 12 mmol), and 10% palladium on carbon (120 mg on a dry basis, 0.12 mmol). The mixture was stirred for 12 h at 5 °C under hydrogen atmosphere at 1 atm. After disappearance of the starting material, the catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 10% NaOH (adjusted to pH 12) for 1 h at room temperature and the reaction mixture was neutralized by 5% HCl. The mixture was chromatographed on synthetic adsorption resin (SP-207, Mitsubishi Kasei Co., eluent 30% MeOH) to give **2b** (401 mg, 1.7 mmol, 71%). By recrystallization from water, an analytical sample was obtained: mp 160-163 °C; $\lambda_{\max}(\text{H}_2\text{O})$ 249 nm (ϵ 1.25x10⁴); $\lambda_{\min}(\text{H}_2\text{O})$ 222 nm (ϵ 2.93x10³); ¹H NMR (D₂O) δ 1.97-2.07 (m, 1H, H-2' β), 2.16-2.24 (m, 1H, H-2' α), 2.47-2.64 (m, 2H, H-3' $\alpha\beta$), 3.64 (dd, 1H, $J=5.1, 12.5$ Hz, H-5'a), 3.80 (dd, 1H,

$J=3.2, 12.5$ Hz, H-5'b), 4.33 (m, 1H, H-4'), 6.29 (dd, 1H, $J=3.4, 6.8$ Hz, H-1'), 8.14 (s, 1H, H-8), 8.28 (s, 1H, H-2); MS m/z 237 (MH⁺). Anal. Calcd for C₁₀H₁₂N₄O₃: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.54; H, 5.06; N, 23.70.

A small amount of 3'-deoxyinosine (**3b**) was obtained as a by-product (36 mg, 0.14 mmol, 6.0%): mp 208-210 °C; $\lambda_{\max}(\text{H}_2\text{O})$ 249 nm (ϵ 1.19x10⁴); $\lambda_{\min}(\text{H}_2\text{O})$ 222 nm (ϵ 2.95x10³); ¹H NMR (Me₂SO-*d*₆) δ 1.87-1.92 (m, 1H, H-3' β), 2.18-2.25 (m, 1H, H-3' α), 3.53 (m, 1H, H-5'a), 3.69 (m, 1H, H-5'b), 4.35 (m, 1H, H-4'), 4.50 (m, 1H, H-2'), 5.03 (s, 1H, 2'-OH), 5.68 (s, 1H, 5'-OH), 5.86 (d, 1H, $J=1.5$ Hz, H-1'), 8.06 (s, 1H, H-8), 8.33 (s, 1H, H-2). MS m/z 253 (MH⁺). Anal. Calcd for C₁₀H₁₂N₄O₄: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.05; H, 4.68; N, 22.07.

2',3'-Dideoxyguanosine (ddG, 2c). **2c** was obtained from **1c** with 5 equiv. of triethylamine and acetonitrile solvent by the similar process described above (65%). By recrystallization from water, an analytical sample was obtained: mp 260 °C; $\lambda_{\max}(\text{H}_2\text{O})$ 253 nm (ϵ 1.25x10⁴); $\lambda_{\min}(\text{H}_2\text{O})$ 224 nm (ϵ 2.79x10³); ¹H NMR (D₂O) δ 1.99-2.09 (m, 1H, H-2' β), 2.16-2.26 (m, 1H, H-2' α), 2.43-2.61 (m, 2H, H-3' $\alpha\beta$), 3.63 (dd, 1H, $J=5.1, 12.4$ Hz, H-5'a), 3.78 (dd, 1H, $J=3.2, 12.5$ Hz, H-5'b), 4.31 (m, 1H, H-4'), 6.12 (dd, 1H, $J=3.5, 6.6$ Hz, H-1'), 8.14 (s, 1H, H-8), 7.98 (s, 1H, H-2); MS m/z 252 (MH⁺). Anal. Calcd for C₁₀H₁₃N₅O₃: C, 47.81; H, 5.22; N, 27.87. Found: C, 47.50; H, 5.12; N, 27.30.

3'-Deoxyguanosine (**3c**) was obtained as a by-product (16%): mp 240 °C; $\lambda_{\max}(\text{H}_2\text{O})$ 253 nm (ϵ 1.26x10⁴); $\lambda_{\min}(\text{H}_2\text{O})$ 224 nm (ϵ 2.66x10³); ¹H NMR (Me₂SO-*d*₆) δ 1.82-1.93 (m, 1H, H-3' β), 2.13-2.25 (m, 1H, H-3' α), 3.48 (m, 1H, H-5'a), 3.62 (m, 1H, H-5'b), 4.29 (m, 1H, H-4'), 4.43 (m, 1H, H-2'), 4.97 (t, 1H, $J=5.5$ Hz, 5'-OH), 5.56 (d, 1H, $J=4.4$ Hz, 2'-OH), 5.67 (d, 1H, $J=2.2$ Hz, H-1'), 6.45 (br s, 2H, 2-NH₂), 7.92 (s, 1H, H-8); MS m/z 268 (MH⁺). Anal. Calcd for C₁₀H₁₂N₄O₄: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.65; H, 4.90; N, 26.07.

(2'R,3'S)-[2'-²H,3'-²H]-2',3'-Dideoxyadenosine (10) and [3'-²H]-3'-deoxyadenosine (11). To a solution of **1a** (1.0 g, 2.4 mmol) in acetonitrile (50 mL) were added triethylamine (1.7 mL, 12 mmol) and 10% palladium on carbon (120 mg, 0.12 mmol). The mixture was stirred for 7 h at room temperature under deuterium atmosphere at 1 atm. The reaction was monitored by HPLC until disappearance of **1a**. The catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 5% NaOH (adjusted to pH 12) for 1 h at room temperature and the reaction mixture was neutralized by 5% HCl. The mixture was chromatographed on synthetic adsorption resin (SP-207, Mitsubishi Kasei Co., eluent 30% MeOH) to give **10** (282 mg, 1.2 mmol, 50%) and **11** (150 mg, 0.6 mmol, 25%).

Physical data for 10: ^1H NMR (D_2O) δ 2.03 (dd, 1H, $J=7.8, 8.3$ Hz, H-3' β), 2.52 (dd, 1H, $J=3.9, 7.8$ Hz H-2' β), 3.67 (dd, 1H, $J=5.1, 12.5$ Hz, H-5'a), 3.84 (dd, 1H, $J=3.2, 12.5$ Hz, H-5'b), 4.36 (dt, 1H, $J=8.3, 4.4$ Hz, H-4'), 6.27 (d, 1H, $J=3.9$ Hz, H-1'), 8.13 (s, 1H, H-8), 8.28 (s, 1H, H-2); MS m/z 238 (MH^+).

Physical data for 11: ^1H NMR (D_2O) δ 2.04 (ddd, reduced H, $J=5.6, 8.5, 13.5$ Hz, H-3' β), 2.29 (ddd, reduced H, $J=3.9, 6.4, 13.5$ Hz, H-3' α), 3.71 (m, 1H, H-5'a), 3.92 (m, 1H, H-5'b), 4.62 (ddt, 1H, $J=6.4, 8.5, 4.0$ Hz, H-4'), 4.83 (ddd, 1H, $J=2.2, 3.9, 5.6$ Hz, H-2'), 6.06 (d, 1H, $J=2.2$ Hz, H-1'), 8.23 (s, 1H, H-8), 8.31 (s, 1H, H-2); MS m/z 253 (MH^+).

Intensity of H-3' proton was reduced and the ratio was calculated $\alpha\text{-D}/\beta\text{-D}=79/21$. For the assignment of the chemical shift at C-2' α,β and C-3' α,β positions, and the coupling constants of C1-C4 protons in the case of ddA (**2**) and 3'-deoxyadenosine (**3**), ^1H NMR, 2D- ^1H NMR and decoupling experiments were performed.

1-(3,5-Di-*O*-acetyl-2-bromo-2-deoxy- β -D-ribofuranosyl)thymine

(12). To 5-methyluridine (5.0 g, 19.3 mmol) in acetic acid (50 mL) was added trimethyl orthoacetate (3.45 mL, 27.1 mmol) and the mixture was stirred at 50 °C for 1 h. The reaction mixture was concentrated to 8.5 g under reduced pressure. To the solution was added 40 mL of acetonitrile and the resulting solution was heated to 50 °C, and at the temperature, a mixture of 15.7g (3 equiv.) of 30% HBr/AcOH and 1.43 mL (1 equiv.) of AcBr was added dropwise over 1 h. The reaction temperature was raised to 60 °C and the mixture was stirred for another 4 h. It was then cooled to 10 °C and 10 mL of water was added. Neutralization with 25% aqueous sodium hydroxide followed by usual workup afforded 7.54 g (17.5 mmol) of 1-(3,5-di-*O*-acetyl-2-bromo-2-deoxy- β -D-ribofuranosyl)-thymine (**12**) (90% yield from 5-methyluridine): mp 128-131 °C; $\lambda_{\text{max}}(\text{H}_2\text{O})$ 264 nm (ϵ 9.59×10^3); $\lambda_{\text{min}}(\text{H}_2\text{O})$ 233 nm (ϵ 2.73×10^3); ^1H NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.81 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 4.28 (m, 2H, H-5'ab), 4.32 (m, 1H, H-4'), 4.99 (dd, 1H, $J=5.9, 7.8$ Hz, H-2'), 5.27 (dd, 1H, $J=2.9, 5.9$ Hz, H-3'), 6.15 (d, 1H, $J=7.82$ Hz, H-1'), 7.53 (s, 1H, H-6), 11.53 (s, 1H, NH); MS m/z 405, 407 (1:1, MH^+). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{BrN}_2\text{O}_7$: C, 41.50; H, 4.23; N, 6.91. Found: C, 40.91; H, 4.19; N, 6.94.

[2'- ^2H]-Thymidine (14) and (2'R,3'S)-[2'- ^2H ,3'- ^2H]-2',3'-dideoxy-5-methyluridine (13). To a solution of **12** (1.0 g, 2.5 mmol) in acetonitrile (50 mL) were added triethylamine (1.7 mL, 12.3 mmol) and 5% palladium on carbon (240 mg, 0.12 mmol). The mixture was stirred for 8 h at room temperature under deuterium atmosphere at 1atm. The reaction was monitored by HPLC until disappearance of **12**. The catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 5% NaOH (adjusted to pH 12) for 1 h at room temperature and the reaction

mixture was neutralized by 5% HCl. The mixture was chromatographed on synthetic adsorption resin (SP-207, Mitsubishi Kasei Co., eluent 15&50% MeOH) to give **14** (277 mg, 1.13 mmol, 46%) and **13** (224 mg, 0.98 mmol, 40%).

Physical data for 14: $^1\text{H NMR}$ (D_2O) δ 1.87 (s, 3H, CH_3), 2.35 (m, 1H, H-2' $\alpha\beta$), 3.74 (dd, 1H, $J=5.1, 12.4$ Hz, H-5'a), 3.82 (dd, 1H, $J=3.4, 12.7$ Hz, H-5'b), 4.00 (dt, 1H, $J=3.9, 5.4$ Hz, H-4'), 4.45 (m, 1H, H-3'), 6.27 (m, 1H, H-1'), 7.62 (s, 1H, H-6); MS m/z 245 (MH^+).

Physical data for 13: $^1\text{H NMR}$ (D_2O) δ 1.83 (m, 1H, H-3' β), 1.87 (s, 3H, CH_3), 2.10 (dd, 1H, $J=3.2, 7.7$ Hz, H-2' β), 3.71 (dd, 1H, $J=5.4, 12.7$ Hz, H-5'a), 3.85 (dd, 1H, $J=3.2, 12.5$ Hz, H-5'b), 4.21 (dt, 1H, $J=9.9, 5.4$ Hz, H-4'), 6.09 (d, 1H, $J=3.2$ Hz, H-1'), 7.70 (s, 1H, H-6); MS m/z 229 (MH^+).

[2'- ^2H]-3',5'-O-(1,1,3,3-Tetraisopropylidisilox-1,3-diy)thymidine (15). To a solution of **14** (120 mg, 0.5 mmol) in pyridine (5 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (TPDS- Cl_2) (172 mg, 0.55 mmol). The reaction mixture was stirred for 3 h at room temperature. Pyridine was evaporated and the residue was partitioned between ethyl acetate (50 mL) and water (10 mL). The organic phase was washed with cold 1N HCl (20 mL two times), water (10 mL), saturated NaHCO_3 (10 mL), and brine (10 mL), dried (MgSO_4), filtered and evaporated. Silica gel chromatography eluted with $\text{CHCl}_3/\text{MeOH}$ (10/1) gave pure **15** (206 mg, 0.43 mmol, 85%). $^1\text{H NMR}$ (CDCl_3) δ 1.01 (m, 28H, isopropyl protons), 1.91 (s, 3H, CH_3), 2.22 (ddd, reduced H, $J=2.4, 5.8, 13.1$ Hz, H-2' β), 2.48 (ddd, reduced H, $J=7.2, 9.6, 13.1$ Hz, H-2' α), 3.76 (dt, 1H, $J=8.2, 2.6$ Hz, H-4'), 4.02 (dd, 1H, $J=3.0, 13.0$ Hz, H-5'a), 4.60 (dd, 1H, $J=2.6, 8.1$ Hz, H-5'b), 4.49 (ddd, 1H, $J=5.8, 8.2, 9.6$ Hz, H-3'), 6.06 (dd, 1H, $J=2.4, 7.2$ Hz, H-1'), 7.43 (s, 1H, H-6); MS m/z 487 (MH^+).

Single-Crystal X-ray Analysis. The cell constants and the reflections were measured with a Rigaku AFC5S diffractometer (graphite monochromator, $\text{CuK}\alpha$ radiation, ω scan, $3^\circ < 2\theta < 160^\circ$). The structures were solved using TEXSAN software package and refined by full-matrix leastsquares to a final $R = 0.058$ (for **1a**) and $R = 0.064$ (for **12**). Compound **1a** was crystallized from acetonitrile. Intensities from a crystal $0.8 \times 0.4 \times 0.2$ mm, space group $\text{P}2_12_1$, orthorhombic, $a = 10.683 \text{ \AA}$, $b = 20.708 \text{ \AA}$, $c = 7.587 \text{ \AA}$, $V = 1678.4 \text{ \AA}^3$, 1697 observed reflections ($I > 3.0\sigma(I)$). Compound **12** was crystallized from acetonitrile. Intensities from a crystal $0.7 \times 0.6 \times 0.3$ mm, space group $\text{P}2_12_1$, orthorhombic, $a = 10.554 \text{ \AA}$, $b = 17.320 \text{ \AA}$, $c = 9.900 \text{ \AA}$, $V = 1809.7 \text{ \AA}^3$, 1632 observed reflections ($I > 3.0\sigma(I)$).

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22. The selective reduction to produce thymidine from 1-(3,5-di-*O*-acetyl-2-bromo-2-deoxy- β -D-ribofuranosyl)thymine (**12**) will be reported later.