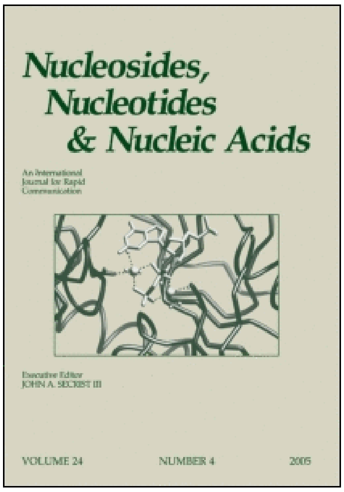

Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

An Efficient Method for the Synthesis of [4-^{15}N]Cytidine, 2'-Deoxy[4-^{15}N]Cytidine, [6-^{15}N]adenosine, and 2'-Deoxy [6-^{15}N]adenosine Derivatives

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To cite this Article Kamaike, Kazuo , Takahashi, Mihoko , Utsugi, Kazuyuki , Tomizuka, Kazue , Okazaki, Yasunori , Tamada, Yuri , Kinoshita, Kazutomo , Masuda, Hiroyuki and Ishido, Yoshiharu(1996) 'An Efficient Method for the Synthesis of [4-^{15}N]Cytidine, 2'-Deoxy[4-^{15}N]Cytidine, [6-^{15}N]adenosine, and 2'-Deoxy [6-^{15}N]adenosine Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 15: 1, 749 — 769

To link to this Article: DOI: 10.1080/07328319608002421

URL: http://dx.doi.org/10.1080/07328319608002421

NUCLEOSIDES & NUCLEOTIDES, 15(1-3), 749-769 (1996)

NOTE

AN EFFICIENT METHOD FOR THE SYNTHESIS OF [4-^{15}N]CYTIDINE, 2'-DEOXY[4-^{15}N]CYTIDINE, [6-^{15}N]ADENOSINE, AND 2'-DEOXY[6-^{15}N]ADENOSINE DERIVATIVES [#,1]

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Abstract: Nucleophilic substitution reactions of 4-azolyl-1-β-D-ribofuranosyl-pyrimidin-2(1*H*)-one and 6-azolyl-9-β-D-ribofuranosyl-9*H*-purine derivatives, which were converted from uridine and inosine, with [^{15}N]phthalimide in the presence of triethylamine or DBU gave *N*^{4}-phthaloyl[4-^{15}N]cytidine and *N*^{6}-phthaloyl[6-^{15}N]-adenosine derivatives, respectively, in high yields. Similar reactions of those azolyl derivatives with succinimide afforded *N*^{4}-succinylcytidine and *N*^{6}-succinyladenosine derivatives in high yields. The corresponding 2'-deoxyribonucleosides were also synthesized efficiently through the same procedure.

INTRODUCTION

Structural analysis, particularly, of dynamic features of biopolymers, e.g., nucleic acids on interaction with a protein, has recently been acknowledged very important, but is impossible to perform without NMR spectroscopy through NMR pulse techniques in combination with the compounds labelled with the stable isotopes of ^{13}C, ^{15}N, and ^{2}H.[2,3]

Two approaches to the chemical synthesis of ^{15}N-labeled nucleosides have been repoted: the first one involves the synthesis of an appropriately ^{15}N-labelled heterocycle, followed by its glycosylation with an appropriately functionalized D-ribofuranosyl or 2-

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[#] This paper is dedicated to Dr. Yoshihisa Mizuno on the occasion of his 75th birthday.

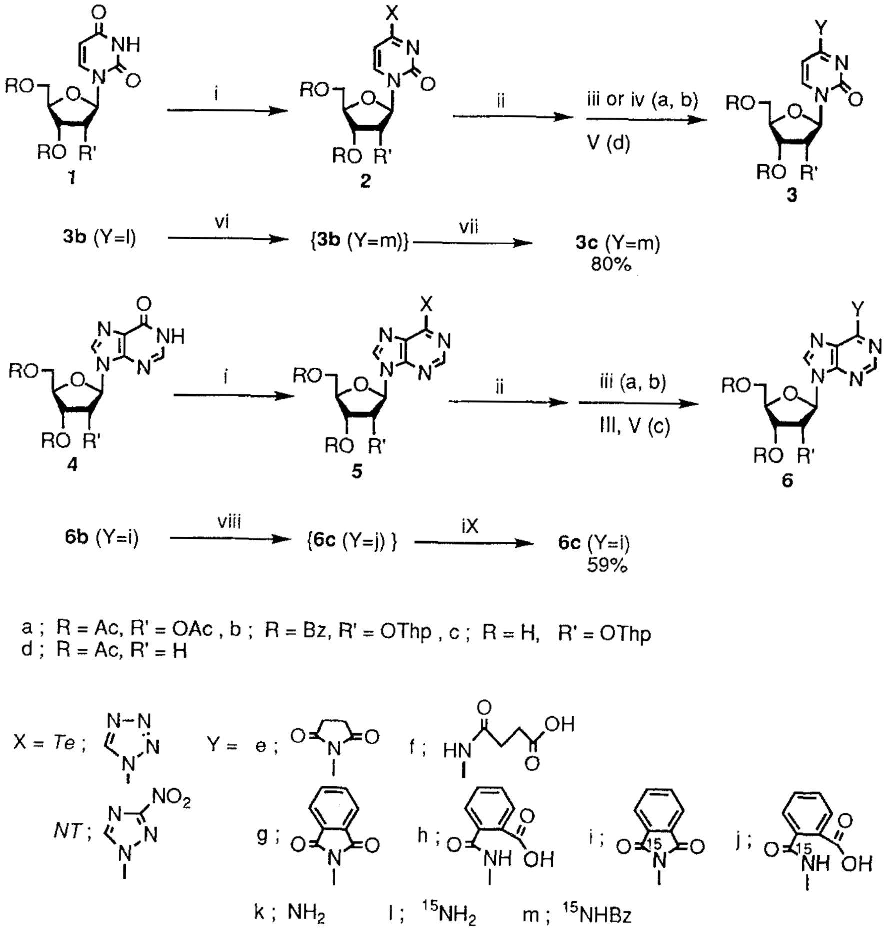
deoxy-D-ribofuranosyl derivative, giving the desired ^{15}N-labeled nucleoside;[4] the second one the chemical derivatization of an intact nucleoside to the corresponding ^{15}N-labelled nucleoside through the reaction of activated intermediates with [^{15}N]ammonia or [^{15}N]benzylamine.[5] The latter approach might be much more promising than the former from the synthetic standpoint of view. It would be further synthetically advantageous if it were possible to perform the latter approach by the use of a small excess amount of a solid nucleophile such as [^{15}N]phthalimide and/or [^{15}N]succinimide, in place of liquid reagents such as [^{15}N]ammonia or [^{15}N]benzylamine, for the introduction of a ^{15}N-label into the exocyclic amino group of a heterocyclic moiety of the nucleosides. This kind of potential approach should also be expected to bring about an alternative method for the introduction of *N*^{6}-phthaloyl and *N*^{6}-succinyl protection of 2'-deoxyadenosine, which has been shown to be beneficial to the automatic DNA oligomer synthesis by minimizing the so-called depurination reaction in the course of an oligodeoxyribonucleotide synthesis.[6]

We now report herein an efficient method for the synthesis of [4-^{15}N]cytidine, 2'-deoxy[4-^{15}N]ycytidine, [6-^{15}N]adenosine, and 2'-deoxy[6-^{15}N]adenosine derivatives from uridine, 2'-deoxyuridine, inosine, and 2'-deoxyinosine derivatives, respectively, which is characterized by the nucleophilic substitution reaction of their azolyl derivatives with [^{15}N]phthalimide or [^{15}N]succinimide in the presence of triethylamine or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (Scheme 1).

RESULTS AND DISCUSSION

Synthesis of Cytidine Derivatives (3a *and* 3b) *from Uridine Derivatives* (1a *and* 1b)

The 4-azolyl derivatives (**2**) were prepared from uridine derivatives (**1**) in a manner similar to that described by Reese *et al.*[7] Treatment of 2',3',5'-tri-*O*-acetyluridine (**1a**) with 1*H*-tetrazole or 3-nitro-1,2,4-triazole (2 mol. equiv.), diphenyl phosphate (1.2 mol. equiv.), and *p*-toluenesulfonyl chloride (2 mol. equiv.) in pyridine at room temperature for 1.5 days gave the corresponding 4-(tetrazol-1-yl) [**2a** (X=*Te*)][7] and 4-(3-nitro-1,2,4-triazol-1-yl) [**2a** (X=*NT*)][7] derivatives in 88% and 94% yields, respectively. Nucleophilic displacement of the 4-(tetrazol-1-yl) group of **2a** (X=*Te*) with succinimide (1.5 mol. equiv.) took place in the presence of triethylamine (5 mol. equiv.) in methylene chloride at room temperature for 1.5 days to give 2',3',5'-tri-*O*-acetyl-*N*^{4}-succinylcytidine [**3a** (Y=e)]. The process of the reaction was followed by TLC and the partial conversion of **3a** (Y=e) to **3a** (Y=f) was indicated, so that acetic anhydride (2 mol. equiv.) and triethylamine (4 mol. equiv.) were added to the reaction mixture to induce the ring closure of **3a** (Y=f) back to **3a** (Y=e). After purification by silica gel



Conditions ; (i) TsCl, $(PhO)_2P(O)OH$, 1*H*-tetrazole or 3-nitro-1,2,4-triazole, pyridine, r.t.
(ii) succinimide, phthalimide or [^{15}N]phthalimide, DBU or Et_3N, CH_2Cl_2, r.t.
(iii) $(CH_3CO)_2O$, Et_3N, CH_2Cl_2, r.t., 1 h
(iv) 1:1 H_2O - pyridine, r.t., 1 h
(V) $NH_2NH_2 \cdot H_2O$, CH_2Cl_2, r.t.
(vi) BzCl, pyridine, r.t., 30 min
(vii) NaOH, H_2O - EtOH - pyridine, 0 °C, 15 min
(viii) NaOH, H_2O - pyridine, 0 °C, 1 h
(iX) $(CF_3CO)_2O$, pyridine, r.t., 30 min

Scheme 1

Table 1 Synthesis of cytidine (**3a** and **3b**) and adenosine (**6a** and **6b**) derivatives.

Entry	Starting Materials	Imide (mol. equiv.)	Base (mol. equiv.)	Time (day)	Products	Yield (%)
1	**2a** (X=*Te*)	Suc (1.5)	Et$_3$N (5.0)	1.5	**3a** (Y=e)	88[a]
2	**2a** (X=*NT*)	Suc (1.5)	Et$_3$N (5.0)	2	**3a** (Y=e)	79[a]
3	**2a** (X=*Te*)	Phth (1.5)	Et$_3$N (5.0)	1	**3a** (Y=k)	94[b]
4	**2a** (X=*NT*)	Phth (1.5)	Et$_3$N (5.0)	1	**3a** (Y=k)	96[b]
5	**2b** (X=*Te*)	Suc (2.0)	Et$_3$N (5.0)	3	**3b** (Y=e)	81[a]
6	**2b** (X=*Te*)	Suc (2.0)	DBU (1.2)	2 h	**3b** (Y=e)	79[a]
7	**2b** (X=*Te*)	Phth (1.5)	Et$_3$N (5.0)	1	**3b** (Y=k)	96[b]
8	**2b** (X=*Te*)	Phth (1.5)	DBU (1.2)	30 min	**3b** (Y=k)	83[b]
9	**2b** (X=*Te*)	$[^{15}\text{N}]$Phth (1.5)	Et$_3$N (5.0)	1	**3b** (Y=l)	96[a]
10	**5a** (X=*NT*)	Suc (2.0)	Et$_3$N (5.0)	2	No Reaction	
11	**5a** (X=*NT*)	Suc (2.0)	DBU (3.0)	2	**6a** (Y=e)	60[a]
12	**5a** (X=*NT*)	Phth (2.0)	Et$_3$N (5.0)	2	No Reaction	
13	**5a** (X=*NT*)	Phth (2.0)	DBU (3.0)	1	**6a** (Y=g)	74[a]
14	**5b** (X=*NT*)	Suc (2.0)	DBU (3.0)	1	**6b** (Y=e)	72[a]
15	**5b** (X=*NT*)	Phth (2.0)	DBU (3.0)	1	**6b** (Y=g)	88[a]
16	**5b** (X=*NT*)	$[^{15}\text{N}]$Phth (2.0)	DBU (3.0)	2	**6b** (Y=i)	99[a]

Suc = Succinimide Phth = Phthalimide $[^{15}\text{N}]$Phth = $[^{15}\text{N}]$Phthalimide

a) Yield of *N*-succinyl or -phthaloyl derivative after the nucleophilic displacement reaction and treatment with acetic anhydride - triethylamine.

b) Yield of cytidine derivative after the nucleophilic displacement reaction and deprotection of the N^4-phthaloyl group by treatment with 1:1 H_2O - pyridine for 1 h.

column chromatography, **3a** (Y=e) was obtained in 88% yield (Entry 1 in Table 1). In a similar manner, the reaction of **2a** (X=*NT*) with succinimide in the presence of triethylamine for 2 days, followed by treatment with acetic anhydride and triethylamine, gave **3a** (Y=e) in 79% yield (Entry 2 in Table 1). Interestingly, after the reaction of **2a** (X=*Te*) or **2a** (X=*NT*) with phthalimide (1.5 mol. equiv.) in the presence of triethylamine (5 mol. equiv.), treatment of the resulting solutions with 1:1 H_2O-pyridine for 1 h induced complete unmasking of the N^4-phthaloyl group of the cytidine derivative [**3a** (Y=g)] to give 2',3',5'-tri-*O*-acetylcytidine **3a** (Y=k) in 94% and 96% yields (Entries 3 and 4 in Table 1), respectively. Similarly, 3',5'-di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)uridine (**1b**),[8] after introducing the tetrazol-1-yl group at its 4-position [**2b** (X=*Te*) in 84% yield], was subjected to the displacement with succinimide or phthalimide in the presence of triethylamine, followed by treatment with acetic anhydride - triethylamine or 1:1 H_2O - pyridine as described above, which gave 3',5'-di-*O*-benzoyl-N^4-succinyl-2'-*O*-(tetrahydropyran-2-yl)cytidine [**3b** (Y=e) in 81% yield] (Entry 5 in Table 1) and 3',5'-di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)cytidine [**3b** (Y=k) in 96%

yield] (Entry 7 in Table 1), respectively. Similar reactions using DBU[9] in place of triethylamine took place more efficiently, although the reactions resulted in inevitable formation of a small amount of several by-products (Entries 6 and 8 in Table 1), which could not be purified.

Synthesis of N^4*-Benzoyl-2'-*O*-(tetrahydropyran-2-yl)*[4-^{15}N]*cytidine* [3c (Y=m)]

3',5'-Di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)[4-^{15}N]cytidine [**3b** (Y=l)] was prepared in 96% yield (Entry 9 in Table 1) by the nucleophilic substitution of **2b** (X=*Te*) with [^{15}N]phthalimide in the presence of triethylamine and subsequent unmasking of the *N*^{4}-phthaloyl group. Compound **3b** (Y=l) was further subjected to *N*^{4}-benzoylation and *O*-debenzoylation as usual to give **3c** (Y=m), which is a useful intermediate for the RNA oligonucleotide synthesis, in 80% yield.

Synthesis of Adenosine Derivatives (6a *and* 6b) *from Inosine Derivatives* (4a *and* 4b)

The successful synthesis of [4-^{15}N]cytidine derivative by the above described approach promoted us to extend our studies to the synthesis of [6-^{15}N]adenosine derivative.

As described in the synthesis of the 4-azolyl derivartives (**2**), 2',3',5'-tri-*O*-acetylinosine (**4a**) was treated with 1*H*-tetrazole or 3-nitro-1,2,4-triazole, diphenyl phosphate, and *p*-toluenesulfonyl chloride in pyridine. Although the reaction with 1*H*-tetrazole was unsuccessful, that with 3-nitro-1,2,4-triazole for 7 days gave 6-(3-nitro-1,2,4-triazol-1-yl) derivative [**5a** (X=*NT*)][10] in 84% yield. The reaction with 3-nitro-1,2,4-triazole at 50 °C exhibited a remarkable effect on the acceleration of the formation of **5a** (X=*NT*) (for 23 h in 92% yield).

Nucleophilic displacement reaction of the 6-(3-nitro-1,2,4-triazol-1-yl) group of **5a** (X=*NT*) with succinimide or phthalimide (2 mol. equiv.) took place in the presence of DBU (3 mol. equiv.) to give 2',3',5'-tri-*O*-acetyl-*N*^{6}-succinyl- [**6a** (Y=e) in 60% yield] (Entry 11 in Table 1) or -phthaloyladenosine [**6a** (Y=g) in 74% yield] (Entry 13 in Table 1), after treatment with acetic anhydride - triethylamine and subsequent purification by silica gel column chromatography.

Similarly, 3',5'-di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)inosine (**4b**)[11] was, after introducing the 3-nitro-1,2,4-triazol-1-yl group at 6-position of the hypoxanthine moiety [**5b** (X=*NT*); in 79 - 80% yield], subjected to the displacement reaction of the 3-nitro-1,2,4-triazol-1-yl group with succinimide or phthalimide in the presence of DBU followed by treatment with acetic anhydride - triethylamine to give 3',5'-di-*O*-benzoyl-*N*^{6}-succinyl- [**6b** (Y=e) in 72% yield] (Entry 14 in Table 1) or -phthaloyl-2'-*O*-(tetrahydropyran-2-yl)adenosine [**6b** (Y=g) in 88% yield] (Entry 15 in Table 1).

Synthesis of N^6*-phthaloyl-2'-*O*-(tetrahydropyran-2-yl)*[6-^{15}N]*adenosine* [6c(Y=i)]

3',5'-Di-*O*-benzoyl-*N*^{6}-phthaloyl-2'-*O*-(tetrahydropyran-2-yl)[6-^{15}N]adenosine [**6a** (Y=i)] was prepared by the displacement reaction of **5b** (X=*NT*) with [^{15}N]phthalimide as described above in 99% yield (Entry 16 in Table 1). O-Debenzoylation of **6b** (Y=i) to **6c** (Y=j), followed by treatment with trifluoroacetic anhydride in pyridine, gave **6c**(Y=i), which is a synthetic intermediate for oligoribonucleotides, in 59% overall yield.

Synthesis of 2'-Deoxy[4-^{15}N]*cytidine Derivative* [3d(Y=l)] *from 2'-Deoxyuridine Derivative* (1d)

The synthesis of 2'-deoxycytidine derivative (**3d**) was achieved as described for cytidine derivative (**3c**). Treatment of 3',5'-di-*O*-acetyl-2'-deoxyuridine (**1d**) with 1*H*-tetrazole, diphenyl phosphate, and *p*-toluenesulfonyl chloride in pyridine gave the corresponding 4-(tetrazol-1-yl) derivative [**2d** (X=*Te*)]^7 in 96% yield. Nucleophilic displacement of the 4-(tetrazol-1-yl) group of **2d** (X=*Te*) with phthalimide (1.5 mol. equiv.) took place in the presence of triethylamine (5 mol. equiv.) or DBU (1.5 mol. equiv.) to give 3',5'-di-*O*-acetyl-*N*^{4}-phthaloylcytidine [**3d** (Y=g)]. After the displacement reaction, treatment of the resulting solutions with 1:1 H_2O - pyridine for 3 days induced complete unmasking of the *N*^{4}-phthaloyl group of **3d** (Y=g) to give 3',5'-di-*O*-acetyl-2'-deoxycytidine **3d** (Y=k) in 96% and 90% yields, respectively (Entries 1 and 2 in Table 2). 3',5'-Di-*O*-acetyl-2'-deoxy[4-^{15}N]cytidine **3d** (Y=l) was prepared in 92% yield (Entry 3 in Table 2) by the displacement reaction of **2d** (X=*Te*) with [^{15}N]phthalimide in the presence of DBU and subsequent unmasking of the *N*^{4}-phthaloyl group by treatment with hydrazine monohydrate instead of 1:1 H_2O - pyridine.

Synthesis of 2'-Deoxy[6-^{15}N]*adenosine Derivative* [6d(Y=l)] *from 2'-Deoxyinosine Derivative* (4d)

The synthesis of 2'-deoxy[6-^{15}N]adenosine derivative (**6d**) was achieved as described for [6-^{15}N]adenosine derivative (**6c**). 3',5'-Di-*O*-acetyl-2'-deoxyinosine (**4d**) was, after introdusing the 3-nitro-1,2,4-triazol-1-yl group at 6-position of the hypoxanthine moiety [**5d** (X=*NT*)^{10} in 69 - 82% yield], subjected to the displacement reaction of the 3-nitro-1,2,4-triazol-1-yl group with [^{15}N]phthalimide in the presence of DBU to give 3',5'-di-*O*-acetyl-*N*^{6}-phthaloyl-2'-deoxy[6-^{15}N]adenosine [**6d** (Y=i)], followed by treatment with acetic anhydride - triethylamine and deprotection of the *N*^{6}-phthaloyl group of **6d** (Y=i) by treatment with hydrazine monohydrate to give 3',5'-di-*O*-acetyl-*N*^{6}-phthaloyl-2'-deoxy[6-^{15}N]adenosine [**6d** (Y=l) in 80% yield] (Entry 4 in Table 2).

Table 2 Synthesis of 2'-deoxycytidine (**3d**) and 2'-deoxyadenosine (**6d**) derivatives.

Entry	Starting Materials	Imide (mol. equiv.)	Base (mol. equiv.)	Time	Products	Yield (%)
1	**2d** (X=*Te*)	Phth (1.5)	Et_3N (5.0)	5 days	**3d** (Y=k)	96[a]
2	**2d** (X=*Te*)	Phth (1.5)	DBU (1.5)	1.5 h	**3d** (Y=k)	90[a]
3	**2d** (X=*Te*)	[^{15}N]Phth (1.5)	DBU (1.5)	2 h	**3d** (Y=l)	92[b]
4	**5d** (X=*NT*)	[^{15}N]Phth (3.0)	DBU (4.0)	5 days	**6d** (Y=l)	80[c]

Phth = Phthalimide [^{15}N]Phth = [^{15}N]Phthalimide

a) Yield of 2'-deoxycytidine derivative [**3d** (Y=k)] after the nucleophilic displacement reaction and deprotection of the N^4-phthaloyl group by treatment with 1:1 H_2O - pyridine for 3 days.

b) Yield of 2'-deoxy[4-^{15}N]cytidine derivative [**3d** (Y=l)] after the nucleophilic displacement reaction and deprotection of the N^4-phthaloyl group by treatment with hydrazine monohydrate for 30 min.

c) Yield of 2'-deoxy[6-^{15}N]adenosine derivative [**6d** (Y=l)] after the nucleophilic displacement reaction, treatment with acetic anhydride - triethylamine, and deprotection of the N^6-phthaloyl group by treatment with hydrazine monohydrate for 30 min.

It is thus concluded the present procedure provides very useful synthetic intermediates leading to an oligonucleotide functionalized by ^{15}N labels in the exocyclic amino groups of cytidine, 2'-deoxycytidine, adenosine and 2'-deoxyadenosine.

EXPERIMENTAL

Column chromatography was performed on silica gel (Wakogel C-300, purchased from Wako Pure Chemicals, Co. Ltd.) by the use of methanol - methylene chloride or methanol - chloroform system. Melting points were determined by a Yanagimoto Micro-melting-point apparatus, and are uncorrected. ^{1}H-N.m.r. spectra were recorded on a Varian GEMINI-300 apparatus with $CDCl_3$ or DMSO-D_6 as an internal standard. ^{15}N-N.m.r. spectra were recorded on a Brucker AM 500 apparatus with liquid $^{15}NH_3$ as an external standard. Mass spectra were recorded on a VG AutoSpecE apparatus. Elemental analyses were achieved with a Perkin-Elmer 240-002 apparatus.

4-(Tetrazol-1-yl)-1-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-pyrimedin-2(1*H*)-one [2a (X=*Te*)].[7] 2',3',5'-Tri-*O*-acetyluridine (**1a**)[12] (2.22 g, 6 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (15 mL), and 1*H*-tetrazole (841 mg, 12 mmol), diphenyl phosphate (1.80 g, 7.2 mmol) and *p*-toluenesulfonyl chloride (2.29 g, 12 mmol) were added to the solution, which was then stirred at room temperature for 1.5 days. The mixture was quenched with water (15 mL) and extracted with methylene chloride (50 mL x 2). The organic layer was, after washing with 5% aqueous sodium hydrogencarbonate solution (50 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **2a** (X=*Te*) (2.23 g, 88% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.10, 2.13, and 2.17 (3s, 9 H, $COCH_3$ x 3), 4.38-4.53 (m, 3 H, H-4', 5', and 5"), 5.29 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 5.4 Hz, H - 3'), 5.47 (dd, 1 H, $J_{1',2'}$ = 3.8 Hz, H - 2'), 6.13 (d, 1 H, H-1'), 7.26 (d, 1 H, $J_{5,6}$ = 7.2 Hz, H-5), 8.37 (d, 1 H, H-6), and 9.61 (br s, 1 H, N=C*H*-N of tetrazolyl moiety).

4-(3-Nitro-1,2,4-triazol-1-yl)-1-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)pyrimedin-2(1*H*)-one [2a (X=*NT*)].[7] 2',3',5'-Tri-*O*-acetyluridine (**1a**) (1.48 g, 4 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (10 mL), and 3-nitro-1,2,4-triazole (913 mg, 8 mmol), diphenyl phosphate (1.20 g, 4.8 mmol) and *p*-toluenesulfonyl chloride (1.53 g, 8 mmol) were added to the solution, which was then stirred at room temperature for 1.5 days. The mixture was quenched with water (10 mL) and extracted with methylene chloride (40 mL x 2). The organic layer was, after washing with 5% aqueous sodium hydrogencarbonate solution (40 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **2a** (X=*NT*) (1.75 g, 94% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.12, 2.16, and 2.17 (3s, 9 H, $COCH_3$ x 3), 4.40-4.55 (m, 3 H, H-4', 5', and 5"), 5.30 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 5.6 Hz, H-3'), 5.47 (dd, 1 H, $J_{1',2'}$ = 3.8 Hz, H-2'), 6.14 (d, 1 H, H-1'), 7.17 (d, 1 H, $J_{5,6}$ = 7.3 Hz, H-5), 8.37 (d, 1 H, H-6), and 9.34 (br s, 1H, N=C*H*-N of 3-nitro-1,2,4-triazolyl moiety).

2',3',5'-Tri-*O*-acetyl-*N*^{4}-succinylcytidine [3a (Y=e)] (Entry 1 in Table 1). Compound **2a** (X=*Te*) (211 mg, 0.5 mmol) was dissolved in dried methylene chloride (1.25 mL) and succinimide (74 mg, 0.75 mmol) and triethylamine (0.35 mL, 2.5 mmol) were added to the solution. After stirring for 1.5 days at room temperature, acetic anhydride (0.09 mL, 1 mmol) and triethylamine (0.28 mL, 2 mmol) were added to the solution, which was then stirred at room temperature for 1 h. The mixture was quenched with water (1 mL), diluted with methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **3a** (Y=e) (198 mg, 88% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.09, 2.14, and 2.17 (3s, 9 H, $COCH_3$ x 3), 2.90 (s, 4 H, $N(COCH_2)_2$), 4.36-4.47 (m, 3 H, H-4', 5', and 5"), 5.36 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 5.4 Hz, H-3'), 5.46 (dd, 1 H, $J_{1',2'}$ = 3.7 Hz, H-2'), 6.14 (d, 1 H, H-1'), 6.54 (d, 1 H, $J_{5,6}$ = 7.2 Hz, H-5), and 8.14 (d, 1 H, H-6). *Anal.* Calcd for $C_{19}H_{21}N_3O_{10} \cdot 0.5H_2O$: C, 49.57; H, 4.82; N, 9.13. Found: C, 49.61; H, 4.82; N, 9.13.

2',3',5'-Tri-*O*-acetylcytidine [3a (Y=k)] (Entry 3 in Table 1).

Compound **2a** (X=*Te*) (211 mg, 0.5 mmol) was dissolved in dried methylene chloride (1.25 mL) and phthalimide (110 mg, 0.75 mmol) and triethylamine (0.35 mL, 2.5 mmol) were added to the solution. After stirring for 1 day at room temperature, 1:1 water - pyridine solution (2 mL) was added to the solution, which was then stirred at room temperature for 1 h. The mixture was evaporated, dilssolved in methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **3a** (Y=k) (174 mg, 94% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.10 (s, 6 H, $COCH_3$ x 2), 2.13 (s, 3 H, $COCH_3$), 4.32- 4.38 (m, 3 H, H-4', 5', and 5"), 5.36 (t, 1 H, $J_{2',3'} = J_{3',4'}$ = 5.6 Hz, H-3'), 5.42 (dd, 1 H, $J_{1',2'}$ = 4.3 Hz, H-2'), 5.99 (d, 1 H, H-1'), 6.02 (d, 1H, $J_{5,6}$ = 7.6 Hz, H-5), and 7.50 (d, 1 H, H-6). *Anal.* Calcd for $C_{15}H_{19}N_3O_8 \cdot 0.1H_2O$: C, 48.54; H, 5.21; N, 11.32. Found: C, 48.46; H, 4.99; N, 11.38.

4-(Tetrazol-1-yl)-1-[3',5'-di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)-β-D-ribofuranosyl]pyrimedin-2(1*H*)-one [2b (X=*Te*)]. 3',5'-Di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)uridine (**1b**) (3.00 g, 5.6 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (14 mL), and 1*H*-tetrazole (785 mg, 11.2 mmol), diphenyl phosphate (1.68 g, 6.72 mmol) and *p*-toluenesulfonyl chloride (2.14 g, 11.2 mmol) were added to the solution, which was then stirred at room temperature for 8 h. The mixture was quenched with water (15 mL) and extracted with methylene chloride (50 mL x 2). The organic layer was, after washing with 5% aqueous sodium hydrogencarbonate solution (50 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **2b** (X=*Te*) (2.76 g, 84% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 1.40-1.80 (m, 6 H, CCH_2C x 3), 3.26-3.33, 3.45-3.60, and 3.76-3.83 (3m, 2 H, OCH_2C), 4.66-4.95 and 5.10-5.14 (2m, 5 H, H - 2', 4', 5', 5", and OC*H*(O)C), 5.38 (dd, *J* = 5.6 and 8.0 Hz, H-3'), 5.57 (t, $J_{2',3'} = J_{3',4'}$ = 5.9 Hz, H-3'), 6.10 and 6.28 (2d, 1 H, $J_{1',2'}$ = 1.4 and 3.6 Hz, H-1'), 6.95 and 7.00 (2d, 1 H, $J_{5,6}$ = 7.2 Hz, H-5), 7.45-7.68 and 8.04-8.08 (2m, 10 H, Ph-*H*), 8.31 and 8.53 (2d, 1 H, H-6), and 9.60 (s, 1 H, N=C*H*-N of tetrazolyl moiety). *Anal.* Calcd for $C_{29}H_{28}N_6O_8 \cdot 0.2H_2O$: C, 58.82; H, 4.80; N, 14.19. Found: C, 58.84; H, 4.62; N, 14.28.

3',5'-Di-*O*-benzoyl-*N*^{4}-succinyl-2'-*O*-(tetrahydropyran-2-yl)-cytidine [3b (Y=e)] (Entry 5 in Table 1). Compound **2b** (X=*Te*) (294 mg, 0.5

mmol) was dissolved in dried methylene chloride (2.5 mL) and succinimide (99 mg, 0.1 mmol) and triethylamine (0.35 mL, 2.5 mmol) were added to the solution. After stirring for 3 days at room temperature, acetic anhydride (0.09 mL, 1 mmol) and triethylamine (0.28 mL, 2 mmol) were added to the solution, which was then stirred at room temperature for 1 h. The mixture was quenched with water (1 mL), diluted with methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **3b** (Y=e) (251 mg, 81% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 1.40-1.80 (m, 6 H, CCH_2C x 3), 2.87 (s, 4 H, $N(COCH_2)_2$), 3.20-3.30, 3.43-3.56, and 3.68-3.78 (3m, 2 H, OCH_2C), 4.66-4.95 and 5.10-5.14 (2m, 5 H, H-2', 4', 5', 5'', and OC*H*(O)C), 5.43 (dd, J = 5.7 and 8.4 Hz, H-3'), 5.58 (t, $J_{2',3'}$ = $J_{3',4'}$ = 6.1 Hz, H-3'), 6.05 (s, H-1'), 6.23 (d, $J_{1',2'}$ = 3.6 Hz, H-1'), 6.29 and 6.32 (2d, 1 H, $J_{5,6}$ = 7.2 Hz, H-5), 7.42-7.62 and 8.01-8.04 (2m, 10 H, Ph-*H*), 8.10 and 8.34 (2d, 1 H, H-6). *Anal.* Calcd for $C_{32}H_{31}N_3O_{10} \cdot 0.7H_2O$: C, 60.99; H, 5.18; N, 6.67. Found: C, 61.02; H, 5.31; N, 6.65.

3',5'-Di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)cytidine [3b (Y=k)] (Entry 7 in Table 1). Compound **2b** (X=*Te*) (294 mg, 0.5 mmol) was dissolved in dried methylene chloride (2.5 mL) and phthalimide (110 mg, 0.75 mmol) and triethylamine (0.35 mL, 2.5 mmol) were added to the solution. After stirring for 1 day at room temperature, 1:1 water - pyridine solution (2 mL) was added to the solution, which was then stirred at room temperature for 1 h. The mixture was evaporated, dilssolved in methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **3b** (Y=k) (256 mg, 96% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 1.36-1.75 (m, 6 H, CCH_2C x 3), 3.28-3.45 and 3.55-3.70 (2m, 2 H, OCH_2C), 4.56-4.81 and 4.99-5.03 (2m, 5 H, H-2', 4', 5', 5'', and OC*H*(O)C), 5.46 (dd, J = 5.7 and 7.2 Hz, H-3'), 5.62 (t, $J_{2',3'}$ = $J_{3',4'}$ = 5.4 Hz, H-3'), 5.72 and 5.82 (2d, 1 H, $J_{5,6}$ = 7.2 Hz, H-5), 6.09 and 6.11 (2d, $J_{1',2'}$ = 5.0 and 3.0 Hz, H-1'), 7.40-7.64 and 8.02-8.10 (2m, 11 H, Ph-*H* and H-6). *Anal.* Calcd for $C_{28}H_{29}N_3O_8 \cdot 0.2H_2O$: C, 62.37; H, 5.50; N, 7.79. Found: C, 62.37; H, 5.25; N, 7.91.

3',5'-Di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)[4-^{15}N]cytidine [3b (Y=l)] (Entry 9 in Table 1). Compound **2b** (X=*Te*) (1.18 g, 2 mmol) was dissolved in dried methylene chloride (10 mL) and [^{15}N]phthalimide (444 mg, 3 mmol;

99.6% ^{15}N-enriched, purchased from Shoko Co. Ltd.) and triethylamine (1.4 mL, 10 mmol) were added to the solution. After stirring for 1 day at room temperature, 1:1 water - pyridine solution (8 mL) was added to the solution, which was then stirred at room temperature for 1 h. The mixture was evaporated, dilssolved in methylene chloride (50 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (25 mL x 2) and water (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **3b** (Y=l) (1.03 g, 96% yield); ^{1}H-n.m.r. (CDCl$_3$): δ 1.26-1.74 (m, 6 H, CCH_2C x 3), 3.27-3.43 and 3.56-3.70 (2m, 2 H, OCH_2C), 4.56-4.78 and 4.98-5.02 (2m, 5 H, H-2', 4', 5', 5'', and OCH(O)C), 5.46 (dd, J = 5.4 and 7.2 Hz, H-3'), 5.63 (t, $J_{2',3'}$ = $J_{3',4'}$ = 5.4 Hz, H-3'), 5.76 and 5.87 (2d, 1 H, $J_{5,6}$ = 7.2 Hz, H-5), 6.07 and 6.11 (2d, $J_{1',2'}$ = 4.9 and 2.8 Hz, H-1'), 7.39-7.63 and 8.02-8.10 (2m, 11 H, Ph-H and H-6); ^{15}N-n.m.r. (CDCl$_3$): δ 98.18 (N^4); Low-resolution FAB mass spectrum, m / z 537.2 (M+H)$^+$.

N^4-Benzoyl-2'-*O*-(tetrahydropyran-2-yl)[4-^{15}N]cytidine[3c (Y=m)].

Compound **3b** (Y=l) (1.03 g, 1.92 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (9.6 mL), and benzoyl chloride (0.33 mL, 2.88 mmol) was added to the solution, which was then stirred at room temperature for 30 min. The mixture was quenched with water (2 mL), diluted with methylene chloride (40 mL) and washed with 5% aqueous sodium hydrogencarbonate solution (20 mL x 2) and water (20 mL). The organic layer was evaporated and the residue was dissolved in 1:2 pyridine - ethanol solution (9.6 mL). The solution was added 2M aqueous sodium hydroxide solution (3 mL) under cooling in an ice-bath. After stirring for 15 min at 0 °C , the resulting mixture was neutralized with Dowex 50Wx8 (H$^+$ form). The resin was filtrated off and washed with 2:1 ethanol - pyridine (*ca.* 50 mL). The filtrate and the washings were combined and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **3c** (Y=m) (the less polar diastereoisomer, 204 mg, and the more polar diastereoisomer, 464 mg, 80% yield); ^{1}H-n.m.r. (CDCl$_3$): δ for the less polar diastereoisomer 1.45-1.60 (m, 6 H, CCH_2C x 3), 3.46-3.55 (m, 2 H, OCH_2C), 3.80 and 4.00 (2dd, 2 H, $J_{4',5'}$ = $J_{4',5''}$ = 1.9 Hz, $J_{5',5''}$ = 12.7 Hz, H-5'and 5''), 4.08-4.11 (m, 1 H, H-4'), 4.19 (dd, 1 H, $J_{2',3'}$ = 4.9 Hz, $J_{3',4'}$ = 6.6 Hz, H-3'), 4.43 (dd, 1 H, $J_{2',3'}$ = 2.7 Hz, H-2'), 4.78 - 4.90 (m, 1 H, OCH(O)C), 5.77 (d,1 H, H-1'), 7.45-7.59 and 7.92-7.95 (2m, 6 H, Ph-H and H-5), and 8.08 (d, 1 H, $J_{5,6}$ = 7.6 Hz, H-6); Low-resolution FAB mass spectrum, m / z 433.2 (M+H)$^+$, and ^{1}H-n.m.r. (CDCl$_3$): δ for the more polar diastereoisomer 1.45-1.86 (m, 6 H, CCH_2C x 3), 3.38-3.48 (m, 2

H, OCH_2C), 3.77 and 3.95 (2dd, 2H, $J_{4',5'} = J_{4',5''} = 2.2$ Hz, $J_{5',5''} = 12.4$ Hz, H-5'and 5"), 4.12-4.14 (m, 1 H, H-4'), 4.41 (t, 1 H, $J_{2',3'} = J_{3',4'} = 5.2$ Hz, H-3'), 4.67 (dd, 1 H, $J_{2',3'} = 4.3$ Hz, H-2'), 4.74-4.77 (m, 1 H, OC*H*(O)C), 5.82 (d,1 H, H-1'), 7.46-7.61 and 7.94-7.97 (2m, 6 H, Ph-*H* and H-5), and 8.08 (d, 1 H, $J_{5,6} = 7.4$ Hz, H-6); Low-resolution FAB mass spectrum, m / z 433.4 $(M+H)^+$.

6-(3-Nitro-1,2,4-triazol-1-yl)-9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine [5a (X=*NT*)].[10] 1) 2',3',5'-Tri-*O*-acetylinosine (**4a**)[13] (1.97 g, 5 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (25 mL), and 3-nitro-1,2,4-triazole (1.14 g, 10 mmol), diphenyl phosphate (1.50 g, 6 mmol) and *p*-toluene- sulfonyl chloride (1.91 g, 10 mmol) were added to the solution, which was then stirred at room temperature for 7 days. The mixture was quenched with water (10 mL) and extracted with methylene chloride (40 mL x 2). The organic layer was, after washing with 5% aqueous sodium hydrogencarbonate solution (40 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **5a** (X=*NT*) (2.060 g, 84% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.11, 2.16, and 2.19 (3s, 9 H, COCH_3 x 3), 4.40-4.55 (m, 3 H, H-4', 5', and 5"), 5.66 (t, 1 H, H-3'), 5.97 (t, 1 H, H-2'), 6.32 (d, 1 H, $J_{1',2'} = 5.0$ Hz , H-1'), 8.48 (s, 1 H, H-2), 9.02 (s, 1 H, H-8), and 9.81 (s, 1 H, N=C*H*-N of 3-nitro-1,2,4-triazolyl moiety).

2) The reaction of **4a** (757 mg, 2.0 mmol) with 3-nitro-1,2,4-triazole (684 mg, 6.0 mmol), diphenyl phosphate (601 mg, 2.4 mmol), and *p*-toluenesulfonyl chloride (763 mg, 4.0 mmol) in dried pyridine (10 mL) at 50°C for 23 h, which was worked up similarly as above, gave **5a** (X=*NT*) in 92% (869 mg) yield.

2',3',5'-Tri-*O*-acetyl-N^6-succinyladenosine [6a (Y=e)] (Entry 11 in Table 1). Compound **5a** (X=*NT*) (245 mg, 0.5 mmol) was dissolved in dried methylene chloride (1.25 mL) and succinimide (99 mg, 1 mmol) and DBU (0.23 mL, 1.5 mmol) were added to the solution. After stirring for 2 days at room temperature, acetic anhydride (0.09 mL, 1 mmol) and triethylamine (0.28 mL, 2 mmol) were added to the solution, which was then stirred at room temperature for 1 h. The mixture was quenched with water (1 mL), diluted with methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **6a** (Y=e) (143 mg, 60% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.10, 2.13, and 2.17 (3s, 9 H, COCH_3 x 3), 3.05 (s, 4 H, N(CH_2)$_2$), 4.40-4.50 (m, 3 H, H-4', 5', and 5"), 5.65 (dd, 1 H, $J_{3',4'} = 4.1$ Hz, H-3'), 5.99 (t, 1 H, $J_{1',2'} = J_{2',3'} = 5.6$ Hz, H-2'), 6.30 (d, 1 H, H-1'), 8.34 (s, 1 H, H-2), and

9.05 (s, 1 H, H-8). *Anal.* Calcd for $C_{20}H_{21}N_5O_9 \cdot 0.5H_2O$: C, 49.59; H, 4.58; N, 14.46. Found: C, 49.30; H, 4.34; N, 14.90.

2',3',5'-Tri-*O*-acetyl-*N*^{6}-phthaloyladenosine [6a (Y=g)] (Entry 13 in Table 1). Compound **5a** (X=*NT*) (245 mg, 0.5 mmol) was dissolved in dried methylene chloride (1.25 mL) and phthalimide (147 mg, 1 mmol) and DBU (0.23 mL, 1.5 mmol) were added to the solution. After stirring for 1 days at room temperature, acetic anhydride (0.09 mL, 1 mmol) and triethylamine (0.28 mL, 2 mmol) were added to the solution, which was then stirred at room temperature for 1 h. The mixture was quenched with water (1 mL), diluted with methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **6a** (Y=g) (0.194 g, 74% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.10, 2.13, and 2.17 (3s, 9 H, $COCH_3$ x 3), 4.40-4.55 (m, 3 H, H-4', 5', and 5"), 5.68 (dd, 1 H, $J_{3',4'}$ = 4.1 Hz, H-3'), 6.02 (t, 1 H, $J_{1',2'} = J_{2',3'}$ = 5.6 Hz, H-2'), 6.32 (d, 1 H, H-1'), 7.83-7.85 and 8.03-8.05 (2m, 4 H, Ph-*H*), 8.33 (s, 1 H, H-2), and 9.08 (s, 1 H, H-8). *Anal.* Calcd for $C_{24}H_{21}N_5O_9 \cdot H_2O$: C, 53.24; H, 4.28; N, 12.93. Found: C, 53.42; H, 4.01; N, 12.65.

6-(3-Nitro-1,2,4-triazol-1-yl)-9-[3',5'-di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)-β-D-ribofuranosyl]-9*H*-purine [5b (X=*NT*)]. 1) 3',5'-Di-*O*-benzoyl-2'-*O*-(tetrahydropyran-2-yl)inosine (**4b**) (2.80 g, 5 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (10 mL), and 3-nitro-1,2,4-triazole (1.14 g, 10 mmol), diphenyl phosphate (1.50 g, 6 mmol) and *p*-toluenesulfonyl chloride (1.91 g, 10 mmol) were added to the solution, which was then stirred at room temperature for 7 days. The mixture was quenched with water (10 mL) and extracted with methylene chloride (40 mL x 2). The organic layer was, after washing with 5% aqueous sodium hydrogencarbonate solution (40 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **5b** (X=*NT*) (2.43 g, 79% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 1.30-1.70 (m, 6 H, CCH_2C x 3), 3.14-3.22, 3.30-3.45, and 3.67-3.76 (3m, 2 H, OCH_2C), 4.61-4.90 (m, 4 H, H-4', 5', 5", and OCH(O)C), 5.41 and 5.48 (2t, 1 H, $J_{1',2'} = J_{2',3'}$ = 5.7 and 5.5 Hz, H-2'), 5.87 and 5.92 (2dd, 1 H, $J_{2',3'}$ = 5.5 Hz, $J_{3',4'}$ = 4.3 Hz, H-3'), 6.35 and 6.36 (2d, 1 H, $J_{1',2'}$ = 5.7 and 5.5 Hz, H-1'), 7.44-7.68 (m, 6 H, Ph-*H*), 8.06-8.18 (m, 4 H, Ph-*H*), 8.42 and 8.46 (2s, 1 H, H-2), 8.77 and 8.80 (2s, 1 H, H-8), and 9.78 (s, 1 H, N=C*H*-N of 3-nitro-1,2,4-triazolyl moiety). *Anal.* Calcd for $C_{31}H_{28}N_8O_7 \cdot 0.3H_2O$: C, 56.24; H, 4.35; N, 16.93. Found: C, 56.25; H, 4.17; N, 16.95.

2) The reaction of **4b** (419 mg, 0.75 mmol) with 3-nitro-1,2,4-triazole (256 mg, 2.25 mmol), diphenyl phosphate (225 mg, 1.50 mmol), and *p*-toluenesulfonyl chloride (285 mg, 1.50 mmol) in dried pyridine (3.25 mL) at 50°C for 24.75 h, which was worked up similarly as above, gave **5b** (X=*NT*) in 80% (393 mg) yield.

3',5'-Di-*O*-benzoyl-*N*^{6}-succinyl-2'-*O*-(tetrahydropyran-2-yl)-adenosine [6b (Y=e)] (Entry 14 in Table 1). Compound **5b** (X=*NT*) (328 mg, 0.5 mmol) was dissolved in dried methylene chloride (1.25 mL) and succinimide (99 mg, 1 mmol) and DBU (0.23 mL, 1.5 mmol) were added to the solution. After stirring for 1 day at room temperature, acetic anhydride (0.09 mL, 1 mmol) and triethylamine (0.28 mL, 2 mmol) were added to the solution, which was then stirred at room temperature for 1 h. The mixture was quenched with water (1 mL), diluted with methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **6b** (Y=e) (231 mg, 72% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 1.30-1.70 (m, 6 H, CCH_2C x 3), 3.05 (s, 4 H, $N(COCH_2)_2$), 3.15-3.34, 3.38-3.47, and 3.70-3.78 (3m, 2 H, OCH_2C), 4.59-4.85 (m, 4 H, H-4', 5', 5'', and $OCH(O)C$), 5.38 and 5.53 (2t, 1 H, $J_{1',2'} = J_{2',3'}$ = 6.0 Hz, H-2'), 5.86 and 5.91 (2dd, 1 H, $J_{3',4'}$ = 3.3 and 3.9 Hz, H-3'), 6.31 (d, 1 H, H-1'), 7.41-7.65 (m, 6 H, Ph-*H*), 8.04-8.16 (m, 4 H, Ph-*H*), 8.34 and 8.36 (2s, 1 H, H-2), 8.80 and 8.89 (2s, 1 H, H-8). *Anal.* Calcd for $C_{33}H_{31}N_5O_9 \cdot 1.5H_2O$: C, 59.28; H, 5.12; N, 10.47. Found: C, 59.19; H, 4.87; N, 10.39.

3',5'-Di-*O*-benzoyl-*N*^{6}-phthaloyl-2'-*O*-(tetrahydropyran-2-yl)-adenosine [6b (Y=g)] (Entry 15 in Table 1). Compound **5b** (X=*NT*) (328 mg, 0.5 mmol) was dissolved in dried methylene chloride (1.25 mL) and phthalimide (147 mg, 1 mmol) and DBU (0.23 mL, 1.5 mmol) were added to the solution. After stirring for 1 day at room temperature, acetic anhydride (0.09 mL, 1 mmol) and triethylamine (0.28 mL, 2 mmol) were added to the solution, which was then stirred at room temperature for 1 h. The mixture was quenched with water (1 mL), diluted with methylene chloride (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **6b** (Y=g) (304 mg, 88% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 1.30-1.70 (m, 6 H, CCH_2C x 3), 3.13-3.22, 3.25-3.34, 3.38-3.46, and 3.67-3.78 (4m, 2 H, OCH_2C), 4.60-4.89 (m, 4 H, H-4', 5', 5'', and $OCH(O)C$), 5.43 and 5.57 (2t, 1 H, $J_{1',2'} = J_{2',3'}$ = 6.1 Hz, H-2'), 5.89 and 5.95 (2dd, 1 H, $J_{3',4'}$ = 3.1

and 3.8 Hz, H-3'), 6.35 (d, 1 H, H-1'), 7.43-7.68, 7.83-7.86 and 8.01-8.20 (3m, 14 H, Ph-*H*), 8.31 (s, 1 H, H-2), 8.85 and 8.93 (2s, 1 H, H-8). *Anal.* Calcd for $C_{37}H_{31}N_5O_9$: C, 64.44; H, 4.53; N, 10.15. Found: C, 64.27; H, 4.57; N, 10.02.

3',5'-Di-*O*-benzoyl-*N*^{6}-phthaloyl-2'-*O*-(tetrahydropyran-2-yl)[6-^{15}N]-adenosine [6b (Y=i)] (Entry 16 in Table 1). Compound **5b** (X=*NT*) (1.31 g, 2 mmol) was dissolved in dried methylene chloride (4 mL) and [^{15}N]phthalimide (593 mg, 4 mmol; 99.6% ^{15}N-enriched, purchased from Shoko Co. Ltd.) and DBU (0.9 mL, 6 mmol) were added to the solution. After stirring for 2 days at room temperature, acetic anhydride (0.38 mL, 4 mmol) and triethylamine (1.12 mL, 8 mmol) were added to the solution, which was then stirred at room temperature for 1 h. The mixture was quenched with water (4 mL), diluted with methylene chloride (50 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (25 mL x 2) and water (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give a mixture of the diastereoisomers of **6b** (Y=i) (1.38 g, 99% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 1.30-1.74 (m, 6 H, CCH_2C x 3), 3.14-3.22, 3.25-3.34, 3.36-3.46, and 3.70-3.80 (4m, 2 H, OCH_2C), 4.60-4.90 (m, 4 H, H-4', 5', 5'', and OC*H*(O)C), 5.43 and 5.57 (2t, 1 H, $J_{1',2'} = J_{2',3'}$ = 6.0 Hz, H-2'), 5.89 and 5.94 (2dd, 1 H, $J_{3',4'}$ = 3.1 and 4.0 Hz, H-3'), 6.35 (d, 1 H, H-1'), 7.43-7.64, 7.83-7.87 and 8.01-8.19 (3m, 14 H, Ph-*H*), 8.31 (s, 1 H, H-2), 8.85 and 8.93 (2s, 1 H, H-8); ^{15}N-n.m.r. ($CDCl_3$): δ 172.03 (N^6); Low-resolution FAB mass spectrum, m / z 690.8 $(M+H)^+$.

***N*^{6}-Phthaloyl-2'-*O*-(tetrahydropyran-2-yl)[6-^{15}N]adenosine [6c (Y=i)]**:

Compound **6b** (Y=i) (1.38 g, 1.99 mmol) was dissolved in 1:2 pyridine - ethanol solution (9.6 mL). The solution was added 2M aqueous sodium hydroxide solution (3 mL) under cooling in an ice-bath. After stirring for 1 h at 0 °C , the resulting mixture was neutralized with Dowex 50Wx8 (H^+ form). The resin was filtrated off and washed with 2 : 1 ethanol - pyridine (*ca.* 50 mL). The filtrate and the washings were combined and evaporated. The residue was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (8 mL), and trifluoroacetic anhydride (1.41 mL, 10 mmol) were added to the solution, which was then stirred at room temperature for 30 min. The mixture was quenched with water (1 mL) and diluted with methylene chloride (50 mL) and washed with 5% aqueous sodium hydrogencarbonate solution (25 mL x 2) and water (25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - methylene chloride eluants to give **6c** (Y=i) (the less polar diastereoisomer, 158 mg, diastereoisomer mixture, 322 mg, and the more polar diastereoisomer, 91 mg, 59% yield); ^{1}H-n.m.r. ($CDCl_3$): δ for the less polar diastereoisomer 1.40-1.85 (m, 6 H, CCH_2C x 3), 3.40-3.53 (m, 2 H, OCH_2C), 3.97-4.05 (m, 2 H, H-5' and 5''), 4.37-4.42 (m, 2 H, H-4' and OC*H*(O)C), 4.58 (t, 1 H, $J_{2',3'} = J_{3',4'} = 4.7$ Hz, H-3'), 4.92 (dd, 1 H, $J_{1',2'} = 7.7$ Hz, H-2'), 6.03 (d, 1 H, H-1'), 7.85-7.88 and 8.02-8.06 (2m, 4 H, Ph-*H*), 8.23 (s, 1 H, H-2), and 9.06 (s, 1 H, H-8); Low-resolution FAB mass spectrum, m / z 483.3 $(M+H)^+$, and ^{1}H-n.m.r. ($CDCl_3$): δ for the more polar diastereoisomer 1.34-1.80 (m, 6 H, CCH_2C x 3), 2.93-2.99 and 3.32-3.37 (2m, 2 H, OCH_2C), 3.79-3.84 and 3.99-4.04 (2m, 2 H, H-5' and 5''), 4.36-4.40 (m, 2 H, H-4' and OC*H*(O)C), 4.61 (t, 1 H, $J_{2',3'} = J_{3',4'} = 5.0$ Hz, H-3'), 5.10 (dd, 1 H, $J_{1',2'} = 7.2$ Hz, H-2'), 6.08 (d, 1 H, H-1'), 7.84-7.87 and 8.01-8.05 (2m, 4 H, Ph-*H*), 8.22 (s, 1 H, H-2), and 9.05 (s, 1 H, H-8); Low-resolution FAB mass spectrum, m / z 483.3 $(M+H)^+$.

4-(Tetrazol-1-yl)-1-(3',5'-di-*O*-acetyl-2'-deoxy-β-D-ribofuranosyl)-pyrimedin-2(1*H*)-one [2d (X=*Te*)].[7] 2'-Deoxyuridine (1.14 g, 5.0 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (25 mL), and acetic anhydride (2.83 mL, 30 mmol) was added to the solution, which was then stirred at room temperature for 12 h. The mixture was evaporated and dissolved in chloroform (100 mL). The organic solution was, after washing with 5% aqueous sodium hydrogencarbonate solution (50 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - chloroform eluants to give 3',5'-di-*O*-acetyl-2'-deoxyuridine (**1d**) (1.50 g, 96% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.10-2.20 (m, 1 H, H-2'), 2.11 and 2.12 (2s, 6 H, $COCH_3$ x 2), 2.54 (ddd, 1 H, $J_{1',2''} = 5.6$ Hz, $J_{2',2''} = 14.2$ Hz, $J_{2'',3'} = 2.0$ Hz, H-2''), 4.26-4.36 (m, 3 H, H-4', 5', and 5''), 5.20-5.24 (m, 1 H, H-3'), 5.79(d, 1 H, $J_{5,6} = 8.2$ Hz, H-5), 6.29 (dd, 1 H, $J_{1',2'} = 8.3$ Hz, $J_{1',2''} = 5.6$ Hz, H-1'), 7.50 (d, 1 H, H-6), and 9.21 (br s, 1 H, N^3-*H*).

Compound **1d** (2.30 g, 7.4 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (18.4 mL), and 1*H*-tetrazole (1.03 g, 14.7 mmol), diphenyl phosphate (2.21 g, 8.85 mmol) and *p*-toluenesulfonyl chloride (2.81 g, 14.7 mmol) were added to the solution, which was then stirred at room temperature for 12 h. The mixture was quenched with water (10 mL) and extracted with chloroform (50 mL x 2). The organic layer was, after washing with 5% aqueous sodium hydrogencarbonate solution (50 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - chloroform eluants to give **2d** (X=*Te*) (2.62 g, 97% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.09, and 2.13 (2s, 6 H, $COCH_3$ x 2), 2.11-2.20 (m, 1 H, H-2'), 2.98 (ddd, 1 H, $J_{1',2''} = 5.8$ Hz, $J_{2',2''} = 14.5$ Hz, $J_{2'',3'}$

= 2.4 Hz, H-2"), 4.37-4.46 (m, 3 H, H-4', 5', and 5"), 5.23-5.26 (m, 1 H, H-3'), 6.25 (dd, 1 H, $J_{1',2'}$ = 7.4 Hz, $J_{1',2''}$ = 5.8 Hz, H-1'), 7.25 (d, 1 H, $J_{5,6}$ = 7.3 Hz. H-5), 8.45 (d, 1 H, H-6), and 9.60 (br s, 1 H, N=C*H*-N of tetrazolyl moiety). *Anal.* Calcd for $C_{14}H_{16}N_6O_6 \cdot 0.5H_2O$: C, 45.04; H, 4.59; N, 22.51. Found: C, 45.26; H, 4.32; N, 22.65.

3',5'-Di-*O*-acetyl-2'-deoxycytidine [3d (Y=k)]. 1) Compound **2d** (X=*Te*) (0.364 g, 1.0 mmol) was dissolved in dried methylene chloride (5 mL) and phthalimide (221 mg, 1.5 mmol) and triethylamine (0.70 mL, 5.0 mmol) were added to the solution. After stirring for 5 days at room temperature, 1:1 H_2O - pyridine (3 mL) was added to the solution, which was then stirred at room temperature for 3 days. After evaporation the residue was subjected to chromatography on a column of silica gel with methanol - chloroform eluants to give **3d** (Y=k) (300 mg, 96% yield) (Entry 1 in Table 2); ^{1}H-n.m.r. ($CDCl_3$): δ 2.04-2.16 (m, 1 H, H-2'), 2.09 and 2.10 (2s, 6 H, COC*H*$_3$ x 2), 2.25-2.31 (m, 1 H, H-2"), 4.28-4.35 (m, 3 H, H-4', 5', and 5"), 5.19-5.22 (m, 1 H, H-3'), 5.78 (d, 1 H, $J_{5,6}$ = 7.4 Hz, H-5), 6.17 (dd, 1 H, $J_{1',2'}$ = 8.0 Hz, $J_{1',2''}$ = 5.5 Hz, H-1'), and 7.60 (d, 1 H, H-6). *Anal.* Calcd for $C_{13}H_{17}N_3O_6 \cdot 0.5H_2O$: C, 48.75; H, 5.35; N, 13.12. Found: C, 48.45; H, 5.36; N, 13.43.

2) Compound **2d** (X=*Te*) (364 mg, 1.0 mmol) was dissolved in dried methylene chloride (5 mL) and phthalimide (221 mg, 1.5 mmol) and DBU (0.22 mL, 1.5 mmol) were added to the solution. After stirring for 1.5 h at room temperature, 1:1 H_2O - pyridine (3 mL) was added to the solution, which was then stirred at room temperature for 3 days. After evaporation the residue was subjected to chromatography on a column of silica gel with methanol - chloroform eluants to give **3d** (Y=k) (281 mg, 90% yield) (Entry 2 in Table 2).

3',5'-Di-*O*-acetyl-2'-deoxy[4-^{15}N]cytidine [3d (Y=l)] (Entry 3 in Table 2). Compound **2d** (X=*Te*) (364 mg, 1.0 mmol) was dissolved in dried methylene chloride (5 mL) and [^{15}N]phthalimide (222 mg, 1.5 mmol, 99.6% ^{15}N-enriched, purchased from Shoko Co. Ltd.) and DBU (0.22 mL, 1.5 mmol) were added to the solution. After stirring for 2 h at room temperature, hydrazine monohydrate (0.12 mL, 2.5 mmol) was added to the solution, which was then stirred at room temperature for 30 min. Acetone (2 mL) was added to the solution. After stirring for 30 min at room temperature,the mixture was evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - chloroform eluants to give **3d** (Y=l) (286 mg, 92% yield); ^{1}H-n.m.r. (DMSO-d_6): δ 2.04 and 2.06 (2s, 6 H, COC*H*$_3$ x 2), 2.25-2.31 (m, 2 H, H-2' and 2"), 4.14-4.17 (m, 1 H, H-4'), 4.21-4.25 (m, 2 H, H-5', and 5"), 5.15-5.18 (m, 1 H, H-3'), 5.78 (d, 1 H, $J_{5,6}$ = 7.5 Hz, H-5), 6.17 (dd, 1 H, $J_{1',2'}$ = 7.8 Hz, $J_{1',2''}$ = 6.4 Hz, H-1'), 7.21 (d, 2 H, $J_{^{15}N,H}$ = 92.4 Hz, ^{15}N-*H*$_2$), and 7.59 (d, 1 H, H-6); ^{15}N-n.m.r. ($CDCl_3$): δ 91.19 (N^4); EI mass spectrum, m / z 313 (M^+).

6-(3-Nitro-1,2,4-triazol-1-yl)-9-(3',5'-di-*O*-acetyl-2'-deoxy-β-D-ribofuranosyl)-9*H*-purine [5d (X=*NT*)].[10] 2'-Deoxyinosine (3.78 g, 15 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (75 mL), and acetic anhydride (5.66 mL, 60 mmol) was added to the solution. After stirring for 12 h at room temperature,the mixture was evaporated. The residue was recrystallized from ethanol to give 3',5'-di-*O*-acetyl-2'-deoxyinosine (**4d**) (4.94 g, 99% yield); m.p. 189 - 192 °C; ^{1}H-n.m.r. ($CDCl_3$): δ 2.10 and 2.14 (2s, 6 H, $COCH_3$ x 2), 2.65 (ddd, 1 H, $J_{1',2''}$ = 6.8 Hz, $J_{2',2''}$ = 14.3 Hz, $J_{2'',3'}$ = 2.5 Hz, H-2"), 2.90 (dt, 1 H, $J_{1',2'}$ = $J_{2',3'}$ = 6.8 Hz, H-2'), 4.33-4.42 (m, 3 H, H-4', 5', and 5"), 5.41-5.43 (m, 1 H, H-3'), 6.29 (t, 1 H, $J_{1',2'}$ = $J_{1',2''}$ = 6.8 Hz, H-1'), 8.03 (s, 1 H, H-2), 8.26 (s, 1 H, H-8), and 13.07 (br s, 1 H, N^1-*H*).

1) Compound **4d** (1.67 g, 5.0 mmol) was, after azeotropic evaporation from pyridine (5 mL x 3), dissolved in dried pyridine (25 mL), and 3-nitro-1,2,4-triazole (1.14 g, 10 mmol), diphenyl phosphate (1.50 g, 6 mmol) and *p*-toluenesulfonyl chloride (1.91 g, 10 mmol) were added to the solution, which was then stirred at room temperature for 8 days. The mixture was quenched with water (10 mL) and extracted with chloroform (50 mL x 2). The organic layer was, after washing with 5% aqueous sodium hydrogencarbonate solution (50 mL x 2) and water (50 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was then subjected to chromatography on a column of silica gel with methanol - chloroform eluants to give **5d** (X=*NT*) (1.49 g, 69% yield); ^{1}H-n.m.r. ($CDCl_3$): δ 2.10 and 2.17 (2s, 6 H, $COCH_3$ x 2), 2.76 (ddd, 1 H, $J_{1',2''}$ = 6.1 Hz, $J_{2',2''}$ = 14.2 Hz, $J_{2'',3'}$ = 2.7 Hz, H-2"), 3.00 (ddd, 1 H, $J_{1',2'}$ = 7.6 Hz, $J_{2',3'}$ = 6.5 Hz, H-2'), 4.41-4.43 (m, 3 H, H-4', 5', and 5"), 5.46-5.49 (m, 1 H, H-3'), 6.32 (dd, 1 H, $J_{1',2'}$ = 7.6 Hz , $J_{1',2''}$ = 6.1 Hz, H-1'), 8.49 (s, 1 H, H-2), 9.00 (s, 1 H, H-8), and 9.81 (s, 1 H, N=C*H*-N of 3-nitro-1,2,4-triazolyl moiety). *Anal.* Calcd for $C_{16}H_{16}N_8O_7$: C, 44.45; H, 3.73; N, 25.92. Found: C, 44.38; H, 3.67; N, 25.83.

2) The reaction of **4d** (623 mg, 2.0 mmol) with 3-nitro-1,2,4-triazole (684 mg, 6.0 mmol), diphenyl phosphate (601 mg, 2.4 mmol), and *p*-toluenesulfonyl chloride (763 mg, 4.0 mmol) in dried pyridine (10 mL) at 50°C for 21.5 h, which was worked up similarly as above, gave **5d** (X=*NT*) in 82% (711 mg) yield.

3',5'-Di-*O*-acetyl-2'-deoxy[6-^{15}N]adenosine [6d (Y=I)] (Entry 4 in Table 2). Compound **5d** (X=*NT*) (216 mg, 0.5 mmol) was dissolved in dried methylene chloride (2.5 mL) and [^{15}N]phthalimide (221 mg, 1.5 mmol, 99.6% ^{15}N-enriched, purchased from Shoko Co. Ltd.) and DBU (0.3 mL, 2.0 mmol) were added to the solution. After stirring for 5 days at room temperature, acetic anhydride (0.19 mL, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol) were added to the solution, which was then stirred at room temperature for 2 h. The mixture was quenched with water (1 mL), diluted with chloroform (30 mL), and washed with 5% aqueous sodium hydrogencarbonate solution (15 mL x 2) and water (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was dissolved in dried methylene chloride (4 mL) and hydrazine monohydrate (0.08 mL, 1.5 mmol) was added to the solution, which was then stirred at room temperature for 30 min. Acetone (1 mL) was added to the solution. After stirring for 30 min at room temperature, the mixture was evaporated, and then subjected to chromatography on a column of silica gel with methanol - chloroform eluants to give **6d** (Y=I) (141 mg, 80% yield); ^{1}H-n.m.r. (CDCl$_3$): δ 2.09 and 2.12 (2s, 6 H, COCH_3 x 2), 2.62 (ddd, 1 H, $J_{1',2''}$ = 5.8 Hz, $J_{2',2''}$ = 14.2 Hz, $J_{2'',3'}$ = 2.5 Hz, H-2"), 2.95 (ddd, 1 H, $J_{1',2'}$ = 8.0 Hz, $J_{2',3'}$ = 6.4 Hz, H-2'), 4.33-4.43 (m, 3 H, H-4', 5', and 5"), 5.41-5.45 (m, 1 H, H-3'), 5.90 (d, 2H, $J_{^{15}N,H}$ = 90.3 Hz, ^{15}N-H_2), 6.43 (dd, 1 H, $J_{1',2'}$ = 8.0 Hz , $J_{1',2''}$ = 5.8 Hz, H-1'), 7.99 (s, 1 H, H-2), and 8.35 (s, 1 H, H-8); ^{15}N-n.m.r. (CDCl$_3$): δ 72.94 (N^6); EI mass spectrum, m / z 337 (M$^+$).

ACKNOWLEDGMENTS

The authors thank Dr. Yasuo Shida for MS measurements, Mrs. Chiseko Sakuma for ^{15}N-NMR measurements, and Mr. Haruhiko Fukaya for elemental analyses, Analytical Center, Tokyo University of Pharmacy and Life Science. One of authors (Y. I.) thanks Ministry of Education, Science and Culture, the Japanse Government, for the Scientific Gran-in-aid (No. 02403011), that on Priority Areas (No. 03242104), and the Science and Technology Agency, the Japanese Government, for Special Coodination Fund, respectively.

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