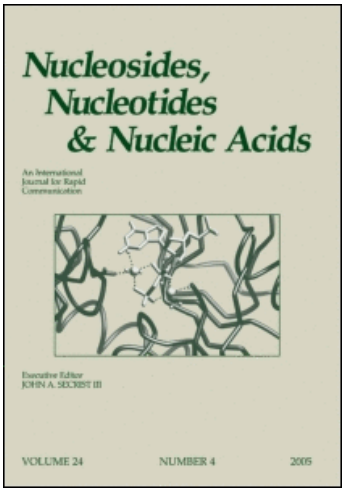

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AN EFFICIENT METHOD FOR THE SYNTHESIS OF β-D-RIBONUCLEOSIDES CATALYZED BY METAL IODIDES

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Abstract: Several β-D-ribonucleosides were synthesized in high yields under mild conditions by *N*-glycosylations of methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) with trimethylsilylated nucleoside bases in acetonitrile using a catalytic amount of metal iodide such as SnI_2, SbI_3 or TeI_4. A deprotection of N^6-benzoyl group of coupling product took place to a considerable extent when N^6-benzoyl-N^6,N^9-bis(trimethylsilyl)adenine was employed as a nucleoside base using SnI_2 or $SnCl_2$ as a catalyst while it was minimized when SbI_3 or TeI_4 was used. Further, the *N*-glycosylation of **1** with 7-trimethylsilyltheophylline in the presence of a catalytic amount of metal iodide was more effectively achieved in nitrile solvents other than acetonitrile.

The chemistry and biochemistry of nucleic acids are getting more and more important because nucleic acids play significant roles on the determination of nature and function of organisms, on the reproduction for conservation of species and on the control of biological processes such as metabolisms and biosyntheses. Nucleosides which are the components of nucleic acids also have many essential functions such as regulating enzyme and cell activities and having physiological control of blood pressure.[1] Therefore, analogs of nucleosides are used as therapeutic agents such as antitumor (araC) and antiviral agents (*e.g.*, ACV, araA, AZT and ddI), and even more

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

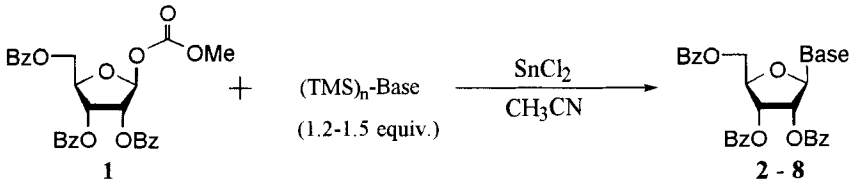
new analogs of nucleosides are being synthesized for the examination of their biological activities now.[2]

At the same time, the methodologies for the synthesis of nucleoside have also been developed and they can be summarized in the following three categories: (1) condensation of sugar moiety and base moiety (*N*-glycosylation), (2) construction of base moiety after introducing functional group to anomeric position of sugar moiety, (3) conversion of naturally occurring nucleoside.[3] In many cases, *N*-glycosylation is frequently carried out by using heavy metal salt or Lewis acid for the synthesis of naturally occurring nucleosides and their analogs because of its applicability to a wide range of their analogs starting from easily available materials.[4] Although this method is well utilized during the past twenty years, there in some cases have been disadvantages as follows: high toxicity of the activators, relatively severe reaction conditions and low yields of the products.

Recently, we reported that several β-D-ribonucleosides had been synthesized in high yields from methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) and trimethylsilylated nucleoside bases catalyzed by the combined use of silver salt such as silver triflate or silver perchlorate, a weak Lewis acid, and diphenyltin sulfide or Lawesson's reagent, a neutral compound under mild reaction conditions.[5] We also reported an useful method for the synthesis of β-D-ribofuranosides from 2,3,5-tri-*O*-benzyl-1-*O*-iodoacetyl-β-D-ribofuranose and trimethylsilylated nucleophiles by using $SnCl_2$ alone or the combination of $SnCl_2$ and $SiCl_4$ as a catalyst.[6] The advantage of this method is the use of $SnCl_2$, a weak Lewis acid and an easily handled crystalline solid. Then, we tried to apply $SnCl_2$ as a catalyst in the *N*-glycosylation.

In the first place, the reaction of **1** with bis(trimethylsilyl)uracil was tried in the presence of a catalytic amount of $SnCl_2$ under several reaction conditions. Effects of the amount of catalyst, of reaction temperature, and of solvent were examined in detail. It was found that the corresponding β-ribonucleoside was obtained in almost quantitative yield by using 20 mol% of $SnCl_2$ in acetonitrile at 80 °C without accompanying an α-isomer by TLC analysis. Next, several trimethylsilylated nucleoside bases were tried (TABLE 1). In the syntheses of both purine and pyrimidine nucleosides, the reactions proceeded smoothly and the desired nucleosides were obtained in high yields.[7] It is noted that N^2-acetyl-2',3',5'-tri-*O*-benzoyl-β-D-guanosine was isolated in better yield compared with the N-glycosylation method previously reported.[6,8] When N^6-benzoyl-N^6,N^9-bis(trimethylsilyl)adenine was used as a nucleoside base, a deprotection of N^6-benzoyl group in the coupling product was observed as a side reaction, and the desired N^6,2',3',5'-tetra-*O*-benzoyl-β-D-adenosine and its N^6-debenzoylated product were obtained in 42% and 44% yields, respectively.

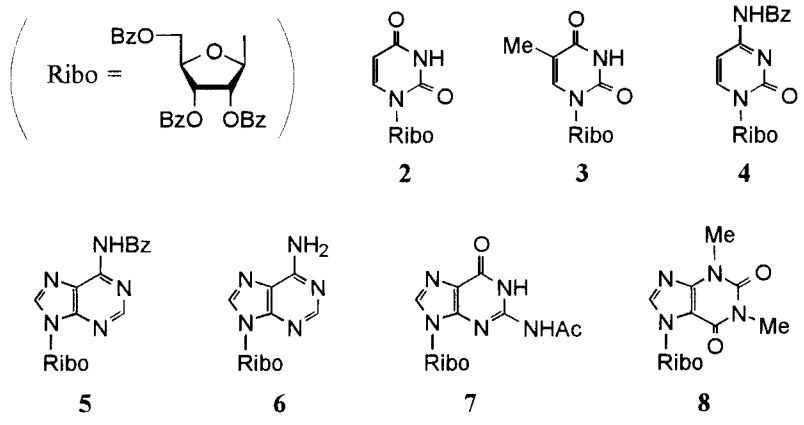
TABLE 1. Synthesis of β-D-Ribonucleosides Catalyzed by $SnCl_2$



Base	Catalyst / mol%	Temp./ °C	Time / hr	Product	Yield / %
Uracil	20	80	6.0	**2**	99
Thymine	20	80	6.5	**3**	quant.
N^4-Benzoylcytosine	50	80	4.3	**4**	84
N^6-Benzoyladenine[a)]	50	reflux	7.0	**5** + **6**	86[b)]
N^2-Acetylguanine	30	80	6.0	**7**	82
Theophylline	20	60	2.75	**8**	99

a) The reaction was carried out in propionitrile.

b) **5** (42%) + **6** (44%).



Next, the activities of four tin(II) halides were examined by taking the reaction of **1** with bis(trimethylsilyl)uracil as a model in order to find effective catalysts by which the *N*-glycosylation proceeded more smoothly under milder reaction conditions compared with the case of using $SnCl_2$ (TABLE 2). The reaction did not proceed at all when SnF_2 was used even though the tin atom had enough Lewis acidity due to the electron withdrawing effect of fluorine atoms. The use of 20 mol% of $SnBr_2$ or SnI_2 was found to give the desired product in better yield compared with $SnCl_2$. In particular,

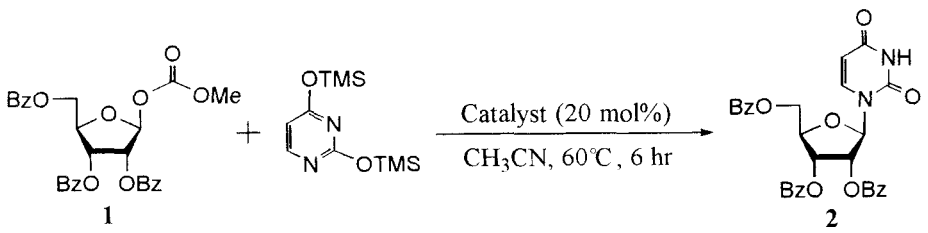


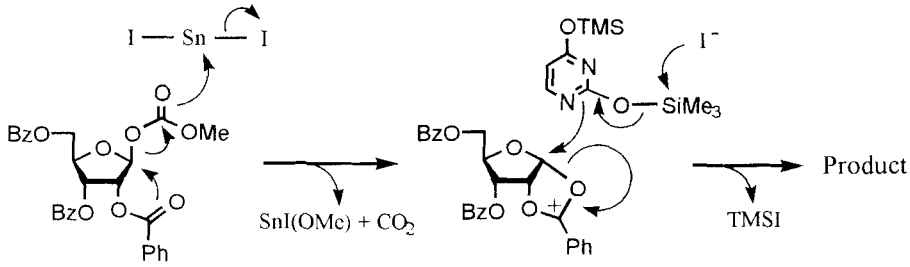
TABLE 2. Effect of Tin(II) Halides in the Synthesis of **2**

Catalyst	Yield / %	Catalyst	Yield / %
SnF_2	NR	$SnBr_2$	93
$SnCl_2$	84	SnI_2	quant.

TABLE 3. Effect of Metal Iodides in the Synthesis of **2**

Catalyst	Yield / %	Catalyst	Yield / %
NaI	NR	SbI_3	96
ZnI_2	32	TeI_4	94
CuI	NR	PbI_2	3
RuI_3	NR	BiI_3	87

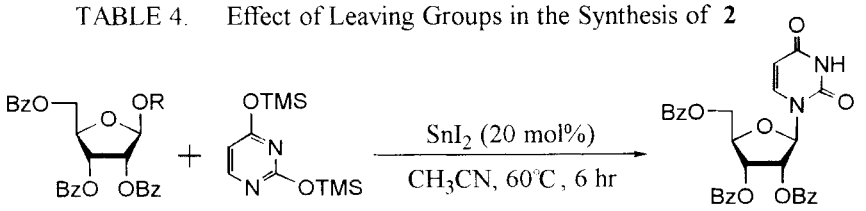
SnI_2, a weak and easily handled Lewis acid, catalyzed this reaction smoothly to give the coupling product in excellent yield. These results indicate that SnI_2 is the most effective catalyst among tin(II) halides. The reactivity sequence of tin(II) halides is found to be in the following order: SnI_2 > $SnBr_2$ > $SnCl_2$ >> SnF_2. The high reactivity of SnI_2 is probably due to the increased nucleophilicity of nucleoside bases by the attack of negatively charged iodide, caused by the smooth interaction of SnI_2 to methoxycarbonyloxy group, toward the silicon atom of nucleoside bases as shown in the following scheme. No reaction took place in the case of SnF_2, probably due to its low solubility in acetonitrile.



These results suggested that metal iodides other than SnI_2 would behave as catalysts in the *N*-glycosylation. Although metal iodides are used widely in organic synthesis, there are only several examples in which a catalytic amount of metal iodide is used as a Lewis acid.[9] Then, various metal iodides were screened based on the expectation that both glycosyl donor and trimethylsilylated nucleoside bases would be activated by the metal iodides described above. The reaction of **1** with bis(trimethylsilyl)uracil was tried in acetonitrile at 60 °C for 6 hr in the presence of various metal iodide catalysts (TABLE 3). When NaI, CuI or RuI_3 was employed as a catalyst, the reaction did not proceed at all whereas a small amount of product was yielded when ZnI_2 or PbI_2 was used. It is noted that the corresponding nucleoside was obtained in 96% and 94% yields, respectively, when SbI_3 or TeI_4 was used as a catalyst. There have been no reports concerning the use of these metal iodides as Lewis acids though these are relatively moisture-stable and easily handled crystals compared with TMSOTf and $SnCl_4$ which are frequently used in the *N*-glycosylation.[10]

The leaving group of glycosyl donor is also an important factor in the *N*-glycosylation. A glycosyl donor which has carbonate group as a leaving group and was first synthesized and employed in the fused method for the *N*-glycosylation by Ishido *et al.*[11] was found to be effective in the *N*-glycosylation catalyzed by the combined use of silver salts and diphenyltin sulfide or Lawesson's reagent under mild reaction conditions.[5] Then several alkyl and aryl β-ribofuranosyl carbonates and their analogs were prepared, and *N*-glycosylation of these glycosyl donors with bis(trimethylsilyl)uracil as a nucleoside base was tried in the presence of 20 mol% of SnI_2 (TABLE 4). It was found that acetate derivative which was frequently used as a glycosyl donor in *N*-glycosylation[3] was less effective compared with methyl carbonate derivative in this reaction condition.[5] The corresponding nucleoside was obtained in moderate yield by using *tert*-butyl or phenyl carbonate derivative. The reaction proceeded smoothly and the desired product was given in high yield when allyl or methoxyethyl carbonate derivative was used wherein methyl carbonate derivative gave the best result. Nearly the same results were observed when glycosyl donors having both phenyl carbonate and phenyl carbamate group were used, while the reactivity decreased when phenyl thiocarbonate group was used as a leaving group. These results indicate that carbonyl oxygen in the carbonate group plays an important role in the activation and the smooth acceleration of the reaction. Different from the formation of trimethylsilyl methoxide from methyl carbonate derivative, the reactivity turned out to be slightly lower than that of methyl carbonate derivative in the case of using *N,N*-dimethyl carbamate derivative, probably because co-product, trimethylsilyl dimethylamide, is basic to reduce the activity of the catalyst.

TABLE 4. Effect of Leaving Groups in the Synthesis of **2**



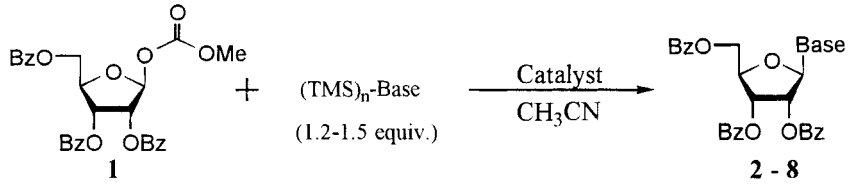
1, 9 - 16 **2**

R	Yield / %	R	Yield / %
-C(O)OCH_3(**1**)	quant.	-C(O)$OCH_2CH{=}CH_2$ (**13**)	96
-C(O)CH_3 (**9**)	21	-C(S)OPh (**14**)	12
-C(O)OPh (**10**)	70	-C(O)NHPh (**15**)	68
-C(O)$OC(CH_3)_3$ (**11**)	68	-C(O)$N(CH_3)_2$ (**16**)	83
-C(O)$OCH_2CH_2OCH_3$ (**12**)	94		

Thus, it was made clear that metal iodides such as SnI_2, SbI_3 and TeI_4 effectively promoted the *N*-glycosylation, and methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) was the most suitable glycosyl donor. Next, *N*-glycosylation was applied to the synthesis of following nucleosides shown in TABLE 5. In the syntheses of uridine, 5-methyluridine, cytidine, adenosine and guanosine derivatives, the corresponding β-D-ribonucleosides were obtained in high yields with complete β-selectivities by using SnI_2, SbI_3 or TeI_4. In every case, the reactions could be carried out under milder reaction conditions compared with that when using $SnCl_2$. It is noted that the reaction between **1** and N^2-acetyl-O,N^2,N^9-tris(trimethylsilyl)guanine afforded the desired product in 93% and 95% yields, respectively, when SnI_2 or SbI_3 was used. The cytidine derivative was also obtained in satisfactory yield (89% - 91% yield) by using every catalyst. Interestingly, the ratio of coupling products, **5** to **6**, in the reaction of **1** with N^6-benzoyl-N^6,N^9-bis(trimethylsilyl)adenine varied according to the catalysts used; that is, either when SnI_2 or $SnCl_2$ was used, a significant amount of the N^6-debenzoylated product was obtained whereas almost no N^6-debenzoylation took place when SbI_3 or TeI_4 was used. These results indicate that the N^6-debenzoylation is characteristic of tin(II) halides, and the mechanism of this side reaction is not yet made clear.[12]

In the case of using 7-trimethylsilyltheophylline as a glycosyl acceptor, the reactivity decreased to a considerable extent by using 20 mol% of SnI_2 or TeI_4 and to a slight extent by using 20 mol% of SbI_3. As shown in TABLE 1, the desired product was

TABLE 5. Synthesis of β-D-Ribonucleosides Catalyzed by Metal Iodides

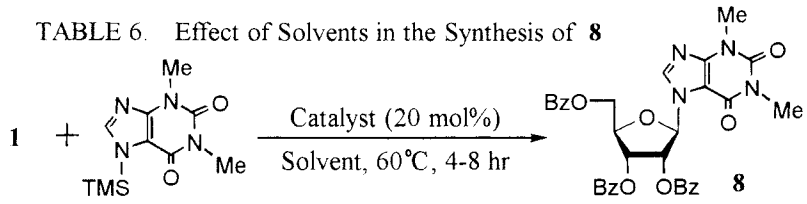


Base	Catalyst / mol%	Temp. /℃	Time / hr	Yield / % [a]		
				SnI_2	SbI_3	TeI_4
Uracil	20	80	6	quant.	96	94
Thymine	20	80	6	quant.	quant.	quant.
N^4-Benzoylcytosine	50	80	5-6	89	91	89[b]
N^6-Benzoyladenine	20	reflux	8	91[b]	88	93
				(49+42)[c]	(82+6)	(93+trace)
N^2-Acetylguanine	30	80	6-10	93	95	81
Theophylline	20	60	5-10	55	84	43

a) The products were shown in TABLE 1.
b) The reaction was carried out using 30 mol% of catalyst.
c) Yields of **5** + **6**.

obtained in 99% yield when 20 mol% of $SnCl_2$ was used under the same reaction condition. In the *N*-glycosylation catalyzed by Lewis acid, a solvent plays an important role on the reactivity to a great extent because the complex formation between nucleoside base and Lewis acid reduces the activity of Lewis acid.[13] In polar solvent such as acetonitrile, it is assumed that the above complex would be dissociated effectively. Then the effect of nitrile solvent was investigated in order to improve the reactivity and the yield (TABLE 6). It is noted that the reactivity is varied by the combination of metal iodide and nitrile solvent. In other words, chloroacetonitrile and benzonitrile were suitable solvent for SnI_2, methoxyacetonitrile, chloroacetonitrile and benzonitrile were just appropriate for SbI_3, and only benzonitrile gave good result for TeI_4. The reaction rate was also influenced by the kind of nitrile solvents. When chloroacetonitrile was used, the reaction proceeded almost completely within 2 hr by using SnI_2 and SbI_3 whereas it took 8 hr when benzonitrile was used. Thus, it was found that metal iodides such as SnI_2, SbI_3 and TeI_4 were also suitable catalysts for the

TABLE 6. Effect of Solvents in the Synthesis of **8**



Solvent	Yield / %		
	SnI_2	SbI_3	TeI_4
CH_3CN	55	84	43
$(CH_3)_3CCN$	51	52	26
CH_3OCH_2CN	63	95	46
$ClCH_2CN$	96	quant.	43
PhCN	91	90	93

synthesis of 7-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)theophylline by choosing the suitable nitrile solvents other than acetonitrile.

In summary, several β-D-ribonucleosides were synthesized in high yields under mild reaction conditions from **1** and trimethylsilylated nucleoside bases in acetonitrile using a catalytic amount of metal iodide such as SnI_2, SbI_3 or TeI_4. It should be noted that in the synthesis of N^6-benzoyladenosine derivative, the deprotection of N^6-benzoyl group of coupling product was minimized by using SbI_3 or TeI_4 while it proceeded to give a considerable amount of N^6-debenzoylated product when tin(II) halide such as SnI_2 or $SnCl_2$ was used. Moreover, it is possible to improve the reactivity in the *N*-glycosylation of **1** with 7-trimethylsilyltheophylline by choosing the suitable nitrile solvents other than acetonitrile when several metal iodide catalysts were used.

Experimental

All melting points were uncorrected. ^1H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JMN-EX270L spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra show only characteristic signals. Mass spectra were recorded on JEOL JMS-HX100, JEOL JMS-SX102A, and Fisons VG-AutoSpec-Q spectrometers. Microanalyses were performed with a Yanako CHN analyzer. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. Purification of products was

performed by silica gel column chromatography (Merck, Art.7734 Kieselgel 60) or preparative TLC on silica gel (Wakogel B-5F).

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose, methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**), and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) were prepared by the methods previously reported.[5] Silylation of nucleoside bases was carried out according to the literature procedures.[10] Bis(trimethylsilyl)uracil was stored as a solution in 1,2-dichloroethane. Other trimethylsilylated nucleoside bases were used immediately as solutions in 1,2-dichloroethane after finishing the silylation and following evaporation of the solvent. SnI_2 was purified by sublimation. SbI_3 was synthesized by the reaction of antimony and iodine in carbon tetrachloride. SnF_2, $SnCl_2$, $SnBr_2$, TeI_4, and other metal iodides were commercially available. Acetonitrile, propionitrile, and 1,2-dichloroethane were distilled successively from P_2O_5 and CaH_2, and stored over molecular sieves. Benzonitrile, chloroacetonitrile, pivalonitrile, and methoxyacetonitrile were distilled from P_2O_5 and stored over molecular sieves.

General Procedure for the *N*-Glycosylation from Glycosyl Donor and Trimethylsilylated Nucleoside Base Using Catalytic Amount of Metal Halide.

A typical reaction procedure is described for the reaction of **1** and bis(trimethylsilyl)uracil; to a suspension of SnI_2 (11.2 mg, 0.03 mmol) in acetonitrile (2.5 ml) was added **1** (78.1 mg, 0.15 mmol) in acetonitrile (2 ml) and bis(trimethylsilyl)uracil in 1,2-dichloroethane (0.315 ml, 0.225 mmol) at room temperature under argon atmosphere, and the mixture was heated at 60 °C for 6 hr. After cooling to room temperature, saturated aqueous $NaHCO_3$ was added to the mixture. The resulting suspension was filtered through celite and the filtrate was extracted with dichloromethane. The extract was washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4 and evaporated. The residue was purified by preparative TLC to give 2',3',5'-tri-*O*-benzoyl-β-D-uridine (**2**) (83.4 mg, quant.): Mp 146.0-146.5 °C (lit.[14] 140-142 °C); $[\alpha]_D^{29}$ -53.6° (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 4.67 (1 H, dd, *J* = 11.9 and 4.0 Hz, 5'A-H), 4.66-4.77 (1 H, m, 4'-H), 4.85 (1 H, dd, *J* = 11.9 and 2.3 Hz, 5'B-H), 5.61 (1 H, dd, *J* = 8.3 and 2.3 Hz, 5-H), 5.75 (1 H, dd, *J* = 5.9 and 5.6 Hz, 2'-H), 5.89 (1 H, dd, *J* = 5.9 and 4.3 Hz, 3'-H), 6.32 (1 H, d, *J* = 5.6 Hz, 1'-H), 7.3-7.7 (10 H, m), 7.9-8.2 (6 H, m), 8.34 (1 H, bs, NH); ^{13}C-NMR ($CDCl_3$) δ : 88.17, 103.41, 139.76, 150.28, 163.21, 165.30, 165.33, 166.07; FAB-MS (NBA+NaI) *m/z* 601 $[M-H+2Na]^+$, 579 $[M+Na]^+$; *Anal.* Calcd for $C_{30}H_{24}N_2O_9$: C, 64.75; H, 4.35; N, 5.03. Found: C, 64.49; H, 4.47; N, 4.90.

Physical properties of other products are as follows:

2',3',5'-Tri-*O*-benzoyl-β-D-5-methyluridine (3): $[\alpha]_D^{31}$ -89.2° (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 1.59 (3 H, s, CH_3), 4.6-4.8 (2 H, m, 4'- and 5'A-H), 4.89 (1 H,

d, J = 10.6 Hz, 5'B–H), 5.77 (1 H, t, J = 6.3 Hz, 2'–H), 5.93 (1 H, dd, J = 6.3 and 3.6 Hz, 3'–H), 6.45 (1 H, d, J = 6.3 Hz, 1'–H), 7.17 (1 H, s, 6–H), 7.3–7.7 (9 H, m), 7.97 (4 H, m), 8.14 (2 H, d, J = 7.9 Hz), 9.48 (1 H, bs, NH); ^{13}C–NMR ($CDCl_3$) δ : 12.04, 86.83, 112.13, 150,42, 163.56, 165.26, 165.34, 165.93; FAB–MS (NBA+NaI) *m/z* 615 $[M-H+2Na]^+$, 593 $[M+Na]^+$; *Anal.* Calcd for $C_{31}H_{26}N_2O_9 \cdot 1.1H_2O$: C, 63.07; H, 4.81; N, 4.75. Found: C, 62.97; H, 4.51; N, 4.65.

N^4,2',3',5'–Tetra–*O*–benzoyl–β–D–cytidine (4): Mp 206.5–208.0 °C (lit.[14] 205–207 °C); $[\alpha]_D^{31}$ −47.1° (*c* 1.00, $CHCl_3$); ^{1}H–NMR ($CDCl_3$) δ : 4.65–4.95 (3 H, m, 4'–, 5'A– and 5'B–H), 5.75–6.0 (2 H, m, 2'– and 3'–H), 6.46 (1 H, d, J = 4.0 Hz, 1'–H), 7.3–7.7 (13 H, m), 7.85–8.15 (9 H, m), 8.92 (1 H, bs, NH); ^{13}C–NMR ($CDCl_3$) δ : 89.56, 144.28, 162.64, 165.16, 165.23, 166.07; FAB–MS (NBA+NaI) *m/z* 704 $[M-H+2Na]^+$, 682 $[M+Na]^+$; *Anal.* Calcd for $C_{37}H_{29}N_3O_9 \cdot 0.4H_2O$: C, 66.64; H, 4.50; N, 6.30. Found: C, 66.61; H, 4.39; N, 6.22.

N^6,2',3',5'–Tetra–*O*–benzoyl–β–D–adenosine (5): $[\alpha]_D^{29}$ −88.0° (*c* 1.00, $CHCl_3$); ^{1}H–NMR ($CDCl_3$) δ : 4.71 (1 H, dd, J = 12.0 and 4.1 Hz, 5'A–H), 4.85 (1 H, m, 4'–H), 4.94 (1 H, dd, J = 12.0 and 3.1 Hz, 5'B–H), 6.27 (1 H, dd, J = 5.6 and 5.3 Hz, 2'–H), 6.42 (1 H, dd, J = 5.6 and 4.6 Hz, 3'–H), 6.50 (1 H, d, J = 5.3 Hz, 1'–H), 7.3–7.5 (12 H, m), 7.9–8.2 (8 H, m), 8.19 (1 H, s, 2–H), 8.70 (1 H, s, 8–H), 9,21 (1 H, bs, NH); ^{13}C–NMR ($CDCl_3$) δ : 87.01, 123.65, 141.74, 149.79, 151.68, 152.92, 164.71, 165.12, 165.32, 166.13; FAB–MS (NBA+DMSO) *m/z* 684 $[M+H]^+$; *Anal.* Calcd for $C_{38}H_{29}N_5O_{11} \cdot H_2O$: C, 60.88; H, 4.17; N, 9.34. Found: C, 60.98; H, 4.07; N, 9.06.

2',3',5'–Tri–*O*–benzoyl–β–D–adenosine (6): $[\alpha]_D^{32}$ −73.7° (*c* 1.00, $CHCl_3$); ^{1}H–NMR ($CDCl_3$) δ : 4.72 (1 H, dd, J = 11.7 and 4.1 Hz, 5'A–H), 4.8–4.9 (1 H, m, 4'–H), 4.91 (1 H, dd, J = 11.7 and 3.1 Hz, 5'B–H), 6.15–6.45 (2 H, br, NH_2), 6.30 (1 H, t, J = 5.0 Hz, 2'–H), 6.41 (1 H, t, J = 5.0 Hz, 3'–H), 6.45 (1 H, d, J = 5.0 Hz, 1'–H), 7.3–7.65 (9 H, m), 7.9–8.2 (6 H, m), 8.00 (1 H, s), 8.28 (1 H, s); ^{13}C–NMR ($CDCl_3$) δ : 86.76, 120.02, 138.96, 149.63, 153.30, 155.72, 165.09, 165.25, 166.09; FAB–MS (NBA+DMSO) *m/z* 580 $[M+H]^+$; *Anal.* Calcd for $C_{31}H_{25}N_5O_7 \cdot H_2O$: C, 62.31; H, 4.55; N, 11.72. Found: C, 62.32; H, 4.31; N, 11.55.

N^2–Acetyl–2',3',5'–tri–*O*–benzoyl–β–D–guanosine (7): $[\alpha]_D^{31}$ −65.2° (*c* 1.00, $CHCl_3$); ^{1}H–NMR ($CDCl_3$) δ : 2.32 (3 H, s, CH_3), 4.60 (1 H, dd, J = 11.6 and 5.6 Hz, 5'A–H), 4.75 (1 H, m, 4'–H), 4.86 (1 H, dd, J = 11.6 and 5.3 Hz, 5'B–H), 6.23 (1 H, dd, J = 5.6 and 5.3 Hz, 3'–H), 6.28 (1 H, d, J = 4.3 Hz, 1'–H), 6.37 (1 H, dd, J = 5.3 and 4.3 Hz, 2'–H), 7.2–7.6 (9 H, m), 7.8–7.95 (6 H, m), 7.96 (1 H, s, 8–H), 10.50 (1 H, s, NH), 12.12 (1 H, s, NH); ^{13}C–NMR ($CDCl_3$) δ : 24.23, 88.23, 122.25, 138.94, 147.66, 147.87, 155.44, 165.16, 165.21, 166.40, 172.70; FAB–MS (NBA+DMSO) *m/z* 638

[M+H]$^+$; *Anal.* Calcd for $C_{33}H_{27}N_5O_9 \cdot 0.7H_2O$: C, 60.96; H, 4.40; N, 10.77. Found: C, 60.74; H, 4.29; N, 10.44.

7-(2',3',5'-Tri-*O*-benzoyl-β-D-ribofuranosyl)theophylline (8): $[a]_D^{29}$ -42.6° (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 3.37 (3 H, s, CH_3), 3.57 (3 H, s CH_3), 4.74 (1 H, dd, *J* = 11.6 and 4.3 Hz, 5'A-H), 4.7-4.9 (1 H, m, 4'-H), 4.89 (1 H, dd, *J* = 11.6 and 3.0 Hz, 5'B-H), 6.05 (1 H, dd, *J* = 5.9 and 5.0 Hz), 6.09 (1 H, dd, *J* = 5.9 and 5.0 Hz), 6.60 (1 H, d, *J* = 5.0 Hz, 1'-H), 7.25-7.65 (9 H, m), 7.85-8.2 (6 H, m), 7.94 (1 H, s, 8-H); ^{13}C-NMR ($CDCl_3$) δ : 28.14, 29.83, 88.73, 106.52, 139.89, 149.54, 151.36, 154.63, 164.96, 165.19, 166.07; FAB-MS (NBA+NaI) *m/z* 647 [M+Na]$^+$; *Anal.* Calcd for $C_{33}H_{28}N_4O_9$: C, 63.46; H, 4.52; N, 8.97. Found: C, 63.33; H, 4.69; N, 8.62.

Procedure for the Preparation of Glycosyl Donor (10 - 14) from 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose.

A typical reaction procedure is described for the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and phenyl chloroformate; to a solution of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (4624.8 mg, 10.00 mmol) and triethylamine (3035.7 mg, 30.00 mmol) in dichloromethane (30 ml) was added phenyl chloroformate (3131.4 mg, 20.00 mmol) at 0 °C under argon atmosphere, and the mixture was stirred at 0 °C for 30 min. Then saturated aqueous $NaHCO_3$ was added to the mixture and the resulting mixture was extracted with dichloromethane. The extract was washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The residue was purified successively by silica gel column chromatography and crystallization (hexane-diethyl ether) to give phenyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**10**) (4245.0 mg, 73 %): Mp 98-99 °C; $[a]_D^{26}$ +16.20° (*c* 1.07, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 4.62 (1 H, dd, *J* = 12.2 and 4.2 Hz, 5A-H), 4.78 (1 H, dd, *J* = 12.2 and 3.6 Hz, 5B-H), 4.88 (1 H, ddd, *J* = 3.6, 3.6, and 7.0 Hz, 4-H), 5.96 (1 H, d, *J* = 5.0 Hz, 2-H), 6.02 (1 H, dd, *J* = 5.0 and 7.0 Hz, 3-H), 6.43 (1 H, s, 1-H), 7.09 (2 H, d, *J* = 7.3Hz), 7.2-7.6 (12 H, m), 7.90 (2 H, d, *J* = 7.3 Hz), 8.03 (2 H, d, *J* = 6.9 Hz), 8.16 (2 H, d, *J* = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ : 101.94, 150.73, 151.91, 164.98, 165.28, 166.16; FAB-MS (NBA+NaCl) *m/z* 605 [M+Na]$^+$, 561 [M-CO_2+Na]$^+$, 445 [M-C_6H_5OCOO]$^+$.

***tert*-Butyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (11)**: Experimental procedure was the same as described for **10**. 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose was treated with di-*tert*-butyl dicarbonate and catalytic amount of 4-dimethylaminopyridine. The residue was purified by silica gel column chromatography to give **11** (97 %): $[a]_D^{27}$ +19.48° (*c* 1.12, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 1.44 (9 H, s), 4.54 (1 H, dd, *J* = 11.9 and 4.0 Hz, 5A-H), 4.7-4.85 (2 H, m, 5B- and 4-H), 5.83 (1 H, d, *J* = 4.6 Hz, 2-H), 5.93 (1 H, dd, *J* = 4.8 and 7.0 Hz, 3-H), 6.27 (1 H, s, 1-H), 7.2-

7.6 (9 H, m), 7.87 (2 H, d, J = 6.9 Hz), 8.02 (2 H, d, J = 7.3 Hz), 8.10 (2 H, d, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ : 27.53, 83.45, 100.61, 151.39, 164.94, 165.16, 166.06; FAB-MS (NBA+NaCl) m/z 585 $[M+Na]^+$, 445 $[M-(CH_3)_3COCOO]^+$.

Methoxyethyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (12): Experimental procedure was the same as described for **10**. 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose was treated with methoxyethyl chloroformate. The residue was purified by silica gel column chromatography to give **12** (89 %): $[\alpha]_D^{27}$ +26.12° (c 1.03, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 3.37 (3 H, s, OCH_3), 3.58 (2 H, t, J = 4.6 Hz), 4.62 (1 H, dt, J = 11.9 and 4.6Hz), 4.38 (1 H, dt, J = 12.0 and 5.3 Hz), 4.57 (1 H, dd, J = 12.2 and 5.4 Hz, 5A-H), 4.70 (1 H, dd, J = 12.3 and 3.6 Hz, 5B-H), 4.82 (1 H, ddd, J = 3.6, 5.4 and 7.0 Hz, 4-H), 5.85 (1 H, d, J = 5.0 Hz, 2-H), 5.92 (1 H, dd, J = 4.9 and 7.0 Hz, 3-H), 6.34 (1 H, s, 1-H), 7.2-7.6 (9 H, m), 7.88 (2 H, d, J = 7.3 Hz), 8.01 (2 H, d, J = 7.2 Hz), 8.10 (2 H, d, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$) δ : 58.85, 67.33, 69.78, 101.38, 153.24, 164.83, 165.09, 166.02; FAB-MS (NBA+NaCl) m/z 587 $[M+Na]^+$, 543 $[M-CO_2+Na]^+$, 445 $[M-CH_3OCH_2CH_2OCOO]^+$.

Allyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (13): Experimental procedure was the same as described for **10**. 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose was treated with allyl chloroformate. The residue was purified by silica gel column chromatography to give **13** (93 %): $[\alpha]_D^{25}$ +24.55° (c 1.07, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 4.5-4.7 (3 H, m), 4.83 (1 H, ddd, J = 4.1, 4.1 and 7.1 Hz, 4-H), 5.27 (1 H, dd, J = 11.0 and 1.1 Hz), 5.35 (1 H, dd, J = 17.2 and 1.1 Hz), 5.8-5.9 (3 H, m), 6.38 (1 H, s, 1-H), 7.2-7.5 (9 H, m), 7.90 (2 H, d, J = 6.9 Hz), 8.00 (2 H, d, J = 6.9 Hz), 8.08 (2 H, d, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ : 69.06, 101.47, 119.52, 130.90, 153.13, 164.98, 165.24, 166.16; FAB-MS (NBA+NaCl) m/z 569 $[M+Na]^+$, 445 $[M-CH_2=CHCH_2OCOO]^+$.

Phenyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl thiocarbonate (14): Experimental procedure was the same as described for **10**. 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose was treated with phenyl chlorothionoformate. The residue was purified by silica gel column chromatography to give **14** (56 %) : $[\alpha]_D^{27}$ +1.38° (c 1.05, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 4.57 (1 H, dd, J = 8.3 and 4.6 Hz, 5A-H), 4.7-4.8 (2 H, m, 5B- and 4-H), 5.89 (1 H, dd, J = 5.0 and 5.2 Hz), 5.97 (1 H, dd, J = 4.9 and 4.3 Hz, 2-H), 6.07 (1 H, d, J = 4.3 Hz, 1-H), 7.2-7.6 (14 H, m), 7.92 (2 H, dd, J = 8.3 and 1.6 Hz), 7.99 (2 H, dd, J = 8.2 and 1.7 Hz), 8.12 (2 H, dd, J = 8.3 and 1.3 Hz); ^{13}C-NMR ($CDCl_3$) δ : 86.23, 121.08, 126.36, 150.76, 164.85, 165.16, 166.00, 166.83; FAB-MS (NBA+NaCl) m/z 621 $[M+Na]^+$, 445 $[M-C_6H_5OCSO]^+$.

Preparation of *N*-Phenyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbamate (15).

To a solution of 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranose (1000.7 mg, 2.16 mmol) and triethylamine (724.5 mg, 7.16 mmol) in dichloromethane (2 ml) was added phenyl isocyanate (514.6 mg, 4.32 mmol) at 0 °C under argon atmosphere, and the mixture was stirred at room temperature for 1 hr. Then saturated aqueous $NaHCO_3$ was added to the mixture and the resulting mixture was extracted with diethyl ether. The extract was washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The residue was purified by crystallization (dichloromethane-diethyl ether) to afforded **15** (658.0 mg, 52 %): Mp 154-155 °C; $[\alpha]_D^{25}$ 4.48° (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 4.53 (1 H, dd, *J* = 8.9 and 2.4 Hz, 5A-H), 4.8-4.9 (2 H, m, 5B- and 4-H), 5.85 (1 H, d, *J* = 5.0 Hz, 2-H), 5.95 (1 H, dd, *J* = 4.9 and 4.2 Hz, 3-H), 6.39 (1 H, s, NH), 6.48 (1 H, s, 1-H), 7.0-7.6 (14 H, m), 7.88 (2 H, d, *J* = 6.5 Hz), 8.00 (2 H, d, *J* = 6.6 Hz), 8.08 (2 H, d, *J* = 5.8 Hz); ^{13}C-NMR ($CDCl_3$) δ : 99.39, 118.90, 123.95, 137.02, 150.94, 165.10, 165.48, 165.98; FAB-MS (NBA+NaCl) *m/z* 604 $[M+Na]^+$, 445 $[M-(CH_3)_2NCOO]^+$.

Preparation of *N,N*-Dimethyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbamate (16).

To a solution of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (1000.5 mg, 2,16 mmol) and 4-dimethylaminopyridine (25.9 mg, 0.21 mmol) in triethylamine (10 ml) was added *N,N*-dimethylcarbamoyl chloride (697.0 mg, 6.48 mmol) at 0 °C under argon atmosphere, and the mixture was stirred at 70 °C for 1 hr. After cooling to room temperature, saturated aqueous $NaHCO_3$ was added to the mixture and the resulting mixture was extracted with diethyl ether. The extract was washed with H_2O and brine, dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography to give **16** (747.2 mg, 65 %): Mp 123-124 °C; $[\alpha]_D^{25}$ +26.52° (*c* 1.03, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ : 2.84 (3 H, s, NCH_3), 2.92 (3 H, s, NCH_3), 4.55 (1 H, dd, *J* = 11.6 and 5.0 Hz, 5A-H), 4.71 (1 H, dd, *J* = 11.6 and 4.3 Hz, 5B-H), 4.78 (1 H, ddd, *J* = 5.0, 4.6, and 4.3 Hz, 4-H), 5.84 (2 H, m, 2- and 3-H), 6.41 (1 H, d, *J* = 1.0 Hz, 1-H), 7.3-7.7 (9 H, m), 7.88 (2 H, dd, *J* = 8.6 and 1.4 Hz), 8.0-8.2 (4 H, m); ^{13}C-NMR ($CDCl_3$) δ : 35.94, 36.46, 99.64, 154.07, 165.05, 165.35, 166.05; FAB-MS (NBA+NaCl) *m/z* 556 $[M+Na]^+$, 445 $[M-(CH_3)_2NCOO]^+$.

REFERENCES

1. M. D. Erion, *Annu. Rep. Med. Chem.*, **28**, 295 (1993).
2. D. M. Huryn and M. Okabe, *Chem. Rev.*, **92**, 1745 (1992); P. A. Bonnet and R. K. Robins, *J. Med. Chem.*, **36**, 635 (1993).

3. Y. Mizuno, "The Organic Chemistry of Nucleic Acids", Kodansha Ltd., Tokyo, 1986, p41–72.
4. K. A. Watanabe, D. H. Hollenberg, and J. J. Fox, *J. Carbohydr. Nucleosides Nucleotides*, **1**, 1 (1974).
5. N. Shimomura, T. Matsutani, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **67**, 3100 (1994).
6. N. Shimomura, M. Saitoh, and T. Mukaiyama, *Chem. Lett.*, **1994**, 433.
7. T. Mukaiyama, T. Matsutani, and N. Shimomura, *Chem. Lett.*, **1994**, 2089.
8. T. Mukaiyama, T. Matsutani, and N. Shimomura, *Chem. Lett.*, **1993**, 1627.
9. C. L. Roux, H. G. Iloughmane, J. Dubac, J. Jaud, and P. Vignaux, *J. Org. Chem.*, **58**, 1835 (1993); T. Mukaiyama, H. Akamatsu, and J. S. Han, *Chem. Lett.*, **1990**, 889; A. Hosomi, S. Iijima, and H. Sakurai, *Tetrahedron Lett.*, **23**, 547 (1982); H. Sakurai, K. Sasaki, and A. Hosomi, *Tetrahedron Lett.*, **22**, 745 (1981); Z. Tocik, R. Earl, and J. Beránek, *Nucleic Acids Res.*, **8**, 4755 (1980).
10. U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654 (1974); F. W. Lichtenthaler, P. Voss, and A. Heerd, *Tetrahedron Lett.*, **24**, 2141 (1974); H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, **114**, 1234 (1981).
11. S. Inaba, M. Yamada, T. Yoshino, and Y. Ishido, *J. Am. Chem. Soc.*, **95**, 2062 (1973).
12. M. Nagai, T. Matsutani, and T. Mukaiyama, *Heterocycles*, submitted for publication.
13. U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **41**, 2084 (1976).
14. K. A. Watanabe and J. J. Fox, *J. Heterocyclic . Chem.*, **6**, 109 (1969).