Stereoselective Syntheses of β-D-Ribonucleosides Catalyzed by the Combined Use of Silver Salts and Diphenyltin Sulfide or Lawesson's Reagent

Naoyuki SHIMOMURA, Takafumi MATSUTANI, and Teruaki MUKAIYAMA*
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162

(Received July 5, 1994)

β-D-Ribonucleosides are stereoselectively synthesized in high yields from methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate and trimethylsilylated nucleoside bases by the use of [diphenyltin sulfide/silver salt] or [Lawesson's reagent/silver salt] combined catalyst system under mild conditions.

The study of pure nucleosides is more and more of growing importance in biological chemistry and related fields. Modified nucleosides, at the same time, are used ever increasingly as therapeutic agents, especially as antiviral (e.g., AZT, ddI, ddC) and antitumor agents (araC).1) They are also expected to be useful for several other purposes such as adenosine receptor antagonist and agonist,2) inhibitor of purine nucleoside phosphorylase,3) etc. Therefore, it is desired to develop further a more efficient method for the synthesis of nucleosides other than the methods already known. Of many methods, glycosylation reaction is the simplest method and is of wide application: for example, the reactions of 1-chlorosugars with silylated nucleoside bases by using bases such as NaH or KOH;4) 1-fluorosugars with silylated nucleoside bases by using $SiF_4$5) or combined use of $CpZrCl_2$ or $CpHfCl_2$ and $AgClO_4$ or silver trifluoromethanesulfonate (AgOTf);6) 1-phenylthiosugars with silylated nucleoside bases by using *N*-bromosuccinimide (NBS)7) or dimethyl(methylthio)sulfonium tetrafluoroborate;8) and 1-*O*-acylsugars (generally 1-*O*-acetylsugars) with silylated nucleoside bases using Friedel–Crafts type catalyst (such as $SnCl_4$),9) trimethylsilyl trifluoromethanesulfonate (TMSOTf), or $TMSClO_4$ developed by Vorbrüggen.10) Especially, the Vorbrüggen modification of the Hilbert–Johnson reaction11) has been used widely for preparation of many modified nucleosides by treating silylated nucleoside bases with sugar derivatives having leaving groups at the anomeric center. According to this method, the desired β-anomers are obtained almost exclusively when α-acyloxy group at C-2 are employed as it stabilizes the anomeric cation by the neighboring effect. However, it is still desired to develop a more efficient method under mild conditions for the synthesis of nucleosides, especially in the case of guanosine.

Recently, a useful method for the stereoselective synthesis of β-D-ribofuranosides from 2,3,5-tri-*O*-benzyl-1-*O*-iodoacetyl-D-ribofuranose and alkyl trimethylsilyl ethers by combined use of diphenyltin sulfide ($Ph_2Sn{=}S$) and silver salts ($AgClO_4$, $AgSbF_6$, AgOTf) was reported from our laboratory.12) Then, the synthesis of ribonucleosides from methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) and silylated nucleoside bases was tried by using the above combined catalyst system, and good results were obtained as reported in the previous communication.13) There, methoxycarbonyloxy group was noted to be an efficient leaving group for *N*-glycosylation and methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) was an effective and stable glycosyl donor. Further, it was shown that Lawesson's reagent was also effective as a partner of silver salts in *O*-glycosylation of 2,3,5-tri-*O*-benzyl-D-ribofuranose with several free alcohols,14) and therefore, the application of [Lawesson's reagent/silver salt] combined catalyst system to the synthesis of nucleosides has been sought for.

In this paper, we would like to describe in full an efficient method for the stereoselective syntheses of β-D-ribonucleosides from **1** and trimethylsilylated nucleoside bases by using [$Ph_2Sn{=}S$/silver salt] or [Lawesson's reagent/silver salt] combined catalyst system under mild conditions.

Results and Discussion

Use of Methyl Ribofuranosyl Carbonates as Glycosyl Donors. In the first place, a search for new glycosyl donors in the synthesis of ribonucleosides under mild conditions was made. It was expected that ribofuranosyl carbonate15) would be activated smoothly even by weak Lewis acids because carbonate has a stronger affinity toward Lewis acids compared with the corresponding ester. Then, the reaction of methyl 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl carbonate (**2**: α/β=ca. 1/4) with 2 equiv of trimethylsilylated uracil (**3**) was tried in the presence of 20 mol% of silver salts such as $AgClO_4$, $AgSbF_6$, AgOTf, or AgOTs and 40 mol% of $Ph_2Sn{=}S$ in acetonitrile at room temperature. The above mentioned silver salts gave good results except in the case of AgOTs ($AgClO_4$: yield 86%, $\alpha/\beta=21/79$; $AgSbF_6$: yield 78%, $\alpha/\beta=19/81$; AgOTf: yield 85%, $\alpha/\beta=21/79$; AgOTs: yield 6%, $\alpha/\beta=52/48$). The better yield and better β-selectivity were given when acetonitrile was used as a solvent although the stereoselectivity did not reach to the enough satisfactory level.

Next, stereoselective synthesis of β-D-ribonucleosides from methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl carbonate (**1**) and trimethylsilylated uracil (**3**) was studied by utilizing the assistance of neighboring effect. In such type of reaction, pure β-anomer must be employed because α-anomer is far less reactive compared with β-anomer. Then, pure β-anomer **1** was prepared by recrystallization since it could not be purified by silica-gel column chromatography. First, the reaction of **1** with trimethylsilylated uracil (**3**: 2 equiv) was tried by using 20 mol% of AgOTf and 40 mol% of $Ph_2Sn{=}S$ at room temperature in acetonitrile, but no reaction took place at all. Since reactivity of **1** is lower than the corresponding 2,3,5-tri-*O*-benzyl compound **2**, the above reaction was carried out at 40, 60, and 80 °C, respectively in order to examine the suitable reaction temperature, and the desired product was obtained in high yield with perfect β-selectivity in each case (Table 1, Entries 1—3). The effect of solvent was screened in the above reaction with 1.2 equiv of **3** at 60 °C (at suitable temperature), and acetonitrile gave the best result (Table 1, Entries 4—6). Further, it was found that the present reaction was efficiently promoted by using even as little as 10 mol% of AgOTf and 20 mol% of $Ph_2Sn{=}S$ (Table 1, Entry 7).

Next, two other leaving groups, acetoxy and iodoacetoxy groups, at the C-1 position of **1** were examined, and it was found that these groups were less effective compared with the methoxycarbonyloxy group (Table 1, Entries 7—9). Several carbonates (phenyl, allyl, methoxyethyl, chloromethyl, etc.) other than methyl carbonate were prepared, but only methyl carbonate (**1**) was purified by recrystallization to give pure β-anomer.

Use of [Diphenyltin Sulfide/Silver Salt] Combined Catalyst System. As mentioned above, combined use of $Ph_2Sn{=}S$ and silver salts effectively promoted the present *N*-glycosylation. Next, the amount of $Ph_2Sn{=}S$ was examined in the reaction of **1** and trimethylsilylated uracil (**3**: 1.2 equiv) by using 10 mol% of AgOTf at 60 °C and the corresponding ribonucleosides were obtained in quantitative yields when not more than 20 mol% of $Ph_2Sn{=}S$ was used (Table 2, Entries 1—4).

Several β-ribonucleosides were prepared by the above procedure in good yields with perfect β-selectivity (Table 3). The reaction of **1** with trimethylsilylated thymine (1.2 equiv) or theophylline (1.5 equiv) also proceeded smoothly like in the case of trimethylsilylated uracil (**3**) (Table 3, Entries 2 and 3).

Concerning the synthesis of N^4-benzoylcytidine derivative (**7**), the reaction conditions such as the kind of silver salts, the molar ratio of silver salts and nucleoside bases, as well as the nature of solvents were carefully examined, and the corresponding nucleoside **7** was isolated along with N^4-debenzoyl compound **8**, which was converted to **7** on heating in xylene with benzoic anhydride (Fig. 1).

In the case of the adenosine derivative (**9**) synthesis, two by-products which might be the isomers were observed by TLC analysis when AgOTf was used as a silver salt. They were slowly converted to the desired compound **9** under the above conditions, but one of them was not perfectly disappeared even after prolonged reaction. The result indicates that severer conditions were required compared with those of the uridine synthesis. Then, the reaction was carried out in the presence of 20 mol% of $AgClO_4$ instead of AgOTf and 40 mol% of $Ph_2Sn{=}S$ in propiononitrile and the corresponding nucleoside **9** was isolated along with N^6-debenzoyl compound (**10**) similar to the case of cytidine (Fig. 1). It is assumed that compounds **8** and **10** were produced by an attack of methoxide anion, generated by decomposition of the methoxycarbonyloxy group, on compounds **7** and **9**, respectively.

The N^2-acetylguanosine derivative (**11**) was also synthesized in good yield from **1** and pertrimethylsilylated N^2-acetylguanine by using propiononitrile as a solvent without accompanying N^2-deacetyl compound.

Syntheses of typical β-ribonucleosides were then successfully performed by using new glycosyl donor **1** and [$Ph_2Sn{=}S$/silver salt] combined catalyst system under mild conditions.

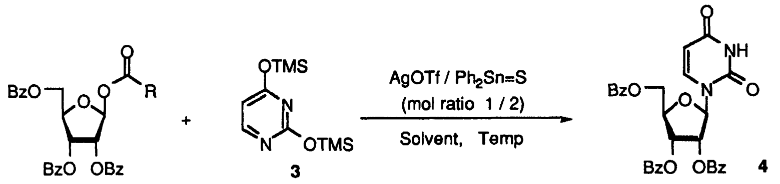
Use of [Lawesson's Reagent/Silver Salt] Combined Catalyst System. First, the reaction of **1** with trimethylsilylated uracil (**3**) was tried at 60 °C by using 10 mol% of AgOTf and 5 mol% of Lawesson's reagent which exists as a dimeric structure, and the corresponding ribonucleoside (**4**) was obtained in 97% yield with perfect β-selectivity (Table 2, Entry 5). Next, it was found that yield of 2′,3′,5′-tri-*O*-benzoyl-β-D-uridine (**4**) was decreased when excess amount, i.e. 20 mol%, of Lawesson's reagent was used (Table 2, Entries 5—7).

The effect of silver salts was examined and the best result was given when AgOTf was used (AgOTf: yield 97%, $AgClO_4$: yield 88%, $AgSbF_6$: yield 91%, other conditions: Lawesson's reagent = 5 mol%, acetonitrile as a solvent, 60 °C) (Table 4, Entries 1—3). The effect of solvents was also screened in the reaction (conditions: AgOTf=20 mol%, Lawesson's reagent=10 mol%, 60 °C), and aliphatic nitrile such as acetonitrile and propiononitrile gave good results (Table 4, Entries 4—8).

Further, several β-ribonucleosides were synthesized by the modified conditions of the procedures previously shown in the reactions using [$Ph_2Sn{=}S$/silver salt] catalyst system. In case of thymidine derivative (**5**) synthesis, the result was almost the same when the reaction was carried out at 80 °C.

Similarly, $AgClO_4$ gave better results compared with AgOTf in cases of syntheses of cytidine (**7**) and adenosine derivatives (**9**). Especially, in case of cytidine derivative (**7**), N^4-debenzoyl compound (**8**) was not isolated and the corresponding ribonucleoside (**7**) was obtained in good yield. Amount of the undesired N^6-debenzoyl adenosine derivative (**10**) also decreased and total yield of **9** and **10** was higher in comparison with the result employing [$Ph_2Sn{=}S$/silver salt] combined catalyst system.

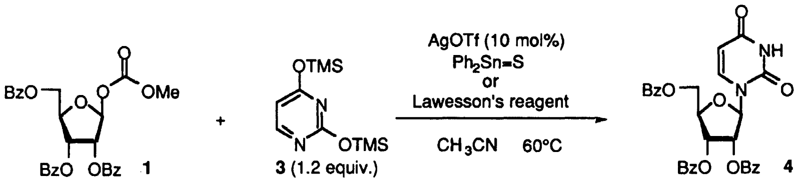
Table 1. Synthesis of 2′,3′,5′-Tri-*O*-benzoyl-*β*-D-uridine by Using [Diphenyltin Sulfide/Silver Salt] Catalyst System



Entry	R	AgOTf/mol%	**3**/equiv	Temp/°C	Time/h	Solvent	Yield/%[a]
1	OMe	20	2.0	40	20.0	CH_3CN	Quant.
2	OMe	20	2.0	60	3.5	CH_3CN	97
3	OMe	20	2.0	80	2.0	CH_3CN	Quant.
4	OMe	20	1.2	60	7.5	1,2-Dichloroethane	Quant.
5	OMe	20	1.2	60	5.0	Benzene	36
6	OMe	20	1.2	60	4.0	CH_3CN	Quant.
7	OMe	10	1.2	60	4.0	CH_3CN	Quant.
8	CH_3	10	1.2	60	6.0	CH_3CN	56
9	CH_2I	10	1.2	60	6.0	CH_3CN	38

a) Isolated yield.

Table 2. Effect of the Amount of Diphenyltin Sulfide or Lawesson's Reagent in Synthesis of 2′,3′,5′-Tri-*O*-benzoyl-*β*-D-uridine



Entry	Partner of AgOTf/mol%		Time/h	Yield/%[a]
1	$Ph_2Sn{=}S$	10	4.0	Quant.
2	$Ph_2Sn{=}S$	20	4.0	Quant.
3	$Ph_2Sn{=}S$	30	4.0	Quant.
4	$Ph_2Sn{=}S$	40	4.0	Quant.
5	Lawesson's reagent	5	6.5	97
6	Lawesson's reagent	10	3.0	96
7	Lawesson's reagent	20	10.0	83

a) Isolated yield.

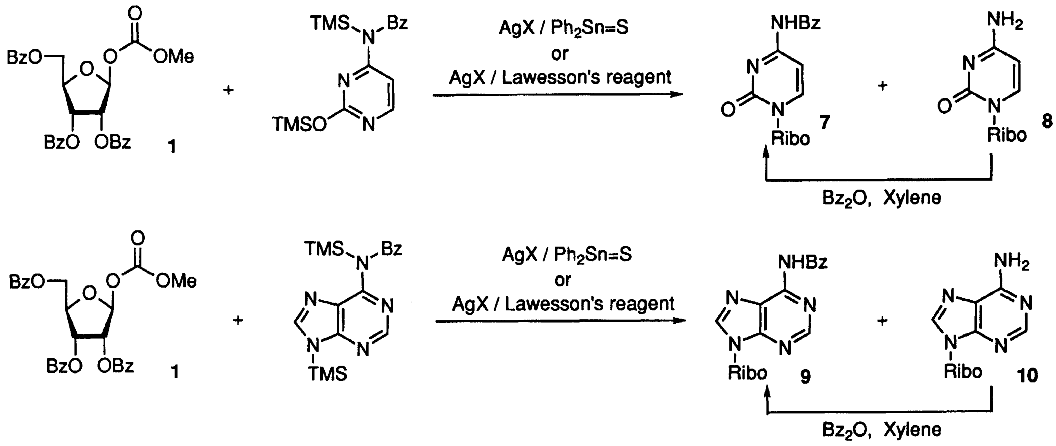
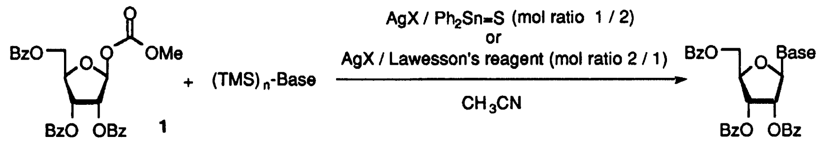


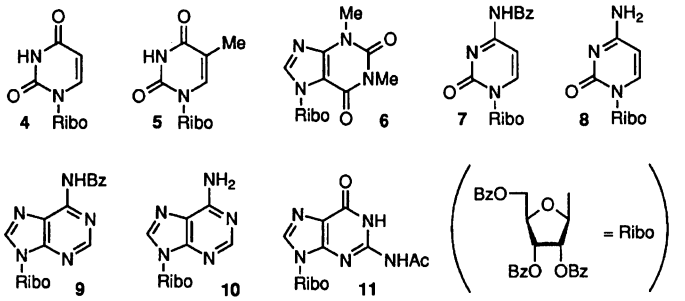
Fig. 1. The cytidine and adenosine derivatives were isolated along with the *N*-debenzoyl compounds.

A better result was attained in synthesis of N^2-acetylguanosine derivative (**11**) under milder conditions even when the amount of AgOTf together with Lawesson's reagent was less and the temperature was lower (60 °C)

Table 3. Synthesis of β-D-Ribonucleosides by Using [Diphenyltin Sulfide/Silver Salt] or [Lawesson's Reagent/Silver Salt] Catalyst System



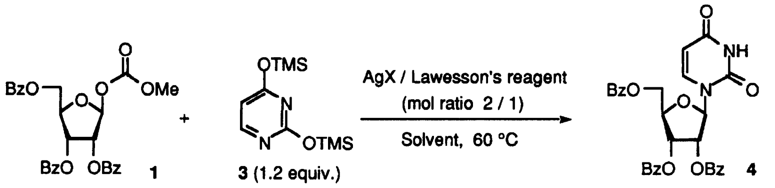
Products in Table. 3



Entry	(TMS)$_n$-Base/equiv	Ph$_2$Sn=S				Lawesson's reagent			
		AgX/mol%	Temp/°C	Time/h	Yield/%[a]	AgX/mol%	Temp/°C	Time/h	Yield/%[a]
1	Uracil 1.2	AgOTf(10)	60	4.0	Quant.	AgOTf(10)	60	6.5	97
2	Thymine 1.2	AgOTf(10)	60	5.0	96	AgOTf(10)	80	5.0	95
3	Theophylline 1.5	AgOTf(10)	60	1.5	96	AgOTf(10)	80	6.5	95
4	N^4-Benzoylcytosine 1.5	AgClO$_4$(30)	80	4.5	89[b]	AgClO$_4$(30)	80	4.0	94
5	N^6-Benzoyladenine 1.5	AgClO$_4$(20)	Reflux[e]	14.0	83[c]	AgClO$_4$(20)	80	4.0	Quant.[d]
6	N^2-Acetylguanine 1.5	AgOTf(30)	Reflux[e]	16.0	77	AgOTf(20)	60	4.0	81

a) Isolated yield. b) The corresponding ribonucleoside was isolated (32%) along with the N-debenzoyl compound (57%). c) The corresponding ribonucleoside was isolated (49%) along with the N-debenzoyl compound (34%). d) The corresponding ribonucleoside was isolated (74%) along with the N-debenzoyl compound (24%). e) Propiononitrile was used instead of acetonitrile as a solvent.

Table 4. Synthesis of 2′,3′,5′-Tri-O-benzoyl-β-D-uridine by Using [Lawesson's Reagent/Silver Salt] Catalyst System



Entry	AgX/mol%	Solvent	Time/h	Yield/%[a]
1	AgOTf 10	CH$_3$CN	6.5	97
2	AgClO$_4$ 10	CH$_3$CN	3.5	88
3	AgSbF$_6$ 10	CH$_3$CN	7.0	91
4	AgOTf 20	Benzene	9.0	71
5	AgOTf 20	Toluene	9.0	87
6	AgOTf 20	1,2-Dichloroethane	9.0	81
7	AgOTf 20	EtCN	4.0	Quant.
8	AgOTf 20	CH$_3$CN	5.0	Quant.

a) Isolated yield.

compared with that by using [Ph$_2$Sn=S/AgOTf] combined catalyst system.

Thus, it was found that [Lawesson's reagent/silver salt] catalyst system was also effective for syntheses of ribonucleosides having either purine and pyrimidine bases.

It is concluded that the combined use of silver salts and Ph$_2$Sn=S or Lawesson's reagent effectively catalyzed the syntheses of β-D-ribonucleosides from **1** and trimethylsilylated nucleoside bases under mild conditions and several ribonucleosides were synthesized in better yields by the present method compared with conventional methods.[9,10] Moreover, it is noted that two combined catalyst systems are prepared by only mixing in situ two stable reagents, $Ph_2Sn{=}S$ and silver salts or Lawesson's reagent and silver salts, which are easier to handle than Lewis acids such as TMSOTf and $SnCl_4$.

Experimental

All melting points are uncorrected. IR spectra were determined on a Horiba FT-300 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-EX270L spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a JMS-HX100 and a JMS-SX102A spectrometer. Microanalyses were performed with a Yanako C, H, N analyzer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Purification of products was performed by column chromatography on silica gel (Merck, Art. 7734 Kieselgel 60) or preparative TLC on silica gel (Wacogel B-5F).

2,3,5-Tri-*O*-benzyl-D-ribofuranose,[16] 2,3,5-tri-*O*-benzoyl-D-ribofuranose,[17] and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[17] were prepared by the previously reported methods. Diphenyltin sulfide (TCI) and AgOTf (Aldrich, TCI, etc.) are commercially available. Dichloromethane, 1,2-dichloroethane, acetonitrile, and propiononitrile were distilled successively from P_2O_5, and CaH_2, and stored over molecular sieves (MS). Toluene and benzene were distilled from P_2O_5 and stored over MS.

Silylations of nucleoside bases were carried out according to the literature method.[10] Persilylated uracil (**3**) was synthesized from uracil, hexamethyldisilazane, and chlorotrimethylsilane, distilled and stored as a solution in 1,2-dichloroethane. In the case of the other persilylated nucleoside bases, distillation was omitted and the residue was dissolved in 1,2-dichloroethane after evaporation of reagents, then used immediately without storage.

Preparation of Methyl 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl Carbonate (2). To a stirred solution of 2,3,5-tri-*O*-benzyl-D-ribofuranose (2.4 mmol) in pyridine (5.0 ml) was added a solution of methyl chloroformate (3.6 mmol) in dichloromethane (3.0 ml) at 0 °C. After being stirred for 1 h at room temperature, the mixture was poured into sat. aqueous $NaHCO_3$, then extracted with AcOEt. The extracts were washed successively with water, sat. aqueous $CuSO_4$, and sat. aqueous NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by deactivated silica-gel column chromatography ($SiO_2/H_2O=3/1$, w/w) to give **2** as a mixture of α- and β-anomers (ca. 1 : 3) in 87% yield. **2β**: IR (neat) 1757 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=3.57$ (1H, dd, $J=11.0$ and 4.8 Hz, 5A-H), 3.67 (1H, dd, $J=11.0$ and 3.5 Hz, 5B-H), 3.74 (3H, s, OCH_3), 3.98 (1H, d, $J=4.3$ Hz, 2-H), 4.14 (1H, dd, $J=7.4$ and 4.3 Hz, 3-H), 4.35—4.45 (1H, m, 4-H), 4.40 and 4.47 (2H, AB, $J=7.1$ Hz, CH_2Ph), 4.51 and 4.56 (2H, AB, $J=8.9$ Hz, CH_2Ph), 4.61 and 4.73 (2H, AB, $J=11.7$ Hz, CH_2Ph), 6.08 (1H, s, 1-H), 7.15—7.5 (15H, m); ^{13}C NMR ($CDCl_3$) $\delta=97.99$ (C-1), 155.02 (C=O); FABMS (NBA+NaI) m/z 501 $[M+Na]^+$. Found: C, 69.87; H, 6.36%. Calcd for $C_{28}H_{30}O_7\cdot 0.15H_2O$: C, 69.88; H, 6.35%. **2α**: ^{1}H NMR ($CDCl_3$) $\delta=3.78$ (3H, s, OCH_3), 6.15 (1H, d, $J=4.3$ Hz, 1-H); ^{13}C NMR ($CDCl_3$) $\delta=101.80$ (C-1), 154.00 (C=O).

Preparation of Methyl 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl Carbonate (1). To a stirred solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranose (5.6 mmol) and methyl chloroformate (11.2 mmol) in dichloromethane (10 ml) was added triethylamine (28.0 mmol) dropwise at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then sat. aqueous $NaHCO_3$ was added to it. The mixture was extracted with dichloromethane, and the extracts were washed with sat. aqueous NaCl, dried over Na_2SO_4, and concentrated. The residue was purified by silica-gel column chromatography to give the crude carbonate (**1**). Recrystallization from benzene–hexane or Et_2O–hexane afforded pure β-anomer (yield 64%). **1β**: Mp 97.5—98.5 °C (benzene–hexane); $[\alpha]_D^{28}$ +30.2° (c 1.00, $CHCl_3$); IR (KBr) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=3.76$ (3H, s, OCH_3), 4.57 (1H, dd, $J=12.2$ and 4.3 Hz, 5A-H), 4.73 (1H, dd, $J=12.2$ and 3.6 Hz, 5B-H), 4.83 (1H, m, 4-H), 5.86 (1H, d, $J=5.0$ Hz, 2-H), 5.94 (1H, dd, $J=7.3$ and 5.0 Hz, 3-H), 6.34 (1H, s, 1-H), 7.25—7.63 (9H, m), 7.85—7.94 (2H, m), 7.96—8.06 (2H, m), 8.06—8.15 (2H, m); ^{13}C NMR ($CDCl_3$) $\delta=101.28$ (C-1), 153.75, 164.83, 165.12, 165.98; FABMS (NAB+NaI) m/z 543 $[M+Na]^+$. Found: C, 64.70; H, 4.71%. Calcd for $C_{28}H_{24}O_{10}$: C, 64.61; H, 4.65%.

Preparation of 2,3,5-Tri-*O*-benzoyl-1-*O*-iodoacetyl-β-D-ribofuranose (12). To a stirred suspension of KF (39 mmol) in acetonitrile (3.8 ml) was added a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranose (2.2 mmol) and iodoacetyl chloride (3.6 mmol) in dichloromethane (10 ml) at 0 °C. After being stirred for 12 h at room temperature, the mixture was filtered through a glass filter, then concentrated. The residue was purified by deactivated silica-gel column chromatography ($SiO_2/H_2O=3/1$, w/w) to give **12** as a mixture of α- and β-anomers in 83% yield. The pure β-anomer (**12β**) was obtained by recrystallization and used as such. **12β**: Mp 136—137 °C (benzene–hexane); $[\alpha]_D^{27}$ +21.2° (c 1.00, $CHCl_3$); IR (KBr) 1726 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=3.56$ and 3.61 (2H, AB, $J=10.2$ Hz, $COCH_2I$), 4.56 (1H, dd, $J=13.0$ and 6.1 Hz, 5A-H), 4.55—4.87 (2H, m, 4- and 5B-H), 5.82 (1H, dd, $J=5.0$ and 0.7 Hz, 2-H), 5.90 (1H, dd, $J=6.6$ and 5.0 Hz, 3-H), 6.44 (1H, d, $J=0.7$ Hz, 1-H), 7.28—7.66 (9H, m), 7.85—7.93 (2H, m), 7.96—8.04 (2H, m), 8.04—8.12 (2H, m); ^{13}C NMR ($CDCl_3$) $\delta=99.61$ (C-1), 164.85, 165.23, 165.86, 166.92; FABMS (NBA+NaI) m/z 653 $[M+Na]^+$. Found: C, 53.54; H, 3.69%. Calcd for $C_{28}H_{23}IO_9$: C, 53.35; H, 3.68%.

Preparation of β-D-Ribonucleosides by Using [$Ph_2Sn{=}S$/Silver Salt] Combined Catalyst System. All ribonucleosides produced by our method were identified by comparison of their infrared and NMR spectra with those of ribonucleosides produced by the Vorbrüggen method. A typical reaction procedure is described for the reaction of **1** and 2,4-bis(trimethylsilyloxy)pyrimidine (**3**); to AgOTf (0.015 mmol) was added a solution of $Ph_2Sn{=}S$ (0.03 mmol) in acetonitrile (2 ml), then **1** (0.15 mmol) and **3** (0.18 mmol) in acetonitrile (3 ml) were added at room temperature. After heating the reaction at 60 °C for 4 h, saturated aqueous $NaHCO_3$ was added at room temperature to quench it. The mixture was filtered through a celite pad, then extracted with AcOEt, and the extracts were washed with sat. aqueous NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by TLC (silica gel) to give 2′,3′,5′-tri-*O*-benzoyl-β-D-uridine (**4**) (quant.): Mp 146— 146.5 °C (dichloromethane–hexane); $[\alpha]_D^{29}$ −53.6° (c 1.00, $CHCl_3$); IR

(KBr) 1722, 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.67 (1H, dd, J=11.9 and 4.0 Hz, 5′A-H), 4.66—4.77 (1H, m, 4′-H), 4.85 (1H, dd, J=11.9 and 2.3 Hz, 5′B-H), 5.61 (1H, dd, J=8.3 and 2.3 Hz, 5-H), 5.75 (1H, dd, J=5.9 and 5.6 Hz, 2′-H), 5.89 (1H, dd, J=5.9 and 4.3 Hz, 3′-H), 6.32 (1H, d, J=5.6 Hz, 1′-H), 7.3—7.7 (10H, m), 7.9—8.05 (4H, m), 8.05—8.15 (2H, m), 8.34 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ=88.17 (C-1′), 103.41, 139.76, 150.28, 163.21, 165.30, 165.33, 166.07; FABMS (NAB+NaI) m/z 601 $[M-H+2Na]^+$ 579 $[M+Na]^+$. Found: C, 64.49; H, 4.47; N, 4.90%. Calcd for $C_{30}H_{24}N_2O_9$: C, 64.75; H, 4.35; N, 5.03%.

Physical properties of other products are as follows:

2′,3′,5′-Tri-*O*-benzyl-β-D-uridine. $[\alpha]^{31}_{D}$ +147.6° (c 1.28, $CHCl_3$); IR (neat) 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.69 (1H, dd, J=10.9 and 1.7 Hz, 5′A-H), 3.8—4.0 (2H, m, 2′- and 5′B-H), 4.03 (1H, dd, J=7.6 and 4.6 Hz, 3′-H), 4.3—4.4 (1H, m, 4′-H), 4.33 and 4.57 (2H, AB, J=11.9 Hz, CH_2Ph), 4.44 and 4.49 (2H, AB, J=11.2 Hz, CH_2Ph), 4.76 and 4.83 (2H, AB, J=12.4 Hz, CH_2Ph), 5.14 (1H, dd, J=8.3 and 2.0 Hz, 5-H), 6.04 (1H, d, J=2.0 Hz, 1′-H), 7.15—7.45 (15H, m), 7.88 (1H, d, J=8.3 Hz, 6-H), 8.8—8.9 (1H, m, NH); ^{13}C NMR ($CDCl_3$) δ=88.25 (C-1′), 101.33, 140.05, 150.26, 164.01; FABMS (NBA+NaI) m/z 559 $[M-H+2Na]^+$ 537 $[M+Na]^+$. Found: C, 69.85; H, 5.91; N, 5.20%. Calcd for $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44%.

2′,3′,5′-Tri-*O*-benzyl-α-D-uridine. $[\alpha]^{29}_{D}$ −10° (c 0.20, $CHCl_3$); IR (neat) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.47 (1H, dd, J=10.9 and 3.6 Hz, 5′A-H), 3.61 (1H, dd, J=10.9 and 2.8 Hz, 5′B-H), 4.09 (1H, t, J=5.0 Hz), 4.35 (1H, t, J=5.0 Hz), 4.3—4.45 (1H, m, 4′-H), 4.45 and 4.54 (2H, AB, J=11.9 Hz, CH_2Ph), 4.46 and 4.56 (2H, AB, J=11.6 Hz, CH_2Ph), 4.47 and 4.62 (2H, AB, J=11.5 Hz, CH_2Ph), 5.64 (1H, dd, J=8.2 and 1.8 Hz, 5-H), 6.31 (1H, d, J=4.9 Hz, 1′-H), 7.15—7.4 (15H, m), 7.69 (1H, d, J=8.2 Hz, 6-H), 9.7—10.0 (1H, m, NH); ^{13}C NMR ($CDCl_3$) δ=84.76 (C-1′), 100.92, 142.43, 150.78, 163.79; FABMS (NBA+NaI) m/z 559 $[M-H+2Na]^+$ 537 $[M+Na]^+$. Found: C, 69.66; H, 5.92; N, 5.19%. Calcd for $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44%.

2′,3′,5′-Tri-*O*-benzoyl-5-methyl-β-D-uridine (5). Mp 98—99.5 °C (dichloromethane–hexane); $[\alpha]^{31}_{D}$ −89.2° (c 1.00, $CHCl_3$); IR (KBr) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.59 (3H, s, CH_3), 4.6—4.8 (2H, m, 4′- and 5′A-H), 4.89 (1H, d, J=10.6 Hz, 5′B-H), 5.77 (1H, t, J=6.3 Hz, 2′-H), 5.93 (1H, dd, J=6.3 and 3.6 Hz, 3′-H), 6.45 (1H, d, J=6.3 Hz, 1′-H), 7.17 (1H, s, 6-H), 7.3—7.7 (9H, m) 7.97 (4H, m), 8.14 (2H, d, J=7.9 Hz) 9.48 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ=12.04, 86.83 (C-1′), 112.13, 150.42, 163.56, 165.26, 165.34, 165.93; FABMS (NBA+NaI) m/z 615 $[M-H+2Na]^+$ 593 $[M+Na]^+$. Found: C, 62.97; H, 4.51; N, 4.65%. Calcd for $C_{31}H_{26}N_2O_9\cdot 1.1H_2O$: C, 63.07; H, 4.81; N, 4.75%.

7-(2′,3′,5′-Tri-*O*-benzoyl-β-D-ribofuranosyl)theophylline (6). Mp 93—96 °C; $[\alpha]^{29}_{D}$ −42.6° (c 1.00, $CHCl_3$); IR (KBr) 1730, 1660, 1603, 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.37 (3H, s, CH_3), 3.57 (3H, s, CH_3), 4.74 (1H, dd, J=11.6 and 4.3 Hz, 5′A-H), 4.7—4.9 (1H, m, 4′-H), 4.89 (1H, dd, J=11.6 and 3.0 Hz, 5′B-H), 6.05 (1H, dd, J=5.9 and 5.0 Hz), 6.09 (1H, dd, J=5.9 and 5.0 Hz), 6.60 (1H, d, J=5.0 Hz, 1′-H), 7.25—7.65 (9H, m), 7.85—8.2 (6H, m), 7.94 (1H, s, 8-H); ^{13}C NMR ($CDCl_3$) δ=28.14, 29.83, 88.73 (C-1′), 106.52, 139.89, 149.54, 151.36, 154.63, 164.96, 165.19, 166.07; FABMS (NBA+NaI) m/z 647 $[M+Na]^+$. Found: C, 63.33; H, 4.69; N, 8.62%. Calcd for $C_{33}H_{28}N_4O_9$: C, 63.46; H, 4.52; N, 8.97%.

***N*^{4}, 2′,3′,5′-Tetra-*O*-benzoyl-β-D-cytidine (7).** Mp 206.5—208 °C; $[\alpha]^{31}_{D}$ −47.1° (c 1.00, $CHCl_3$); IR (KBr) 1734, 1666, 1620, 1554, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 4.65—4.95 (3H, m, 4′-, 5′A-, and 5′B-H), 5.75—6.0 (2H, m, 2′- and 3′-H), 6.46 (1H, d, J=4.0 Hz, 1′-H), 7.3—7.67 (13H, m), 7.85—8.15 (9H, m), 8.92 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ=89.56 (C-1′), 144.28, 162.64, 165.16, 165.23, 166.07; FABMS (NBA+NaI) m/z 704 $[M-H+2Na]^+$ 682 $[M+Na]^+$. Found: C, 66.61; H, 4.39; N, 6.22%. Calcd for $C_{37}H_{29}N_3O_9\cdot 0.4H_2O$: C, 66.64; H, 4.50; N, 6.30%.

2′,3′,5′-Tri-*O*-benzoyl-β-D-cytidine (8). Mp 182—183 °C; $[\alpha]^{32}_{D}$ −25.5° (c 1.00, $CHCl_3$); IR (KBr) 1726, 1657, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.6—4.85 (3H, m), 5.85—6.05 (3H, m), 6.12 (1H, d, J=4.0 Hz, 1′-H), 6.90 (1H, br, NH), 7.25—7.6 (10H, m), 7.85—8.0 (4H, m), 8.07 (2H, d, J=7.8 Hz), 8.05 (1H, br, NH); ^{13}C NMR ($CDCl_3$) δ=91.03 (C-1′), 96.30, 141.40, 155.62, 165.23, 165.41, 166.22; FABMS (NBA+NaI) m/z 600 $[M-H+2Na]^+$ 578 $[M+Na]^+$. Found: C, 64.41; H, 4.59; N, 7.24%. Calcd for $C_{30}H_{25}N_3O_8\cdot 0.2H_2O$: C, 64.44; H, 4.58; N, 7.52%.

***N*^{6},2′,3′,5′-Tetra-*O*-benzoyl-β-D-adenosine (9).** Mp 88—92 °C; $[\alpha]^{29}_{D}$ −88.0° (c 1.00, $CHCl_3$); IR (KBr) 1728, 1608, 1587 cm^{-1}; ^{1}H NMR ($CDCl_3$)[18] δ=4.71 (1H, dd, J=12.0 and 4.1 Hz, 5′A-H), 4.85 (1H, m, 4′-H), 4.94 (1H, dd, J=12.0 and 3.1 Hz, 5′B-H), 6.27 (1H, dd, J=5.6 and 5.3 Hz, 2′-H), 6.42 (1H, dd, J=5.6 and 4.6 Hz, 3′-H), 6.50 (1H, d, J=5.3 Hz, 1′-H), 7.3—7.5 (12H, m), 7.9—8.2 (8H, m), 8.19 (1H, s, 2-H), 8.70 (1H, s, 8-H), 9.21 (1H, bs, NH); ^{13}C NMR ($CDCl_3$) δ=87.01 (C-1′), 123.65, 141.74, 149.79, 151.68, 152.92, 164.71, 165.12, 165.32, 166.13; FABMS (NBA+DMSO) m/z 684 $[MH]^+$. Found: C, 60.98; H, 4.07; N, 9.06%. Calcd for $C_{38}H_{29}N_5O_{11}\cdot H_2O$: C, 60.88; H, 4.17; N, 9.34%.

2′,3′,5′-Tri-*O*-benzoyl-β-D-adenosine (10). Mp 90—94 °C; $[\alpha]^{32}_{D}$ −73.7° (c 1.00, $CHCl_3$); IR (KBr) 1728, 1641, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.72 (1H, dd, J=11.7 and 4.1 Hz, 5′A-H), 4.8—4.9 (1H, m, 4′-H), 4.91 (1H, dd, J=11.7 and 3.1 Hz, 5′B-H), 6.15—6.45 (2H, br, NH_2), 6.30 (1H, t, J=5.0 Hz, 2′-H), 6.41 (1H, t, J=5.0 Hz, 3′-H), 6.45 (1H, d, J=5.0 Hz, 1′-H), 7.3—7.65 (9H, m), 7.9—8.15 (6H, m), 8.00 (1H, s), 8.28 (1H, s); ^{13}C NMR ($CDCl_3$) δ=86.76 (C-1′), 120.02, 138.96, 149.63, 153.30, 155.72, 165.09, 165.25, 166.09; FABMS (NBA+DMSO) m/z 580 $[MH]^+$. Found: C, 62.32; H, 4.31; N, 11.55%. Calcd for $C_{31}H_{25}N_5O_7\cdot H_2O$: C, 62.31; H, 4.55; N, 11.72%.

***N*^{2}-Acetyl-2′,3′,5′-tri-*O*-benzoyl-β-D-guanosine (11).** Mp 130—135 °C; $[\alpha]^{31}_{D}$ −65.2° (c 1.00, $CHCl_3$); IR (KBr) 1726, 1684, 1610, 1558 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 2.32 (3H, s, CH_3CO), 4.60 (1H, dd, J=11.6 and 5.6 Hz, 5′A-H), 4.75 (1H, m, 4′-H), 4.86 (1H, dd, J=11.6 and 5.3 Hz, 5′B-H), 6.23 (1H, dd, J=5.6 and 5.3 Hz, 3′-H), 6.28 (1H, d, J= 4.3 Hz, 1′-H), 6.37 (1H, dd, J=5.3 and 4.3 Hz, 2′-H), 7.2—7.4 (6H, m), 7.4—7.6 (3H, m), 7.8—7.95 (6H, m), 7.96 (1H, s, 8-H), 10.50 (1H, s, NH), 12.12 (1H, s, NH); ^{13}C NMR ($CDCl_3$) δ=24.23, 88.23 (C-1′), 122.25, 138.94, 147.66, 147.87, 155.44, 165.16, 165.21, 166.40, 172.70; FABMS (NBA+DMSO) m/z 638 $[MH]^+$. Found: C, 60.74; H, 4.29; N, 10.44%. Calcd for $C_{33}H_{27}N_5O_9\cdot 0.7H_2O$: C, 60.96; H, 4.40; N, 10.77%.

Preparation of β-D-Ribonucleosides by Using

[Lawesson's Reagent/Silver Salt] Combined Catalyst System. A typical reaction procedure is described for the reaction of **1** and 2,4-bis(trimethylsilyloxy)pyrimidine (**3**); to AgOTf (0.015 mmol) was added a suspension of Lawesson's reagent (0.0075 mmol) in acetonitrile (2 ml). After stirring this mixture for 15 min at room temperature, a solution of **1** (0.15 mmol) and **3** (0.18 mmol) in acetonitrile (3 ml) was added to it at room temperature. After heating the reaction at 60 °C for 6.5 h, saturated aqueous $NaHCO_3$ was added at room temperature to quench it. The mixture was filtered through a celite pad, then extracted with AcOEt, and the extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. Then residue was purified by TLC (silica gel) to give 2′,3′,5′-tri-*O*-benzoyl-β-D-uridine (**4**: 97% yield).

References

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

2) K. A. Jacobson, P. J. M. van Galen, and M. Williams, *J. Med. Chem.*, **35**, 407 (1992); V. Nair and A. J. Fasbender, *Tetrahedron*, **49**, 2169 (1993).

3) M. D. Erion, S. Niwas, J. D. Rose, S. Ananthan, M. Allen, J. A. Secrist, III, Y. S. Babu, C. E. Bugg, W. C. Guida, S. E. Ealick, and J. A. Montgomery, *J. Med. Chem.*, **36**, 3771 (1993).

4) F. Seela, H. Rosemeyer, and S. Fischer, *Helv. Chim. Acta*, **73**, 1602 (1990).

5) R. Noyori and M. Hayashi, *Chem. Lett.*, **1987**, 57.

6) M. I. Matheu, R. Echarri, and S. Castillón, *Tetrahedron Lett.*, **33**, 1093 (1992).

7) H. Sugimura, K. Sujino, and K. Osumi, *Tetrahedron Lett.*, **33**, 2515 (1992).

8) K. Sujino and H. Sugimura, *Chem. Lett.*, **1993**, 1187.

9) U. Niedballa and H. Vorbrüggen, *J. Org. Chem.*, **39**, 3654, 3660, 3664, 3668, and 3672 (1974); F. W. Lichtenthaler, P. Voss, and A. Heerd, *Tetrahedron Lett.*, **24**, 2141 (1974); M. Saneyoshi and E. Satoh, *Chem. Pharm. Bull.*, **27**, 2518 (1979).

10) H. Vorbrüggen and K. Krolikiewicz, *Angew. Chem., Int. Ed. Engl.*, **14**, 421 (1975); H. Vorbrüggen, K. Krolikiewicz, and B. Bennua, *Chem. Ber.*, **114**, 1234 (1981); H. Vorbrüggen and G. Höfle, *Chem. Ber.*, **114**, 1256 (1981); H. Vorbrüggen and B. Bennua, *Chem. Ber.*, **114**, 1279 (1981).

11) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 4489 (1930).

12) T. Mukaiyama and N. Shimomura, *Chem. Lett.*, **1993**, 781.

13) T. Mukaiyama, T. Matsutani, and N. Shimomura, *Chem. Lett.*, **1993**, 1627.

14) N. Shimomura and T. Mukaiyama, *Chem. Lett.*, **1993**, 1941.

15) Concerning the use of alkyl or aryl carbonates as glycosyl donors, equimolar amounts of catalysts or pyrolytic conditions are required to achieve the glycosylation reactions to form the corresponding glycosides: K. Suzuki, H. Maeta, T. Matsumoto, and G. Tsuchihashi, *Tetrahedron Lett.*, **29**, 3571 (1988); A. Marra, J. Esnault, A. Veyrieres, and P. Sinaÿ, *J. Am. Chem. Soc.*, **114**, 6354 (1992); Y. Ishido, S. Inaba, A. Matsuno, T. Yoshino, and H. Umezawa, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1382.

16) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

17) R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **76**, 763 (1954).

18) M.-C. Chapeau and L. J. Marnett, *J. Org. Chem.*, **58**, 7258 (1993).