

Y. Tarumi\*, K. Moriguchi and T. Atsumi

Takarazuka Research Center, Pharmaceuticals Research Laboratory, Sumitomo Chemical Co.,  
2-1, 4-chome, Takatsukasa, Takarazuka-shi, Hyogo-ken, 665 Japan  
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In the synthesis of glycosyl derivatives of 4-carbamoylimidazolium-5-olate (**2**) by the silyl-Hilbert-Johnson method using trimethylsilyl trifluoromethanesulfonate as catalyst, we obtained *N*-3 nucleosides **5** as major products and *N*-1, *N*-3-bis-nucleosides **6** as minor ones. The desired *N*-1 nucleosides **4** were isolated in only low yields. However, the yields of **4** were improved by adding *ca.* one equivalent of stannic chloride to the silylated 4-carbamoylimidazolium-5-olate (**3**). On the basis of nuclear magnetic resonance ( $^{13}\text{C}$  and  $^{29}\text{Si}$ ) and ultraviolet spectroscopic studies, we verify the formation of  $\sigma$ -complexes between the silylated base **3** and the Lewis acid (stannic chloride or trimethylsilyl trifluoromethanesulfonate), and we propose the structures of these complexes and the reaction mechanism.

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Bredinin (**1**), one of imidazole nucleosides [1], was isolated in 1974 from the culture filtrate of *Eupenicillium brefeldianum* [2] and its structure was determined as 4-carbamoyl-1- $\beta$ -D-ribofuranosylimidazolium-5-olate by X-ray crystallographic analysis [3]. The aglycone, 4-carbamoylimidazolium-5-olate (**2**) [4], of bredinin (**1**) has been known to possess cytotoxicity against L5178Y cells, as well as bredinin (**1**) [2]. Meanwhile, the antitumor activities of **2** against various experimental tumors were reported [5a-c] and this compound **2** is currently undergoing clinical evaluation as an antitumor agent. We have been interested in the antitumor activities of **2** and have undertaken the synthetic study to obtain its more active and water-soluble de-

rivatives including nucleosides.

Here we describe a regioselective glycosylation of **2** including the improved synthesis of bredinin (**1**), and discuss the formation and the structures of the  $\sigma$ -complexes between the silylated base **3** and stannic chloride or trimethylsilyl trifluoromethanesulfonate (TMS triflate), respectively.

### 1. Regioselective Glycosylation of **2**.

In the previous papers [6a,b], we reported that compound **2** has four reactive sites for electrophilic substitution such as acylation and alkylation; two ring nitrogens, 5-hydroxyl oxygen and an amide nitrogen (Figure 1). This

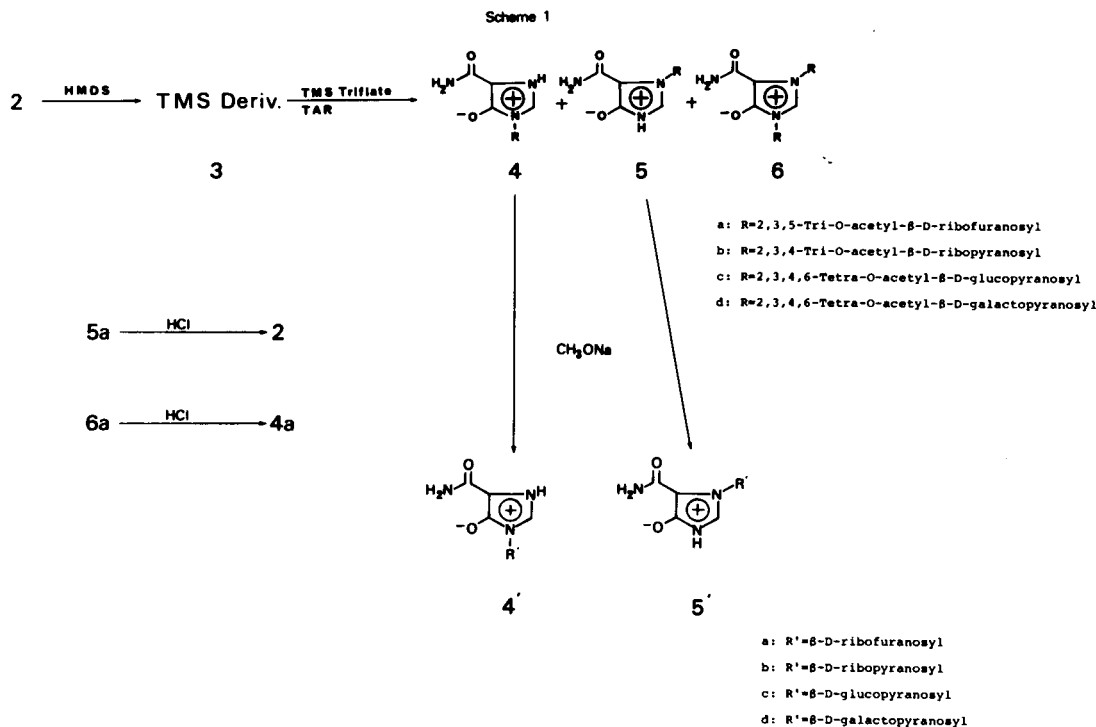


Table 1  
 Analytical Data for Nucleoside Derivatives of 2

Compound No.	R <sub>1</sub> and R <sub>2</sub>	Mp, °C (Solvent) [a]	Yield %	[α] <sub>D</sub> <sup>25</sup>	Formula (Molecular Weight)	Analysis, % Calcd./Found			Mass (m/e)
						C	H	N	
4a	R <sub>1</sub> = 2',3',5'-Tri- <i>O</i> -acetyl-β-D-ribofuranosyl, R <sub>2</sub> = H	201 dec (EtOH)	82.5 [b] 17.4 [c]	-26.3 (C 0.75, DMSO) [a]	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>9</sub> (385.33)	46.75	4.97	10.91	385, 259
						46.38	5.00	10.79	139, 127
4b	R <sub>1</sub> = 2',3',4'-Tri- <i>O</i> -acetyl-β-D-ribofuranosyl, R <sub>2</sub> = H	217.5 dec (EtOH-IPE)	54.5 [b] 11.0 [c]	+21.5 (C 0.10, H <sub>2</sub> O)	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>9</sub> (385.33) ¼H <sub>2</sub> O	46.21	5.04	10.78	385, 259
						46.18	4.96	10.69	127
4c	R <sub>1</sub> = 2',3',4',6'-Tetra- <i>O</i> -acetyl-β-D-glucopyranosyl, R <sub>2</sub> = H	222.5 dec (EtOH)	64.6 [b] 22.1 [c]	-26.5 (C 0.10, H <sub>2</sub> O)	C <sub>18</sub> H <sub>23</sub> N <sub>3</sub> O <sub>11</sub> (457.39) ¾CH <sub>3</sub> CO <sub>2</sub> H	45.91	5.24	8.92	457, 331
						45.84	5.06	8.76	169, 127
4d	R <sub>1</sub> = 2',3',4',6'-Tetra- <i>O</i> -acetyl-β-D-galactopyranosyl, R <sub>2</sub> = H	130-135 (MeOH)	66.7 [b] 5.9 [c]	+5.1 (C 0.10, H <sub>2</sub> O)	C <sub>18</sub> H <sub>23</sub> N <sub>3</sub> O <sub>11</sub> (457.39) ¾CH <sub>3</sub> CO <sub>2</sub> H	46.61	5.22	8.36	457, 331
						46.63	5.26	8.39	169, 127
5a	R <sub>1</sub> = 2',3',5'-Tri- <i>O</i> -acetyl-β-D-ribofuranosyl, R <sub>2</sub> = H	177-179 (EtOH-IPE)	60.7 [c]	+26.2 (C 0.11, H <sub>2</sub> O)	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>9</sub> (385.33) ½H <sub>2</sub> O	45.68 45.66	5.11 4.82	10.66 10.65	385, 259 139, 127
5b	R <sub>1</sub> = 2',3',4'-Tri- <i>O</i> -acetyl-β-D-ribofuranosyl, R <sub>2</sub> = H	242 dec (CHCl <sub>3</sub> -MeOH)	49.5 [c]	+26.7 (C 0.11, H <sub>2</sub> O)	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>9</sub> (385.33) ¼H <sub>2</sub> O	46.21	5.04	10.78	385, 259
						46.39	5.01	10.72	139, 127
5c	R <sub>1</sub> = 2',3',4',6'-Tetra- <i>O</i> -acetyl-β-D-glucopyranosyl, R <sub>2</sub> = H	218 dec (CHCl <sub>3</sub> -IPE)	49.2 [c]	-26.5 (C 0.10, H <sub>2</sub> O)	C <sub>18</sub> H <sub>23</sub> N <sub>3</sub> O <sub>11</sub> (457.39) ½H <sub>2</sub> O	46.35	5.19	9.01	457, 331
						46.22	5.14	8.82	271, 169
5d	R <sub>1</sub> = 2',3',4',6'-Tetra- <i>O</i> -acetyl-β-D-galactopyranosyl, R <sub>2</sub> = H	235 dec (MeOH)	47.4 [c]	+31.2 (C 0.09, H <sub>2</sub> O)	C <sub>18</sub> H <sub>23</sub> N <sub>3</sub> O <sub>11</sub> (457.39) ½H <sub>2</sub> O	46.35	5.19	9.01	457, 397
						46.13	5.06	8.95	169, 127
6a	R <sub>1</sub> = R <sub>2</sub> = 2',3',5'-Tri- <i>O</i> -acetyl-β-D-ribofuranosyl	91 (EtOH-IPE)	8.8 [c]	-9.0 (C 0.09, MeOH)	C <sub>26</sub> H <sub>33</sub> N <sub>3</sub> O <sub>16</sub> (643.55) ½IPE	50.14	5.80	6.05	643, 385
						49.78	5.80	6.05	259, 139
6b	R <sub>1</sub> = R <sub>2</sub> = 2',3',4'-Tri- <i>O</i> -acetyl-β-D-ribofuranosyl	160-167 (CHCl <sub>3</sub> -MeOH)	14.7 [c]	+1.9 (C 0.10, H <sub>2</sub> O)	C <sub>26</sub> H <sub>33</sub> N <sub>3</sub> O <sub>16</sub> (643.55) 3/2H <sub>2</sub> O	46.57	5.41	6.27	643, 514
						46.75	5.40	6.07	259, 127
6c	R <sub>1</sub> = R <sub>2</sub> = 2',3',4',6'-Tetra- <i>O</i> -acetyl-β-D-glucopyranosyl	148-153 (CHCl <sub>3</sub> -MeOH)	13.9 [c]	-25.3 (C 0.10, H <sub>2</sub> O)	C <sub>32</sub> H <sub>41</sub> N <sub>3</sub> O <sub>20</sub> (787.67) H <sub>2</sub> O	47.70	5.38	5.22	787, 456
						47.87	5.41	5.18	331, 169
6d	R <sub>1</sub> = R <sub>2</sub> = 2',3',4',6'-Tetra- <i>O</i> -acetyl-β-D-galactopyranosyl	128-132 CHCl <sub>3</sub> -MeOH)	9.7 [c]	-5.0 (C 0.10, H <sub>2</sub> O)	C <sub>32</sub> H <sub>41</sub> N <sub>3</sub> O <sub>20</sub> (787.67) H <sub>2</sub> O	47.70	5.38	5.22	727(M <sup>+</sup> -AcOH)
						48.02	5.39	5.13	457, 169
1	R <sub>1</sub> = β-D-Ribofuranosyl, R <sub>2</sub> = H	203.5 dec (H <sub>2</sub> O-CH <sub>3</sub> COCH <sub>3</sub> )	96.0	-24.4 (C 1.01, H <sub>2</sub> O)	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> O <sub>6</sub> (259.22) H <sub>2</sub> O	38.99 38.99	5.45 5.59	15.16 15.10	
4' b	R <sub>1</sub> = β-D-Ribopyranosyl, R <sub>2</sub> = H	271 dec (EtOH)	81.1	-31.4 (C 0.10, H <sub>2</sub> O)	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> O <sub>6</sub> (259.22) ¼H <sub>2</sub> O	40.99	5.16	15.93	
						41.07	5.17	16.03	
4' c	R <sub>1</sub> = β-D-Glucopyranosyl, R <sub>2</sub> = H	248 dec (MeOH)	85.1	-21.8 (C 0.09, H <sub>2</sub> O)	C <sub>10</sub> H <sub>15</sub> N <sub>3</sub> O <sub>7</sub> 289.24 3/2 H <sub>2</sub> O	40.76	5.34	14.26	
						41.05	5.40	13.93	
4' d	R <sub>1</sub> = β-D-Galactopyranosyl, R <sub>2</sub> = H	188 dec (MeOH-IPE)	80.9	+12.0 (C 0.09, H <sub>2</sub> O)	C <sub>10</sub> H <sub>15</sub> N <sub>3</sub> O <sub>7</sub> (289.24) ¾H <sub>2</sub> O	37.97	5.74	13.29	
						37.98	5.47	12.86	
5' a	R <sub>1</sub> = H, R <sub>2</sub> = β-D-Ribofuranosyl	193.5 dec (MeOH)	65.4	+62.1 (C 0.09, H <sub>2</sub> O)	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> (259.22) ½CH <sub>3</sub> OH	41.45	5.49	15.27	
						41.30	5.18	15.18	
5' b	R <sub>1</sub> = H, R <sub>2</sub> = β-D-Ribopyranosyl	162 dec (H <sub>2</sub> O)	98.9	-18.4 (C 0.10, H <sub>2</sub> O)	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> O <sub>6</sub> (259.22) H <sub>2</sub> O	38.99	5.45	15.16	
						38.68	5.07	14.96	

5'c	R <sub>1</sub> = H, R <sub>2</sub> =	261 dec	79.1	-6.9	C <sub>10</sub> H <sub>15</sub> N <sub>3</sub> O <sub>7</sub>	40.89	5.32	14.31
	β-D-Glucopyr- anosyl	(MeOH)		(C 0.09, H <sub>2</sub> O)	(289.24)	41.15	5.34	14.34
5'd	R <sub>1</sub> = H, R <sub>2</sub> =	245 dec	79.0	+23.1	C <sub>10</sub> H <sub>15</sub> N <sub>3</sub> O <sub>7</sub>	40.89	5.32	14.31
	β-D-Galactopyr- anosyl	(MeOH)		(C 0.11, H <sub>2</sub> O)	(289.24)	40.98	5.44	14.37

[a] EtOH: Ethanol, IPE: Diisopropyl Ether, MeOH: Methanol, DMSO: Dimethyl sulfoxide. [b] Using stannic chloride and TMS triflate. [c] Using TMS triflate only.

Table 2

<sup>13</sup>C and <sup>1</sup>H NMR Chemical Shifts [a] for Nucleoside Derivatives of 2

Compound No.	<sup>13</sup> C Chemical Shifts (ppm)						<sup>1</sup> H Chemical Shifts (ppm)		
	C-2	C-4	C-5	C-6	C-1'	C-1''	C-2-H	C-1'-H [b]	C-1''-H
4a	125.0	99.5	155.4	162.2	84.7		8.20	5.50 (d, J = 4.5 Hz)	
4b	124.4	98.2	155.0	161.8	75.2		8.39	5.64 (d, J = 9.1 Hz)	
4c	124.8	97.8	154.9	161.8	76.6		8.44	5.81 (d, J = 8.8 Hz)	
4d	124.7	98.1	155.0	161.9	77.1		8.40	5.76 (d, J = 6.5 Hz)	
5a	129.7	100.9	157.3	161.6	88.8		8.03	6.52 (d, J = 2.9 Hz)	
5b	131.9	101.1	156.5	161.7	78.8		8.03	6.82 (d, J = 9.4 Hz)	
5c	132.5	101.0	156.4	161.5	80.8		8.07	6.73 (d, J = 7.5 Hz)	
5d	132.2	101.2	156.8	161.7	80.9		7.97	6.76 (d, J = 7.7 Hz)	
6a	125.1	98.5	155.6	161.5	86.8	90.1	8.45	5.53 (d, J = 5.4 Hz)	6.49 (s)
6b	127.0	97.3	155.1	161.6	80.1	82.2	9.05	5.66 (d, J = 8.6 Hz)	6.97 (d, J = 9.4 Hz)
6c	127.9	97.1	154.8	161.6	78.5	81.0	9.03	5.85 (d, J = 8.5 Hz)	7.08 (d, J = 8.1 Hz)
6d	126.8	97.4	155.0	161.7	80.0	81.4	8.69	5.88 (d, J = 7.1 Hz)	7.06 (d, J = 7.9 Hz)
4'a	124.9	99.2	155.3	162.0	87.2		8.29	5.53 (d, J = 5.1 Hz)	
4'b	124.9	98.3	155.6	161.9	77.1		8.28	5.31 (d, J = 9.3 Hz)	
4'c	125.1	98.4	155.5	162.1	80.2		8.34	5.07 (d, J = 9.2 Hz)	
4'd	125.0	98.6	155.7	162.3	80.5		8.23	5.03 (d, J = 9.0 Hz)	
5'a	126.8	99.9	157.9	162.3	90.8		8.42	6.36 (s)	
5'b	130.5	100.7	159.4	162.8	81.1		7.91	6.31 (d, J = 9.2 Hz)	
5'c	130.1	100.6	157.3	162.4	83.8		8.14	6.22 (d, J = 9.0 Hz)	
5'd	131.6	100.4	159.5	162.6	85.8		7.98	5.81 (d, J = 8.8 Hz)	

[a] In δ units in deuteriodimethyl sulfoxide with TMS as internal standard. [b] d: doublet, s: singlet.

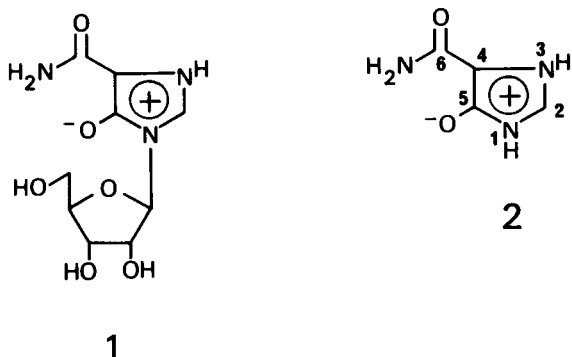


Figure 1

multiplicity was also the case for glycosylation of 2 as shown in Scheme 1. In this reaction we used the silyl-Hilbert-Johnson method; treatment of the silylated base 3 with per-acetylated sugars in the presence of a catalytic amount of TMS triflate as Lewis acid [7a,b]. Compound 2 was silylated by refluxing it with hexamethyldisilazane

and a catalytic amount of ammonium sulfate in dry xylene for two hours. The silylated base 3 was obtained in a quantitative yield as crystalline mass after concentration of the above reaction solution. The structure of 3 will be verified in the next section. This glycosylation is represented by ribosylation of 2 as follows. A solution of the silylated base 3 (1 equivalent), 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (TAR) (1 equivalent) and TMS triflate (0.15 equivalent) in 1,2-dichloroethane was refluxed for one hour. The reaction mixture was neutralized by the addition of sodium bicarbonate and purified by silica gel column chromatography. The major product was *N*-3-nucleoside 5a (61% isolated yield) and *N*-1,*N*-3-bis-nucleoside 6a was also obtained as minor one in a yield of 9%. The monosubstituted compound 4a was obtained in 17% yield and was proved to be the desired *N*-1-nucleoside by leading it to commercially available bredinin (1); deacylation of 4a with sodium methoxide gave bredinin (1) in a yield of 96%. The anomeric configuration of other nucleosides 5a and 6a was assumed to be β from the above fact and the mechanism of nucleo-

side formation *via* 1,2-acyloxonium ion to give 1,2-*trans* compounds [8]. The results of elemental and mass spectroscopic analyses proved **5a** and **6a** to be mono- and di-substituted derivatives, respectively (Table 1). The sites of substitution of **5a** and **6a** were assigned mainly by comparing their uv spectra with those of their corresponding methyl derivatives of **2** (**7**: *N*-1-methyl derivative, **8**: *N*-3-

methyl one, **9**: *N*-1,*N*-3-dimethyl one) (Table 3). The spectra of **5a** and **6a** are essentially identical with those of *N*-3-methyl derivative **8** and *N*-1,*N*-3-dimethyl one **9**, respectively. This assignment is well consistent with the results of acid hydrolysis of **5a** and **6a**. The *N*-3-nucleoside **5a** was treated with *N*-hydrochloric acid at 50° to give **2** in a yield of 73%. The substituent at *N*-3 of the bis-nucleoside **6a**

Table 3  
Ultraviolet Spectra of Nucleoside Derivatives of **2**

Compound No.	Neutral (H <sub>2</sub> O)		Acidic (aq <i>N</i> -HCl)		Basic (aq <i>N</i> -NaOH)	
	max (nm)	$\epsilon \times 10^{-3}$	max (nm)	$\epsilon \times 10^{-3}$	max (nm)	$\epsilon \times 10^{-3}$
<b>4a</b>	278	13.0	280	11.4	276	14.8
	245	6.3	244	5.9		
<b>4b</b>	278	12.8	280	12.0	275	15.0
	245	6.6	244	6.5		
<b>4c</b>	277	13.8	280	12.9	276	15.9
	247	7.1	244	7.3		
<b>4d</b>	279	11.3	281	10.9	275	14.0
	244	6.4	244	6.1		
<b>5a</b>	279	9.3	277	3.4	288	10.1
	235	4.1	242	6.5	234	2.6
<b>5b</b>	285	9.8	282	6.1	288	11.7
	236	5.0	240	5.8	230	sh [a]
<b>5c</b>	280	7.1	280	3.1	289	9.3
	236	3.9	243	6.2	228	2.8
<b>5d</b>	285	9.3	284	6.0	288	11.7
	236	5.5	239	5.5	230	sh
<b>6a</b>	284	7.9	282	8.6	268	17.9
	241	4.0	244	4.6		
<b>6b</b>	288	3.8	288	3.7	262	22.3
	240	2.8	241	2.7		
<b>6c</b>	290	8.8	286	4.0	266	22.6
	241	6.0	241	2.7		
<b>6d</b>	290	9.1	290	5.7	266	22.0
	241	5.8	246	3.7		
<b>4'a</b>	278	14.3	279	12.3	276	16.3
	244	6.5	243	6.5		
<b>4'b</b>	278	14.1	280	12.1	275	15.7
	245	6.3	244	6.7		
<b>4'c</b>	278	12.3	280	11.2	276	14.5
	243	6.2	243	6.3		
<b>4'd</b>	278	12.0	280	10.8	275	14.0
	243	6.1	243	6.1		
<b>5'a</b>	278	10.4	278	4.4	288	11.1
	239	3.6	243	6.3	232	3.0
<b>5'b</b>	283	8.4	279	4.3	288	10.2
	236	4.0	242	5.5		
<b>5'c</b>	282	10.0	281	4.6	288	11.8
	235	4.8	242	6.3	232	2.1
<b>5'd</b>	283	11.1	279	4.1	288	12.3
	235	5.1	242	7.5	231	2.2
4-Carbamoyl-1-methylimidazolium-5-olate ( <b>7</b> )	278	12.8	278	7.3	277	13.3
5-Carbamoyl-1-methylimidazolium-4-olate ( <b>8</b> )	239	4.6	240	6.5	240	sh
4-Carbamoyl-1,3-dimethylimidazolium-5-olate ( <b>9</b> )	277	11.7	275	sh	287	12.2
	237	4.0	244	7.7	231	2.5
	279	11.1	280	7.8	279	10.1
	239	3.5	240	4.5	240	sh

[a] Shoulder.

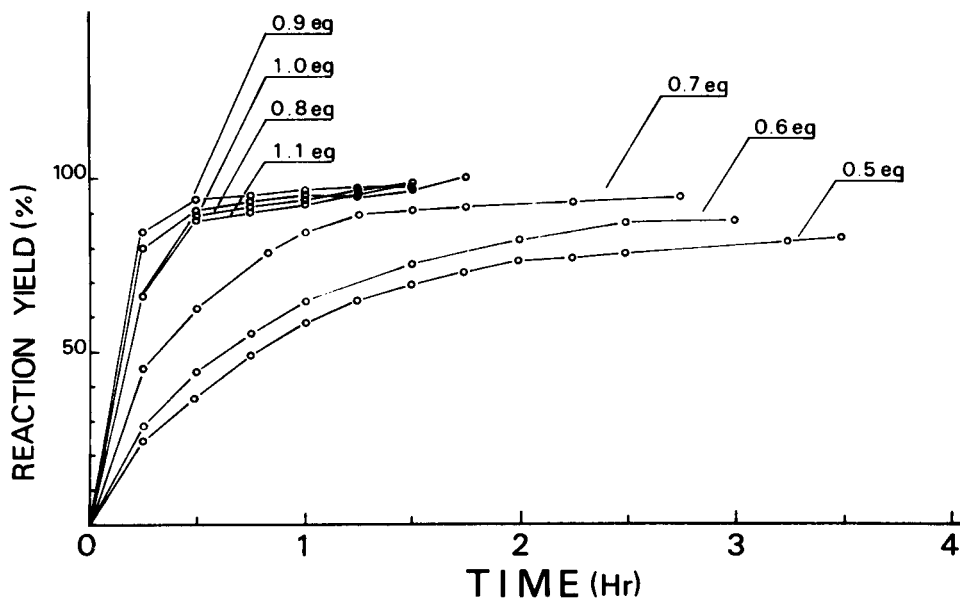


Figure 2. Production of 4a upon incremental addition of stannic chloride  
[2 : 1.2eq, TAR : 1eq, TMS triflate : 0.1eq]

was selectively removed with the acid to room temperature to afford **4a** in 96% yield. This procedure was also applied to other sugars to afford the *N*-3-nucleosides **5b-d** and *N*-1,*N*-3-bis-nucleosides **6b-d** (Table 1). We used 1,2-dichloroethane or acetonitrile as a glycosylation solvent, but there was no difference in the ratio of the products and the yields between these solvents except that the reaction proceeded faster in acetonitrile than in 1,2-dichloroethane [7a,b]. Contrary to this result, Hayashi *et al.* reported the isolation of only *N*-1 isomers using stannic chloride or titanium chloride as catalyst; they obtained 2',3',5'-tri-*O*-acetylbredinin (**4a**) in 14% yield by use of **3**, TAR and stannic chloride, and 2',3',5'-tri-*O*-benzoylbredinin in 52% yield using **3**, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranose and titanium chloride [9]. We assumed that there occurs the formation of a complex between the silylated base **3** and stannic chloride or titanium chloride [10a], and the substitution site is restricted to *N*-1 position. We examined the production of **4a** upon incremental addition of stannic chloride to ascertain this speculation and the results were depicted in Figure 2. The isolated yields of the desired product **4a** were clearly increased to 80-85% by adding stannic chloride and the optimum amount of stannic chloride was about one molar equivalent to **2**. This result suggests the complex formation between the silylated base **3** and stannic chloride. This procedure using one equivalent of stannic chloride to **2** and a catalytic amount of TMS triflate was successfully applied to other sugars to obtain *N*-1-nucleosides **4b-d** (Table 1). The acyl groups of sugar moieties of *N*-1-**4** and *N*-3-**5**-nucleosides were removed by

alcoholysis with sodium methoxide to give free *N*-1-**4'** and *N*-3-**5'**-nucleosides, respectively. The analytical data and nmr chemical shifts of these nucleosides are shown in Table 1 and 2, respectively.

## 2. Structure of the Complex.

The formation of such  $\sigma$ -complex has already been postulated or indicated in the case of pyrimidines, purines [7b-c] and imidazoles [10a-b]. And the spectroscopic studies of  $\sigma$ -complex on the structure and the role in the reaction mechanism have recently been reported [8,10a,11].

Based on the analyses of ultraviolet absorption spectra,  $^{13}\text{C}$  and  $^{29}\text{Si}$  nmr spectra of the silylated base **3** and its  $\sigma$ -complex, we could elucidate the structures of the complexes and propose the reaction mechanism.

First of all, we determined the structure of the silylated base **3**. The spectral data concerning the structure analysis of **3** are tabulated in Table 4. On the basis of mass [ $m/e = 343$  ( $M^+$ ):  $\text{C}_{13}\text{H}_{29}\text{N}_3\text{O}_2\text{Si}_3$  (343.64)] and nmr spectroscopic studies, it was proved that three TMS residues are introduced to compound **2**. Comparison of the  $^{13}\text{C}$  nmr chemical shifts and the ultraviolet spectra of **3** with those of three methyl derivatives **9**, **10**, **11** [12] reveals the spectral resemblance between **3** and **10**. This observation indicates that two of the three TMS residues substitute at *N*-3 and 5-*O*. Another TMS substitution is occurred on the amide nitrogen; in proton non-decoupled spectra of  $^{29}\text{Si}$  nmr, the peak at 4.8 ppm appears as a X pattern of  $\text{XA}_2\text{B}$  spin system, which identify this peak as silicon of TMS-NH partial structure. On the other hand, the peaks at 13.0 and 24.8



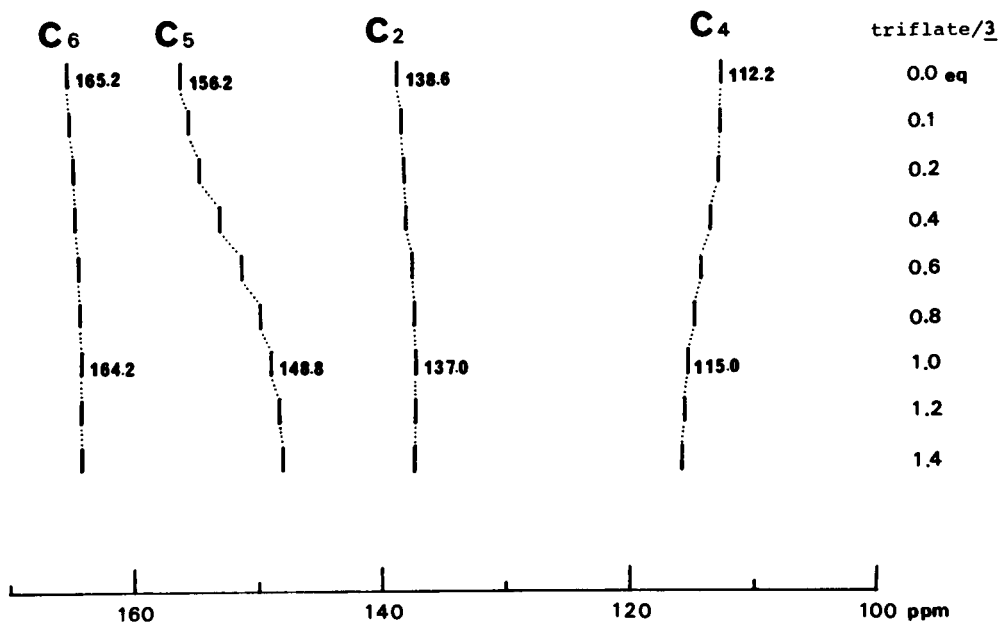
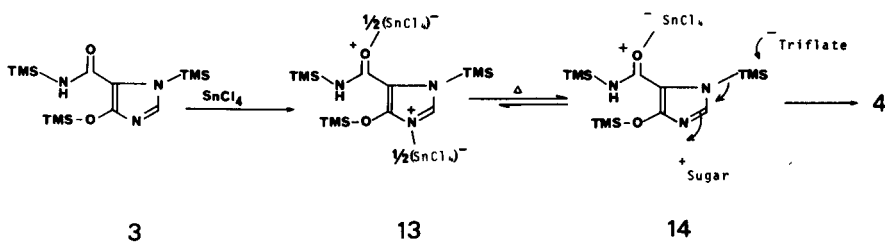


Figure 4.  $^{13}\text{C}$  Nmr chemical shifts of **3** upon addition of TMS triflate

1.  $\text{SnCl}_4$  and catalytic amount of TMS Triflate



2. TMS Triflate only



Figure 5 Proposed reaction mechanism

ppm appear as a X pattern of  $\text{XA}_9$  system. The latter two peaks are assigned as shown in Table 4 in the comparison of its chemical shifts with those of **12**. From these results, the structure of **3** is identified as 1-trimethylsilyl-4-trimethylsilyloxy-1*H*-imidazole-5-trimethylsilylcarboxamide (Table 4).

Next we examined the changes in the  $^{13}\text{C}$  nmr spectra of **3** upon incremental addition of stannic chloride or TMS triflate in perdeuteriodichloromethane, Figure 3 and Figure 4 show visual representations of the spectra in each case. In the case of stannic chloride (Figure 3), the intensity of the new peaks increased in proportion to the amount

Table 5  
<sup>13</sup>C Relaxation Times [a] (T<sub>1</sub>, T<sub>2</sub>) of **3** and its Complex with Stannic Chloride

	<b>3</b>		<b>3</b> + SnCl <sub>4</sub> [b]	
	T <sub>1</sub> [c] (s) [e]	T <sub>2</sub> [d] (s)	T <sub>1</sub> (s)	T <sub>2</sub> (s)
C-4	35.5 ± 1.2	0.8 ± 0.1	15.7 ± 1.3	0.3 ± 0.04
C-2	1.1 ± 0.1	0.7 ± 0.02	0.5 ± 0.1	< 0.1
C-5	30.4 ± 0.8	2.6 ± 0.2	10.2 ± 0.5	0.3 ± 0.07
C-6	20.0 ± 0.3	1.9 ± 0.1	7.0 ± 0.4	0.3 ± 0.04

[a] Concentration, 27% in perdeuteriodichloromethane. [b] 0.4 Molar equivalent. [c] Inversion recovery method. [d] Carr-Purcell-Meiboom-Gill method. [e] Second.

of the Lewis acid added. The appearance of such new peaks indicates that stannic chloride of strong acidity forms so tight complex with **3** that the exchange between **3** and its complex is very slow on the nmr time scale. The peaks of **3** completely disappear after the addition of one molar equivalent of stannic chloride and no changes occur after further addition except decrease in peak intensity. These results indicate a 1 silylated base: 1 stannic chloride stoichiometry. The position of the peaks derived from C-6 and C-4 show large downfield and upfield shifts, respectively. These shifts may successfully be explained by the complexation with stannic chloride at carbonyl oxygen; electron density is decreased at C-6 and increased at C-4. We also examined the changes in the relaxation times (T<sub>1</sub> and T<sub>2</sub>) by the addition of stannic chloride to **3** (Table 5). Here we again confirmed the complex formation based on the reduction (1/2-1/3) of the spin-lattice relaxation times (T<sub>1</sub>) at all carbons. The decrease in the spin-spin relaxation times (T<sub>2</sub>) of C-6 and C-4 is in good agreement with the complexation at carbonyl oxygen suggested by the shifts of absorption peaks (C-6 and C-4). The relaxation times T<sub>2</sub> of C-2 and C-5 tend to shorten more than those of C-6 and C-4. This result supports the other liganding site to be the ring nitrogen, N-1. These observations based on <sup>13</sup>C nmr analyses implicate that the liganding sites on **3** with stannic chloride are carbonyl oxygen and N-1 (**13** in Figure 5) and 1:1 stoichiometry is well consistent with two valences of stannic chloride molecule [11].

When stannic chloride and a catalytic amount of TMS triflate are used, the  $\sigma$ -complex **13** should be a reacting species (Figure 5-1). However, as this complex **13** is not so reactive at room temperature (e.g. **4a**: 61% yield after four days), it is necessary to reflux the reaction mixture to obtain the desired nucleosides **4**. The binding at N-1 may dissociate to give **14** at high temperature. Then the triflate anion, which was generated by the reaction between peracylated sugar and TMS triflate, reacts with TMS residue at N-3 to give *N*-1-nucleosides **4**.

Figure 4 depicts the changes in <sup>13</sup>C nmr chemical shifts of **3** upon addition of increasing amount of TMS triflate. In this case, on the contrary to the case of stannic chloride,

all peaks shifted continuously upon addition and ultimately almost no changes are observed after the addition of one molar equivalent of TMS triflate. This time-averaged spectra implicate that the equilibrium between **3** and its complex is a rapid process on the nmr time scale because of the weak acidity of TMS triflate. The peaks for C-4 and C-5 shift markedly towards downfield and upfield, respectively. This pattern of chemical shifts resembles that of compound **11** and the ultraviolet absorption spectrum of this complex (TMS triflate:one equivalent) exhibits the maximum at 239 nm which is also in good agreement with that of compound **11** at 237 nm (Table 4).

From the above results, we assume that the  $\sigma$ -complex **15** is in equilibrium with the *N*-1-silyl compound **16** (Figure 5-2). Compound **16** should then react readily with the sugar cation to give the *N*-3-nucleosides **5** as major products. In this equilibrium, a part of **3** itself may react to produce *N*-1-nucleosides **4**.

## EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet absorption spectra were obtained on a Shimadzu UV-300 spectrophotometer. Nuclear magnetic resonance spectra using tetramethylsilane as an internal standard were measured in DMSO-d<sub>6</sub> on a JEOL FX-100 FT-NMR spectrometer at 99.60 (<sup>1</sup>H) and 25.20 (<sup>13</sup>C) MHz and in perdeuteriodichloromethane on a Varian XL-200 FT-NMR spectrometer at 39.75 (<sup>29</sup>Si) MHz. Electron impact mass spectra were determined on a Shimadzu LKB-9000 mass spectrometer operating at 12 and 70 eV.

4-Carbamoylimidazolium-5-olate (**3**), mp 237° dec was prepared by the method described in the literature [4].

Melting points, recrystallization solvents and analytical data of the nucleoside derivatives of **2** are listed in Table 1.

Glycosylation of **2**.

(A) In the Absence of Stannic Chloride.

The example given below is representative for preparation of the compounds **4b-d**, **5b-d** and **6b-d**.

4-Carbamoyl-1-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)imidazolium-5-olate (**4a**), 5-Carbamoyl-1-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)imidazolium-4-olate (**5a**) and 4-Carbamoyl-1,3-bis(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)imidazolium-5-olate (**6a**).

A mixture of 254 mg (2.0 mmoles) of **2**, 4 ml of hexamethyldisilazane, 4 ml of dry xylene and 2 mg of ammonium sulfate was stirred for two hours under reflux. The clear solution obtained was concentrated *in vacuo* with



protection against moisture to give trimethylsilyl derivative **3** as crystalline mass. To the solution of **3** in 8 ml of dry 1,2-dichloroethane was added 637 mg (2.0 mmoles) of 1,2,3,5-tetra-*O*-acetyl- $\beta$ -D-ribofuranose and 55  $\mu$ l (0.3 mmole) of trimethylsilyl trifluoromethanesulfonate, and the mixture was refluxed for one hour. The reaction mixture was allowed to cool to room temperature and poured into the suspension of 4 g of sodium bicarbonate in 20 ml of methanol. After completeness of neutralization, the mixture was filtered over celite. Evaporation of the filtrate *in vacuo* gave an oily residue, which was chromatographed on a column of silica gel. The initial fraction eluted with a mixture of chloroform and methanol (15:1) afforded 113 mg (9%) of **6a** and then 468 mg (61%) of **5a**. The following fraction eluted with a mixture of the same solvents (4:1) gave 134 mg (17%) of **4a**.

#### (B) In the Presence of Stannic Chloride.

The example given below is representative for preparation of the *N*-1-nucleosides **4b-d**.

#### 4-Carbamoyl-1-(2,3,5-tri-*O*-acetyl- $\beta$ -D-ribofuranosyl)imidazolium-5-olate (**4a**).

To a solution of **3** [prepared from 254 mg (2.0 mmoles) of **2** as described in (A)] in 8 ml of dry 1,2-dichloroethane was added 0.21 ml (1.8 mmoles) of stannic chloride, 532 mg (1.67 mmoles) of 1,2,3,5-tetra-*O*-acetyl- $\beta$ -D-ribofuranose and 55  $\mu$ l (0.3 mmoles) of trimethylsilyl triflate, and the reaction mixture was stirred for one hour under reflux. This mixture was allowed to cool to room temperature and poured into the suspension of 8 g of sodium bicarbonate in 20 ml of methanol. After completeness of neutralization, the mixture was filtered over celite. Evaporation of the filtrate *in vacuo* gave a residue like caramel, which was purified by reversed phase column chromatography [Merck RP-8 eluted with aqueous 40% methanol containing acetic acid (1%)] to give 530 mg (83%) of **4a**.

#### Deacylation of **4** and **5**.

##### 4-Carbamoyl-1- $\beta$ -D-ribofuranosylimidazolium-5-olate (**1**).

To a mixture of 9.449 g (36.45 mmoles) of **4a** and 400 ml of dry methanol was added 6.480 g (120 mmoles) of sodium methoxide in 20 ml of dry methanol under ice-cooling. The reaction mixture was further stirred for one hour at room temperature and concentrated to dryness *in vacuo*. The residue was dissolved in 10 ml of water and charged on a column of cation-exchange resin [800 ml of Dowex 50 $\times$ 4 (H<sup>+</sup> form) eluted with water] to give 7.44 g of crude desired product. Recrystallization from methanol afforded 6.397 g (96%) of **1**.

The other free nucleosides **4'b-d**, **5'a-d** were prepared by the same manner described above except that ammonium form of ion-exchange resin was used for the removal of sodium ion in the case of *N*-3-nucleosides **5'a-d** to avoid the hydrolysis of the glycosyl bond.

#### Hydrolysis of **5a**.

A solution of 385 mg (1.0 mmole) of **5a** and 1.1 ml (1.1 mmoles) of *N*-hydrochloric acid in 6 ml of 1,4-dioxane was stirred for one and a half hour at 50°. The reaction mixture was allowed to cool to room temperature and the crystals were collected by filtration, washed with diisopropyl ether to give 145 mg (73%) of the hydrochloride dihydrate of **2** [mp 210° dec (lit mp 211° dec)] [13]. The ir spectrum of this product was identical with that of the authentic sample prepared from **2**.

#### Hydrolysis of **6a**.

A solution of 322 mg (0.5 mmole) of **6a** and 0.5 ml (0.5 mmole) of *N*-hydrochloric acid in 10 ml of 1,4-dioxane was stirred for one and a half hours at room temperature and neutralized by the addition of the saturated solution of sodium bicarbonate. Evaporation of the reaction mixture *in vacuo* gave the crude product, which was purified by reversed phase column chromatography [Merck RP-8 eluted with aqueous 40% methanol containing acetic acid (1%)] to give 189 mg (96%) of **4a**. The ir spectrum of this product was identical with that of the authentic sample prepared by the ribosylation of **2**.

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