STEREOSELECTIVITIES IN THE COUPLING REACTION BETWEEN SILYLATED PYRIMIDINE BASES AND 1-HALO-2,3-DIDEOXYRIBOSE

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Abstract --- Coupling reactions between 1-chloro-2,3-dideoxyribose and silylated pyrimidines have been examined from the point of stereoselectivity. When the reaction was carried out in chloroform, the selectivity was in the anomeric ratio of $\alpha : \beta = 4 : 6$. On the other hand, the presence of tertiary amine raises the selectivity to $\alpha : \beta = 3 : 7$.

Nucleoside analogues have been considered as useful materials because of their biological activities.[1] Some of them have uses in pharmacology.[1] In many cases, naturally occurring nucleosides were the starting material for these nucleosides analogues.[2] It is, however, rather disadvantageous since the material with a particular nucleic base cannot be obtained preferentially. From this viewpoint, we have been interested in the synthesis of a wide variety of nucleosides starting from other resources. Our attention has mainly focused on the stereoselectivity in the coupling reaction between a nucleic base and a sugar.[3]

In recent years, 2',3'-dideoxynucleosides have received a lot of attention because of their antiviral activities against the HIV, which causes the acquired immune deficiency syndrome (AIDS).[4] A lot of methods for the preparation of these nucleosides have been reported; deoxygenation of the 3'-hydroxy group of 2'-deoxy-nucleosides,[5] double deoxygenation of vicinal diol of ribonucleosides,[6] and the coupling reaction between activated nucleic bases and 2,3-dideoxyribose derivatives.[7] Two types of this coupling reaction have already been reported; Lewis acids catalyzed reactions[7a] and S_N2-like reaction of 1-bromosugar.[7b] In the former case,

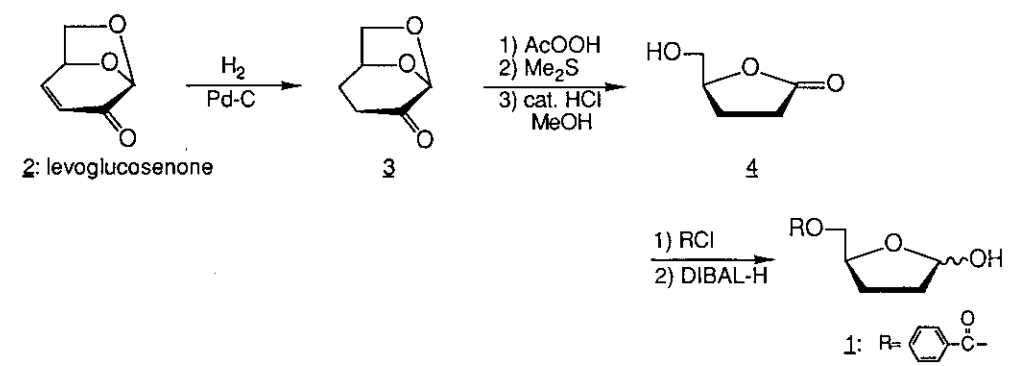
the stereoselectivities of the reaction were up to $\alpha : \beta = 4 : 6$. In the latter case, 1-bromosugar was unstable and the reaction resulted in the formation of a mixture of equal amounts of both anomers. It has been reported by Hubbard *et al.* that the coupling reactions between 1-α-chloro-2-deoxyribose and silylated nucleic bases in chloroform proceed with S_N2 displacement to give mainly the β-anomers.[8] We have focused our attention on this result, and here we report the stereoselectivities in the coupling reactions between 1-chloro-2,3-dideoxyribose and silylated pyrimidine bases.

1-Halosugar

2,3-Dideoxyribose (**1**) was prepared as follows (Scheme 1). We used levoglucosenone (**2**) as a starting material.[9] This compound is known as the main product from the pyrolysis of cellulose. Compound **3** derived from **2** by hydrogenation was subjected to the Baeyer-Villiger reaction with peracetic acid to give the lactone **4**.[10] Benzoylation of **4** followed by reduction with DIBAL-H gave the sugar (**1**).

2,3-Dideoxyribose (**1**) was halogenated under the conditions described in Table 1. Two sets of conditions for the preparation of 1-chlorosugar (**5a**) were adopted as indicated in Table 1. In both cases, however, the anomeric mixtures have almost the same anomeric ratio, 6 : 4, which was determined by ^{1}H-nmr (entries 1 and 2). It was not possible to determine directly which anomer was the major isomer, but afterwards the anomeric ratio was deduced from the results of the coupling reaction (*vide infra*). We also prepared 1-bromo-2,3-dideoxyribose (**5b**). 1-Bromosugar (**5b**), which was prepared from **1** and acetyl bromide and after the removal of the low-boiling point materials, exists in a 6 : 4 anomeric mixture in chloroform (entries 3 and 4). It is in the same ratio as

Scheme 1



2: levoglucosenone 3 4

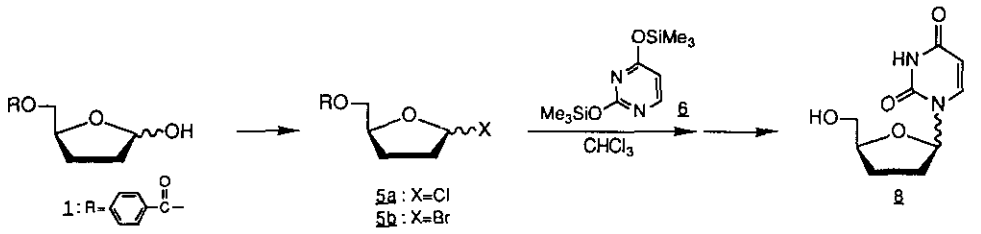


Table 1. Preparation of 1-halosugar (5) and coupling reaction between 5 and silylated uracil (6)[a]

Entry	X	Conditions of halogenation[b]	Anomeric ratio of 5[c]	Yield/%[d] ($\alpha + \beta$)	Stereoselectivity[d] ($\alpha : \beta$)
1	Cl	HCl (gas)/$MgSO_4$/PhH/2 h	57 : 43	76	43 : 57
2	Cl	$SOCl_2$ (1.5)/$CHCl_3$/5 h	60 : 40	62	42 : 58
3	Br	AcBr (1.5)/$PhCH_3$/5 h	64 : 36	26	52 : 48
4	Br	AcBr (1.5)/$CHCl_3$/5 h	62 : 38	28	51 : 49

a) Coupling reactions were carried out under the following conditions; 0.5 mmol scale, sugar : base=1 : 2, in 4 ml of chloroform, room temperature, overnight.

b) The numbers in parentheses refer to the equivalent of reagents.

c) Determined by ^{1}H-nmr.

d) Yields and stereoselectivities were determined by hplc (uv detection, 254 nm; compared to uracil as an internal standard) after deprotection by sodium methoxide in methanol.

in a solution after the treatment of 1-acetylsugar with trimethylsilyl bromide as reported by Farina and Benigni.[7b] As Hubbard *et al.* have reported, the coupling reaction between 1-chlorosugar and silylated uracil (6) in chloroform without catalysts present proceeded completely in an S_N2 mode,[8] and 1-chlorosugar (5a) was subjected to these reaction conditions. The crude coupling product was analyzed by hplc after deprotection. The ratio of resulting 2',3'-dideoxyuridine (8) and its anomer was $\alpha : \beta = 4 : 6$ (entries 1 and 2). This result indicates that the coupling reaction between 5a and 6 proceeds in an S_N2 manner, and the anomers of 1-chloro-2,3-dideoxyribose (5a) exists in chloroform in the ratio of $\alpha : \beta = 6 : 4$. On the other hand, 1-bromosugar (5b) was subjected to the same reaction conditions, but it gave equal amounts of both anomers as was also reported

by Farina and Benigni.[7b] In the case of 1-bromosugar (**5b**), the coupling reaction involved the S_N1 character to some extent.

Tertiary amines

In order to further improve the β-selectivity, we examined the effect of additives in the coupling reaction. Among the additives primarily examined, pyridine affected the selectivity and increased the β-selectivity (α : β=31 : 69). In order to investigate this effect, coupling reactions were carried out in the presence of other tertiary amines and the results are summarized in Table 2.

Table 2. Coupling reaction between 1-chlorosugar (**5a**) and silylated uracil (**6**) in the presence of tertiary amines[a,b]

Entry	Tertiary Amine	Yield/%[c] (α + β)	Stereoselectivity[c] (α : β)
1	--	62	42 : 58
2	pyridine	77	31 : 69
3	2-picoline	65	31 : 69
4	2,6-lutidine	70	32 : 68
5	2,4,6-collidine	49	35 : 65
6	4-(*N*,*N*-dimethylamino)pyridine	37	31 : 69
7	triethylamine	58	30 : 70
8	*N*,*N*-dimethylaniline	73	38 : 62
9	1,8-diazabicyclo[5.4.0]undec-7-ene	36	31 : 69

a) 1-Chlorosugar was prepared under the following conditions; 0.5 mmol scale, 0.75 mmol of thionyl chloride, in 4 ml of chloroform, room temperature, 5 h.

b) Coupling reactions were carried out under the following conditions; 0.5 mmol scale, sugar : base=1 : 2, 0.25 mmol of tertiary amines, in 4 ml of chloroform, room temperature, overnight.

c) Yields and stereoselectivities were determined by hplc (uv detection, 254 nm; compared to uracil as an internal standard) after deprotection by sodium methoxide in methanol.

All of these amines had a similar effect in raising the β-selectivity, except for *N*,*N*-dimethylaniline (entry 8). On the other hand, the amines with relatively strong basicity such as 2,4,6-collidine, 4-(*N*,*N*-dimethylamino)-pyridine, and 1,8-diazabicyclo[5.4.0]undec-7-ene caused low yield (entries 5, 6, and 9). Anyway, the best β-selectivity in the coupling reaction between 1-chlorosugar (**5a**) and silylated uracil (**6**) was obtained when the reaction was carried out in the presence of pyridine.

Protecting group of 5-hydroxy group

Since the participation effect of the protecting group of 5-hydroxy group could be assumed, some of the acyl-protected 2,3-dideoxyribose (**9**) was prepared and used in the coupling reactions. These results are summarized in Table 3. Their 1-chloro derivatives (**10**) existed as anomeric mixtures in the ratio of about 6 : 4, almost equal to the bezoylated sugar (**5a**). When the coupling reactions with silylated uracil were performed in chloroform without additives, the anomeric ratios of the products completely reflected those of 1-chlorosugar (**10**). These results suggested that the reactions also proceeded in an S_N2 manner and that there was no significant participation effect of the protecting groups. Furthermore, addition of pyridine similarly raised the β-selectivities in all cases. As a result, there was no distinct difference in the stereoselectivity when the protecting group of the sugar hydroxy group was changed. It was possible to obtain the β-anomer in pure form by a much easier

Scheme 2

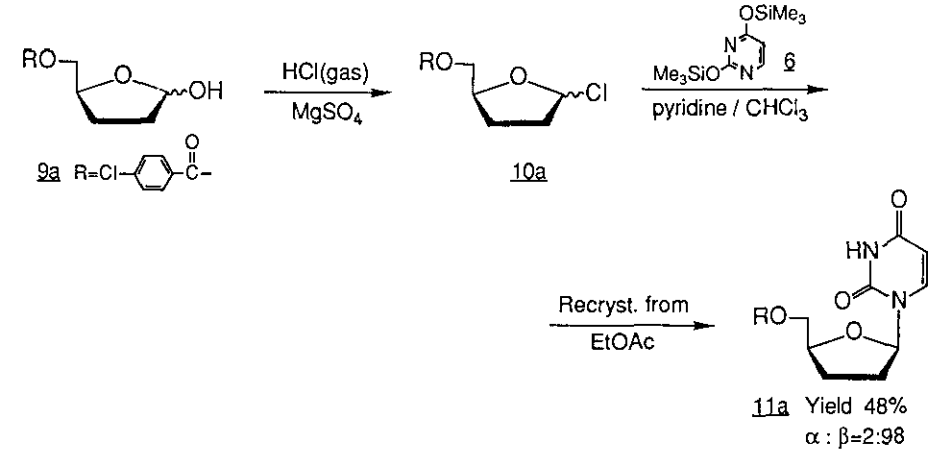


Table 3. Coupling reaction between 1-chlorosugar (**9**) and silylated uracil (**6**)[a,b]

Entry	Sugar	Anomeric ratio of **10**[c]	Without amines		With pyridine[d]	
			Yield/%[e] ($\alpha + \beta$)	Selectivity[e] ($\alpha : \beta$)	Yield/%[e] ($\alpha + \beta$)	Selectivity[e] ($\alpha : \beta$)
1	**1**	57 : 43	76[f]	43 : 57	77[f]	31 : 69
2	**9a**	54 : 46	61[f]	45 : 55	85[f]	34 : 66
3	**9b**	52 : 48	63[f]	47 : 53	78	39 : 61
4	**9c**	59 : 41	79	40 : 60	66	31 : 69
5	**9d**	57 : 43	57	40 : 60	51	30 : 70
6	**9e**	56 : 44	94	42 : 58	89	33 : 67
7	**9f**	61 : 39	33[f]	38 : 62	72	34 : 66

a) 1-Chlorosugar was prepared under the following conditions; 0.5 mmol scale, 0.75 mmol of thionyl chloride, in 4 ml of chloroform, room temperature, 5 h.

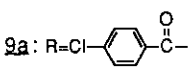
b) Coupling reactions were carried out under the following conditions; 0.5 mmol scale, sugar : base=1 : 2, in 4 ml of chloroform, room temperature, overnight.

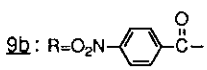
c) Determined by ^{1}H-nmr.

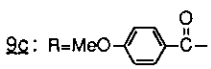
d) Coupling reactions were performed in the presence of 0.25 mmol of pyridine.

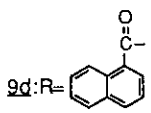
e) Yields and stereoselectivities were determined by hplc (uv detection, 254 nm; compared to uracil as an internal standard) after deprotection by sodium methoxide in methanol.

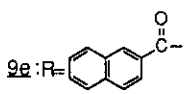
f) 1-Chlorosugar was prepared under the following conditions; 0.5 mmol scale, 0.5 g of anhydrous magnesium sulfate, in 6 ml of benzene, under hydrogen chloride atmosphere, room temperature, 2 h.

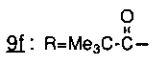










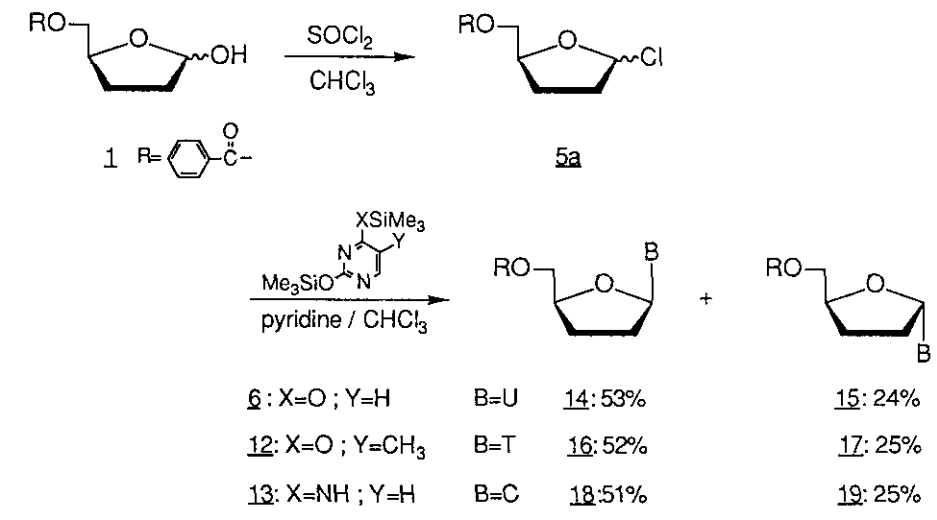


procedure as follows (Scheme 2). The coupling reaction between silylated uracil (**6**) and 1-chloro-5-*O*-(*p*-chlorobenzoyl)-2,3-dideoxyribose (**10a**) in chloroform in the presence of 0.5 equivalent of pyridine gave the product as an anomeric mixture in the ratio of α : β=34 : 66 in 85% yield (entry 2). Protected 2',3'-dideoxy-β-uridine (**11a**) can be simply obtained in 98% purity by recrystallization from ethyl acetate in 48% yield (based on the sugar **9a**).

Other silylated pyrimidines

As described above, we have clearly determined that the coupling reaction between 1-chloro-2,3-dideoxyribose and silylated uracil in chloroform in the presence of pyridine proceeded stereoselectively to give the desired β-anomer in 70% purity. To test the applicability of these reaction conditions, we carried out this reaction with other silylated pyrimidine bases such as thymine (**12**) and cytosine (**13**) as well as uracil (**6**) in preparative scale (4 mmol scale). Each of the anomers was isolated by the use of hplc. These results are summarized in Scheme 3. Determinations of the α/β-anomers were made by ^{1}H-nmr.[11] Furthermore, all of the β-anomers were deprotected and were confirmed by comparison to those synthesized by other methods.[5,12] It is clear that relatively higher β-selectivity in the coupling reaction with silylated uracil (**6**) under the conditions described above was equally general to those reactions using other silylated pyrimidine bases.

Scheme 3



6 : X=O ; Y=H	B=U	14: 53%	15: 24%
12: X=O ; Y=CH_3	B=T	16: 52%	17: 25%
13: X=NH ; Y=H	B=C	18: 51%	19: 25%

Conclusion

It is clear that the S_N2 type displacement at sugar C-1 proceeded in the coupling reaction between 1-chloro-2,3-dideoxyribose and silylated uracil in chloroform to give the product as an anomeric mixture in the ratio of α : β=4 : 6. Here we also have shown that the presence of tertiary amines, especially pyridine, in the coupling reaction improved the β-selectivity to α : β=3 : 7, and that similar results were obtained with other silylated pyrimidine bases. The effect of tertiary amines is not clear at the present time. We now assume the intermediate of 1-ammonium sugar, because (1) Aoyama reported the similar cases with 1-chloro-2-deoxyribose,[13] (2) *N,N*-dimethylaniline, which has relatively weak nucleophilicity, had no such effect, (3) H-1 protons of 1-chlorosugar in ^{1}H-nmr disappeared completely from the normal field of anomeric protons on addition of excess pyridine.

EXPERIMENTAL

1-Chloro-5-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pentofuranose (**5a**)

Under an argon atmosphere, 0.48 ml (6.6 mmol) of thionyl chloride was added to a solution of 0.89 g (4.0 mmol) of 5-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pentofuranose (**1**)[14] in 25 ml of dry chloroform, and the mixture was stirred at room temperature for 5 h. The solvent and low-boiling point materials were evaporated off under reduced pressure (2 mmHg) at room temperature for 30 min. The residual oil was used in the next step without further purification; ^{1}H-nmr ($CDCl_3$) δ: 6.43 (0.6H, t, J=1.7 Hz, H-1), 6.37 (0.4H, d, J=4.1 Hz, H-1).

1-Chloro-5-*O*-(*p*-chlorobenzoyl)-2,3-dideoxy-D-*glycero*-pentofuranose (**10a**)

To a solution of 1.3 g (5.0 mmol) of 5-*O*-(*p*-chlorobenzoyl)-2,3-dideoxy-D-*glycero*-pentofuranose (**9a**)[14] in 60 ml of dry benzene, 5.0 g of anhydrous magnesium sulfate was added and the mixture was stirred at room temperature for 3 h under a hydrogen chloride atmosphere. After the solids were filtered off, the filtrate was evaporated under reduced pressure (2 mmHg) at room temperature for 30 min. The residual oil was used in the next step without further purification; ^{1}H-nmr ($CDCl_3$) δ: 6.42 (0.6H, t, J=1.7 Hz, H-1), 6.36 (0.4H, d, J=4.2 Hz, H-1).

1-(5-*O*-Benzoyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)uracil (**14**) and 1-(5-*O*-Benzoyl-2,3-dideoxy-α-D-*glycero*-pentofuranosyl)uracil (**15**)

To a suspension of 0.87 g (7.8 mmol) of uracil in 15 ml of hexamethyldisilazane was added 0.2 ml of chlorotrimethylsilane, and the mixture was refluxed under an argon atmosphere for 30 min. After the crystals dissolved, the solvent was evaporated under reduced pressure (2 mmHg) at room temperature for 30 min. The residual oil was dissolved in 20 ml of dry chloroform. To this solution, a solution of 0.63 g (4.0 mmol) of 1-chloro-5-*O*-

benzoyl-2,3-dideoxy-D-*glycero*-pentofuranose (**5a**) and 160 ml (2.0 mmol) of pyridine in 10 ml of dry chloroform was added, and the mixture was stirred under an argon atmosphere at room temperature overnight. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with chloroform three times. The organic layer was dried over anhydrous magnesium sulfate, and then the solvent was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography (chloroform : methanol=96 : 4, v/v) to give an anomeric mixture of 1-(5-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pentofuranosyl)uracil. These anomers were separated by hplc (ODS; 30 mmϕ X 250 mm; acetonitrile : water=35 : 65, v/v; 7.5 ml/min.) to give 1-(5-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)uracil (0.65 g, 52%) and its α-anomer (0.29 g, 24%).

1-(5-*O*-Benzoyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)uracil; mp 146.0-149.0°C (ethyl acetate); $[\alpha]_D^{23}$ +18.5° (c 1.00, $CHCl_3$); ir (KBr) 2990(m), 1723(s), 1680(s), 1464(m), 1410(m), 1392(m), 1361(m), 1321(m), 1272(s), 1257(s), 1181(m), 1100(s), 870(m), 708(s), 526(m) cm^{-1}; uv ($CHCl_3$) 264 nm (log ε 3.98); ^{1}H-nmr ($CDCl_3$) δ: 9.81 (1H, br, NH), 8.03 (2H, d, *J*=7.2 Hz, aromatic H), 7.68 (1H, d, *J*=8.1 Hz, H-6), 7.61 (1 H, t, *J*=7.4 Hz, aromatic H), 7.47 (2H, t, *J*=7.5 Hz, aromatic H), 6.10 (1H, dd, *J*=6.6 and 3.2 Hz, H-1'), 5.56 (1H, d, *J*=8.1 Hz, H-5), 4.65 (1H, dd, *J*=12.4 and 2.9 Hz, H-5'), 4.57 (1H, dd, *J*=12.3 and 4.3 Hz, H-5'), 4.49-4.40 (1H, m, H-4'), 2.58-2.44 (1H, m, H-2'), 2.20-2.05 (2H, m, H-2', H-3'), 2.05-1.87 (1H, m, H-3'); ^{13}C-nmr ($CDCl_3$) δ: 166.17 (C=O), 163.59 (C-4), 150.37 (C-2), 139.41 (C-6), 133.49 (aromatic C), 129.47 (aromatic C), 129.36 (aromatic C), 128.57 (aromatic C), 101.85 (C-5), 86.44 (C-1'), 79.13 (C-4'), 64.75 (C-5'), 32.78 (C-3'), 25.47 (C-2'); ms *m/z* 316 (M^+), 205 (sugar), 113 (base unit + 1), and 105 (benzoyl unit); Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.09; N, 8.85. Found C, 60.72; H, 5.02; N, 8.86.

1-(5-*O*-Benzoyl-2,3-dideoxy-α-D-*glycero*-pentofuranosyl)uracil; mp 133.0-135.5°C (ethyl acetate); $[\alpha]_D^{26}$ -42.7° (c 1.04, $CHCl_3$); ir (KBr) 3242(m), 1707(s), 1686(s), 1452(m), 1288(m), 1270(m), 1098(m), 717(m) cm^{-1}; uv ($CHCl_3$) 264 nm (log ε 4.02); ^{1}H-nmr ($CDCl_3$) δ: 10.08 (1H, br, NH), 8.06 (2H, d, *J*=7.1 Hz, aromatic H), 7.59 (1H, t, *J*=7.4 Hz, aromatic H), 7.46 (2H, t, *J*=7.5 Hz, aromatic H), 7.39 (1H, d, *J*=8.1 Hz, H-6), 6.14 (1H, dd, *J*=6.1 and 4.2 Hz, H-1'), 5.76 (1H, d, *J*=7.9 Hz, H-5), 4.78-4.69 (1H, m, H-4'), 4.55 (1 H, dd, *J*=11.9 and 3.7 Hz, H-5'), 4.35 (1H, dd, *J*=11.9 and 5.6 Hz, H-5'), 2.65-2.53 (1H, m, H-2'), 2.27-1.94 (3H, m, H-2', H-3'); ^{13}C-nmr ($CDCl_3$) δ: 166.20 (C=O), 163.78 (C-4), 150.35 (C-2), 139.30 (C-6), 133.19 (aromatic C), 129.54 (aromatic C), 129.45 (aromatic C), 128.39 (aromatic C), 101.99 (C-5), 87.82 (C-1'), 78.87 (C-4'), 66.04 (C-5'), 32.39 (C-3'), 26.29 (C-2'); ms *m/z* 316 (M^+), 205 (sugar), 113 (base unit +

1), and 105 (benzoyl unit); Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.09; N, 8.85. Found C, 60.76; H, 5.00; N, 8.88.

1-(5-*O*-Benzoyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)thymine (**16**) and 1-(5-*O*-Benzoyl-2,3-dideoxy-α-D-*glycero*-pentofuranosyl)thymine (**17**)

To a suspension of 1.01 g (8.0 mmol) of thymine in 40 ml of 1,2-dichloroethane were added 4 ml of hexamethyldisilazane and 3.5 ml of chlorotrimethylsilane, and the mixture was refluxed under an argon atmosphere for 3 h. After the crystals dissolved, the solvent was evaporated under reduced pressure (2 mmHg) at room temperature for 30 min. The residual oil was dissolved in 20 ml of dry chloroform. To this solution, a solution of 0.63 g (4.0 mmol) of 1-chloro-5-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pentofuranose (**5a**) and 160 ml (2.0 mmol) of pyridine in 10 ml of dry chloroform was added, and the mixture was stirred under an argon atmosphere at room temperature overnight. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with chloroform three times. The organic layer was dried over anhydrous magnesium sulfate, and then the solvent was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography (chloroform:methanol=97 : 3, v/v) to give an anomeric mixture of 1-(5-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pentofuranosyl)thymine. These anomers were separated by hplc (ODS; 30 mmϕ X 250 mm; acetonitrile:water=38 : 62, v/v; 7.5 ml/min.) to give 1-(5-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-thymine (0.69 g, 52%) and its α-anomer (0.33 g, 25%).

1-(5-*O*-Benzoyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)thymine; mp 106.0-109.0°C (ethyl acetate); $[\alpha]_D^{23}$ -8.6° (c 1.01, $CHCl_3$); ir ($CHCl_3$) 3022(m), 1688(s), 1470(m), 1454(m), 1274(s), 1122(m), 1087(m), 1071(m) cm^{-1}; uv ($CHCl_3$) 269 nm (log ε 4.00); ^{1}H-nmr ($CDCl_3$) δ: 10.05 (1H, br, NH), 8.05 (2H, d, *J*=7.1 Hz, aromatic H), 7.60 (1H, t, *J*=7.4 Hz, aromatic H), 7.46 (2H, t, *J*=7.5 Hz, aromatic H), 7.36 (1H, s, H-6), 6.12 (1H, dd, *J*=6.5 and 4.3 Hz, H-1'), 4.65 (1H, dd, *J*=12.1 and 2.8 Hz, H-5'), 4.53 (1H, dd, *J*=12.2 and 4.6 Hz, H-5'), 4.48-4.42 (1H, m, H-4'), 2.55-2.38 (1H, m, H-2'), 2.25-1.92 (3H, m, H-2', H-3'), 1.70 (3H, s, Me); ^{13}C-nmr ($CDCl_3$) δ: 166.14 (C=O), 164.10 (C-4), 150.52 (C-2), 134.94 (C-6), 133.30 (aromatic C), 129.37 (aromatic C), 128.45 (aromatic C), 110.54 (C-5), 85.90 (C-1'), 78.17 (C-4'), 65.19 (C-5'), 32.06 (C-3'), 25.77 (C-2'), 12.21 (CH_3); ms *m/z* 330 (M^+), 205 (sugar), 127 (base unit + 1), and 105 (benzoyl unit); Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found C, 61.77; H, 5.38; N, 8.47.

1-(5-*O*-Benzoyl-2,3-dideoxy-α-D-*glycero*-pentofuranosyl)thymine; $[\alpha]_D^{27}$ -37.5° (c 1.18, $CHCl_3$); ir ($CHCl_3$) 3028 (m), 1688 (s), 1470 (m), 1454 (m), 1270 (s), 1122 (m), 1071 (m) cm^{-1}; uv ($CHCl_3$) 271 nm (log ε 4.02); ^{1}H-nmr ($CDCl_3$) δ: 9.92 (1H, br, NH), 8.06 (2H, d, *J*=7.0 Hz, aromatic H), 7.60 (1H, t, *J*=7.4 Hz, aromatic

H), 7.59 (2H, t, *J*=7.4 Hz, aromatic H), 7.46 (2H, t, *J*=7.5 Hz, aromatic H), 7.17 (1H, s, H-6), 6.16 (1H, dd, *J*=6.1 and 4.8 Hz, H-1'), 4.79-4.70 (1H, m, H-4'), 4.45 (1H, dd, *J*=11.8 and 3.8 Hz, H-5'), 4.36 (1H, dd, *J*=11.8 and 5.6 Hz, H-5'), 2.63-2.50 (1H, m, H-2'), 2.32-2.17 (1H, m, H-3'), 2.17-1.90 (5H, m, H-2', H-3', Me); ^{13}C-nmr ($CDCl_3$) δ: 166.23 (C=O), 164.19 (C-4), 150.42 (C-2), 135.10 (C-6) ,133.17 (aromatic C), 129.54 (aromatic C), 129.48 (aromatic C), 128.37 (aromatic C), 110.55 (C-5), 87.36 (C-1'), 78.64 (C-4'), 66.11 (C-5'), 32.17 (C-3'), 26.48 (C-2'), 12.55 (CH_3); ms *m/z* 330 (M^+), 205 (sugar), 127 (base unit + 1), and 105 (benzoyl unit); hrms Calcd for $C_{17}H_{18}N_2O_5$ (M^+): 330.1215. Found 330.1181.

(5-*O*-Benzoyl-2,3-dideoxy-β-**D**-*glycero*-pentofuranosyl)cytosine (**18**) and (5-*O*-Benzoyl-2,3-dideoxy-α-**D**-*glycero*-pentofuranosyl)cytosine (**19**)

A suspension of 0.89 g (8.0 mmol) of cytosine in 16 ml of hexamethyldisilazane was refluxed under an argon atmosphere for 30 min. After the crystals dissolved, the solvent was evaporated under reduced pressure (2 mmHg) at room temperature for 30 min. The residual oil was dissolved in 150 ml of dry chloroform. To this solution, a solution of 0.63 g (4.0 mmol) of 1-chloro-5-*O*-benzoyl-2,3-dideoxy-**D**-*glycero*-pentofuranose (**5a**) and 160 ml (2.0 mmol) of pyridine in 10 ml of dry chloroform was added, and the mixture was stirred under an argon atmosphere at room temperature overnight. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with chloroform three times. The organic layer was dried over anhydrous magnesium sulfate, and then the solvent was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography (dichloromethane:methanol=85 : 15, v/v) to give an anomeric mixture of 1-(5-*O*-benzoyl-2,3-dideoxy-**D**-*glycero*-pentofuranosyl)cytosine. These anomers were separated by hplc (ODS; 30 mmϕ X 250 mm; acetonitrile:water=28 : 72, v/v; 10 ml/min.) to give 1-(5-*O*-benzoyl-2,3-dideoxy-β-**D**-*glycero*-pentofuranosyl)cytosine (0.65 g, 51%) and its α-anomer (0.31 g, 25%).

(5-*O*-Benzoyl-2,3-dideoxy-β-**D**-*glycero*-pentofuranosyl)cytosine; mp 141.5-143.0°C (ethyl acetate); $[\alpha]_D^{27}$ +85.0° (c 0.99, $CHCl_3$); ir (KBr) 3376 (m), 3108 (m), 1719 (s), 1657 (s), 1620 (s), 1524 (m), 1485 (s), 1274 (s), 1120 (m), 1091 (m), 1071 (m), 791 (m), 708 (m) cm^{-1}; uv ($CHCl_3$) 280 nm (log ε 3.84); ^{1}H-nmr ($CDCl_3$) δ: 8.02 (2H, d, *J*=7.1 Hz, aromatic H), 7.69 (1H, d, *J*=7.4 Hz, H-6), 7.57 (1H, t, *J*=7.4 Hz, aromatic H), 7.44 (2 H, t, *J*=7.5 Hz, aromatic H), 6.06 (1H, dd, *J*=6.6 and 3.1 Hz, H-1'), 5.77 (1H, d, *J*=7.4 Hz, H-5), 4.58 (1H, dd, *J*=12.3 and 3.5 Hz, H-5'), 4.54 (1H, dd, *J*=12.2 and 4.6 Hz, H-5'), 4.45-4.37 (1H, m, H-4'), 2.53-2.38 (1 H, m, H-2'), 2.13-1.99 (2H, m, H-2', H-3'), 1.87-1.73 (1H, m, H-3'); ^{13}C-nmr ($CDCl_3$) δ: 166.21 (C=O), 166.04 (C-4), 155.98 (C-2), 139.93 (C-6), 133.30 (aromatic C), 129.48 (aromatic C), 129.43 (aromatic C), 128.44 (aromatic C), 94.36 (C-5), 87.17 (C-1'), 78.88(C-4'), 65.25(C-5'), 32.97 (C-3'), 25.52 (C-2'); ms

m/z 315 (M^+), 205 (sugar), 112 (base unit + 1), and 105 (benzoyl unit); Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.32. Found C, 60.77; H, 5.23; N, 13.30.

(5-*O*-Benzoyl-2,3-dideoxy-α-**D**-*glycero*-pentofuranosyl)cytosine; $[\alpha]_D^{27}$ -95.6° (c 1.25, $CHCl_3$); ir (KBr) 3330 (m), 3200 (m), 1719 (s), 1649 (s), 1522 (m), 1491 (s), 1274 (s), 1120 (m), 1071 (m), 789 (m), 712 (m) cm^{-1}; uv ($CHCl_3$) 278 nm (log ε 3.84); ^{1}H-nmr ($CDCl_3$) δ: 8.05 (2H, d, *J*=7.0 Hz, aromatic H), 7.58 (1H, t, *J*= 7.4 Hz, aromatic H), 7.45 (2H, t, *J*=7.5 Hz, aromatic H), 7.43 (1H, d, *J*=7.4 Hz, H-6), 6.14 (1H, dd, *J*=6.1 and 3.3 Hz, H-1'), 5.83 (1H, d, *J*=7.4 Hz, H-5), 4.75-4.66 (1H, m, H-4'), 4.43 (1H, dd, *J*=11.8 and 4.0 Hz, H-5'), 4.35 (1H, dd, *J*=11.8 and 5.5 Hz, H-5'), 2.66-2.52 (1H, m, H-2'), 2.19-2.03 (2H, m, H-2', H-3'), 2.03-1.90 (1H, m, H-3'); ^{13}C-nmr ($CDCl_3$) δ: 166.35 (C=O), 165.99 (C-4), 155.94 (C-2), 139.98 (C-6), 133.24 (aromatic C), 129.64 (aromatic C), 129.62 (aromatic C), 128.46 (aromatic C), 94.18 (C-5), 88.54 (C-1'), 78.72 (C-4'), 66.29 (C-5'), 32.76 (C-3'), 26.12 (C-2'); ms *m/z* 315 (M^+), 205 (sugar), 112 (base unit + 1), and 105 (benzoyl unit); hrms Calcd for $C_{16}H_{17}N_3O_4$ (M^+): 315.1219. Found 315.1194.

1-[5-*O*-(*p*-Chlorobenzoyl)-β-**D**-*glycero*-pentofuranosyl]uracil (**11**)

To a suspension of 1.1 g (10 mmol) of uracil in 20 ml of hexamethyldisilazane was added 0.5 ml of chlorotrimethylsilane, and the mixture was refluxed under an argon atmosphere for 30 min. After the crystals dissolved, the solvent was evaporated under reduced pressure (2 mmHg) at room temperature for 30 min. The residual oil was dissolved in 50 ml of dry chloroform. To this solution, a solution of 0.96 g (5.0 mmol) of 1-chloro-5-*O*-(*p*-chlorobenzoyl)-2,3-dideoxy-**D**-*glycero*-pentofuranose (**10a**) and 200 ml (2.5 mmol) of pyridine in 10 ml of dry chloroform was added, and the mixture was stirred under an argon atmosphere at room temperature overnight. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with chloroform three times. The organic layer was dried over anhydrous magnesium sulfate, and then the solvent was distilled away under reduced pressure. The residue obtained was purified by silica gel column chromatography (chloroform:methanol=97 : 3, v/v) and by recrystallization from ethyl acetate to give 1-[5-*O*-(*p*-chlorobenzoyl)-β-**D**-*glycero*-pentofuranosyl]uracil (0.85 g, 48% yield);mp 165.0-167.0°C; $[\alpha]_D^{27}$ +35.1° (c 1.00, $CHCl_3$); ir (KBr) 1725 (m), 1680 (s), 1276 (m), 1255 (m), 1094 (m), 760 (m) cm^{-1}; uv ($CHCl_3$) 248 nm (log ε 4.31); ^{1}H-nmr ($CDCl_3$) δ: 9.19 (1H, br, NH), 7.97 (2H, d, *J*=8.7 Hz, aromatic H), 7.62 (1H, d, *J*=8.2 Hz, H-6), 7.45 (2H, d, *J*=8.7 Hz, aromatic H), 6.08 (1H, dd, *J*=6.6 and 3.5 Hz, H-1'), 5.62 (1H, d, *J*=8.2 Hz, H-5), 4.62 (1H, dd, *J*=13.6 and 3.6 Hz, H-5'), 4.55 (1H, dd, *J*=13.6 and 5.3 Hz, H-5'), 4.49-4.40 (1H, m, H-4'), 2.58-2.44 (1H, m, H-2'), 2.20-2.06 (2H, m, H-2', H-3'), 1.98-1.83 (1H, m, H-3'); ^{13}C-nmr ($CDCl_3$) δ: 165.27 (C=O), 162.95 (C-4), 150.05 (C-2), 140.02 (aromatic C), 139.26 (C-6), 130.91 (aromatic

C), 128.92 (aromatic C), 127.89 (aromatic C), 101.97 (C-5), 86.67 (C-1'), 78.95 (C-4'), 65.35 (C-5'), 32.67 (C-3'), 25.90 (C-2'); ms *m/z* 350 (M^+), 239 (sugar), 139 (*p*-chlorobenzoyl unit), and 113 (base unit + 1); Anal. Calcd for $C_{16}H_{15}N_2O_5Cl$: C, 54.79; H, 4.31; N, 7.99; Cl, 10.11. Found C, 54.84; H, 4.16; N, 8.01; Cl, 9.86.

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