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Stereoselective Synthesis of Anomers of 5-Substituted 2′-Deoxyuridines

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The substitution reaction of 5-substituted 2,4-bis(trimethylsilyloxy)pyrimidines with 3,5-bis(*O*-*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl chloride was investigated. In the presence of *p*-nitrophenol, β anomers were formed stereoselectively, whereas the addition of organic bases brought forth stereoselective formation of α anomers. Stereoselectivity of the reaction depends on the substituents at 5-position of disilylpyrimidines, additives, and the concentration of each reagent. The α and β anomers of 5-substituted 2′-deoxy-uridines were synthesized through the deacylation of α and β anomers of 5-substituted 3′,5′-di-*O*-(*p*-chlorobenzoyl)-2′-deoxyuridines.

It is well-known that 5-substituted 2′-deoxy-β-uridines (**6a—f**) have useful physiological activity for antitumor[1,2] and anti-viral[3-5] drugs. Usually, only β anomers show the physiological activity. Many investigations have been carried out to synthesize β anomers under different conditions by the Hilbert-Johnson reaction, such as reactions of sugar halide with mercury salt of uracils,[6-8] 2,4-dimethoxypyrimidines,[9-14] silylpyrimidines by fusion,[15,16] and silylpyrimidines in the presence of $SnCl_4$.[17] But up to date, no general and efficient methods have been reported for the stereoselective synthesis of 2′-deoxyuridines.

We reported recently that the reaction of 5-fluoro-2,4-bis(trimethylsilyloxy)pyrimidine (**1c**) with 3,5-bis(*O*-*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl chloride (**2**) in the presence of Brönsted acids selectively gives 3′,5′-di-*O*-(*p*-chlorobenzoyl)-5-fluoro-2′-deoxy-β-uridine (**4c**).[18] Further studies on stereoselectivity of the reaction of **1c** with **2** suggested that the addition of a base such as pyridine changed the stereoselectivity of the reaction from β- to α-selectivity in proportional degrees to the concentration of the base.

This paper describes the stereoselective synthetic method of both the α and β anomers of 5-substituted 2′-deoxyuridines (**5a—f** and **6a—f**) based on the following observation. 1) In the presence of *p*-nitrophenol, **1a—f** reacts with **2** to give β anomers stereoselectively in high yields. 2) Combined use of *p*-nitrophenol and pyridine as catalyst changes β-stereoselective reaction of **1c** with **2** to an α-stereoselective reaction. 3) In the presence of other organic bases or their salts, reaction of **1c** with **2** also gives an α anomer (**3c**) stereoselectively. 4) Similarly to the reactin of **1c**, 5-substituted 2,4-bis(trimetylsilyloxy)-pyrimidines reacts with **2** in the presence of pyridine to give α anomers in high yields.

Results

Identification of Anomers of 2′-Deoxyuridine Derivatives. Rapid identification of the anomers of 2′-deoxyuridine derivatives in the reaction mixture was carried out by mean of ^{1}H NMR spectroscopy and chromatography. The properties of 5-substituted 3′,5′-di-*O*-(*p*-chlorobenzoyl)-2′-deoxyuridines are summarized in Table 1. The anomeric protons of all β anomers **4a—f** were observed as triplet at δ 6.15—6.40, whereas those of α anomers **3a—f** were multiplet.

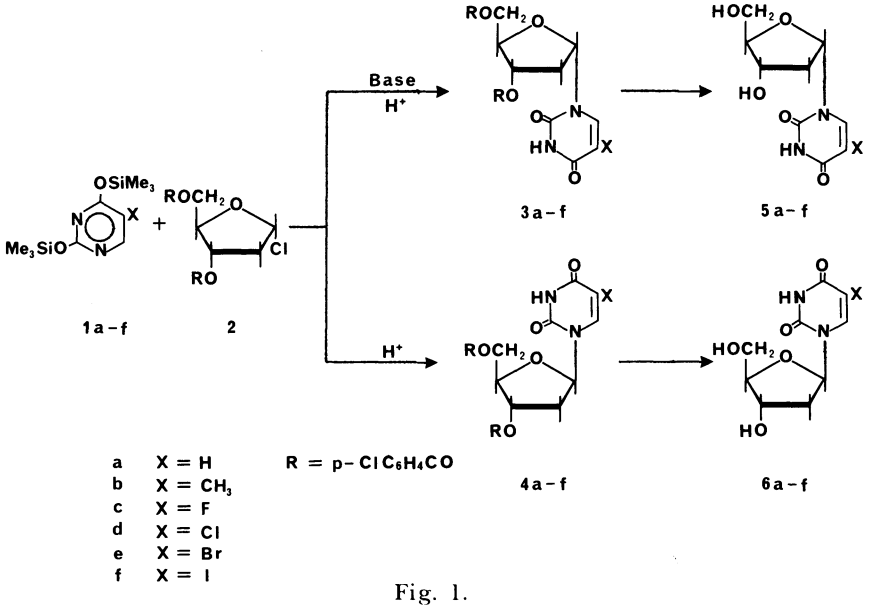

Fig. 1.

Table 1. 5-Substituted 3′,5′-Di-*O*-(*p*-chlorobenzoyl)-2′-deoxyuridines

Compound No.	Substituent and Anomer	Mp θ_m/°C	TLC R_f Value	HPLC Retention time/min	$[\alpha]_D^{20}$ (C2, dioxane) (°)	IR (KBr) $\nu_{C=O}$/cm^{-1}	^{1}H NMR[a] δ(ppm) Anomeric H
3a	H, α	190.5—191	0.29	9.25	−46.2	1720, 1690, 1670	6.17—6.37m
4a	H, β	212 —213	0.25	11.47	−14.7	1718, 1685	6.25 t, *J*=8 Hz
3b	CH_3, α	179 —180	0.34	11.45	−23.7	1725, 1685	6.18—6.42m
4b	CH_3, β	197.5—198.5	0.38	14.02	−30.7	1715, 1675	6.33 t, *J*=8 Hz
3c	F, α	176 —177	0.41	11.89	−67.4	1725, 1690, 1670	6.15—6.41m
4c	F, β	198 —199	0.45	14.59	− 4.7	1710, 1700, 1665	6.25 t, *J*=7 Hz
3d	Cl, α	184 —185	0.48	13.65	− 1.2	1725, 1690	6.11—6.35m
4d	Cl, β	189.5—190	0.59	16.39	−28.4	1710, 1692	6.37 t, *J*=8 Hz
3e	Br, α	168 —170	0.49	14.38	+22.5	1720, 1690	6.14—6.34m
4e	Br, β	188 —189	0.61	17.18	−35.4	1715, 1680	6.30 t, *J*=8 Hz
3f	I, α	182 —183	0.50	15.43	+56.1	1715, 1665	6.24—6.36m
4f	I, β	187 —188	0.64	18.33	−50.3	1712, 1675, 1650	6.18 t, *J*=8 Hz

a) DMSO-d_6.

Table 2. 5-Substituted 2′-Deoxyuridines

Compound No.	Substituent and Anomer	Mp θ_m/°C	TLC R_f Value	$[\alpha]_D^{20}$ (C2, N-NaOH) (°)	IR (KBr) $\nu_{C=O}$/cm^{-1}	^{1}H NMR[a] δ(ppm) H_6	^{1}H NMR[a] δ(ppm) Anomeric H
5a	H, α	oil	0.25	− 4.2	1700, 1690	7.72 d, *J*=8Hz	6.09 dd, *J*=5 and 6Hz
6a	H, β	164 —165	0.27	+50.4	1690, 1660	7.60 d, *J*=8Hz	6.24 t, *J*=Hz
5b	CH_3, α	187.5—188	0.32	+19.3	1682	7.60s	6.15 dd, *J*=5 and 6Hz
6b	CH_3, β	192 —193	0.34	+30.8	1700, 1655	7.43s	6.28 t, *J*=6.5Hz
5c	F, α	177 —178	0.39	−13.7	1722, 1690	7.80 d, *J*=7Hz	6.09m
6c	F, β	150 —151	0.44	+55.1	1710, 1685	7.70 d, *J*=7Hz	6.18 t, *J*=7Hz
5d	Cl, α	194 —196	0.44	+ 4.6	1695, 1680(sh)	7.93s	6.11 dd, *J*=3.5 and 7Hz
6d	Cl, β	177 —178	0.50	+49.4	1730, 1672	7.86s	6.15 t, *J*=7Hz
5e	Br, α	197 —199	0.47	+11.2	1682	8.04s	6.05 dd, *J*=3.5 and 7Hz
6e	Br, β	186 —187	0.52	+39.4	1710, 1685	7.99s	6.24 t, *J*=8Hz
5f	I, α	188.5—189.5	0.51	+21.5	1685	8.09s	6.03 dd, *J*=4 and 7Hz
6f	I, β	187 —188	0.55	+27.4	1700, 1672	8.08s	6.16 t, *J*=7Hz

a) N-NaOD.

Thin-layer chromatograph using a precoated silica-gel plate (Art 5715, $60F_{254}$) and a mixted solvent of hexane, benzene, and ethyl acetate (1 : 1 : 2) as well as HPLC were successfully used for separating α and β anomers (**3a—f** and **4a—f**).

The properties of 5-substituted 2′-deoxyuridines are shown in Table 2. ^{1}H NMR spectra of the anomeric protons show triplet about δ 6.03—6.28 for all β anomers, and double doublet or multiplet for α anomers. ^{1}H NMR spectra of H_6 of pyrimidine ring show doublet or singlet peaks and those of β anomers appear at higher magnetic fields in comparison with those of α anomers. The α and β anomers (**5a—f and 6a—f**) were identified by thin-layer chromatogrph using a precoated silica-gel plate (HPTLC, Art 5628, $60F_{254}$) with a mixed solvent of ethyl acetate, formic acid, and water (65 : 5 : 5).

Reaction of 1a—f with 2 in the Presence of *p*-Nitrophenol. Pyrimidine derivatives **1a—f** reacted with **2** in the presence of *p*-nitrophenol to give β anomers **4a—f** in high yields. Among Brönsted acids used, *p*-nitrophenol gave β anomer most efficiently in the reaction of **1c** with **2**.[18] The results are shown in Table 3. The β-stereoselectivity was affected by a substituent in 5-position of silylpyrimidine; electron-releasing substituents seem to give more β anomer.

Table 3. β-Selective Synthesis of 5-Substituted 3′,5′-Di-*O*-(*p*-chlorobenzoyl)-2′-deoxy-β-uridines

Run	Substituent group	Yield/%[a] α Anomer	Yield/%[a] β Anomer
1	H	2.5	96.5
2	CH_3	trace	96
3	F	4.5	92
4	Cl	4.5	92
5	Br	10	85
6	I	9	87

a) Yields refer to isolated products.

Reaction of 1c with 2 in the Presence of Base and *p*-Nitrophenol. During investigation of the reaction of **1c** with **2** it was happened that β anomer **4c** is not formed, but formed α anomer **3c** when **1c** and/or **2** containing a trace of trietylamine hydrochloride[20] and/or pyridine were used. This result made the author to examine the effect of base on the stereoselectivity.

First, the effect of concentration of pyridine on the

stereoselectivity was investigated. The results are shown in Fig. 2. In the presence of a trace of pyridine, β-stereoselective reaction changed to α-stereoselective reaction in proportion to the concentration of pyridine.

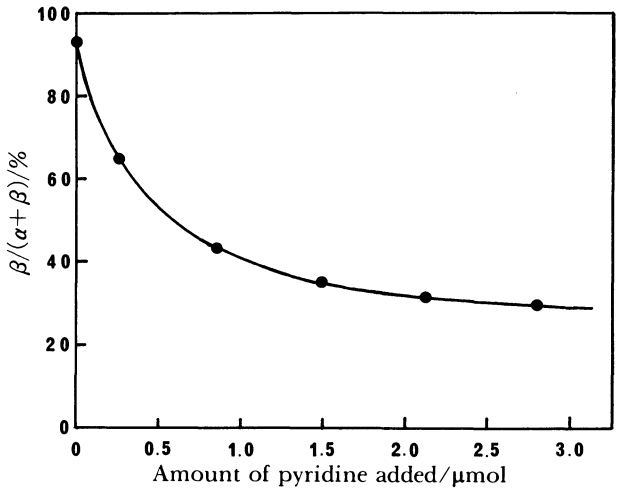

Fig. 2. The effect of the concentration of pyridine on the stereoselectivity of the reaction **1c** with **2**. Reaction conditions; **1c**: 0.197 g (0.768 mmol), **2**: 0.300 g (0.698 mmol), *p*-nitrophenol: 0.034 g (0.244 mmol), chloroform: 2.1 cm³, reaction temp: 25 °C, reaction time: 12 h.

Table 4. Effect of Additives on the Formation of **3c**[a)]

Run	Additive	Amount[b)]	Yield/%[c)]
1	Pyridine	0.1	77.8
2	α-Picoline	0.1	76.5
3	β-Picoline	0.1	78.1
4	2,6-Lutidine	0.1	62.3
5	Triethylamine	0.1	73.4
6	Triethylamine Hydrochloride	0.35	77.5
7	*N*,*N*-Dimethylformamide	0.1	39.7
8	Acetamide	0.1	50.9

a) Reaction conditions; **1c**: 1.1 mmol, **2**: 1.0 mmol, *p*-nitrophenol: 0.35 mmol, chloroform: 3.0 cm³, reaction temp: 25 °C, reaction time: 12 h. b) Based on 2. c) Yield is measured by HPLC.

Table 5. α-Selective Synthesis of 5-Substituted 3′,5′-Di-*O*-(*p*-chlorobenzoyl)-2′-deoxy-α-uridines

Run	Substituent group	Yield/%[a)]	
		α Anomer	β Anomer
1	H	74.8	21.1
2	CH_3	67.4	32.5
3	F	79.3	14.6
4	Cl	77.3	10.4
5	Br	77.0	21.0
6	I	81.5	15.4

a) Yields refer to isolated products.

Second, the effect of additives such as organic bases or triethylamine hydrochloride in the reaction of **1c** with **2** on the stereoselectivity was investigated. The results are shown in Table 4. Pyridine showed higher α-stereo-selectivity than lutidine. This seems to be due to steric hindrance of methyl radicals of 2,6-lutidine to sugar halide. On the other hand, triethylamine hydrochloride showed considerable α-stereoselectivity, but *N*,*N*-dimethylformamide and acetamide showed no stereoselectivity.

α-Stereoselective Synthesis. The effect of substituents at 5-position of silylpyrimidine on α-stereoselective reactions of **1a—f** with **2** was investigated and α anomers **3a—f** were synthesized. In the presence of pyridine, **1a—f** reacted with **2** α-stereoselectively to give **3a—f** in high yields. The results are shown in Table 5.

The α-stereoselectivity was affected by the substituents at 5-position of silylpyrimidine and halogen substituents showed higher selectivity than methyl group. It is, therefore, considered that electron-attracting substituents cause higher α-stereoselectivity than electron-releasing substituents.

Deprotection by the treatment of ammonia-methanol solution to **3a—f** or **4a—f** smoothly gave **5a—f** or **6a—f**, respectively, in high yields.

Discussion

On the substitution reactions of **1a—f** with **2**, it became apparent that the stereoselectivity varies with

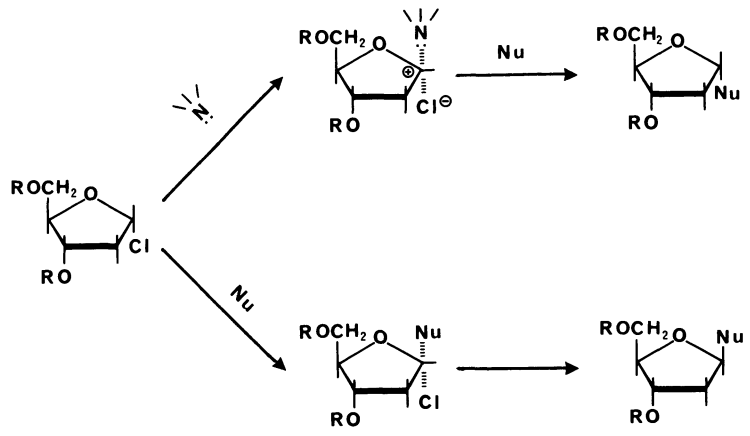

Fig. 3.

the substituent group of 5-position of silylpyrimidine, the additives, and concentration of additives.

It is improbable that both the α and β nucleosides are stereoselectively formed in the substituting reaction, by the Hilbert-Johnson reaction through nucleophilic attack of a sugar cation on aromatic pyrimidine ring.[13] In the preceding work,[18] it was proposed that β-stereoselective reaction occurs between silylpyrimidine as nucleophilic reagent and the β-face of sugar halide which is pure α anomer, in the presence of Brönsted acid.

On the other hand, the presence of organic base or its salt turned β-stereoselective substitution reaction into α-stereoselective reaction.

α-Stereoselectivity. The α-stereoselective reaction mechanism can be depicted in Fig. 3. While nucleophilic reagent attacks the β-face of sugar halide, a base attacks the nucleophilic reagent competitively. If the base has higher active in nucleophilicity than the nucleophilic reagent, the base coordinates with the β-face of sugar halide predominantly. Then the nucleophilic reagent cannot attack the β-face of sugar halide but attacks the α-face to produce an α-nucleoside. Thus, nucleophilicity of reagent seems to contribute to the stereoselectivity in substitution reaction.

Experimental

Apparatus. All the melting points measured were not corrected. IR spectra were recorded by a Hitachi 260—30 infrared spectrophotometer using KBr disk method. ^{1}H NMR spectra were obtained by a Hitachi Perkin-Elmer P-24 (60 MHz) using TMS as the internal standard. The specific rotation was measured by a JASCO DIP-181 digital polarimeter. The spectrophotometric measurement of TLC spots was done on a Shimadzu High-Speed TLC Scanner CS-920. High-performance liquid chromatography was experimented by a Shimadzu LC-3A equipped with a Shimadzu variable length spectrophotometric detector SPD-2A and a Shimadzu Chromatopac C-RIA.

Analysis by Thin-Layer Chromatography. The anomeric ratio of nucleoside was monitored during the reaction by thin-layer chromatography. Anomers were separated on the plates precoated with silica-gel $60F_{254}$ (Merck, Art 5715) with a mixed solvent of hexane, benzene, and ethyl acetate (1 : 1 : 2). R_f values of anomers **3a—f** and **4a—f**, are shown in Table 1. Measurements were run according to the preceding work[18] by using of high-speed TLC scanner.

Anomers **5a—f** and **6a—f**, were separated the plates precoated with silica-gel $60F_{254}$ (HPTLC, Merck, Art 5628) a mixed solvent of ethyl acetate, formic acid, and water (65 : 5 : 5). R_f values of the anomers are shown in Table 2.

Analysis by High-Performance Liquid Chromatography. A column (25 cm×4 mm i.d.) was packed with RP-18 chemically bonded silica-gel (LiChrosorb, 10 μm, Merck). The mobil phase was a 45 : 55 mixture of 0.03 mol dm^{-3} ammonium dihydrogenphosphate solution and acetonitrile, which was made to 1 cm^3 min^{-1} and 25 °C. The retention time values of each compound of **3a—f** and **4a—f** are shown in Table 1.

Materials. Chloroform were refluxed for 2 h over P_2O_5 and distilled. Uracil, thymine, and 5-fluorouracil purchased were used without further purification. 5-Chlorouracil, 5-bromouracil, and 5-iodouracil were prepared by the reaction of uracil with the corresponding *N*-halosuccinimide[19] in acetic acid. 3,5-Bis(*O*-*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl chloride (**2**) was prepared as described in the preceding report.[18]

Table 6. Boiling Point of 5-Substituted 2,4-Bis-(trimethylsilyloxy)pyrimidines

Compound		Bp/θ_b/°C/mmHg†
No.	Substituent group	
1a	H	113—114/16
1b	CH_3	124—131/16
1c	F	110—111/15
1d	Cl	130—131/16
1e	Br	138—139/16
1f	I	124—132/4

5-Substituted 2,4-Bis(trimethylsilyloxy)pyrimidines (1a—f). These compounds were all prepared in an analogous manner.[18] A mixture of appropriate uracil (1 mol), hexamethyldisilazane (260 cm^3, 1.25 mol), and trimethylsilyl chloride (1 cm^3, 7.8 mmol) was refluxed in dry atomosphere. Ammonia gas vigorously evolved. The excess of hexamethyldisilazane was removed after 2 h of the reaction under 50 mmHg† and finally 12 mmHg at 90 °C. The residue was distilled in vacuo to give **1a—f**. The boiling point values are shown in Table 6.

Synthesis of β Anomers (4a—f). To a mixture of **1a—f** (17.9 mmol), *p*-nitrophenol (0.8 g, 5.77 mmol) in dry chloroform (49 cm^3), was added **2** (7 g, 16.3 mmol) and stirred for 12 h at 30 °C. The reaction mixture was then evaporated under a reduced pressure to give crystalline residue, which was recrystallized from acetic acid to give β anomers. From mother liquor, anomers were isolated by fractional crystallization. Results are shown in Table 3.

Effect of Pyridine on the Reaction of 1c with 2. To a mixture of **1c** (0.197 g, 0.768 mmol), *p*-nitrophenol (0.034 g, 0.244 mmol), and pyridine in chloroform (2.1 cm^3), was added **2** (0.300 g, 0.698 mmol) and stirred for 12 h at 25 °C. The ratio of each anomer was analyzed by TLC scanner. The result is shown in Fig. 2.

Effect of Additives on the Formation of 3c. To a mixture of **1c** (0.302 g, 1.1 mmol), *p*-nitrophenol (0.049 g, 0.35 mmol), and additives in chloroform (3.0 cm^3), was added **2** (0.430 g, 1.0 mmol) and stirred for 12 h at 25 °C. The ratio of each anomer was analyzed by HPLC. The results are shown in Table 4.

Synthesis of α Anomers (3a—f). To a mixture of **1a—f** (17.9 mmol), *p*-nitrophenol (0.8 g, 5.77 mmol), and pyridine (0.4 g, 5.05 mmol) in dry chloroform (49 cm^3), was added **2** (7 g, 16.3 mmol) and stirred for 12 h at 30. The reaction mixture was then evaporated under a reduced pressure to give an oily residue, which was subjected to crystallization with ethanol to give α anomers. The anomers were isolated from mother solutions by fractional crystallization. The results are shown in Table 5.

5-Substituted 2′-Deoxyuridines (5a—f, 6a—f). To a saturated ammonia-methanol solution (20 cm^3), was added 1 g of each anomer **3a—f** and **4a—f**, and stirred for 16 h at 30 °C. The reaction mixture was then treated similarly to the

† 1 mmHg=133.3 Pa.

manner as described in preceding report.[18] The 2′-deoxyuridine derivatives were isolated in 90—99% yield, of which physical properties are shown in Table 2.

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