  Bull. Chem. Soc. Jpn., 64, 2266—2269 (1991) [Vol. 64, No. 7

A Synthesis of 5′-*O*-Acryloyl-5-fluorouridine by Use of *p*-Methoxybenzyl Group as an N^3-Imide Protecting Group of 5-Fluorouridine[1)]

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(Received February 18, 1991)

5′-*O*-Acryloyl-5-fluorouridine was prepared by use of *p*-methoxybenzyl (PMB) group as an N^3-imide protecting group of 5-fluorouridine. PMB group was introduced chemoselectively by use of *N*,*N*-diisopropylethylamine or DBU as a base. A new deprotection method was developed by means of $AlCl_3$–anisole system at room temperature.

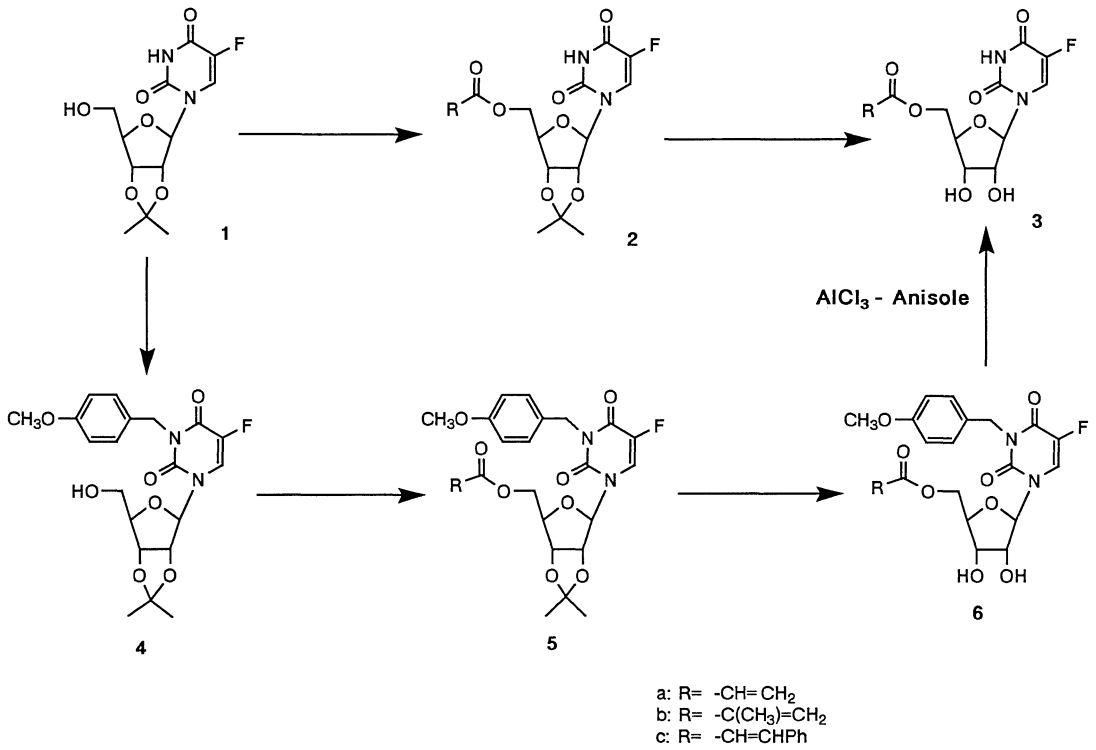
In our laboratory, as part of a continuing synthetic program designed to develop antitumor agents with high antitumor activity and low toxicity, we have synthesized various kinds of 5-fluorouracil (5-FU) derivatives such as 1-carbamoyl-,[2)] 1-acyloxyalkyl-,[3)] 1-alkylthiocarbamoyl-,[4)] 1-alkoxyalkyl-5-fluorouracils,[5)] and also functional polymers bearing 5-FU as a side chain.[6)] Recently, functional polymers containing 5-FU have attracted considerable attention from the standpoint of polymeric drugs. Polymeric drugs bearing 5-fluorouridine (FUR) as a side chain, however, have not been developed so far. In previous papers,[1,7)] we reported syntheses and antitumor activity of 5′-*O*-acyl-5-fluorouridines, which showed high antitumor activity against L-1210 leukemia in mice. These results prompted us to synthesize functional polymers containing FUR as a side chain. We focused on 5′-*O*-acryloyl-5-fluorouridine (**3a**) as a promising ester monomer containing FUR and attempted to synthesize it. Unexpectedly, **3a** was not obtained by the usual method (5′-*O*-acylation of 2′,3′-*O*-isopropylidene-5-fluorouridine (**1**) followed by acidic hydrolysis). In order to synthesize it efficiently, protection of the N^3-imide function was necessary. Protection of N^3-imide function in uridine moiety has attracted considerable attention in nucleotide chemistry and various kinds of protecting groups such as benzoyl,[8)] 2-(4-nitrophenyl)ethyl,[9)] 2-(4-nitrophenylsulfonyl)-ethyl,[10)] phenyl,[11)] and 2-(methoxy)ethoxymethyl[12)] groups have been developed. Because N-glycosidic bonds are acid labile and *O*-acryloyl moiety is unstable in basic conditions, an N^3-imide protecting group removable under mild conditions is desirable. We have found that *p*-methoxybenzyl (PMB) group meets above requirements. The PMB group has following features; 1) selective introduction is possible in the presence of free OH group with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base, 2) deprotection was effected smoothly by the action of $AlCl_3$ in anisole at room temperature under mild conditions.[13)] In this paper we wish to describe a synthesis of **3a** by use of PMB group as a N^3-imide protecting group removable under weakly acidic conditions by means of $AlCl_3$–anisole system.[14)]

Results and Discussion

A variety of 5′-*O*-acyl-5-fluorouridines were synthesized by 5′-*O*-acylation of **1** followed by acidic hydrolysis of the isopropylidene moiety.[1)] However, when **1** was treated with acryloyl chloride in the presence of tertiary amine, corresponding 5′-*O*-acylated compound **2a** was obtained in a very low yield and was too labile to purify by column chromatography. All our attempts to synthesize **2a** in a pure form failed. We therefore speculated that **2a** could be obtained by protecting N^3-imide function in advance and sought a protecting group for the N^3-imide function. We have found that a PMB group meets above requirements.

Introduction of a PMB group was carried out as follows. Treatment of **1** with *p*-methoxybenzyl bromide (1.5 equiv) in the presence of *N*,*N*-diisopropylethylamine (2.0 equiv) as a base in CH_3CN at room temperature for 3 h gave 2′,3′-*O*-isopropylidene-3-(4-methoxybenzyl)-5-fluorouridine (**4**) quantitatively. The PMB group was introduced more conveniently by use of commercially available *p*-methoxybenzyl chloride in the presence of DBU as a base in CH_3CN without protecting 5′-OH group to afford **4** in a good yield. No formation of 5′-*O*-alkylated compound was observed under these conditions. Next, acylation of N^3-protected derivative **4** with acryloyl chloride proceeded smoothly to obtain 5′-*O*-acryloyl-2′,3′-*O*-isopropylidene-3-(4-methoxybenzyl)-5-fluorouridine (**5a**) in a good yield. Acidic hydrolysis of the isopropylidene moiety afforded 5′-*O*-acryloyl-3-(4-methoxybenzyl)-5-fluorouridine (**6a**).

An $AlCl_3$–anisole system has been utilized in the deprotection of benzyl esters.[15)] We employed the $AlCl_3$–anisole system for the deprotection of N^3-benzyl moieties of FUR. Deprotection of the PMB group was achieved by treatment of **6a** with $AlCl_3$ (10 equiv) in anisole at room temperature overnight to obtain 5′-*O*-acryloyl-5-fluorouridine (**3a**) in 96% yield. When ammonium cerium(IV) nitrate was used for the deprotection of PMB moiety,[13)] **3a** was not obtained at all presumably due to the decomposition of **3a** or **6a** under the reaction conditions. This result demonstrates mild conditions of our deprotection methods.



Scheme 1.

Table 1. Deprotection of the *p*-Methoxybenzyl Group[a)]

Run	R_1	R_2	R_3	Product	Yield/%
1	**6a** $-COCH=CH_2$	H	H	**3a**	96
2	**6b** $-COC(CH_3)=CH_2$	H	H	**3b**	81
3	**6c** $-COCH=CHPh$	H	H	**3c**	93
4	**5c** $-COCH=CHPh$	$C(CH_3)_2$		**2c**	81

a) 10 equiv of $AlCl_3$ was used in anisole at room temperature.

The present method was successfully applied to other PMB-protected 5-fluorouridine derivatives as shown in Table 1. In the case of cinnamoyl (**6c**), methacryloyl (**6b**) derivatives, PMB groups were also cleaved without harming N-glycosidic bond to afford the NH free compounds in good yields. It is noted that PMB group was cleaved in preference to the 2′,3′-*O*-isopropylidene moiety (Run 4).

Finally, we tested an unsubstituted benzyl group. When 5′-*O*-cinnamoyl-3-benzyl-5-fluorouridine (**9**) was treated with $AlCl_3$ (10 equiv) in anisole at room temperature, no reaction took place. Deprotection of the benzyl group proceeded at a higher temperature (80 °C, 4 h) with concurrent cleavage of the N-glycosidic bond to afford **3c** in a low yield (<10%). Thus, presence of the *p*-methoxy substituent is essential for the smooth cleavage of N^3-benzyl moiety in the present method.

Experimental

Melting points were determined on a Yamato melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a JEOL GSX-270 spectrometer with tetramethylsilane as an internal standad. IR spectra were recorded on a Hitachi EPI G-3 spectrometer. $AlCl_3$ was ground into fine powder and stored under N_2 atmosphere. Anisole was distilled over CaH_2 and stored over Molecular Sieves 4A. *p*-Methoxybenzyl bromide[17)] was prepared by NBS-mediated bromination[18)] of *p*-methoxytoluene and used immediately. Purification of products was performed by column chromatography on silica gel (Wako gel C-300) or preparative TLC on silica gel (Wako gel B-5F).

2′,3′-*O*-Isopropylidene-3-(4-methoxybenzyl)-5-fluorouridine (4). To a solution of 2′,3′-*O*-isopropylidene-5-fluorouridine[19)] (**1**) (1.35 g, 4.47 mmol) in CH_3CN (15 ml) was added *p*-methoxybenzyl chloride (1.12 ml, 8.94 mmol) and DBU (1.34 ml, 8.94 mmol). The mixture was allowed to reflux at 50—60 °C for 3 h. After the mixture was cooled to room temperature, H_2O was added. The mixture was extracted with ethyl acetate. The combined organic layers were successively washed with 1 M HCl (1 M=1 mol dm^{-3}) and brine, and then concentrated to dryness to give an oil, which was purified by column chromatography on silica gel (CH_2Cl_2 : ethyl acetate=5.5 : 1, v/v) to afford an oil. Recrystallization of it from a mixture of hexane and ethyl acetate (v/v=1 : 1) gave **4** as crystals (1.85 g, 98%): Mp 118—119 °C; ^1H NMR ($CDCl_3$) δ=1.36 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.46—2.51 (1H, m, OH), 3.78 (3H, s, OCH_3), 3.81 (1H, ddd, $J_{5',5''}$=11.9 Hz, $J_{4',5'}$=2.7 Hz, $J_{5',OH}$=6.1 Hz, H-5′), 3.94 (1H, dt, $J_{4',5''}$=2.7 Hz, H-5″), 4.33 (1H, q, $J_{3'4'}$=2.7 Hz, H-4′), 4.88—4.95 (2H, m, H-2′,3′), 5.02, 5.08 (2H, ABq, J=13.6 Hz, CH_2), 5.68 (1H, d, $J_{1',2'}$= 2.4 Hz, H-1′), 6.80—6.86 (2H, m, aromatic), 7.42—7.48 (2H, m, aromatic), and 7.59 (1H, d, J=5.8 Hz, H-6); IR (nujol) 3420, 1690, 1660, and 1640 cm^{-1}. Found: C, 56.81; H, 5.51; N,

6.41%. Calcd for $C_{20}H_{23}N_2O_7F$: C, 56.87; H, 5.49; N, 6.63%.

General Procedure for the 5′-*O*-Acylation of 4. A typical procedure is described for 5′-*O*-acryloyl-2′,3′-*O*-isopropylidene-3-(4-methoxybenzyl)-5-fluorouridine (**5a**). To a solution of **4** (1.53 g, 3.63 mmol) in CH_3CN (2 ml) was added successively *N*,*N*-diisopropylethylamine (1.26 ml, 7.25 mmol) and acryloyl chloride (0.884 ml, 10.9 mmol) at room temperature. The mixture was stirred at that temperature for 4 h, and 5% $KHSO_4$ solution was added. Organic phase was separated and aqueous layers were extracted with ethyl acetate. The combined orgaic layers were successively washed with brine, 2.5% $NaHCO_3$ solution, and brine, dried over anhydrous Na_2SO_4, and concentrated to leave an oil, which was purified by column chromatography on silica gel (CH_2Cl_2 : ethyl acetate=2 : 1, v/v) to give **5a** (1.66 g, 96%): ^{1}H NMR ($CDCl_3$) δ=1.36 (3H, s, CH_3), 1.58 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 4.32—4.51 (3H, m, H-4′,5′), 4.79 (1H, dd, $J_{3',4'}$=2.1 Hz, $J_{2',3'}$=6.4 Hz, H-3′), 4.89 (1H, dd, $J_{1',2'}$=2.1 Hz, H-2′), 4.99, 5.10 (2H, ABq, J=13.6 Hz, CH_2), 5.74 (1H, d, H-1′), 5.84 (1H, dd, J=10.4 Hz, 1.4 Hz, vinyl-H), 6.08 (1H, dd, J=10.4 Hz, 17.3 Hz, =CHCO), 6.41 (1H, dd, J=1.4 Hz, 17.3 Hz, vinyl-H), 6.87 (2H, d, J=8.9 Hz, aromatic), 7.39 (2H, d, J=5.5 Hz, H-6), and 7.47 (2H, d, J=8.9 Hz, aromatic); IR (nujol) 3000, 1700, 1680, and 1650 cm^{-1}. Found: C, 57.75; H, 5.31; N, 5.77%. Calcd for $C_{23}H_{25}N_2O_8F$: C, 57.98; H, 5.29; N, 5.88%.

2′,3′-*O*-Isopropylidene-5′-methacryloyl-3-(4-methoxybenzyl)-5-fluorouridine (5b): ^{1}H NMR ($CDCl_3$) δ=1.37 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.91 (3H, s, =CCH_3), 3.78 (3H, s, OCH_3), 4.28—4.50 (3H, m, H-4′,5′), 4.79 (1H, dd, $J_{3',4'}$=3.4 Hz, $J_{2',3'}$=6.4 Hz, H-3′), 4.86 (1H, dd, $J_{1',2'}$=2.1 Hz, H-2′), 5.01, 5.09 (2H, ABq, J=13.4 Hz, CH_2), 5.51—5.55 (1H, m, vinyl-H), 5.72 (1H, d, H-1′), 6.03 (1H, brs, vinyl-H), 6.80—6.85 (2H, m, aromatic), 7.36 (1H, d, J=5.8 Hz, H-6), 7.42—7.49 (2H, m, aromatic; IR ($CHCl_3$) 2990, 1700, 1645, 1490, and 1400 cm^{-1}. Found: C, 58.98; H, 5.78; N, 5.63%. Calcd for $C_{24}H_{27}N_2O_8F$: C, 58.77; H, 5.55; N, 5.71%.

5′-*O*-Cinnamoyl-2′,3′-*O*-isopropylidene-3-(4-methoxybenzyl)-5-fluorouridene (5c): ^{1}H NMR ($CDCl_3$) δ=1.37 (3H, s, CH_3), 1.59 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 4.42—4.51 (3H, m, H-4′,5′), 4.82—4.85 (1H, m, H-3′), 4.89 (1H, dd, $J_{1',2'}$=1.8 Hz, $J_{2',3'}$=6.4 Hz, H-2′), 4.99, 5.05 (2H, ABq, J=13.4 Hz, CH_2), 5.79 (1H, d, H-1′), 6.42 (1H, d, J=15.8 Hz, PhCH=), 6.79—6.84 (2H, m, aromatic), 7.37—7.52 (7H, m, aromatic), and 7.72 (1H, d, =CHCO); IR ($CHCl_3$) 2950, 1700, 1650, 1500, 1440, 1360, 1260, and 1240 cm^{-1}. Found: C, 62.79; H, 5.34; N, 5.00%. Calcd for $C_{29}H_{29}N_2O_8F$: C, 63.04, H, 5.29; N, 5.07%.

General Procedure for the Cleavage of Isopropylidene Moiety. A typical procedure is described for 5′-*O*-acryloyl-3-(4-methoxybenzyl)-5-fluorouridine (**6a**). A solution of **5a** (1.65 g, 3.45 mmol) in an 80% methanolic solution of trifluoroacetic acid (4.0 ml) was stirred at room temperature for 10 min. The reaction mixture was concentrated in vacuo to leave an oil, which was purified by column chromatography on silica gel (hexane : ethyl acetate=1 : 2, v/v) to give **6a** (1.32 g, 88%) as an amorphous solid: ^{1}H NMR ($CDCl_3$: CD_3OD=95 : 5, v/v) δ=2.70 (2H, brs, OH), 3.79 (3H, s, OCH_3), 4.00—4.10 (2H, m, H-2′,3′), 4.22—4.30 (1H, m, H-4′), 4.50 (1H, brs, H-5′), 4.51 (2H, brs, H-5″), 5.03, 5.09 (2H, ABq, J=13.7 Hz, CH_2), 5.79 (1H, brs, H-1′), 5.93 (1H, dd, J=1.2 Hz, J=10.4 Hz, vinyl-H), 6.14 (1H, dd, J=10.4 Hz, 17.2 Hz, =CHCO), 6.46 (1H, dd, J=1.2 Hz, J=17.2 Hz, vinyl-H), 6.78—6.88 (2H, m, aromatic), 7.35—7.48 (2H, m, aromatic), and 7.73 (1H, d, J=6.1 Hz, H-6); IR (nujol) 3400, 3000, 1690, 1660, and 1630 cm^{-1}. Found: C, 54.93; H, 4.91; N, 6.08%. Calcd for $C_{20}H_{21}N_2O_8F$: C, 55.05, H, 4.85; N, 6.42%.

5′-*O*-Methacryloyl-3-(4-methoxybenzyl)-5-fluorouridine (6b): ^{1}H NMR ($CDCl_3$: CD_3OD=95 : 5, v/v) δ=1.95 (3H, brs, CH_3), 2.46 (2H, brs, OH), 3.79 (3H, s, OCH_3), 4.02—4.15 (2H, m, H-2′,3′), 4.23—4.52 (1H, m, H-4′), 4.46 (1H, dd, $J_{4',5'}$=3.4 Hz, $J_{5',5''}$=12.5 Hz, H-5′), 4.51 (1H, dd, $J_{4',5''}$=2.7 Hz, H-5″), 5.03, 5.08 (2H, ABq, J=13.7 Hz, CH_2), 5.63—5.67 (1H, m, vinyl-H), 5.75—5.81 (1H, m, H-1′), 6.09 (1H, brs, vinyl-H), 6.77—6.88 (2H, m, aromatic), 7.39—7.49 (2H, m, aromatic), and 7.62 (1H, d, J=5.8 Hz, H-6); IR (nujol) 3350, 1700, 1630, and 1260 cm^{-1}. Found: C, 56.13; H, 5.15; N, 5.92%. Calcd for $C_{21}H_{23}N_2O_8F$: C, 56.00; H, 5.15; N, 6.22%.

5′-*O*-Cinnamoyl-3-(4-methoxybenzyl)-5-fluorouridine (6c): ^{1}H NMR ($CDCl_3$: CD_3OD=95 : 5, v/v) δ=3.76 (3H, s, OCH_3), 4.10—4.16 (2H, m, H-2′,3′), 4.32 (1H, m, H-4′), 4.48—4.51 (2H, m, H-5′, 5″), 5.01, 5.06 (2H, ABq, J=13.7 Hz, CH_2), 5.85 (1H, brs, H-1′), 6.46 (1H, d, J=15.9 Hz, =CHCO), 6.81 (2H, d, J=8.5 Hz, aromatic), 7.39—7.42 (5H, m, aromatic), 7.50—7.54 (2H, m, aromatic), 7.75 (1H, d, PhCH=), and 7.89 (1H, d, J=6.1 Hz, H-6); IR (nujol) 3450, 1700, 1620, 1290, 1230, 1160, and 1090 cm^{-1}. Found: C, 60.10; H, 5.31; N, 5.15%. Calcd for $C_{26}H_{25}N_2O_8F \cdot 0.5H_2O$: C, 59.88, H, 5.03, N, 5.37%.

General Procedure for the Cleavage of PMB Group. A typical procedure is described for 5′-*O*-acryloyl-5-fluorouridine (**3a**). To a solution of **6a** (208 mg, 0.477 mmol) in anisole (1 ml) and $AlCl_3$ (636 mg, 4.77 mmol) in anisole (1 ml). After stirring at that temperature overnight, methanol (1.0 ml) was added to the reaction mixture at 0 °C, the mixture was evaporated by rotary evaporator at a bath temperature below 40 °C. The resultant anisole solution was subjected to short column chromatography on silica gel (methanol: CH_2Cl_2=1 : 10 (v/v)) to afford an oil, which was further purified by TLC on silica gel (methanol : CH_2Cl_2=1 : 10 (v/v)) to give **3a** (144 mg, 96%): ^{1}H NMR ($CDCl_3$: DMSO-d_6=95 : 5, v/v) δ=3.33 (2H, s, H-2′,3′), 4.09—4.17 (1H, m, H-5′), 4.17—4.28 (1H, m, H-4′), 4.39—4.53 (2H, m, H-2′,3′), 5.93 (1H, dd, J=1.5 Hz, 10.4 Hz, vinyl-H), 6.21 (1H, dd, J=17.0 Hz, 10.4 Hz, =CHCO), 6.46 (1H, dd, J=1.5 Hz, 17.0 Hz, vinyl-H), 7.65 (1H, d, J=6.4 Hz, H-6), and 11.51 (1H, brs, H-3); IR (nujol) 3450, 3370, 3330, 1700, 1680, and 1660 cm^{-1}. Found: C, 45.52; H, 4.44; N, 8.51%. Calcd for $C_{12}H_{13}N_2O_7F$: C, 45.58; H, 4.14; N, 8.86%.

3-Benzyl-2′,3′-*O*-isopropylidene-5-fluorouridine (7). This was obtained by the similar procedure as described for the preparation of **4** in a quantitative yield: Mp 124—125 °C; ^{1}H NMR ($CDCl_3$) δ=1.36 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.45—2.49 (1H, m, OH), 3.81 (1H, ddd, $J_{5',5''}$=12.0 Hz, $J_{4',5'}$=2.6 Hz, $J_{5',OH}$=5.8 Hz, H-5′), 3.94, (1H, dt, $J_{4',5''}$=2.6 Hz, H-5″), 4.33 (1H, q, $J_{3',4'}$=2.6 Hz, H-4′), 4.87—4.95 (2H, m, H-2′3′), 5.08, 5.15 (2H, ABq, J=13.9 Hz, CH_2), 5.69 (1H, d, $J_{1',2'}$=2.5 Hz, H-1′), 7.23—7.35 (3H, m, aromatic), 7.45—7.55 (2H, m, aromatic), and 7.62 (1H, d, J=5.8 Hz, H-6); IR (nujol) 3400, 1700, 1675, and 1640 cm^{-1}. Found: C, 58.18; H, 5.33; N, 6.95%. Calcd for $C_{19}H_{21}N_2O_6F$: C, 58.16; H, 5.39; N, 7.14%.

3-Benzyl-5′-*O*-cinnamoyl-2′,3′-*O*-isopropylidene-5-fluorouridine (8). This was obtained by the similar procedure as described for the preparation of **5a** in 75% yield: ^{1}H NMR ($CDCl_3$) δ=1.37 (3H, s, CH_3), 1.56 (3H, s, CH_3), 4.42—4.55 (3H, m, H-4′,5′), 4.80—4.86 (1H, m, H-3′), 4.88 (1H, dd, $J_{1',2'}$=1.8 Hz, $J_{2',3'}$=6.4 Hz, H-2′), 5.05, 5.12 (2H, ABq,

J=13.7 Hz, CH_2), 5.79 (1H, d, H-1′), 6.42 (1H, d, J=15.9 Hz, PhCH=), 7.20—7.75 (10H, m, aromatic), and 7.72 (1H, d, =CHCO); IR ($CHCl_3$) 1700, 1650, 1250, 1150, and 1040 cm^{-1}. Found: C, 63.75; H, 5.06; N, 5.47%. Calcd for $C_{24}H_{27}N_2O_7F$: C, 63.52; H, 5.33; N, 5.49%.

3-Benzyl-5′-*O*-cinnamoyl-5-fluorouridine (9). This was obtained by the similar procedure as described for the preparation of **6a** in 93% yield: ^1H NMR ($CDCl_3$: CD_3OD (v/v=95/5)) δ=2.62 (2H, s, OH), 4.03—4.17 (2H, m, H-2′,3′), 4.23—4.33 (1H, m, H-4′), 4.51 (1H, dd, $J_{4',5'}$=2.4 Hz, $J_{5',5''}$=12.8 Hz, H-5′), 4.60 (1H, dd, $J_{4',5''}$=3.1 Hz, H-5″), 5.09, 5.14 (2H, ABq, J=13.7 Hz, CH_2), 5.81 (1H, brs, H-1′), 6.47 (1H, d, J=15.9 Hz, PhCH=), 7.20—7.60 (10H, m, aromatic), 7.76 (1H, d, =CHCO), and 7.93 (1H, d, J=6.1 Hz, H-6); IR ($CHCl_3$) 3600, 1720, 1650, and 1200 cm^{-1}. Found: C, 61.24; H, 4.81; N, 5.68%. Calcd for $C_{24}H_{23}N_2O_7F$: C, 61.27; H, 4.93; N, 5.95%.

The authors wish to thank the Advanced Center for Chemical Analysis, Ehime University, for elemental analyses.

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