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Synthesis of 6-Aroyluridine from Uridine *via* Regiospecific Lithiation

HIROMICHI TANAKA, HIROYUKI HAYAKAWA, and TADASHI MIYASAKA*

School of Pharmaceutical Sciences, Showa University, Hatanodai
1-5-8, Shinagawa-ku, Tokyo 142, Japan

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6-Aroyluridines, a hitherto unknown class of uridine derivatives, were synthesized from 2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine *via* regiospecific lithiation.

Keywords——uridine; 6-aroyluridine; 6-arylhydroxymethyluridine; regiospecific lithiation; oxidation; ^{1}H-NMR

In view of their various biological activities, a wide range of 5-substituted pyrimidine ribosides and deoxyribosides has been prepared. On the other hand, in spite of the antiviral activities of 6-methyluridine and 6-methylcytidine reported by Diwan and his co-workers,[1] pyrimidine nucleosides bearing a carbon functionality at C-6 have received only scant attention, probably due to the difficulty of synthesizing them. Condensation of 6-substituted pyrimidines with appropriately protected sugar derivatives has almost always resulted in the predominant formation of N^3-ribosylated products.[2-4] Such undesired reactions should be eliminated by using naturally occurring pyrimidine nucleosides as starting material.[5] Among several methods available for the transformation of uridine to 6-substituted analogs,[6-8] lithiation at C-6 offers the most direct means of general introduction of diverse carbon substituents. As described in previous reports concerning the preparation of 6-alkyluridines[9] and 5'-deoxy-6-alkyluridines,[10] both 2',3'-*O*-isopropylideneuridine (1) and 5'-deoxy-2',3'-*O*-isopropylideneuridine were metalated at C-6 of the uracil ring in a regiospecific manner by lithium diisopropylamide (LDA),[11] which is thought to function effectively by an "acid-base" mechanism.[12]

As a part of studies designed to define the scope and limitations of our earlier work, we have examined the addition reaction of a lithiated uridine derivative to aromatic aldehydes and the successive oxidation of the resulting 6-arylhydroxymethyl derivatives leading to 6-aroyluridines.

The previous investigations[9,10] suggested that 5'-*O*-protection of **1** would provide good solubility to the lithiated species, thus rendering the metalation more effective. Consequently, we decided to protect the 5'-hydroxyl group of **1** with a methoxymethyl group, which is considered to be compatible with the lithiation conditions and removable simultaneously with the isopropylidene group. Treatment of **1** with a large excess of dimethoxymethane in the presence of *p*-toluenesulfonic acid gave 2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (2) in 82.8% yield. That **2** contains an *O*-methoxymethyl group rather than an *N*-methoxymethyl group, is clear from the ^{1}H-nuclear magnetic resonance (NMR) spectrum which shows an NH resonance at δ 9.80 (disappears on addition of D_2O).

As expected, when the metalation of **2** with LDA was carried out at -78—-70°C in tetrahydrofuran, a clear solution of the dilithio derivative (3) resulted. Subsequent addition of benzaldehyde to this solution furnished the 6-phenylhydroxymethyl derivative (**4a**). The ^{1}H-NMR spectrum of the crude product showed no signal in the range of δ 6.2—9.0 attributable to the C-6 hydrogen; only the phenyl protons (δ 7.39, 5H, s) were detected. This observation indicated that the presence of the methoxymethyl substituent in **2** did not affect the regiospecificity of the lithiation. As summarized in Table I, heteroaromatic aldehydes react equally well to give the corresponding 6-arylhydroxymethyl derivatives (**4b**—**f**) in good yields.

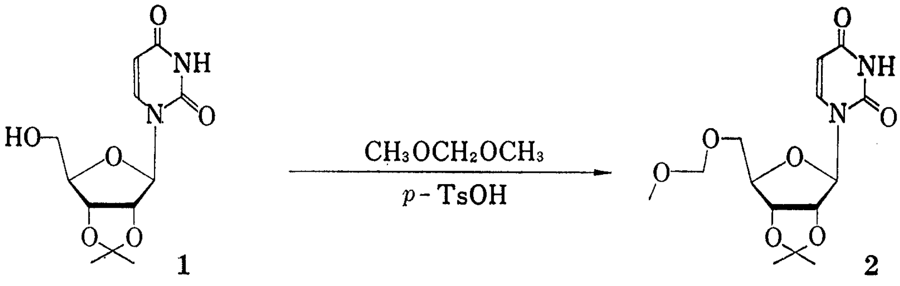


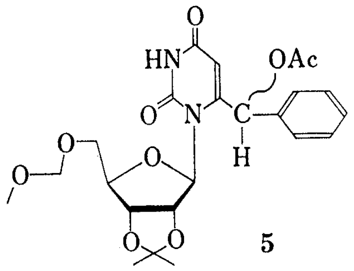
Chart 1

TABLE I. Yields (%)[a] of Compounds **4**, **6**, and **8**

	Ar	4	6	8
a	Phenyl	86.3(90.1)	85.0	83.6
b	Furan-2-yl	72.4(89.0)	65.3	96.1
c	Thiophen-2-yl	67.6(82.7)	82.0	90.5
d	Pyridin-2-yl	57.2(86.7)	83.5	81.6
e	Pyridin-3-yl	87.2(96.8)	53.7	77.1
f	Pyridin-4-yl	66.9(88.1)	70.6	67.6

a) Yields were not optimized, and those in parentheses are based on consumed **2**.

The rather complicated ^{1}H-NMR features of the 6-arylhydroxymethyl derivatives (**4**) suggested that they consist of a pair of epimers. We have examined the spectrum in some detail in the case of the phenylhydroxymethyl derivative (**4a**). Among the peaks observed, the signals due to the isopropylidene (*exo* and *endo*) and the methoxymethyl groups, each appearing as two singlets, were easily assignable from their chemical shifts; isopropylidene Me (*exo*) δ 1.23 and 1.26, isopropylidene Me (*endo*) δ 1.41 and 1.46, $CH_2OC\underline{H}_3$ δ 3.35 and 3.37, $C\underline{H}_2$-OCH_3 δ 4.65 and 4.67. However, other signals, involving H-5, H-1', H-2' and methine ($C\underline{H}OH$–Ph) resonances, were hardly resolved. This difficulty was readily circumvented by converting **4a** to the corresponding acetate (**5**), whose ^{1}H-NMR spectrum was measured.



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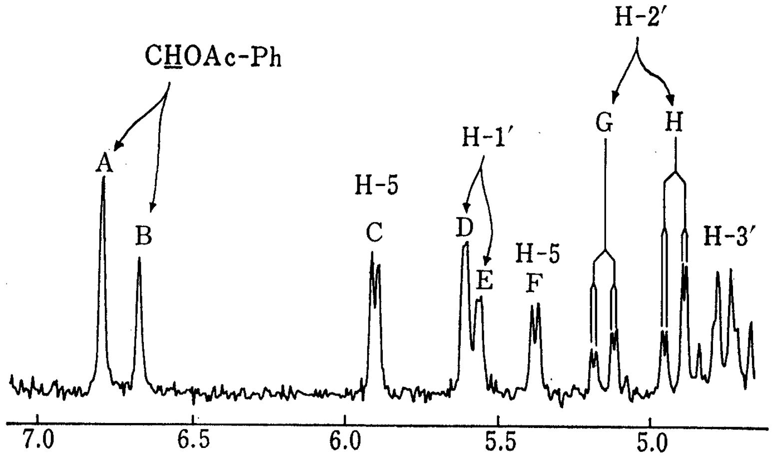


Fig. 1. ^{1}H-NMR Spectrum of **5** in the Region of δ 4.70—7.00 (100 MHz, $CDCl_3$)

Figure 1 shows an expansion of the region of δ 4.70—7.00. Two methine signals ($C\underline{H}OAc$–Ph), A and B, appear at lower field by *ca.* 1 ppm compared to that of **4a**. The remaining signals were assigned as given in Figure 1 by D_2O addition and homonuclear proton-proton decoupling experiments. The following two results were derived from the ^1H-NMR evidence; (1) the ratio of epimers is approximately 1.7: 1.0, (2) the major epimer exhibited the signals A, C, D, and H, while the minor one showed the signals marked B, E, F, and G.

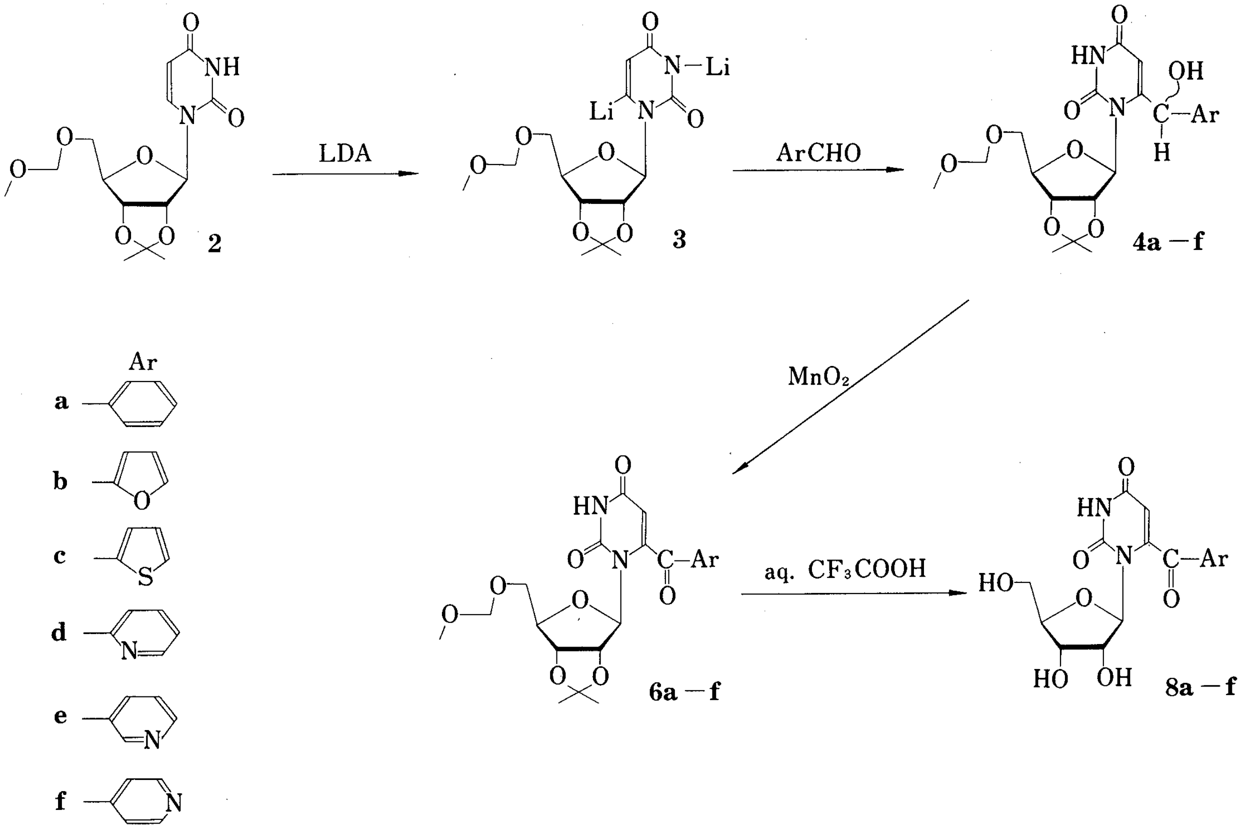
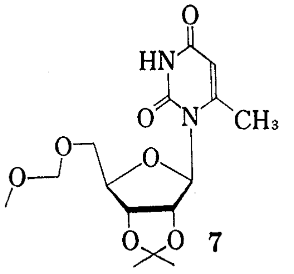


Chart 2

Oxidation of the arylhydroxymethyl group in **4** was effected by using activated manganese dioxide (MnO_2).[13] Thus, treatment of a chloroform solution of **4** with finely powdered MnO_2 at room temperature produced the protected 6-aroyluridines (**6**) in good yields as shown in Table I. Interestingly, in the ^1H-NMR spectrum of **6**, the signal for methylene protons ($C\underline{H}_2OCH_3$) appeared as an AB quartet ($J_{gem}=6.3$—6.8 Hz), which is indicative of an interaction between the methylene group and a carbonyl (C-2 or aroyl carbonyl). It is well known that 6-substituted uridines, *e.g.*, 6-methyluridine[14] and orotidine,[15] are in the *syn* conformation in solution, so it would be reasonable to suppose that compound **6** prefers the *syn* conformation thus favoring interaction between the methylene and the C-2 carbonyl. To substantiate our reasoning, 2′,3′-*O*-isopropylidene-5′-*O*-methoxymethyl-6-methyluridine (**7**) was prepared from 2′,3′-*O*-isopropylidene-6-methyluridine which, from ^1H-NMR and CD evidence,[10] is thought to exist preferentially in the *syn* form in solution. The fact that the chemical shifts of H-2′ in **6** are quite similar to that of **7** (Table II) is consistent with our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reasoning, but the methylene protons in **7** appeared as a sharp singlet at δ 4.65. Since the "*syn* range" covers somewhat more than 90°, centered about ϕ_{CN} *ca.* +150°,[16] and a through-space coupling effect[17] is observable only when an sp^2 hybridized atom (carbonyl oxygen) intervenes between remote protons ($C\underline{H}_2OCH_3$) with a specially fixed geometrical arrangement, these ^{1}H-NMR results would not be contradictory to the *syn* conformation of **6**, though the precise orientation of the base moiety in **6** around the sugar portion remains uncertain. Another ^{1}H-NMR feature of particular interest is the differences in chemical shift ($\Delta\delta$) between the methyl signals of the isopropylidene moiety. For the compounds having 6-aroyl substituents listed in Table II, $\Delta\delta$ values are relatively small compared to that of 6-unsubstituted (**2**) or 6-methyl (**7**) derivatives. Above all, the value of the 6-picolinyl derivative (**6d**), 0.11 ppm, is noteworthy, and does not meet Imbach's criterion for a β-anomer.[18,19]

TABLE II. ^{1}H-NMR Data for Protected 6-Aroyluridines in $CDCl_3$

C-6 Substituent	Chemical shifts δ				$J_{1',2'}$	Isop. Me	$\Delta\delta$
	H-5	H-1'	H-2'	H-3'			
H(**2**)	5.70	5.86	4.83∼4.68		1.5	1.59, 1.36	0.23
Benzoyl (**6a**)	5.69	5.97	5.24	4.62	2.4	1.52, 1.37	0.15
2-Furoyl (**6b**)	5.89	5.95	5.22	4.67	2.4	1.53, 1.36	0.17
2-Thenoyl (**6c**)	5.89	5.96	5.22	4.64	2.4	1.55, 1.36	0.19
Picolinyl (**6d**)	5.72	5.61	5.18	4.66	2.0	1.42, 1.31	0.11
Nicotinyl (**6e**)	5.69	5.98	5.21	4.61	2.9	1.54, 1.37	0.17
Isonicotinyl (**6f**)	5.68	5.98	5.19	4.59	2.4	1.54, 1.37	0.17
CH_3 (**7**)	5.57	5.72	5.22	4.88	1.0	1.56, 1.35	0.21

Finally, as we intended, concurrent deprotection of the isopropylidene and methoxymethyl groups in **6** was successfully accomplished. Treatment of **6** with 50% aqueous trifluoroacetic acid at room temperature gave the free 6-aroyluridines (**8a**—**f**) in good to excellent yields. Partial ^{1}H-NMR data of **8** are listed in Table III, together with those of uridine and 6-methyluridine.

TABLE III. ^{1}H-NMR Data for 6-Aroyluridines in D_2O

C-6 Substituent	Chemical Shifts δ				$J_{1',2'}$
	H-5	H-1'	H-2'	H-3'	
H	5.88	5.90	4.32	4.21	4.4
Benzoyl (**8a**)	5.90	5.58	4.63	4.04	4.4
2-Furoyl (**8b**)	6.10	5.64	4.65	4.08	3.9
2-Thenoyl (**8c**)	6.08	5.61	4.67	4.11	3.9
Picolinyl (**8d**)	5.94	5.60	4.58	3.98	3.9
Nicotinyl (**8e**)	5.96	5.70	4.62	4.02	3.9
Isonicotinyl (**8f**)	5.95	5.72	4.60	3.99	3.9
CH_3	5.75	5.65	4.81	4.37	3.4

We believe that reaction of lithiated 2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine with electrophiles provides a general, regiospecific, and simple route from uridine to various 6-substituted uridines as illustrated herein by synthesizing 6-arylhydroxymethyl and 6-aroyluridines. Further extension of this method is presently under investigation.

Experimental

Melting points were determined with Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured with an appropriate internal standard of tetramethylsilane (TMS) or sodium-

2,2-dimethyl-2-silapentane 5-sulfonate (DSS), with a JEOL JNM-FX 100 NMR spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. UV and IR spectra were recorded on Hitachi 340 and JASCO A-102 spectrophotometers, respectively. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was purchased from E. Merck and was titrated before use according to the published procedure.[20] Column chromatography was carried out on Merck Silica Gel 60.

2′,3′-*O*-Isopropylidene-5′-*O*-methoxymethyluridine (2)——Anhydrous *p*-toluenesulfonic acid (2 g) was added to a suspension of finely powdered **1** (11.5 g) in dry dimethoxymethane (160 ml) and the mixture, protected from moisture by a positive pressure of dry nitrogen, was stirred at room temperature until dissolution was complete. The reaction mixture was poured into 28% aqueous NH_3 (200 ml) and was evaporated to dryness. The whole residue was chromatographed on a silica gel (150 g) column with 1% EtOH in $CHCl_3$ as an eluent to give 11.0 g (82.8%) of **2** as a foam. High resolution MS *m/z*: 328.1248 (M^+) Calcd for $C_{14}H_{20}N_2O_7$ 328.1268. UV $\lambda_{\max}^{\text{methanol}}$ nm: 259, $\lambda_{\min}^{\text{methanol}}$ nm: 228. NMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.59 (3H, s, isop.Me), 3.37 (3H, s, $CH_2OC\underline{H}_3$), 3.36—3.88 (2H, m, CH_2-5′), 4.20—4.48 (1H, m, H-4′), 4.66 (2H, s, $C\underline{H}_2OCH_3$), 4.68—4.83 (2H, m, H-2′ and H-3′), 5.70 (1H, dd, H-5), 5.86 (1H, d, J=1.5 Hz, H-1′), 7.49 (1H, d, J=8.3 Hz, H-6), 8.07 (1H, br, NH).

General Procedures for the Reaction of 3 with Aromatic Aldehydes——LDA in THF was placed in a three-necked flask fitted with a nitrogen inlet adapter, thermometer, and serum stopper. To this, a solution of **2** in THF was added, under positive pressure of dry nitrogen, at a rate such that the temperature did not exceed −70°C. After the mixture had been stirred for 1 h, the freshly distilled aromatic aldehyde was added neat, dropwise, while maintaining the temperature below −70°C. After an appropriate reaction period, the reaction mixture was quenched with acetic acid and was allowed to warm to room temperature. The whole was evaporated to dryness and the residue was chromatographed on a silica gel column. This afforded **4** as a syrupy epimeric mixture.

2′,3′-*O*-Isopropylidene-5′-*O*-methoxymethyl-6-phenylhydroxymethyluridine (4a)——The following amounts of reagents and 725 mg (2.21 mmol) of **2** in THF (11 ml) were employed: 5.53 mmol of LDA in THF (10 ml), 0.45 ml (4.42 mmol) of benzaldehyde. The reaction was continued for 2 h. This afforded 829 mg (86.3%) of **4a** and 30 mg of **2** after column chromatography (2—3% EtOH in $CHCl_3$). MS *m/z*: 434 (M^+), 419 (M−15), 218 (B+1). UV $\lambda_{\max}^{\text{methanol}}$ nm: 259, $\lambda_{\min}^{\text{methanol}}$ nm: 233. NMR ($CDCl_3$) δ for the major epimer: 1.23 (3H, s, isop.Me), 1.41 (3H, s, isop.Me), 3.37 (3H, s, $CH_2OC\underline{H}_3$), 4.68 (2H, s, $C\underline{H}_2OCH_3$).

Acetylation of **4a** (318 mg, 0.73 mmol) in pyridine (5 ml) with acetic anhydride (0.2 ml) gave the acetate **5** (340 mg, 97.5%) as a foam. High resolution MS *m/z*: 476.1784 (M^+) Calcd for $C_{23}H_{28}N_2O_9$: 476.1792. NMR ($CDCl_3$) δ for the major epimer: 1.20 (3H, s, isop.Me), 1.40 (3H, s, isop.Me), 2.17 (3H, s, CH_3CO), 4.77 (1H, t, H-3′), 4.95 (1H, dd, H-2′), 5.64 (1H, d, J=1.5 Hz, H-1′), 5.93 (1H, d, H-5), 6.83 (1H, s, $C\underline{H}OAc$-Ph). NMR ($CDCl_3$) δ for the minor epimer: 1.33 (3H, s, isop.Me), 1.50 (3H, s, isop.Me), 2.19 (3H, s, CH_3CO), 4.81 (1H, t, H-3′), 5.18 (1H, dd, H-2′), 5.41 (1H, d, H-5), 5.59 (1H, d, J=1.5 Hz, H-1′), 6.71 (1H, s, $C\underline{H}OAc$-Ph). The following signals are indistinguishable for both epimers: 3.35 (3H, s, CH_2OCH_3), 3.66—3.78 (2H, m, CH_2-5′), 4.08—4.26 (1H, m, H-4′), 4.63 (2H, s, $C\underline{H}_2OCH_3$), 7.40 (5H, s, phenyl), 9.10 (1H, br, NH).

6-Benzoyl-2′,3′-*O*-isopropylidene-5′-*O*-methoxymethyluridine (6a)——Finely powdered activated MnO_2 (2 g) was added to a solution of **4a** (104 mg) in $CHCl_3$ (50 ml). The whole was stirred for 21 h at room temperature, then MnO_2 was removed by filtration and the resulting filtrate was purified by passage through a short column of silica gel (5% EtOH in $CHCl_3$). Compound **6a** (88 mg, 85%) was obtained as a foam. MS *m/z*: 432 (M^+), 417 (M−15), 216 (B+1), 105 ($PhC\equiv O^+$). NMR ($CDCl_3$) δ: 1.37 (3H, s, isop.Me), 1.52 (3H, s, isop.Me), 3.20 (3H, s, $CH_2OC\underline{H}_3$), 3.36—3.59 (2H, m, CH_2-5′), 3.90—4.12 (1H, m, H-4′), 4.07 and 4.33 (2H, each as d, J_{gem}=6.8 Hz, $C\underline{H}_2OCH_3$), 4.62 (1H, t, H-3′), 5.24 (1H, dd, H-2′), 5.69 (1H, d, H-5), 5.97 (1H, d, J=2.4 Hz, H-1′), 7.46—7.72 (3H, m, phenyl), 7.90—7.99 (2H, m, phenyl), 9.36 (1H, br, NH).

6-(2-Furoyl)-2′,3′-*O*-isopropylidene-5′-*O*-methoxymethyluridine (6b)——The following amounts of reagents and 969 mg (2.95 mmol) of **2** in THF (15 ml) were employed for the preparation of **4b**: 7.38 mmol of LDA in THF (10 ml), 0.49 ml (5.90 mmol) of furfural. The procedure was identical with that used for the preparation of **4a** and the reaction was continued for 3 h. Silica gel column chromatography (2% EtOH in $CHCl_3$) gave **4b** (907 mg, 72.4%) and 181 mg of **2**. MS *m/z*: 424 (M^+), 409 (M−15), 208 (B+1). The ^1H-NMR spectrum showed that **4b** was an equimolar mixture of two epimers. NMR ($CDCl_3$) δ: 1.26 and 1.31 (3H, each as s, isop.Me), 1.46 and 1.50 (3H, each as s, isop.Me), 3.34 and 3.36 (3H, each as s, $CH_2OC\underline{H}_3$), 3.69—3.86 (2H, m, CH_2-5′), 4.12—4.41 (1H, m, H-4′), 4.64 and 4.65 (2H, each as s, $C\underline{H}_2OCH_3$), 4.68—4.87 (1H, m, H-3′), 4.99—5.17 (1H, m, H-2′), 5.61 and 6.01 (1H, each as s, H-5), 5.72 and 6.18 (1H, each as s, H-1′), 5.75 and 5.79 (1H, each as s, $C\underline{H}OH$-Ar), 6.29—6.50 (2H, m, furan H-3 and H-4), 7.36—7.44 (1H, m, furan H-5), 9.60 (1H, br, NH).

Treatment of **4b** (180 mg) in $CHCl_3$ (30 ml) with MnO_2 (369 mg) for 24 h gave the furoyl derivative **6b** (117 mg, 65.3%). Crystallization from methanol–ether afforded an analytical sample: mp 183—185°C. *Anal.* Calcd for $C_{19}H_{22}N_2O_9$: C, 54.02; H, 5.25; N, 6.63. Found: C, 54.32; H, 5.27; N, 6.55. MS *m/z*: 422 (M^+), 407 (M−15), 207 (B+2), 206 (B+1). UV $\lambda_{\max}^{\text{methanol}}$ nm (ε): 289 (18300), $\lambda_{\min}^{\text{methanol}}$ nm (ε): 252 (6600). NMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.53 (3H, s, isop.Me), 3.28 (3H, s, $CH_2OC\underline{H}_3$), 3.20—3.70

(2H, m, CH_2-5′), 3.80—4.10 (1H, m, H-4′), 4.40 and 4.50 (2H, each as d, $J_{gem}=6.4$ Hz, $C\underline{H}_2OCH_3$), 4.67 (1H, dd, H-3′), 5.22 (1H, dd, H-2′), 5.89 (1H, d, H-5), 5.95 (1H, d, $J=2.4$ Hz, H-1′), 6.67 (1H, dd, furan H-4), 7.38 (1H, dd, furan H-5), 7.80 (1H, m, furan H-3), 8.23 (1H, br, NH).

2′,3′-*O*-Isopropylidene-5′-*O*-methoxymethyl-6-(2-thenoyl)uridine (**6c**)——The following amounts of reagents and 416 mg (1.27 mmol) of **2** in THF (15 ml) were employed for the preparation of **4c**: of 3.80 mmol ofLDA in THF (10 ml) and 0.58 ml (6.34 mmol) of 2-thiophenecarbaldehyde. The procedure was identical with that used for the preparation of **4a**, and the reaction was continued for 16.5 h. Silica gel column chromatography (2% EtOH in $CHCl_3$) gave **4c** (377 mg, 67.6%) and 76 mg of **2**. The ^{1}H-NMR spectrum showed that **4c** was a mixture of two epimers (approximately 3: 2). NMR ($CDCl_3$) δ: 1.25 (3H, s, isop.Me), 1.43 (3H, s, isop.Me), 3.34 and 3.37 (3H, each as s, $CH_2OC\underline{H}_3$), 3.76—3.83 (2H, m, CH_2-5′), 4.20—4.37 (1H, m, H-4′), 4.64 and 4.67 (2H, each as s, $C\underline{H}_2OCH_3$), 4.69—4.81 (1H, m, H-3′), 4.99—5.11 (1H, m, H-2′), 5.66 and 6.09 (1H, s, H-5), 5.81 and 6.20 (1H, s, H-1′), 5.92 and 5.96 (1H, s, C$\underline{H}$OH–Ar), 6.94—7.07 (2H, m, thiophene H-3 and H-4), 7.28—7.39 (1H, m, thiophene H-5), 9.60 and 9.64 (1H, each br, NH).

Treatment of **4c** (169 mg) in $CHCl_3$ (30 ml) with MnO_2 (334 mg) for 23.5 h gave the thenoyl derivative **6c** (138 mg, 82.0%) as a foam after chromatography on a short column of silica gel (10% EtOH in $CHCl_3$). NMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 3.25 (3H, s, $CH_2OC\underline{H}_3$), 3.29—3.72 (2H, m, CH_2-5′), 3.90—4.12 (1H, m, H-4′), 4.29 and 4.45 (2H, each as d, $J_{gem}=6.4$ Hz, $C\underline{H}_2OCH_3$), 4.64 (1H, t, H-3′), 5.22 (1H, dd, H-2′), 5.89 (1H, d, H-5), 5.96 (1H, d, $J=2.4$ Hz, H-1′), 7.18—7.23 (1H, m, thiophene H-4), 7.79 (1H, dd, thiophene H-5), 7.90 (1H, dd, thiophene H-3), 8.25 (1H, br, NH).

2′,3′-*O*-Isopropylidene-5′-*O*-methoxymethyl-6-picolinyluridine (**6d**)——The following amounts of reagents and 1.07 g (3.26 mmol) of **2** in THF (20 ml) were employed for the preparation of **4d**: 8.20 mmol of LDA in THF (10 ml) and 0.62 ml (6.56 mmol) of 2-pyridinecarbaldehyde. The procedure was identical with that used for the preparation of **4a**, and the reaction was continued for 15 h. Silica gel column chromatography (3% EtOH in $CHCl_3$) gave **4d** (812 mg, 57.2%) and 364 mg of **2**. The ^{1}H-NMR spectrum indicated that **4d** was a mixture of two epimers. Partial ^{1}H-NMR data are shown below. NMR ($CDCl_3$) δ: 1.31 (3H, s, isop.Me), 1.50 (3H, s, isop.Me), 3.33 and 3.37 (3H, each as s, $CH_2OC\underline{H}_3$), 3.68—3.83 (2H, m, CH_2-5′), 4.12—4.40 (1H, m, H-4′), 4.61 and 4.67 (2H, each as s, $C\underline{H}_2OCH_3$), 4.70—4.89 (1H, m, H-3′), 7.32—7.43 (2H, m, pyridine H-3 and H-5), 7.71—7.86 (1H, m, pyridine H-4), 8.60—8.65 (1H, m, pyridine H-6), 9.25 (1H, br, NH).

Treatment of **4d** (752 mg) in $CHCl_3$ (70 ml) with MnO_2 (1.50 g) for 48 h gave the picolinyl derivative **6d** (625 mg, 83.5%) as a foam after column chromatography on silica gel (2% EtOH in $CHCl_3$). NMR ($CDCl_3$) δ: 1.31 (3H, s, isop.Me), 1.42 (3H, s, isop.Me), 3.28 (3H, s, $CH_2OC\underline{H}_3$), 3.33—3.68 (2H, m, CH_2-5′), 3.96—4.18 (1H, m, H-4′), 4.39 and 4.51 (2H, each as d, $J_{gem}=6.8$ Hz, $C\underline{H}_2OCH_3$), 4.66 (1H, dd, H-3′), 5.18 (1H, dd, H-2′), 5.61 (1H, d, $J=2.0$ Hz, H-1′), 5.72 (1H, d, H-5), 7.40—7.58 (1H, m, pyridine H-5), 7.78—7.96 (1H, m, pyridine H-4), 8.00—8.16 (1H, m, pyridine H-3), 8.55 (1H, br, NH), 8.60—8.74 (1H, m, pyridine H-6).

2′,3′-*O*-Isopropylidene-5′-*O*-methoxymethyl-6-nicotinyluridine (**6e**)——The following amounts of reagents and 996 mg (3.03 mmol) of **2** in THF (20 ml) were employed for the preparation of **4e**: 7.58 mmol of LDA in THF (10 ml) and 0.57 ml of 3-pyridinecarbaldehyde. The procedure was identical with that used for the preparation of **4a**, and the reaction was continued for 4 h. Silica gel column chromatography (3—5% EtOH in $CHCl_3$) gave **4e** (1.15 g, 87.2%) and 100 mg of **2**. Without identification, the whole of **4e** was oxidized in $CHCl_3$ (80 ml) with MnO_2 (3.42 g) at room temperature for 62 h. The nicotinyl derivative **6e** (615 mg, 53.7%) was obtained after column chromatography on silica gel (1% EtOH in $CHCl_3$). NMR ($CDCl_3$) δ: 1.37 (3H, s, isop.Me), 1.54 (3H, s, isop.Me), 3.20 (3H, s, $CH_2OC\underline{H}_3$), 3.08—3.70 (2H, m, CH_2-5′), 3.90—4.12 (1H, m, H-4′), 4.13 and 4.31 (2H, each as d, $J_{gem}=6.4$ Hz, $C\underline{H}_2OCH_3$), 4.61 (1H, t, H-3′), 5.21 (1H, dd, H-2′), 5.69 (1H, d, H-5), 5.98 (1H, d, $J=2.9$ Hz, H-1′), 7.40—7.58 (1H, m, pyridine H-5), 8.12—8.26 (1H, m, pyridine H-4), 8.81 (1H, br, NH), 8.90 (1H, dd, pyridine H-6), 9.14 (1H, d, pyridine H-2).

6-Isonicotinyl-2′,3′-*O*-isopropylidene-5′-*O*-methoxymethyluridine (**6f**)——The following amounts of reagents and 987 mg (3.01 mmol) of **2** in THF (20 ml) were employed for the preparation of **4f**: 7.50 mmol of LDA in THF (10 ml) and 0.56 ml (6.0 mmol) of 4-pyridinecarbaldehyde. The procedure was identical with that used for the preparation of **4a**, and the reaction was continued for 17 h. Silica gel column chromatography (3—5% EtOH in $CHCl_3$) gave **4f** (876 mg, 66.9%) and 238 mg of **2**. Without identification, the whole of **4f** was treated with MnO_2 (2.22 g) in $CHCl_3$ (80 ml) for 63 h. Purification through column chromatography on silica gel (2% EtOH in $CHCl_3$) gave the isonicotinyl derivative **6f** (616 mg, 70.6%) as a foam. NMR ($CDCl_3$) δ: 1.37 (3H, s, isop.Me), 1.54 (3H, s, isop.Me), 3.18 (3H, s, $CH_2OC\underline{H}_3$), 3.02—3.70 (2H, m, CH_2-5′), 3.90—4.16 (1H, m, H-4′), 4.09 and 4.30 (2H, each as d, $J_{gem}=6.8$ Hz, $C\underline{H}_2OCH_3$), 4.59 (1H, t, H-3′), 5.19 (1H, dd, H-2′), 5.68 (1H, s, H-5), 5.98 (1H, d, $J=2.4$ Hz, H-1′), 7.65—7.77 (2H, m, pyridine H-3 and H-5), 8.81—8.93 (2H, m, pyridine H-2 and H-6).

2′,3′-*O*-Isopropylidene-5′-*O*-methoxymethyl-6-methyluridine (**7**)——In a manner similar to that described for **2**, 2′,3′-*O*-isopropylidene-6-methyluridine (50 mg) was transformed to its 5′-*O*-methoxymethyl derivative **7** (38 mg, 66.2%), which crystallized from methanol–hexane: mp 156—158°C. *Anal.* Calcd for $C_{15}H_{22}N_2O_7$: C, 52.62; H, 6.48; N, 8.18. Found: C, 52.66; H, 6.71; N, 8.20. MS *m/z*: 342 (M^+), 327 (M−15), 126 (B+1). UV $\lambda_{max}^{methanol}$ nm (ε): 258 (11100), $\lambda_{min}^{methanol}$ nm (ε): 228 (2700). NMR ($CDCl_3$) δ: 1.35 (3H, s, isop.Me), 1.56 (3H, s, isop.Me), 2.34 (3H, s, CH_3), 3.35 (3H, s, $CH_2OC\underline{H}_3$), 3.70—3.79 (2H, m, CH_2-5′), 4.17—4.30 (1H, m, H-4′), 4.65 (2H, s, $C\underline{H}_2OCH_3$), 4.88 (1H, dd, H-3′), 5.22 (1H, dd, H-2′), 5.57 (1H, d, H-5), 5.72 (1H, d,

$J=1.0$ Hz, H-1′), 10.24 (1H, br, NH).

6-Benzoyluridine (8a)——A solution of **6a** (236 mg) in 50% aqueous CF_3COOH (10 ml) was stirred overnight at room temperature. Evaporation followed by column chromatography (7% EtOH in $CHCl_3$) afforded 159 mg (83.6%) of **8a**, which crystallized from water: mp 193—195°C. *Anal.* Calcd for $C_{16}H_{16}N_2O_7$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.16; H, 4.52; N, 8.03. Field desorption MS *m/z*: 348 (M^+), 330 ($M-H_2O$), 216 (B+1), 105 ($PhC\equiv O^+$). UV λ_{max}^{water} nm (ε): 264 (16600), λ_{min}^{water} nm (ε): 230 (6400). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O), 1680 (CONH). NMR (D_2O) δ: 3.19—3.85 (3H, m, CH_2-5′ and H-4′), 4.04 (1H, t, H-3′), 4.63 (1H, dd, H-2′), 5.58 (1H, d, $J=4.4$ Hz, H-1′), 5.90 (1H, s, H-5), 7.53—7.90 (3H, m, phenyl), 7.96—8.06 (2H, m, phenyl).

6-(2-Furoyl)uridine (8b)——A solution of **6b** (226 mg) in 50% aqueous CF_3COOH (5 ml) was stirred for 18 h at room temperature. Chromatographic purification (5—10% EtOH in $CHCl_3$) afforded 174 mg (96.1%) of **8b**, which crystallized from EtOH: mp 177—179°C. *Anal.* Calcd for $C_{14}H_{14}N_2O_8$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.54; H, 4.09; N, 8.34. Field desorption MS *m/z*: 339 (M+1), 338 (M^+), 320 ($M-H_2O$), 206 (B+1). UV λ_{max}^{water} nm (ε): 294 (18400), λ_{min}^{water} nm (ε): 256 (6800). IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O), 1680 (CONH). NMR (D_2O) δ: 3.28—3.94 (3H, m, CH_2-5′ and H-4′), 4.08 (1H, t, H-3′), 4.65 (1H, dd, H-2′), 5.64 (1H, d, $J=3.9$ Hz, H-1′), 6.10 (1H, s, H-5), 6.79 (1H, dd, furan H-4), 7.60 (1H, d, furan H-5), 8.03 (1H, d, furan H-3).

6-(2-Thenoyl)uridine (8c)——Treatment of **6c** (134 mg) with 50% aqueous CF_3COOH for 40 h followed by chromatographic purification (10% EtOH in $CHCl_3$) gave **8c** (98 mg, 90.5%) as a foam. UV λ_{max}^{water} nm: 274, λ_{min}^{water} nm: 228. NMR (D_2O) δ: 3.33—3.86 (3H, m, CH_2-5′ and H-4′), 4.11 (1H, t, H-3′), 4.67 (1H, dd, H-2′), 5.61 (1H, d, $J=3.9$ Hz, H-1′), 6.08 (1H, s, H-5), 7.32 (1H, t, thiophene H-4), 7.96 (1H, d, thiophene H-5), 8.18 (1H, d, thiophene H-3).

Compound **8c** was converted to its triacetate, whose high resolution MS was measured. High resolution MS *m/z*: 480.0801 (M^+) Calcd for $C_{20}H_{20}N_2O_{10}S$: 480.0836. NMR ($CDCl_3$) δ: 2.00 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 3.96—4.34 (3H, m, CH_2-5′ and H-4′), 5.34 (1H, t, H-3′), 5.70 (1H, d, $J=3.9$ Hz, H-1′), 5.83—5.95 (2H, m, H-2′ and H-5), 7.18—7.28 (1H, m, thiophene H-4), 7.81 (1H, dd, thiophene H-5), 7.91 (1H, dd, thiophene H-3), 9.00 (1H, br, NH).

6-Picolinyluridine (8d)——Treatment of **6d** (602 mg) with 50% aqueous CF_3COOH (15 ml) for 69 h followed by chromatographic purification (12% EtOH in $CHCl_3$) gave **8d** (396 mg, 81.6%), which crystallized from EtOH: mp 177—179°C. *Anal.* Calcd for $C_{15}H_{15}N_3O_7$: C, 51.58; H, 4.33; N, 12.03. Found: C, 51.94; H, 4.36; N, 11.91. UV λ_{max}^{water} nm (ε): 246 (12000), 274 (10600), λ_{min}^{water} nm (ε): 227 (8100), 264 (10500). NMR (D_2O) δ: 3.19—3.89 (3H, m, CH_2-5′ and H-4′), 3.98 (1H, t, H-3′), 4.58 (1H, dd, H-2′), 5.60 (1H, d, $J=3.9$ Hz, H-1′), 5.94 (1H, s, H-5), 7.65—7.87 (1H, m, pyridine H-5), 7.98—8.31 (2H, m, pyridine H-3 and H-4), 8.61—8.75 (1H, m, pyridine H-6).

6-Nicotinyluridine (8e)——Treatment of **6e** (610 mg) with 50% aqueous CF_3COOH (16 ml) for 73 h followed by chromatographic purification (12% EtOH in $CHCl_3$) gave **8e** (379 mg, 77.1%) as a foam. UV λ_{max}^{water} nm: 242, $\lambda_{shoulder}^{water}$ nm: 274, λ_{min}^{water} nm: 225. NMR (D_2O) δ: 3.12—3.87 (3H, m, CH_2-5′ and H-4′), 4.02 (1H, t, H-3′), 4.62 (1H, dd, H-2′), 5.70 (1H, d, $J=3.9$ Hz, H-1′), 5.96 (1H, s, H-5), 7.61—7.74 (1H, m, pyridine H-5), 8.35—8.48 (1H, m, pyridine H-4), 8.66—8.90 (1H, br, pyridine H-6), 8.90—9.16 (1H, br, pyridine H-2).

Compound **8e** was converted to its triacetate, whose high resolution MS was measured. High resolution MS *m/z*: 475.1222 (M^+) Calcd for $C_{21}H_{21}N_3O_{10}$: 475.1225. NMR (D_2O) δ: 1.94 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.08 (3H, s, CH_3CO), 3.69—4.23 (3H, m, CH_2-5′ and H-4′), 5.21—5.37 (1H, m, H-3′), 5.77—5.89 (2H, m, H-1′ and H-2′), 5.72 (1H, d, H-5), 7.53 (1H, m, pyridine H-5), 8.26 (1H, d, pyridine H-4), 8.92 (1H, br, pyridine H-6), 9.14 (1H, br, pyridine H-2), 9.76 (1H, br, NH).

6-Isonicotinyluridine (8f)——Treatment of **6f** (600 mg) with 50% aqueous CF_3COOH (16 ml) for 73 h followed by chromatographic purification (12% EtOH in $CHCl_3$) gave **8f** (327 mg, 67.6%), which crystallized from EtOH: mp 162—165°C (dec.). *Anal.* Calcd for $C_{15}H_{15}N_3O_7$: C, 51.58; H, 4.33; N, 12.03. Found: C, 51.58; H, 4.15; N, 11.96. UV $\lambda_{shoulder}^{water}$ nm (ε): 231 (15100), 257 (9300), 300 (5200). NMR (D_2O) δ: 3.07—3.90 (3H, m, CH_2-5′ and H-4′), 3.99 (1H, t, H-3′), 4.60 (1H, dd, H-2′), 5.72 (1H, d, $J=3.9$ Hz, H-1′), 5.95 (1H, s, H-5), 7.88—7.95 (2H, m, pyridine H-3 and H-5), 8.78—8.85 (2H, m, pyridine H-2 and H-6).

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