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"UMPOLUNG" OF REACTIVITY AT THE C-6 POSITION OF URIDINE: A SIMPLE AND GENERAL METHOD FOR 6-SUBSTITUTED URIDINES

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Abstract—— Lithiated 2',3'-O-isopropylidene-5'-O-methoxymethyl-uridine was found to react with a variety of electrophilic reagents regiospecifically at the C-6 position. The protecting groups of the ribose moiety in the 6-functionalized products were concurrently removed under mild conditions with aqueous trifluoroacetic acid. Consequently, the present method permits simple and general syntheses of 6-substituted uridines.

Introduction of a carbon functionality to the C-6 position of uridine has been known to be of limited success. To date, several attempts[1-5] to effect this transformation have been reported, but a general method is still lacking.

The C-6 position of uridine could be regarded as the beta position in the enone system, and as such most of the earlier syntheses are based on the susceptibility to nucleophilic reactions at this position. However, if "Umpolung" of reactivity[5] at the C-6 position were possible, a new strategy would be available, which could permit a general introduction of diverse substituents upon subjecting electrophiles to the C-6 anionic species.

In the course of our studies on the lithiation of uridine derivatives,[6,7,8] we found that the metalation of 2',3'-O-isopropylidene-5'-O-methoxymethyl-uridine (1)[7,8] with lithium diisopropylamide (LDA) takes place at the C-6 position in an essentially regiospecific manner[8] and that the resulting dilithio derivative (2) is quite soluble in THF. Thus, this methodology (Chart 1) becomes relevant to the conversion of uridine to 6-substituted analogs. In this paper, we describe the synthesis of various types of 6-substituted uridines, proving the usefulness of the above methodology.

Disulfides are used as a label for estimating the extent of metalation, especially in the case of lithiation with

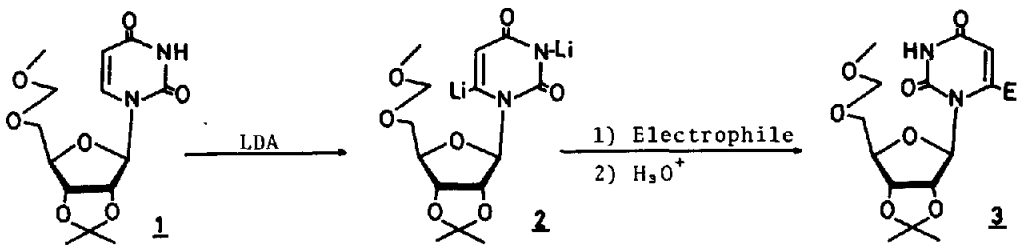
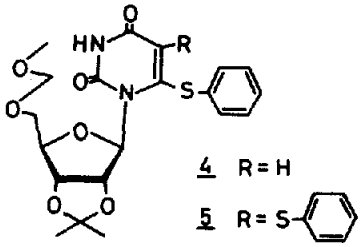


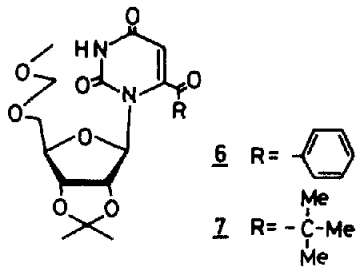
Chart 1

lithium dialkylamides, where substitution by deuterium may be low.[10] We examined first the reaction of 2, prepared from 1 with 2.5 eq. of LDA in THF, with diphenyl disulfide in order to evaluate the extent of lithiation. Treatment of 2 with 2.0 eq. of diphenyl disulfide (below -70° for 2 h) furnished 2',3'-O-isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (4) in 82.7% yield along with a 5.3% yield of 5,6-disubstituted derivative (5). Compound 4 was readily crystallized from MeOH-ether (mp 157~158°). Thus, the extent of lithiation was estimated at 88.0%.



We then investigated the reaction of 2 with various types of carbon electrophiles.

Of the electrophiles for the reaction of 2, we have already reported the effectiveness of aromatic aldehydes in yielding 6-arylhydroxymethyl derivatives, which are readily oxidized with activated manganese dioxide (MnO_2) to give 6-aroyluridines.[7] We were next interested to see whether 2 could be directly aroylated with an ester or acid halide. The reaction of 2 with ethyl benzoate resulted in complete recovery of 1 after quenching with acetic acid, while benzoyl chloride gave 6-benzoyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (6)[7] in 80.0% yield. Thus, this appears to be an alternative and even more direct route to 6-aroyluridines. Treatment of 2 with pivaloyl chloride was also fruitful in affording the corresponding 6-pivaloyl derivative (7) in 71.5% yield. However, only the starting material (1) was recovered when acetyl chloride was employed as the acid halide. On the other hand, in the case of propionyl and isobutyryl chlorides, PMR and high resolution mass spectra of the corresponding products, obtained in 6.9 and 45.1% yields respectively, showed that further acylation occurred on the introduced C-6 acyl groups. These results indicated that the direct introduction of acyl groups was unsuccessful when the acyl halide used had an alpha hydrogen.



As a general route to 6-acyluridines, we tried the addition reaction of 2 to aliphatic aldehydes, with subsequent oxidation of the resulting carbinols. When 2 in THF was treated with acetaldehyde or propionaldehyde below -70° for 3 h, the carbinol 8 (76.8%) or 9 (75.7%) was isolated after chromatography on silica gel. Langley reported a high-yield conversion of 2,4-diethoxy-6-α-hydroxyethylpyrimidine to 6-acetyl-2,4-diethoxypyrimidine by MnO_2 oxidation,[11] but our attempts to oxidize the carbinols (8 and 9) with MnO_2 failed. Therefore, we examined Sarett oxidation.[12] A mixture of the carbinol (8 or 9) and chromium trioxide in pyridine was

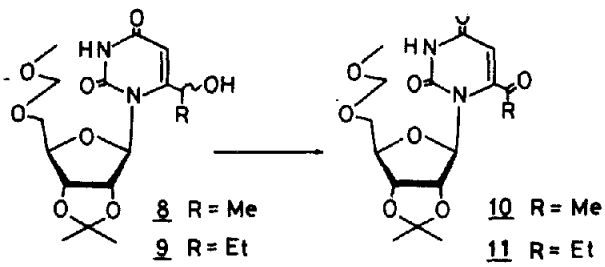
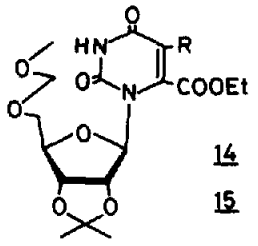


Chart 2

stirred overnight at room temperature, followed by the usual work up, and chromatography afforded the C-6 acyl derivative (10: 85.4%, 11: 63.5%). The isopropylidene and methoxymethyl protecting groups are compatible under these oxidation conditions. That the PMR spectra of the 6-acyl derivatives (7, 10, and 11) revealed a sharp singlet around δ 4.6 assignable to the methylene protons of the methoxymethyl group is a striking difference from those of the 6-aroyl derivatives, which exhibited an AB quartet.[7]

Among the 6-acyluridines, the synthesis of the 6-formyl derivative has already been accomplished by selenium dioxide oxidation of 6-methyluridine[13] and by alkylative hydrolysis of 5,6-dihydro-6-(1,3-dithian-2-yl)uridine derivatives.[8] A more straightforward way to 6-formyluridine can be easily anticipated: the formylation of 2 with ethyl formate as an electrophile. The reaction of 2 with ethyl formate was conducted below -70° for 1 h, after which TLC analysis ($CHCl_3$:EtOH= 15:1) of the reaction mixture indicated the presence of a product with a low R_f value (0.36, R_f value of 1: 0.50), expected to be 12. Because of the reported instability of 6-formyl derivatives, we did not try to isolate 12, but instead attempted to convert it to 13 in a one-pot manner. The reaction mixture containing 12 was quenched with acetic acid, followed by dilution with ethanol. Treatment of the above mixture with sodium borohydride at room temperature for 10 min revealed that the initial product was completely converted to a new product having an R_f value of 0.28. On the basis of data from the PMR (doublet at δ 4.33: CH_2OH, triplet at δ 5.84: CH_2OH) and mass spectra (M^+: m/z 358) of this material, the structure was assigned as 6-hydroxymethyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (13). The yield of 13 from 1 was 65.7%. Because the published methods for the preparation of 6-formyl[8,13] and 6-hydroxymethyluridines[2,4] suffer from the disadvantage of requiring several steps, this method using ethyl formate might be the most convenient one currently available.

So far, only one report[2] has been published concerning the conversion of uridine to orotidine, the sole naturally occurring 6-substituted pyrimidine nucleoside. This fact prompted an examination of the reaction of 2 with ethyl chloroformate. Compound 1 was metalated with 2.5 eq. of LDA and the resulting metalated species was treated with 2.0 eq. of ethyl chloroformate below -70° for 5 h. Interestingly, the PMR spectrum of the crude product indicated that it was a mixture of the 5,6-bis-ethoxycarbonyl (14) and 6-ethoxycarbonyl (15) derivatives, with a preponderance of the former (ca. 3:1). Compound 14 was isolated from the mixture by crystallization (ether-hexane: mp 101~103°). Since under similar con-



14 R = COOEt

15 R = H

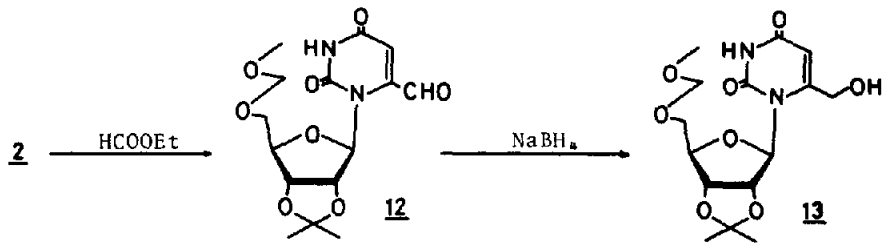


Chart 3

ditions above, such a 5,6-disubstituted product was not obtained in any detectable amount when using benzoyl chloride, pivaloyl chloride, or ethyl formate, we believe that the dominant formation of 14 is not attributable simply to the increased acidity of H-5 but to coordination by the ester carbonyl oxygen, thereby facilitating the generation of C-5 lithiated species (Fig. 1). When

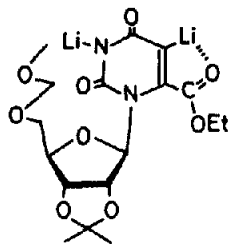
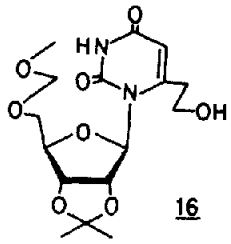


Fig. 1

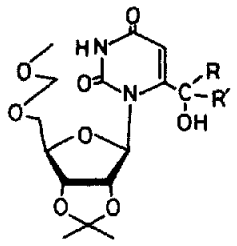
2.0 eq. of LDA and 1.0 eq. of ethyl chloroformate were used in this reaction, 15 was obtained as the sole product in 52.9% yield.

The β-hydroxyethylation was performed by adding ethylene oxide in THF to 2 (below -70° for 17 h). Presumably due to the poor reactivity of this electrophile at such a low temperature, 16 was obtained in only 25.6% yield (90.5% based on consumed 1).



16

Reaction of 2 with ketones was next investigated. Benzophenone reacted with 2 (in THF, below -70° for 3 h) to produce the 6-diphenylhydroxymethyl derivative (17) in 74.4% yield. Enolizable ketones such as acetone and cyclohexanone, in contrast, gave lower yields of the carbinols (18: 19.3%, 19: 30.4%), and most of 1 was left unchanged after quenching. Compounds 17 and 18 show the following two characteristics in their PMR spectra. The methylene protons of the 5'-O-methoxymethyl group behave magnetically non-equivalent, thereby exhibiting an AB quartet; this is seen in 6-aroyluridine derivatives.[7] Remarkable downfield shifts of H-1' (18: δ 7.07, 19: δ 7.11) are observed compared with those of the 6-hydroxymethyl derivative (13: δ 5.55) and other 6-substituted analogs. A detailed discussion of the relationship between these PMR results and conformational analysis will be published elsewhere.

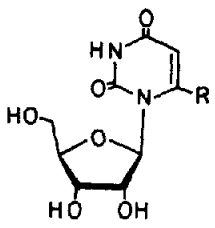


17 R=R'= 

18 R=R'= Me

19 R=R'= -$(CH_2)_5$-

Concurrent deprotection of the isopropylidene and methoxymethyl groups was successfully accomplished without any appreciable side reaction. Thus, treatment of the protected nucleosides with 50% aqueous trifluoroacetic acid (room temperature) gave the corresponding free nucleosides (20~28) in 73.1~98.6% yields.



20 R= phenylthio
21 R= benzoyl
22 R= pivaloyl
23 R= acetyl
24 R= propionyl
25 R= hydroxymethyl
26 R= diphenylhydroxymethyl
27 R= dimethylhydroxymethyl
28 R= 1-hydroxycyclohexyl

In conclusion, it is evident that our methodology successfully synthesizes a wide variety of 6-substituted uridines, and we believe that it will prove to be a method of choice.

Further applications are presently under investigation.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. PMR spectra were measured with an appropriate internal standard of tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-sila-

pentane-5-sulfonate (DSS), with a JEOL JNM-FX 100 NMR spectrometer. UV spectra were recorded on a Hitachi 340 spectrophotometer. The abbreviation used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; sh, shoulder. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use according to the published procedure.[18] Column chromatography was carried out on Merck Silica Gel 60. TLC was performed on silica gel (precoated silica gel plate 60 F_{254}, Merck).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (4) and 5,6-diphenylthio-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (5)—— LDA (15.2 mmol) in THF (30 ml) was placed in a three-necked flask fitted with a nitrogen inlet adapter, thermometer, and rubber septum. To this, a solution of 1 (1.992 g: 6.07 mmol) in THF (25 ml) was added, under positive pressure of dry nitrogen, at a rate such that the temperature did not exceed -70°. After the mixture was stirred for 1 h, diphenyl disulfide (2.690 g: 12.32 mmol) in THF (15 ml) was added, while maintaining the temperature below -70°. The mixture was stirred for 2 h below -70°, quenched with AcOH (2 ml), and allowed to warm to room temperature. The whole was evaporated to dryness and the residue was chromatographed on a silica gel (150 g) column (1% EtOH in $CHCl_3$). This afforded 2.191 g (82.7%) of 4, which was crystallized from MeOH-ether (mp 157∿158°), and 176 mg (5.3%) of 5.

Physical data of 4 are as follows. Anal. Calcd. for $C_{20}H_{24}N_2O_7S$: C, 55.04; H, 5.54; N, 6.42. Found: C, 55.14; H, 5.57; N, 6.31. MS m/z: 436 (M^+), 421 (M-Me). UV absorption in MeOH: max 279 nm (ε 11300), min 242 nm (ε 5500). PMR ($CDCl_3$) δ: 1.35 (3H, s, isop.Me), 1.58 (3H, s, isop.Me), 3.36 (3H, s, CH_2OCH_3), 3.77 (2H, m, CH_2-5'), 4.31 (1H, m, H-4'), 4.66 (2H, s, CH_2OCH_3), 4.88 (1H, dd, H-3'), 4.93 (1H, d, H-5), 5.23 (1H, dd, H-2'), 6.14 (1H, d, J=1.0 Hz, H-1'), 7.52 (5H, s, phenyl), 10.43 (1H, br, NH).

Physical data of 5 are as follows. MS m/z: 544 (M^+), 529 (M-Me), 328 (B+1). UV absorption in MeOH: max 244 nm, sh 276 and 310 nm, min 228 nm. PMR ($CDCl_3$) δ: 1.18 (3H, s, isop.Me), 1.43 (3H, s, isop.Me), 3.34 (3H, s, CH_2OCH_3), 3.63∿3.78 (2H, m, CH_2-5'), 4.00∿4.23 (1H, m, H-4'), 4.63 (2H, s, CH_2OCH_3), 4.67∿4.89 (2H, m, H-2' and H-3'), 6.68 (1H, d, J=1.0 Hz, H-1'), 7.22 (5H, s, phenyl), 7.30 (5H, s, phenyl), 8.87 (1H, br, NH).

6-Benzoyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (6)—— The following amounts of reagents and 395 mg (1.20 mmol) of 1 in THF (10 ml) were employed: 3.00 mmol of LDA in THF (10 ml), 0.28 ml (2.40 mmol) of freshly distilled benzoyl chloride. The procedure was identical with that used for the preparation of 4, and the reaction was continued for 19 h. Silica gel column chromatography (1% EtOH in $CHCl_3$) gave 6 (414 mg, 80.0%). For physical data of 6, see reference 7.

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-pivaloyluridine (7)—— The following amounts of reagents and 650 mg (1.98 mmol) of 1 in THF (10 ml) were employed: 4.95 mmol of LDA in THF (10 ml), 0.48 ml (3.96 mmol) of freshly distilled pivaloyl chloride. The reaction was continued for 19 h. Silica gel column chromatography (1% EtOH in $CHCl_3$) gave 7 (584 mg, 71.5%). MS m/z: 412 (M^+), 397 (M-Me), 197 (B+2). UV absorption in MeOH: max 260 nm, min 235 nm. PMR ($CDCl_3$) δ: 1.23 (3H, s, CMe_3), 1.31 (9H, s, isop.Me and CMe_3), 1.51 (3H, s, isop.Me), 3.36 (3H, s, CH_2OCH_3), 3.60∿3.80 (2H, m, CH_2-5'), 4.19∿4.30 (1H, m, H-4'), 4.64 (2H, s, CH_2OCH_3), 4.85 (1H, dd, H-3'), 5.19 (1H, dd, H-2'), 5.08 (1H, d, J=1.5 Hz, H-1'), 5.23 (1H, s, H-5), 9.35 (1H, br, NH).

6-Acetyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (10)—— The following amounts of reagents and 539 mg (1.64 mmol) of 1 in THF (10 ml) were employed for the preparation of the carbinol 8: 4.10 mmol of LDA in THF (10 ml), a THF solution of freshly distilled acetaldehyde (3.28 mmol). The reaction was continued for 3 h. Silica gel column chromatography (2.5% EtOH in $CHCl_3$) gave 8 (470 mg, 76.8%). MS m/z: 373 (M+1), 357 (M-Me), 156 (B+1). PMR ($CDCl_3$) δ: 1.34 (3H, s, isop.Me), 1.56 (6H, s, isop.Me and CHOH-Me), 3.37 and 3.38 (3H, each as s, CH_2OCH_3), 3.74∿3.84 (2H, m, CH_2-5'), 4.21∿4.34 (1H, m, H-4'), 4.67 and 4.68 (2H, each as s, CH_2OCH_3), 4.76∿4.89 (2H, m, H-3' and CHOH-Me), 5.19 (1H, d, H-2'), 5.81 and 6.15 (1H, each as s, H-1'), 5.77 and 5.90 (1H, each as s, H-5).

A pyridine (6 ml) solution of 8 (304 mg) was added to the complex prepared from CrO_3 (816 mg) and pyridine (8.2 ml). The mixture was stirred at room temperature overnight. The whole was poured into ice water. The product was extracted with $CHCl_3$ and chromatographed on silica gel (3% EtOH in $CHCl_3$). This afforded 10 (258 mg, 85.4 %). MS m/z: 370 (M^+), 355 (M-Me), 155 (B+2). UV absorption in MeOH: max 271 nm, min 236 nm. PMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 2.52 (3H, s, $COCH_3$), 3.37 (3H, s, CH_2OCH_3), 3.65∿3.73 (2H, m, CH_2-5'), 4.04∿4.21 (1H, m, H-4'), 4.65 (2H, s, CH_2OCH_3), 4.65 (1H, t, H-3'), 5.12 (1H, dd, H-2'), 5.92 (1H, d, J=2.5 Hz, H-1'), 5.84 (1H, d, H-5), 8.64 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-propionyluridine (11)—— The following amounts of reagents and 1.50 g (4.57 mmol) of 1 in THF (25 ml) were employed for the preparation of the carbinol 9: 22.8 mmol of LDA in THF (15 ml), 3.3 ml (46.0 mmol) of freshly distilled propionaldehyde. The reaction was continued for 3 h. Silica gel column chromatography (1% EtOH in $CHCl_3$) gave 9 (1.34 g, 75.7%). MS m/z: 386 (M^+), 371 (M-Me), 171 (B+2). High resolution MS m/z: 386.1644 (M^+) Calcd. for $C_{17}H_{26}N_2O_8$ 386.1682. PMR ($CDCl_3$) δ: 0.88∿1.13 (3H, m, CH_2CH_3), 1.34 (3H, s, isop.Me), 1.56 (3H, s, isop.Me), 1.63∿1.92 (2H, m, CH_2CH_3), 3.37 (3H, s, CH_2OCH_3), 3.78∿3.84 (2H, m, CH_2-5'), 4.22∿4.61 (2H, m, H-4' and CHOH-Et), 4.68 (2H, s, CH_2OCH_3), 4.83∿4.89 (1H, m, H-3'), 5.21 (1H, d, H-2'), 5.72 and 5.88 (1H, each as s, H-5), 5.79 and 6.17 (1H, each as s, H-1'), 9.61 (1H, br, NH).

A pyridine (14 ml) solution of 9 (718 mg) was added to the complex prepared from CrO_3 (1.86 g) and pyridine (18.6 ml). The mixture was stirred at room temperature for 30 h. The whole was poured into ice water. The product was extracted with $CHCl_3$ and chromatographed on silica gel (1% EtOH in $CHCl_3$). This afforded 11 (453 mg, 65.3 %) which was crystallized from ether: mp 117∿118°. Anal. Calcd. for $C_{17}H_{24}N_2O_8$: C, 53.12; H, 6.29; N, 7.29. Found: C, 53.35; H, 6.43; N, 7.13. MS m/z: 384 (M^+), 369 (M-Me), 169 (B+2). UV absorption in MeOH: max 272 nm (ε 7300), min 237 nm (ε 2200). PMR ($CDCl_3$) δ: 1.20 (3H, t, $COCH_2CH_3$), 1.36 (3H, s, isop.Me), 1.56 (3H, s, isop.Me), 2.83 (2H, q, $COCH_2CH_3$), 3.36 (3H, s, CH_2OCH_3), 3.60∿3.72 (2H, m, CH_2-5'), 4.04∿4.22 (1H, m, H-4'), 4.64 (2H, s, CH_2OCH_3), 4.68 (1H, t, H-3'), 5.15 (1H, dd, H-2'), 5.78 (1H, d, J=2.0 Hz, H-1'), 5.80 (1H, d, H-5), 9.10 (1H, br, NH).

6-Hydroxymethyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (13)—— The following amounts of reagents and 786 mg (2.39 mmol) of 1 in THF (12 ml) were employed for the preparation of 12: 5.99 mmol of LDA in THF (10 ml), 0.39 ml (4.79 mmol) of freshly distilled ethyl formate. The formylation reaction was continued for 3.5 h. After quenching with AcOH (0.36 ml), the mixture was allowed to warm to room temperature. The reaction mixture containing 12 was diluted with EtOH (45 ml) and then treated with $NaBH_4$ (114 mg) for 10 min at room temperature. After evaporation, the whole residue was chromatographed on silica gel (2% EtOH in $CHCl_3$). This afforded 13 (564 mg, 65.7% from 1), which was crystallized from MeOH-hexane: mp 219∿220°. Anal. Calcd. for $C_{15}H_{22}N_2O_8$: C, 50.27; H, 6.19; N, 7.82. Found: C, 50.48; H, 6.21; N, 7.91. MS m/z: 358 (M^+), 343 (M-Me), 143 (B+2). UV absorption in MeOH: max 258 nm (ε 10500), min 228 nm (ε 2700). PMR (DMSO-d_6) δ: 1.28 (3H, s, isop.Me), 1.47 (3H, s, isop.Me), 3.23 (3H, s, CH_2OCH_3), 3.55∿3.64 (2H, m, CH_2-5'), 4.00∿4.13 (1H, m, H-4'), 4.33 (2H, d, CH_2OH), 4.54 (2H, s, CH_2OCH_3), 4.76 (1H, dd, H-3'), 5.21 (1H, d, H-2'), 5.69 (1H, s, H-5), 5.77 (1H, s, H-1'), 5.84 (1H, t, CH_2OH), 11.38 (1H, br, NH).

5,6-Bis(ethoxycarbonyl)-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (14)—— The following amounts of reagents and 756 mg (2.30 mmol) of 1 in THF (11 ml) were employed: 5.76 mmol of LDA in THF (11 ml), 0.44 ml (4.61 mmol) of the freshly distilled ethyl chloroformate. The reaction was continued for 5 h. Silica gel column chromatography (0.5% EtOH in $CHCl_3$) gave 687 mg of the crude mixture (14/15= ca. 3), from which 14 was isolated as crystals by treating with ether-hexane: mp 101∿103°. Anal. Calcd. for $C_{20}H_{28}N_2O_{11}$: C, 50.85; H, 5.97; N, 5.93. Found: C, 50.73; H, 5.99; N, 5.79. MS m/z: 472 (M^+), 457 (M-Me), 257 (B+2). UV absorption in MeOH: max 275 nm (ε 10900), min 236 nm (ε 2400). PMR ($CDCl_3$) δ: 1.33 (3H, s, isop.Me), 1.34 (3H, t, $CO_2CH_2CH_3$), 1.40 (3H, t, $CO_2CH_2CH_3$), 1.53 (3H, s, isop.Me), 3.37 (3H, s, CH_2OCH_3), 3.68∿3.75 (2H, m, CH_2-5'), 4.16∿4.56 (5H, m, $CO_2CH_2CH_3$ and H-4'), 4.65 (2H, s, CH_2OCH_3), 4.81 (1H, dd, H-3'), 5.18 (1H, dd, H-2'), 5.53 (1H, d, J=1.5 Hz, H-1'), 8.85 (1H, br, NH).

6-Ethoxycarbonyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (15)—— The following amounts of reagents and 712 mg (2.17 mmol) of 1 in THF (12 ml) were employed: 4.34 mmol of LDA in THF (11 ml), 0.21 ml (2.17 mmol) of the freshly distilled ethyl chloroformate. The reaction was continued for 5 h. Silica gel column chromatography (1% EtOH in $CHCl_3$) gave 15 (459 mg, 52.9%). MS m/z: 400 (M^+), 385 (M-Me), 185 (B+2). UV absorption in MeOH: max 271 nm, min 231 nm. PMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.40 (3H, t, $CO_2CH_2CH_3$), 1.56 (3H, s, isop.Me), 3.36 (3H, s, CH_2OCH_3), 3.69∿3.76 (2H, m, CH_2-5'), 4.12∿4.30 (1H, m, H-4'), 4.40 (2H, q, $CO_2CH_2CH_3$), 4.65 (2H, s, CH_2OCH_3), 4.81 (1H, dd, H-3'), 5.21 (1H, dd, H-2'), 5.97 (1H, d, J= 1.5 Hz, H-1'), 6.10 (1H, d, H-5), 9.83 (1H, br, NH).

6-β-Hydroxyethyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (16)—— The following amounts of reagents and 265 mg (0.81 mmol) of 1 in THF (10 ml) were employed: 5.00 mmol of LDA in THF (10 ml), a THF solution of freshly distilled ethylene oxide (4.95 mmol). The reaction was continued for 17 h. Silica gel column chromatography (1∿2% EtOH in $CHCl_3$) gave 77 mg (25.6%) of 16 and 190 mg of 1. MS m/z: 372 (M^+), 357 (M-Me). High resolution MS m/z: 372.1520 (M^+) Calcd. for $C_{16}H_{24}N_2O_8$ 372.1530. UV absorption in MeOH: max 259 nm, min 229 nm. PMR ($CDCl_3$) δ: 1.34 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 2.84 (2H, t, CH_2CH_2OH), 3.35 (3H, s, CH_2OCH_3), 3.73∿3.80 (2H, m, CH_2-5'), 3.92 (2H,

t, CH_2CH_2OH), 4.22∿4.27 (1H, m, H-4'), 4.65 (2H, s, CH_2OCH_3), 4.86 (1H, t, H-3'), 5.21 (1H, d, H-2'), 5.67 (1H, s, H-5), 5.79 (1H, s, H-1').

6-Diphenylhydroxymethyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (17)—— The following amounts of reagents and 691 mg (2.10 mmol) of 1 in THF (10 ml) were employed: 5.25 mmol of LDA in THF (10 ml), a THF solution of benzophenone (765 mg: 4.20 mmol). The reaction was continued for 3 h. Silica gel column chromatography (0.5% EtOH in $CHCl_3$) gave 17 (798 mg, 74.4%). MS m/z: 510 (M^+), 495 (M-Me), 294 (B+1). UV absorption in MeOH: max 261 nm, min 235 nm. PMR ($CDCl_3$) δ: 1.09 (3H, s, isop.Me), 1.20 (3H, s, isop.Me), 3.39 (3H, s, CH_2OCH_3), 3.64∿3.91 (2H, m, CH_2-5'), 4.16∿4.30 (1H, m, H-4'), 4.50∿4.87 (4H, m, H-2', H-3', and CH_2OCH_3), 4.97 (1H, d, H-5), 6.41 (1H, d, H-1'), 7.10∿7.38 (10H, m, phenyl), 9.30 (1H, br, NH).

6-Dimethylhydroxymethyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (18)—— The following amounts of reagents and 643 mg (1.96 mmol) of 1 in THF (10 ml) were employed: 4.90 mmol of LDA in THF (10 ml), 0.29 ml (3.93 mmol) of freshly distilled acetone. The reaction was continued for 3 h. Silica gel column chromatography (2% EtOH in $CHCl_3$) gave 146 mg (19.3%) of 18 and 513 mg of 1. MS m/z: 387 (M+1), 371 (M-Me), 171 (B+2). UV absorption in MeOH: max 260 nm, min 228 nm. PMR ($CDCl_3$) δ: 1.34 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 1.59 (3H, s, COH-Me_2), 1.62 (3H, s, COH-Me_2), 3.39 (3H, s, CH_2OCH_3), 3.80∿3.95 (2H, m, CH_2-5'), 4.20∿4.42 (1H, m, H-4'), 4.65 and 4.75 (2H, each as d, J=6.4 Hz, CH_2OCH_3), 4.79 (1H, dd, H-3'), 5.15 (1H, dd, H-2'), 5.61 (1H, d, H-5), 7.07 (1H, d, J=1.5 Hz, H-1'), 9.43 (1H, br, NH).

6-(1-Hydroxycyclohexyl)-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (19)—— The following amounts of reagents and 598 mg (1.82 mmol) of 1 in THF (10 ml) were employed: 4.55 mmol of LDA in THF (10 ml), 0.38 ml (3.64 mmol) of distilled cyclohexanone. The reaction was continued for 3.5 h. Silica gel column chromatography (1.5% EtOH in $CHCl_3$) gave 236 mg (30.4%) of 19 and 369 mg of 1. Compound 19 was crystallized from ether-hexane: mp 131 ∿132°. Anal. Calcd. for $C_{20}H_{30}N_2O_8$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.42; H, 6.97; N, 6.73. MS m/z: 427 (M+1), 411 (M-Me), 210 (B+1). UV absorption in MeOH: max 261 nm (ε 10400), min 230 nm (ε 2800). PMR ($CDCl_3$) δ: 1.33 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 1.00∿2.20 (10H, m, $-(CH_2)_5-$), 3.39 (3H, s, CH_2OCH_3), 3.80∿3.94 (2H, m, CH_2-5'), 4.25∿4.38 (1H, m, H-4'), 4.65 and 4.75 (2H, each as d, J=6.8 Hz, CH_2OCH_3), 4.78 (1H, t, H-3'), 5.14 (1H, dd, H-2'), 5.58 (1H, d, H-5), 7.11 (1H, d, J=1.5 Hz, H-1'), 9.16 (1H, br, NH).

General procedures for the deprotection of 2',3'-O-isopropylidene-5'-O-methoxymethyl-6-substituted uridines—— To the protected nucleoside (1 mmol), 50% aqueous CF_3COOH (10 ml) was added. The mixture was stirred at room temperature. After completion of the reaction (TLC analysis), the mixture was evaporated to dryness and chromatographed on a silica gel column. This afforded the corresponding free nucleoside.

6-Phenylthiouridine (20)—— A mixture containing 455 mg of 4 was stirred overnight. After chromatography (4∿5% EtOH in $CHCl_3$), 283 mg (77.0%) of 20 was obtained. UV absorption in H_2O: max 281 nm, min 242 nm. PMR (D_2O) δ: 3.78∿4.03 (3H, m, H-4' and CH_2-5'), 4.41 (1H, t, H-3'), 4.86 (1H, dd, H-2'), 5.12 (1H, s, H-5), 6.07 (1H, d, J=3.4 Hz, H-1'), 7.60 (5H, s, phenyl).

Compound 20 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 478.1077 (M^+) Calcd. for $C_{21}H_{22}N_2O_9S$ 478.1046. PMR ($CDCl_3$) δ: 2.09 (6H, s, Ac), 2.13 (3H, s, Ac), 4.13∿4.62 (3H, m, H-4' and CH_2-5'), 5.04 (1H, d, H-5), 5.60 (1H, t, H-3'), 5.88 (1H, dd, H-2'), 6.02 (1H, d, J=2.9 Hz, H-1'), 7.52 (5H, s, phenyl), 9.29 (1H, br, NH).

6-Benzoyluridine (21)—— A mixture containing 236 mg of 6 was stirred overnight. After chromatography (7% EtOH in $CHCl_3$), 159 mg (83.6%) of 21 was obtained. Crystallization from H_2O gave an analytical sample: mp 193∿195°. For physical data of 21, see reference 7.

6-Pivaloyluridine (22)—— A mixture containing 500 mg of 7 was stirred overnight. After chromatography (5% EtOH in $CHCl_3$), 378 mg (95.0%) of 22 was obtained. UV absorption in H_2O: max 260 nm, min 228 nm. PMR (D_2O) δ: 1.32 (9H, s, $COMe_3$), 3.68∿3.99 (3H, m, H-4' and CH_2-5'), 3.43 (1H, t, H-3'), 4.78 (1H, dd, H-2'), 4.89 (1H, d, J=2.9 Hz, H-1'), 5.80 (1H, s, H-5).

Compound 22 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 454.1555 (M^+) Calcd. for $C_{20}H_{26}N_2O_{10}$ 454.1585. PMR ($CDCl_3$) δ: 1.30 (9H, s, $COMe_3$), 2.06 (3H, s, Ac), 2.08 (3H, s, Ac), 2.09 (3H, s, Ac), 4.17∿4.47 (3H, m, H-4' and CH_2-5'), 5.00 (1H, d, J= 3.9 Hz, H-1'), 5.49∿5.62 (2H, m, H-3' and H-5), 5.97 (1H, dd, H-2'), 9.03 (1H, br, NH).

6-Acetyluridine (23)—— A mixture containing 79 mg of 10 was stirred for 24 h. After chromatography (7% EtOH in $CHCl_3$), 60 mg (98.6%) of 23 was obtained. High resolution MS m/z: 286.0784 (M^+) Calcd. for $C_{11}H_{14}N_2O_7$ 286.0799. UV absorption in H_2O: max 272 nm, min 236 nm. PMR (D_2O) δ: 2.60 (3H, s, $COCH_3$), 3.53∿4.01 (3H, m, H-4' and CH_2-5'), 4.14 (1H, t, H-3'), 4.60 (1H, dd, H-2'), 5.59 (1H, d, J= 3.9 Hz, H-1'), 6.12 (1H, s, H-5).

6-Propionyluridine (24)—— A mixture containing 100 mg of 11 was stirred for 24 h. After chromatography (7% EtOH in $CHCl_3$), 72 mg (92.3%) of 24 was obtained. High resolution MS m/z: 300.0927 (M^+) Calcd. for $C_{12}H_{16}N_2O_7$ 300.0955. UV absorption in H_2O: max 271 nm, min 237 nm. PMR (D_2O) δ: 1.05∿1.23 (3H, m, $COCH_2CH_3$), 2.83∿3.01 (2H, m, $COCH_2CH_3$), 3.54∿3.99 (3H, m, H-4' and CH_2-5'), 4.14 (1H, t, H-3'), 4.63 (1H, dd, H-2'), 5.48 (1H, d, J=3.9 Hz, H-1'), 6.06 (1H, s, H-5).

6-Hydroxymethyluridine (25)—— A mixture containing 100 mg of 13 was stirred for 2 days. After chromatography (9% EtOH in $CHCl_3$), 56 mg (73.1 %) of 25 was obtained. Crystallization from EtOH gave an analytical sample: mp 177∿178°. Anal. Calcd. for $C_{10}H_{14}N_2O_7$: C, 43.80; H, 5.15; N, 10.22. Found: C, 43.62; H, 5.20; N, 9.94. MS m/z: 443 (M+1), 185 (B+2). UV absorption in H_2O: max 258 nm (ε 10700), min 227 nm (ε 2800). PMR (D_2O) δ: 3.62∿4.03 (3H, m, H-4' and CH_2-5'), 4.39 (1H, t, H-3'), 4.59 (2H, s, CH_2OH), 4.79 (1H, dd, H-2'), 5.55 (1H, d, J=3.4 Hz, H-1'), 5.97 (1H, s, H-5).

6-Diphenylhydroxymethyluridine (26) —— A mixture containing 386 mg of 17 was stirred for 20 h. After chromatography (6% EtOH in $CHCl_3$), 281 mg (87.2 %) of 26 was obtained. Crystallization from MeOH-H_2O gave an analytical sample: mp 188∿189°. Anal. Calcd. for $C_{22}H_{22}N_2O_7$: C, 61.96; H, 5.20; N, 6.57. Found: C, 61.78; H, 5.37; N, 6.40. MS m/z: 408 (M-H_2O), 294 (B+1). UV absorption in MeOH: max 265 nm (ε 9300), min 237 nm (ε 3500). PMR (DMSO-d_6, after addition of D_2O) δ: 3.17∿3.63 (3H, m, H-4' and CH_2-5'), 3.99∿4.26 (2H, m, H-3' and H-2'), 4.69 (1H, s, H-5), 5.91 (1H, d, J=1.5 Hz, H-1'), 7.30 (10H, s, phenyl).

6-Dimethylhydroxymethyluridine (27) —— A mixture containing 60 mg of 18 was stirred for 22 h. After chromatography (7% EtOH in $CHCl_3$), 41 mg (87.7 %) of 27 was obtained. UV absorption in H_2O: max 262 nm, min 231 nm. PMR (D_2O) δ: 1.66 (6H, s, COH-Me_2), 3.69∿3.98 (3H, m, H-4' and CH_2-5'), 4.41 (1H, t, H-3'), 4.73 (1H, dd, H-2'), 5.97 (1H, s, H-5), 6.65 (1H, d, J=2.9 Hz, H-1').

Compound 27 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 429.1507 (M+1) Calcd. for $C_{18}H_{25}N_2O_{10}$ 429.1507. PMR ($CDCl_3$) δ: 1.61 (6H, s, COH-Me_2), 2.07 (3H, s, Ac), 2.09 (3H, s, Ac), 2.12 (3H, s, Ac), 3.49 (1H, br, COH-Me_2), 4.12∿4.52 (3H, m, CH_2-5' and H-4'), 5.60 (1H, t, H-3'), 5.62 (1H, s, H-5), 5.99 (1H, dd, H-2'), 6.73 (1H, d, J=1.5 Hz, H-1'), 9.52 (1H, br, NH).

6-(1-Hydroxycyclohexyl)uridine (28) —— A mixture containing 32 mg of 19 was stirred for 24 h. After chromatography (7% EtOH in $CHCl_3$), 22 mg (85.3 %) of 28 was obtained. UV absorption in H_2O: max 261 nm, min 233 nm. PMR (D_2O) δ: 1.10∿2.25 (10H, m, -$(CH_2)_5$-), 3.61∿4.01 (3H, m, H-4' and CH_2-5'), 4.40 (1H, t, H-3'), 4.73 (1H, dd, H-2'), 5.97 (1H, s, H-5), 6.73 (1H, d, J=2.9 Hz, H-1').

Compound 28 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 468.1768 (M^+) Calcd. for $C_{21}H_{28}N_2O_{10}$ 468.1743. PMR ($CDCl_3$) δ: 1.00∿2.20 (10H, m, -$(CH_2)_5$-), 2.09 (6H, s, Ac), 2.12 (3H, s, Ac), 4.07∿4.55 (3H, m, CH_2-5' and H-4'), 5.59 (1H, t, H-3'), 5.66 (1H, s, H-5), 5.93 (1H, dd, H-2'), 6.78 (1H, d, J=2.0 Hz, H-1'), 9.00 (1H, br, NH).

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