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LITHIATION OF 5,6-DIHYDROURIDINE: A NEW ROUTE TO 5-SUBSTITUTED URIDINES

HIROYUKI HAYAKAWA, HIROMICHI TANAKA AND TADASHI MIYASAKA*

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

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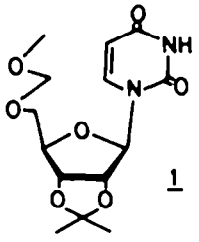
Summary——2',3'-O-Isopropylidene-5'-O-methoxymethyl-5,6-dihydrouridine (2) was found to serve as an "amide α-anion" upon lithiation with LDA. Reactions of the anion with acid chlorides followed by phenylselenation and oxidative elimination furnished 5-acyluridines. For the preparation of 5-alkyluridines, initial introduction of phenylselenenyl group at the C-5 of 2 appeared to be effective. Alkylation of its α-selenenyl carbanion and subsequent generation of 5,6-double bond produced 5-alkyluridines. These routes constitute a new entry to 5-substituted uridines.

Lithiation of organic molecules has been studied extensively as an increasingly important tool for carbon-carbon bond forming reactions.[1] In the field of nucleoside chemistry, however, this method has only recently become recognized to be practically useful.
In the course of our studies on the lithiation of uridine derivatives, we found that the metallation of 2',3'-O-isopropylidene-5'-O-methoxymethyluridine (1) with LDA took place at the C-6 position in an essentially regio-

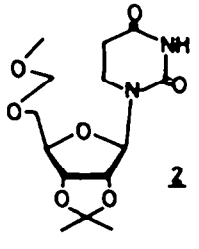


1

specific manner. We have already reported the usefulness of this method for the general synthesis of 6-substituted uridines.[2,3] In continuation of our work on the utilization of lithiation for synthetic purpose in nucleoside field, we now report here a new method which has been devised for the transformation of uridine to 5-substituted uridines.[4,5]

Since butyllithium is known to act through a "coordination mechanism"[6] which could be advantageous for the generation of the C-5 anion of uridine, we first examined the lithiation of 1 with butyllithium. Compound 1 was treated with 2.5 eq of butyllithium in THF below -70°C. After quenching with CD_3OD, the PMR spectrum of the product showed, however, that the deuterium incorporation occurred with a preference of about 2:1 for the C-6 position. Although this is quite interesting as compared with the result reported by Pichat and co-workers[7] in the case of tris-trimethylsilyluridine, lack of desired regioselectivity in the above reaction prompted us to devise another route.

As the C-5 position in 1 is alpha to the C-4 carbonyl function, we reasoned that saturation of the 5,6-double bond would provide a good possibility to generate an "amide α-anion" upon lithiation, despite the presence of the NH proton.[8]



2

Catalytic hydrogenation of 1 was carried out in MeOH in the presence of 5% Rh on alumina[9] to give 2',3'-O-isopropylidene-5'-O-methoxymethyl-5,6-dihydrouridine (2) in virtually quantitative yield. Disappearance of the UV absorption at 260 nm was used as a criterion of the reduction. In the PMR spectrum of 2, the signals of the olefinic protons were missing and the two CH_2 protons appeared as well separated triplets at 2.68 (CH_2-6) and 3.52 (CH_2-5) ppm.

When 2 in THF was treated with 2.5 eq of LDA below -70°C, a clear solution of N,α-dianion (3) resulted. The dianion was then treated with benzoyl chloride at the same temperature for 1 h to afford 4a in 79.6% yield after column chromatography on silica gel. PMR spectrum indicated that 4a is a 6:5 diastereomeric mixture, showing two anomeric protons at 5.69 and 5.93 ppm. As expected, no N-benzoylated product was observed due to a poor nucleophilicity of the conjugate base at low temperature.

Other acylating agents, including ethyl chloroformate, work equally well to provide 4b~e in high yields as tabulated in Table 1.

The next stage to be accomplished was regeneration of the 5,6-double bond. Liotta *et al.* reported an efficient method for the conversion of β-dicarbonyl compounds to their corresponding unsaturated derivatives where PhSeCl-pyridine complex was used for selenation.[10] Although they used this complex only for β-ketoaldehydes, β-diketones and β-ketoesters, namely for easily enolizable compounds, we found that this reagent worked satisfactorily in the case of 4 leading to 5.

Thus, 4 was added to the preformed complex in CH_2Cl_2 at 0°C and the mixture was allowed to stir at ambient temperature overnight. After removal of pyridine, the mixture was treated with 30% H_2O_2 in CH_2Cl_2 at 0°C for 2 h without isolating the intermediate selenoderivative. Chromatographic purification gave rise to 5 in high yields as given in Table 1. The phenylselenation of 5-pivaloyl derivative (4d) did not proceed under the above conditions and required heating at 60~70°C. Although 4 reacted rather sluggishly with the complex, the addition of excess reagent was unnecessary[10] even in the case of 4d. The PMR spectra of all the products (5) exhibited sharp singlets in aromatic region corresponding to their H-6, providing evidence of regeneration of the 5,6-double bonds.

Our next intention was to prepare 5-alkyluridines from 2.[11] As the introduction of an alkyl group at the C-5 of 2 decreases the acidity of H-5, one will find difficuty in the successive phenylselenation. In fact, phenylselenation of 5-methyl-5,6-dihydrouridine

Table 1 yields (%) of products

	RCOX	4	5
a	$PhCOCl$	79.6	89.7
b	CH_3CH_2COCl	72.3	82.7
c	$(CH_3)_2CHCOCl$	80.0	88.0
d	$(CH_3)_3CCOCl$	94.4	64.4
e	CH_3CH_2OCOCl	80.5	99.2

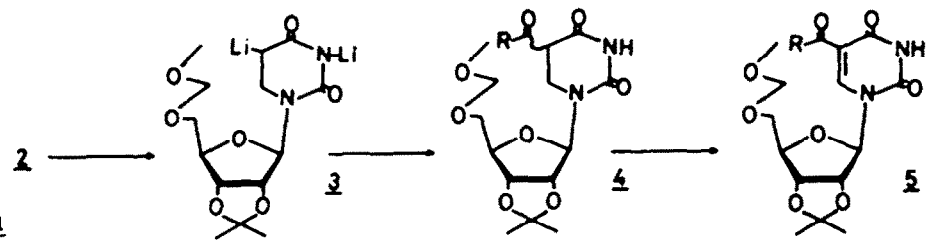
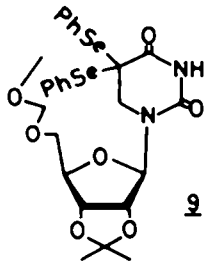


Chart 1

derivative (6), obtained in 87.4% yield by methylation of 3, with PhSeCl-pyridine complex resulted in complete recovery of the starting material. Compound 7 was produced only when 6 was lithiated with LDA and then selenated with PhSeCl, but the yield (35.7%) was poor. A solution of the problem encountered above might be to reverse this reaction sequence, since several selenium stabilized carbanions have been reported.[12]

Thus, 2 was subjected to metallation with LDA and treated with PhSeCl. The isolated yield of the requisite product (8) was, however, only moderate (42~50 %) due to the formation of bis-phenylseleno derivative (9: 19~22%). On the other hand, when the reaction mixture



9

containing 8 and 9 was further treated with 1.0 eq of butyllithium in a one-pot manner, the greater part of 9 was converted to 8.[13] After chromatography on a silica gel column, 8 was isolated in 71.0% yield along with a small amount of 9 (2.6%). Indeed, the lithiation of 8 with LDA[14] and successive methylation with MeI gave a higher yield of 7 (87.0%). Reactions with allyl bromide, benzyl bromide and methyl bromoacetate were also carried out in a similar manner to afford the corresponding products (10a~c) in good yields (Table 2).

Although a selenium stabilized anion derived from $PhSeCH_2CO_2Et$ has been reported,[15] we are not aware of any example similar to our system, PhSeCHRCONHR'.

Oxidative elimination with 10 was conducted in CH_2Cl_2-30% H_2O_2 from 0°C to room temperature for a couple of hours. The yields of protected 5-alkyluridines (11 and 12a~c) were excellent as shown in Table 2.

Finally, concurrent deprotection of the isopropylidene and methoxymethyl groups in 5, 11 and 12 was successfully accomplished in 50% aqueous CF_3CO_2H at room temperature without any appreciable side reaction, except in the case of 12c where partial hydrolysis of the ester function occurred. The yields of free 5-substituted uridines are shown in parentheses. Compound 22 was prepared from 21 by ammonolysis.

In conclusion, our results provide

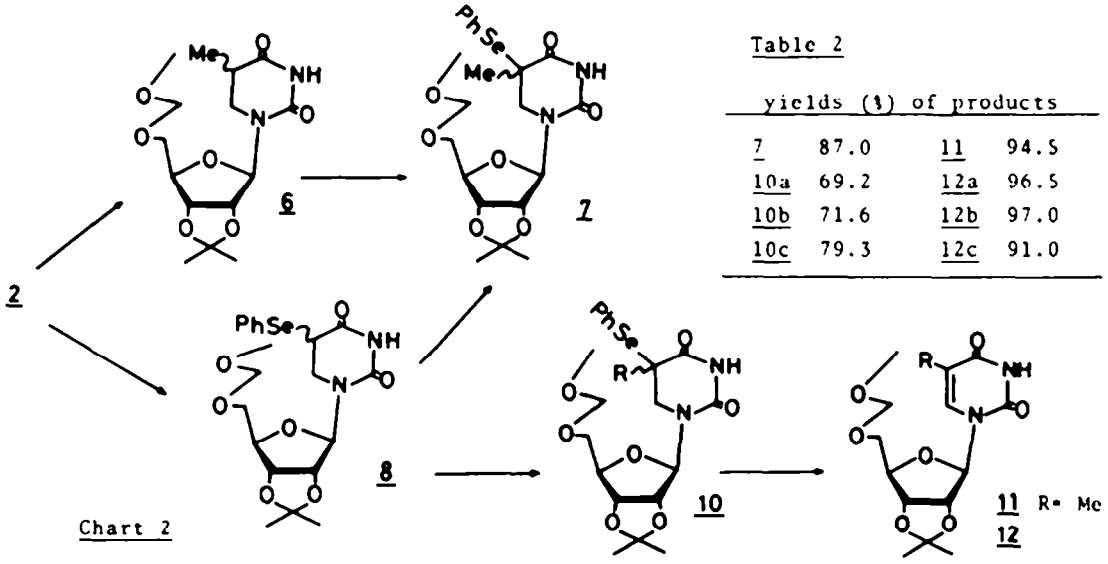
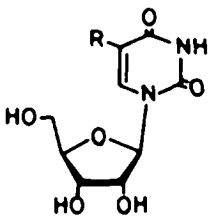


Chart 2

Table 2

yields (%) of products			
7	87.0	11	94.5
10a	69.2	12a	96.5
10b	71.6	12b	97.0
10c	79.3	12c	91.0

a) R= $CH_2CH{=}CH_2$, b) R= CH_2Ph, c) R= CH_2CO_2Me.



13 R= COPh (84.3%)
14 R= COC_2H_5 (83.0%)
15 R= CO-iPr (90.6%)
16 R= $COCMe_3$ (82.3%)
17 R= CO_2Et (93.4%)
18 R= Me (87.0%)
19 R= $CH_2CH{=}CH_2$ (80.0%)
20 R= CH_2Ph (81.0%)
21 R= CH_2CO_2Me (55.8%)
22 R= CH_2CONH_2 (61.6%)*

*yield from 21.

the first successful example of utilizing 5,6-dihydrouridine derivative for the synthesis of 5-substituted uridines. We believe that our method will be effective for the preparation of modified nucleosides in transfer RNA, since many of them are 5-substituted uridine derivatives.[16,17]

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-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; q, quartet; m, multiplet; br, broad. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer. Reactions at low temperature were performed using a CryoCool CC-100 (NESLAB Instrument, Inc.). Butyllithium in hexane was titrated before use by diphenylacetic acid in THF. THF was distilled from sodium benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200). TLC was performed on silica gel (precoated silica gel plate 60 F_{254}, Merck).

An improved preparation of 2',3'-O-isopropylidene-5'-O-methoxymethyluridine (1)—— Methanesulfonic acid (4.0 ml) was added to a suspension of finely powdered isopropylideneuridine (15.0 g), dry dimethoxymethane (400 ml) and dry acetone (200 ml). The mixture was stirred at room temperature overnight. The resulting clear solution was poured into 28% NH_4OH (200 ml) and was evaporated to dryness. The residue was partitioned between $CHCl_3$ and aqueous NaCl. The organic layer was separated, dried (Na_2SO_4), evaporated and chromatographed on a silica gel column (0.5 ~1% EtOH in $CHCl_3$) to give 1 (15.7 g, 90.4%). Physical data of 1: see reference 2.

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5,6-dihydrouridine (2)—— A MeOH (60 ml) solution of 1 (2.40 g) was hydrogenated at atmospheric pressure in the presence of 5% Rh on alumina (300 mg) as a catalyst. The theoretical amount of H_2 was taken up within 1~2 h. The catalyst was removed by filtration. Evaporation of the solvent followed by chromatographic purification on a short column of silica gel (5% EtOH in $CHCl_3$) gave 2 (2.39 g, 99.0%) as syrup. MS m/z: 330 (M^+), 315 (M-Me). PMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.58 (3H, s, isop.Me), 2.68 (2H, t, H-6), 3.37 (3H, s, CH_2OCH_3), 3.52 (2H, t, H-5), 3.69~3.74 (2H, m, CH_2-5'), 4.14~4.32 (1H, m, H-4'), 4.66 (2H, s, CH_2OCH_3), 4.71~4.87 (2H, m, H-2' and H-3'), 5.71 (1H, d, H-1'), 7.74 (1H, br, NH).

5-Benzoyl-2',3'-O-isopropylidene-5'-methoxymethyl-5,6-dihydrouridine (4a)—— LDA (11.7 mmol) in THF (15 ml) was placed in a three-necked flask equipped with a gas inlet adaptor, thermometer and rubber septum. To this, a solution of 2 (1.54 g, 4.66 mmol) in THF (18 ml) was added, under positive pressure of dry argon, at a rate such that the temperature did not exceed -70°. After the mixture was stirred for 1 h, freshly distilled benzoyl chloride (1.09 ml, 9.32 mmol) was added neat, while maintaining the temperature below -70°. The reaction mixture was stirred for 3 h, quenched with AcOH, and evaporated to dryness. The whole residue was chromatographed on a silica gel column (1% EtOH in $CHCl_3$) to give 4a (1.61 g, 79.6%). MS m/z: 434 (M^+), 419 (M-Me). PMR ($CDCl_3$) δ: 1.34 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 3.24 and 3.32 (3H, each as s, CH_2OCH_3), 3.51~3.92 (4H, m, H-6 and CH_2-5'), 4.11~4.23 (1H, m, H-5), 4.47~4.83 (5H, m, H-2', H-3', H-4' and CH_2-5'), 5.69 and 5.93 (1H, each as d, H-1'), 7.41~7.73 (3H, m, Ph), 7.92~8.04 (2H, m, Ph).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-propionyl-5,6-dihydrouridine (4b)—— The following amounts of reagents and 526 mg (1.59 mmol) of 2 were used: 3.98 mmol of LDA in THF (10 ml), 0.28 ml (3.18 mmol) of freshly distilled CH_3CH_2COCl. After adding the electrophile, the reaction was continued for 1.5 h. Chromatographic purification on a silica gel column (1% EtOH in $CHCl_3$) gave 4b (443 mg, 72.3%). MS m/z: 386 (M^+), 371 (M-Me). PMR ($CDCl_3$) δ: 1.09 (3H, t, CH_2CH_2CO), 1.35 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 2.68~2.80 (2H, m, H-6), 3.36 and 3.38 (3H, each as s, CH_2OCH_3), 3.49~3.86 (5H, m, H-5, CH_2-5' and $COCH_2Me$), 4.12~4.22 (1H, m, H-4'), 4.64 and 4.66 (2H, each as s, CH_2OCH_3), 4.71~4.82 (2H, m, H-2' and H-3'), 5.65 and 5.92 (1H, each as d, H-1'), 7.77 (1H, br, NH).

5-Isobutyryl-2',3'-O-isopropylidene-5'-O-methoxymethyl-5,6-dihydrouridine (4c)—— The following amounts of reagents and 971 mg (2.94 mmol) of 2 were

used: 7.35 mmol of LDA in THF (15 ml), 0.61 ml (5.88 mmol) of freshly distilled $(CH_3)_2CHCOCl$. After adding the electrophile, the reaction was continued for 1 h. Chromatographic purification on a silica gel column (1~2% EtOH in $CHCl_3$) gave 4c (941 mg, 80.0%). MS m/z: 400 (M^+), 385 (M-Me). PMR ($CDCl_3$) δ: 1.07~1.23 (6H, m, Me_2CHCO), 1.35 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 2.92~3.24 (1H, m, Me_2CHCO), 3.35 and 3.37 (3H, each as s, CH_2OCH_3), 3.48~3.89 (4H, m, H-6 and CH_2-5'), 4.10~4.27 (2H, m, H-5 and H-4'), 4.63 and 4.65 (2H, each as s, CH_2OCH_3), 4.70~4.80 (1H, m, H-3'), 4.86~4.98 (1H, m, H-2'), 5.63 and 5.91 (1H, each as d, H-1'), 8.30 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-pivaloyl-5,6-dihydrouridine (4d) — The following amounts of reagents and 939 mg (2.84 mmol) of 2 were used: 7.10 mmol of LDA in THF (15 ml), 0.69 ml (5.68 mmol) of freshly distilled $(CH_3)_3CCOCl$. After adding the electrophile, the reaction was continued for 1 h. Chromatographic purification on a silica gel column (1% EtOH in $CHCl_3$) gave 4d (1.11 g, 94.4%). MS m/z: 415 (M+1), 399 (M-Me). PMR ($CDCl_3$) δ: 1.21 (9H, s, Me_3CCO), 1.36 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 3.35 (3H, s, CH_2OCH_3), 3.40~3.88 (4H, m, H-6 and CH_2-5'), 4.11~4.27 (2H, m, H-5 and H-4'), 4.61 (2H, s, CH_2OCH_3), 4.64~4.82 (2H, m, H-2' and H-3'), 5.66 and 5.79 (1H, each as d, H-1'), 8.15 (1H, br, NH).

5-Ethoxycarbonyl-2',3'-O-isopropylidene-5'-O-methoxymethyl-5,6-dihydrouridine (4e) — The following amounts of reagents and 1.0 g (3.03 mmol) of 2 were used: 7.58 mmol of LDA in THF (15 ml), 0.58 ml (6.06 mmol) of freshly distilled $ClCO_2Et$. After adding the electrophile, the reaction was continued for 1 h. Chromatographic purification on a silica gel column (1% EtOH in $CHCl_3$) gave 4e (980 mg, 80.5%). MS m/z: 403 (M+1), 402 (M^+), 387 (M-Me). PMR ($CDCl_3$) δ: 1.29 and 1.31 (3H, each as t, $COOCH_2CH_3$), 1.35 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 3.37 (3H, s, CH_2OCH_3), 3.48~3.92 (5H, m, H-5, H-6 and CH_2-5'), 4.12~4.39 (3H, m, H-4' and $CO_2CH_2CH_3$), 4.65 (2H, s, CH_2OCH_3), 4.69~4.85 (2H, m, H-2' and H-3'), 5.65 and 5.89 (1H, each as d, H-1'), 8.08 (1H, br, NH).

5-Benzoyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (5a) — PhSeCl-pyridine complex (1.29 mmol), prepared from 247 mg of PhSeCl and 104 μl of pyridine, in CH_2Cl_2 (7 ml) was cooled to 0°. After 15 min, 4a (510 mg, 1.17 mmol) in CH_2Cl_2 (7 ml) was added to the above solution and the mixture was stirred for 24 h. The reaction mixture was evaporated and coevaporated with EtOH to remove the last trace of pyridine. The residue was dissolved in CH_2Cl_2 (10 ml) and cooled back to 0°, at which time 0.2 ml of 30% H_2O_2 was added. After 2 h, the organic layer was separated, washed with aqueous $NaHCO_3$, dried (Na_2SO_4) and chromatographed on a silica gel column (1% EtOH in $CHCl_3$) to give 5a (456 mg, 89.7%). MS m/z: 433 (M+1), 417 (M-Me). PMR ($CDCl_3$) δ: 1.38 (3H, s, isop.Me), 1.61 (3H, s, isop.Me), 3.28 (3H, s, CH_2OCH_3), 3.70~3.80 (2H, m, CH_2-5'), 4.50~4.55 (1H, m, H-4'), 4.55 (2H, s, CH_2OCH_3), 4.77~4.89 (2H, m, H-2' and H-3'), 6.04 (1H, d, H-1'), 7.34~7.60 (3H, m, Ph), 7.69~7.81 (2H, m, Ph), 8.39 (1H, s, H-6), 8.61 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-propionyluridine (5b) — PhSeCl-pyridine complex (1.18 mmol) in CH_2Cl_2 (10 ml), 4b (412 mg, 1.07 mmol) in CH_2Cl_2 (7 ml) and 0.2 ml of 30% H_2O_2 were used. Phenylselenation and oxidation were continued for 24 h and for 2 h, respectively. Chromatographic purification on a silica gel column ($CHCl_3$) gave 5b (340 mg, 82.7%). MS m/z: 384 (M^+), 369 (M-Me). PMR ($CDCl_3$) δ: 1.11 (3H, t, $COCH_2CH_3$), 1.37 (3H, s, isop.Me), 1.60 (3H, s, isop.Me), 3.02 (2H, q, $COCH_2CH_3$), 3.36 (3H, s, CH_2OCH_3), 3.70~3.86 (2H, m, CH_2-5'), 4.44~4.60 (1H, m, H-4'), 4.70 (2H, s, CH_2OCH_3), 4.78~4.90 (2H, m, H-2' and H-3'), 5.99 (1H, d, H-1'), 8.63 (1H, s, H-6), 8.76 (1H, br, NH).

5-Isobutyryl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (5c) — PhSeCl-pyridine complex (0.83 mmol) in CH_2Cl_2 (15 ml), 4c (300 mg, 0.75 mmol) in CH_2Cl_2 (6 ml) and 0.2 ml of 30% H_2O_2 were used. Phenylselenation and oxidation were continued overnight and for 1 h, respectively. Chromatographic purification on a silica gel column (2% EtOH in $CHCl_3$) gave 5c (263 mg, 88.0%). MS m/z: 398 (M^+), 383 (M-Me). PMR ($CDCl_3$) δ: 1.11 (6H, d, $COCHMe_2$), 1.37 (3H, s, isop.Me), 1.60 (3H, s, isop.Me), 3.35 (3H, s, CH_2OCH_3), 3.62~3.90 (3H, m, $COCHMe_2$), 4.48~4.52 (1H, m, H-4'), 4.64 and 4.72 (2H, each as d, CH_2OCH_3), 4.82~4.89 (2H, m, H-2' and H-3'), 5.98 (1H, d, H-1'), 8.60 (1H, s, H-6), 8.77 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-pivaloyluridine (5d) — PhSeCl-pyridine complex (1.12 mmol) in CH_2Cl_2 (20 ml), 4d (424 mg, 1.02 mmol) in CH_2Cl_2 (7 ml) and 0.2 ml of 30% H_2O_2 were used. Phenylselenation was conducted at 60~70° for 24 h. Oxidation was continued for 1 h. Chromatographic purification on a silica gel column ($CHCl_3$) gave 5d (271 mg, 64.4%). MS m/z: 413 (M+1), 397 (M-Me). PMR ($CDCl_3$) δ: 1.28 (9H, s, $COCMe_3$), 1.37 (3H, s, isop.Me), 1.60 (3H, s, isop.Me), 3.36 (3H, s, CH_2OCH_3), 3.78 (2H, d, CH_2-5'), 4.42~4.50 (1H, m, H-4'), 4.61 and 4.69 (2H, each as d, CH_2OCH_3), 4.80~4.82 (2H, m, H-2' and H-3'), 5.94 (1H, d, H-1'), 8.10 (1H, s, H-6), 8.53 (1H, br, NH).

5-Ethoxycarbonyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (5e)—— PhSeCl-pyridine complex (1.42 mmol) in CH_2Cl_2 (25 ml), 4e (520 mg, 1.29 mmol) in CH_2Cl_2 (8 ml) and 0.2 ml of 30% H_2O_2 were used. Phenylselenation and oxidation were continued overnight and 1 h, respectively. Chromatographic purification on a silica gel column (3% EtOH in $CHCl_3$) gave 5e (512 mg, 99.2%). MS m/z: 401 (M+1), 385 (M-Me). PMR ($CDCl_3$) δ: 1.35 (3H, t, $CO_2CH_2CH_3$), 1.37 (3H, s, isop.Me), 1.60 (3H, s, isop.Me), 3.36 (3H, s, CH_2OCH_3), 3.79 (2H, d, CH_2-5'), 4.33 (2H, q, $CO_2CH_2CH_3$), 4.48~4.54 (1H, m, H-4'), 4.67 (2H, s, CH_2OCH_3), 4.82 (2H, m, H-2' and H-3'), 5.93 (1H, s, H-1'), 8.59 (1H, s, H-6), 8.76 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-methyl-5,6-dihydrouridine (6)—— Compound 2 (707 mg, 2.14 mmol) in THF (10 ml) was treated with LDA (5.35 mmol) in THF (10 ml) below -70° for 1 h. Freshly distilled MeI (0.27 ml, 4.28 mmol) was added to the above solution and the reaction mixture was stirred for 1.5 h. Chromatographic purification on a silica gel column (1% EtOH in $CHCl_3$) gave 6 (644 mg, 87.4%). MS m/z: 344 (M^+), 329 (M-Me). PMR ($CDCl_3$) δ: 1.22 and 1.29(3H, each as d, 5-Me), 1.35 (3H, s, isop.Me), 1.57 (3H, s, isop.Me), 2.72 and 3.24 (2H, each as m, H-6), 3.37 (3H, s, CH_2OCH_3), 3.50 (1H, m, H-5), 3.71 (2H, m, CH_2-5'), 4.18 (1H, m, H-4'), 4.65 (2H, s, CH_2OCH_3), 4.75 (2H, m, H-2' and H-3'), 5.68 and 5.77 (1H, each as d, H-1'), 7.77 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-phenylselenenyl-5,6-dihydrouridine (8)—— Compound 2 (1.06 g, 3.20 mmol) in THF (17 ml) was treated with LDA (11.2 mmol) in THF (15 ml) below -70° for 1 h. PhSeCl (1.84 g, 9.60 mmol) in THF (10 ml) was added to the solution and the mixture was stirred for 2 h below -70°. The reaction mixture was further treated with butyllithium (3.20 mmol) in hexane and kept below -70° for 1.5 h. After being quenched with AcOH, the mixture was evaporated. The whole residue was chromatographed on a silica gel column (1% EtOH in $CHCl_3$) to give 8 (1.10 g, 71.0%) and 9 (53 mg, 2.6%).

PMR data ($CDCl_3$) of 8 are as follows. δ: 1.36 and 1.39 (3H, each as s, isop.Me), 1.66 (3H, s, isop.Me), 3.35 and 3.37 (3H, each as s, CH_2OCH_3), 3.44~3.78 (3H, m, H-5 and CH_2-5'), 3.87~4.05 (2H, m, H-6), 4.10~4.27 (1H, m, H-4'), 4.61 and 4.65 (2H, each as s, CH_2OCH_3), 4.58~4.86 (2H, m, H-2' and H-3'), 5.47 and 5.87 (1H, each as d, H-1'), 7.29~7.42 (3H, m, Ph), 7.53 (1H, br, NH), 7.60~7.72 (2H, m, Ph).

PMR data ($CDCl_3$) of 9 are as follows. δ: 1.35 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 3.35 (3H, s, CH_2OCH_3), 3.42 and 3.79 (2H, each as d, H-6), 3.60 (2H, d, CH_2-5'), 4.06~4.20 (1H, m,H-4'), 4.52~4.76 (2H, m, H-2' and H-3'), 4.61 (2H, s, CH_2OCH_3), 5.36 (1H, d, H-1'), 7.28~7.45 (6H, m, Ph), 7.65~7.76 (4H, m, Ph).

Preparation of 2',3'-O-isopropylidene-5'-O-methoxymethyl-5-methyluridine (11) from 8 via its 5-methyl-5-phenylselenenyl intermediate (7)—— Compound 8 (931 mg, 1.92 mmol) in THF (15 ml) was lithiated with LDA (4.80 mmol) in THF (12 ml) below -70° for 1 h. Freshly distilled MeI (0.24 ml, 3.84 mmol) was added to the above solution and the reaction mixture was stirred below -70° for 3 h. An additional 0.24 ml of MeI was then added and stirring was continued for another 1 h. After being quenched with AcOH, the reaction mixture was evaporated. The residue was chromatographed on a silica gel column ($CHCl_3$) to give 7 (836 mg, 87.0%). The intermediate (7, 836 mg) was oxidized by 30% H_2O_2 (0.4 ml) in CH_2Cl_2 (20 ml) for 2 h. Chromatographic purification on a silica gel column (2% EtOH in $CHCl_3$) gave 11 (542 mg, 94.5% from 7). MS m/z: 342 (M^+), 327 (M-Me). PMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.59 (3H, s, isop.Me), 1.91 (3H, d, 5-Me), 3.38 (3H, s, CH_2OCH_3), 3.75~3.80 (2H, m, CH_2-5'), 4.28~4.39 (1H, m, H-4'), 4.68 (2H, s, CH_2OCH_3), 4.82 (2H, m, H-2' and H-3'), 5.85 (1H, d, H-1'), 7.29 (1H, d, H-6), 8.69 (1H, br, NH).

Preparation of 5-allyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (12a) from 8 via its 5-allyl-5-phenylselenenyl intermediate (10a)—— Compound 8 (976 mg, 2.01 mmol) in THF (12 ml) was lithiated with LDA (5.03 mmol) in THF (10 ml). After addition of freshly distilled allyl bromide (2.8 ml, 32.4 mmol), the reaction mixture was kept below -70° overnight. Chromatographic purification on a silica gel column (benzene:AcOEt = 2:1) gave 10a (732 mg, 69.2%). The intermediate (10a, 732 mg) was oxidized by 30% H_2O_2 (0.4 ml) in CH_2Cl_2 (15 ml) for 4 h. Column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 12a (495 mg, 96.5% from 10a). MS m/z: 368 (M^+), 353 (M-Me). PMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.59 (3H, s, isop.Me), 3.08 (2H, dd, CH_2CH=CH_2), 3.37 (3H, s, CH_2OCH_3), 3.77 (2H, d, CH_2-5'), 4.28~4.40 (1H, m, H-4'), 4.66 (2H, s, CH_2OCH_3), 4.73~4.93 (2H, m, H-2' and H-3'), 5.02~5.08 and 5.18~5.22 (2H, m, CH_2CH=CH_2), 5.65~6.05 (1H, m, CH_2CH=CH_2), 5.82 (1H, d, H-1'), 7.21 (1H, s, H-6), 8.74 (1H, br, NH).

Preparation of 5-benzyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (12b) from 8 via its 5-benzyl-5-phenylselenenyl intermediate (10b)—— Compound 8 (954 mg, 1.97 mmol) in THF (12 ml) was lithiated with LDA (4.93 mmol) in THF (10 ml). After addition of freshly distilled benzyl bromide (3.75 ml, 31.5 mmol), the reaction mixture was kept below -70° overnight. Chromatographic purification on a silica gel column (benzene:AcOEt = 10:1) gave 10b

(810 mg, 71.6%). The intermediate (10b, 700 mg) was oxidized by 30% H_2O_2 (0.3 ml) in CH_2Cl_2 (15 ml) for 3 h. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 12b (494 mg, 97.0% from 10b). MS m/z: 418 (M^+), 403 (M-Me). PMR ($CDCl_3$) δ: 1.34 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 3.32 (3H, s, CH_2OCH_3), 3.64 (2H, s, CH_2Ph), 3.66 (2H, d, CH_2-5'), 4.16~4.35 (1H, m, H-4'), 4.53 (2H, s, CH_2OCH_3), 4.67~4.94 (2H, m, H-2' and H-3'), 5.68 (1H, d, H-1'), 6.99 (1H, s, H-6), 7.19~7.49 (5H, m, Ph), 8.46 (1H, br, NH).

Preparation of 2',3'-O-isopropylidene-5-methoxycarbonylmethyl-5'-O-methoxymethyluridine (12c) from 8 via its 5-methoxycarbonylmethyl-5-phenylselenenyl intermediate (10c)—— Compound 8 (1.29 g, 2.66 mmol) in THF (17 ml) was lithiated with LDA (6.65 mmol) in THF (15 ml). After addition of freshly distilled methyl bromoacetate (0.5 ml, 5.32 mmol), the reaction mixture was kept below -70° for 2 h. Chromatographic purification on a silica gel column ($CHCl_3$) gave 10c (1.17 g, 79.3%). The intermediate (10c, 1.17 g) was oxidized by 30% H_2O_2 (0.4 ml) in CH_2Cl_2 (20 ml) for 2 h. Short column chromatography on silica gel (1% EtOH in $CHCl_3$) gave 12c (765 mg, 91.0% from 10c). MS m/z: 400 (M^+), 385 (M-Me), 184 (B+1). PMR ($CDCl_3$) δ: 1.36 (3H, s, isop.Me), 1.58 (3H, s, isop.Me), 3.37 (3H, s, CH_2OCH_3), 3.74 (2H, d, CH_2-5'), 3.80 (3H, s, CO_2Me), 4.16~4.29 (1H, m, H-4'), 4.69 (2H, s, CH_2OCH_3), 4.69~4.79 (1H, m, H-3'), 4.78 (2H, d, CH_2CO_2Me), 4.89 (1H, dd, H-2'), 5.81 (1H, d, H-1'), 6.99 (1H, t, H-6), 8.01 (1H, br, NH).

5-Benzoyluridine (13)—— Compound 5a (360 mg) in 50% aqueous CF_3CO_2H (8 ml) was stirred at room temperature for 3 days. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 13 (245 mg, 84.3%) which was crystallized from EtOH (mp 210~211°C). Anal. Calcd. for $C_{16}H_{14}N_2O_7$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.23; H, 4.63; N, 7.85. UV absorption in MeOH: max 283 nm (ε 15200) and 251 nm (ε 12400), min 264 nm (ε 11500) and 225 nm (ε 6500). PMR (D_2O) δ: 3.49~3.84 (2H, m, CH_2-5'), 4.10~4.14 (2H, m, H-3' and H-4'), 4.32~4.36 (1H, m, H-2'), 5.93 (1H, d, J= 2.9 Hz, H-1'), 7.45~7.79 (5H, m, Ph), 8.52 (1H, s, H-6).

5-Propionyluridine (14)—— Compound 5b (204 mg) in 50% aqueous CF_3CO_2H (5 ml) was stirred at room temperature for 19 h. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 14 (131 mg, 83.0%) which was crystallized from EtOH (mp 180~181°C). Anal. Calcd. for $C_{12}H_{14}N_2O_7$: C, 48.00; H, 5.37; N, 9.33. Found: C, 47.85; H, 5.41; N, 9.16. UV absorption in MeOH: max 283 nm (ε 12000) and 225 nm (ε 9800), min 247 nm (ε 1700). PMR (D_2O) δ: 1.06 (3H, t, $COCH_2CH_3$), 2.93 (2H, q, $COCH_2CH_3$), 3.88~3.97 (2H, m, CH_2-5'), 4.08~4.39 (3H, m, H-2', H-3' and H-4'), 5.91 (1H, d, J= 2.4 Hz, H-1'), 8.88 (1H, s, H-6).

An alternative method for the preparation of 14 has been reported: ref. 18.

5-Isobutyryluridine (15)—— Compound 5c (253 mg) in 50% aqueous CF_3CO_2H (5 ml) was stirred at room temperature for 2 days. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 15 (183 mg, 90.6%) which was crystallized from AcOEt (mp 168~169°C). Anal. Calcd. for $C_{13}H_{18}N_2O_7$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.40; H, 5.82; N, 8.70. UV absorption in MeOH: max 283 nm (ε 11700) and 226 nm (ε 9100), min 249 nm (ε 1900). PMR (D_2O) δ: 1.09 (6H, d, $COCHMe_2$), 3.43~3.71 (1H, m, $COCHMe_2$), 3.74~3.97 (2H, m, CH_2-5'), 4.09~4.35 (3H, m, H-2', H-3' and H-4'), 5.92 (1H, d, J= 2.0 Hz, H-1'), 8.86 (1H, s, H-6).

5-Pivaloyluridine (16)—— Compound 5d (217 mg) in 50% aqueous CF_3CO_2H (5 ml) was stirred at room temperature for 2 days. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 16 (142 mg, 82.3%) which was crystallized from EtOH-hexane (mp 129~130°C). Anal. Calcd. for $C_{14}H_{20}N_2O_7 \cdot 1/3H_2O$: C, 50.30; H, 6.23; N, 8.38. Found: C, 50.28; H, 6.25; N, 8.40. UV absorption in MeOH: max 273 nm (ε 10700), min 245 nm (ε 4900). PMR (D_2O) δ: 1.22 (9H, s, $COCMe_3$), 3.70~4.03 (2H, m, CH_2-5'), 4.08~4.37 (3H, m, H-2', H-3' and H-4'), 5.91 (1H, d, J= 3.4 Hz, H-1'), 8.22 (1H, s, H-6).

5-Ethoxycarbonyluridine (17)—— Compound 5e (490 mg) in 50% aqueous CF_3CO_2H (10 ml) was stirred at room temperature for 16 h. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 17 (359 mg, 93.4%) which was crystallized from EtOH (mp 205~206°C). Anal. Calcd. for $C_{12}H_{16}N_2O_8$: C, 45.57; H, 5.10; N, 8.86. Found: C, 45.49; H, 5.21; N, 8.90. UV absorption in MeOH: max 276 nm (ε 13200), min 239 nm (ε 1700). PMR (D_2O) δ: 1.31 (3H, t, $CO_2CH_2CH_3$), 3.87~3.98 (2H, m, CH_2-5'), 4.09~4.41 (4H, m, H-3', H-4' and $CO_2CH_2CH_3$), 4.78 (1H, m, H-2'), 5.91 (1H, d, J= 2.0 Hz, H-1'), 9.00 (1H, s, H-6).

An alternative method for the preparation of 17 has been reported: ref. 19.

5-Methyluridine (18)—— Compound 11 (180 mg) in 50% aqueous CF_3CO_2H (5 ml) was stirred at room temperature for 19 h. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 18 (120 mg, 87.0%) which was crystallized from acetone (mp 181~182°C). Anal. Calcd. for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.63; H, 5.50; N, 10.69. UV absorption in MeOH: max 267 nm (ε 9500), min 234 nm (ε 2000). PMR (D_2O) δ: 1.88 (3H, d, 5-Me), 3.81~3.88 (2H, m, CH_2-5'), 3.98~4.39 (3H, m, H-2', H-3' and H-4'), 5.90 (1H, d, J= 4.4 Hz, H-1'), 7.68 (1H, d, H-6).

An alternative method for the preparation of 18 has been reported: ref. 20.

5-Allyluridine (19)—— Compound 12a (110 mg) in 50% aqueous CF_3CO_2H (3 ml) was stirred at room temperature for 15 h. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 19 (69 mg, 80.0%) which was crystallized from acetone (mp 169~171°C). Other physical data of 19: see ref. 21.

5-Benzyluridine (20)—— Compound 12b (468 mg) in 50% aqueous CF_3CO_2H (10 ml) was stirred at room temperature for 21 h. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 20 (303 mg, 81.0%) which was crystallized from EtOH (mp 188~190°C). Anal. Calcd. for $C_{16}H_{16}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.31; H, 5.35; N, 8.43. UV absorption in MeOH: max 267 nm (ε 9900), min 237 nm (ε 2700). PMR (D_2O) δ: 3.65 (2H, s, CH_2Ph), 3.54~3.89 (2H, m, CH_2-5'), 4.07~4.24 (3H, m, H-2', H-3' and H-4'), 5.88 (1H, d, J= 3.9 Hz, H-1'), 7.54 (1H, s, H-6).

5-Methoxycarbonylmethyluridine (21) and 5-carbamylmethyluridine (22)—— Compound 12c (496 mg) in 50% aqueous CF_3CO_2H (10 ml) was stirred at room temperature for 22 h. Short column chromatography on silica gel (5% EtOH in $CHCl_3$) gave 21 (219 mg, 55.8%) which was slightly impure. UV absorption in MeOH: max 265 nm, min 236 nm. PMR (DMSO-d_6) δ: 3.51~4.02 (8H, m, H-2', H-3', H-4', CH_2-5', 2'-OH, 3'-OH and 5'-OH), 3.75 (3H, s, CH_2CO_2Me), 4.58 (2H, d, CH_2CO_2Me), 5.77 (1H, d, J= 5.4 Hz, H-1'), 6.70 (1H, t, H-6), 10.89 (1H, br, NH).

Compound 21 (185 mg) was dissolved in 28% aqueous NH_4OH (7 ml) and the mixture was stirred at room temperature overnight. The solvent was evaporated and the solid residue was washed with MeOH to give 22 (109 mg, 61.6%). Recrystallization from MeOH-H_2O gave crystals of 22 (mp 228~230°C). Anal. Calcd. for $C_{11}H_{15}N_3O_7$: C, 43.85; H, 5.02; N, 13.95. Found: C, 44.10; H, 5.07; N, 13.68. UV absorption in H_2O: max 267 nm (ε 8800), min 233 nm (ε 500). PMR (D_2O) δ: 3.33 (2H, s, CH_2CONH_2), 3.86 (2H, m, CH_2-5'), 4.00~4.40 (3H, m, H-2', H-3' and H-4'), 5.92 (1H, d, J= 3.9 Hz, H-1'), 7.86 (1H, s, H-6).

An alternative method for the preparation of 21 and 22 has been reported: ref. 22.

REFERENCES AND NOTES

1) P. Beak and V. Sniekus, Acc. Chem. Res., 15, 306 (1982).

2) H. Tanaka, H. Hayakawa and T. Miyasaka, Tetrahedron, 38, 2635 (1982).

3) An application of our method has been reported: H. Ikehira, T. Matsuura and I. Saito, Tetrahedron Lett., 25, 3325 (1984).

4) A part of this study has been published as a communication: H. Hayakawa, H. Tanaka and T. Miyasaka, Chem. Pharm. Bull., 30, 4589 (1982).

5) Several methods so far available for the conversion of uridine to 5-substituted uridines, except those cited as ref. 18 and 21, are given below: K. H. Scheit, Chem. Ber., 99, 3884 (1966); E. I. Budowsky, V. N. Shibaev and G. I. Elisceva, "Synthetic Procedures in Nucleic Acids Chemistry", Vol. 1, ed. by W. W. Zorbach and R. S. Tipson, John Wiley and Sons, Inc., New York, London, Sydney and Toronto, 1968, pp.436~438; D. E. Bergstrom and M. K. Ogawa, J. Am. Chem. Soc., 100, 8106 (1978); H. Inoue and T. Ueda, Chem. Pharm. Bull., 26, 2657 (1978); K. Hirota, M. Suematsu, Y. Kuwabara, T. Asao and S. Senda, Chem. Commun., 1981, 623.

6) H. W. Gschwend and H. R. Rodriguez, "Organic Reactions", Vol. 26, ed. by W. G. Dauben, John Wiley and Sons, Inc., New York, Chichester, Brisbane and Toronto, 1979, pp. 1~360.

7) L. Pichat, J. Godbillon and M. Herbert, Bull. Soc. Chim. Fr., 1973, 2715.

8) As an example of N,α-dianion of lactams: J-P. Deprès, A. E. Greene and P. Crabbé, Tetrahedron Lett., 1978, 2191.

9) W. E. Cohn and D. G. Doherty, J. Am. Chem. Soc., 78, 2863 (1956).

10) D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer and H. S. Kezar, III, J. Org. Chem., 46, 2920 (1981).

11) Alkylation at the C-5 of 1,3-disubstituted 5,6-dihydrouracils has been reported: S. J. Hannon, N. G. Kundu, R. P. Hertzberg, R. S. Bhatt and C. Heidelberger, Tetrahedron Lett., 21, 1105 (1980).

12) D. Seebach and N. Peleties, Angew. Chem., 81, 465 (1969); idem, Chem. Ber., 105, 511 (1972).

13) The cleavage of selenoacetals and selenoketals with butyllithium has been reported: W. Dumont, P. Bayet and A. Krief, Angew. Chem. Int. Ed. Engl., 13, 804 (1974).

14) Lithium dialkylamides are known to be the preferred bases for deprotonation of selenides: H. J. Reich and S. K. Shah, J. Am. Chem. Soc., 97, 3250 (1975).

15) K. B. Sharpless, R. F. Lauer and A. Y. Teranishi, J. Am. Chem. Soc., 95, 6137 (1973).

16) Compounds 18, 21 and 22 are modified nucleosides in transfer RNA.

17) As a recent example of the synthesis of a C-5 modified uridine found in trasfer RNA: T. Kondo, T. Fukami, T. Goto, M. Kawakami and S. Takemura, Nucleic Acids Symposium Series, 12,

127 (1983).

18) H. Inoue, M. Takada, M. Takahashi and T. Ueda, Heterocycles, 8, 427 (1977).

19) A. Holý, Collect. Czech. Chem., Commun., 37, 1555 (1972).

20) J. J. Fox, N. Yung, J. Davoll and G. B. Brown, J. Am. Chem. Soc., 78, 2117 (1956).

21) J. L. Ruth and D. E. Bergstrom, J. Org. Chem., 43, 2870 (1978).

22) J. D. Fissekis and F. Sweet, Biochemistry, 9, 3136 (1970).