Tetrahedron Vol. 42, No. 15, pp. 4187 to 4195, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

SYNTHETIC ROUTE TO 5-SUBSTITUTED URIDINES VIA A NEW TYPE OF DESULFURIZATIVE STANNYLATION[1)]

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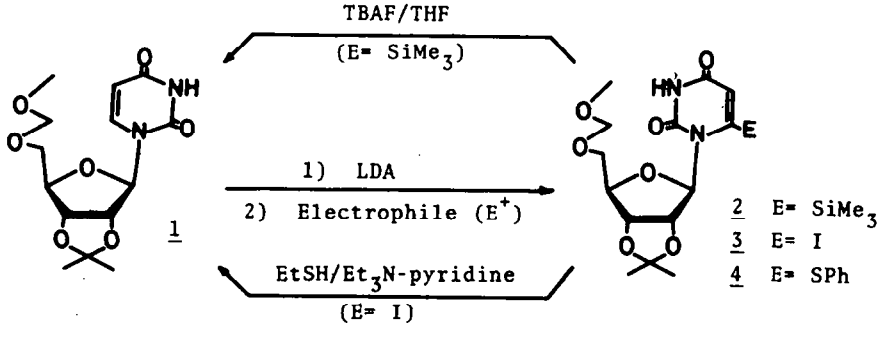
(*Received in Japan* 30 *April* 1986)

Abstract – phenylthio group at the C-6 position of uridine serves as the protecting group during lithiation at the C-5 position with lithium 2,2,6,6-tetramethylpiperidide. Reactions of the resulting C-5 lithiated species with various types of electrophiles furnish 5-substituted 6-phenylthiouridine derivatives. The phenylthio group in these products can be removed by a new type of desulfurizative stannylation with tributyltin hydride followed by protonolysis. The whole sequence constitutes a new route to 5-substituted uridines. Application of this method to 2'-deoxyuridine is also described.

In an earlier paper,[2)] we demonstrated the usefulness of 2',3'-O-isopropylidene-5'-O-methoxymethyluridine (1) for the synthesis of various types of 6-substituted uridines. During the course of this work, it occurred to us that some of these 6-substituted uridine derivatives, such as 2,[3)] 3,[4)] and 4,[2)] might serve as precursors for the preparation of 5-substituted uridines if their C-5 positions could be lithiated to a practical extent, and if appropriate conditions could be found which permit removal of the C-6 substituent.[5)]

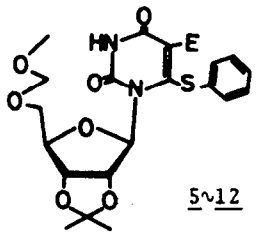


Although the trimethylsilyl group in the C-6 position of 2 was removed by treatment with tetrabutylammonium fluoride (TBAF) in THF, no appreciable deuterium incorporation at the C-5 position was observed upon lithiation of 2 with lithium diisopropylamide (LDA), butyllithium (BuLi), or lithium 2,2,6,6-tetramethylpiperidide (LTMP) followed by deuteration. Despite its successful deiodination with EtSH in Et_3N-pyridine, results of lithiation of 3 with several lithiating agents were also discouraging mainly due to its susceptibility to halogen-lithium exchange reaction. It should be noted that, in the case of 3, halogen-metal exchange was observed to the extent of 49% even by the use of LDA (3 equiv) which had been effective for the C-6 lithiation of 5-iodo-2',3'-O-isopropylidene-5'-O-methoxymethyluridine.[6)]

In contrast to the above two cases, lithiation of the 6-phenylthiouridine derivative (4) with LTMP, which is non-nucleophilic and a more basic lithiating agent[7] than LDA,[8] appeared to meet our requirement.

Compound 4 was metallated with 3 equiv of LTMP at below -70 °C for 1 h and then quenched with CD_3OD. After short-column chromatography on silica gel, the dueterated product was isolated (recovery: 95%). Its PMR spectrum in $CDCl_3$ showed no appreciable signal corresponding to H-5 of 4 (δ 4.93 ppm), indicating that the C-5 position was lithiated in an essentially quantitative yield.

In Table 1 are summarized the results of reactions of the C-5 lithiated species of 4 with various types of electrophiles.



5∿12

Table 1. Synthesis of compounds 5∿12

Electrophile	E	Product	Yield (%)*
CD_3OD	D	5	100†
MeI	Me	6	81
EtI	Et	7	30
BuI	Bu	8	13
$ClCO_2Et$	CO_2Et	9	86
ClCOPh	COPh	10	92
$ClSiMe_3$	$SiMe_3$	11	91
PhSSPh	SPh	12	94

* yields of isolated products
† D-incorporation calculated by PMR

These reactions were carried out for a couple of hours below -70 °C after addition of the corresponding electrophile. In the cases of EtI and BuI, however, prolonged reaction time (19∿21 h) was necessary due to their poor electrophilicity at low temperature.

Table 2. Isopropylidene Me chemical shifts

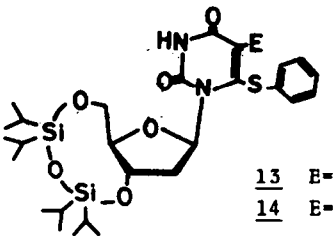
Compd.	Chemical shifts δ (ppm) of isop. Me	
	Endo-Me	Exo-Me
1	1.59	1.36
4	1.58	1.35
6	1.46	1.23
7	1.40	1.18
8	1.40	1.17
9	1.45	1.19
10	1.43	1.19
11	1.34	1.10
12	1.43	1.18

Chemical shifts of the endo and exo methyl signals of the isopropylidene group in the 5-substituted 6-phenylthiouridine derivatives (6∿12) were measured in $CDCl_3$ and are listed in Table 2, together with those of 1 and 4.

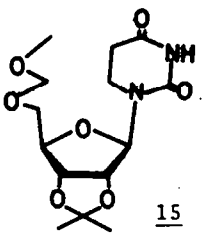
As we have already reported, the phenyl ring of 6-phenylthio group in 4 lies perpendicular to the uracil ring.[9] This contention is supported by the observation that its δ values of the endo and exo methyl signals are not affected by the ring current effect.[10] On the other hand, introduction of a substituent into the C-5 position of 4 caused shielding of both signals by ca. 0.1∿0.2 ppm. This would be due to the conformational change of the 6-phenylthio group and the more bulky group such as the trimethylsilyl in the C-5 position is likely to exert the greater influence on both signals.

This method of C-5 functionalization is, of course, applicable to 2'-deoxyuridine. Thus, 6-phenylthio-3',5'-O-(tetraisopropyldisiloxan-1,3-diyl)-2'-deoxyuridine (13) prepared via our previously reported route[11] was subjected to the LTMP lithiation followed by methylation with MeI to furnish 14 in 66% yield.

We next searched for an efficient method for removing the phenylthio group. Although aluminum amalgam has been used to remove a phenylthio group,[12] treatment of 4 with Al-Hg[13] in 3% aqueous EtOH gave a mixture of 1 and its 5,6-dihydrogen-



13 E= H
14 E= Me

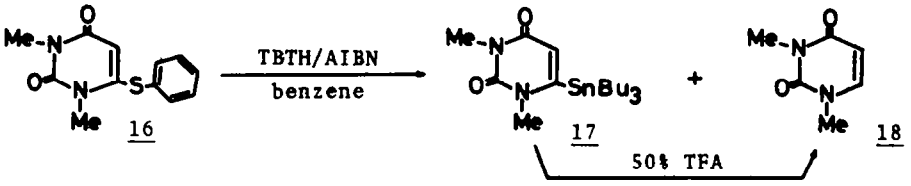


15

ated product (15).[5] Especially in the reaction of 9, no UV-absorbing spot was detected even immediately after the Al-Hg treatment. Use of Raney nickel also failed, resulting in either recovery of the starting material or decrease in UV absorption depending on the conditions used.

We found that tributyltin hydride (TBTH) was a superior reagent for removing the phenylthio group in this system.[14]

When a benzene solution of 6-phenylthio-1,3-dimethyluracil (16),[15] a model compound, was treated with 5 equiv of TBTH in the presence of α,α'-azobisisobutyronitrile (AIBN), the starting material disappeared after refluxing for 8 h. The PMR spectrum of the main product isolated by preparative TLC on basic alumina showed the presence of three butyl groups (δ 0.90, 9H, t, $CH_2CH_2CH_2\underline{Me}$; δ 1.80∿1.56, 18H, m, $\underline{CH_2}\,\underline{CH_2}\,\underline{CH_2}Me$) and H-5 (δ 5.77, 1H, s). The MS spectrum of this product (M-1 m/z:429,

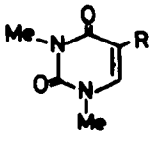


16 17 18

427, and 425; M-Bu m/z: 373, 371, and 369) was characteristic of an organotin compound, giving a cluster of isotope peaks corresponding to Sn.[16] These data are best accommodated by structure 17. The yield of 6-tributylstannyl-1,3-dimethyluracil (17) was 97%. 1,3-Dimethyluracil (18) was also obtained in 2% yield in this reaction.

During the isolation of these products, we noticed that the isolated yield of 18 increased when silica gel was used as an adsorbent. This suggests that 17 might be susceptible to protonolysis, though only tributylstannyl group alpha to carbonyl or at allylic position has been reported to be removable by acidic treatment.[17,18] Compound 17 which is quite stable in AcOH (at room temperature for 24 h) proved to undergo the expected protonolysis of the 6-tributylstannyl group upon treatment with 50% aqueous trifluoroacetic acid (TFA) to furnish 18 in 89% yield (at room temperature for 7 h).

We have also examined the desulfurizative stannylation and successive protonolysis in the case of 5-phenylthio-1,3-dimethyluracil (19).[15] Compound 19 was allowed to react with 2 equiv of TBTH for 1 h to afford the corresponding 5-tributylstannylated product (20) in 96% yield. Compound 20 possesses even a higher propensity to undergo protonolysis. Thus, when 20 was treated with 50% TFA at room temperature, 18 was obtained in 92% yield within 10 min, while the treatment with AcOH gave 18 in 88% yield after 1 h.



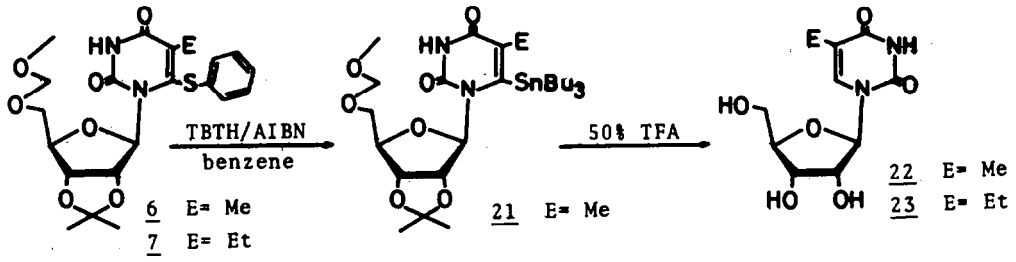
19 R= SPh
20 R= $SnBu_3$

Although Ueno and Okawara[19] have reported the reaction of 2-(allylthio)-1,3-benzothiazole with TBTH to yield an allyltin product, formation of a stannylated

product can be observed only in the TBTH reaction which proceeds through the S_H' mechanism.[20] This type of organotin-mediated direct desulfurizative substitution with a tributylstannyl radical is unprecedented to the best of our knowledge.[21]

The above mentioned results in hand, we then prepared 5-substituted uridines from the 6-phenylthiouridine derivatives (6~12).

When 6 was treated with 3 equiv of TBTH for 3 h, the corresponding 6-stannylated product 21 was obtained in 81% yield. In contrast to the case of 6-tributylstannylated 1,3-dimethyluracil (17), silica gel column chromatography can be used for the purification of 6-stannylated uridines. Subsequent treatment of 21 with

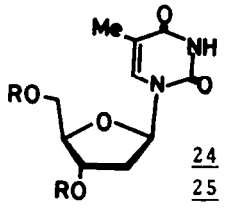


6 E= Me
7 E= Et

21 E= Me

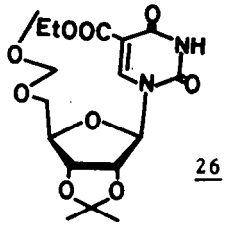
22 E= Me
23 E= Et

50% aqueous TFA effected concurrent removal of the 2',3'-O-isopropylidene, 5'-O-methoxymethyl, and 6-tributylstannyl groups to furnish 5-methyluridine (22).[5] The overall yield of 22 from 6 was 79%. Similarly, 5-ethyluridine (23)[22] was prepared in 82% yield from 7. The derivative of 5-methyl-6-phenylthio-2'-deoxyuridine (14) also followed this reaction sequence. Compound 14 was stannylated with 3 equiv of TBTH for 4 h and the reaction mixture was treated with 50% aqueous TFA in dioxane at room temperature for 4 h to remove, again, the tributylstannyl and 3',5'-O-tetraisopropyldisiloxan-1,3-diyl groups[23] simultaneously. The resulting thymidine (24) was isolated as its diacetate (25) in 58% yield from 14 after acetylation.



24 R= H
25 R= Ac

On the other hand, the reaction of TBTH with 5-ethoxycarbonyl derivative (9) gave a different result. When 9 was allowed to react with 2 equiv of TBTH, the starting material disappeared within 10 min and the product proved to be 5-ethoxycarbonyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (26: 91%)[5] instead of a 6-tributylstannyl derivative. At present, the formation of 26 from 9 is mechanistically unclear because a similar TBTH reaction with the 5-benzoyl derivative (10) resulted in an intractable mixture of products.



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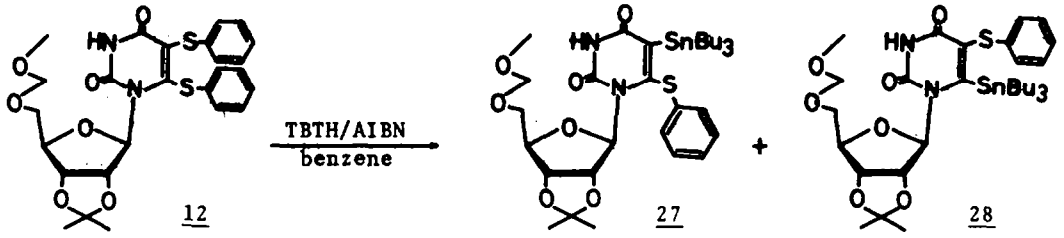
The TBTH reaction did not proceed with the 5-trimethylsilyl derivative (11), the starting material being recovered completely. This failure is probably ascribable to the bulkiness of the 5-trimethylsilyl group since, in a similar reaction of the 5,6-diphenylthiouridine derivative (12) described below, no trace of the 5,6-bis(tributylstannyl)uridine derivative formed.

Finally, the TBTH reaction of 12 was investigated from a viewpoint of a competitive stannylation between the 5- and 6-phenylthio groups.

After a reaction with 2 equiv of TBTH for 40 min, TLC analysis (benzene:EtOAc = 1:1) of the reaction mixture indicated two products. The MS spectra of both products showed fragment ion peaks at m/z 669, 667, and 665 attributable to a cluster of M-Bu ions from the mono-stannylated product.



12 27 28

For the structural elucidation of these products, the above stated PMR criterion for the 5-substituted 6-phenylthiouridine derivatives (Table 2) was useful: the faster moving product showed isopropylidene methyl signals at 1.33 and 1.11 ppm suggestive of the presence of a bulky substituent in the C-5 position, while the δ values of the slower moving one, 1.55 and 1.36 ppm, are indicative of the absence of a phenylthio group in the C-6 position. The former isolated in 40% yield was, therfore, identified as 6-phenylthio-5-tributylstannyluridine derivative 27 and the latter isolated in 22% yield was proved to be a 6-stannylated product (28). These structures were further confirmed by 50% aqueous TFA treatment which gave 6-phenylthiouridine[9] and 5-phenylthiouridine,[24] respectively.

The above result is consistent with those of the 1,3-dimethyluracil derivatives (16 and 19) and the 5-phenylthio group of the uracil moiety seems to be more susceptible to the TBTH-mediated desulfurizative stannylation.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. PMR spectra were measured with an internal standard of tetramethylsilane (TMS) with a JEOL JNM-FX 100 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 benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200). Preparative TLC was performed on basic alumina (precoated aluminum oxide plate 60 F_{254}, type E, Merck). Analytical TLC was carried out on silica gel (precoated silica gel 60 F_{254}, Merck).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-trimethylsilyluridine (2)—— This compound was prepared from 1 (681 mg, 2.1 mmol) in THF (12 ml) according to the published procedure: see reference 2. The following amounts of reagents were used: LDA (5.2 mmol) in THF (10 ml), $ClSiMe_3$ (0.53 ml, 4.2 mmol). The reaction was continued for 1.5 h at below -70 °C. Silica gel column chromatography (1% EtOH in $CHCl_3$) gave 2 (676 mg, 82%) as a syrup.

MS m/z: 400 (M^+), 385 (M-Me), 184 (B+1). UV absorption in MeOH: max 260 nm, min 230 nm. PMR ($CDCl_3$) δ: 0.42 (9H, s, $SiMe_3$), 1.35 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 3.78 (2H, m, CH_2-5'), 4.18~4.35 (1H, m, H-4'), 4.88 (1H, dd, H-3'), 5.22 (1H, dd, H-2'), 5.64 (1H, d, J= 1.5 Hz, H-1'), 5.84 (1H, d, H-5), 9.73 (1H, br, NH).

Desilylation of 2—— Compound 2 (70 mg, 0.18 mmol) in THF (3 ml) was treated with TBAF·$3H_2O$ (85 mg, 0.27 mmol) at room temperature for 30 min. The solvent was evaporated and the whole residue was chromatographed on a silica gel (1% EtOH in $CHCl_3$) column to give 1 (55 mg, 94%).

Deiodination of 3—— Compound 3 (99 mg, 0.22 mmol) was dissolved in Et_3N (2 ml) and pyridine (1 ml). To this was added EtSH (0.4 ml, 5.55 mmol) and the resulting solution was stirred for 15 min at room temperature. Evaporation of the solvents followed by chromatographic purification on a silica gel column (1% EtOH in $CHCl_3$) gave 1 (71 mg, 99%).

5-Deuterio-2',3'-O-isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (5) —— LTMP (1.50 mmol) prepared from 2,2,6,6-tetramethylpiperidine (0.25 ml) and butyllithium (1.50 mmol) in THF (5 ml) was placed in a three-necked flask fitted with a nitrogen inlet adapter, thermometer, and rubber septum. To this, a solution of 4 (218 mg, 0.5 mmol) in THF (5 ml) was added, under positive pressure of dry argon, at a rate such that the temperature did not exceed -70 °C. After the mixture was stirred for 1 h, CD_3OD (0.5 ml) was added, while maintaining the temperature below -70 °C. The mixture was stirred for 1 h below -70 °C, quenched with AcOH

(0.09 ml), and allowed to warm to room temperature. The whole was evaporated to dryness and the residue was chromatographed on a short column of silica gel (1% EtOH in $CHCl_3$) to give 5 (208 mg, recovery 95%).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-methyl-6-phenylthiouridine (6) —— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 873 mg (2.0 mmol) of 4 in THF (15 ml) were used: LTMP (6.0 mmol) in THF (15 ml), MeI (0.25 ml, 4.0 mmol). The reaction was continued for 2 h at below -70 °C. Silica gel column chromatography (benzene:EtOAc = 8:1) gave 6 (732 mg, 81%) as a foam.

Anal. Calcd. for $C_{21}H_{26}N_2O_7S$: C, 55.98; H, 5.82; N, 6.22. Found: C, 56.04; H, 6.04; N, 6.10. UV absorption in MeOH: max 275 nm (ε 9100) and 243 nm (ε 9800), min 258 nm (ε 7600) and 233 nm (ε 8800), shoulder 313 nm (ε 3600). MS m/z: 450 (M^+), 435 (M-Me), 234 (B+1), 217 (M-B). PMR ($CDCl_3$) δ: 1.23 (3H, s, isop.Me), 1.46 (3H, s, isop.Me), 2.14 (3H, s, 5-Me), 3.34 (3H, s, CH_2OCH_3), 3.72 (2H, m, CH_2-5'), 4.07∿4.25 (1H, m, H-4'), 4.63 (2H, s, CH_2OCH_3), 4.80 (1H, dd, H-3'), 5.00 (1H, dd, H-2'), 6.69 (1H, d, J= 1.5 Hz, H-1'), 7.18∿7.38 (5H, m, SPh), 9.29 (1H, br, NH).

5-Ethyl-2',3'-O-isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (7) —— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 873 mg (2.0 mmol) of 4 in THF (15 ml) were used: LTMP (6.0 mmol) in THF (15 ml), EtI (1.12 ml, 14.0 mmol). The reaction was continued for 21 h at below -70 °C. Silica gel column chromatography (benzene:EtOAc = 10:1) gave 7 (278 mg, 30%) as a foam.

Anal. Calcd. for $C_{22}H_{28}N_2O_7S$: C, 56.88; H, 6.07; N, 6.03. Found: C, 56.73; H, 6.17; N, 5.78. UV absorption in MeOH: max 276 nm (ε 9500) and 243 nm (ε 9700), min 257 nm (ε 7500) and 233 nm (ε 8700), shoulder 313 nm (ε 3700). MS m/z: 464 (M^+), 449 (M-Me), 248 (B+1), 217 (M-B). PMR ($CDCl_3$) δ: 1.04 (3H, t, CH_2Me), 1.18 (3H, s, isop.Me), 1.40 (3H, s, isop.Me), 2.73 (2H, q, CH_2Me), 3.34 (3H, s, CH_2OCH_3), 3.66∿3.74 (2H, m, CH_2-5'), 4.04∿4.20 (1H, m, H-4'), 4.63 (2H, s, CH_2OCH_3), 4.77 (1H, dd, H-3'), 4.87 (1H, dd, H-2'), 6.59 (1H, d, J= 1.5 Hz, H-1'), 7.24∿7.32 (5H, m, SPh), 8.59 (1H, br, NH).

5-Butyl-2',3'-O-isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (8) —— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 873 mg (2.0 mmol) of 4 in THF (15 ml) were used: LTMP (6.0 mmol) in THF (15 ml), BuI (1.6 ml, 14.0 mmol). The reaction was continued for 19 h at below -70 °C. Silica gel column chromatography (benzene:EtOAc = 10:1) gave 8 (129 mg, 13%) as a syrup.

Anal. Calcd. for $C_{24}H_{32}N_2O_7S$: C, 58.52; H, 6.55; N, 5.69. Found: C, 58.77; H, 6.65; N, 5.60. UV absorption in MeOH: max 276 nm (ε 9500) and 243 nm (ε 9400), min 257 nm (ε 7300) and 234 nm (ε 8700), shoulder 312 nm (ε 4000). MS m/z: 492 (M^+), 477 (M-Me), 276 (B+1), 217 (M-B). PMR ($CDCl_3$) δ: 0.88 (3H, t, $CH_2CH_2CH_2Me$), 1.17 (3H, s, isop.Me), 1.26∿1.34 (4H, m, $CH_2CH_2CH_2Me$), 1.40 (3H, s, isop.Me), 2.61∿2.77 (2H, br, $CH_2CH_2CH_2Me$), 3.33 (3H, s, CH_2OCH_3), 3.73 (2H, m, CH_2-5'), 4.04∿4.21 (1H, m, H-4'), 4.63 (2H, s, CH_2OCH_3), 4.71∿4.91 (2H, m, H-2' and H-3'), 6.59 (1H, d, J= 1.5 Hz, H-1'), 7.22∿7.32 (5H, m, SPh).

5-Ethoxycarbonyl-2',3'-O-isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (9) —— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 873 mg (2.0 mmol) of 4 were used: LTMP (6.0 mmol) in THF (15 ml), $ClCO_2Et$ (0.38 ml, 4.0 mmol). The reaction was continued for 1 h at below -70 °C. Silica gel column chromatography (benzene:EtOAc = 5:1) gave 9 (875 mg, 86%) as a foam.

Anal. Calcd. for $C_{23}H_{28}N_2O_9S$: C, 54.32; H, 5.55; N, 5.51. Found: C, 54.41; H, 5.65; N, 5.48. UV absorption in MeOH: max 274 nm (ε 9800) and 243 nm (ε 8800), min 257 nm (ε 7900) and 231 nm (ε 7800), shoulder 312 nm (ε 3500). MS m/z: 493 (M-Me), 292 (B+1), 217 (M-B). PMR ($CDCl_3$) δ: 1.19 (3H, s, isop.Me), 1.27 (3H, t, CH_2Me), 1.45 (3H, s, isop.Me), 3.33 (3H, s, CH_2OCH_3), 3.60∿3.75 (2H, m, CH_2-5'), 4.04∿4.21 (1H, m, H-4'), 4.27 (2H, q, CH_2Me), 4.62 (2H, s, CH_2OCH_3), 4.67∿4.87 (2H, m, H-2' and H-3'), 6.53 (1H, d, J= 1.0 Hz, H-1'), 7.30∿7.54 (5H, m, SPh), 9.43 (1H, br, NH).

5-Benzoyl-2',3'-O-isopropylidene-5'-O-methoxymethyl-6-phenylthiouridine (10) —— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 873 mg (2.0 mmol) of 4 in THF (15 ml) were used: LTMP (6.0 mmol) in THF (15 ml), ClCOPh (0.47 ml, 4.0 mmol). The reaction was continued for 3 h at below -70 °C. Silica gel column chromatography (benzene:EtOAc = 7:1) gave 10 (999 mg, 92%) as a foam.

MS m/z: 540 (M^+), 525 (M-Me), 324 (B+1), 217 (M-B). UV absorption in MeOH: max 250 nm, min 225 nm, shoulder 271 nm. PMR ($CDCl_3$) δ: 1.19 (3H, s, isop.Me), 1.43 (3H, s, isop.Me), 3.36 (3H, s, CH_2OCH_3), 3.68∿3.76 (2H, m, CH_2-5'), 4.06∿4.24 (1H, m, H-4'), 4.65 (2H, s, CH_2OCH_3), 4.69∿4.90 (2H, m, H-2' and H-3'), 6.57 (1H, d, J= 1.0 Hz, H-1'), 7.21∿7.91 (10H, m, SPh and COPh), 9.06 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5-trimethylsilyl-6-phenylthiouridine (11) —— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 873 mg (2.0 mmol) of 4 in THF (15 ml) were used: LTMP (6.0 mmol) in THF (15 ml), $ClSiMe_3$ (0.51 ml, 4.0 mmol). The reaction was continued for 2 h at below -70 °C. Silica gel column chromatography (benzene:EtOAc = 8:1) gave 11 (929 mg, 91%) as a foam.

Anal. Calcd. for $C_{28}H_{32}N_2O_7SSi$: C, 54.31; H, 6.34; N, 5.51. Found: C, 54.59; H, 6.51; N, 5.38. UV absorption in MeOH: 277 nm (ε 10100) and 245 nm (ε 9500), min 258 nm (ε 7700) and 233 nm (ε 7500), shoulder 313 nm (ε 3800). MS m/z: 508 (M^+), 493 (M-Me), 292 (B+1), 217 (M-B). PMR ($CDCl_3$) δ: 0.35 (9H, s, $SiMe_3$), 1.10 (3H, s, isop.Me), 1.34 (3H, s, isop.Me), 3.32 (3H, s, CH_2OCH_3), 3.63∿3.70 (2H, m, CH_2-5'), 3.97∿4.06 (1H, m, H-4'), 4.61 (2H, s, CH_2OCH_3), 4.66∿4.76 (2H, m, H-2' and H-3'), 6.52 (1H, s, H-1'), 7.16∿7.41 (5H, m, SPh), 9.04 (1H, br, NH).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-5,6-diphenylthiouridine (12) —— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 873 mg (2.0 mmol) of 4 in THF (15 ml) were used: LTMP (6.0 mmol) in THF (15 ml), PhSSPh (873 mg, 4.0 mmol) in THF (10 ml). The reaction was continued for 1 h at below -70 °C. Silica gel column chromatography (benzene: EtOAc = 10:1) gave 12 (1.024 g, 94%) which was crystallized from EtOH-hexane (mp 116.5∿118.5 °C).

Anal. Calcd. for $C_{26}H_{28}N_2O_7S_2$: C, 57.33; H, 5.18; N, 5.14. Found: C, 57.61; H, 5.29; N, 5.05. UV absorption in MeOH: max 244 nm (ε 14800), min 228 nm (ε 12200), shoulder 310 nm (ε 5800) and 276 nm (ε 10200). Other physical data of 12: see reference 2.

5-Methyl-6-phenylthio-3',5'-O-(tetraisopropyldisiloxan-1,3-diyl)-2'-deoxyuridine (14)—— This compound was prepared by the procedure for deuteration of 4. The following amounts of reagents and 603 mg (1.04 mmol) of 13 in THF (12.5 ml) were used: LTMP (3.12 mmol) in THF (10 ml), MeI (0.5 ml, 8.0 mmol). The reaction was continued for 5 h at below -70 °C. Silica gel column chromatography (benzene: EtOAc = 9:1) gave 14 (409 mg, 66%) as a foam.

Anal. Calcd. for $C_{28}H_{44}N_2O_6SSi_2$: C, 56.74; H, 7.48; N, 4.73. Found: C, 57.00; H, 7.62; N, 4.53. UV absorption in MeOH: max 278 nm (ε 8800) and 245 nm (ε 8300), min 259 nm (ε 6900) and 235 nm (ε 7100). MS m/z: 549 (M-i-Pr), 359 (M-B), 234 (B+1). PMR ($CDCl_3$) δ: 1.02 (28H, m, iso-Pr), 2.15 (3H, s, 5-Me), 2.08∿2.31 and 2.48∿2.69 (2H, each as m, H-2'), 3.60∿3.77 (1H, m, H-4'), 3.96 (2H, m, CH_2-5'), 4.77∿5.03 (1H, m, H-3'), 6.67 (1H, dd, H-1'), 7.23∿7.36 (5H, m, SPh), 8.03 (1H, br, NH).

6-Tributylstannyl-1,3-dimethyluracil (17)—— To a solution of 16 (124 mg, 0.5 mmol) and AIBN (25 mg) in dry benzene (5 ml) was added TBTH (0.66 ml, 2.5 mmol). The mixture was refluxed for 7 h and then evaporated to dryness. The residue was dissolved in $CHCl_3$ and purified by preparative TLC (benzene:EtOAc = 30:1). This gave 17 (208 mg, 97%) and 18 (2 mg, 2%).

Physical data of 17 are as follows. UV absorption in MeOH: max 273 nm, min 241 nm. MS m/z: 429, 427, and 425 (M-1), 373, 371, and 369 (M-Bu). PMR ($CDCl_3$) δ: 0.90 (9H, t, $CH_2CH_2CH_2Me$), 1.08∿1.56 (18H, m, $CH_2CH_2CH_2Me$), 3.34 (3H, s, N^1-Me), 3.42 (3H, s, N^3-Me), 5.77 (1H, s, H-5).

5-Tributylstannyl-1,3-dimethyluracil (20)—— To a solution of 19 (124 mg, 0.5 mmol) and AIBN (25 mg) in dry benzene (5 ml) was added TBTH (0.27 ml, 1.0 mmol). The mixture was refluxed for 1 h and then evaporated to dryness. The residue was dissolved in $CHCl_3$ and purified by preparative TLC (benzene:EtOAc = 30:1). This gave 20 (206 mg, 96%) as an oil.

UV absorption in MeOH: max 271 nm, min 240 nm. MS m/z: 431, 429, and 427 (M+1), 373, 371, and 369 (M-Bu). PMR ($CDCl_3$) δ: 0.89 (9H, t, $CH_2CH_2CH_2Me$), 1.03∿1.47 (18H, m, $CH_2CH_2CH_2Me$), 3.33 (3H, s, N^1-Me), 3.37 (3H, s, N^3-Me), 6.88 (1H, s, H-6).

2',3'-O-Isopropylidene-5'-O-methoxymethyl-6-tributylstannyl-5-methyluridine (21)—— To a solution of 6 (101 mg, 0.22 mmol) and AIBN (30 mg) in dry benzene (5 ml) was added TBTH (0.18 ml, 0.67 mmol). The mixture was refluxed for 3 h and then evaporated to dryness. The residue was chromatographed on a silica gel column (benzene:EtOAc = 7:1) to give 21 (112 mg, 81%) as an oil.

UV absorption in MeOH: max 274 nm, min 256 nm. MS m/z: 617, 615, and 613 (M-Me), 575, 573, and 571 (M-Bu), 359, 357, and 355 (B+1-Bu), 217 (M-B). High resolution MS m/z: 575.17713 (M-Bu) Calcd. for $C_{23}H_{39}N_2O_7Sn$ 575.17783. PMR ($CDCl_3$) δ: 0.91 (9H, t, $CH_2CH_2CH_2Me$), 1.18∿1.62 (18H, m, $CH_2CH_2CH_2Me$), 1.36 (3H, s, isop.Me), 1.54 (3H, s, isop.Me), 2.00 (3H, s, 5-Me), 3.36 (3H, s, CH_2OCH_3), 3.73∿3.79 (2H, m, CH_2-5'), 4.12∿4.29 (1H, m, H-4'), 4.66 (2H, s, CH_2OCH_3), 4.88 (1H, dd, H-3'), 5.21 (1H, dd, H-2'), 5.45 (1H, d, J= 1.0 Hz, H-1'), 9.31 (1H, br, NH).

5-Methyluridine (22)—— Compound 6 (175 mg, 0.39 mmol) was treated with AIBN (50 mg) and TBTH (0.31 ml, 1.19 mmol) in dry benzene (8 ml) in a similar manner as above. After column chromatography, the resulting 21 was dissolved in 50% TFA (15 ml) and the mixture was stirred at room temperature for 2 days. Evaporation of the solvent followed by column chromatography (10% EtOH in $CHCl_3$) gave 22 (80 mg, 79% from 6), which was crystallized from acetone (mp 182∿183 °C).

PMR (DMSO-d_6) δ: 1.77 (3H, d, J= 1.0 Hz, 5-Me), 3.53∿3.64 (2H, m, CH_2-5'), 3.77∿3.89 (1H, m, H-4'), 3.94∿4.06 (2H, m, H-2' and H-3'), 5.02∿5.13 (2H, m, 2'- or 3'-OH and 5'-OH), 5.30 (1H, d, 2'- or 3'-OH), 5.77 (1H, d, J= 4.9 Hz, H-1'), 7.73 (1H, d, H-6), 11.27 (1H, br, NH).

5-Ethyluridine (23)—— Compound 7 (140 mg, 0.30 mmol) was treated with AIBN (30 mg) and TBTH (0.24 ml, 0.92 mmol) in dry benzene (8 ml) for 3 h at refluxing temperature. After evaporation of the solvent followed by short-column chromatography ($CHCl_3$), the resulting oil was dissolved in 50% TFA (10 ml) and the mixture was stirred at room temperature for 2 days. Column chromatographic purification

(10% EtOH in $CHCl_3$) of the mixture gave 23 (67 mg, 82% from 7) which was crystallized from EtOH (mp 185~186 °C).

PMR (DMSO-d_6) δ: 1.03 (3H, t, CH_2CH_3), 2.21 (2H, q, CH_2CH_3), 3.54~3.65 (2H, m, CH_2-5'), 3.78~3.90 (1H, m, H-4'), 3.95~4.12 (2H, m, H-2' and H-3'), 5.02~5.15 (2H, m, 2'- or 3'-OH and 5'-OH), 5.31 (1H, d, 2'- or 3'-OH), 5.78 (1H, d, J= 4.9 Hz, H-1'), 7.73 (1H, s, H-6), 11.24 (1H, br, NH).

Desulfurizative stannylation of 14 and the successive protonolysis—— To a solution of 14 (140 mg, 0.24 mmol) and AIBN (20 mg) in dry benzene (5 ml) was added TBTH (0.19 ml, 0.7 mmol). The mixture was refluxed for 4 h. After evaporation of the solvent, the residue was dissolved in dioxane (3 ml) containing 50% TFA (3 ml) and the mixture was stirred at room temperature for 4 h. The whole mixture was poured into NH_3/MeOH, evaporated, and acetylated with Ac_2O in pyridine. Purification by preparative TLC ($CHCl_3$:EtOH = 40:1) gave 3',5'-di-O-acetylthymidine (25: 45 mg, 58% from 14).

5-Ethoxycarbonyl-2',3'-O-isopropylidene-5'-O-methoxymethyluridine (26)—— To a solution of 9 (97 mg, 0.19 mmol) and AIBN (30 mg) in dry benzene (5 ml) was added TBTH (0.1 ml, 0.39 mmol). The mixture was refluxed for 10 min and then evaporated to dryness. The residue was chromatographed on a silica gel column (benzene: EtOAc = 3:1) to give 26 (69 mg, 91%).

For physical data of 26: see reference 5.

Desulfurizative stannylation of 12—— To a solution of 12 (102 mg, 0.19 mmol) and AIBN (25 mg) in dry benzene (5 ml) was added TBTH (0.1 ml, 0.39 mmol). The mixture was refluxed for 40 min and then evaporated to dryness. Purification by preparative TLC (benzene:EtOAc = 7:1) gave 54 mg (40%) of 2',3'-O-isopropylidene-5'-O-methoxymethyl-5-tributylstannyl-6-phenylthiouridine (27), the faster moving product, and 30 mg (22%) of 2',3'-O-isopropylidene-5'-O-methoxymethyl-6-tributylstannyl-5-phenylthiouridine (28), the slower moving product.

Physical data of 27 are as follows. UV absorption in MeOH: max 274 nm and 246 nm, min 257 nm and 235 nm. MS m/z: 711, 709, and 707 (M-Me), 669, 667, and 665 (M-Bu), 453, 451, and 449 (B+1-Bu), 217 (M-B). PMR ($CDCl_3$) δ: 0.85 (9H, t, $CH_2CH_2CH_2$-Me), 1.01~1.53 (18H, m, $CH_2CH_2CH_2$Me), 1.11 (3H, s, isop.Me), 1.33 (3H, s, isop.Me), 3.33 (3H, s, CH_2OCH_3), 3.64~3.71 (2H, m, CH_2-5'), 3.79~4.06 (1H, m, H-4'), 4.61 (2H, s, CH_2OCH_3), 4.65~4.74 (2H, m, H-2' and H-3'), 6.43 (1H, s, H-1'), 7.16~7.37 (5H, m, SPh), 8.27 (1H, br, NH).

Physical data of 28 are as follows. UV absorption in MeOH: max 274 nm and 242 nm, min 267 nm and 228 nm. MS m/z: 669, 667, and 665 (M-Bu), 453, 451, and 449 (B+1-Bu), 217 (M-B). PMR ($CDCl_3$) δ: 0.84 (9H, t, $CH_2CH_2CH_2$Me), 1.11~1.50 (18H, m, $CH_2CH_2CH_2$Me), 1.36 (3H, s, isop.Me), 1.55 (3H, s, isop.Me), 3.38 (3H, s, CH_2OCH_3), 3.75~3.81 (2H, m, CH_2-5'), 4.23~4.27 (1H, m, H-4'), 4.87 (1H, dd, H-3'), 5.22 (1H, dd, H-2'), 5.63 (1H, d, J= 1.1 Hz, H-1'), 7.19~7.29 (5H, m, SPh), 8.31 (1H, br, NH).

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