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LITHIATION OF 3',5'-O-(TETRAISOPROPYLDISILOXANE-1,3-DIYL)-2'-DEOXYURIDINE: SYNTHESIS OF 6-SUBSTITUTED 2'-DEOXYURIDINES

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Abstract—— Synthesis of 6-substituted 2'-deoxyuridines can be effected by lithiation of 3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine with LDA followed by the reaction of its lithio derivative with electrophiles. This method provides a general, regiospecific and simple route to various types of 6-substituted 2'-deoxyuridines which have, so far, been known to be difficult to prepare.

In the field of nucleoside chemistry, the lithiation reaction has only recently become recognized as a practically useful method for introducing various functionalities to the base moiety. We have already reported the synthesis of 5- and/or 6-substituted uridines and 8-substituted purine nucleosides based on the lithiation.[1] As a part of our program to search for biologically active nucleosides, it was necessary to prepare the title compounds, since some of the 6-substituted uridines previously synthesized exhibited highly promising antileukemic activity.[2]

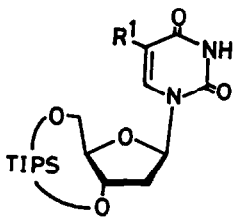
Although the condensation reaction of the base and an appropriately protected sugar derivative is frequently used in nucleoside synthesis, this method is not applicable to the preparation of 6-substituted 2'-deoxyuridines due to the production of mixtures of regio- and stereoisomers. For example, the reaction of silylated 6-methyluracil with 1,3,5-tri-O-acetyl-2-deoxyribofuranose in the presence of $SbCl_5$ afforded the α- and β-anomers of the corresponding N^1- and N^3-ribosylated products.[3,4]

Thus, the synthesis of the title compounds might be best carried out by using 2'-deoxyuridine as a starting material, which would avoid the concomitant formation of such undesired products. In addition, the lithiation of a 2'-deoxyuridine derivative appears to present the method of choice, as a wide range of electrophiles are available for the reaction with organolithium compounds. To our knowledge, only one report has appeared in the literature on the conversion of 2'-deoxyuridine to 6-substituted derivative by means of lithiation.[5] These authors reported, however, that following treatment of a lithiated 2'-deoxyuridine derivative with MeI, 6-methyluridine was obtained in a low yield along with thymidine as a main product.

In this paper, we describe a simple and regiospecific method for synthesizing 6-substituted 2'-deoxyuridines, as well as a 6-substituted 2'-deoxy-5-fluorouridine on the basis of lithiation.

Since desired 6-substituted products were expected to be rather unstable, hydroxyl groups of the sugar moiety

were protected by TIPS (1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) group which was removable by fluoride anion under mild conditions. Treatment of 2'-deoxyuridine or 2'-deoxy-5-fluorouridine with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[6] in pyridine gave the



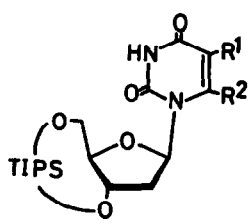
1a R^1= H
1b R^1= F

TIPS= 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl

corresponding TIPS derivatives (1a and 1b) in almost quantitative yields. The regioselectivity of lithiation was examined by using 2.5 eq of lithiating agent such as BuLi, BuLi/TMEDA or LDA in THF below -70°C. After quenching the lithiated species of 1a with CD_3OD, ^{1}H-NMR spectrum of the deuterated product was measured.[7]

In the case of BuLi or BuLi/TMEDA, preferential lithiation at the C-5 was observed. On the other hand, the use of LDA resulted in the exclusive formation of the 6-deuterated product in 20.0% yield. When 5.0 eq of LDA was used in this reaction, the highest deuterium incorporation (52.8%) was accomplished with complete regioselectivity at the C-6 position. The use of 10 eq of LDA, however, resulted in the loss of the regiospecificity to give both C-6 and C-5 deuterated products.

The reactions of the C-6 lithiated species (2) with various electrophiles were next carried out. Treatment of 2 with 1.5 eq of diphenyl disulfide below -70°C for 2 h produced a protected 6-phenylthio-2'-deoxyuridine (4) in 54.6% yield after silica gel column chromatography. Since disulfides are recommended as "label reactants" in the case of lithiation with lithium dialkylamides where substitution by deuterium may be low,[8] we believe that the actual extent of this lithiation should be estimated at 54.6%. When MeI was employed in this reaction, the TIPS derivative could not be isolated in a pure form, therefore it was further deprotected by Bu_4NF in THF to give 6-methyl-2'-deoxyuridine (5)[5,9] in 33.2% yield. The formation of 6-ethyl-2'-deoxyuridine (6: 1.8%) was also observed as was anticipated from the acidic nature of the 6-methyl protons.



4 R^1= H, R^2= SPh
7 R^1= H, R^2= CO_2Me
8 R^1= H, R^2= CH(OH)Ph
9 R^1= H, R^2= CH_2OH
10 R^1= H, R^2= I
11 R^1= F, R^2= SPh

The results with other carbon-electrophiles such as $ClCO_2Me$, PhCHO or HCO_2Et leading to the corresponding 6-substituted TIPS-2'-deoxyuridines are summarized in Table 1. 6-Formyl-TIPS-2'-deoxyuridine resulting from initial reaction of 2 with HCO_2Et was reduced by $NaBH_4$ in a one-pot manner to furnish 6-hydroxymethyl derivative (9) in 45.7% yield. The preparation of carbon-halogen bond at the C-6 position is illustrated by the formation of 6-iodo-TIPS-2'-deoxyuridine which was formed through

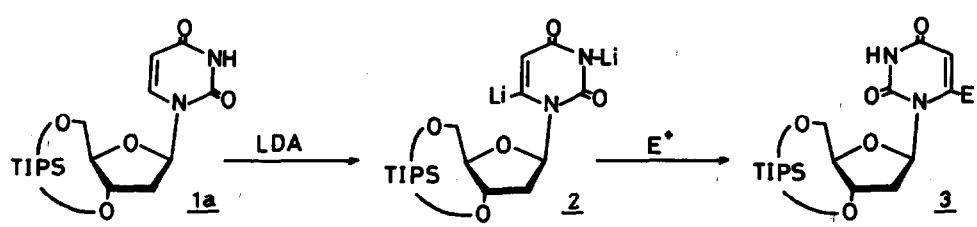


Table 1

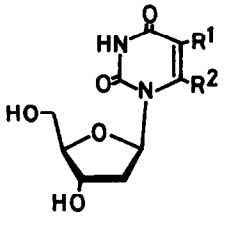
electrophile	R^1	R^2		yield (%)		
MeI	H	Me			5	33.2*
	H	Et			6	1.8*
$(PhS)_2$	H	SPh	4	54.6	12	41.6
$ClCO_2Me$	H	CO_2Me	7	44.0	13	52.9
PhCHO	H	CH(OH)Ph	8	51.5	14	65.0
HCO_2Et	H	CH_2OH	9	45.7	15	61.0
I_2	H	I	10	51.0		
$(PhS)_2$	F	SPh	11	58.4	16	55.8

* overall yield from 1a

the reaction of 2 with I_2.

To demonstrate the applicability of this method, 1b was converted to its 6-phenylthio derivative (11) in a similar manner. This is the first example of the modification at C-6 of 5-fluoro-2'-deoxyuridine, a biologically active nucleoside.

Finally deprotection of 6-substituted TIPS-2'-deoxyuridines was investigated. The TIPS derivative was treated with Bu_4NF in THF at room temperature. In the case of 10, 6-iodo-2'-deoxyuridine could not be detected in any appreciable amount on TLC ($CHCl_3$:EtOH = 15:1). The glycosidic bond of 10 appeared to be extremely labile toward nucleophilic reaction even under neutral conditions. For example, in refluxing EtOH, 10 was completely converted to 6-iodouracil within 2 h. As seen in Table 1, other 6-substituted 2'-deoxyuridines were isolated in reasonable yields by column chromatography on magnesium silicate. It should be noted that, in the cases of 4, 7 and 11, the use of silica gel decreased the isolated yields of products.



5 R^1= H, R^2= Me
6 R^1= H, R^2= Et
12 R^1= H, R^2= SPh
13 R^1= H, R^2= CO_2Me
14 R^1= H, R^2= CH(OH)Ph
15 R^1= H, R^2= CH_2OH
16 R^1= F, R^2= SPh

The instability of some 6-substituted 2'-deoxyuridines might be generally explicable in terms of electron-withdrawing nature of the introduced substituent which increases leaving ability of the base moiety.

In conclusion, the present method provides a general, regiospecific and simple access to 6-substituted or 5,6-disubstituted 2'-deoxyuridines which have, so far, been known to be difficult to synthesize.

Further work is in progress to evaluate biological activities of the compounds prepared in this study.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured with an appropriate internal standard of tetramethylsilane (TMS) or sodium-2,2-dimethyl-2-silapentane 5-sulfonate (DSS), with a JEOL JNM-FX 100 NMR spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet ; t, triplet; m, multiplet; br, broad. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. UV 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 either on silica gel (Wakogel® C-200) or on magnesium silicate (Florisil®). TLC was performed on silica gel (precoated silica gel plate 60 F_{254}, Merck).

3',5'-O-(Tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine (1a)—— To a solution of 2'-deoxyuridine (10.0 g, 43.8 mmol) in pyridine (130 ml), 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (15.3 g, 48.5 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 h and partitioned between $CHCl_3$ and H_2O. The organic layer was separated, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed on a silica gel column (1% EtOH in $CHCl_3$) to give 1a (19.0 g, 91.5%) which was crystallized from EtOH-H_2O (mp 119∿120°C).

Physical data of 1a are as follows. Anal. Calcd. for $C_{21}H_{38}N_2O_6Si_2$: C,53.46; H, 8.13; N, 5.77. Found: C, 53.52; H, 8.13; N, 5.95. MS m/z: 471 (M+1), 427 (M-iso-Pr), 112 (B+1). UV absorption in MeOH: max 263 nm (ε 10900), min 231 nm (ε 3100). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (28H, m, iso-Pr), 2.21∿2.54 (2H, m, H-2'), 3.71∿3.80 (1H, m, H-4'), 4.04∿4.07 (2H, m, CH_2-5'), 4.10∿4.50 (1H, m, H-3'), 5.69 (1H, dd, H-5), 6.02 (1H, dd, H-1'), 7.76 (1H, d, H-6), 8.57 (1H, br, NH).

5-Fluoro-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine (1b)——Compound 1b was prepared from 5-fluoro-2'-deoxyuridine (7.1 g, 28.84 mmol) by a similar method as above. Crystallization from EtOH-H_2O gave an analytical sample (mp 76∿77°C). Anal. Calcd. for $C_{21}H_{37}N_2O_6FSi_2$: C, 51.64; H, 7.64; N, 5.74. Found: C, 51.45; H,7.72; N, 5.54. MS m/z: 445 (M-iso-Pr), 130 (B+1). UV absorption in MeOH: max 269nm (ε 8900), min 235 nm (ε 2800). ^{1}H-NMR ($CDCl_3$) δ: 1.01∿1.10 (28H, m, iso-Pr), 2.13∿2.69 (2H, m, H-2'), 3.69∿3.82 (1H, m, H-4'), 3.91∿4.26 (2H, m, CH_2-5'), 4.26∿4.58 (1H, m, H-3'), 6.01 (1H, d, H-1'), 7.89 (1H, d, H-6), 9.00 (1H, br, NH).

6-Phenylthio-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl-2'-deoxyuridine (4)—— LDA (31.5 mmol) in THF (35 ml) was placed in a three-necked flask equipped with a gas inlet adaptor, thermometer and rubber septum. To this, a solution of 1a (2.96 g, 6.30 mmol) in THF (35 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, diphenyl disulfide (2.06 g, 9.45 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, and evaporated. The residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was separated, dried with Na_2SO_4 and chromatographed on a silica gel column ($CHCl_3$) to give 4 (1.98 g, 54.6%). MS m/z: 535 (M-iso-Pr), 220 (B+1). UV absorption in MeOH: max 282 nm, min 244 nm. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (28H, s, iso-Pr), 2.20∿2.57 and 2.75∿3.11 (2H, each as m, H-2'), 3.81∿3.86 (1H, m, H-4'), 3.91∿4.07 (2H, m, CH_2-5'), 4.87∿5.11 (1H, m, H-3'), 4.97 (1H, s, H-5), 6.34 (1H, dd, H-1'), 7.51 (5H, s, Ph), 8.29 (1H, br, NH).

6-Methyl-2'-deoxyuridine (5) and 6-ethyl-2'-deoxyuridine (6)—— The following amounts of reagents and 2.35 g (5.0 mmol) of 1a in THF (30 ml) were employed: 25.0 mmol of LDA in THF (30 ml), 0.47 ml (7.50 mmol) of freshly distilled MeI. The reaction was continued for 2 h. Chromatographic purification on a silica gel column ($CHCl_3$) gave a mixture of TIPS derivatives (1.51 g). The whole mixture was treated with Bu_4NF (1.90 g) in THF (22.5 ml) at room temperature for 1 h. After being evaporated, the residue was purified through a Florisil column (5% EtOH in $CHCl_3$) which gave 5 (402 mg, 33.2%) and 6 (23 mg, 1.8%). Compound 5 was crystallized from EtOH (mp 164∿165°C). For physical data of 5, see references 5 and 9. ^{1}H-NMR data of 6 (D_2O, DSS) are as follows. δ: 1.22 (3H, t, CH_2CH_3), 2.11∿2.39 and 2.87∿3.09 (2H, each as m, H-2'), 2.68 (2H, q, CH_2CH_3), 3.62∿4.01 (3H, m, CH_2-5' and H-4'), 4.43∿4.63 (1H, m, H-3'), 5.77 (1H, s, H-5), 6.18 (1H, dd, H-1').

6-Methoxycarbonyl-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine (7)—— The following amounts of reagents and 2.35 g (5.0 mmol) of 1a in THF (30 ml) were employed: 25.0 mmol of LDA in THF (30 ml), 0.58 ml (7.50 mmol) of freshly distilled $ClCO_2Me$. The reaction was continued for 2 h. Chromatographic purification on a silica gel column (benzene:AcOEt = 10:1) gave 7 (1.16 g, 44.0%). MS m/z: 485 (M-iso-Pr), 170 (B+1). ^{1}H-NMR ($CDCl_3$) δ: 1.00∿1.13 (28H, m, iso-Pr), 2.29∿2.56 and 2.71∿2.99 (2H, each as m, H-2'), 3.72∿4.04 (3H, m, CH_2-5' and H-4'), 3.92 (3H, s, CO_2Me), 4.64 (1H, m, H-3'), 5.92 (1H, d, H-5), 5.97 (1H, dd, H-1'), 8.66 (1H, br, NH).

6-Phenylhydroxymethyl-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine (8)—— The following amounts of reagents and 2.35 g (5.0 mmol) of 1a in THF (30 ml) were employed: 25.0 mmol of LDA in THF (30 ml), 0.76 ml (7.50 mmol) of freshly distilled PhCHO. The reaction was continued for 2 h. Chromatographic purification on a silica gel column (1% EtOH in $CHCl_3$) gave 8 (1.48 g, 51.5%) as an epimeric mixture. MS m/z: 533 (M-iso-Pr). ^{1}H-NMR ($CDCl_3$) δ: 0.97∿1.26 (28H, m, iso-Pr), 1.59∿1.92 and 2.44∿2.67 (2H, each as m, H-2'), 3.61∿3.74 (1H, m, H-4'), 3.91∿3.98 (2H, m, CH_2-5'), 4.76∿4.99 (1H, m, H-3'),

5.60∿6.15 (3H, m, H-5, H-1' and PhCHOH), 7.38 (5H, s, Ph).

6-Hydroxymethyl-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine (9)—— The following amounts of reagents and 2.35 g (5.0 mmol) of 1a in THF (30 ml) were employed: 25.0 mmol of LDA in THF (30 ml) and freshly distilled HCO_2Et. The reaction was continued for 2 h. After being quenched with AcOH, the mixture was diluted with EtOH (50 ml) and reduced by $NaBH_4$ (600 mg). Excess of $NaBH_4$ was decomposed by adding AcOH. The mixture was then evaporated and partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4) and chromatographed on a silica gel column (4% EtOH in $CHCl_3$) to give 9 (1.15 g, 45.7%). MS m/z: 457 (M-iso-Pr). ^{1}H-NMR ($CDCl_3$) δ: 1.00∿1.13 (28H, m, iso-Pr), 2.15∿2.52 and 2.73∿3.01 (2H, each as m, H-2'), 3.68∿3.85 (1H, m, H-4'), 3.98∿4.06 (2H, m, CH_2-5'), 4.50 (2H, br, CH_2OH), 4.83∿5.05 (1H, m, H-3'), 5.80 (1H, s, H-5), 5.98 (1H, dd, H-1'), 8.77 (1H, br, NH).

6-Iodo-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine (10) —— The following amounts of reagents and 2.35 g (5.0 mmol) of 1a in THF (30 ml) were employed: 25.0 mmol of LDA in THF (30 ml), iodine (3.8 g, 15.0 mmol). The reaction was continued for 2 h. Chromatographic purification on a silica gel column ($CHCl_3$) gave 10 (1.52 g, 51.0%). MS m/z: 553 (M-iso-Pr), 238 (B+1). ^{1}H-NMR ($CDCl_3$) δ: 1.04∿1.13 (28H, m, iso-Pr), 2.52∿3.02 and 2.24∿2.45 (2H, each as m, H-2'), 3.79∿4.04 (3H, m, CH_2-5' and H-4'), 4.87∿5.09 (1H, m, H-3'), 6.17 (1H, dd, H-1'), 6.39 (1H, d, H-5), 8.39 (1H, br, NH).

5-Fluoro-6-phenylthio-3',5'-O-(tetraisopropyldisiloxane-1,3-diyl)-2'-deoxyuridine (11)—— The following amounts of reagents and 2.44g (5.0 mmol) of 1b were employed: 25.0 mmol of LDA in THF (30 ml), 1.64 g (7.5 mmol) of diphenyl disulfide. The reaction was continued for 2 h. Chromatographic purification on a silica gel column ($CHCl_3$) gave 11 (1.74 g, 58.4%). MS m/z: 553 (M-iso-Pr), 238 (B+1). ^{1}H-NMR ($CDCl_3$) δ: 0.98∿1.05 (28H, m, iso-Pr), 1.95∿2.25 and 2.56∿2.83 (2H, each as m, H-2'), 3.58∿3.82 (1H, m, H-4'), 3.95∿3.99 (2H, m, CH_2-5'), 4.80∿5.02 (1H, m, H-3'), 6.61 (1H, dd, H-1'), 7.37 (5H, s, Ph).

6-Phenylthio-2'-deoxyuridine (12)—— Compound 4 (697 mg, 1.20 mmol) was treated with Bu_4NF (757 mg) in THF (15 ml) at room temperature for 1 h. The solvent was evaporated and the whole residue was chromatographed on a Florisil column (5% EtOH in $CHCl_3$) to give 12 (168 mg, 41.6%) which was crystallized from EtOH (mp 270∿271°C). Anal. Calcd. for $C_{15}H_{16}N_2O_5S$: C, 53.56; H, 4.79; N, 8.33. Found: C, 53.86; H,4.76; N, 8.22. MS m/z: 220 (B+1). UV absorption in MeOH: max 284 nm (ε 10800), min 246 nm (ε 5900). ^{1}H-NMR (DMSO-d_6) δ: 1.85∿2.12 and 2.70∿3.08 (2H, each as m, H-2'), 3.62 (3H, m, CH_2-5' and H-4'), 4.27 (1H, m, H-3'), 4.66 (1H, t, 5'-OH), 4.72 (1H, d, H-5), 5.16 (1H, d, 3'-OH), 6.31 (1H, dd, H-1'), 7.60 (5H, s, Ph), 11.32 (1H, br, NH).

6-Methoxycarbonyl-2'-deoxyuridine (13)—— Compound 7 (754 mg, 1.38 mmol) was treated with Bu_4NF (871 mg) in THF (15 ml) at room temperature for 1 h. The solvent was evaporated and the whole residue was chromatographed on a Florisil column (5% EtOH in $CHCl_3$) to give 13 (208 mg, 52.9%). MS m/z: 269 (M+1-H_2O), 170 (B+1). UV absorption in MeOH: max 285 nm, min 239 nm. ^{1}H-NMR (DMSO-d_6) δ1.95∿2.66 (2H, m, H-2'), 3.32∿3.76 (3H, m, CH_2-5' and H-4'), 3.85 (3H, s, CO_2Me), 4.10 (1H, m, H-3'), 4.78 (1H, t, 5'-OH), 5.17 (1H, d, 3'-OH), 5.86 (1H, t, H-1'), 6.05 (1H, s, H-5), 11.39 (1H, br, NH).

Compound 13 was converted to its diacetate, whose high resolution MS was measured. High resolution MS m/z: 370.1005 (M^+) Calcd. for $C_{15}H_{18}N_2O_9$ 370.1010. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (6H, s, Ac), 2.33∿2.54 and 2.87∿3.16 (2H, each as m, H-2'), 3.92 (3H, s, CO_2Me), 4.12∿4.45 (3H, m, CH_2-5' and H-4'), 5.18∿5.33 (1H, m, H-3'), 6.01 (1H, s, H-5), 6.08 (1H, t, H-1'), 8.93 (1H, br, NH).

6-Phenylhydroxymethyl-2'-deoxyuridine (14)—— Compound 8 (1.48 g, 2.57 mmol) was treated with Bu_4NF (1.62 g) in THF (22.5 ml) at room temperature for 1 h. The solvent was evaporated and the whole residue was chromatographed on a Florisil column (3∿5% EtOH in $CHCl_3$) to give 14 (559 mg, 65.0%) as an epimeric mixture. UV absorption in MeOH: max 260 nm, min 232 nm. ^{1}H-NMR (DMSO-d_6) δ: 0.84∿1.31 and 2.22∿2.54 (2H, each as m, H-2'), 3.37∿3.57 (3H, m, CH_2-5' and H-4'), 4.17 (1H, m,H-3'), 4.47 (1H, m, 5'-OH), 4.87 and 4.90 (1H, each as d, 3'-OH), 5.59∿6.11 (3H, m, H-5, H-1' and PhCHOH), 6.47 and 6.76 (1H, each as d, PhCHOH), 7.38 (5H, s, Ph), 11.29 (1H, br, NH).

Compound 14 was converted to its tri-acetate, whose high resolution MS was measured. High resolution MS m/z: 460.1449 (M^+) Calcd. for $C_{22}H_{24}N_2O_9$ 460.1479. ^{1}H-NMR ($CDCl_3$) δ: 2.01 (3H, s, Ac), 2.05 (3H, s, Ac), 2.16 and 2.25 (3H, each as s, PhCHOAc), 1.26∿1.53 and 2.65∿2.98 (2H, each as m, H-2'), 3.99∿4.45 (3H, m, CH_2-5' and H-4'), 5.19∿5.43 (1H, m, H-3'), 5.72∿5.92 (1H, m, H-1'), 6.05 (1H, s, H-5), 6.75 and 6.89 (1H, each as s, PhCHOAc), 7.32∿7.40 (5H, m, Ph), 9.55 (1H, br, NH).

6-Hydroxymethyl-2'-deoxyuridine (15) —— Compound 9 (1.15 g, 2.29 mmol) was treated with Bu_4NF (1.45 g) in THF (22.5 ml) at room temperature for 1 h. The solvent was evaporated and the whole residue was chromatographed on a Florisil column (5∿10% EtOH in $CHCl_3$) to give 15 (364 mg, 61.0%). UV ab-

sorption in H_2O: max 259 nm, min 228 nm. ^{1}H-NMR (D_2O) δ: 2.11∿2.39 and 2.79∿3.07 (2H, each as m, H-2'), 3.63∿4.01 (3H, m, CH_2-5' and H-4'), 4.43∿4.51 (1H, m, H-3'), 4.59 (2H, s, CH_2OH), 5.93 (1H, s, H-5), 6.04 (1H, dd, H-1').

Compound 15 was converted to its triacetate, whose high resolution MS was measured. High resolution MS m/z: 384.1187 (M^+) Calcd. for $C_{16}H_{20}N_2O_9$ 384.1169. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, Ac), 2.09 (3H, s, Ac), 2.18 (3H, s, Ac), 2.24∿2.43 and 2.98∿3.26 (2H, each as m, H-2'), 4.07∿4.55 (3H, m, CH_2-5' and H-4'), 4.95 and 5.11 (2H, each as d, CH_2-OAc), 5.32∿5.50 (1H, m, H-3'), 5.97 (1H, t, H-1'), 5.83 (1H, s, H-5), 10.09 (1H, br, NH).

5-Fluoro-6-phenylthio-2'-deoxyuridine (16)—— Compound 11 (1.39 g, 2.33 mmol) was treated with Bu_4NF (1.47 g) in THF (22.5 ml) at room temperature for 1 h. The solvent was evaporated and the whole residue was chromatographed on a Florisil column (5% EtOH in $CHCl_3$) to give 16 (461 mg, 55.8%). UV absorption in MeOH: max 296 nm, min 257nm, shoulder 235 nm. ^{1}H-NMR (DMSO-d_6) δ: 1.55∿1.73 and 2.47∿2.66 (2H, each as m, H-2'), 3.45∿3.65 (3H, m, CH_2-5' and H-4'), 4.13∿4.21 (1H, m, H-3'), 4.57 (1H, t, 5'-OH), 5.04 (1H, d, 3'-OH), 6.44 (1H, dd, H-1'), 7.32∿7.57 (5H, m, Ph).

Compound 16 was converted to its diacetate, whose high resolution MS was measured. High resolution MS m/z: 438.0925 (M^+) Calcd. for $C_{19}H_{19}N_2O_7FS$ 438.0897. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, Ac), 2.08 (3H, s, Ac), 1.64∿1.91 and 2.71∿3.07 (2H, m, H-2'), 4.02∿4.45 (3H, m, CH_2-5' and H-4'), 6.66 (1H,dd, H-1'), 7.38 (5H, s, Ph), 7.55 (1H, br, NH).

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