Introduction of an Alkyl Group into the Sugar Portion of Uracilnucleosides by the Use of Gilman Reagents

Hiroyuki Hayakawa, Hiroshi Ashizawa, Hiromichi Tanaka, and Tadashi Miyasaka*

School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan. *Received July 14, 1989*

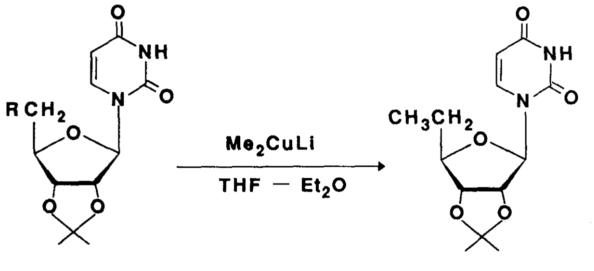
Substitution of a *p*-toluenesulfonyloxy group in the sugar portion of uracilnucleosides by an alkyl group was investigated by using Gilman reagents (R_2CuLi). In the cases of 5′-*O*-tosyl derivatives of 2′,3′-*O*-isopropylideneuridine, moderate yields of 5′-alkylated products were obtained. In contrast to this, the reactions of the corresponding 2′-deoxyuridine derivatives gave higher yields of products. A similar substitution reaction at the 3′-position of 2′-deoxyuridine derivatives was also examined.

Keywords organometallic reagent; Gilman reagent; uracilnucleoside; 5′-alkyl-5′-deoxyuridine; *C*-alkylated dideoxyuridine; nucleophilic substitution

We are interested in the use of organometallic reagents in the field of synthetic chemistry of nucleosides. For the modification of their base moiety, a lithiation approach has been found to be highly efficient, providing a general method for introducing various substituents including carbon functionalities.[1-7] On the other hand, surprisingly little synthetic methodology is available for effecting C–C bond formation at the sugar portion of nucleosides, and hence the vast majority of reports have dealt with either the Wittig reaction or nucleophilic addition reactions using keto or aldehyde derivatives of appropriately protected nucleosides.[8,9] Although the ring cleavage of oxirane[10] or oxetane[11] with carbanions can also be used in this context, the simplest approach would be nucleophilic substitution of nucleoside derivatives carrying a leaving group in the sugar portion. To our knowledge, however, there seem to be only two reports in which 5′-deoxy-5′-iodothymidine or 2′,3′-*O*-isopropylidene-5′-*O*-tosyladenosine was allowed to react with cyanide ion to produce the corresponding 5′-cyano-5′-deoxy derivative.[12,13]

A major concern in performing a similar substitution reaction by using organometallics would be the inherent propensity of nucleosides to undergo elimination reaction or cyclonucleoside formation.[14] In this paper, we would like to describe the use of Gilman reagents, mainly Me_2CuLi, for the introduction of an alkyl group into the sugar portion of uracil nucleosides without the above-mentioned side reactions.

The reaction of Me_2CuLi, prepared from MeLi and CuI, with the 2′,3′-*O*-isopropylideneuridine derivatives (**1**—**4**) was first investigated. When a tetrahydrofuran (THF) solution of **1** was treated with Me_2CuLi (3 eq in ether) at 0 °C for 20 h, the proton nuclear magnetic resonance (^1H-NMR) spectrum of the crude product isolated by silica gel column chromatography showed that it was contaminated by a considerable amount of the starting material (**1**). After treatment of this with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_3CN at refluxing temperature for 6 h, a pure product (**5**) was obtained in 35% yield.[15] During the DBU treatment, a small amount of a by-product [MS *m/z*: 533 ($M^+ - Me$), ^1H-NMR ($CDCl_3$): two anomeric protons at δ 5.60 ($J = 1.5$ Hz) and 5.68 ppm ($J = 2.6$ Hz)], which was assumed to have been formed by intermolecular substitution between **1** and **5**, was also formed. The reactions of **2**—**4** were conducted under conditions similar to those described above, and **5** was isolated in the following yields: 13% from **2**, 0% from **3**, and 31% from **4**. In the case of the 5′-*O*-(*p*-nitrobenzenesulfonyl) derivative (**3**), an intractable mixture of products resulted, indicating the incompatibility of a nitro group with these reaction conditions.[16] Althought the yield of **5** is not high enough, a significant amount of the starting material remained unchanged, except in the case of **3**, and the formation of elimination products or cyclonucleoside was not observed even in trace amounts throughout these reactions.



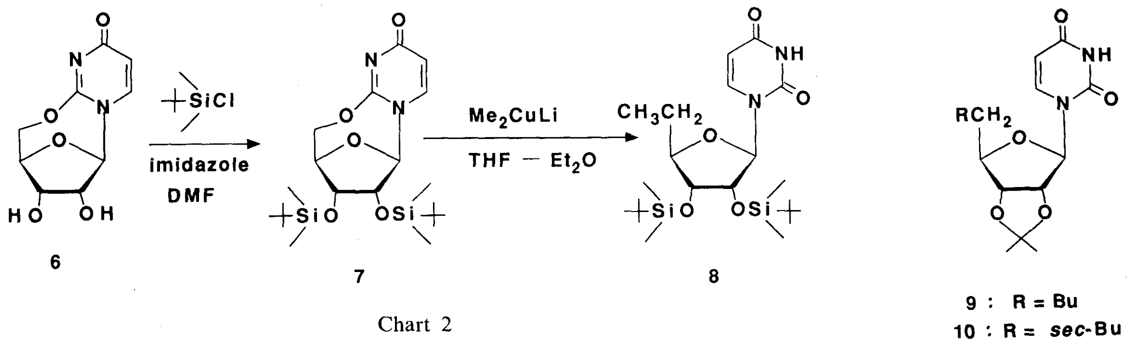
1 : R = OTs
2 : R = OMs
3 : R = $OSO_2C_6H_4NO_2$-*p*
4 : R = I

5

Chart 1

Since source of Cu(I) salt is known to exert profound effects on the reactivity of organocopper reagents,[17] salts such as CuBr, CuBr·SMe_2, CuCN, and CuSCN were also examined in the reaction of **1**, but the reagents prepared from these salts and MeLi gave uniformly lower yield of **5**: CuBr (8%), CuBr·SMe_2 (22%), CuCN (5%), and CuSCN (0%). A high-yield introduction of a methyl group into the 5′-position of uridine can be accomplished, however, with Me_2CuLi by a different route. Thus, starting from O^2,5′-cyclouridine (**6**), the 2′,3′-bis-*O*-*tert*-butyldimethylsilyl derivative (**7**) was prepared and subjected to the reaction with Me_2CuLi prepared from CuI (3 eq, 0 °C for 1 h). After column chromatographic purification, the corresponding 5′-deoxy-5′-methylated product (**8**) was isolated in 80% yield (Chart 2). Slow addition of **7** appeared to be indispensable to achieve this yield of **8**.

Use of other Gilman reagents (R_2CuLi, where R = Bu, *sec*-Bu, *tert*-Bu, or Ph), prepared from CuI, in the reaction of **1** was rather discouraging, either resulting in recovery of a large amount of the starting material (when R = Bu, *sec*-Bu, and *tert*-Bu) or giving a mixture of unknown products (when R = Ph). The sole case from which the desired



6

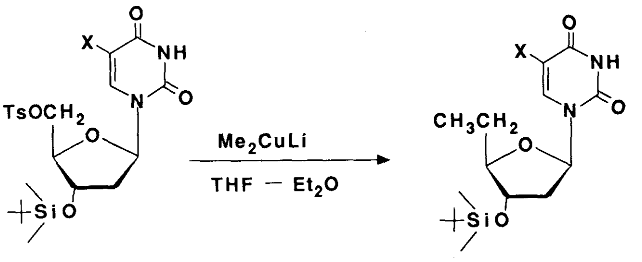
7

8

9 : R = Bu
10 : R = *sec*-Bu

Chart 2

product could be isolated was the reaction of Bu_2CuLi, but the ^1H-NMR spectrum of the product (**9**) revealed that it contained the corresponding 5,6-dihydro derivative. In contrast to this result, change of the salt to $CuBr \cdot SMe_2$ offered an advantage in allowing isolation of the pure **9** in 30% yield. A *sec*-butyl group could also be introduced by using this salt as a Cu(I) source to provide **10** in 16% yield as an equimolar mixture of two diastereomers about a tertiary carbon of the introduced *sec*-butyl group.

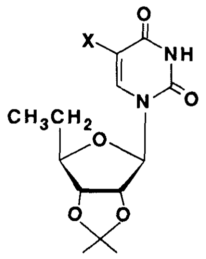


15 : X = H
16 : X = Me
17 : X = F

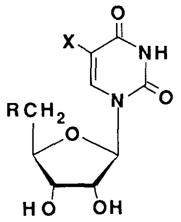
18 : X = H (90%)
19 : X = Me (86%)
20 : X = F (74%)

Chart 3

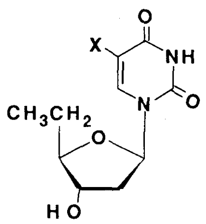
Introduction of a methyl group at the 5′-position of 5-substituted uridines was also carried out in a similar manner by using their 5′-tosylates and Me_2CuLi prepared from CuI. The yields of 5′-deoxy-5′-methylated products (**11**—**14**) are shown in parentheses. Formation of a trace amount of **13** was confirmed by examining the ^1H-NMR spectrum of the recovered 5′-tosylate (recovery, 89%) wherein the presence of a triplet (δ 1.02 ppm) assignable to the introduced C5′-methyl group of the contaminating **13** was evident. In the case of the formation of **14**, **5** was also isolated as a main product, indicating that the preferential pathway in this reaction was halogen–metal exchange reaction.



11 : X = Me (37%)
12 : X = F (51%)
13 : X = Cl (trace)
14 : X = Br (22%)



21 : X = H , R = Me
22 : X = H , R = Bu
23 : X = H , R = *sec*-Bu
24 : X = Me , R = Me
25 : X = F , R = Me
26 : X = Br , R = Me



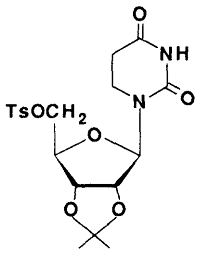
27: X = H
28: X = Me
29: X = F

Interestingly, when the substitution reaction with Me_2CuLi was extended to 2′-deoxyuridine derivatives (**15**—**17**), the C5′-methylated products (**18**—**20**) were obtained in good yields (the yields are shown in parentheses in Chart 3), which were significantly higher as compared with those of their ribosyl counterparts (**5**, **11**, and **12**).

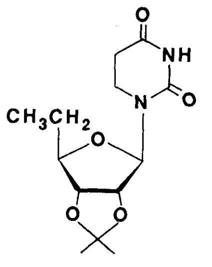
The 5′-alkylated products prepared in the above reactions were deprotected by treatment with either 50% aqueous CF_3CO_2H in the cases of 2′,3′-*O*-isopropylidene derivatives or tetrabutylammonium fluoride in the cases of 3′-*O*-*tert*-butyldimethylsilyl derivatives to give the respective free nucleosides (**21**—**29**).

Since the precise mechanistic interpretation of substitution reactions with Gilman reagents still remains uncertain even in the system of simple tosylates,[18] the reactions dealt with herein are presumably not simple one with an additional "enone system" in the base moiety, which has the possibility to interact with the reagents to form d-π complex.[19] Among various possible factors intervening in the present reactions, we thought the conformational difference in the sugar portion between 2′,3′-*O*-isopropylideneuridine and 2′-deoxyuridine would be a possible determinant of the efficiency of the present reactions. That is, we reasoned that 2′,3′-bis-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-tosyluridine ($J_{1',2'} = 7.3$ Hz), which would favour the C2′-*endo* conformation, might be more prone to undergo the substitution than the 2′,3′-*O*-isopropylidene derivative (**1**: $J_{1',2'} = 2.2$ Hz). However, upon subjecting this tosylate to the reaction of Me_2CuLi, a large amount of the starting material was recovered (recovery 84%).

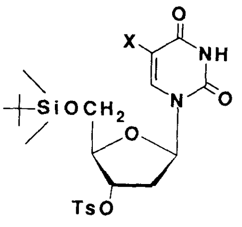
Another experiment undertaken to cast light on the mechanism has to do with the complexation of the base



30

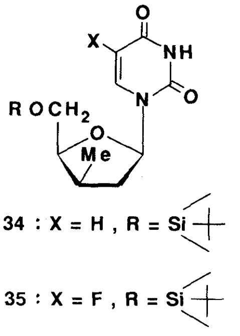


31



32 : X = H

33 : X = F



34 : X = H , R = Si

35 : X = F , R = Si

36 : X = H , R = H

37 : X = F , R = H

moiety to the reagent. Thus, 5,6-dihydro-2′,3′-*O*-isopropylidene-5′-*O*-(*p*-toluenesulfonyl)uridine (**30**) was prepared from 2′,3′-*O*-isopropylideneuridine by catalytic hydrogenation (5% Rh on alumina, in MeOH, for 3 h)[20] followed by tosylation. When **30** was treated with Me_2CuLi under the same reaction conditions as employed for **1**, a significantly higher yield (69%) of the corresponding *C*5′-methylated product (**31**) was formed, suggesting that the presence of the 5,6-double bond in **1** might be responsible for the complexation, which could thwart the nucleophilic substitution at the 5′-position.

Finally, to examine the applicability of this approach to the introduction of an alkyl group to a secondary alcoholic carbon, the 3′-*O*-tosyl derivatives (**32** and **33**) of 2′-deoxyuridine and of 5-fluoro-2′-deoxyuridine were subjected to the reaction of Me_2CuLi (3 eq) in THF–ether. Column chromatography followed by preparative TLC of the reaction mixture provided 3′-deoxy-3′-methyl derivatives **34** (27%) and **35** (25%), respectively. In the reaction of **32**, a 12% yield of 5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyuridine was also formed. The *β*-stereochemistry of the introduced methyl group was confirmed by ^{1}H-NMR spectroscopy after converting them to the corresponding free nucleosides (**36** and **37**). That is, in their two dimensional nuclear Overhauser enhancement spectra (NOESY-spectra) measured in dimethyl sulfoxide (DMSO)-d_6, the enhancement correlation of the methyl group was observed with a 2′-proton that was correlated to H-6.

In conclusion, from the present preliminary study, it became apparent that nucleophilic substitution of tosyl derivatives of nucleosidic alcohol with Gilman reagent could offer a straightforward method for effecting C–C bond formation in the sugar moiety of nucleosides, especially in the reaction at the 5′-position of 2′-deoxyuridine derivatives. Further application of this methodology to the introduction of functionalized substituents is currently under investigation in our laboratory.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured at 23 °C (internal standard, Me_4Si) with either a JEOL JNM-FX 100 or a JEOL JNM-GX 400 spectrometer. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-240 spectrophotometer. Commercially available solutions of alkyllithiums were titrated before use with diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out on silica gel (Wakogel® C-200). Thin layer chromatography (TLC) was performed on silica gel (precoated Silica gel plate F_{254}, Merck).

2′,3′-*O*-Isopropylidene-5′-*O*-(*p*-nitrobenzenesulfonyl)uridine (3) A pyridine (2 ml) solution of *p*-nitrobenzenesulfonyl chloride (441 mg, 1.99 mmol) was added dropwise to a solution of 2′,3′-*O*-isopropylideneuridine (379 mg, 1.33 mmol) in pyridine (4 ml) at 0 °C, and the resulting mixture was kept in a refrigerator overnight. The reaction was quenched with ice, and the reaction mixture was partitioned between H_2O and $CHCl_3$. The organic layer was separated, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on a silica gel column (2% EtOH in $CHCl_3$). This gave **3** (431 mg, 69%) as a foam.

^{1}H-NMR ($CDCl_3$) δ: 1.33 and 1.53 (3H each, s, $CH\underline{Me_2}$), 4.33—4.40 (3H, m, CH_2-5′ and H-4′), 4.80 (1H, dd, $J=3.7$, 6.4 Hz, H-3′), 5.04 (1H, dd, $J=1.1$, 6.4 Hz, H-2′), 5.47 (1H, d, $J=1.1$ Hz, H-1′), 5.74 (1H, d, $J=8.1$ Hz, H-5), 7.17 (1H, d, $J=8.1$ Hz, H-6), 8.10 and 8.38 (4H, each as d, $J=9.2$ Hz, Ph), 9.40 (1H, br, NH). MS *m/z*: 469 (M^+), 454 (M^+-Me). UV absorption in MeOH: max 254 nm, min 225 nm.

5′-Deoxy-5′-methyl-2′,3′-*O*-isopropylideneuridine (5) MeLi (11.7 mmol) in ether (12.9 ml) was added dropwise to an ether (10 ml) suspension of CuI (1.11 g, 5.85 mmol) at 0 °C under positive pressure of dry argon. After 10 min, a THF (10 ml) solution of **1** (856 mg, 1.95 mmol) was added dropwise to the above solution of Me_2CuLi and the reaction mixture was stirred at 0 °C for 20 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), evaporated, and chromatographed on a silica gel column (4% EtOH in $CHCl_3$). The fractions containing **1** and **5** were evaporated to dryness and treated with DBU (0.44 ml, 2.93 mmol) in CH_3CN (10 ml) at refluxing temperature for 6 h. Evaporation of the solvent followed by column chromatographic purification (2% EtOH in $CHCl_3$) gave **5** (192 mg, 35%) as a foam.

^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, $J=7.3$ Hz, Me-5′), 1.35 and 1.57 (3H each, s, $CH\underline{Me_2}$), 1.67—1.74 (2H, m, CH_2-5′), 3.97—4.00 (1H, m, H-4′), 4.57 (1H, dd, $J=4.8$, 6.6 Hz, H-3′), 4.90 (1H, dd, $J=2.2$, 6.6 Hz, H-2′), 5.67 (1H, d, $J=2.2$ Hz, H-1′), 5.74 (1H, dd, $J=2.2$, 8.1 Hz, H-5), 7.25 (1H, d, $J=8.1$ Hz, H-6), 8.89 (1H, br, NH). MS *m/z*: 282 (M^+), 267 (M^+-Me). UV absorption in MeOH: max 259 nm, min 228 nm.

2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-O^2,5′-cyclouridine (7) A mixture of **6** (2.76 g, 12.2 mmol), *tert*-butyldimethylsilyl chloride (5.52 g, 36.6 mmol), and imidazole (5.0 g, 73.3 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) was stirred at room temperature for 25 h. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer separated was dried (Na_2SO_4), evaporated, and chromatographed on a silica gel column (2% EtOH in $CHCl_3$). This gave **7** (3.08 g, 57%) as a powder.

^{1}H-NMR ($CDCl_3$) δ: 0.03, 0.09, 0.14, and 0.15 (12H, each as s, SiMe), 0.91 and 0.94 (18H, each as s, SiBu-*tert*), 4.17 and 4.39 (2H, each as dd, $J=1.1$, 11.7 Hz, CH_2-5′), 4.46—4.49 (2H, m, H-3′ and H-4′), 4.59 (1H, dd, $J=1.1$, 5.9 Hz, H-2′), 5.23 (1H, s, H-1′), 6.12 (1H, d, $J=7.7$ Hz, H-5), 7.29 (1H, d, $J=7.7$ Hz, H-6). MS *m/z*: 454 (M^+), 397 (M^+-Bu-*tert*). UV absorption in MeOH: max 237 nm, min 213 nm.

2′,3′-Bis-*O*-(*tert*-butyldimethylsilyl)-5′-deoxy-5′-methyluridine (8) MeLi in ether (3.0 ml, 3.0 mmol) was added to an ether (5 ml) suspension of CuI (286 mg, 1.5 mmol) at 0 °C. A THF (5 ml) solution of **7** (227 mg, 0.5 mmol) was added to the above clear solution of the reagent during 15 min and the reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with $CHCl_3$, and then the extract was dried (Na_2SO_4), and evaporated. Chromatographic purification of the residue gave **8** (188 mg, 80%), which was crystallized from EtOH to give an analytical sample (mp 199—200 °C).

Anal. Calcd for $C_{22}H_{42}N_2O_5Si_2$: C, 56.16; H, 9.00; N, 5.95. Found: C, 56.31; H, 9.19; N, 5.99. ^{1}H-NMR ($CDCl_3$) δ: 0.08 and 0.09 (12H, each as s, SiMe), 0.90 and 0.91 (18H, each as s, SiBu-*tert*), 1.07 (3H, t, $J=7.3$ Hz, 5′-

Me), 1.51—1.57 and 1.72—1.77 (2H, each as m, CH_2-5′), 3.68—3.70 (1H, m, H-4′), 3.93—3.98 (1H, m, H-3′), 4.14 (1H, t, J=4.0 Hz, H-2′), 5.69 (1H, d, J=4.0 Hz, H-1′), 5.75 (1H, dd, J=2.2, 8.1 Hz, H-5), 7.33 (1H, d, J=8.1 Hz, H-6), 8.21 (1H, br, NH). MS *m/z*: 455 (M^+ − Me), 413 (M^+ − Bu-*tert*). UV absorption in MeOH: max 261 nm (ε 9800), min 230 nm (ε 2600).

5′-Butyl-5′-deoxy-2′3′-*O*-isopropylideneuridine (9) BuLi in hexane (4.6 ml, 6.0 mmol) was added dropwise to a THF (8 ml) solution of CuBr·Me_2S (617 mg, 3.0 mmol) at −50 °C under positive pressure of dry argon. To the above mixture, a THF (8 ml) solution of **1** (438 mg, 1.0 mmol) was added dropwise at −50 °C and the whole was stirred for 9 h at −20 °C. The reaction was quenched with aqueous NH_4Cl. $CHCl_3$ was added to the mixture and the whole was sonicated. The organic layer was separated, dried (Na_2SO_4), and chromatographed on a silica gel column (4% EtOH in $CHCl_3$). This gave **9** (97 mg, 30%) as a foam.

^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.2 Hz, Me in Bu), 1.35 and 1.57 (3H each, s, CHMe_2), 1.26—1.42 and 1.65—1.71 (8H, each as m, CH_2-5′ and $(CH_2)_3$ in Bu), 4.02 (1H, dd, J=6.6, 11.9 Hz, H-4′), 4.55 (1H, t, J=6.6 Hz, H-3′), 4.89 (1H, dd, J=2.2, 6.6 Hz, H-2′), 5.66 (1H, d, J=2.2 Hz, H-1′), 5.74 (1H, d, J=8.1 Hz, H-5), 7.24 (1H, d, J=8.1 Hz, H-6), 8.86 (1H, br, NH). MS *m/z*: 324 (M^+), 309 (M^+ − Me). UV absorption in MeOH: max 259 nm, min 229 nm.

5′-*sec*-Butyl-5′-deoxy-2′,3′-*O*-isopropylideneuridiene (10) This compound was obtained in 16% yield as a foam from **1** (219 mg, 0.5 mmol) in THF (5 ml) by the same procedure as described for the preparation of **9**. The following amounts of reagents and solvents were used: CuBr·Me_2S (308 mg, 1.5 mmol) in THF (5 ml), *sec*-butyllithium in cyclohexane (3.3 ml, 3.0 mmol). The reaction was continued for 8 h at −30 °C.

^{1}H-NMR ($CDCl_3$) δ: 0.88 and 0.90 (3H, each as t, J=7.3 Hz, ω-Me in *sec*-Bu), 0.93 (3H, d, J=6.6 Hz, α-Me in *sec*-Bu), 1.35 and 1.57 (3H, each, s, CHMe_2), 1.17—1.74 (5H, m, CH_2-5′ and CH + CH_2 in *sec*-Bu), 4.10—4.15 (1H, m, H-4′), 4.50—4.54 (1H, m, H-3′), 4.86—4.89 (1H, m, H-2′), 5.67 (1H, m, H-1′), 5.73 (1H, dd, J=2.2, 8.1 Hz, H-5), 7.23 and 7.24 (1H, each as d, J=8.1 Hz, H-6), 8.17 (1H, br, NH). MS *m/z*: 324 (M^+), 309 (M^+ − Me). UV absorption in MeOH: max 259 nm, min 233 nm.

5′-Deoxy-2′,3′-*O*-isopropylidene-5,5′-dimethyluridine (11) This compound was obtained in 37% yield as a foam from 2′,3′-*O*-isopropylidene-5′-*O*-(*p*-toluenesulfonyl)-5-methyluridine (204 mg, 0.45 mmol) in THF (1.5 ml) by the same procedure as described for the preparation of **5** from **1**. The following amounts of reagents and solvents were used: CuI (257 mg, 1.35 mmol) in ether (1.5 ml), MeLi in ether (3.16 ml, 2.7 mmol). The reaction was continued for 22 h at 0 °C. DBU treatment of the crude product followed by column chromatographic purification (4% EtOH in $CHCl_3$) gave **11**.

^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.3 Hz, 5′-Me), 1.26 and 1.48 (3H each, s, CHMe_2), 1.61—1.68 (2H, m, CH_2-5′), 1.84 (3H, s, 5-Me), 3.83—3.87 (1H, dd, J=7.0, 11.7 Hz, H-4′), 4.50—4.53 (1H, m, H-3′), 4.87 (1H, dd, J=2.2, 6.6 Hz, H-2′), 5.58 (1H, d, J=2.2 Hz, H-1′), 7.22 (1H, s, H-6), 9.99 (1H, br, NH). MS *m/z*: 296 (M^+), 281 (M^+ − Me). UV absorption in MeOH: max 262 nm, min 231 nm.

5′-Deoxy-5-fluoro-2′,3′-*O*-isopropylidene-5′-methyluridine (12) This compound was obtained in 51% yield as a foam from 5-fluoro-2′,3′-*O*-isopropylidene-5′-*O*-(*p*-toluenesulfonyl)uridine (283 mg, 0.52 mmol) in THF (2 ml) by the same procedure as described for the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (297 mg, 1.56 mmol) in ether (2 ml), MeLi in ether (2.78 ml, 3.12 mmol). The reaction was continued for 28 h at 0 °C.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.3 Hz, 5′-Me), 1.35 and 1.57 (3H each, s, CHMe_2), 1.67—1.79 (2H, m, CH_2-5′), 3.96—4.01 (1H, m, H-4′), 4.53 (1H, dd, J=4.6, 6.6 Hz, H-3′), 4.85 (1H, dd, J=2.2, 6.6 Hz, H-2′), 5.71 (1H, d, J=2.2 Hz, H-1′), 7.35 (1H, d, J=5.5 Hz, H-6), 9.73 (1H, br, NH). MS *m/z*: 300 (M^+), 285 (M^+ − Me). UV absorption in MeOH: max 265 nm, min 232 nm.

5-Bromo-5′-deoxy-2′,3′-*O*-isopropylidene-5′-methyluridine (14) This compound was obtained in 22% yield as a foam from 5-bromo-2′,3′-*O*-isopropylidene-5′-*O*-(*p*-toluenesulfonyl)uridine (259 mg, 0.5 mmol) in THF (1.5 ml) by the same procedure as described for the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (286 mg, 1.5 mmol) in ether (1.5 ml). MeLi in ether (2.67 ml, 3.0 mmol). The reaction was continued for 26 h at 0 °C.

^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7.3 Hz, 5′-Me), 1.35 and 1.57 (3H each, s, CHMe_2), 1.68—1.80 (2H, m, CH_2-5′), 3.97—4.00 (1H, m, H-4′), 4.55 (1H, dd, J=4.8, 6.6 Hz, H-3′), 4.87 (1H, dd, J=2.2, 6.6 Hz, H-2′), 5.67 (1H, d, J=2.2 Hz, H-1′), 7.58 (1H, s, H-6), 8.87 (1H, br, NH). MS *m/z*: 362 and 360 (M^+), 347 and 345 (M^+ − Me), 192 and 190 (B + 1). UV absorption in MeOH: max 272 nm, min 241 nm.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-5′-*O*-(*p*-toluenesulfonyl)uridine (15) A mixture of 2′-deoxy-5′-*O*-(*p*-toluenesulfonyl)uridine (423 mg, 1.1 mmol), *tert*-butyldimethylsilyl chloride (331 mg, 2.2 mmol), and imidazole (449 mg, 6.6 mmol) in DMF (5 ml) was stirred at room temperature for 22 h. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer was separated, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on a silica gel column (2% EtOH in $CHCl_3$). This gave **15** (536 mg, 98%) as a powder.

^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s, SiMe), 0.86 (9H, s, SiBu-*tert*), 1.99—2.28 (2H, m, CH_2-2′), 2.46 (3H, s, Me in tosyl), 3.99 (1H, m, H-4′), 4.20 (2H, m, CH_2-5′), 4.29—4.42 (1H, m, H-3′), 5.68 (1H, d, J=8.1 Hz, H-5), 6.24 (1H, t, J=6.6 Hz, H-1′), 7.37 and 7.79 (4H, each as d, J=8.1 Hz, Ph), 7.41 (1H, d, J=8.1 Hz, H-6), 9.10 (1H, br, NH). MS *m/z*: 496 (M^+), 481 (M^+ − Me), 439 (M^+ − Bu-*tert*). UV absorption in MeOH: max 260 nm, min 240 nm.

3′-*O*-(*tert*-Butyldimethylsilyl)-5′-*O*-(*p*-toluenesulfonyl)thymidine (16) This compound was obtained in 92% yield as a foam from 5′-*O*-(*p*-toluenesulfonyl)thymidine (1.36 g, 3.44 mmol) by the same procedure as described for the preparation of **15**.

^{1}H-NMR ($CDCl_3$) δ: 0.03 and 0.05 (6H, each as s, SiMe), 0.86 (9H, s, SiBu-*tert*), 1.95 (3H, s, 5-Me), 2.09—2.26 (2H, m, CH_2-2′), 2.47 (3H, s, Me in tosyl), 3.97—4.02 (1H, m, H-4′), 4.18—4.24 (2H, m, CH_2-5′), 4.30—4.40 (1H, m, H-3′), 6.30 (1H, t, J=6.6 Hz, H-1′), 7.37 and 7.80 (4H, each as d, J=8.1 Hz, Ph), 7.37 (1H, s, H-6), 8.91 (1H, br, NH). MS *m/z*: 453 (M^+ − Bu-*tert*), 126 (B + 1). UV absorption in MeOH: max 265 nm, min 240 nm.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-5-fluoro-5′-*O*-(*p*-toluenesulfonyl)uridine (17) This compound was obtained in 88% yield as a foam from 2′-deoxyl-5-fluoro-5′-*O*-(*p*-toluenesulfonyl)uridine (850 mg, 2.31 mmol) by the same procedure as described for the preparation of **15**.

^{1}H-NMR ($CDCl_3$) δ: 0.06 and 0.07 (6H, each as s, SiMe), 0.87 (9H, s, SiBu-*tert*), 2.01—2.08 and 2.26—2.32 (2H, each as m, CH_2-2′), 2.47 (3H, s, Me in tosyl), 4.03 (1H, m, H-4′), 4.19—4.27 (2H, m, CH_2-5′), 4.38—4.41 (1H, m, H-3′), 6.23 (1H, t, J=6.2 Hz, H-1′), 7.38 and 7.81 (4H, each as d, J=8.1 Hz, Ph), 7.51 (1H, d, J=6.2 Hz, H-6), 8.36 (1H, br, NH). MS *m/z*: 541 (M^+), 457 (M^+ − Bu-*tert*). UV absorption in MeOH: max 265 nm, min 240 nm.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′,5′-dideoxy-5′-methyluridine (18) This compound was obtained in 90% yield as a powder from **15** (199 mg, 0.4 mmol) in THF (1.5 ml) by the same procedure as described for the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (229 mg, 1.2 mmol) in ether (1.5 ml), MeLi in ether (2.3 ml, 2.4 mmol). The reaction was continued for 26 h at 0 °C.

^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s, SiMe), 0.90 (9H, s, SiBu-*tert*), 1.04 (3H, t, J=7.3 Hz, 5′-Me), 1.59—1.69 (2H, m, CH_2-5′), 1.97—2.04 and 2.31—2.37 (2H, each as m, CH_2-2′), 3.74—3.79 (1H, m, H-4′), 4.04—4.08 (1H, m, H-3′), 5.75 (1H, dd, J=2.2, 8.1 Hz, H-5), 6.15 (1H, t, J=6.6 Hz, H-1′), 7.38 (1H, d, J=8.1 Hz, H-6), 8.41 (1H, br, NH). MS *m/z*: 283 (M^+ − Bu-*tert*). UV absorption in MeOH: max 260 nm, min 232 nm.

3′-*O*-(*tert*-Butyldimethylsilyl)-5′-deoxy-5′-methylthymidine (19) This compound was obtained in 86% yield as a foam from **16** (255 mg, 0.5 mmol) in THF (1.5 ml) by the same procedure as described for the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (286 mg, 1.5 mmol) in ether (1.5 ml), MeLi in ether (2.67 ml, 3.0 mmol). The reaction was continued for 24 h at 0 °C.

^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s, SiMe), 0.89 (9H, s, SiBu-*tert*), 1.04 (3H, t, J=7.3 Hz, 5′-Me), 1.56—1.73 (2H, m, CH_2-5′), 1.94 (3H, s, 5-Me), 1.99—2.06 and 2.26—2.33 (2H, each as m, CH_2-2′), 3.72—3.76 (1H, m, H-4′), 4.06—4.09 (1H, m, H-3′), 6.19 (1H, t, J=6.6 Hz, H-1′), 7.16 (1H, s, H-6), 9.50 (1H, br, NH). MS *m/z*: 354 (M^+), 297 (M^+ − Bu-*tert*). UV absorption in MeOH: max 264 nm, min 235 nm.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′,5′-dideoxy-5-fluoro-5′-methyluridine (20) This compound was obtained in 74% yield as a foam from **17** (257 mg, 0.5 mmol) in THF (2 ml) by the same procedure as described for the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (286 mg, 1.5 mmol) in ether (1.5 ml), MeLi in ether (2.67 ml, 3.0 mmol). The raction was continued for 24 h at 0 °C.

^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s, SiMe), 0.89 (9H, s, SiBu-*tert*), 1.05 (3H, t, J=7.3 Hz, 5′-Me), 1.57—1.72 (2H, m, CH_2-5′), 1.95—2.05 and 2.33—2.39 (2H, each as m, CH_2-2′), 3.75—3.99 (1H, m, H-4′), 4.05—4.08 (1H, m, H-3′), 6.14—6.17 (1H, m, H-1′), 7.44 (1H, d, J=5.9 Hz, H-6), 9.93

(1H, br, NH). MS *m/z*: 301 (M^+ − Bu-*tert*). UV absorption in MeOH: max 260 nm, min 242 nm.

General Procedure for Deprotection of 5 and 9—14 The respective 5′-alkylated 5′-deoxy-2′,3′-*O*-isopropylidene derivative was dissolved in 50% aqueous CF_3CO_2H and the solution was stirred for 1—5 h. The reaction mixture was evaporated to dryness and the residue was chromatographed on a silica gel column (5—10% EtOH in $CHCl_3$). This gave the corresponding free nucleoside.

5′-Deoxy-5′-methyluridine (21) This compound was obtained from **5** in 60% yield. Crystallization from EtOH gave an analytical sample (mp 183—184 °C).

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.59; H, 5.88; N, 11.57. Found: C, 49.30; H, 5.82; N, 11.67. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7.3 Hz, 5′-Me), 1.53–1.69 (2H, m, CH_2-5′), 3.62—3.67 (1H, m, H-4′), 3.74 (1H, dd, J=5.5 Hz, H-3′), 4.03 (1H, q, J=5.5 Hz, H-2′), 5.03 and 5.30 (2H, each as d, J=5.5 Hz, OH), 5.63 (1H, dd, J=2.2, 8.1 Hz, H-5), 5.70 (1H, d, J=5.5 Hz, H-1′), 7.55 (1H, d, H-6), 11.31 (1H, br, NH). MS *m/z*: 242 (M^+), 131 (M^+ − B), 112 (B + 1). UV absorption in MeOH: max 262 nm (e 10200), min 231 nm (e 2700).

5′-Butyl-5′-deoxyuridine (22) This compound was obtained from **9** in 73% yield. Crystallization from EtOH gave an analytical sample (mp 160—161 °C).

Anal. Calcd for $C_{13}H_{20}N_2O_5$: C, 54.92; H, 7.09; N, 9.85. Found: C, 55.05; H, 7.10; N, 9.85. ^{1}H-NMR (DMSO-d_6) δ: 0.87 (3H, t, J=6.6 Hz, α-Me in Bu), 1.25—1.33 and 1.50—1.65 (8H, each as m, CH_2-5′ and CH_2 in Bu), 3.17—3.32 (1H, overlapped with H_2O, H-4′), 3.69—3.74 (1H, m, H-3′), 4.03 (1H, t, J=4.8 Hz, H-2′), 4.95—5.10 (1H, m, OH), 5.25—5.38 (1H, m, OH), 5.63 (1H, dd, J=2.2, 8.1 Hz, H-5), 5.69 (1H, d, J=4.8 Hz, H-1′), 7.55 (1H, d, J=8.1 Hz, H-6), 11.32 (1H, br, NH). MS *m/z*: 284 (M^+), 173 (M^+ − B), 112 (B + 1). UV absorption in MeOH: max 261 nm (ε 10000), min 230 nm (ε 2700).

5′-*sec*-Butyl-5′-deoxyuridine (23) This compound was obtained as a foam from **10** in 79% yield.

Anal. Calcd for $C_{13}H_{20}N_2O_5$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.67; H, 7.32; N, 9.75. ^{1}H-NMR (DMSO-d_6) δ: 0.83—0.89 (6H, m, α-Me and ω-Me in *sec*-Bu), 1.07—1.62 (5H, m, CH_2-5′ and CH + CH_2 in *sec*-Bu), 3.67—3.71 (1H, m, H-4′), 3.76—3.82 (1H, m, H-3′), 4.02 (1H, m, H-2′), 4.96—5.48 (2H, m, OH), 5.59 (1H, d, J=7.7 Hz, H-5), 5.70 (1H, d, J=4.4 Hz, H-1′), 7.50 and 7.51 (1H, each as d, J=7.7 Hz, H-6), 11.33 (1H, br, NH). MS *m/z*: 284 (M^+), 173 (M^+ − B), 112 (B + 1). UV absorption in MeOH: max 262 nm (ε 10000), min 230 nm (ε 2400).

5′-Deoxy-5,5′-dimethyluridine (24) This compound was obtained from **11** in 80% yield. Crystallization from EtOH gave an analytical sample (mp 175—176 °C).

Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.27; H, 6.24; N, 10.80. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7.3 Hz, 5′-Me), 1.54—1.69 (2H, m, CH_2-5′), 1.80 (3H, s, 5-Me), 3.60—3.62 (1H, m, H-4′), 3.74—3.77 (1H, m, H-3′), 4.05—4.06 (1H, m, H-2′), 4.98 and 5.25 (2H, each as br, OH), 5.70 (1H, d, J=5.1 Hz, H-1′), 7.38 (1H, s, H-6), 11.28 (1H, br, NH). MS *m/z*: 256 (M^+), 131 (M^+ − B), 126 (B + 1). UV absorption in MeOH: max 266 nm (ε 9000), min 234 nm (ε 2000).

5′-Deoxy-5-fluoro-5′-methyluridine (25) This compound was obtained from **12** in 75% yield. Crystallization from EtOH gave an analytical sample (169—170 °C).

Anal. Calcd for $C_{10}H_{13}FN_2O_5$: C, 46.16; H, 5.04; N, 10.77. Found: C, 46.45; H, 5.41; N, 10.61. ^{1}H-NMR (DMSO-d_6) δ: 0.94 (3H, t, J=7.3 Hz, 5′-Me), 1.56—1.70 (2H, m, CH_2-5′), 3.61—3.64 (1H, m, H-4′), 3.72—3.75 (1H, m, H-3′), 4.93 and 5.21 (2H, each as br, OH), 5.66 (1H, d, J=5.1 Hz, H-1′), 7.81 (1H, d, J=5.9 Hz, H-6), 11.80 (1H, br, NH). MS *m/z*: 260 (M^+). UV absorption in MeOH: max 267 nm (ε 8500), min 234 nm (ε 2100).

5-Bromo-5′-deoxy-5′-methyluridine (26) This compound was obtained from **14** in 83% yield. Crystallization from EtOH gave an analytical sample (mp 207—208 °C).

Anal. Calcd for $C_{10}H_{13}BrN_2O_5$: C, 37.40; H, 4.08; N, 8.72. Found: C, 37.56; H, 4.30; N, 8.80. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, t, J=7.3 Hz, 5′-Me), 1.54—1.70 (2H, m, CH_2-5′), 3.58—3.63 (1H, m, H-4′), 3.75—3.77 (1H, m, H-3′), 4.03—4.05 (1H, m, H-2′), 5.06 and 5.33 (2H, each as br, OH), 5.69 (1H, d, J=5.5 Hz, H-1′), 7.35 (1H, s, H-6), 11.24 (1H, br, NH). MS *m/z*: 190 and 192 (B + 1), 131 (M^+ − B). UV absorption in MeOH: max 278 nm (ε 9200), min 240.5 nm (ε 1700).

General Procedure for Deprotection of 18—20 The respective 2′,5′-dideoxy-3′-*O*-(*tert*-butyldimethylsilyl)-5′-methyluridine derivative was dissolved in THF and treated with 2 eq of tetrabutylammonium fluoride trihydrate at room temperature for 3 h. The reaction mixture was diluted with EtOH and evaporated to dryness. The residue was chromatographed on a silica gel column (5—10% EtOH in $CHCl_3$). This gave the respective free nucleoside.

2′,5′-Dideoxy-5′-methyluridine (27) This compound was obtained from **18** in 85% yield. Crystallization from EtOH gave an analytical sample (mp 148—149 °C).

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.33; H, 6.47; N, 12.43. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7.3 Hz, 5′-Me), 1.49—1.64 (2H, m, CH_2-5′), 2.04—2.15 (2H, m, CH_2-2′), 3.59 (1H, m, H-4′), 4.02 (1H, m, H-3′), 5.23 (1H, d, J=3.7 Hz, OH), 5.63 (1H, d, J=8.1 Hz, H-5), 6.10 (1H, t, J=6.6 Hz, H-1′), 7.54 (1H, d, J=8.1 Hz, H-6), 11.30 (1H, br, NH). MS *m/z*: 115 (M^+ − B), 112 (B + 1). UV absorption in MeOH: max 262 nm (ε 10000), min 228 nm (ε 2500).

5′-Deoxy-5′-methylthymidine (28) This compound was obtained from **19** in 89% yield. Crystallization from EtOH gave an analytical sample (mp 191—192 °C).

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.92; H, 6.70; N, 11.67. Found: C, 55.09; H, 6.86; N, 11.65. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (3H, t, J=7.3 Hz, 5′-Me), 1.51—1.61 (2H, m, CH_2-5′), 1.79 (3H, s, 5-Me), 2.00—2.05 and 2.08—2.17 (2H, each as m, CH_2-2′), 3.53—3.57 (1H, m, H-4′), 3.99—4.03 (1H, m, H-3′), 5.17 (1H, br, OH), 6.11 (1H, t, J=6.2 Hz, H-1′), 7.34 (1H, s, H-6), 11.24 (1H, br, NH). MS *m/z*: 240 (M^+), 126 (B + 1), 115 (M^+ − B). UV absorption in MeOH: max 266 nm (ε 9000), min 234 nm (ε 2000).

2′,5′-Dideoxy-5-fluoro-5′-methyluridine (29) This compound was obtained from **20** in 73% yield. Crystallization from EtOH gave an analytical sample (mp 182—183 °C).

Anal. Calcd. for $C_{10}H_{13}FN_2O_4$: C, 49.18; H, 5.37; N, 11.47. Found: C, 48.91; H, 5.34; N, 11.30. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, J=7.3 Hz, 5′-Me), 1.52—1.66 (2H, m, CH_2-5′), 2.02—2.07 and 2.14—2.21 (2H, m, CH_2-2′), 3.55—3.60 (1H, m, H-4′), 4.01—4.04 (1H, m, H-3′), 5.21 (1H, d, J=2.6 Hz, OH), 6.08 (1H, m, H-1′), 7.80 (1H, d, J=5.1 Hz, H-6), 11.83 (1H, br, NH). MS *m/z*: 244 (M^+), 130 (B + 1), 115 (M^+ − B). UV absorption in MeOH: 269 nm (ε 8800), min 235 nm (ε 2100).

5,6-Dihydro-2′,3′-*O*-isopropylidene-5′-*O*-(*p*-toluenesulfonyl)uridine (30) 2′,3′-*O*-Isopropylideneuridine (568 mg, 2 mmol) was dissolved in MeOH (60 ml) and hydrogenated in the presence of 5% Rh on Al_2O_3 (121 mg) for 3 h, after which disappearance of the UV absorption at 260 nm was confirmed. The catalyst was removed from the mixture containing the corresponding 5,6-dihydro derivative by filtration. The filtrate was evaporated to dryness and dissolved in dry pyridine (5 ml). The resulting solution was treated with a pyridine (3 ml) solution of *p*-toluenesulfonyl chloride (572 mg, 2.0 mmol) at 0 °C overnight. The reaction mixture was treated with ice and extracted with $CHCl_3$. The extract was dried (Na_2SO_4), and evaporated, and the residue was chromatographed on a silica gel column ($CHCl_3$). This gave **30** (527 mg, 60% yield from 2′,3′-*O*-isopropylideneuridine) as a foam.

^{1}H-NMR ($CDCl_3$) δ: 1.32 and 1.53 (3H each, s, $CH\underline{Me_2}$), 2.46 (3H, s, Me in tosyl), 2.66 (2H, t, J=5.9 Hz, CH_2-6), 3.42—3.49 (2H, m, CH_2-5), 4.20 (3H, m, H-4′ and CH_2-5′), 4.70 (1H, dd, J=2.0, 5.9 Hz, H-3′), 4.86 (1H, dd, J=2.9, 5.9 Hz, H-2′), 5.56 (1H, d, J=2.9 Hz, H-1′), 7.35 and 7.77 (4H, each as d, J=8.1 Hz, Ph). MS *m/z*: 440 (M^+), 425 (M^+ − Me).

5′-Deoxy-5,6-dihydro-2′,3′-*O*-isopropylidene-5′-methyluridine (31) This compound was prepared in 69% yield as a foam from **30** (159 mg, 0.36 mmol) in THF (2 ml) by the same procedure as described for the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (206 mg, 1.08 mmol) in ether (1 ml), MeLi in ether (1.92 ml, 2.16 mmol). The reaction was continued for 24 h at 0 °C.

^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.3 Hz, 5′-Me), 1.34 and 1.55 (3H each, s, $CH\underline{Me_2}$), 1.64—1.70 (2H, m, CH_2-5′), 2.65—2.75 (2H, m, CH_2-6), 3.42—3.52 (2H, m, CH_2-5), 3.81—3.86 (1H, m, H-4′), 4.43 (1H, dd, J=4.8, 6.8 Hz, H-3′), 4.88 (1H, dd, J=3.3, 6.8 Hz, H-2′), 5.64 (1H, d, J=3.3 Hz, H-1′), 7.84 (1H, br, NH). MS *m/z*: 269 (M^+ − Me), 171 (M^+ − B), 114 (B + 1).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-3′-*O*-(*p*-toluenesulfonyl)uridine (32) A mixture of 5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyuridine (454 mg, 1.33 mmol), *p*-toluenesulfonyl chloride (760 mg, 3.99 mmol), and 4-(dimethylamino)pyridine (DMAP) (309 mg, 2.53 mmol) in pyridine (5 ml) was stirred at room temperature for 2 d. The reaction was quenched with ice, and the mixture was extracted with $CHCl_3$. Column chromatographic purification (2% EtOH in $CHCl_3$) of the extract gave **32** (463 mg, 70%) as a foam.

^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, SiMe), 0.89 (9H, s, SiBu-*tert*), 1.89—2.18 (2H, m, CH_2-2′), 2.47 (3H, s, Me in tosyl), 3.74 and 3.86 (2H, each as dd, J=1.8, 11.5 Hz, CH_2-5′), 4.29 (1H, d, J=1.8 Hz, H-4′), 5.07 (1H, d,

$J=6.2$ Hz, H-3′), 5.67 (1H, dd, $J=2.2$, 8.4 Hz, H-5), 6.30 (1H, dd, $J=2.4$, 8.3 Hz, H-1′), 7.37 and 7.80 (4H, each as d, $J=8.4$ Hz, Ph), 7.75 (1H, d, $J=8.4$ Hz, H-6), 8.64 (1H, br, NH). MS m/z: 439 (M^+−Bu-*tert*), 112 (B+1). UV absorption in MeOH: max 260 nm, min 240 nm.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-5-fluoro-3′-*O*-(*p*-toluenesulfonyl)-uridine (33) This compound was obtained in 59% yield as a foam from 5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5′-fluorouridine (1.40 g, 3.88 mmol) by the same procedure as described for the preparation of **32**. The following amounts of reagents and 10 ml of pyridine were used: *p*-toluenesulfonyl chloride (2.21 g, 3.88 mmol), DMAP (900 mg, 7.37 mmol).

^{1}H-NMR ($CDCl_3$) δ: 0.12 (6H, s, SiMe), 0.91 (9H, s, SiBu-*tert*), 2.03—2.17 (2H, m, CH_2-2′), 2.48 (3H, s, Me in tosyl), 3.70—3.86 (2H, m, CH_2-5′), 4.31 (1H, d, $J=1.5$ Hz, H-4′), 5.06 (1H, d, $J=6.2$ Hz, H-3′), 6.30 (1H, m, H-1′), 7.38 and 7.80 (4H, each as d, $J=8.1$ Hz, Ph), 7.91 (1H, d, $J=5.9$ Hz, H-6), 8.58 (1H, br, NH). MS m/z: 457 (M^+−Bu-*tert*). UV absorption in MeOH: max 265 nm, min 240 nm.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-3′(*R*)-methyluridine (34) This compound was obtained in 27% yield as a foam from **32** (249 mg, 0.5 mmol) in THF (1 ml) by the same procedure as described in the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (286 mg, 1.5 mmol) in ether (1.5 ml), MeLi in ether (3.5 ml 3.0 mmol). The reaction was continued for 20 h at 0 °C. The starting material (**32**, 40%) and 5′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyuridine (12% yield) were also isolated.

^{1}H-NMR ($CDCl_3$) δ: 0.11 (6H, s, SiMe), 0.92 (9H, s, SiBu-*tert*), 1.17 (3H, d, $J=7.0$ Hz, 3′-Me), 1.72—1.80 and 2.37—2.43 (2H, each as m, $CH_2$2′), 2.58—2.63 (1H, m, H-3′), 3.71 and 3.90 (2H, each as dd, $J=2.6$, 11.2 Hz, CH_2-5′), 4.06—4.08 (1H, m, H-4′), 5.67 (1H, d, $J=8.1$ Hz, H-5), 6.07 (1H, dd, $J=5.5$, 8.8 Hz, H-1′), 8.03 (1H, d, $J=8.1$ Hz, H-6), 8.11 (1H, br, NH). MS m/z: 340 (M^+), 283 (M^+−Bu-*tert*). UV absorption in MeOH: max 260 nm, min 232 nm.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-5-fluoro-3′(*R*)-methyluridine (35) This compound was obtained in 25% yield as a foam from **33** (514 mg, 1.0 mmol) in THF (4 ml) by the same procedure as described for the preparation of **5** from **1**, except DBU treatment. The following amounts of reagents and solvents were used: CuI (571 mg, 3.0 mmol) in ether (4 ml), MeLi in ether (5.34 ml, 6.0 mmol). The reaction was continued for 24 h at 0 °C. The starting material (**33**) was also isolated in 38% yield.

^{1}H-NMR ($CDCl_3$) δ: 0.13 and 0.14 (6H, each as s, SiMe), 0.93 (9H, s, SiBu-*tert*), 1.19 (3H, d, $J=7.0$ Hz, 3′-Me), 1.73—1.81 and 2.37—2.47 (2H, each as m, CH_2-2′), 2.57—2.64 (1H, m, H-3′), 3.72 and 3.93 (2H, each as dd, $J=2.6$, 11.5 Hz, CH_2-5′), 4.07 (1H, dt, $J=2.6$, 8.4 Hz, H-4′), 6.06 (1H, ddd, $J_{1',2'}=5.5$, 8.8 Hz, $J_{1',F}=1.8$ Hz, H-1′), 8.17 (1H, d, $J=6.2$ Hz, H-6), 8.91 (1H, br, NH). MS m/z: 358 (M^+), 301 (M^+−Bu-*tert*). UV absorption in MeOH: max 268 nm, min 236 nm.

2′,3′-Dideoxy-3′(*R*)-methyluridine (36) This compound was obtained in 80% yield as a powder from **34** by the general procedure.

^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, d, $J=7.0$ Hz, 3′-Me), 1.66—1.74 and 2.23—2.29 (2H, each as m, CH_2-2′), 2.50 (1H, m, H-3′), 3.51 and 3.61 (2H, each as dd, $J=3.7$, 11.7 Hz, CH_2-5′), 3.94—3.98 (1H, m, H-4′), 4.89 (1H, br, 5′-OH), 5.61 (1H, d, $J=8.1$ Hz, H-5), 5.94 (1H, dd, $J=5.5$, 8.2 Hz, H-1′), 8.01 (1H, d, $J=8.1$ Hz, H-6), 11.18 (1H, br, NH). High resolution MS m/z: 226.0993 (M^+) Calcd for $C_{10}H_{14}N_2O_4$: 226.0953. UV absorption in MeOH: max 260 nm, min 230 nm.

2′,3′-Dideoxy-5-fluoro-3′(*R*)-methyluridine (37) This compound was obtained in 88% yield as a powder from **35** by the general procedure.

^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, d, $J=5.5$ Hz, 3′-Me), 1.70—1.77 and 2.21—2.27 (2H, each as m, CH_2-2′), 2.50 (1H, m, H-3′), 3.54 and 3.64 (2H, each as d, $J=11.7$ Hz, CH_2-5′), 3.98 (1H, d, $J=8.4$ Hz, H-4′), 5.05 (1H, br, 5′-OH), 5.95 (1H, t, $J=6.2$ Hz, H-1′), 8.39 (1H, d, H-6), 11.71 (1H, br, NH). High resolution MS m/z: 244.0852 Calcd for $C_{10}H_{13}FN_2O_4$: 244.0857. UV absorption in MeOH: max 269 nm, min 234 nm.

Acknowledgement Generous financial support (to H. H.) from Uehara Memorial Foundation is gratefully acknowledged.

References and Notes

1) H. Tanaka, H. Hayakawa, and T. Miyasaka, *Tetrahedron*, **38**, 2635 (1982).
2) H. Tanaka, H. Hayakawa, S. Iijima, K. Haraguchi, and T. Miyasaka, *Tetrahedron*, **41**, 861 (1985).
3) H. Hayakawa, H. Tanaka, and T. Miyasaka, *Tetrahedron*, **41**, 1675 (1985).
4) H. Tanaka, M. Hirayama, M. Suzuki, T. Miyasaka, A. Matsuda, and T. Ueda, *Tetrahedron*, **42**, 1971 (1986).
5) H. Tanaka, H. Hayakawa, K. Obi, and T. Miyasaka, *Tetrahedron*, **42**, 4187 (1986).
6) H. Hayakawa, H. Tanaka, K. Obi, M. Itoh, and T. Miyasaka, *Tetrahedron Lett.*, **28**, 87 (1987).
7) H. Hayakawa, K. Haraguchi, H. Tanaka, and T. Miyasaka, *Chem. Pharm. Bull.*, **35**, 72 (1987).
8) J. G. Moffatt, "Nucleoside Analogues," ed. by R. T. Walker, E. De Clercq, and F. Eckstein, Plenum Publishing Corporation, London, 1979, pp. 71—164.
9) For recent examples: H. Hayakawa, H. Tanaka, N. Itoh, M. Nakajima, T. Miyasaka, K. Yamaguchi, and Y. Iitaka, *Chem. Pharm. Bull.*, **35**, 2605 (1987); A. Matsuda, K. Takenuki, H. Itoh, T. Sasaki, and T. Ueda, *ibid.*, **35**, 3967 (1987).
10) A. Mete, J. B. Hobbs, D. I. C. Scopes, and R. F. Newton, *Tetrahedron Lett.*, **26**, 97 (1985); M. Ashwell, A. S. Jones, and R. T. Walker, *Nucleic Acids Res.*, **15**, 2157 (1987).
11) H. Tanaka, M. Fukui, K. Haraguchi, M. Masaki, and T. Miyasaka, *Tetrahedron Lett.*, **30**, 2567 (1989).
12) G. Etzolt, G. Kowwollik, and P. Langen, *J. Chem. Soc., Chem. Commun.*, **1968**, 422.
13) W. Meyer, E. Bohnke, and H. Follmann, *Angew. Chem. Int. Ed. Engl.*, **15**, 499 (1976).
14) Formation of cyclonucleosides during nucleophilic substitution reaction with cyanide ion has been reported: see references 12 and 13.
15) Use of 2 eq of Me_2CuLi decreased the yield to 15%.
16) Me_2CuLi has been used to convert *p*-nitrobenzoyl chloride to *p*-nitroacetophenone (in ether, at −78 °C, for 15 min): G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, **1970**, 4647.
17) B. H. Lipshutz, R. S. Wilhelm, and D. M. Floyd, *J. Am. Chem. Soc.*, **103**, 7672 (1981); B. H. Lipshutz, S. Whitney, J. Kozlowski, and C. M. Breneman, *Tetrahedron Lett.*, **1986**, 4273; S. H. Berrtz, C. P. Gibson, and G. Dabbagh, *ibid.*, **28**, 4251 (1987).
18) C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95**, 7783 (1973).
19) E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6015 (1985) and references cited therein.
20) Catalytic hydrogenation of **1** under the same conditions was found to be very sluggish, giving **30** (56%) after 4 d.