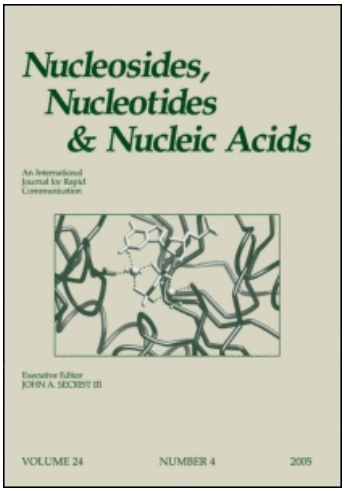

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Synthesis of 6-Methyluridine via Palladium-Catalyzed Cross-Coupling Between A 6-Iodouridine Derivative and Tetramethylstannane

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SYNTHESIS OF 6-METHYLURIDINE *VIA* PALLADIUM-CATALYZED CROSS-COUPLING BETWEEN A 6-IODOURIDINE DERIVATIVE AND TETRAMETHYLSTANNANE

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Abstract: 6-Methyluridine can be synthesized from 5'-*O*-(*tert*-butyldimethylsilyl)-6-iodo-2',3'-*O*-isopropylideneuridine *via* palladium-catalyzed cross-coupling with Me_4Sn followed by deprotection. Application of this method for the synthesis of 6-phenyluridine was also carried out.

Lithiation has now been recognized as an important method for the modification of nucleosides at the base moiety, since the lithio intermediate reacts with a wide range of electrophiles. Our study on the LDA (lithium diisopropylamide) lithiation of 2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (**1**) revealed that the C-6 position of **1** can be metallated regiospecifically to an extent of 88%. As a result, this method furnished a highly general entry to 6-substituted uridines as shown in Chart 1.[1)]

This paper is dedicated to the memory of the late Professor Tohru Ueda, an excellent scientist and a great teacher.

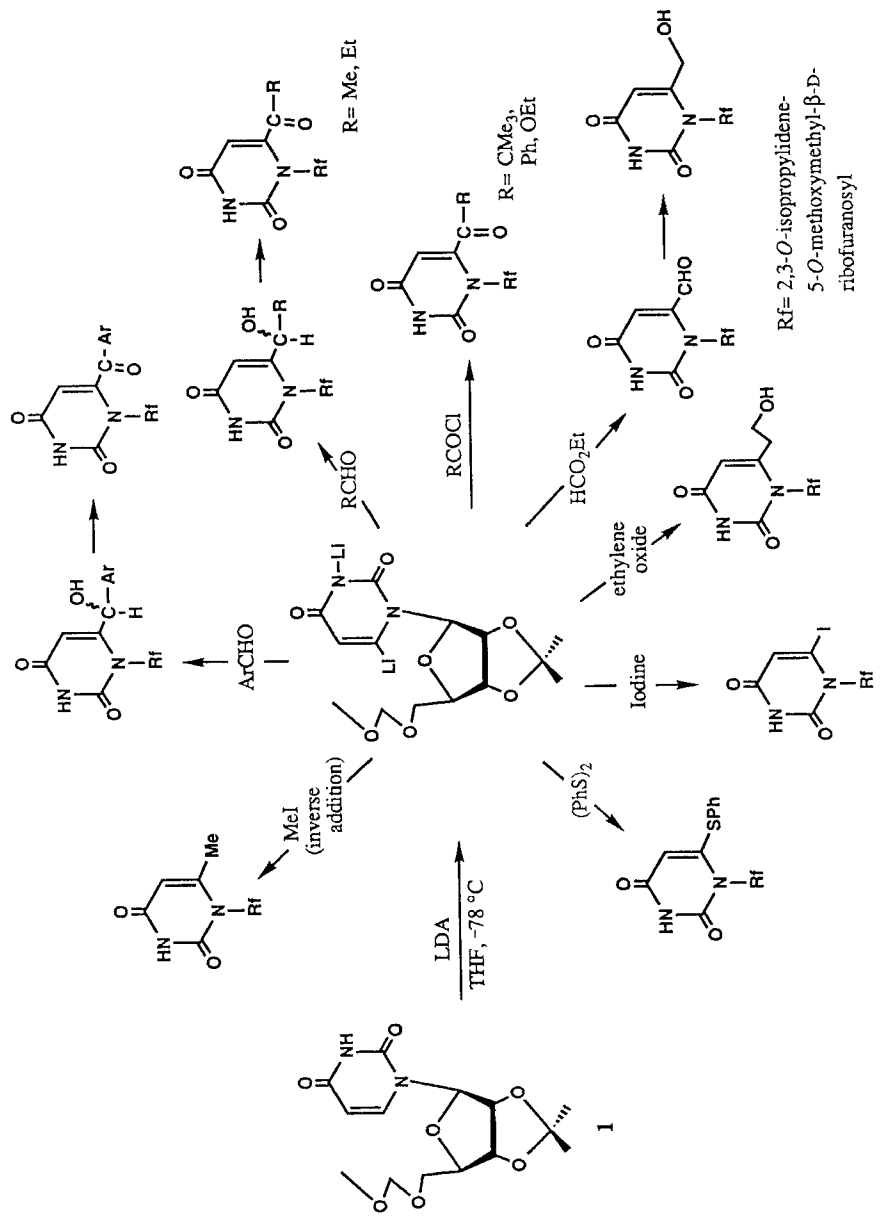
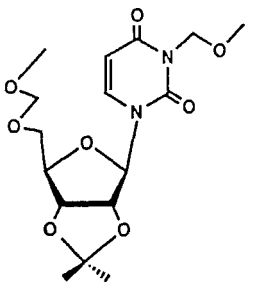


Chart 1

However, there have been several drawbacks in this method, which are in order: 1) though the starting material (**1**) has been prepared by treating 2',3'-*O*-isopropylideneuridine with dimethoxymethane in the presence of an acid,[2,3] it cannot be crystallized and also has to be separated from a by-product, 2',3'-*O*-isopropylidene-N^3,5'-*O*-bis(methoxymethyl)uridine (**2**); 2) for the preparation of



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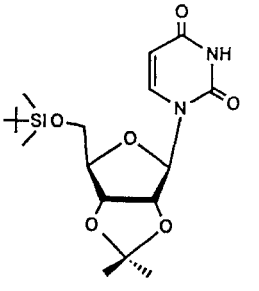


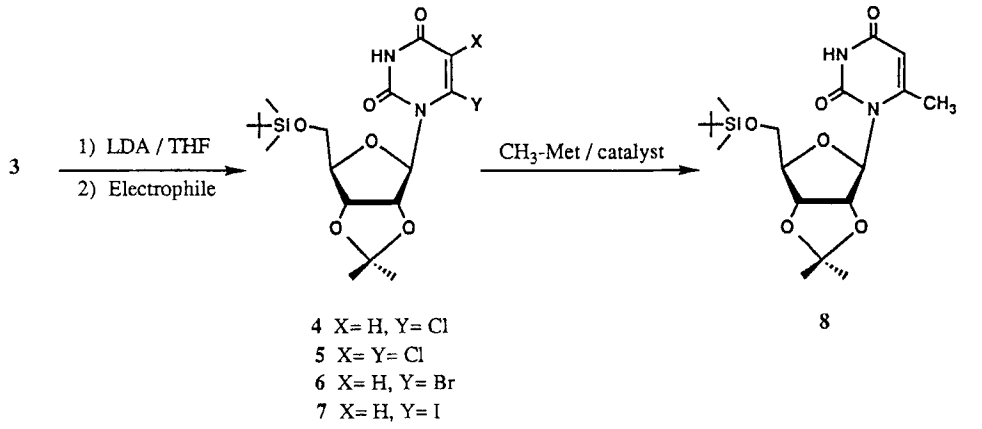
3

6-methyluridine, reaction between the lithiated of **1** and MeI has to be carried out by "inverse addition" method[4] to avoid further methylation of the introduced 6-methyl group which forms the 6-ethyl as well as 6-isopropyl derivatives.

One of the authors recently reported a palladium-catalyzed cross-coupling between 5-bromouridine and Me_3Al for synthesizing 5-methyluridine.[5] In the present study, by employing a crystalline starting material, 5'-*O*-(*tert*-butyldimethylsilyl)-2',3'-*O*-isopropylideneuridine (**3**),[6] as a substrate for the LDA lithiation, preparation of 6-halogeno derivatives was carried out and then their conversion to 6-methyluridine[7,8] was investigated based on the cross-coupling reaction.

Compound **3** was prepared in quantitative yield simply by treating 2',3'-*O*-isopropylideneuridine with *tert*-butyldimethylsilyl chloride in pyridine and crystallized from EtOH (mp 136-137 °C).

For the C-6 chlorination of **3**, tosyl chloride (TsCl) was used as an electrophile.[9] When **3** was treated with LDA (2.5 equiv) in THF below −70 °C and then reacted with TsCl (2.5 equiv) for 1 h, two products were formed. The desired 6-chloro derivative **4** was isolated as a main product in 52% yield.[10] The ^1H NMR spectrum of a minor product was devoid of a signal corresponding to the H-5. On the basis of its MS spectrum, the structure was deduced to be 5,6-



4 X= H, Y= Cl
5 X= Y= Cl
6 X= H, Y= Br
7 X= H, Y= I

8

Chart 2

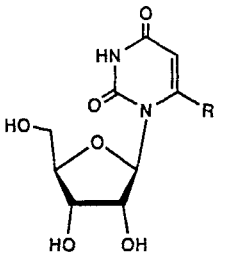
dichlorinated product (**5**). The yield was 31%. Although the formation of **5** could be reduced to a trace amount, when 1.2 equiv of TsCl was used, a considerable amount (45%) of the starting material (**3**) was recovered. The C-6 bromination was carried out by using phenacyl bromide. However, the yield of the 6-bromo derivative (**6**) was only 12%.

In contrast to the above results, 5'-*O*-(*tert*-butyldimethylsilyl)-6-iodo-2',3'-*O*-isopropylideneuridine (**7**) can be prepared in 88% yield as crystals (mp 99-101 °C) simply by employing iodine as an electrophile. We were unable to detect even a trace amount of 5,6-diiodinated product. Since 5,6-diiodouridine has been synthesized by the LDA lithiation of a 5-iodouridine derivative,[11] the sole formation of **7** in this reaction, which contrasts to the case of the above-mentioned chlorination, is not attributable to steric hindrance of the introduced iodine atom but would be explicable in terms of a poor electron-withdrawing inductive effect of the 6-iodo substituent.

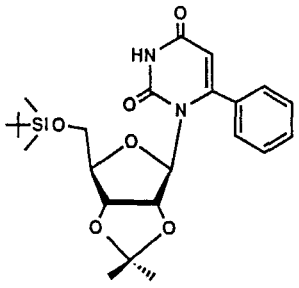
We next examined the synthesis of 6-methyluridine from **4** or **7**. When **4** was reacted with Me_3Al (2.0 equiv) in the presence of $(Ph_3P)_2PdCl_2$ (5 mol%) in THF at refluxing temperature, a significant amount of **4** remained even after 12 h and the desired **8** was obtained only in 15% yield together with an unknown product. Compound **7**, on the other hand, gave **8** in 61% yield under the same reaction conditions.[12]

In an alternative method to synthesize **8**, MeMgBr was used in combination with $Ni(dppp)Cl_2$.[13] When **7** was treated with MeMgBr (2.5 eq) in the presence of the catalyst (10 mol%) in refluxing THF for 5 h, the starting material was completely consumed. However, the major reaction path was found to be reductive removal of the iodine atom, forming **3** and **8** in a ratio of approximately 6:1. Although the use of **4** completely suppressed the formation of **3**, almost equal amounts of **4** and **8** resulted even after 12 h's reflux in dioxane.[14]

We found that tetramethylstannane, an organometallic with the less carbanionic character, is the most appropriate reagent for the conversion of **7** to **8**. Thus, when a dioxane solution of **7** was gently refluxed for 3 h in the presence of $(Ph_3P)_2PdCl_2$ (10 mol%) and Me_4Sn (10 equiv),[15] **8** was obtained in quantitative yield simply by evaporation of the solvent followed by column chromatography. An additional point to be mentioned is that the reaction proceeds much cleaner than the other two coupling reactions examined. Concurrent removal of the isopropylidene and *tert*-butyldimethylsilyl protecting groups of **8** was accomplished by the treatment with 50% aqueous trifluoroacetic acid to give **9** in high yield.



9 R= Me
11 R= Ph



10

Finally, as an application of this method, the introduction of a phenyl substituent was also carried out by the use of Ph_4Sn (5 equiv) and again the desired product (**10**) was obtained in almost quantitative yield (95%).[16-18] Deprotection of **10** gave 6-phenyluridine (**11**, mp 181-183 °C), which has previously been synthesized by photochemical reaction of a 6-iodouridine derivative but not in a crystalline form.[19] We believe the present approach has provided an entry to 6-substituted uridines which cannot be synthesized directly by the LDA lithiation.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. ^1H NMR spectra were measured with tetramethylsilane as an internal standard, with a JEOL JNM-FX 100 (100 MHz) NMR spectrometer. 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 used for the preparation of LDA was titrated by diphenylacetic acid in THF. THF was distilled from benzophenone ketyl. Column chromatography was carried out on a silica gel (Wakogel® C-200). TLC was performed on precoated silica gel plates F_{254}, Merck.

5'-*O*-(*tert*-Butyldimethylsilyl)-2',3'-*O*-isopropylideneuridine (3) To a pyridine (70 ml) solution of 2',3'-*O*-isopropylideneuridine (15.76 g, 55.4 mmol), *tert*-butyldimethylsilyl chloride (9.04 g, 60.0 mmol) was added and the resulting mixture was stirred overnight at room temperature. After addition of EtOH, the reaction mixture was evaporated and chromatographed on a short column of silica gel (1% EtOH in $CHCl_3$). This afforded **3** (21.8 g, 99%), which was crystallized from EtOH (mp 136-137 °C). *Anal.* Calcd for $C_{18}H_{30}N_2O_6Si$: C, 54.26; H, 7.59; N, 7.03. Found: C, 54.19; H, 7.89; N, 6.75. UV absorption in MeOH: λ_{max} 259 nm (ε 9600), λ_{min} 228 nm (ε 2000). ^1H NMR ($CDCl_3$) δ: 0.09 (6H, s, SiMe), 0.91 (9H, s, SiBu-*t*), 1.36 (3H, s, isop. Me), 1.59 (3H, s, isop. Me), 3.78 and 3.94 (2H, each as dd, $J_{4',5'}$= 2.4, J_{gem}= 11.4 Hz, CH_2-5'), 4.31 (1H, m, H-4'), 4.64-4.82 (2H, m, H-2' and H-3'), 5.68 (1H, dd, $J_{5,6}$= 8.0 Hz, H-5), 5.98 (1H, d, $J_{1',2'}$= 1.9 Hz, H-1'), 7.68 (1H, d, H-6), 9.17 (1H, br, NH). MS *m/z*: 383 (M^+–Me), 341 (M^+–Bu-*t*).

5'-*O*-(*tert*-Butyldimethylsilyl)-6-chloro-2',3'-*O*-isopropylideneuridine (4) and 5'-*O*-(*tert*-butyldimethylsilyl)-5,6-dichloro-2',3'-*O*-isopropylideneuridine (5) In a three-necked flask equipped with a gas-inlet adaptor, thermometer, and rubber septum, a THF (35 ml) solution of LDA (37.5 mmol) was prepared from BuLi and diisopropylamine below −70 °C. To this, **3** (5.99 g, 15.0 mmol) in THF (20 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, TsCl (7.20 g, 37.8 mmol) in THF (20 ml) was added, while maintaining the temperature below −70 °C. The reaction mixture was stirred for 1 h and quenched with AcOH (3.8 ml), and allowed to warm to room temperature. The whole was evaporated and partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic layer separated was dried (Na_2SO_4), evaporated, and chromatographed on a silica gel

column. Compound **4** (3.11 g, 52%, as a foam) and **5** (2.16 g, 31%, as a foam) were obtained by elution with 4% and 3% EtOAc in benzene, respectively.

Physical data of **4** are as follows. *Anal.* Calcd for $C_{18}H_{29}ClN_2O_6Si$: C, 49.95; H, 6.77; N, 6.47. Found: C, 50.10; H, 6.87; N, 6.40. UV absorption in MeOH: λ_{max} 260 nm (ε 8900), λ_{min} 231 nm (ε 3000). ^1H NMR ($CDCl_3$) δ: 0.05 (6H, s, SiMe), 0.89 (9H, s, SiBu-*t*), 1.34 (3H, s, isop. Me), 1.55 (3H, s, isop. Me), 3.80 (2H, m, CH_2-5'), 4.15 (1H, m, H-4'), 4.82 (1H, dd, $J_{2',3'}$= 6.3, $J_{3',4'}$= 4.8 Hz, H-3'), 5.20 (1H, d, H-2'), 5.90 (1H, d, $J_{3,5}$= 1.4 Hz, H-5), 6.25 (1H, s, H-1'), 9.43 (1H, br, NH). MS *m/z*: 419 and 417 (M^+–Me), 377 and 375 (M^+–Bu-*t*), 287 (M^+–B), 148 and 146 (B+1).

Physical data of **5** are as follows. *Anal.* Calcd for $C_{18}H_{28}Cl_2N_2O_6Si$: C, 46.26; H, 6.04; N, 5.99. Found: C, 46.56; H, 5.79; N, 5.92. UV absorption in MeOH: λ_{max} 274 nm (ε 9600), λ_{min} 241 nm (ε 2500). ^1H NMR ($CDCl_3$) δ: 0.05 (6H, s, SiMe), 0.88 (9H, s, SiBu-*t*), 1.34 (3H, s, isop. Me), 1.55 (3H, s, isop. Me), 3.79 (2H, m, CH_2-5'), 4.15 (1H, m, H-4'), 4.81 (1H, dd, $J_{2',3'}$= 6.5, $J_{3',4'}$= 4.4 Hz, H-3'), 5.19 (1H, d, H-2'), 6.28 (1H, s, H-1'), 9.38 (1H, br, NH). MS *m/z*: 455, 453, and 451 (M^+–Me), 413, 411, and 409 (M^+–Bu-*t*), 287 (M^+–B), 184, 182, and 180 (B+1).

6-Bromo-5'-*O*-(*tert*-butyldimethylsilyl)-2',3'-*O*-isopropylideneuridine (6) This compound was synthesized by the same procedure as described for the preparation of **4** and **5**. The following amounts of reagents and 410 mg (1.02 mmol) of **3** in THF (10 ml) were used: 2.55 mmol of LDA in THF (10 ml), 810 mg (4.07 mmol) of $PhCOCH_2Br$ in THF (10 ml). Silica gel column chromatography (5% EtOAc in benzene) gave **6** (57 mg, 12%) as a foam. UV absorption in MeOH: λ_{max} 264 nm, λ_{min} 231 nm. ^1H NMR ($CDCl_3$) δ: 0.05 (6H, s, SiMe), 0.88 (9H, s, SiBu-*t*), 1.34 (3H, s, isop. Me), 1.54 (3H, s, isop. Me), 3.79 (2H, m, CH_2-5'), 4.16 (1H, m, H-4'), 4.81 (1H, dd, $J_{2',3'}$= 6.3, $J_{3',4'}$= 4.4 Hz, H-3'), 5.19 (1H, d, H-2'), 6.11 (1H, s, H-5), 6.25 (1H, s, H-1'), 9.68 (1H, br, NH). MS *m/z*: 463 and 461 (M^+–Me), 421 and 419 (M^+–Bu-*t*), 287 (M^+–B), 191 and 189 (B^+). High resolution MS *m/z*: 463.0749 and 461.0754 (M^+–Me) Calcd. for $C_{17}H_{26}BrN_2O_6Si$ 463.0723 and 461.0743.

5'-*O*-(*tert*-Butyldimethylsilyl)-6-iodo-2',3'-*O*-isopropylideneuridine (7) This compound was synthesized by the same procedure as described for the preparation of **4** and **5**. The following amounts of reagents and 4.67 g (11.7 mmol) of **3** in THF (40 ml) were used: 29.3 mmol of LDA in THF (100 ml), 6.84 g (26.9 mmol as I_2) in THF (30 ml). Silica gel column chromatography (7% EtOAc in benzene) gave **7** (5.39 g, 88%), which was crystallized from

Et_2O-hexane (mp 99-101 °C). *Anal.* Calcd for $C_{18}H_{29}IN_2O_6$: C, 41.23; H, 5.58; N, 5.34. Found: C, 41.33; H, 5.51; N, 5.05. UV absorption in MeOH: λ_{max} 278 nm (ε 12000), λ_{min} 248 nm (ε 5200). ^1H NMR ($CDCl_3$) δ: 0.05 (6H, s, SiMe), 0.89 (9H, s, SiBu-*t*), 1.34 (3H, s, isop. Me), 1.53 (3H, s, isop. Me), 3.79 (2H, m, CH_2-5'), 4.16 (1H, m, H-4'), 4.81 (1H, dd, $J_{2',3'}$= 6.3, $J_{3',4'}$= 4.4 Hz, H-3'), 5.18 (1H, d, H-2'), 6.08 (1H, s, H-1'), 6.44 (1H, d, $J_{3,5}$= 1.5 Hz, H-5), 9.63 (1H, br, NH). MS *m/z*: 509 (M^+–Me), 467 (M^+–Bu-*t*), 287 (M^+–B), 238 (B+1).

5'-*O*-(*tert*-Butyldimethylsilyl)-2',3'-*O*-isopropylidene-6-methyluridine (8) A mixture of **7** (523 mg, 1.0 mmol), Me_4Sn (1.4 ml, 10.1 mmol), and $(Ph_3P)_2PdCl_2$ (80 mg, 0.1 mmol) in dioxane (12.5 ml) was heated, under positive pressure of dry argon, with stirring at 110 °C for 3 h. The reaction mixture was evaporated to dryness and the whole residue was chromatographed on a silica gel column (10-15% EtOAc in benzene). This afforded **8** (412 mg, 100%), which was crystallized from Et_2O-hexane (mp 115-117 °C). *Anal.* Calcd for $C_{19}H_{32}N_2O_6Si$: C, 55.32; H, 7.82; N, 6.79. Found: C, 55.30; H, 8.09; N, 6.76. UV absorption in MeOH: λ_{max} 258 nm (ε 10300), λ_{min} 209 nm (ε 2500). ^1H NMR ($CDCl_3$) δ: 0.04 (6H, s, SiMe), 0.88 (9H, s, SiBu-*t*), 1.33 (3H, s, isop. Me), 1.53 (3H, s, isop. Me), 2.33 (3H, s, 6-Me), 3.80 (2H, m, CH_2-5'), 4.14 (1H, m, H-4'), 4.82 (1H, dd, $J_{2',3'}$= 6.3, $J_{3',4'}$= 4.4 Hz, H-3'), 5.21 (1H, dd, $J_{1',2'}$= 0.9 Hz, H-2'), 5.55 (1H, s, H-5), 5.70 (1H, d, H-1'), 9.28 (1H, br, NH). MS *m/z:* 397 (M^+–Me), 355 (M^+–Bu-*t*), 287 (M^+–B), 126 (B+1).

6-Methyluridine (9) Compound **8** (324 mg) was dissolved in THF (5 ml). To this, 50% aqueous CF_3CO_2H (10 ml) was added and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and cold EtOH was added to the residue. This gave **9** (168 mg, 83%) as a precipitate, which was crystallized from EtOH (mp 177-178 °C, lit.[8] mp 172-173 °C).

5'-*O*-(*tert*-Butyldimethylsilyl)-2',3'-*O*-isopropylidene-6-phenyluridine (10) This compound was synthesized by the same procedure as described for the perparation of **8**. The following amounts of reagents and 538 mg (1.03 mmol) of **7** in dioxane (30 ml) were used: 2.28 g (5.34 mmol) of Ph_4Sn, 88 mg (0.11 mmol) of $(Ph_3P)_2PdCl_2$. The reaction was continued overnight. After evaporation of the solvent, EtOH was added to the residue and insoluble materials were removed by filtration. Silica gel column chromatography (10% EtOAc in benzene) of the filtrate gave **10** (461 mg, 95%) as a foam. UV absorption in MeOH: λ_{max} 270 nm, λ_{min} 240 nm. ^1H NMR ($CDCl_3$) δ: 0.06 (6H, s, SiMe), 0.89 (9H, s, SiBu-*t*), 1.27 (3H, s, isop. Me), 1.34 (3H, s, isop. Me), 3.83 (2H, m, CH_2-5'), 4.01 (1H, m, H-4'),

4.79 (1H, dd, $J_{2',3'}$= 6.3, $J_{3',4'}$= 4.4 Hz, H-3'), 5.20 (1H, d, H-2'), 5.46 (1H, s, H-1'), 5.64 (1H, s, H-5), 7.48 (5H, s, Ph), 9.97 (1H, br, NH). MS *m/z*: 459 (M^+–Me), 417 (M^+–Bu-*t*), 188 (B+1). High resolution MS *m/z*: 459.1981 (M^+–Me) Calcd. for $C_{23}H_{31}N_2O_6Si$ 459.1952.

6-Phenyluridine (11) This compound was prepared from **10** (304 mg) by the same procedure as described for the preparation of **9**. After evaporation, silica gel column chromatography (5% EtOH in $CHCl_3$) of the reaction mixture gave **11** (155 mg, 76%), which was crystallized from EtOAc-MeOH to give an analytical sample (mp 181-183 °C). *Anal.* Calcd. for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.13; H, 5.05; N, 8.62. UV absorption in MeOH: λ_{max} 272 nm (ε 11000), λ_{min} 241 nm (ε 5500). MS *m/z*: 188 (B+1). For ^1H NMR data of **11**: see reference 19.

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14) The yields of **4** and **8** were 38 and 31%, respectively. When **4** was treated with 5.0 equiv of MeMgBr in dioxane for 2 h, a complex mixture of highly polar products resulted along with a 37% yield of **8**.
15) Though this particular reaction was carried out with 10 equiv of $SnMe_4$, the use of 3.0 equiv effects almost complete conversion under these conditions; only partial conversion to **8** (16%) was observed by using 1.2 equiv of $SnMe_4$.
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17) Organostannanes have been used for the coupling reaction with 2',3',5'-tri-*O*-acetyl-5-trifluoromethanesulfonyloxyuridine: G. T. Crisp and B. L. Flynn, *Tetrahedron Lett.*, **31**, 1347 (1990).
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