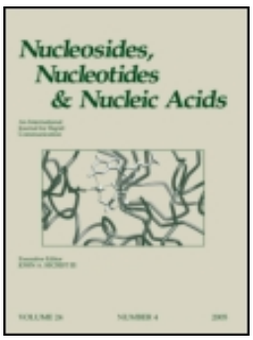

Nucleosides, Nucleotides and Nucleic Acids

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SULFOXIDE-METAL EXCHANGE FOR THE SYNTHESIS OF THE 2′-TRIBUTYLSTANNYL DERIVATIVE OF 2′,3′-DIDEHYDRO-2′,3′-DIDEOXYURIDINE (d4U): A GENERAL ENTRY TO 2′-CARBON-SUBSTITUTED ANALOGUES OF d4U

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ABSTRACT

Methods are described for the synthesis of the 2′-tributylstannyl derivative of 2′,3′-didehydro-2′,3′-dideoxyuridine (d4U). Two approaches were investigated: radical-mediated desulfonylative stannylation of the 2′-benzenesulfonyl derivative of d4U and sulfoxide-metal exchange reaction of the 2′-benzenesulfinyl derivative. The latter approach was found to give the desired 2′-stannyl derivative in good yield. It was also shown that manipulations of the stannyl group allowed the introduction of a variety of carbon-substituents to the 2′-position by applying the Stille reaction. The whole reaction sequence has opened up a highly general entry to 2′-carbon-substituted analogues of d4U.

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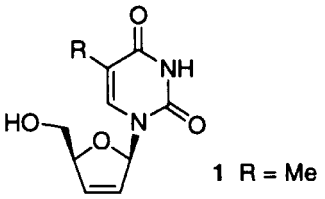
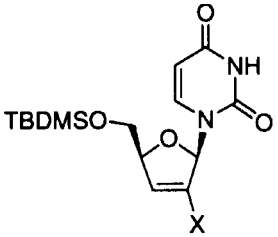
INTRODUCTION

The potent anti-HIV activity of 3′-deoxy-2′,3′-didehydrothymidine (d4T, **1**) has stimulated the synthesis and evaluation of variety of 2′,3′-didehydro-2′,3′-dideoxyribonucleosides (d4Ns).[1] In spite of the fact that several d4Ns substituted at the 2′- or 3′-position possess significant anti-HIV activity,[2,3] structure-activity relationship studies have been limited to a narrow range of carbon-substituents.[4,5]



1 R = Me
2 R = H



3 X = SO_2Ph
4 X = SOPh

With the aim of developing a general method for the synthesis of 2′-carbon-substituted analogues of 2′,3′-didehydro-2′,3′-dideoxyuridine (d4U, **2**), we investigated in this study a radical-mediated desulfonylative stannylation of the 2′-benzenesulfonyl derivative (**3**) as well as a sulfoxide-metal exchange reaction of the corresponding 2′-benzenesulfinyl derivative (**4**).

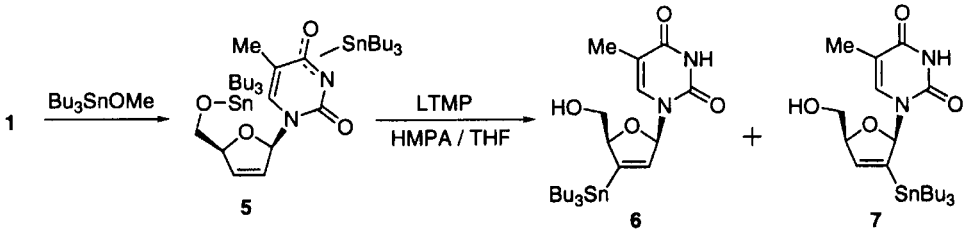
RESULTS AND DISCUSSION

Radical Approach to Stannylation at the 2′-Position of d4U

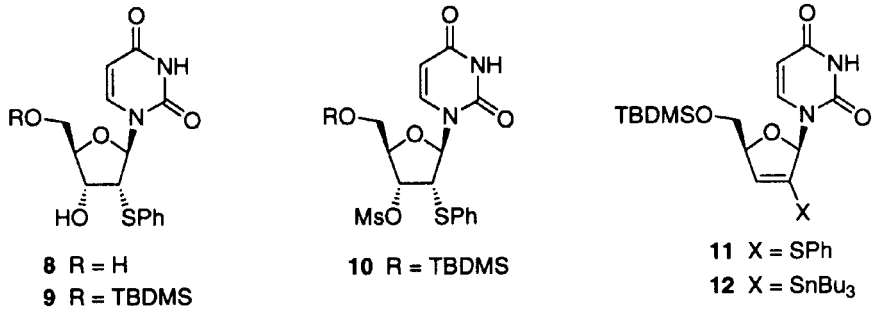
Based on organotin chemistry,[6] a variety of manipulations are feasible to transform a trialkylstannyl group attached to sp^2-carbon atom. Therefore, introduction of a trialkylstannyl group at the 2′-position of d4U would provide diversity for a variety of substituents to be introduced. We recently reported that reaction between Bu_3SnOMe and d4T (**1**) yielded the trans-alkoxylation product **5**, which underwent an anionic O→C stannyl migration upon treatment with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in the presence of HMPA in THF (Sch. 1).[7] This approach is, however, not appropriate for the present purpose, since the migration occurs preferentially at the 3′-position to give **6** as the major product, with only 10% of **7** being formed. Since a phenylthio group is reported to be readily introduced to the 2′-position of uridine by way of its O^2,2′-anhydro derivative,[8] radical-mediated desulfonylative stannylation[9] was considered as an alternative approach.

The starting material **8** was prepared according to the published procedure by reacting O^2,2′-anhydrouridine with benzenethiol in DMF.[8] Compound **8** was selectively silylated with *tert*-butyldimethylsilyl chloride

(TBDMSCl) in pyridine to give **9**. The 3′-*O*-mesylated derivative (**10**) was prepared by a conventional method (MsCl/pyridine, at 0°C), and then it was treated with DBN in refluxing CH_3CN to give the vinyl sulfide **11** (80% overall yield from **8**). Oxidation of **11** with 2 equiv of *m*-CPBA in MeOH furnished the vinyl sulfone **3** in 79% yield. When the radical reaction of **3** with Bu_3SnH (4 equiv) was carried out for 6 h in refluxing benzene in the presence of AIBN, the desired 2′-stannyl derivative (**12**)[10] was isolated only in 35% yield after flash silica gel column chromatography. The starting material (**3**) was recovered in 40% yield from this reaction. The fact that no improvement was seen in the yield of **12** even at higher temperatures (refluxing toluene, 31%; refluxing xylene, 32%) led us to investigate an alternative approach.

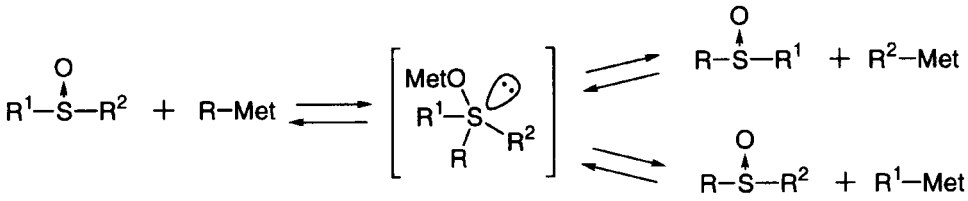


Scheme 1.



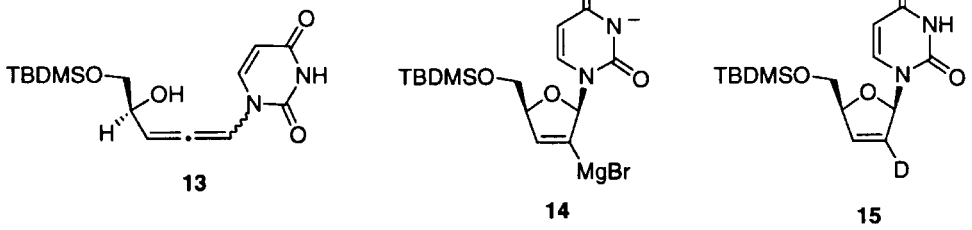
Sulfoxide-metal Exchange Reaction for the Introduction of 2′-Stannyl Group to d4U

Ligand-exchange reaction of sulfoxides with organometallic reagents, mostly RLi or RMgX, has been known for a long time.[11] It is assumed that a penta-coordinate sulfrane intermediate would be involved in this reaction as shown in Sch. 2. As a consequence, a new organometallic species either R^1-Met or R^2-Met is generated. Which S-C bond is cleaved is dependent on the structure of ligands, and it seems likely from several precedents[12,13] that alkenyl aryl sulfoxides undergo preferential S-alkenyl bond cleavage.



Scheme 2.

We intended to generate the 2′-metallated species of d4U to be reacted with Bu_3SnCl by applying the above sulfoxide-metal exchange reaction. The sulfoxide **4** was prepared in 81% yield as a mixture of two diastereomers (*ca.* 1:1) by oxidation of **11** with 1.1 equiv of *m*-CPBA in CH_2Cl_2 at −40°C. For the exchange reaction of **4**, alkyllithiums would not be suitable reagents, since the generated 2′-lithio intermediate is anticipated to give the allene derivative **13**, as reported in our previous study of d4T.[7] Therefore, Grignard reagent EtMgBr was used in the reaction of **4** (THF at −70°C), and the extent of generating **14** was verified by deuterium incorporation, the results of which are summarized in Table 1.



13 **14** **15**

In the reactions shown in entries 1 and 2, the yields of **15**[14] were not high enough due to the presence of the starting material (**4**). This was improved either by prolonging the reaction time (entry 3) or by increasing the

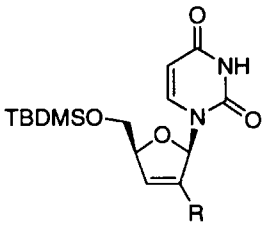
Table 1. Sulfoxide-metal Exchange Reaction of **4** with EtMgBr, and Subsequent Deuteration[a]

Entry	EtMgBr (equiv)	NaH (equiv)	Time (min)[b]	Yield (%) of **15**	D-incorporation (%)
1	2.2	–	0.5	47	56
2	3.0	–	0.5	72	68
3	3.0	–	20	85	63
4	5.0	–	0.5	98	73
5	2.2	2.0	20	98	81

[a]All reactions were carried out in THF at −70°C.
[b]Time required between addition of EtMgBr and quenching with MeOD.

amount of EtMgBr (entry 4). Although almost quantitative conversion to **15** was achieved in entry 4, the observed deuterium level was not as high. Also, the presence of excess Grignard reagent is certainly disadvantageous for the reaction of **14** with Bu_3SnCl in that it has to be carried out in a one-pot manner. Since the sulfoxide-exchange is reported to be a faster process,[15] it is conceivable that, in the present case, the generated 2′-magnesium intermediate undergoes protonation from the N^3H. As shown in entry 5, simply by pre-treatment of **4** with NaH, the best result was obtained both in terms of yield of **15** and incorporation level of deuterium.

The preparation of the 2′-tributylstannyl derivative (**12**) was carried out under the above reaction conditions of entry 5. Reaction of the 2′-magnesium intermediate **14** with Bu_3SnCl did not proceed at $-70°C$, and required stirring for 1 h at room temperature. By this procedure, the desired **12** was obtained in 62% yield. In addition to Bu_3SnCl, some other electrophiles can also be used in the reaction of **14**. Thus, the 2′-cyano derivative (**16**) was prepared in 48% yield by reacting **14** with *p*-toluenesulfonyl cyanide at 0°C for 1 h. Iodination with iodine can be carried out at $-70°C$, forming **17** in 71% yield after 0.5 h. It would be worthy to mention that, in sulfoxide-metal exchange reaction of alkenyl aryl sulfoxides, incipient alkenylmetal species are spontaneously protonated because of its highly basic character.[16] To the best of our knowledge, there has been only one precedent wherein alkenylmetal species derived from α-halovinyl aryl sulfoxides reacted with added electrophiles.[17]



16 R = CN (48%)
17 R = I (71%)
18 R = Ph (80%)
19 R = styryl (64%)
20 R = allyl (69%)
21 R = benzyl (50%)
22 R = (trimethylsilyl)ethynyl (71%)

Finally, the utility of the 2′-tributylstannyl derivative (**12**) as well as the 2′-iodo derivative (**17**) was briefly exemplified by the preparation of 2′-carbon-substituted analogues. The Stille coupling reaction[18] between **12** and organic halides (iodobenzene, β-bromostyrene, allyl bromide, and benzyl bromide) was carried out in DMF at room temperature using $Pd(PPh_3)_4/CuI$ to give the respective products (**18**–**21**, yields are given in parentheses). Compound **17** also serves as a useful substrate especially for cross-coupling reaction with terminal alkynes.[19] The reaction of **17** with (trimethylsilyl)acetylene gave **22** in 71% yield.

In conclusion, starting from readily available 2′-phenylthiouridine (**8**), the 2′-tributylstannyl derivative (**12**) of d4U was synthesized by applying the sulfoxide-metal exchange reaction to the 2′-benzenesulfinyl-d4U (**4**). Since

the stannyl group of **12** can be transformed into a variety of carbon functionalities, the present study has disclosed a general entry to the 2′-carbon-substituted analogues of d4U.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were measured at 500 MHz. Chemical shifts are reported relative to Me_4Si. Mass spectra (MS) were taken in FAB mode (*m*-nitrobenzyl alcohol as a matrix). Column chromatography was carried out on silica gel (Silica Gel 60, Merck). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck). Where necessary, analytical samples were purified by high-performance liquid chromatography (HPLC). HPLC was carried out on a Shimadzu LC-6AD with a Shim-pack PREP-SIL (H). KIT column (2×25 cm). THF was distilled from benzophenone ketyl.

5′- *O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-2′-phenylthiouridine (9). A mixture of **8** (3.0 g, 8.92 mmol) and TBDMSCl (1.61 g, 10.7 mmol) in pyridine (40 mL) was stirred at room temperature for 15 h. The reaction mixture was evaporated, and then coevaporated with EtOH. The residue was partitioned between $CHCl_3$ and 0.5 M hydrochloric acid. Column chromatography ($CHCl_3$/MeOH = 30/1) of the organic layer gave **9** (4.01 g, 100%) as a foam: UV (MeOH) λ_{max} 256 nm (ε 10,200), λ_{min} 231 nm (ε 2700); ^{1}H NMR ($CDCl_3$) δ 0.02 and 0.07 (6H, each as s, SiMe), 0.83 (9H, s, SiBu-*t*), 2.98 (1H, d, $J = 2.4$ Hz, 3′-OH), 3.72 (1H, dd, $J = 4.4$ and 8.8 Hz, H-2′), 3.79 (1H, dd, $J = 2.0$ and 11.6 Hz, H-5′), 3.92 (1H, dd, $J = 2.0$ and 11.6 Hz, H-5′), 4.24–4.25 (1H, m, H-4′), 4.27–4.29 (1H, m, H-3′), 5.65 (1H, dd, $J = 2.0$ and 8.0 Hz, H-5), 6.29 (1H, d, $J = 8.8$ Hz, H-1′), 7.26–7.30 (3H, m, Ph), 7.37–7.41 (2H, m, Ph), 7.81 (1H, d, $J = 8.0$, H-6), 8.55 (1H, br, NH); FAB-MS *m/z* 451 ($M^+ + H$). Anal. Calcd for $C_{21}H_{30}N_2O_5SSi$: C, 55.85; H, 6.92; N, 6.16. Found: C, 55.72; H, 6.75; N, 6.16.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-deoxy-3′-*O*-methanesulfonyl-2′-phenylthiouridine (10). To a solution of **9** (33 g, 73 mmol) in pyridine (300 mL), MsCl (17 mL, 220 mmol) was added at 0°C. After stirring for 12 h at room temperature, the reaction mixture was poured into ice-water (*ca.* 500 mL). The resulting precipitate was collected and dried under reduced pressure. This gave **10** (30.9 g, 80%) as a solid: mp 145–148°C; UV (MeOH) λ_{max} 255 nm (ε 10,600), λ_{min} 230 nm (ε 2900); ^{1}H NMR ($CDCl_3$) δ 0.10 and 0.11 (6H, each as s, SiMe), 0.88 (9H, s, SiBu-*t*), 3.19 (3H, s, SO_2Me), 3.74 (1H, dd, $J = 5.2$ and 9.6 Hz, H-2′), 3.84–3.91 (2H, m, H-5′), 4.46–4.47 (1H, m, H-4′), 5.28 (1H, d, $J = 5.2$ Hz, H-3′), 5.49 (1H, dd, $J = 2.0$ and 8.0 Hz, H-5), 6.39 (1H, d, $J = 9.6$ Hz, H-1′), 7.23–7.32 (3H, m, Ph), 7.39–7.42 (2H, m, Ph), 7.49

(1H, d, $J = 8.0$ Hz, H-6), 7.91 (1H, br, NH); FAB-MS m/z 529 (M^++H). Anal. Calcd for $C_{22}H_{32}N_2O_7S_2Si$: C, 49.88; H, 6.28; N, 5.29. Found: C, 49.92; H, 6.09; N, 5.28.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-2′-phenylthiouridine (11). A mixture of **10** (500 mg, 0.95 mmol) and DBN (350 μL, 2.84 mmol) in CH_3CN (10 mL) was refluxed for 2 h. The reaction mixture was partitioned between 0.5 M hydrochloric acid and $CHCl_3$. Column chromatography (hexane/EtOAc = 2/1) of the organic layer gave **11** (420 mg, 100%) as a foam: UV (MeOH) λ_{max} 259 nm (ε 12,300), λ_{min} 230 nm (ε 7600); ^{1}H NMR ($CDCl_3$) δ 0.05 and 0.06 (6H, each as s, SiMe), 0.90 (9H, s, SiBu-*t*), 3.76 (1H, dd, $J = 2.4$ and 11.6 Hz, H-5′), 3.87 (1H, dd, $J = 2.8$ and 11.6 Hz, H-5′), 4.87–4.89 (1H, m, H-4′), 5.62 (1H, dd, $J = 1.6$ and 8.0 Hz, H-5), 5.84–5.85 (1H, m, H-3′), 6.89–6.90 (1H, m, H-1′), 7.32–7.37 (3H, m, Ph), 7.38–7.46 (2H, m, Ph), 7.79 (1H, d, $J = 8.0$, H-6), 8.22 (1H, br, NH); FAB-MS m/z 433 (M^++H). Anal. Calcd for $C_{21}H_{28}N_2O_4SSi$: C, 58.30; H, 6.52; N, 6.48. Found: C, 58.05; H, 6.49; N, 6.28.

2′-Benzenesulfonyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyuridine (3). A mixture of **11** (500 mg, 1.16 mmol) and *m*-CPBA (purity 70698 mg, 2.43 mmol) in MeOH (20 mL) was stirred at room temperature for 3 h. The reaction mixture was neutralized by adding Et_3N and partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Column chromatography (hexane/
EtOAc = 1/1) of the organic layer gave **3** (425 mg, 79%) as a foam: UV (MeOH) λ_{max} 230 nm (ε 13,900) and 260 nm (ε 8000), λ_{min} 219 nm (ε 12,300) and 250 nm (ε 7000); ^{1}H NMR ($CDCl_3$) δ 0.07 and 0.10 (6H, each as s, SiMe), 0.90 (9H, s, SiBu-*t*), 3.94 (1H, dd, $J = 2.4$ and 12.0 Hz, H-5′), 3.99 (1H, dd, $J = 2.0$ and 12.0 Hz, H-5′), 4.99–5.01 (1H, m, H-4′), 5.30 (1H, dd, $J = 2.4$ and 8.0 Hz, H-5), 7.15–7.16 (1H, m, H-1′), 7.24 (1H, t, $J = 1.6$ Hz, H-3′), 7.51–7.55 (2H, m, Ph), 7.57 (1H, d, $J = 8.0$ Hz, H-6), 7.64–7.68 (1H, m, Ph), 7.84–7.87 (2H, m, Ph), 8.42 (1H, br, NH); FAB-MS m/z 465 ($M^+ + H$). Anal. Calcd for $C_{21}H_{28}N_2O_6SSi$: C, 54.29; H, 6.07; N, 6.03. Found: C, 54.46; H, 6.00; N, 5.88.

Radical-mediated desulfonylative stannylation of 3: formation of the 2′-tributylstannyl derivative (12). A mixture of **3** (400 mg, 0.86 mmol), Bu_3SnH (925 μL, 3.44 mmol), and AIBN (71 mg, 0.43 mmol) in benzene (20 mL) was heated at 80°C for 6 h. The reaction mixture was evaporated. Flash column chromatography (hexane/EtOAc = 3/1) of the residue gave **12** (184 mg, 35%) as an oil. Elution with hexane/EtOAc = 2/1 gave the recovered **3** (211 mg, 40%). Physical data for **12** are as follows: UV (MeOH) λ_{max} 260 nm (ε 8400), λ_{min} 232 nm (ε 3000); ^{1}H NMR ($CDCl_3$) δ 0.07 and 0.08 (6H, each as s, SiMe), 0.85–0.89 (9H, m, $Sn(CH_2)_3C\underline{H}_3$), 0.90 (9H, s, SiBu-*t*), 0.90–0.95

and 1.22–1.48 (18H, each as m, $Sn(C\underline{H}_2)_3$ CH_3), 3.85 (1H, dd, $J = 2.4$ and 12.0 Hz, H-5′), 3.93 (1H, dd, $J = 2.4$ and 12.0 Hz, H-5′), 4.82–4.85 (1H, m, H-4′), 5.64 (1H, dd, $J = 2.0$ and 8.4 Hz, H-5), 6.17–6.23 (1H, m, H-3′), 7.05–7.06 (1H, m, H-1′), 7.84 (1H, d, $J = 8.4$ Hz, H-6), 8.00 (1H, br, NH); FAB-MS (^{120}Sn) m/z 653 (M^++K). Anal. Calcd for $C_{27}H_{50}N_2OSiSn$: C, 52.86; H, 8.22; N, 4.57. Found: C, 52.88; H, 8.37; N, 4.40.

2′-Benzenesulfinyl-5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyuridine (4). Compound **11** (400 mg, 0.92 mmol) in CH_2Cl_2 (10 mL) was treated with *m*-CPBA (293 mg, 1.02 mmol) at −40°C for 0.5 h. After neutralization with Et_3N, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. Column chromatograhy (hexane/AcOEt = 1/1) of the organic layer gave **4** (335 mg, 81%, a mixture of two diastereomers; *ca*. 1:1) as a foam: UV (MeOH) λ_{max} 259 nm (ε 8200), λ_{min} 246 nm (ε 6900); ^{1}H NMR ($CDCl_3$) δ 0.08, 0.09, 0.11, and 0.12 (6H, each as s, SiMe), 0.91 and 0.92 (9H, each as s, SiBu-*t*), 3.90–4.01 (2H, m, H-5′), 4.97–5.00 and 5.01–5.03 (1H, each as m, H-4′), 5.17 (0.5H, dd, $J = 2.0$ and 8.4 Hz, H-5), 5.41 (0.5 H, dd, $J = 2.0$ and 8.0 Hz, H-5), 6.93–6.95 (1H, m, H-3′ and H-1′), 7.00–7.02 and 7.06–7.07 (1H, each as m, H-3′ and H-1′), 7.41–7.45 and 7.48–7.53 (3H, each as m, Ph), 7.54 (0.5 H, d, $J = 8.4$ Hz, H-6), 7.55–7.62 (2H, m, Ph), 7.69 (0.5H, d, $J = 8.0$ Hz, H-6), 8.19 and 8.39 (1H, each as br, NH); FAB-MS m/z 449 (M^++H). Anal. Calcd for $C_{21}H_{28}N_2O_5SSi$: C, 56.22; H, 6.29; N, 6.24. Found: C, 56.23; H, 6.34; N, 6.14.

Reaction of 4 with EtMgBr and subsequent deuteration: formation of 15. To a solution of **4** (200 mg, 0.45 mmol) in THF (8 mL), NaH (60% oil-dispersion, 36 mg, 0.9 mmol) was added at room temperature under positive pressure of dry Ar. After stirring for 20 min, the resulting suspension was cooled to −70°C, and reacted with EtMgBr (0.9 M in THF, 1.1 mL, 0.99 mmol). After stirring for 20 min at −70°C, the reaction mixture was quenched by adding MeOD (0.75 mL). The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. Column chromatography (hexane/EtOAc = 2/1) of the organic layer gave **15** (144 mg, 98%) as a foam. The extent of deuterium incorporation (81%) at the 2′-position was calculated based on ^{1}H NMR spectroscopy.

Preparation of the 2′-tributylstannyl derivative (12) by sulfoxide-metal exchange reaction by using 4. A solution of **4** (300 mg, 0.67 mmol) in THF (8 mL) was treated with NaH followed by EtMgBr by the procedure described for the preparation of **15**. To the resulting mixture containing **14** was added Bu_3SnCl (814 μL, 3.0 mmol) at below −70°C. After stirring for 1 h at room temperature, the reaction mixture was treated with saturated aqueous NH_4Cl. Extraction with $CHCl_3$ followed by flash column chromatography (hexane/EtOAc = 3/1) gave **12** (253 mg, 62%).

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-cyano-2′,3′-didehydro-2′,3′-dideoxyuridine (16). A solution of **4** (416 mg, 0.93 mmol) in THF (15 mL) was treated with NaH followed by EtMgBr by the procedure described for the preparation of **15**. To the resulting mixture containing **14** was added *p*-toluenesulfonyl cyanide (709 mg, 3.91 mmol) at below −70°C. After stirring for 1 h at 0°C, the reaction mixture was treated with saturated aqueous NH_4Cl. Extraction with $CHCl_3$ followed by column chromatography (hexane/EtOAc = 1/1) gave **16** (156 mg, 48%) as a foam : UV (MeOH) λ_{max} 258 nm (ε 8900), λ_{min} 237 nm (ε 5800); ^{1}H NMR ($CDCl_3$) δ 0.10 and 0.11 (6H, each as s, SiMe), 0.91 (9H, s, SiBu-*t*), 3.93 (1H, dd, J = 2.4 and 12.0 Hz, H-5′), 3.99 (1H, dd, J = 2.4 and 12.0 Hz, H-5′), 5.06–5.09 (1H, m, H-4′), 5.75 (1H, dd, J = 2.0 and 8.4 Hz, H-5), 7.07–7.08 (1H, m, H-3′), 7.13–7.15 (1H, m, H-1′), 7.76 (1H, d, J = 8.4 Hz, H-6), 8.55 (1H, br, NH); FAB-MS m/z 350 (M^++H). Anal. Calcd for $C_{16}H_{23}N_3O_4Si$: C, 54.99; H, 6.63; N, 12.02. Found: C, 55.12; H, 6.65; N, 11.87.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-2′-iodouridine (17). A solution of **4** (300 mg, 0.67 mmol) in THF (15 mL) was treated with NaH followed by EtMgBr by the procedure described for the preparation of **15**. To the resulting mixture containing **14** was added iodine (766 mg, 3.0 mmol as I_2) at below −70°C. After stirring for 0.5 h at below −70°C, the reaction mixture was treated with saturated aqueous NH_4Cl. Extraction with $CHCl_3$ followed by column chromatography (hexane/EtOAc = 2/1) gave **17** (213 mg, 71%) as a foam: UV (MeOH) λ_{max} 259 nm (ε 8900), λ_{min} 234 nm (ε 3000); ^{1}H NMR ($CDCl_3$) δ 0.07 and 0.09 (6H, each as s, SiMe), 0.90 (9H, s, SiBu-*t*), 3.84 (1H, dd, J = 2.8 and 11.6 Hz, H-5′), 3.90 (1H, dd, J = 2.8 and 11.6 Hz, H-5′), 4.85–7.86 (1H, m, H-4′), 5.72 (1H, dd, J = 2.0 and 8.0 Hz, H-5), 6.54–6.55 (1H, m, H-3′), 6.92–6.93 (1H, m, H-1′), 7.74 (1H, d, J = 8.0 Hz, H-5), 8.84 (1H, br, NH); FAB-MS m/z 451 (M^++H). Anal. Calcd for $C_{15}H_{23}IN_2O_4Si$: C, 40.01; H, 5.15; N, 6.22. Found: C, 40.30; H, 5.06; N, 6.12.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-2′-phenyluridine (18). A mixture of **12** (784 mg, 1.28 mmol), PhI (360 μL, 3.20 mmol), $Pd(Ph_3P)_4$ (150 mg, 0.13 mmol), and CuI (50 mg, 0.26 mmol) in DMF (3 mL) was stirred at room temperature for 20 h. The resulting suspension was partitioned between brine and EtOAc. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **18** (407 mg, 80%) as a foam: UV (MeOH) λ_{max} 254 nm (ε 21,500), λ_{min} 224 nm (ε 6600); ^{1}H NMR ($CDCl_3$) δ 0.10 and 0.12 (6H, each as s, SiMe), 0.92 (9H, s, SiBu-*t*), 3.91 (1H, dd, J = 2.8 and 11.6 Hz, H-5′), 3.97 (1H, dd, J = 2.8 and 11.6 Hz, H-5′), 5.02–5.03 (1H, m, H-4′), 5.56 (1H, dd, J = 2.0 and 8.0 Hz, H-5), 6.49–6.50 (1H, m, H-3′), 7.32–7.36 (5H, m, Ph), 7.48–7.50 (1H, m, H-1′), 7.79 (1H, d, J = 8.0 Hz, H-6), 8.14 (1H, br, NH); FAB-MS m/z 401 (M^++H). Anal.

Calcd for $C_{21}H_{28}N_2O_4Si$: C, 62.97; H, 7.05; N, 6.99. Found: C, 62.94; H, 7.23; N, 6.91.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-2′-styryluridine (19). A mixture of **12** (296 mg, 0.48 mmol), β-bromostyrene ($E/Z = 7/1$, 154 μL, 1.21 mmol), $Pd(Ph_3P)_4$ (55 mg, 0.048 mmol), and CuI (18 mg, 0.096 mmol) in DMF (1.5 mL) was stirred at room temperature for 48 h. The resulting suspension was partitioned between brine and EtOAc. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **19** (132 mg, 64%, a mixture of two geometrical isomers: $E/Z = ca.$ 8/1) as a foam: UV (MeOH) λ_{max} 226 nm (ε 14400) and 277 nm (ε 27800), λ_{min} 238 nm (ε 5800); ^{1}H NMR ($CDCl_3$) of *E*-isomer δ 0.09 and 0.10 (6 H, each as s, SiMe), 0.91 (9H, s, SiBu-*t*), 3.87 (1H, dd, $J = 2.8$ and 11.6 Hz, H-5′), 3.93 (1H, dd, $J = 2.8$ and 11.6 Hz, H-5′), 4.92–4.94 (1H, m, H-4′), 5.64 (1H, dd, $J = 2.4$ and 8.0 Hz, H-5), 6.24–6.25 (1H, m,H-3′), 6.52 and 6.78 (2H, each as d, $J = 16.8$ Hz, C<u>H</u>=C<u>H</u>Ph), 7.25–7.39 (6H, m, H-1′ and Ph), 7.58 (1H, d, $J = 8.0$ Hz, H-6), 8.18 (1H, br, NH); ^{1}H NMR ($CDCl_3$) of *Z*-isomer (0.02 and 0.04 (6H, each as s, SiMe), 0.88 (9H, s, SiBu-*t*), 3.73 (1H, dd, $J = 3.2$ and 12.0 Hz, H-5′), 3.79 (1H, dd, $J = 3.2$ and 12.0 Hz, H-5′), 4.81–4.82 (1H, m, H-4′), 5.59 (1H, dd, $J = 2.4$ and 8.0 Hz, H-5), 5.99 and 6.69 (2H, each as d, $J = 12.0$ Hz, C<u>H</u>=C<u>H</u>Ph), 6.17–6.18 (1H, m, H-3′), 6.86–6.87 (1H, m, H-1′), 7.25–7.39 (5H, m, Ph), 7.49 (1H, d, $J = 8.0$ Hz, H-6), 7.88 (1H, br, NH); FAB-MS m/z 427 (M^++H). Anal. Calcd for $C_{23}H_{30}N_2O_4Si \cdot 1/2H_2O$: C, 63.42; H, 7.17; N, 6.43. Found: C, 63.04; H, 6.99; N, 6.46.

2′-Allyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyuridine (20). A mixture of **12** (280 mg, 0.62 mmol), allyl bromide (134 μL, 1.55 mmol), $Pd(Ph_3P)_4$ (72 mg, 0.062 mmol), and CuI (24 mg, 0.124 mmol) in DMF (1.5 mL) was stirred at room temperature for 24 h. The resulting suspension was partitioned between brine and EtOAc. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **20** (155 mg, 69%) as a foam: UV (MeOH) λ_{max} 261 nm (ε 8300), λ_{min} 230 nm (ε 1100); ^{1}H NMR ($CDCl_3$) δ 0.07 and 0.08 (6H, each as s, SiMe), 0.90 (9H, s, SiBu-*t*), 2.68–2.81 (2H, m, C<u>H</u>$_2$CH=CH$_2$), 3.80 (1H, dd, $J = 2.4$ and 11.6 Hz, H-5′), 3.92 (1H, dd, $J = 2.4$ and 11.6 Hz, H-5′), 4.84–4.85 (1H, m, H-4′), 5.07–5.09 and 5.11–5.12 (2H, each as m, CH$_2$CH=C<u>H</u>$_2$), 5.67 (1H, dd, $J = 2.0$ and 8.0 Hz, H-5), 5.69–5.80 (1H, m, CH$_2$C<u>H</u>=CH$_2$), 5.85–5.86 (1H, m, H-3′), 6.88–6.89 (1H, m, H-1′), 7.89 (1H, d, $J = 8.0$ Hz, H-6), 8.09 (1H, br, NH); FAB-MS m/z 365 (M^++H). Anal. Calcd for $C_{18}H_{28}N_2O_4Si$: C, 59.48; H, 7.49; N, 7.71. Found: C, 59.29; H, 7.88; N, 7.50.

2′-Benzyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxyuridine (21). A mixture of **12** (2.24 g, 3.66 mmol), benzyl bromide (1.3 mL, 10.97 mmol), $Pd(Ph_3P)_4$ (422 mg, 0.37 mmol), and CuI (139 mg, 0.73 mmol) in

DMF (9 mL) was stirred at room temperature for 40 h. The resulting suspension was partitioned between brine and EtOAc. Column chromatography (hexane/EtOAc = 1/1) of the organic layer gave **21** (757 mg, 50%) as a foam: UV (MeOH) λ_{max} 261 nm (ε 7800), λ_{min} 232 nm (ε 1400); ^{1}H NMR ($CDCl_3$) δ 0.06 and 0.07 (6H, each as s, SiMe), 0.90 (9H, s, SiBu-*t*), 3.24 and 3.46 (2H, each as d, J = 15.6 Hz, C$\underline{H}_2$Ph), 3.77 (1H, dd, J = 2.4 and 11.6 Hz, H-5′), 3.92 (1H, dd, J = 2.0 and 11.6 Hz, H-5′), 4.83–4.85 (1H, m, H-4′), 5.44 (1H, dd, J = 2.4 and 8.0 Hz, H-5), 5.76–5.77 (1H, m, H-3′), 6.90–6.91 (1H, m, H-1′), 7.10–7.12 (2H, m, Ph), 7.20–7.27 (3H, m, Ph), 7.79 (1H, d, J = 8.0 Hz, H-6), 8.01 (1H, br, NH); FAB-MS m/z 415 (M^++H). Anal. Calcd for $C_{22}H_{30}N_2O_4Si \cdot 1/5H_2O$: C, 63.19; H, 7.33; N, 6.70. Found: C, 63.15; H, 7.38; N, 6.56.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-didehydro-2′,3′-dideoxy-2′-(trimethylsilyl)ethynyluridine (22). A mixture of **17** (300 mg, 0.67 mmol), (trimethylsilyl)acetylene (280 μL, 2.0 mmol), $Cl_2Pd(Ph_3P)_2$ (47 mg, 0.067 mmol), CuI (13 mg, 0.067 mmol), and Et_3N (280 μL, 2.0 mmol) in DMF (3 mL) was stirred at 80°C for 1 h. The resulting suspension was partitioned between brine and EtOAc. Column chromatography (hexane/EtOAc = 2/1) of the organic layer gave **22** (195 mg, 71%) as a foam: UV (MeOH) λ_{max} 236 nm (ε 17,300) and 247 nm (ε 18,200), λ_{min} 241 nm (ε 15,200); ^{1}H NMR ($CDCl_3$) δ 0.07 and 0.08 (6H, each as s, $SiMe_2$), 0.16 (9H, s, $SiMe_3$), 0.90 (9H, s, SiBu-*t*), 3.82 (1H, dd, J = 2.4 and 11.6 Hz, H-5′), 3.87 (1H, dd, J = 2.8 and 11.6 Hz, H-5′), 4.92–4.95 (1H, m, H-4′), 5.69 (1H, dd, J = 2.4 and 8.0 Hz, H-5), 6.40–6.41 (1H, m, H-3′), 6.91–6.93 (1H, m, H-1′), 7.69 (1H, d, J = 8.0 Hz, H-6), 8.23 (1H, br, NH); FAB-MS m/z 421 (M^++H). Anal. Calcd for $C_{20}H_{22}N_2O_4Si_2$: C, 57.05; H, 7.67; N, 6.66. Found: C, 57.25; H, 7.71; N, 6.61.

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	^{13}C NMR Chemical Shifts (δ ppm) in $CDCl_3$				
Compd.	C1′	C2′	C3′	C4′	C5′
d4U	95.0	141.1	142.6	88.1	64.2
12	89.6	126.6	134.2	87.3	64.1
Δδ	5.4	14.5	8.4	0.8	0.1

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