# Stannyl Migration from the Base to the Sugar Portion of 1',2'-Unsaturated Uridine: the First Example of Substitution at the 2'-Position

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*Abstract:* We report that TBDMS-protected 1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)-6-(tributyl-stannyl)uracil, when treated with LDA or LTMP, undergoes an anionic stannyl migration to yield the 2'-stannylated product. Optimization of the reaction conditions has disclosed an efficient entry to compounds variously substituted at the 2'-position. Desilylation of these compounds caused no further elimination, and furnished a hitherto unknown series of nucleoside analogues.
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*Keywords:* Lithiation; Tin and compounds; Migration; Uridine.

Although nucleosides having an unsaturated sugar moiety have been known for a long time, the majority of their reactions have been simple electrophilic additions with which only non-carbon substituents can be introduced.[1] We have demonstrated through a series of publications that this class of compounds are useful substrates for constructing C-C bonds in the sugar portion.[2] Among possible four types of unsaturated-sugar nucleosides, the 1',2'-unsaturated derivatives, 1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl) derivatives,[3-7] have attracted scant attention presumably due to their reported instability, during deprotection, to undergo further elimination which results in the formation of furan derivatives.[3] Since the first report in 1974 by Robins *et al.*[3] on the preparation of 1',2'-unsaturated uridine **1**[8] from the $O^2$,2'-anhydrouridine **2**, chemistry regarding 1',2'-unsaturated nucleosides had been unexploited until recently,[2] except for simple catalytic hydrogenation.
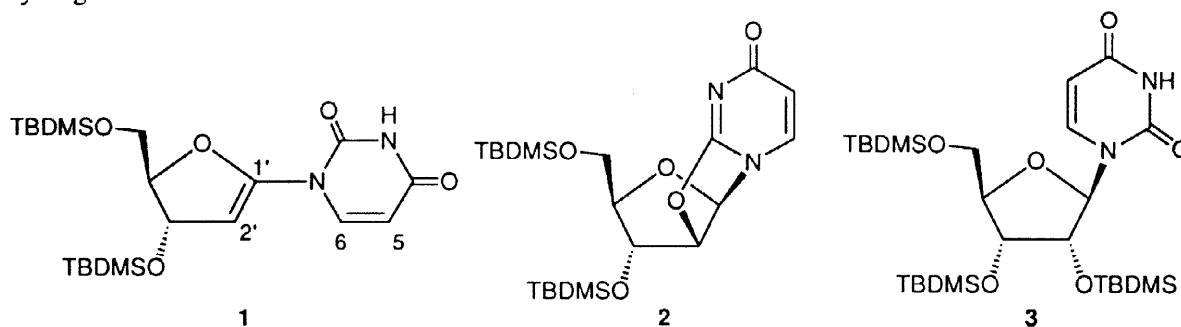


We planned to develop a method for introducing substituents at the 2'-position of **1**, which furnishes hitherto unknown type of nucleoside analogues. This plan was motivated by the fact that the UV absorption maximum of **1** in MeOH appears at a longer wavelengh of 276 nm as compared with those of usual uridine

analogues, for an example, 2',3',5'-tris-O-TBDMS-uridine (3: $\lambda_{max}$ 262 nm). It can be readily assumed, therefore, that the aforementioned difficulty in deprotecting 1 would be attributable, at least in part, to the coplanarity of the base and the sugar moieties. If substituents can be introduced to the 2'-position, conformational change around the N1-C1' pivot bond would occur to avoid sterically unfavourable coplanarity, which might render the molecules more stable.

It has been demonstrated in our previous lithiation studies of uridine derivatives that LDA effects specific deprotonation of the more acidic H-6.[10] Being consistent with this, LDA lithiation of 1 (3 equiv, THF, below −70 °C) took place exclusively at the 6-position, which was confirmed by deuteration of the lithiated species. However, when the same lithiated species was reacted with Bu$_3$SnCl (3 equiv), two products 4 (75%) and 5 (10%) were formed (Scheme 1).
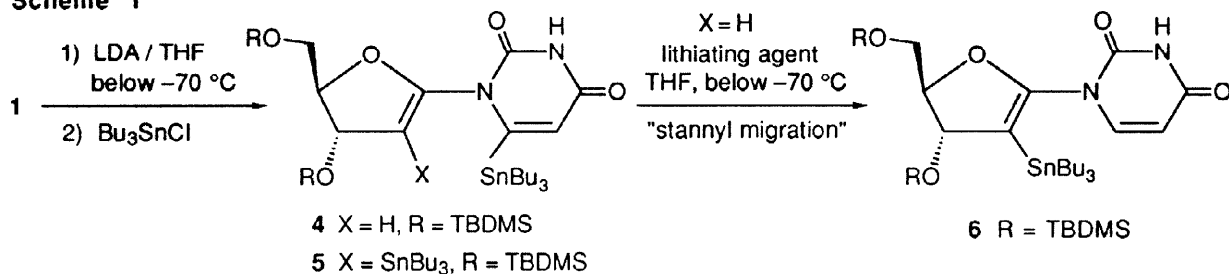
**Scheme 1**



4 X = H, R = TBDMS
5 X = SnBu$_3$, R = TBDMS

6 R = TBDMS

**Table 1.** Synthesis of 6 from 4 *via* an anionic stannyl migration.[a]

| entry | lithiating agent | HMPA (equiv) | reaction time (h) | combined yield (%)[b] of 4 plus 6 | ratio of 4 / 6[c] |
|-------|------------------|--------------|-------------------|------------------------------------|-------------------|
| 1 | LDA | — | 0.5 | 73 | 2 / 1 |
| 2 | LDA | 10 | 0.5 | 72 | 1 / 3 |
| 3 | LTMP | — | 0.5 | 68 | 1 / 1 |
| 4 | LTMP | 10 | 0.5 | 73 | 1 / 5 |
| 5 | LTMP | 10 | 1.0 | 77 | 4 / 96 |
| 6 | LTMP | 10 | 3.0 | 62[d] | 0 / 100 |

[a] All reactions were carried out by using 3 equiv of lithiating agent (THF, below −70 °C).
[b] The yields refer to those obtained after silica gel flush column chromatography (hexane/EtOAc = 10/1).
[c] Calculated based on $^1$H NMR spectroscopy by integrating H-5 of 4 and 6.
[d] Compound 1 was isolated in 11% yield.

As to the formation of the 6,2'-bis(tributylstannyl) derivative (5), we simply considered the possibility of further deprotonation at the 2'-position of 4 and subsequent stannylation, although the literature survey showed that lithiation of the β-position of alkyl vinyl ethers occurs only when the anion is stabilized by the presence of an adjacent halogen atom.[11,12] Quite unexpectedly, however, upon treatment of 4 with LDA (3 equiv, for 0.5 h) and then with MeOD, a mixture of 4 (no D-incorporation at the 2'-position) and the 2'-stannyl derivative 6 (D-incorporation at the 6-position: 96%) resulted in a ratio of 2/1 (entry 1 in Table 1). This result clearly indicates that the 2'-stannyl group of 5 had been introduced through C2'-lithiation of 4 which

was followed by an instantaneous stannyl migration from the 6-position. The fact that use of a more basic LTMP (entries 3-6) encourages the formation of **6** also supports involvement of the C2'-lithio intermediate. The presence of HMPA in the reaction medium (entries 2 and 4-6) was also advantageous for the formation of **6**. Complete conversion of **4** to **6** was attainable by prolonging the reaction time, but only at the expense of the yield (entry 6).

An analytical sample of **6**[13] was obtained by HPLC purification (hexane/EtOAc = 4/1), but this compound showed a propensity to undergo protodestannylation to form **1** during chromatography. The data in Table 1, therefore, do not perfectly reflect the actual reaction outcomes but are somewhat underestimated. In fact, when the reaction mixture resulted from entry 5 was subjected to a simple extractive workup (EtOAc/$H_2O$) and then reacted with iodine (1.2 equiv as $I_2$/THF/rt/40 min), the 2'-iodo derivative **7**[14] was isolated in 87% overall yield from **4**. Other halogen atoms can also be introduced by using **6**: **8** (NBS/THF/rt/ 0.5 h); **9** (NCS/THF/80 °C/0.5 h then at rt for 17 h); yields and UV absorption maxima in MeOH are given in parentheses.
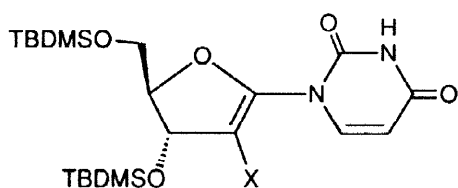


**7** X = I (87% from **4**, $\lambda_{max}$ 252 nm)

**8** X = Br (75% from **6**, $\lambda_{max}$ 255 nm)

**9** X = Cl (83% from **6**, $\lambda_{max}$ 254 nm)

**10** X = Ph (66% from **6**, $\lambda_{max}$ 253 nm)

**11** X = CH$_2$Ph (29% from **6**, $\lambda_{max}$ 254 nm)

**12** X = Me (67% from **7**, $\lambda_{max}$ 255 nm)

**13** X = CH=CH$_2$ (80% from **7**, $\lambda_{max}$ 251 nm)
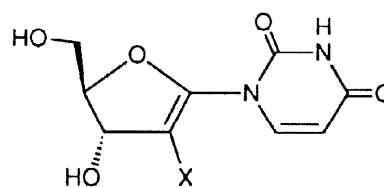
**14** X = I (82%)

**15** X = Br (93%)

**16** X = Cl (97%)

**17** X = Ph (97%)

**18** X = CH$_2$Ph (95%)

**19** X = Me (98%)

**20** X = CH=CH$_2$ (89%)

The introduction of carbon-substituents to the 2'-position was performed based on the Stille reaction by using either **6** or the more stable **7**: **10** (PhI/CuI/PdCl$_2$(PPh$_3$)$_2$/DMF/80 °C/5 min); **11** (PhCH$_2$Br/CuI/ Pd(PPh$_3$)$_4$/HMPA/80 °C/14 h); **12** (Me$_4$Sn/CuI/PdCl$_2$(MeCN)$_2$/DMF/60 °C/120 h); **13** (CH$_2$=CHSnBu$_3$/ CuI/Pd(PPh$_3$)$_4$/THF/reflux/22 h).

Finally, deprotection of the 2'-substituted 1',2'-unsaturated uridines (**7-13**) with NH$_4$F (in MeOH at 60 °C) was examined. As anticipated from the observed $\lambda_{max}$ of these compounds, which appeared at 251-255 nm, formation of the furan derivatives was not detected by TLC and the corresponding free nucleosides **14-20** were isolated uniformly in good yields after usual silica gel column chromatography (CHCl$_3$/EtOH = 10/1).[15] Biological evaluation of **14-20** and application of the present chemistry to other 1',2'-unsaturated nucleosides are currently under investigation in our laboratory.

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13) Physical data of **6** obtained as a syrup are as follows: $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.08, 0.12, and 0.13 (12H, each as s, SiMe), 0.87 (9H, t, *J*= 7.3 Hz, SnBu), 0.89 and 0.90 (18H, each as s, SiBu-*t*), 0.89-0.92 (6H, m, SnBu), 1.24-1.32 (6H, m, SnBu), 1.41-1.48 (6H, m, SnBu), 3.60 (1H, dd, *J*= 7.0 and 10.4 Hz, H-5'), 3.76 (1H, dd, *J*= 5.1 and 10.4 Hz, H-5'), 4.37-4.40 (1H, m, H-4'), 4.99 (1H, d, *J*= 2.1 Hz, H-3'), 5.73 (1H, d, *J*= 8.2 Hz, H-5), 7.25 (1H, d, *J*= 8.2 Hz, H-6), 8.38 (1H, br, NH); FAB-MS ($^{118}Sn$) *m/z* 745 ($M^++H$). Anal. Calcd for $C_{33}H_{64}N_2O_5Si_2Sn$: C, 53.29; H, 8.67; N, 3.77. Found: C, 53.38; H, 8.79; N, 3.78.

14) Physical data of **7** obtained as a solid (mp 150 °C) are as follows: $^1$H NMR ($CDCl_3$, 500 MHz) δ 0.08, 0.15, and 0.20 (12H, each as s, SiMe), 0.90 and 0.92 (18H, each as s, SiBu-*t*), 3.74 (1H, dd, *J*= 5.8 and 11.2 Hz, H-5'), 3.80 (1H, dd, *J*= 4.8 and 11.2 Hz, H-5'), 4.48-4.51 (1H, m, H-4'), 4.90 (1H, d, *J*= 3.0 Hz, H-3'), 5.79 (1H, d, *J*= 8.0 Hz, H-5), 7.18 (1H, d, *J*= 8.0 Hz, H-6); FAB-MS *m/z* 581 ($M^++H$). Anal. Calcd for $C_{21}H_{37}IN_2O_5Si_2$: C, 43.44; H, 6.42; N, 4.74. Found: C, 43.68; H, 6.44; N, 4.74.

15) As a typical example, physical data of **14** obtained as a solid (mp 89-96 °C) are given below: $^1$H NMR (DMSO-$d_6$, 500 MHz, after addition of $D_2O$) δ 3.53 (2H, d, *J*= 5.2 Hz, H-5'), 4.34-4.36 (1H, m, H-4'), 4.58 (1H, d, *J*= 4.3 Hz, H-3'), 5.75 (1H, d, *J*= 7.9 Hz, H-5), 7.51 (1H, *J*= 7.9 Hz, H-6); FAB-MS *m/z* 353 ($M^++H$). Anal. Calcd for $C_9H_9IN_2O_5$: C, 30.70; H, 2.58; N, 7.97. Found: C, 30.83; H, 2.38; N, 7.76.