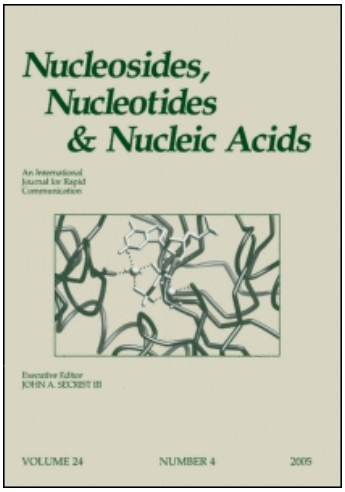

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Nucleophilic Substitution Reactions of 5-Bromo-6-methyluridines

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NUCLEOPHILIC SUBSTITUTION REACTIONS OF 5-BROMO-6-METHYLURIDINES.

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Abstract: The reactions of the 5-bromo-6-methyl-2′,3′-*O*-isopropylideneuridines **9** and **10** with a number of nucleophiles in hot DMF have been investigated. With acetate ion as the nucleophile, either the 5-acetoxy- (**11**,**12**) or the 6-acetoxymethyl- (**15**) products can be obtained in modest yield depending upon the exact reaction conditions. With nitrogen nucleophiles (aniline or *p*-methoxybenzylamine) reaction takes place at the 6-methyl carbon, whereas with sulfur nucleophiles (thiophenol, thioacetate) only the 5-substituted products are obtained.

In work published a number of years ago, Hirota and co-workers[1] demonstrated that the reaction between 5-bromo-6-methyluracils (**1**) and nucleophiles such as aromatic amines or acetate ion in hot *N,N*-dimethylformamide leads efficiently to the corresponding 6-(substituted-methyl)uracils **3** (X = NHAr or OAc, R_1 = alkyl, R_2 = alkyl or H). These interesting transformations are thought to proceed as shown *via* the methylene tautomer **2**. Although a number of related reactions have been reported for various 1,3-dialkyluracil bases,[2] we are aware of only a single example from the area of nucleoside chemistry. That example concerns our own work with the cyclonucleoside **4**, where the triflate group was found[3] to undergo an allylic displacement by formate ion to give **5**. Extension of these reactions to more conventional nucleosides such as **6** could afford potentially useful syntheses of 6-substituted products of type **7**, and provide an alternative to the lithiation approach[4] to 6-substituted uridines. Furthermore, the allylic displacement reaction suggests an attractive method for functionalizing the methylene

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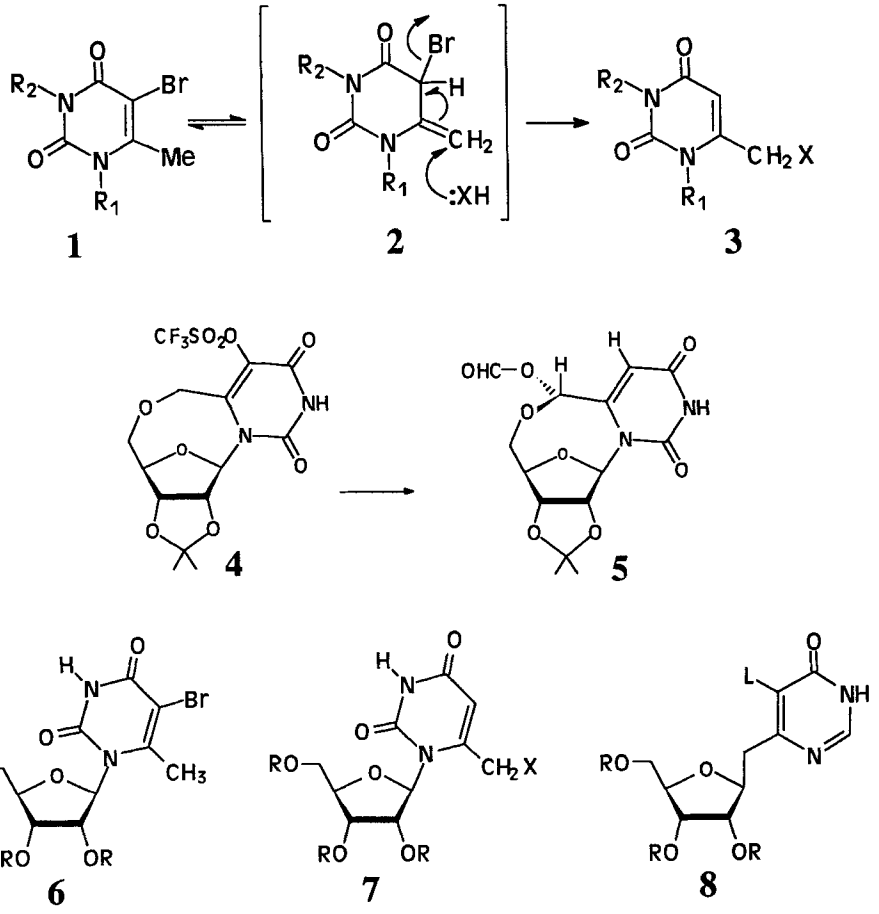
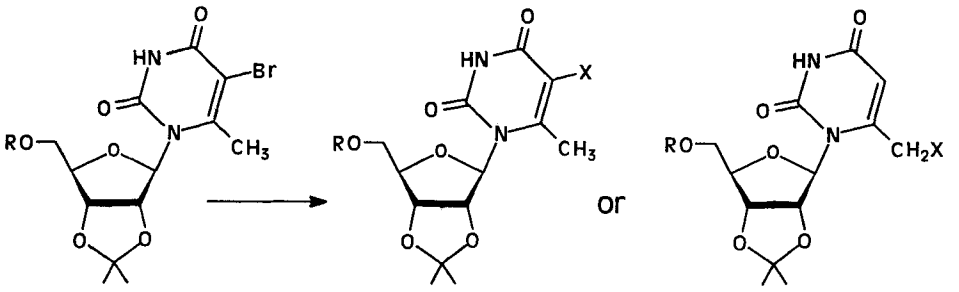
This paper is dedicated to the memory of Professor Roland K. Robins.



group of homo-nucleosides such as **8**, thereby providing intermediates for further elaboration into bicyclic C-nucleosides.

We have recently developed a high-yielding synthesis of the 5-bromo-6-methyluridines **6** (R = Bz or H) for another study.[5] Rather surprisingly, these simple nucleosides have not been reported before. Nucleoside **6** (R = H) has been further converted into the protected compounds **9** and **10**, and we report in the present paper the results of a preliminary survey of their reactions with a variety of nucleophiles.

Nucleoside **9** reacts sluggishly with sodium acetate in DMF at 70 °C and more rapidly at 100 °C (table entry 1), but the product is the 5-acetoxy nucleoside **11** rather than the desired 6-acetoxymethyl compound. Nucleoside **11** is easily recognized from



9 R = H

10 R = $(CH_3)_3C$, $(CH_3)_2$ Si– (TBDMS)

	X	R
11	$OCOCH_3$	H
12	$OCOCH_3$	TBDMS
13	$SCOCH_3$	TBDMS
14	SC_6H_5	H

	X	R
15	$OCOCH_3$	TBDMS
16	$NHCH_2C_6H_4OMe$	TBDMS
17	$N(CH_3)_2$	TBDMS
18	NHC_6H_5	H

Entry	Starting material	Nucleophile	Equiv.	Temp °C	Time Hrs	Product	Yield %
1	**9**	Anhyd. NaOAc	1.0	100	2	**11**	43*
2	**10**	Anhyd. NaOAc	1.2‡	70	10	**12**	23*
3	**10**	Anhyd. NaOAc	1.2	150	1	**15**	40
4	**9**	$C_6H_5NH_2$	1.2	150	2	**18**	29
5	**10**	para–OMe-$C_6H_4CH_2NH_2$	2.0	150	1	**16** and **17**	29 15
6	**9**	C_6H_5SH†	1.2	150	2	**14**	40
7	**10**	$KSCOCH_3$	1.2	70	1	**13**	56

* Yield corrected for recovered starting material. ‡ An additional 1.2 equiv. of NaOAc was added at 5 hrs. † The reaction mixture also contained 1 equivalent of triethylamine.

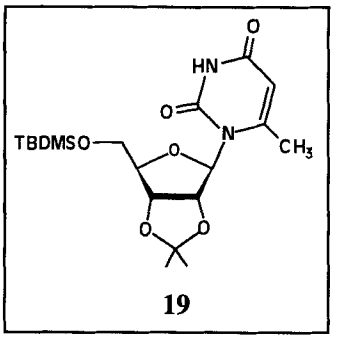
its NMR and UV spectral properties. Increasing the reaction temperature leads only to intractable mixtures. Nucleoside **10** similarly affords the 5-acetoxy nucleoside **12** at 70 °C (entry 2). However, careful examination of the reaction mixture by TLC, using multiple developments, revealed *trace* amounts of another component that was found to be the 6-acetoxymethyl product **15**. The 6-substituted product **15** was obtained in much higher yield by adding sodium acetate to a boiling (150 °C) solution of **10** in DMF (entry 3), and under these conditions it is the 5-acetoxy nucleoside **12** that is present in only trace amounts. At intermediate temperatures, for example 100 °C, TLC analysis indicates that both **12** and **15** are formed from **10**. In order to investigate the possibility that **15** might arise *via* a rearrangement process, we heated samples of **12** in DMF at 150 °C under nitrogen for 1 hr, both in the presence and absence of sodium acetate. However, **12** is essentially stable under these conditions, and nucleoside **15** was not detectable in either reaction mixture. We conclude that **15** is formed from **10** by a mechanism that operates efficiently only at higher temperatures.

The striking temperature dependence seen for the formation of **12** and **15** is similar to the results reported by Hirota *et al*[1b] for the reaction of **1** (R_1 = R_2 = Me) with amines such as morpholine in DMF. Thus, the 5-morpholino product was formed in reactions run at 100 and 150 °C, but the 6-morpholinomethyl product was obtained only at the higher temperature.

The reaction of the TBDMS nucleoside **10** with aniline in hot DMF is complicated by extensive desilylation: however, nucleoside **9** affords the 6-anilinomethyl product **18** in low yield (entry 4). The TBDMS group of **10** survives when *p*-methoxybenzylamine is used as the nucleophile (entry 5) and the 6-substituted product **16** was obtained, again in low yield. In addition, we isolated a significant amount of a second product which we have identified as the *N,N*-dimethylaminomethyl nucleoside **17** from its ^{1}H- and ^{13}C-NMR spectra. Compound **17** is not evident in any of the other reaction mixtures listed in the table, and its dimethylamino group presumably derives ultimately from DMF. In fact, various amines are known[6] to undergo exchange reactions with DMF, and it appears that *p*-methoxybenzylamine, being a much stronger base than aniline (entry 4), releases dimethylamine which can compete in the substitution reaction. A separate experiment established that **16** is stable under the conditions of its formation, and that it is therefore not a precursor of **17**. Interestingly, reducing the temperature of the reactions of either

of the amine nucleophiles with **10** does not lead to the formation of the corresponding 5-substituted products, so in this regard the amine reactions differ from their acetate ion counterparts.

Finally, the sulfur nucleophile thiophenol (entry 6) appears to afford only the 5-substituted product (**14**), even at 150 °C. Extensive desilylation accompanies the reaction of **10** with thiophenol, but the products are again the 5-substituted compounds. Potassium thioacetate (entry 7) likewise leads to a fair yield of the 5-thioacetyl nucleoside **13**, but only at lower temperatures. At 150 °C, the reaction mixture of **10** with potassium thioacetate is very complex, with substantial amounts of the debrominated product **19**[4] being formed together with smaller amounts of an unidentified product, which is definitely not a 6-(substituted-methyl) compound. The reaction between **10** and sodium cyanide (data not shown) also results in debromination to form **19** with no other recognizable products.



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In summary, 5-bromo-6-methyluridines react with sodium acetate in DMF to give either the 5-acetoxy- or 6-acetoxymethyl- products in a temperature dependent manner. On the other hand, the amine nucleophiles examined gave only the 6-substituted products whereas sulfur nucleophiles have thus far afforded only 5-substituted products. It is possible that the observed yields could be improved by using other solvents or other reaction conditions. Studies toward that end are planned, together with a more detailed examination of the temperature dependency of the reactions with oxygen nucleophiles.

EXPERIMENTAL SECTION

^{1}H- and ^{13}C-NMR spectra were obtained in $CDCl_3$ solution on a Varian XL-200 spectrometer. Internal TMS was used as a reference for proton spectra: ^{13}C-spectra were referenced to the solvent resonance. UV spectra were recorded on a Gilford Response II spectrophotometer. EI-Mass spectra were obtained on a Kratos Profile mass spectrometer; FAB-MS spectra were obtained on a Finegan MAT-90 instrument using glycerol as the matrix. Preparative TLC separations were performed on 1000 μm 20 X

20 cm silica gel plates (Uniplates from Analtech, Inc.). Microanalyses were performed by M.H.W. Laboratories, Phoenix, Arizona. All evaporations were carried out under reduced pressure in a rotary evaporator.

5-Bromo-6-methyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine (10). *tert*-Butyldimethylsilyl chloride (0.56 g, 3.73 mmol) was added to a solution of **9** (0.7 g, 1.86 mmol)[5] in dry pyridine (20 mL), and the mixture was stirred at room temperature for 16 h. The reaction mixture was then evaporated to dryness and the residue was partitioned between water and chloroform. The organic phase was washed with water, dried and concentrated. Crystallization of the residue from hexane-ethyl acetate (4:1) afforded pure **10** (0.76 g, 83%), mp 119 - 120 °C; UV (70% MeOH) λ_{max} 277 nm, λ_{min} 244 nm, UV (pH 12) λ_{max} 277 nm, λ_{min} 255 nm; ^{1}H-NMR δ 9.02 (1H, br s, N3-H), 5.81 (1H, d, H-1′)[7], 5.20 (1H, dd, H-2′), 4.83 (1H, dd, H-3′), 4.15 (1H, 8-line m, H-4′), 3.82 and 3.78 (2H, 8-line m, H-5′ and H-5″), 2.64 (3H, s, 6-Me), 1.55 and 1.34 (two 3H s, *MeCMe*), 0.89 (9H, s, SiBu-*t*), 0.05 (6H, s, SiMe), $J_{1',2'}$ = 1.3, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 4.5, $J_{4',5'}$ = 3.7, $J_{4',5''}$ = 8.3, $J_{5',5''}$ = 10.8 Hz.[8]

Anal. Calcd. for $C_{19}H_{31}BrN_2O_6Si$: C, 46.43; H, 6.36; Br, 16.26; N, 5.70. Found: C,46.63, H, 6.35; Br, 16.11; N, 5.57.

General Procedures for Reactions of 9 and 10 with Nucleophiles.

(1) High temperature reactions (table entries 3-6). A sample of **9** or **10** (300 - 450 mg) was dissolved in dry *N,N*-dimethylformamide (10 - 15 mL) and the solution was heated under nitrogen to the reflux point. The nucleophilic reagent was then added and refluxing was continued for the time indicated in the table. The cooled reaction mixture was evaporated to dryness and dichloromethane (60 mL) was added to the residue. The dichloromethane solution was washed with water, dried and concentrated. The products were purified by preparative TLC, using two or three developments in hexane:ethyl acetate (1:1, v/v) containing 0.5% acetic acid.

(2) Lower temperature reactions (table entries 1,2 and 7). In these cases, both **9** (or **10**) *and* the nucleophilic reagent were dissolved in DMF at room temperature, and the mixture was heated to the indicated temperature. After the appropriate reaction period, the mixture was worked-up as described above.

Many of the above reaction mixtures are complex and only the major components were isolated. The yields of the various products have not necessarily been optimized. The following products were obtained as colorless foams:

5-Acetoxy-6-methyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine (12): UV (70% MeOH) λ_{max} 266 nm, λ_{min} 236 nm. In alkaline solution, the UV absorption maximum shifts in a time-dependent manner to 306 nm, reflecting hydrolysis to the monoanion of the corresponding 5-hydroxy nucleoside. On subsequent acidification, the absorption shifts to 278 nm, as expected for the neutral 5-hydroxy product. ^{1}H-NMR for **12**: δ 9.16 (1H, br s, N3-H), 5.68 (1H, d, H-1′), 5.22 (1H, dd, H-2′), 4.83 (1H, dd, H-3′), 4.15 (1H, 8-line m, H-4′), 3.80 (2H, 8-line m, H-5′ and H-5″), 2.32 (3H, s, OAc), 2.26 (3H, s, 6-Me), 1.54 and 1.34 (two 3H s, *MeCMe*), 0.89 (9H, s, SiBu-*t*) 0.06 (6H, s, SiMe), $J_{1',2'}$ = 1.3, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 4.5 Hz; EI-MS *m/z*: 455.18497, [M-Me]$^+$, ($C_{20}H_{31}N_2O_8Si$ calcd. 455.18433); 413.13916 [M-Bu-*t*]$^+$, ($C_{17}H_{25}N_2O_8Si$ calcd. 413.13806).

5-Acetoxy-6-methyl-2′,3′-*O*-isopropylideneuridine (11): UV (30% MeOH) λ_{max} 264 nm, λ_{min} 234 nm. The UV spectral changes observed in alkaline solution and on subsequent reacidification are essentially identical to those described above for **12**. ^{1}H-NMR for **11**: δ 9.22 (1H, br s, N3-H), 5.62 (1H, d, H-1′), 5.27 (1H, dd, H-2′), 5.04 (1H, dd, H-3′), 4.23 (1H, m, H-4′), 3.88 and 3.80 (2H, 8-line m, H-5′ and H-5″), 2.33 (3H, s, OAc), 2.26 (3H, s, 6-Me), 1.56 and 1.36 (two 3H s, *MeCMe*), $J_{1',2'}$ = 2.4, $J_{2',3'}$ = 6.6, $J_{3',4'}$ = 4.0, $J_{4',5'}$ = 2.7, $J_{4',5''}$ = 4.4, $J_{5',5''}$ = 12.1 Hz.[9]

Anal. Calcd. for $C_{15}H_{20}N_2O_8$: C, 50.56; H, 5.66; N, 7.86. Found: C, 50.38, H, 5.79; N, 7.64.

6-Acetoxymethyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine (15): UV (70% MeOH) λ_{max} 261 nm, λ_{min} 231 nm, UV (pH 12) λ_{max} 262 nm, λ_{min} 248 nm; ^{1}H-NMR δ 9.12 (1H, br s, N3-H), 5.81 (1H, d, H-5, $J_{NH,5}$ = 2.2 Hz), 5.57 (1H, d, H-1′), 5.21 (1H, dd, H-2′), 5.04 and 4.94 (two 1H dd, CH_2, J_{gem} = 14.4 Hz, $J_{allylic}$ $\approx$ 0.7Hz), 4.81 (1H, dd, H-3′), 4.12 (1H, 8-line m, H-4′), 3.81 (2H, 8-line m, H-5′ and H-5″), 2.18 (3H, s, OAc), 1.54 and 1.39 (two 3H s, *MeCMe*), 0.89 (9H, s, SiBu-*t*) 0.05 (6H, s, SiMe), $J_{1',2'}$ = 1.5, $J_{2',3'}$ = 6.5, $J_{3',4'}$ = 4.6 Hz.

Anal. Calcd. for $C_{21}H_{34}N_2O_8Si$: C, 53.60; H, 7.28; N, 5.95. Found: C, 53.45, H, 7.07; N, 5.86.

6-(*N*-Phenylaminomethyl)-2′,3′-*O*-isopropylideneuridine (18): UV (30% MeOH) λ_{max} 242, sh260 nm, λ_{min} 222 nm, UV (pH 12) λ_{max} 237, sh266 nm, λ_{min} 226 nm; ^{1}H-NMR δ 9.08 (1H, br s, N3-H), 7.21 (2H, m, *m*-Ph), 6.81 (1H, m, *p*-Ph), 6.62 (2H, m, *o*-Ph), 5.89 (1H, s, H-5), 5.70 (1H, d, H-1′), 5.29 (1H, dd, H-2′), 5.02 (1H, dd, H-3′), 4.24 (3H, m, H-4′ and CH_2), 3.88 (1H, m, H-5′), 3.81 (1H, m, H-5″), 3.30 (1H, br s, 5′-OH), 1.51 and 1.35 (two 3H s, *MeCMe*), $J_{1',2'}$ = 2.7, $J_{2',3'}$ = 6.6, $J_{3',4'}$ = 3.8, $J_{4',5'}$ = 2.6, $J_{4',5''}$ = 4.7, $J_{5',5''}$ = 12.2 Hz.[9]

Anal. Calcd. for $C_{19}H_{23}N_3O_6$: C, 58.60; H, 5.95; N, 10.79. Found: C, 58.78, H, 6.00; N, 10.56.

6-(*N*-*p*-Methoxybenzylaminomethyl)-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine (16): UV (70% MeOH) λ_{max} 261 nm, λ_{min} 235 nm, UV (pH 12) λ_{max} 264 nm, λ_{min} 248 nm; ^{1}H-NMR δ 9.43 (1H, br s, N3-H), 7.29 and 6.86 (two 2H m, C_6H_4) 6.06 (1H, d, H-1′), 5.76 (1H, s, H-5), 5.22 (1H, dd, H-2′), 4.82 (1H, dd, H-3′), 4.13 (1H, 8-line m, H-4′), 3.87-3.84 (7H, m, H5′, H5″, CH_2 and OMe), 3.66(2H, q, CH_2, J_{gem} = 14.6Hz), 1.58 and 1.37 (two 3H s, *MeCMe*), 0.89 (9H, s, SiBu-*t*) 0.06 (6H, s, SiMe), $J_{1',2'}$ = 1.1, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 4.2 Hz.

Anal. Calcd. for $C_{27}H_{41}N_3O_7Si$: C, 59.21; H, 7.54; N, 7.67. Found: C, 59.00, H, 7.43; N, 7.49.

6-(*N,N*-dimethylaminomethyl)-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneuridine (17) was obtained as a side-product in the preparation of **16**; UV (70% MeOH) λ_{max} 262 nm, λ_{min} 233 nm, UV (pH 12) λ_{max} 263 nm, λ_{min} 247 nm; ^{1}H-NMR δ 8.76 (1H, br s, N3-H), 6.14 (1H, d, H-1′), 5.69 (1H, s, H-5), 5.22 (1H, dd, H-2′), 4.81 (1H, dd, H-3′), 4.16 (1H, 8-line m, H-4′), 3.80 (2H, 8-line m, H5′ and H5″), 3.47 and 3.06 (two 1H d, CH_2, J_{gem} = 14.0 Hz), 2.29 (6H, s, NMe_2), 1.53 and 1.34 (two 3H s, *MeCMe*), 0.88 (9H, s, SiBu-*t*) 0.04 (6H, s, SiMe); ^{13}C-NMR ($CDCl_3$ + 1 drop D_2O) δ 162.6(C-4), 153.1(C-2), 150.5(C-6), 113.4 (MeCMe), 103.9 (C-5, J_{gem} = 173 Hz), 91.4 (C-1′), 89.6(C-4′), 84.3(C-2′), 82.2(C-3′), 64.3(C-5′, J_{gem} = 142 Hz), 60.9(CH_2, J_{gem} =133 Hz), 45.0(NMe_2, J_{gem} = 135 Hz), 27.2 and 25.5

(*MeCMe*), 25.9 (SiC*Me*$_3$), 18.5 (Si*C*Me$_3$), -5.2 (Si*Me*$_2$), $J_{1',2'}$ = 1.1, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 4.2 Hz; EI-MS *m/z* 455.24454 (8.1, $M^+[C_{21}H_{37}N_3O_6Si]$ = 455.24517).

***S*-Acetyl-6-methyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-5-mercaptouridine (13)**: UV (50% MeOH) λ_{max} 216.5 and 272 nm, λ_{min} 242 nm. Adjustment of the pH to 12 results in the gradual shift of UV absorption to 256 nm and 321 nm, which corresponds to the values expected for the dianion of the parent 5-mercapto nucleoside[10]. The 321.5 nm absorption then decreases with time, reflecting the formation of the disulfide. However, in the presence of dithiothreitol, which stabilizes 5-mercaptouracils[10], spectra for the monoanion (λ_{max} 330 nm, λ_{min} 294 nm) and the neutral molecule (λ_{max} 290, λ_{min} 274 nm) were obtained at pH 8 and pH 4, respectively. ^{1}H-NMR for **13**: δ 10.25 (1H, br s, N3-H), 5.81 (1H, br s, H-1′), 5.24 (1H, dd, H-2′), 4.82 (1H, dd, H-3′), 4.14 (1H, 8-line m, H-4′), 3.80 (2H, 8-line m, H5′ and H5″), 2.53 (3H, s, 6-Me), 2.42 (3H, s, SAc), 1.53 and 1.34 (two 3H s, *MeCMe*), 0.87 (9H, s, SiBu-*t*) 0.04 (6H, s, SiMe), $J_{1',2'}$ = 1.2, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 4.4 Hz.

Anal. Calcd. for $C_{21}H_{34}N_2O_7SSi$: C, 51.83; H, 7.04; N, 5.76; S, 6.59. Found: C, 52.00, H, 7.18; N, 5.73; S, 6.41.

***S*-Phenyl-6-methyl-2′,3′-*O*-isopropylidene-5-mercaptouridine (14)**: UV (30% MeOH) λ_{max} 246, sh268, sh306 nm, λ_{min} 224 nm, UV (pH 12) λ_{max} 246, sh270 nm, λ_{min} 230 nm; ^{1}H-NMR δ 9.90 (1H, br s, N3-H), 7.11-7.33 (5H, m, Ph), 5.79 (1H, d, H-1′), 5.28 (1H, dd, H-2′), 5.05 (1H, dd, H-3′), 4.24 (1H, m, H-4′), 3.88 and 3.81 (2H, 8-line m, H-5′ and H-5″), 2.77 (3H, s, 6-Me), 1.56 and 1.35 (two 3H s, *MeCMe*), $J_{1',2'}$ = 2.2, $J_{2',3'}$ = 6.6, $J_{3',4'}$ = 4.2, $J_{4',5'}$ = 2.7, $J_{4',5''}$ = 4.8, $J_{5',5''}$ = 12.2 Hz;[9] FAB-MS (negative ion) *m/z* 405.1, $[M-H]^-$, (calcd. for $C_{19}H_{21}N_2O_6S$, $[M-H]^-$ 405.1).

Anal. Calcd. for $C_{19}H_{22}N_2O_6S$: C, 56.15; H, 5.46; N, 6.89; S, 7.89. Found: C, 55.96, H, 5.62; N, 6.60; S, 7.66.

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(7) The H-1′ resonances of 6-methyl and 6-(substituted-methyl)-2′,3′-*O*-isopropylideneuridines are broadened by two previously unreported five-bond couplings, namely $^5J_{\text{H-1}',\text{N3-H}}$ and $^5J_{\text{H-1}',\text{Me}}$ (or $^5J_{\text{H-1}',\text{CH}_2\text{R}}$). These small couplings, which can be detected by decoupling experiments, can obscure the splitting of the H-1′ resonances such that accurate values of $J_{1',2'}$ can be extracted only from the H-2′ resonances. These couplings will be discussed in more detail in a forthcoming publication.

(8) The chemical shifts of H-5′ and H-5″ and values of $J_{4',5'}$, $J_{4',5''}$, and $J_{5',5''}$ were obtained by spectral simulation. Essentially identical splitting patterns for H-4′, H-5′ and H-5″ were seen for all of the 5′-*O*-(*tert*-butyldimethylsilyl) nucleosides used in this study.

(9) The chemical shifts for H-5′ and H-5″ and the coupling constants involving these two protons were obtained by simulation of the spectrum recorded after the addition of D_2O.

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