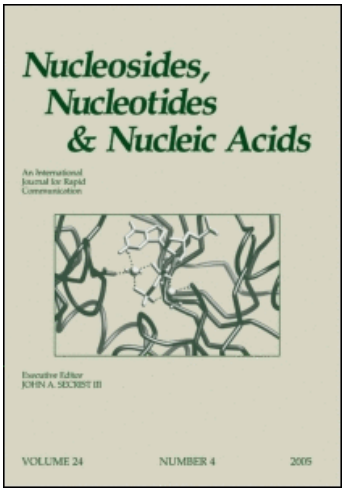

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Studies on the Synthesis of $S^{5'}$,6-Methano-5'-Thiourldines

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STUDIES ON THE SYNTHESIS OF $S^{5'}$,6-METHANO-5'-THIOURIDINES.

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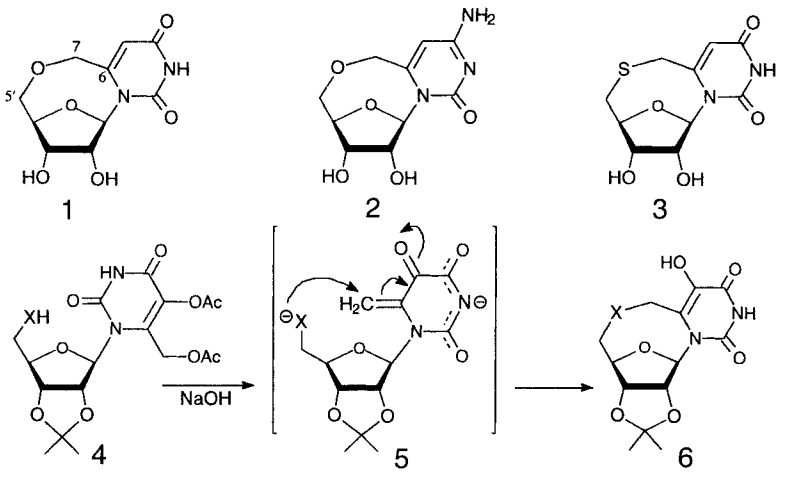
Abstract: Two approaches to the synthesis of the title compounds are described. In the first route, a reactive 5-oxo-6-methylene pyrimidine intermediate that is generated by treating the *bis*-acetylated or *bis*-benzoylated nucleosides **10** and **11** with sodium hydroxide undergoes intramolecular attack by the 5'-thiol group to afford the 5-hydroxy cyclonucleoside **12**. In the second and higher yielding approach, the $S^{5'}$,6-methano linkage is established by an internal allylic displacement reaction that occurs when the 5-bromo-6-methyl nucleoside **24** is treated with base. The conformational properties of $S^{5'}$,6-methano-5'-thiouridine (**3**) and certain long-range spin-spin couplings observed in the NMR spectra of the intermediate nucleosides are discussed.

In previous investigations with semi-flexible cyclonucleosides that retain a full complement of the normal pyrimidine hydrogen-bonding sites, we have synthesized $O^{5'}$,6-methanouridine (**1**)[1] and $O^{5'}$,6-methanocytidine (**2**).[2] Such compounds are useful probes of the conformational specificities of the enzymes of pyrimidine nucleoside metabolism. For example, our observations that **2** is a substrate for cytidine deaminase from mouse liver,[2] whereas **1** is unaffected by uridine phosphorylase from *Toxoplasma gondii,*[3] have contributed to the evidence that these enzymes require their normal substrates to adopt the *anti* and *syn* conformations respectively. As an extension of these studies, we have been interested in preparing the corresponding $S^{5'}$,6-methano compounds of type **3**, and we report in the present paper two different synthetic approaches to this new class of cyclonucleosides. Our interest in them stems from the possibility of obtaining sulfones and chiral sulfoxides that might extend the range of attainable conformations, as well as the possibility that sulfur-extrusion reactions might afford an interesting route to carbon-linked cyclonucleosides.

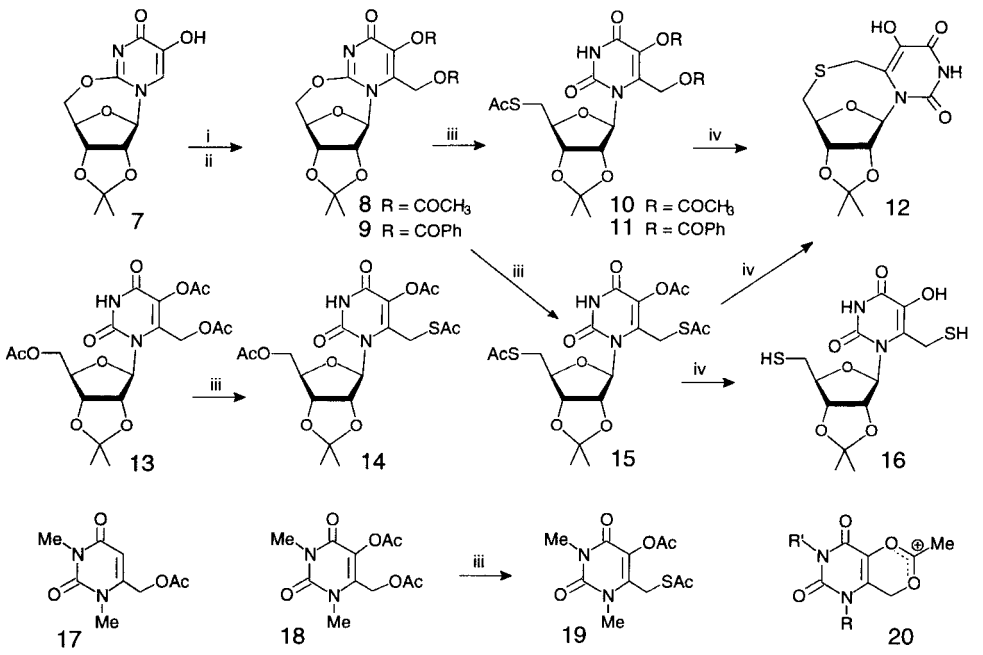
The synthesis of $O^{5'}$,6-methanouridine (**1**) exploits the fact that treatment of 5-acetoxy-6-(acetoxymethyl)uridines such as **4** (X = O) with sodium hydroxide



generates a reactive enone (**5**) that, at pH 14, undergoes capture by the 5'-oxy anion to give the intermediate 5-hydroxy nucleoside **6** (X = O).[1] We expected that the same strategy with 5'-thio nucleosides would lead to the $S^{5'}$,6-methano system (**6**, X = S), so our initial target compound was the 5'-thioacetate **10**.

A suitable precursor, namely the 2,5'-anhydro nucleoside **8**, was prepared in crystalline form *via* a modified procedure from **7** and treated with potassium thioacetate in refluxing acetone. When only a small excess (1.1 equivalents) of potassium thioacetate was used, the major product was indeed the expected **10**. However, the reaction mixture contained a second product that was found to be the *bis*-thioacetate **15**, and this compound became the major product when a larger excess of potassium thioacetate was used. The surprising incorporation of the thioacetyl group into the pyrimidine 6-substituent seems to be a general reaction of 5-acetoxy-6-(acetoxymethyl)-uracils. Thus, treatment of both the nucleoside **13** and the free base **18** with potassium thioacetate leads smoothly to the corresponding 6-(thioacetoxy-methyl) compounds **14** and **19**, respectively. Since the simple 5-unsubstituted-6-(acetoxymethyl)-uracil **17** was recovered unchanged after treatment with potassium thioacetate in hot acetone, it is possible that the formation of **14**, **15**, and **19** proceed *via* the intermediacy of acetoxonium ions of type **20**. The scope of this reaction with nucleophiles other than thioacetate remains to be determined.[4] Interestingly, the analogous *bis*-benzoyl 2,5'-anhydro nucleoside **9**, which was prepared in modest yield from **7** by a two-

step hydroxymethylation-benzoylation procedure,[5] afforded *only* the 5'-thioacetate **11**, even when a large excess of potassium thioacetate was used. The locations of the thioacetyl groups in the various nucleosides were readily determined from the NMR spectra. In the ^{13}C-NMR spectra (Table 1), for example, the presence of *S*-acetyl groups shifts the C5' and/or C7 resonances upfield by more than 30 ppm relative to their *O*-acetyl counterparts.



Reagents: i) NaOH, HCHO, 50°C. ii) HOAc, $(RCO)_2O$. iii) KSAc, acetone, reflux. iv) 1*N* NaOH.

Treatment of **10** with aqueous sodium hydroxide does promote formation of the $S^{5'}$,6-methano nucleoside **12** as anticipated. However, the formation of numerous side products reduces the yield of **12** to only 11%. In contrast, the *O*-acetyl nucleoside **13** affords the corresponding $O^{5'}$,6-methano nucleoside in 57% yield.[1] Somewhat better yields of **12** (24%) were obtained from the benzoyl nucleoside **11**. Treatment of the *bis*-thioacetate **15** with sodium hydroxide also affords **12** (14%), but the major product **16** (35%) is simply the result of deacetylation.

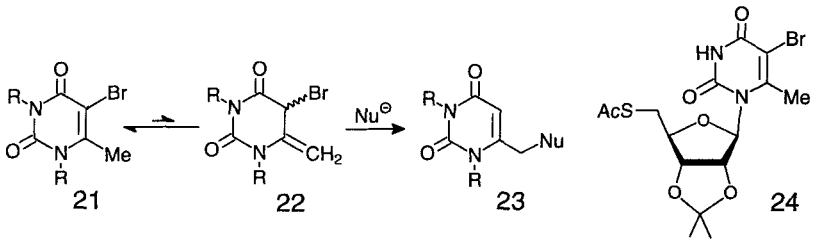
Although the foregoing work demonstrated that a stable $S^{5'}$,6-methano-uridine could be obtained, the combination of disappointing yields of **12** and the

TABLE 1. ^{13}C-NMR Data for Selected Nucleosides.

Cpd	C4	C2	C6	C5	C1'	C2'	C3'	C4'	C5'	C7/ Me†	OAc	SAc
13	157.7	149.3	140.0	127.7	93.0	84.6	82.0	86.8	64.6	55.0	170.7, 20.8 169.7, 20.4 168.2, 20.2	-
10	157.5	149.3	140.1	127.5	93.1	84.8	84.1	88.1	31.3	54.9	170.3, 20.9 168.2, 20.2	194.8, 30.5
15	157.3	149.3	143.2	126.4	93.0	84.9	84.2	88.2	31.2	23.5	168.2, 20.2	194.8, 30.6 192.1, 30.1
14	157.2	149.2	143.1	126.4	92.8	84.6	82.0	86.8	64.8	23.5	170.7, 20.9 168.2, 20.2	192.2, 30.1
11	157.5	149.4	140.4	127.7	93.3	84.9	84.1	88.1	31.4	55.5	-	194.8, 30.6
29*	158.8	149.8	151.3	99.8	92.9	70.9	69.3	84.6	61.5	20.3†	-	-
30	158.3	150.0	150.7	101.0	93.8	83.5	80.4	88.0	62.8	20.7†	-	-
24	158.7	149.6	150.9	100.7	93.7	84.9	84.3	88.4	30.6	20.6†	-	194.8, 31.4
16*	159.7	148.9	133.2	129.7	91.5	84.1	83.4	89.9	26.0	17.8	-	-
12*	159.5	149.1	131.3	130.3	96.8	87.8	82.9	89.3	33.8	26.5	-	-
34*	162.0	151.3	152.7	102.9	96.8	88.0	83.0	89.6	35.1	34.9	-	-
3*	162.0	151.3	153.8	103.9	94.5	76.6	70.4	85.7	33.2	34.2	-	-

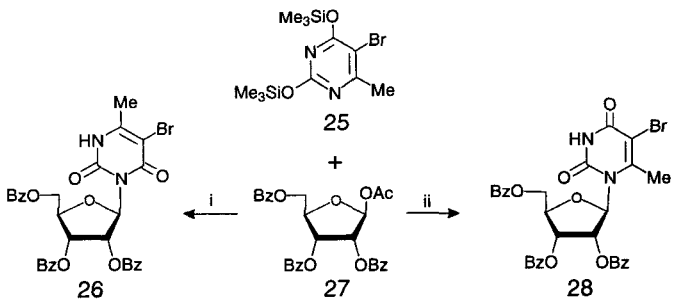
$CDCl_3$ was used as solvent except for the compounds marked with an asterisk, where DMSO-d_6 was used instead. For compounds with isopropylidene groups, MeCMe resonances occur in the ranges δ113.9-114.2, 27.0-27.3 and 25.1-25.4 for spectra obtained in $CDCl_3$, and 112.5-114.4, 26.5-26.9 and 24.7-24.9 for spectra obtained in DMSO-d_6. Benzoyl resonances for compound **11** appear at δ165.1, 163.9, 133.7, 134.2, 130.7, 130.2, 128.6 and 128.3 ppm.

modest yield of the most effective precursor (**11**) prompted us to examine an alternative approach. This approach is based on the work of Hirota and coworkers,[6] who showed that 5-bromo-6-methyluracils (**21**) afford the 6-substituted uracils **23** when treated with oxygen and nitrogen nucleophiles, apparently *via* an allylic displacement reaction of the tautomer **22.** Indeed, the 6-acetoxymethyluracil



17 used to investigate the thioacetylation reaction described above was prepared by this procedure. In later work, we found that **21** reacts with sulfur nucleophiles to give 5- rather than 6-substituted products.[7] However, it seemed possible that the constraints of an intramolecular reaction would induce the 5'-thiol derived from a precursor such as **24** to participate in an allylic displacement reaction leading to the $S^{5'}$,6-methano linkage. Also, the 5-unsubstituted nature of the product would represent a distinct advantage over our first approach, where it would be necessary to remove the 5-hydroxy group from the initial product **12** in a separate series of reactions.

In order to evaluate the allylic displacement route, we first needed to prepare the appropriate 5-bromo-6-methyluridines, which, rather surprisingly, had not been reported before. In their studies with silylated 5,6-disubstituted uracils, Vorbrüggen and coworkers[8] found that high yields of the N-1 nucleosides could be



Reagents: i) $SnCl_4$, MeCN, 22°C. ii) $Me_3SiOSO_2CF_3$, MeCN, 0°C.

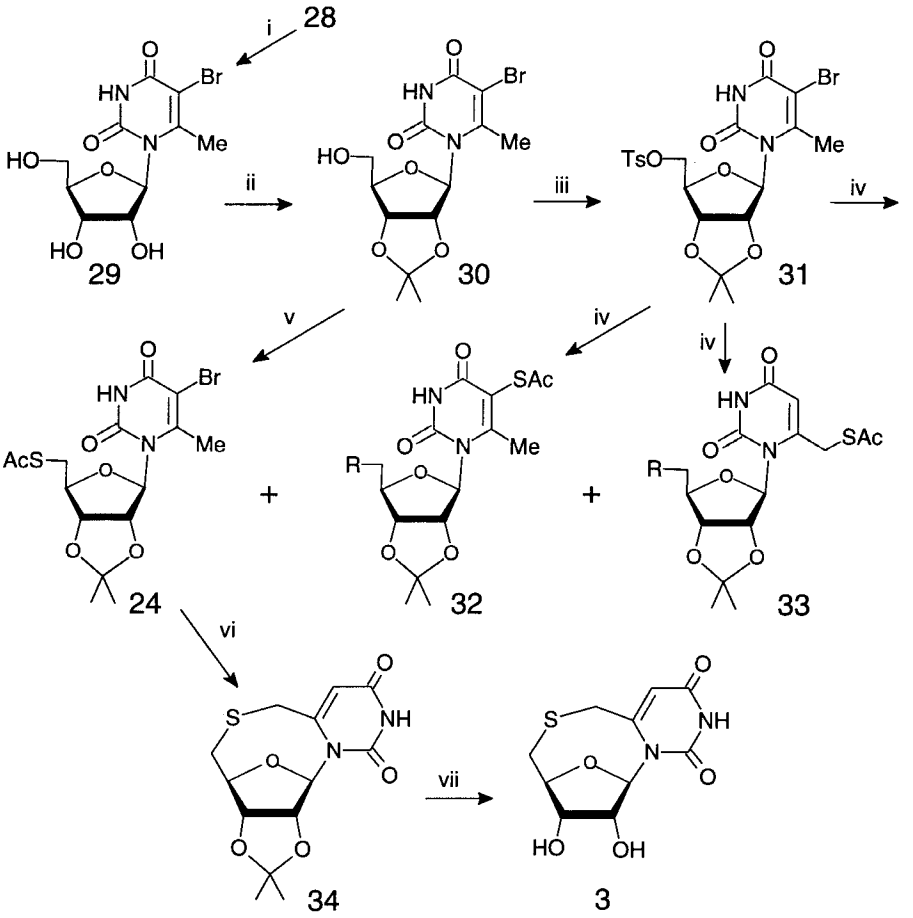
obtained in Lewis acid-catalyzed condensation reactions, probably because bulky 5-substituents tend to push the 4-*O*-trimethylsilyl group towards N-3, which

therefore becomes hindered. We have found that the 5-bromo-6-methyluracil **25** can also be ribosylated selectively at N-1, although some experimentation was necessary to find an appropriate catalyst/solvent combination. For example, stannic chloride/acetonitrile, which afforded the N-1 nucleoside efficiently with silylated 5,6-dimethyluracil,[8] promotes the formation of the N-3 isomer **26** as the major product in the condensation of **25** with **27**. On the other hand, a combination of trimethylsilyl triflate and acetonitrile does afford the required N-1 nucleoside **28** in yields approaching 80%. Debenzoylation to give 5-bromo-6-methyluridine (**29**) and formation of the intermediates **30** and **31** were then accomplished using standard methods.

Since intermediate **31** has the potential of undergoing nucleophilic attack at multiple sites, it was not surprising to find that treatment with potassium thioacetate in hot acetone led to several products in addition to the required 5'-thioacetate **24**, which was isolated in 36% yield. The various side products could not be entirely separated by chromatography, but it was clear from the NMR spectra that two of the fractions contained the 5-thioacetoxy nucleosides **32** (R = SAc and OTs), respectively. These side products, which were expected on the basis of our earlier studies,[7] were each obtained in about 20% yield, and were accompanied by much smaller amounts of the 6-thioacetoxymethyl nucleosides **33** (R = SAc and OTs). Fortunately, these side products can be avoided by subjecting the 5'- alcohol **30** to a Mitsunobu-like reaction[9] with potassium thioacetate. Under these conditions, **24** was obtained in 58% yield from a much less-complex reaction mixture.

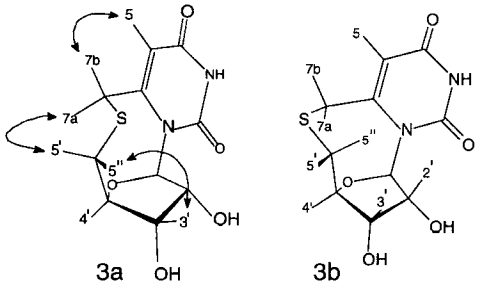
Ring-closure to the desired $S^{5'}$,6-methano system occurred smoothly on treatment of **24** with sodium hydroxide in ethanol at reflux temperature, and **34** was obtained in 59% yield by direct crystallization from the neutralized reaction mixture. In contrast, attempts to induce the 5'-alcohol **30** to cyclize in base to give the corresponding $O^{5'}$,6-methano nucleoside have not been successful thus far. Conventional deblocking of **34** then afforded the parent cyclonucleoside **3**, which was obtained in an overall yield of 15% for the five steps starting from **27**.

In previous conformational studies, we concluded that although $O^{5'}$,6-methano nucleosides such as **1** and **2** cannot adopt the full range of normal furanose conformations, they nevertheless exist in an equilibrium of N-type (C2'-*exo*) and S-type (C3'-*exo*) conformers. This sets them apart from conventional 5'-linked cyclonucleosides with smaller bridging systems, which are held rigidly in the normally unpopulated ${}_0E$ conformation. It appears that the $S^{5'}$,6-methano nucleoside **3** also exists in a two-state equilibrium, but judging from the values of $J_{1',2'}$ and $J_{3',4'}$ (2.3 and 5 Hz) relative to those of **1** (4.2 and 3.7 Hz), a larger



Reagents: i) NaOMe, MeOH. ii) *p*-TsOH, $Me(OMe)_2Me$, acetone. iii) *p*-TsCl, pyridine. iv) KSAc, acetone. v) Ph_3P, DEAD, KSAc, THF. vi) NaOH, EtOH. vii) HCl, MeOH.

proportion of N-type conformers is present. With regard to the orientation of the *S*-methano bridge, molecular modeling studies suggest that the three lowest energy structures have the two basic types of conformations shown in structures **3a** and **3b**. These conformers include the 2'-*exo* and 3'-*exo* forms of **3a**, which features the gauche-gauche (+sc) orientation about the C4'-C5' bond, and the 4'-*endo* form of **3b**, where the orientation is gauche-trans (ap).[10] These conformations would be distinguishable in solution by different NOE interactions, and it is clear from the observed pattern that **3a** predominates. The same NOE pattern was observed previously for $O^{5'}$,6-



methanouridine (**1**).[1] If **3b** were to predominate, NOE contacts would be expected between H5'' and H2', and between H3' and *both* of the C5' protons, and a much larger value for the coupling constant $J_{4',5''}$ would be expected as well. Of course, it is possible that **3b** is a minor contributor to the population of conformers. In an average conformation that tends towards 2'-exo **3a**, with a possible minor contribution from **3b**, the average value of the glycosyl rotation angle χ would tend to increase relative to the $O^{5'}$,6-methano case, and it is possible that χ in **3** could approach -170°. The observed molar ellipticity found for **3** ([θ] =27,700), which exceeds the value found for **1** ([θ] = 20,500), is consistent with this conclusion since the magnitude of the CD spectrum is known [1,11] to increase with increasing values of χ for *anti* nucleosides.

Finally, we wish to report some interesting features observed in the NMR spectra of the various intermediate 6-substituted-2',3'-*O*-isopropylidene nucleosides. In routine NMR characterization of these compounds, we found that the H1' resonances in spectra determined in deuteriochloroform are invariably broader than neighboring resonances such as H2'. In some cases, for example **24**, the H1' resonance in the unperturbed spectrum shows none of the 1.1 Hz splitting due to $J_{1',2'}$. In other cases, for example **10**, the H1' splitting is significantly less than expected from the value of $J_{1',2'}$ extracted from the H2' resonance. The observed broadening of the H1' resonance is caused by two hitherto unreported five bond couplings, namely $^5J_{NH,1'}$ and $^5J_{1',CH_2R}$. The existence of a $^5J_{NH,1'}$ is demonstrated by the partial sharpening of the H1' resonance that occurs on addition of D_2O or irradiation of the NH resonance. This small coupling (≤0.5 Hz), which is analogous to the $^5J_{5,1'}$ that has been detected for certain *anti* pyrimidine nucleosides,[12] probably requires that H1' and N^3-H lie close to the same plane. This would imply a value of χ of about 65° for these compounds. The existence of the second ≤ 0.5 Hz coupling ($^5J_{1',CH_2R}$) is demonstrated by the sharpening of H1' that occurs on irradiation of the methyl or methylene protons after exchange of N^3-H by deuterium. Under these conditions, the splitting of the H1'-resonances reflect the full value of $J_{1',2'}$.

EXPERIMENTAL

General Procedures: ^{1}H-NMR were obtained relative to internal tetramethylsilane on a Varian XL-200 spectrometer. Except where noted, spectra were obtained at ambient temperature (22 °C). Values given for coupling constants and chemical shifts that pertain to non first-order portions of the spectra were obtained by spin simulation using

Varian software. Iteration was continued until the root-mean-square frequency error between the observed and calculated lines was less than 0.1 Hz. NOESY spectra were generated using a mixing time of 0.5 sec. ^{13}C-NMR spectra were recorded on a Varian XL-200 instrument (50.3 MHz), and the solvent resonance was used as a reference. Selective irradiation experiments and peak multiplicity in coupled spectra were used to confirm peak assignments. UV and CD spectra were recorded on Gilford Response II and JASCO J-720 instruments, respectively. Preparative TLC separations were performed on 1000 μm 20 X 20 cm silica gel plates (Uniplates from Analtech, Inc.). Unless stated otherwise, all evaporations were carried out under reduced pressure (water aspirator) in a rotary evaporator. Microanalyses were performed by M. H. W. Laboratories, Phoenix, Arizona.

5-Acetoxy-6-(acetoxymethyl)-2',3'-*O*-isopropylidene-2,5'-anhydrouridine (**8**). 1*N* sodium hydroxide solution (10 mL) was added to a suspension of 2.82 g (10 mmol) of 5-hydroxy-2',3'-*O*-isopropylidene-2,5'-anhydrouridine (**7**)[13] in water (90 mL). Aqueous formaldehyde (2 mL of 37% solution, 13 mmol) was added when solution was complete and the mixture was heated at 50 °C for 6 h, during which time the UV maximum of diluted samples (pH 10) shifts from 295 nm to 310 nm. The reaction mixture was stored at room temperature overnight and then neutralized with acetic acid prior to evaporation of solvents (oil pump). Two 50 mL batches of ethanol were evaporated from the residue, and acetic anhydride (30 mL)[14] was added to the final gelatinous white solid. The mixture was stirred at room temperature for 1 h, the acetic anhydride was removed by rotary evaporation (oil pump), and the residue was partitioned between sodium bicarbonate solution and ethyl acetate. Concentration of the washed and dried (Na_2SO_4) organic phase to about 25 mL afforded 2.6 g (66%) of crystalline **8** in two crops. A sample recrystallized from aqueous ethanol showed the following properties: mp 183-186 °C; UV (5% aq. ethanol) λ_{max} = 253.5, λ_{min} = 224 nm; ^{1}H NMR ($CDCl_3$) δ 5.69(1H, s, H1'), 5.23 (1H, d, H7a), 5.06 (1H, d, H7b), 5.03 and 4.95 (2H, dd, H2' and H3'), 4.72 (1H, t, H4'), 4.48 (1H, dd, H5'), 4.23 (1H, dd, H5''), 2.36 and 2.15 (two 3H s, acetyls), 1.53 and 1.37 (two 3H s, MeCMe), $J_{1',2'} = J_{3',4'} \approx 0$, $J_{2',3'}$ = 5.7, $J_{4,5'}$ = 1.4, $J_{4',5''}$ = 1.2, $J_{5'gem}$ = 12.8, J_{7gem} = 13.9 Hz. *Anal.* Calcd. for $C_{17}H_{20}N_2O_9$: C, 51.52; H, 5.09; N, 7.07. Found: C, 51.70; H, 5.22; N, 6.81.

5-Benzoyloxy-6-(benzoyloxymethyl)-2',3'-*O*-isopropylidene-2,5'-anhydrouridine (**9**). 5-Hydroxy-2',3'-*O*-isopropylidene-2,5'-anhydrouridine (**7**) (2.82 g) was hydroxymethylated as described above. After evaporation of the neutralized reaction mixture, the residue was dried by the azeotropic removal of water with ethanol and pyridine, the final residue was dissolved in dry pyridine (50 mL) containing benzoic anhydride (20 g),[5,14] and the mixture was stirred at room temperature for 2 h. Methanol was added, and stirring was continued for an additional 1 h. Solvents were removed by rotary evaporation and a solution of the dark residue in ethyl acetate was loaded onto a short column of silica gel. Elution with ethyl acetate and concentration of the appropriate fractions afforded pure **9**, which crystallized (1.46 g, 28%) from ethanol, mp 198-202 °C; ^{1}H NMR ($CDCl_3$) δ 8.25-8.07 (4H,

m,*o*-Ph), 7.69-7.40 (6H, m, *m*-and *p*-Ph), 5.99 (1H, s, H1'). 5.65 (1H, d, H7a), 5.33 (1H, d, H7b), 5.05 and 5.01 (2H, dd, H2' and H3'), 4.74 (1H, t, H4'), 4.51 (1H, dd, H5'), 4.28 (1H, dd, H5"), 1.49 and 1.34 (two 3H s, MeCMe), $J_{1',2'} = J_{3',4'} \approx 0$, $J_{2',3'} = 5.6$, $J_{4,5'} = 1.4$, $J_{4',5''} = 1.0$, $J_{5'gem} = 12.8$, $J_{7gem} = 13.9$ Hz. *Anal.* Calcd. for $C_{27}H_{24}N_2O_9$: C, 62.30; H, 4.65; N, 5.38. Found: C, 62.10; H, 4.65; N, 5.31.

5-Acetoxy-6-(acetoxymethyl)-5'-*S*-acetyl-2',3'-*O*-isopropylidene-5'-thiouridine (10). Potassium thioacetate (62.8 mg, 0.55 mmol) was added to a solution of **8** (0.5 mmol) in acetone (10 mL) and the mixture was heated at reflux temperature for 1 h, at which time TLC (ethyl acetate-hexanes 1:1 containing 0.5% acetic acid) indicated a predominance of **10** together with much smaller amounts of **15**. The neutralized (HOAc) reaction mixture was evaporated to dryness and a solution of the residue in dichloromethane was applied to a preparative TLC plate. Triple development in the above solvent system and removal of the appropriate band afforded 146 mg (62%) of pure **10**, mp153-155 °C (from ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$) δ 9.07 (1H, br s, NH), 5.61 (1H, d, H1'), 5.26 and 5.22 (2H, dd overlapped by d, H2' and H7a), 4.90 and 4.85 (2H, d overlapped by dd, H7b and H3'), 4.14 (1H, 6-line m, H4'), 3.27 and 3.24 (2H, AB part of ABX, H5' and H5"), 2.35 and 2.34 (two 3H s, COMe) 2.13 (3H, s, COMe), 1.52 and 1.34 (two 3H s, MeCMe), $J_{1',2'} = 1.3$, $J_{2',3'} = 6.5$, $J_{3',4'} = 3.95$, $J_{4,5'} = 6.9$, $J_{4',5''} = 7.4$, $J_{5'gem} = 13.7$, $J_{7gem} = 13.5$ Hz. *Anal.* Calcd. for $C_{19}H_{24}N_2O_{10}S$: C, 48.30; H, 5.12; N, 5.93; S, 6.79. Found: C, 48.40; H, 5.27; N, 5.77; S, 7.19.

5-Acetoxy-6-(thioacetoxymethyl)-5'-*S*-acetyl-2',3'-*O*-isopropylidene-5'-thiouridine (15) was prepared and isolated as described above for **10** except that a larger excess of potassium thioacetate (342 mg, 3 mmol, 6 equivalents) was used. Crystalline **15** (180 mg, 74%) was obtained from aqueous ethanol, mp 138-141 °C (with prior shrinking); ^{1}H-NMR ($CDCl_3$) δ 9.34 (1H, br s, NH), 5.10 (1H, d, H1'), 5.23 (1H, dd, H2'), 4.84 (1H, dd, H3'), 4.22 (1H, d, H7a), 4.13 (1H, 6-line m, H4'), 4.02 (1H, d, H7b), 3.25 (2H, pseudo d with 7.2 Hz splitting, H5' and H5"), 2.40 (3H, s, COMe), 2.35 and 2.34 (two 3H s, COMe), 1.51 and 1.34 (two 3H s, MeCMe), $J_{1',2'} = 1.3$, $J_{2',3'} = 6.5$, $J_{3',4'} = 3.9$, $J_{7gem} = 14.5$ Hz. *Anal.* Calcd. for $C_{19}H_{24}N_2O_9S_2$: C, 46.71; H, 4.95; N, 5.73; S, 13.13. Found: C, 46.90; H, 5.09; N, 5.74; S, 13.14.

5-Acetoxy-6-(thioacetoxymethyl)-5'-*O*-acetyl-2',3'-*O*-isopropylideneuridine (14). was prepared from **13**[13] and potassium thioacetate (4 equivalents) as described above for **10**. Crystalline **14** was obtained in 81% yield, mp 145-146 °C (from ethanol); ^{1}H NMR ($CDCl_3$) δ 8.38 (1H, br s, NH), 5.44 (1H, d, H1'), 5.20 (1H, dd, H2'), 4.80 (1H, dd with virtual coupling since δH4' = δ5', H3'), 4.42-4.18 (4H, m, H4', H5' H5" overlapping H7a d at δ4.24), 4.03 (1H, d, H7b), 2.40, 2.34 and 2.09 (three 3H, s, COMe), 1.53 and 1.35 (two 3H, s, MeCMe), $J_{1',2'} = 1.3$, $J_{2',3'} = 6.5$, $J_{3',4'} = 3.9$, $J_{7gem} = 14.5$ Hz. *Anal.* Calcd. for $C_{19}H_{24}N_2O_{10}S$: C, 48.30; H, 5.12; N, 5.93; S, 6.79. Found: C, 48.47; H, 5.35; N, 5.87; S, 6.87.

5'-*S*-Acetyl-5-benzoyloxy-6-(benzoyloxymethyl)-2',3'-*O*-isopropylidene-5'-thiouridine (**11**) was prepared from **9** and potassium thioacetate (1.2 equivalents) as described above for **10**. Pure **11** was obtained as a foam in 91% yield, ^{1}H NMR ($CDCl_3$) δ 9.05 (1H, br s, NH), 8.22-8.09 (4H, m, *o*-Ph), 7.65-7.40 (6H, m, *m*- and *p*-Ph), 5.89 (1H, d, H1'), 5.78 (1H, d, H7a), 5.32 (1H, dd, H2'), 5.20 (1H, d, H7b), 4.87 (1H, dd, H3'), 4.15 (1H, 6-line m, H4'), 3.31 and 3.27 (2H, AB part of ABX, H5' and H5''), 2.35 (3H, s, COMe), 1.44 and 1.30 (two 3H s, MeCMe), $J_{1',2'}$ = 1.3, $J_{2',3'}$ = 6.5, $J_{3',4'}$ = 4.3, $J_{4,5'}$ = 6.9, $J_{4',5''}$ = 7.3, $J_{5'gem}$ = 13.7, J_{7gem} = 13.5 Hz. *Anal.* Calcd. for $C_{29}H_{28}N_2O_{10}S$: C, 58.38; H, 4.73; N, 4.70; S, 5.37. Found: C, 58.19; H, 4.78; N, 4.60; S, 5.17.

5-Acetoxy-1,3-dimethyl-6-(thioacetoxymethyl)uracil (**19**) was prepared from **18** (90 mg)[15] and potassium thioacetate (114 mg) in refluxing acetone (6 mL) as described above, and isolated *via* preparative TLC in 88% yield (corrected for recovered starting material); mp 143-145 °C (from ethyl acetate-hexane), ^{1}H NMR ($CDCl_3$) δ 4.08 (2H, s, CH_2), 3.42 and 3.36 (two 3H s, NMe), 2.21 and 2.35 (two 3H s, COMe). For comparison, the methylene resonance of starting material **18** appears at δ 5.03. *Anal.* Calcd. for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.93; N, 9.78; S,11.20. Found: C, 45.98; H, 4.85; N, 9.51; S, 11.39.

5-Hydroxy-2',3'-*O*-isopropylidene-$S^{5'}$,6-methano-5'-thiouridine (**12**). ***Method A:*** A 97 mg (0.2 mmol) sample of the 5'-thioacetyl nucleoside **10** was dissolved in 1*N* sodium hydroxide solution (6 mL). After 30 min, the reaction mixture was acidified with acetic acid (0.4 mL) and extracted with several batches of ethyl acetate. The dried organic phase was concentrated and subjected to preparative TLC in ethyl acetate-hexane -acetic acid (1:1:0.05) to afford 7 mg (11%) of **12** after crystallization from ethyl acetate hexane, mp > 300 °C (with darkening above 290 °C), UV (water) λ_{max} = 291.5 nm, λ_{min} = 248.5 nm; UV (pH 12) λ_{max} = 323.5 nm and 250 nm(sh), λ_{min} = 276 nm; ^{1}H-NMR (DMSO-d_6) δ 11.56 (1H, br s, NH), 8.72 (1H, br s, OH), 6.17 (1H, d, H1'), 4.88 (1H, dd, H2'), 4.81 (1H, t, H4'), 4.66 (1H, d, H3'), 4.28 (1H, d, H7a), 3.73 (1H, d, H7b), 3.04 (1H, dd, H5'), 2.75 (1H, dd, H5''), 1.44 and 1.26 (two 3H s, MeCMe), $J_{1',2'}$ = 1.6, $J_{2',3'}$ = 6.2, $J_{3',4'} \approx 0$, $J_{4,5'} = J_{4',5''}$ = 3.6, $J_{5'gem}$ = 14.8, J_{7gem} = 14.5 Hz. *Anal.* Calcd. for $C_{13}H_{16}N_2O_6S$: C, 47.56; H, 4.91; N, 8.53; S, 9.76. Found: C, 47.59; H, 5.00; N, 8.39; S, 9.76.

Method B: A solution of the benzoylated anhydro nucleoside **9** (520 mg, 1 mmol) in acetone (25 mL) containing potassium thioacetate (342 mg, 3 mmol) was heated at reflux temperature for 1 h. The solvent was then removed and the residue containing **11** was suspended in 10 mL of water and 3 mL of 10*N* sodium hydroxide solution. Solution was complete within 10 min. After 30 min, the yellow reaction mixture was acidified with acetic acid. Cyclonucleoside **12** was obtained in 24% yield (80 mg) as described above except that a small column of silica gel was used instead of preparative TLC.

Method C: A solution of the acetylated anhydro nucleoside **8** (792 mg, 2 mmol) in acetone (40 mL) containing potassium thioacetate (800 mg, 7 mmol) was heated at reflux temperature for 3 h. The solvent was then removed and the residue containing **15** was treated with 60 mL of 1*N* sodium hydroxide solution for 15 min. Work-up as described

above and column chromatography afforded (in reverse order of elution) 66 mg of unidentified material, 94 mg (14%) of **12**, and 253 mg (35%) of **5-Hydroxy-6-(thiomethyl)-2',3'-*O*-isopropylidene-5'-thiouridine** (**16**), which crystallizes readily from aqueous ethanol, mp indistinct (with shrinkage over a broad range, 135-155 °C); UV (pH 1) λ_{max} = 287.5 nm, λ_{min} = 248 nm; UV (pH 14) λ_{max} = 321 nm, λ_{min} = 278 nm; ^{1}H-NMR (DMSO-d_6, 28 °C) δ 11.71 (1H, br s, NH), 9.04 (1 br s, OH), 3.03 (1H, v br s, 7SH), 2.45 (1H, dd, 5'SH); $J_{5',SH}$ = 7.5 and 9.4 Hz; ^{1}H-NMR (DMSO-d_6 + D_2O, 45 °C) δ 5.69 (1H, d, H1'), 5.25 (1H, dd, H2'), 4.80 (1H, dd, H3'), 4.02 (1H, 6-line m, H4'), 3.88 (1H, d, H7a), 3.54 (1H, d, H7b), 2.74 and 2.69 (2H, AB part of ABX, H5' and H5"), 1.47 and 1.29 (two 3H s, MeCMe). $J_{1',2'}$ = *1.2*, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 3.8, $J_{4,5'}$ = 7.5, $J_{4',5''}$ = 6.8, $J_{5'gem}$ = 13.2, J_{7gem} = 14.1 Hz. *Anal.* Calcd. for $C_{13}H_{18}N_2O_6S_2 \cdot 0.75\ H_2O$: C, 41.53; H, 5.23; N, 7.45; S,17.06. Found: C, 41.48; H, 5.22; N, 7.27; S, 17.00.

2',3',5'-Tri-*O*-benzoyl-5-bromo-6-methyluridine (**28**). 5-Bromo-6-methyluracil (1.5 g, 7.32 mmol) and ammonium sulfate (21 mg) were added to hexamethyldisilazane (50 mL) and the mixture was heated at reflux temperature for 2 h. The excess HMDS was then removed and the resulting **25** was dissolved in acetonitrile (50 mL). A solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**27**) (3.7 g, 7.34 mmol) in acetonitrile (50 mL) was added, and the mixture was cooled in an ice bath. Following addition of trimethylsilyl triflate (1.7 g, 7.65 mmol), the light yellow mixture was stirred at 0°C for 45 min. and then quenched by the addition of water (20 mL) and saturated sodium bicarbonate solution (30 mL). The acetonitrile was removed by rotary evaporation and the residue was partitioned between water and dichloromethane (100 mL). The organic phase was washed with water, dried and evaporated to give crude **28**, which was purified by column chromatography on silica gel using hexane-ethyl acetate (7:3). The yield of pure **28**, which crystallized from a 2:1 mixture of ethyl acetate and hexane, was 3.77 g (79 %): mp 197-198 °C; ^{1}H-NMR ($CDCl_3$) δ 9.00 (1H, s, NH), 7.6-7.25 (6H, m, Ph), 8.10-7.80 (9H, m, Ph), 6.10 (2H, m, H2',H3'), 5.81 (1H, narrow m, H1'), 4.59-4.85 (3H, m, H4',H5',H5"), 2.59 (3H, s, Me). *Anal.* Calcd. for $C_{31}H_{25}BrN_2O_9$: C, 57.33; H, 3.88; N, 4.31; Br, 12.30. Found: C, 57.42; H, 4.09; N, 4.24; Br, 12.41.

5-Bromo-6-methyluridine (**29**). *Sodium methoxide in methanol* (0.94 mL, 4.1 mmol, of 25% w/v solution) was added to a solution of **28** (2.6 g, 4 mmol) in methanol (40 mL), and the mixture was stirred at room temperature for 20 h. Water (10-15 mL) was added to dissolve the separated solid and the solution was neutralized with Amberlite CG-50 (H^+) ion exchange resin. The filtrate was evaporated to dryness and the residue was thoroughly washed with ether (4 X 50 mL) to afford 1.30 g (96%) of **29**, mp 179-180°C (from ethanol); UV (water) λ_{max} = 213 (ε 6120) and 277.5 nm (ε 8980), λ_{min} = 244 nm (ε 1600); UV (pH 12) λ_{max} = 277 nm (ε 6030), λ_{min} = 253 nm (ε 2860); ^{1}H-NMR (DMSO-d_6, 28 °C) δ 11.80 (1H, br s, NH), 5.19 (1H, d, 2'OH), 4.95 (1H, d, 3'OH), 4.67 (1H, dd, 5'OH), $J_{2',OH}$ = 5.3, $J_{3',OH}$ = 6.4, $J_{5',OH}$ = 5.3 and 6.1 Hz; ^{1}H-NMR (DMSO-d_6 +D2O, 50 °C) δ 5.62 (1H, d, H1'), 4.52 (1H, dd, H2'), 4.08 (1H, dd, H3'), 3.73 (1H, 6-line m, H4'), 3.62 (1H, dd, H5'), 3.47 (1H, dd, H5"), 2.54 (3H, s, Me), $J_{1',2'}$ = 4.4, $J_{2',3'}$ = 6.3, $J_{3',4'}$ = 5.9, $J_{4,5'}$ = 3.4, $J_{4',5''}$ = 5.9, $J_{5'gem}$ = 11.8 Hz. *Anal.* Calcd. for $C_{10}H_{13}BrN_2O_6$: C, 35.63; H, 3.89; N, 8.31; Br, 23.70. Found: C, 35.82; H, 4.00; N, 8.12; Br, 23.59.

5-Bromo-2',3'-*O*-isopropylidene-6-methyluridine (30). *p*-Toluenesulfonic acid monohydrate (0.37 g) was added to a suspension of **29** (1.3 g, 3.85 mmol) in acetone (36 mL) containing dimethoxypropane (1.6 mL), and the mixture was stirred rapidly at room temperature. The solid essentially dissolved within 10 min, at which time TLC (CH_2Cl_2-MeOH, 9.5:0.5) indicated that the formation of **30** was complete. The reaction mixture was filtered and evaporated to dryness, and the residue was partitioned between water (15 mL) containing sodium bicarbonate (170 mg) and ethyl acetate (3 X 25 mL). Evaporation of the dried (Na_2SO_4) organic phase afforded 1.42 g (98%) of **30**, mp 185-188 °C (from aqueous ethanol); ^{1}H NMR ($CDCl_3$) δ 9.31 (1H, br s, NH), 5.75 (1H, d, H1'), 5.25 (1H, dd, H2'), 5.03 (1H, dd, H3'), 4.24 (1H, 6-line m, H4'), 3.89 (1h, dd, H5'), 3.80 (1H, dd, H5") 2.95 (1H, v br s, 5'OH), 2.63 (3H, s, Me), 1.57 and 1.35 (two 3H s, MeCMe), $J_{1',2'}$ = 2.4, $J_{2',3'}$ = 6.5, $J_{3',4'}$ = 4.1, $J_{4,5'}$ = 2.9, $J_{4',5"}$ = 4.7, $J_{5'gem}$ = 12.1 Hz. *Anal.* Calcd. for $C_{13}H_{17}BrN_2O_6$: C, 41.40; H, 4.54; N, 7.43; Br, 21.18. Found: C, 41.54; H, 4.76; N, 7.14; Br, 21.37.

5-Bromo-2',3'-*O*-isopropylidene-6-methyl-5'-*O*-(*p*-toluenesulphonyl)uridine (31). *p*-Toluenesulfonyl chloride (0.57 g, 3 mmol) was added to a solution of **30** (1 g, 2.65 mmol) in dry pyridine (15 mL) and the mixture was stirred at room temperature for 24 h. Following evaporation of solvents and a conventional chloroform/water work-up, the product was purified by silica gel chromatography using dichloromethane-methanol (98:2) as the eluting solvent. Evaporation of the appropriate fractions afforded **31** (1.2 g, 86%) as a foam, ^{1}H-NMR ($CDCl_3$) δ 9.53 (1H, br s, NH), 7.74 and 7.28 (two 2H m, *p*-C_6H_4-), 5.74 (1H, br s, H1'), 5.16 (1H, dd, H2'), 4.82 (1H, dd, H3'), 4.2-4.4 (3H, m, H4',H5',H5"), 2.59 (3H, s, Me), 1.52 and 1.32 (two 3H s, MeCMe), $J_{1',2'}$ = 1.0, $J_{2',3'}$ = 6.3, $J_{3',4'}$ = 3.7 Hz. *Anal.* Calcd. for $C_{20}H_{23}BrN_2O_8S$: C, 45.21; H, 4.36; N, 5.27; Br,15.04; S, 6.03. Found: C, 44.96; H, 4.46; N, 5.21; Br, 15.27; S, 5.88.

5'-*S*-Acetyl-5-Bromo-2',3'-*O*-isopropylidene-6-methyl-5'-thiouridine(24). ***Method A***: A mixture of tosylate **31** (930 mg, 1.75 mmol) and potassium thioacetate (200 mg, 1.75 mmol) in dry acetone (20 mL) was heated at reflux temperature under a nitrogen atmosphere for 5 h. Evaporation of solvents afforded a residue that contains several products in addition to **24** and unchanged **31**. After a conventional dichloromethane/water work-up, the residue was subjected to silica gel chromatography. Elution with hexane-ethyl acetate-acetic acid (4:1:0.01) afforded 246 mg (36%, corrected for recovered starting material) of **24**, which crystallized from methanol, mp 131-133 °C; ^{1}H NMR ($CDCl_3$) δ 8.99 (1H, br s, NH), 5.75 (1H, br s, H1') 5.25 (1H, dd, H2'), 4.87 (1H, dd, H3'), 4.16 (1H, 6-line m, H4'), 3.23 (2H, pseudo d with 7.2 Hz splitting, H5' and H5"), 2.63 (3H, s, Me) 1.53 and 1.34 (two 3H s, MeCMe), $J_{1',2'}$ = 1.1, $J_{2',3'}$ = 6.3, $J_{3',4'}$ = 3.8 Hz. *Anal.* Calcd. for $C_{15}H_{19}BrN_2O_6S$: C, 41.39; H, 4.40; N, 6.44; Br,18.36; S, 7.37. Found: C, 41.53; H, 4.51; N, 6.24; Br, 18.19; S, 7.16.

Further elution of the column with hexane-ethyl acetate-acetic acid (7.5:2.5:0.02) afforded 118 mg of starting material **31**. Increasing the polarity of the eluting solvent (to 7:3:0.02 and then 3:2:0.02) afforded two additional fractions (152 mg and 171 mg) that contained (NMR), respectively, the 5-thioacetoxy nucleosides **32** (R = SAc and OTs) as

the major components, together with much smaller amounts (about 10%) of the corresponding 6-(thioacetoxymethyl) nucleosides **33** (R = SAc and OTs). Attempts to further purify these fractions by preparative TLC were unsuccessful.

Method B: Diethyl azodicarboxylate (166 mg, 0.95 mmol) was added over a 15 min period to a solution of triphenylphosphine (250 mg, 0.95 mmol) in tetrahydrofuran (5 mL) at 5 °C. The reaction mixture was warmed to room temperature and allowed to stand for an additional 15 min prior to the addition of **30** (300 mg, 0.79 mmol) and potassium thioacetate (110 mg, 0.96 mmol). Stirring was continued for 2 h, at which time TLC (CH_3Cl-MeOH, 15:1) indicated the presence of **24** with only a minor amount of starting material remaining. The residue obtained after a conventional dichloromethane/water work-up was purified by preparative TLC in the same solvent system. The 5'-thioacetate **24**, which was identical to the material described above, was obtained in 58% yield (200 mg).

2',3'-*O*-Isopropylidene-*S*$^{5'}$,6-methano-5'-thiouridine (34). 1*N* Sodium hydroxide solution (5 mL) was added to a solution of **24** (130 mg, 0.3 mmol) in ethanol (5 mL) and the mixture was heated at reflux temperature for 3 h. The cooled reaction mixture was neutralized with acetic acid and then evaporated to dryness. Addition of water (15 mL) to the residue and cooling to 4 °C for 20 h resulted in crystallization of **34** (55 mg, 59%), mp > 260 °C; ^{1}H-NMR (DMSO-d_6) δ 11.37 (1H, br s, NH), 6.18 (1H, d, H1'), 5.54 (1H, d, H5), 4.88 (2H, m overlapped by dd, H4' and H2'), 4.60 (1H, dd, H3'), 3.97 (1H, d, H7a), 3.82 (1H, d, H7b), 3.14 (1H, dd, H5'), 2.81 (1H, dd, H5''), 1.46 and 1.29 (two 3H s, MeCMe), $J_{5,NH}$ = 2.2, $J_{1',2'}$ = 1.7, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 0.9, $J_{4,5'}$ = 3.8, $J_{4',5''}$ = 2.4, $J_{5'gem}$ = 14.7, J_{7gem} = 14.6 Hz. *Anal.* Calcd. for $C_{13}H_{16}N_2O_5S$: C, 49.99; H, 5.16; N, 8.97; S,10.26. Found: C, 50.18; H, 5.34; N, 8.93; S, 10.44.

S$^{5'}$,6-Methano-5'-thiouridine (3). A solution of **34** (15 mg) in 6% methanolic hydrochloric acid (20 mL) was stirred at room temperature for 3 h. The reaction mixture was neutralized by the addition of methanolic ammonia and the residue obtained after removal of solvents was purified by preparative HPLC on a 2.5 X 30 cm Waters Dynamax™ C-18 reversed phase column with 30% methanol (10 mL/min) as the eluting solvent. The yield of pure **3** (retention time 9 min) was 12 mg (92%). In larger scale runs (125 mg of **34**), cyclonucleoside **3** was obtained in 60% yield by crystallization directly from the neutralized reaction mixture. The initially obtained monomethanolate (long silky needles) becomes anhydrous on drying at 110 °C for a few hours, mp > 260 °C; UV (water) λ_{max} = 273.5 (ε 11300) , λ_{min} = 236 nm (ε 1600); UV (pH 12) λ_{max} = 273.5 nm (ε 8800), λ_{min} = 245 nm (ε 4000); CD (water) $[\theta]_{max}$ (nm) 27,700 (271); ^{1}H NMR (DMSO-d_6, 60 °C) δ 11.16 (1H, br s, NH), 5.23 (1H, d, 2'OH), 4.87 (1H, d, 3'OH), $J_{2',OH}$ = 5, $J_{3',OH}$ = 5.5 Hz; ^{1}H NMR (DMSO-d_6 + D_2O, 65 °C) δ 5.95 (1H, d, H1'), 5.52 (1H, s, H5), 4.49 (1H, m, H4'), 4.45 (1H, dd, H2'), 4.34 (1H, pseudo t, H3'), 4.12 (1H, d, H7a), 3.68 (1H, d, H7b), 3.32 (1H, dd, H5'), 2.62 (1H, dd, H5''), $J_{1',2'}$ = 2.3, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 5.0, $J_{4,5'}$ = 3.6, $J_{4',5''}$ = 1.5, $J_{5'gem}$ = 14.7, J_{7gem} = 14.7 Hz. *Anal.* Calcd. for $C_{10}H_{12}N_2O_5S$: C, 44.11; H, 4.44; N, 10.29; S,11.77. Found: C, 44.15; H, 4.61; N, 10.14; S, 11.91.

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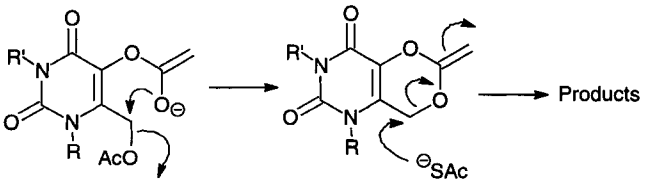
REFERENCES AND NOTES

(1) B. A. Otter, S. A. Patil, M. R. Spada, L. A. Jelicks, Y. Yoshimura, A. Matsuda, and R. S. Klein, Synthesis and Conformational Studies of $O^{5'}$,6-Methanouridine — A New Type of Pyrimidine Cyclonucleoside. *Nucleosides & Nucleotides*, **11**, 615-635 (1992).

(2) S. Megati, S. E. Ealick, F. N. M. Naguib, M. H. el Kouni, R. S. Klein and B. A. Otter. $O^{5'}$,6-Methanocytidine – Synthesis, Conformational Properties and Deamination by Cytidine Deaminase. *Nucleosides & Nucleotides* **13**, 2151-2168 (1994). In addition, **1** does not bind to human uridine phosphorylase (personal communication from M. H. el Kouni and F. N. M. Naguib).

(3) M. H. el Kouni, F. N. M. Naguib, R. P. Panzica, B. A. Otter, S-H Chu, G. Gosselin, C. K. Chu, R. F. Schinazi, Y. F. Shealy, N. Goudgaon, A. A. Ozerov, T. Ueda and M. Iltzsch. Effects of Modifications in the Pentose Moiety and Conformational Changes on the Binding of Nucleoside Ligands to Uridine Phosphorylase from *Toxoplasma gondii. Biochem. Pharmacol.,* **51**, 1687-1700 (1996).

(4) In an alternative mechanism, kindly suggested by a reviewer, the enolate anion derived from the 5-acetoxy group could facilitate the displacement reaction *via* intermediates of the following type:



(5) Benzoylation was accomplished with benzoic anhydride because use of benzoyl chloride leads to a mixture of **9** and the *bis*-benzoylated-5'-chloro nucleoside formed by cleavage of the 2,5'-anhydro linkage. Other examples that illustrate the marked susceptibility of the anhydro linkage to ring opening include the unexpected formation of the 5'-*O*-tosyl nucleoside when 5-hydroxy-6-hydroxymethyl-2',3'-*O*-isopropylidene-2,5'-anhydrouridine (**8**, but R = H) is treated with *p*-toluenesulfonic acid and acetone in order to form the 5,7-*O*- isopropylidene compound. Similarly, **8** (R = OAc) undergoes cleavage on treatment with silver trifluoroacetate in pyridine at room temperature to afford an intermediate ester that hydrolyzes during aqueous work-up to give the 5'-unsubstituted product. This latter reaction represents a new method for converting 2,5'-anhydro nucleosides into the parent alcohols under very mild conditions.

(6) K. Hirota, Y. Yamada, Y. Kitade and S. Senda, Pyrimidine Derivatives and Related Compounds. Part 37. Novel Nucleophilic Substitutions of 5-Bromo-6-Methyluracils or 5-Bromo-6-Bromomethyluracils with Aromatic Amines. *J. Chem. Soc. Perkin 1.* 2943-2947 (1981).

(7) M. S. P. Sarma, R. S. Klein and B. A. Otter, Nucleophilic Substitution Reactions of 5-Bromo-6-Methyluridines. *Nucleosides & Nucleotides* **13**, 369-378 (1994).

(8) H. Vorbrüggen, K. Krolikiewicz and B. Bennua. Nucleoside Synthesis with Trimethylsilyl Triflate and Perchlorate as Catalysts. *Chem. Ber.*, **114**, 1234-1255 (1981).

(9) O. Mitsunobu. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* 1-28 (1981). D. L. Hughes. Mitsunobu Reaction. *Org. Reactions* ***42***, 335-636 (1992).

(10) Molecular modeling studies using the Hyperchem™ implementation of the MM2 force field were conducted along the lines described earlier.[2] The three low energy structures found have the following conformational parameters:

3a (2'-*exo* form), 20.8 Kcal, γ (S5',C5',C4',C3') = 62°, χ (O4'-C1'-N1-C2) = -173°;
3a (3'-*exo* form), 19.2 Kcal, γ = 72°, χ = -156°;
3b (4'-*endo* form), 19.1 Kcal, γ = 165° χ = 179°.

(11) Y. Yoshimura, A. Matsuda and T. Ueda. *Chem. Pharm. Bull.* **37**, 660 (1989) and references therein.

(12) F. E. Hruska. Long-Range Spin-Spin Coupling in Pyrimidine Nucleosides. *Can. J. Chem.*, **49**, 2111-8 (1971).

(13) R. S. Sodum and B. A. Otter. Studies on the Chemistry of 5-Acetoxy-6-(acetoxymethyl)-uridines: Synthesis of a New Type of 5'-Cyclonucleoside. *Nucleosides & Nucleotides* **5**, 385-397 (1986).

(14) Large excesses of acetic anhydride and benzoic anhydride were used in the syntheses of **8** and **9**, respectively, in order to promote rapid *bis-O*-acylation of the intermediate 5-hydroxy-6-(hydroxymethyl)uridines. Partial acylation is known to lead to the formation of 5-oxo-6-methylenepyrimidines that readily dimerize under these conditions. See: I. M. Sasson, R. P. Gagnier and B. A. Otter. The Chemistry of 5-Hydroxy-6-(Hydroxyalkyl)uracils. Synthesis of Spiro[pyrimidine-4,2'-pyrano[3,2-*d*]pyrimidines]. *J. Heterocyclic Chem.*, **20**, 753-757 (1983).

(15) B. A. Otter, I. M. Sasson, and R. P. Gagnier. New Hydantoin Synthesis *via* a Reactive 5-oxo-6-methylenepyrimidine Intermediate. *J. Org. Chem.*, **47**, 508-513 (1982).

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