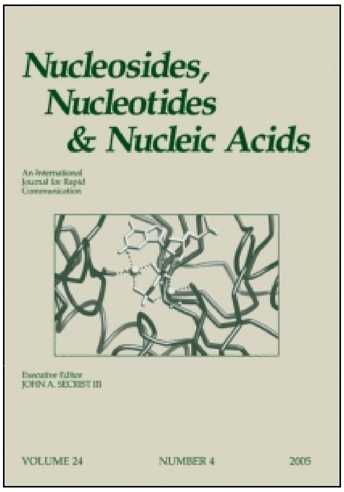

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Synthesis and Conformational Studies of $O^{5'}$, 6-Methanouridine—A New Type of Pyrimidine Cyclonucleoside

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SYNTHESIS AND CONFORMATIONAL STUDIES OF $O^{5'}$,6-METHANOURIDINE — A NEW TYPE OF PYRIMIDINE CYCLONUCLEOSIDE.

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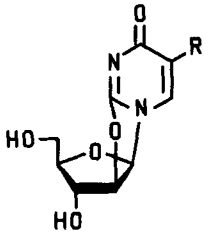
Abstract: The 5-oxo-6-methylene-pyrimidine-2,4-dione intermediate (**6**) that is formed when 5-acetoxy-6-acetoxymethyl-1-β-D-(5-*O*-acetyl-2,3-*O*-isopropylidene)-ribofuranosyluracil (**5**) is treated with sodium hydroxide undergoes cyclization at pH 14 to give 2′,3′-*O*-isopropylidene-5-hydroxy- $O^{5'}$,6-methanouridine (**8**) in good yield. Conversion of **8** into the 5-triflate ester **14** followed by reduction with $[(Ph)_3P]_4Pd/Bu_3SnH$ and deblocking with acetic acid then affords $O^{5'}$,6-methanouridine (**4**). Conformational studies (NOE difference spectra, vicinal ^1H-^{13}C coupling constants, NOESY and CD spectra, molecular modeling) indicate that the C7-methylene group of **4** projects towards the furanose ring oxygen atom, producing a glycosyl rotation angle of about -160°.

Information about the conformational aspects of nucleoside-enzyme interactions can often be obtained by studying the propensity of cyclonucleosides — compounds in which the conformation about the glycosidic bond is constrained by an extra covalent linkage between the sugar and the base — to act as enzyme substrates or inhibitors. For example, the finding that the *anti-* cyclonucleosides **2** (R = H, *R*-CH_2OH or *S*-CH_2OH) and **3** have no affinity for human uridine phosphorylase,[1] coupled with the observation that *syn-*

This paper is dedicated to the memory of Professor Tohru Ueda.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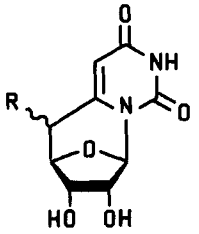
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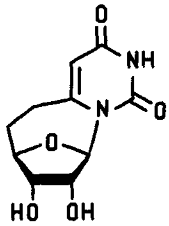
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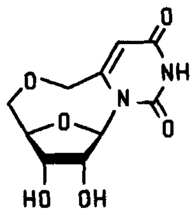
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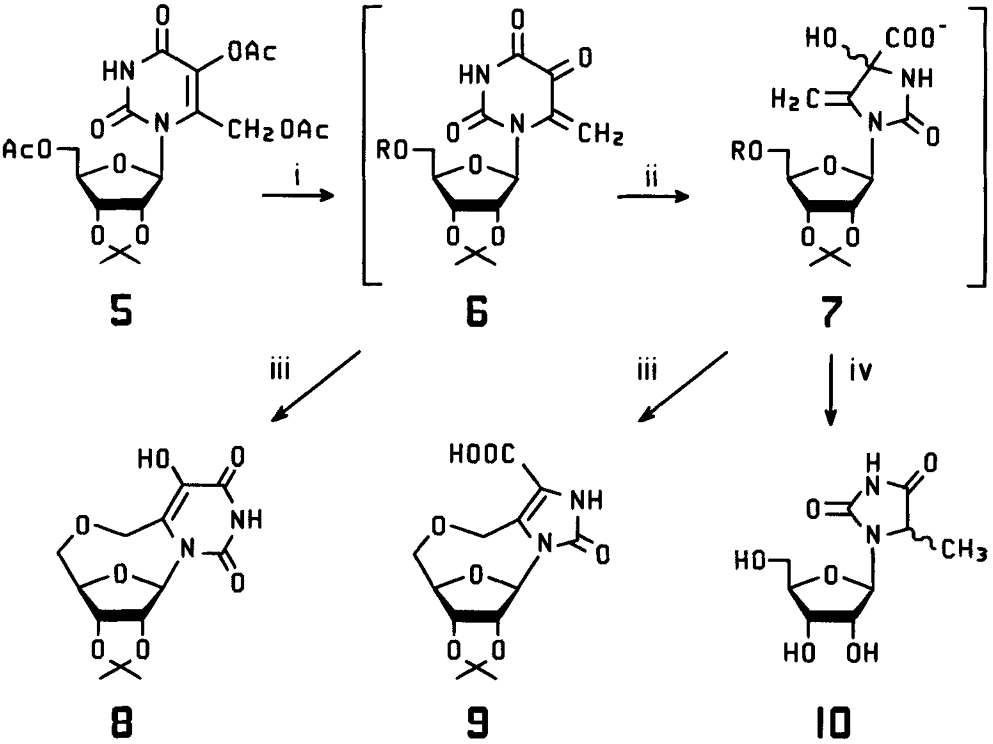
2,2'-anhydro nucleosides of type **1** are potent inhibitors,[1,2] particularly when R = Et, is consistent with the idea that the enzyme requires its substrates to adopt the *syn* conformation. Similarly, the findings[3] that the 2',3'-cyclic phosphates of cyclonucleosides **2** and **3** are substrates for ribonuclease A, and that the resulting 3'-phosphates are good inhibitors, suggests that the *anti* conformation is a normal requirement for that particular enzyme.

A wide variety of nucleosides with restricted conformations is now available, with many of the most interesting having come from Ueda's program on the synthesis of carbon-bridged cyclonucleosides. These compounds cover a wide range of values for the glycosyl rotation angle χ but they are invariably rigid, and the sugar ring is frequently forced to adopt a conformation that is not normally seen in unconstrained nucleosides. As a next step, it would be of interest to devise cyclonucleosides where the base is still held in a particular orientation, but where the sugar ring is sufficiently flexible to adopt whatever puckering the enzyme normally imposes on its substrates. These requirements might be achieved in compounds where the length of the bridge system has been increased, and we report in the present paper the synthesis and initial conformational studies of $O^{5'}$,6-methanouridine (**4**), a pyrimidine cyclonucleoside with a larger-than-usual ring size.[4]

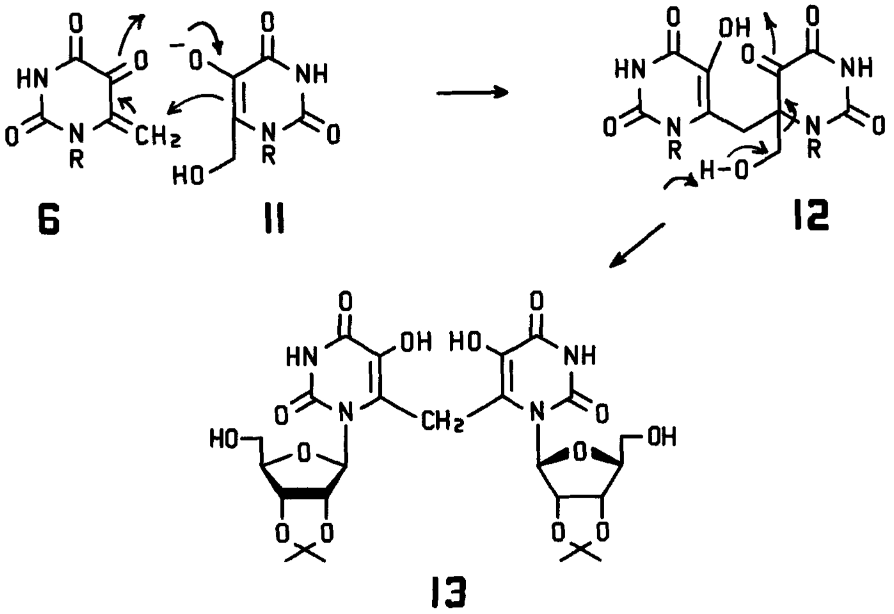
Our synthesis of the title compound exploits a basic property of 5-acetoxy-6-acetoxymethyluracils, namely, the fact that they are converted with remarkable ease into quinone methide-like intermediates when treated with bases in protic solvents (scheme 1). Nucleoside **5**, for example, serves as a precursor of enone **6**. Such enones are highly reactive substances and their fate depends upon the conditions under which they are generated. In some cases, pyrimidine enones of type **6** readily undergo a Diels-Alder type of dimerization;[5] in others, they rapidly undergo a benzilic acid type of rearrangement.[6] An example of the latter process is the formation of the imidazolidine-



i) NaOH. ii) pH << 14. iii) pH > 14. iv) pH 4.

SCHEME 1

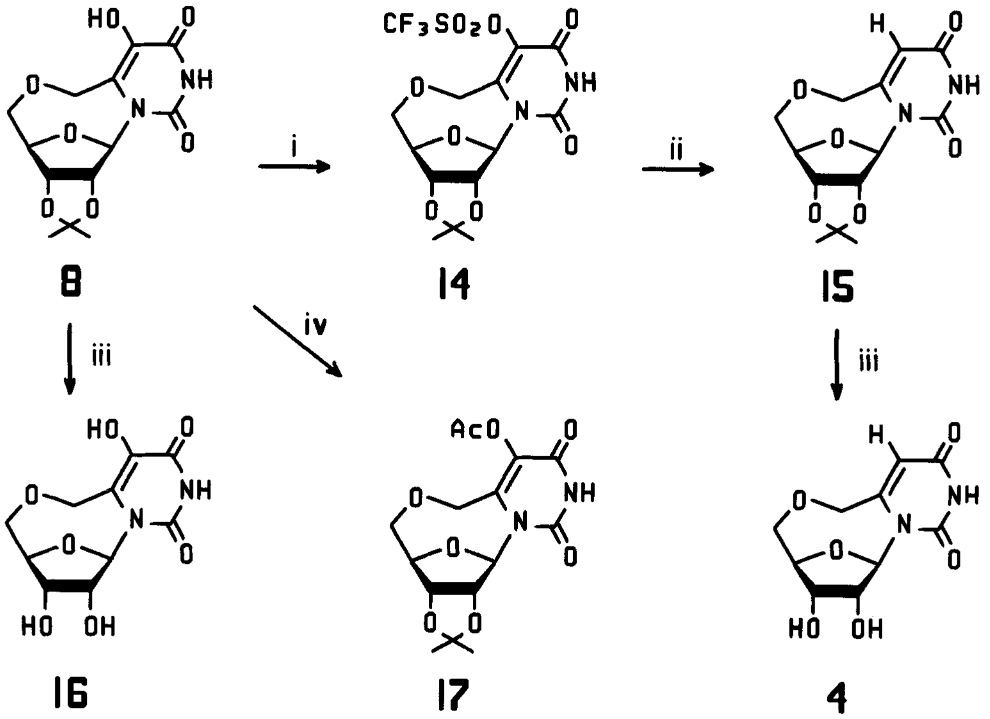
-4-carboxylic acid **7** upon treatment of **5** with three equivalents of sodium hydroxide. Intermediate **7**, in turn, can undergo stabilization in a number of ways, including a decarboxylative rearrangement on subsequent acidification to give[7] (after blocking group removal) the separate 5*R*- and 5*S*-methylhydantoin nucleosides **10**. However, when **7** (R = mixed Ac and H) is subjected to stronger alkaline conditions (pH 14) to ensure complete removal of the 5′-*O*-acetyl group, it readily cyclizes[8] to give the $O^{5'}$,5- methano nucleoside **9**. This result suggested that if the ring contraction **6** ⟶ **7** could be prevented, intermediate **6** (R = H) might undergo a similar cyclization to give the desired $O^{5'}$,6-methano nucleoside **8**. This result has now been realized by the simple expedient of conducting the reaction of **5** with sodium hydroxide at pH 14 or above. Under these conditions, **8** was obtained in better than 50% yield by



SCHEME 2

direct crystallization after neutralization of the reaction mixture. The pyrimidine NH of **6** (R = H) is obviously ionized at pH 14, and the 5′-hydroxyl group probably is as well, and these seem to be the key factors that promote cyclization to **8** rather than ring contraction to **7**.

The generation of **6** (R = H) at pH 14 also leads to the formation of the symmetrical methylenebis-nucleoside **13** (scheme 2). The structure of **13** is evident from its mass spectrum and from its ^{1}H-NMR spectrum, where the methylene protons resonate as a broad singlet at δ4.09 that integrates for 1H relative to the ribosyl protons. This product presumably arises *via* a mechanism in which the alcohol **11** (R = 2′,3′-*O*-isopropylidene-β-D-ribofuranosyl), formed either by complete hydrolysis of **5** or by attack of hydroxide ion on the methylene group of **6**, alkylates enone **6** to give intermediate **12**. A retro-aldol loss of formaldehyde from **12** would then afford **13**. The formation of the intramolecular product **8** can be maximized at the expense of the intermolecular product **13** by conducting the reaction of **5** with base in more dilute solution. In practice, this can be achieved by adding solid **5** in small portions over a period of time to 2*N* sodium hydroxide solution, a procedure that affords **8** in a total yield of 57%. When the same amount of **5** was added *all at once* to the same volume of 2*N* sodium hydroxide, **8** was obtained in only 35% yield.



i) K_2CO_3, $(CF_3SO_2)_2NPh$, dioxane-water. ii) $[(Ph)_3P]_4Pd$, LiCl, Bu_3SnH, THF, reflux. iii) 80% HOAc, reflux. iv) NaOH, Ac_2O.

SCHEME 3

In order to remove the 5-hydroxy group from **8**, we first converted the cyclonucleoside into the intermediate triflate ester **14** (scheme 3). This was achieved in excellent yield by using the conditions reported by Crisp and Flynn[9] for the preparation of the triflate of 5-hydroxyuridine, namely treatment of the potassium salt of **8** with N-phenyltriflimide in aqueous dioxane. Treatment of triflate **14** with tributyltin hydride and lithium chloride in the presence of tetrakis(triphenylphosphine)palladium(0) — conditions that were devised by Stille and coworkers[10] for the reduction of enol triflates — afforded the 5-unsubstituted nucleoside **15** in better than 80% yield. Removal of the isopropylidene blocking group from **15** then gave the title compound **4**. The corresponding 5-hydroxy nucleoside **16** was similarly obtained from **8**, and the latter compound was further characterized as the acetate **17**.

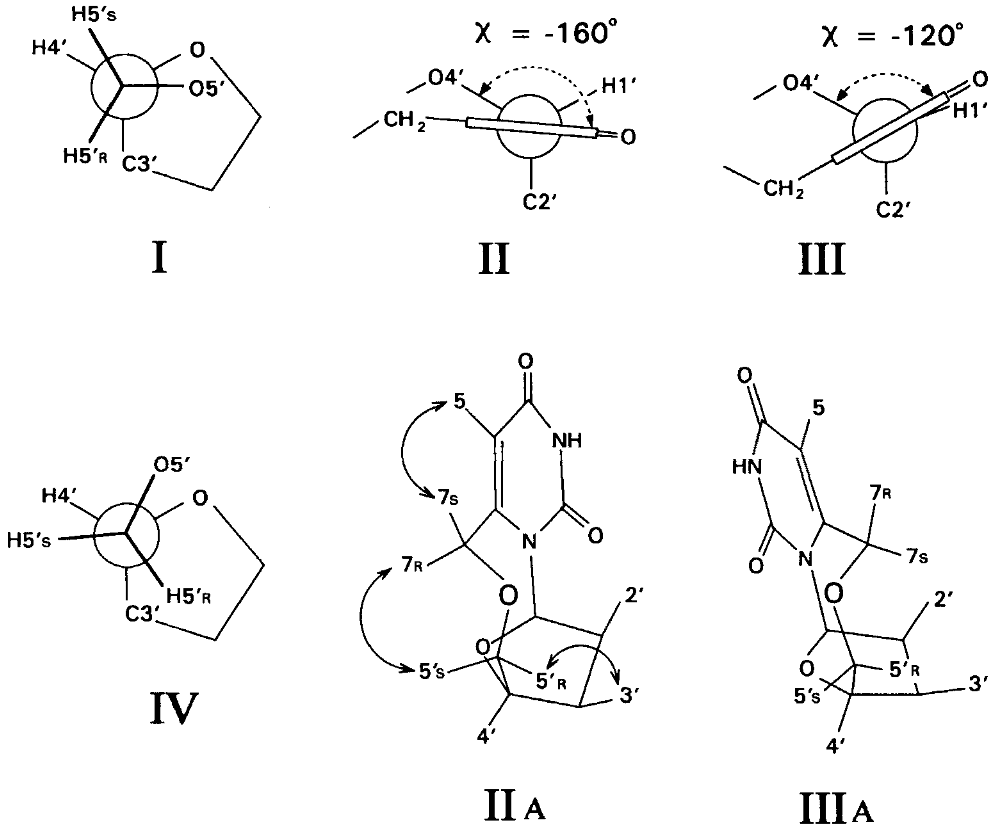


FIGURE 1

That the compounds illustrated in scheme 3 are indeed $O^{5'}$,6- methanouridines is convincingly demonstrated by their ^{1}H- and ^{13}C-NMR characteristics. A common feature in the ^{1}H-spectra of all of these $O^{5'}$,6-methanouridines is that H4' is coupled to only *one* of the prochiral C5' methylene protons, namely the upfield H5'*S*. It therefore appears that the average C4'-C5' rotamer population is as shown in projection **I** (figure 1), where the 90° angle between H4' and H5'*R* would accommodate a zero coupling. Conformations of the *gauche,trans* (*ap*)[11] type such as **IV**, where the coupling between H4' and H5'-*R* would be large, are apparently not populated to any appreciable extent. Confirmation of the NMR assignments for H5'*R* and H5'*S* was obtained by using NOE difference spectroscopy, which has been done for compounds **4**, **8**, and **16**. In each case, irradiation of H3' produces an enhancement at H5'*R* of about 5%, and vice versa.

With the bridging oxygen atom (*O*5′) oriented as shown in **I**, the C7-methylene group can project towards either the furanose ring oxygen or the 2′,3′-edge of the furanose ring. These arrangements, which are shown, respectively, as projections **II** and **III**, and as the corresponding conformational drawings **IIA** and **IIIA**, lead to glycosyl torsion angles (χ) of approximately -160° and -120° as judged from molecular models. The observation of NOEs between H5 and H7*S* (for **4**) and between H7*R* and H5′*S* (for **4**, **8** and **16**) provides strong evidence that these compounds adopt conformation **II/IIA**. Conversely, the failure to detect any NOEs between H7*S* and H2′(or 3′), or between H7*S* and H5′*R*, is equally strong evidence that **III/IIIA** does not contribute significantly to the overall conformation.

The various enhancements seen in the 1D NOE difference spectra of compounds **4**, **8** and **16** are also apparent in 2D phase-sensitive NOESY spectra. An example is shown in figure 2, which illustrates part of the NOESY spectrum of the title compound (**4**), where the diagnostic cross- peaks between H5 and H7*S*, H7*R* and H5′*S*, and H5′*R* and H3′ are clearly visible. In addition to the NOE enhancements discussed above, both the 1D NOE difference spectra and the 2D NOESY spectra reveal small NOEs between H1′ and H4′ for compounds **4**, **8** and **16**. This suggests that the distance between H1′ and H4′ must approach the range seen for normal β-D-nucleosides, where such NOEs are also seen[12]. In contrast, H1′⟷ H4′ NOEs are not observable in rigid 5′-cyclonucleosides such as $O^{5'}$,6-cyclo-5-bromo-2′-deoxy-tubercidin,[12] where the sugar rings are forced into the normally unpopulated $_0E$ conformation, and where H1′ and H4′ are relatively far apart. Clearly, increasing the ring size from that of cyclonucleoside **3** (which has an abnormal sugar conformation[3b] similar to that of the cyclotubercidin just mentioned) to that of cyclonucleoside **4** produces a sugar ring conformation that is closer to those of unconstrained nucleosides. In fact, judging from the vicinal coupling constants observed for **4**, the furanose ring favors the S conformation.[11,13]

Two additional lines of evidence support the conclusion from the NOE studies that $O^{5'}$,6-methanouridines adopt conformation **II** with $\chi \approx -160°$. The first is an evaluation of the vicinal coupling constant $^3J_{C2,H1'}$, the magnitude of which shows[15] an approximate Karplus dependence with the dihedral angle C2,N1,C1′,H1′. Using the Karplus parameters derived by Davies and coworkers,[15] it is seen that $^3J_{C2,H1'}$ should be 1.4 Hz for conformation **II** (with a dihedral angle of about - 40°) and 3.0 Hz for conformation **III** (with a dihedral angle of about 5°). The average $^3J_{C2,H1'}$ found for compounds **8**, **15**,

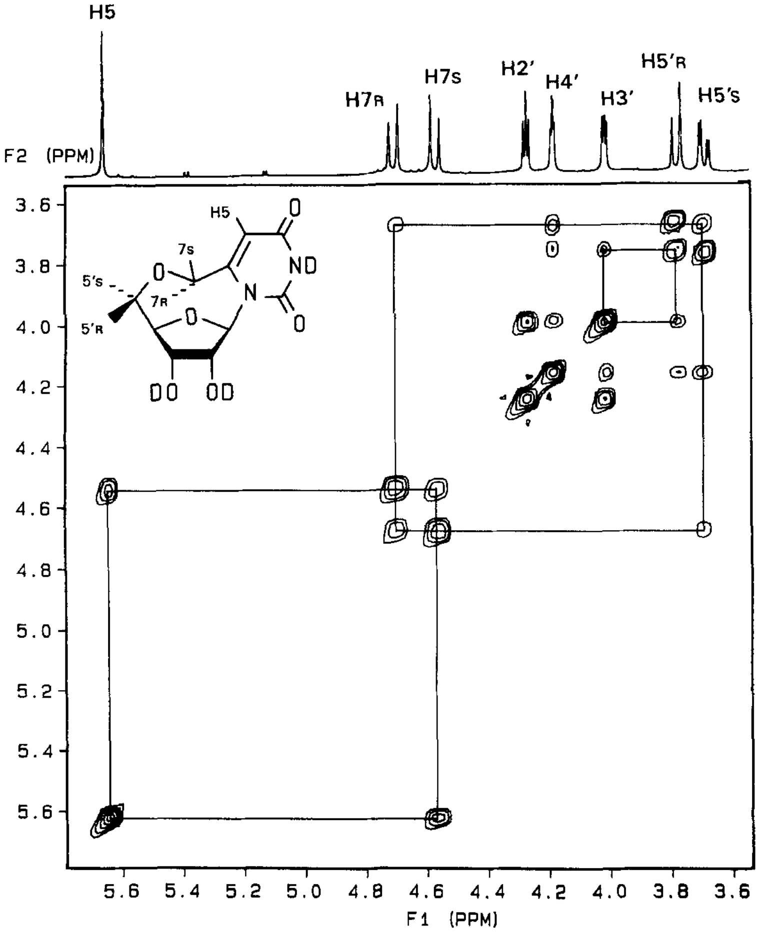


FIGURE 2

Part of the 500 MHz. phase-sensitive NOESY spectrum of $O^{5'}$,6-methanouridine (**4**) in DMSO-d_6 plus D_2O, with a mixing time of 1 sec. The diagonal contours (negative) were plotted at a lower level than the cross-peaks (positive). The small doublets near δ5.1 and δ 5.4 in the 1D spectrum are the residual 2'- and 3'-hydroxyl peaks. Size: 2K X 2K; number of acquisitions: 16; number of increments: 256.

16, and **17** is 1.7 Hz, which is reasonably close to the value expected for conformation **II**.[16]

The second line of evidence that supports conformation **II** is based on the work of Ueda and coworkers[18], who established that the sign and magnitude of the CD spectra of carbon-bridged cyclopyrimidine nucleosides is a function of the glycosyl rotation angle χ. As seen in figure 3, the CD band for *anti*-cyclonucleosides undergoes a sign reversal as χ is varied from -150° to -74°, with the curve approaching zero (at the position of the UV maximum) at a point that corresponds to a value of about -120° for χ, as exemplified by the 6,5'-methano nucleoside.[19] The CD spectrum of *O*$^{5'}$,6-methanouridine (**4**) is therefore expected to be strongly positive if $\chi \approx -160°$ (conformation **II**) or extremely weak if $\chi \approx$ the transitional value of -120° (conformation **III**). In fact, the molar ellipticity [θ] found for **4** exceeds 20,000 at a position corresponding to the main UV absorption band, clearly indicating that χ must be greater than the -150° of the 6,5'-cyclonucleoside, which was previously the limiting value. The [θ] value found for the isopropylidene nucleoside **15** is somewhat smaller than that of **4**, but still substantial at 14,300. It is possible that the presence of the fused dioxolane ring in **15** causes small changes in χ that are reflected in the CD spectrum. In this regard, the CD method appears to be more sensitive than the NMR methods that rely on NOEs or the magnitudes of ^{1}H-^{13}C coupling constants.

Since the various methods discussed above each point to **II** as the preferred conformation for *O*$^{5'}$,6-methanouridines, it was of interest to determine whether molecular modeling would also lead to the same conclusion. Based on preliminary studies,[21] this seems to be the case. Thus conformer **III** apparently corresponds to a local minimum, and it is of considerably higher energy than conformers where the methylene group is located over the furanose ring oxygen, as it is in **II**. Interestingly, low energy conformers of type **II**/**IIA** are seen with a variety of sugar puckerings, including C2'-exo and C3'-exo, which is perhaps an indication that the furanose ring does retain some flexibility. Additional modeling studies using molecular dynamics simulations will be used to address this question further.

Returning now to a discussion of some of the synthetic aspects, it should be noted that the Bu_3SnH-$[(Ph)_3P]_4Pd$ method described above for reducing triflate **14** appears to be superior to our earlier techniques for deoxygenating 5-hydroxyuracils. These earlier methods relied on the Pd/C-catalyzed hydrogenolysis of the corresponding 5-(1-phenyltetrazolyl) ethers,[22] or of the mesyl[23] or tosyl[20] esters. Another potential method[24] for deoxygenation

CD Spectra and Glycosyl Rotation Angles (χ) of some *anti* - Cyclonucleosides.

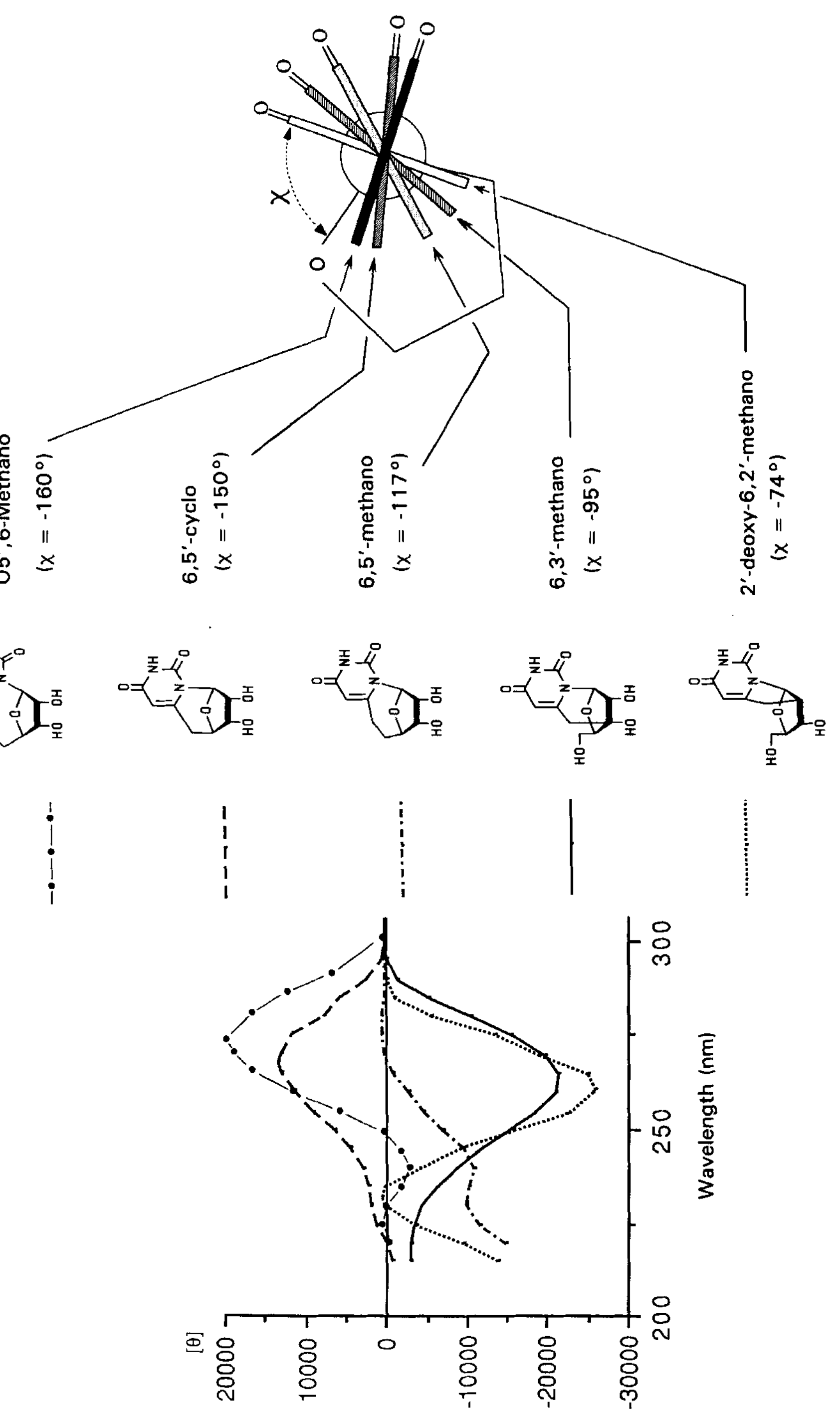
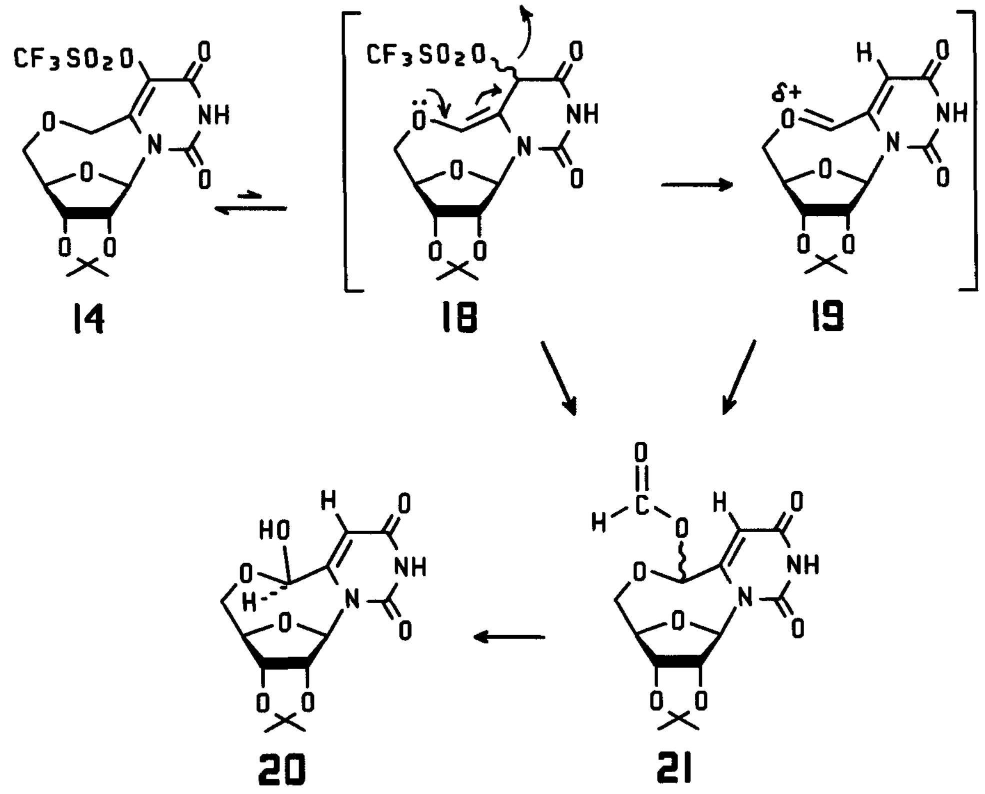


FIGURE 3



SCHEME 4

involves treating enol triflates with tributylammonium formate and bis(triphenylphosphine)palladium(II) acetate in DMF at 60 °C. We have found that this method works well when applied to the model triflate derived from 1,3-dimethyl- 5-hydroxyuracil, affording 1,3-dimethyluracil in excellent yield. However, the reaction takes a surprisingly different course when applied to triflate **14** (scheme 4) since it affords the formate ester **21**, which is partially hydrolyzed during work-up to give a mixture containing the hemiacetal **20** and **21**. Following separation by preparative TLC, **20** was obtained as the crystalline hemihydrate. Further study showed that the palladium reagent plays no role in the reaction, and that the same mixture of products can be obtained by treating **14** with either tributylammonium formate or sodium formate in warm DMF. This result is reminiscent of the findings of Hirota and coworkers[25] with various 1-substituted-6-methyl-5-bromouracils. These compounds undergo an allylic displacement of the 5-bromo group *via* a nucleophilic attack on the exocyclic carbon atom, apparently by involvement of the methylene tautomer. In our case, it seems possible that the analogous tautomer **18** could undergo nucleophilic attack at C7 to give **21** directly, or it could lose its trifluoromethanesulfonyloxy group to generate the oxonium ion **19**, which would also be susceptible to attack at C7. Evidence for the structure of **20** includes the observation of the hydroxy resonance in the ^{1}H-NMR spectrum as an exchangeable doublet at δ 7.29, coupled (6.4Hz) to H7 at δ 5.73. In the ^{13}C-NMR spectrum, the α- shift of 21 ppm observed for C7 of **20** relative to C7 of **15**, together with a β-shift of 2.2 ppm for C6 and γ-shifts of -3.3 ppm and -2.2 ppm for C5′ and C5, respectively, is diagnostic for the presence of a C7 substituent. Finally, the observation of NOEs between 7-OH and H5, between H7 and H5′*S*, and between H5′*R* and H3′ confirms the *S* configuration at C7 and demonstrates that the basic conformation of the $O^{5'}$,6- methano bridge of **20** is unaltered relative to the 7-unsubstituted compounds discussed above. Further studies on the scope of the reactions shown in scheme 4, together with studies of the properties of **20** (a novel internal hemiacetal derived from 6-formyluridine) are planned.

EXPERIMENTAL SECTION

Melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. Ultraviolet spectra were recorded on Gilford Response II and Shimadzu UV-2100S spectrophotometers; CD spectra were measured on a JASCO J-500A recording spectropolarimeter. ^{1}H-NMR spectra were determined at 200 MHz or 500 MHz with Varian XL-200 and VXR-500 spectrometers, respectively. Except where noted, spectra were obtained in DMSO-d_6 at ambient temperature (ca. 22 °C). DMSO-d_6 and DMSO-d_6 + D_2O solutions used to obtain phase-sensitive NOESY and NOE difference spectra were degassed by five freeze-pump-thaw cycles prior to sealing in vacuum. ^{13}C-NMR spectra were measured at 50.31 MHz on a Varian XL-200 spectrometer and, unless stated otherwise, DMSO-d_6 containing 3-5% D_2O was used as solvent. The DMSO resonance, which was used as an internal reference peak in all cases, was set at 39.44 ppm relative to TMS. Coupled spectra were obtained with a data resolution of 0.3Hz per point. Peak assignments for non-quaternary carbons were verified by selective decoupling experiments. Mass spectra were obtained on a Finnegan MAT-90 instrument using Fast Atom Bombardment (FAB$^+$) with glycerol and/or thioglycerol as the matrix. Thin layer chromatography was performed on 250 μm silica gel GH plates (Analtech, Inc.) and the substances were visualized with short wavelength (254 nm) light and/or by spraying with 10% ethanolic sulfuric acid followed by charring. Preparative TLC was performed on 1000 μm 20 X 20 cm Uniplates (Analtech Inc.). Microanalyses were performed by M. H. W. Laboratories, Phoenix, Arizona. In cases where microanalysis indicated a solvated product, the identity and approximate amount of solvent was verified by NMR spectroscopy. All evaporations were carried out under reduced pressure in a rotary evaporator.

5-Hydroxy-2',3'-*O*-isopropylidene-$O^{5'}$,6-methanouridine (8). A finely- ground sample of the triacetyl nucleoside 5 (1.52 g, 3.33 mmoles)[8] was added in small portions, over a 5-6 min period, to 100 mL of *vigorously* stirred 2*N* sodium hydroxide solution. The colorless solution was kept at room temperature for 30 min and then neutralized with 11.5 mL of glacial acetic acid. Crystallization of **8** commenced rapidly and was completed by storing the mixture overnight at 5 °C. The collected solid, which was homogenous on TLC (methanol-dichloromethane, 1:9), weighed 543 mg (52%) after drying. The combined filtrate and washings were concentrated to about 75 mL and extracted with 500 mL of ethyl acetate in a continuous extractor for 5 h. Removal of solvent and recrystallization of the residue from hot water then afforded an additional 50 mg of **8** (total yield 57%), mp indistinct at about 235 °C (dec); UV (water) λ_{max} = 286nm (ϵ 9,510), λ_{min} = 245.5nm (ϵ 1,982); UV (pH 12) λ_{max} = 318nm (ϵ 6,560), 222nm (ϵ 11,300) and 250 sh (ϵ 4,200), λ_{min} 275 nm (ϵ 1,980); MS (FAB) *m/z* [MH$^+$] 313.1 (calcd. for $C_{13}H_{17}N_2O_7$, [MH$^+$] 313.096);[26] ^{1}H-NMR (500MHz) δ11.67 (1H, s, NH), 8.80 (1H, s, 5-OH), 6.40 (1H, d, H1'), 5.28 (1H, d, H7*S*), 4.73 (1H, d, H3'), 4.70 (1H, dd, H2'), 4.56 (1H, d, H4'), 4.32 (1H, d, H7*R*), 3.89 (1H, d, H5'*R*), 3.68 (1H, dd, H5'*S*), 1.46 (3H, s) and 1.27 (3H, s, *Me*C*Me*), $J_{1',2'} = 1.8$, $J_{2',3'} = 6.0$, $J_{3',4'} = J_{4',5'R} \approx 0$, $J_{4',5'S} = 3.1$, $J_{5'gem} = 12.8$, $J_{7gem} = 14.3$Hz; ^{13}C- NMR, δ 159.5 (C4), 149.1 (C2), 130.4 (C5), 129.1 (C6), 111.4 (Me*C*Me), 95.6 (C1'), 87.3 (C4'), 86.8 (C2'), 83.2 (C3'), 72.1 (C5'), 66.0 (C7), 26.8 and 24.9 (*Me*C*Me*), $^3J_{C2,H1'} = 1.7$, $^1J_{C1',H1'} = 172.5$Hz.

Anal. Calcd. for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.15; N, 8.97. Found: C, 50.10; H, 5.08; N, 8.84.

6,6'-Methylenebis[5-hydroxy-2',3'-*O*-isopropylideneuridine] (13).

The preparation of **8** was repeated on the scale described above except that the extraction step with ethyl acetate was omitted. Instead, after removal of the first crop of **8**, the filtrate and washings were lyophilized to remove the bulk of the water. After thawing and filtering the solution through a 4.5μm nylon filter, the volume was adjusted to 30 mL. HPLC in 35% methanol (using the conditions described below) revealed seven uv-absorbing compounds, of which the dimer **13** (22.5 min) was present in the largest amounts. Residual cyclonucleoside **8** (30.3 min) and small amounts of the deacetylated starting material **11** (R = 2′,3′-*O*-isopropylidene-β-D-ribofuranosyl, 12.7 min) were also identified. Four minor products with retention times of 25, 37.5, 45.5 and 65 min, respectively, were not investigated further other than to establish (by uv) that they did not contain the 5-hydroxyuridine chromophore. Six 1 mL aliquots were subjected to preparative HPLC (35% methanol, 10 mL per min., 21.4 mm ID Rainin Dynamax Macro HPLC C18 column) and the peaks corresponding to dimer **13** (22 - 24 min) were collected. After removal of solvents, 32 mg of **13** was obtained as a foam. This would correspond to a yield of 160 mg (15%) if the entire solution was subjected to HPLC. A solution of **13** in moist methanol deposited well-formed cubic crystals on standing, mp 210-214 °C (dec); UV (pH 5) λ_{max} 285nm; UV (pH 10) λ_{max} 324nm; MS (FAB) *m/z* [MH$^+$] 613.3 (calcd. for $C_{25}H_{33}N_4O_{14}$, [MH$^+$] 613.19); ^{1}H-NMR (200MHz, 50 °C) δ11.52 (2H, br s, NH), 9.02 (2H, s, 5-OH), 5.25 (2H, d, H1′), 4.88 (2H, dd, H2′), 4.64 (2H, dd, H3′), 4.54 (2H, t, 5′- OH), 4.09 (2H, bs, CH_2), 3.82 (2H, 4-line m, H4′), 3.53 and 3.46 (4H, 7- line m, H5′ and H5″), 1.35 (6H, s) and 1.20 (6H, s, *Me*C*Me*), $J_{1',2'} \approx 0.8$, $J_{2',3'} = 6.4$, $J_{3',4'} = 4.7$, $J_{4',5'} = 4.0$, $J_{4',5''} = 6.0$, $J_{5',5''} = 10.6$Hz[28]; ^{13}C-NMR, δ 159.7 (C4), 148.0 (C2), 131.7 (C6), 127.9 (C5), 112.9 (Me*C*Me), 91.6 (C1′), 88.3 (C4′), 84.5 (C2′), 81.6 (C3′), 61.7 (C5′), 26.7 and 25.1 (*Me*C*Me*), 21.9 (CH_2), $^3J_{C2,H1'} = 6.7$, $^1J_{C1',H1'} = 162.8$Hz.

Anal. Calcd. for $C_{25}H_{32}N_4O_{14}\cdot0.5MeOH\cdot0.5H_2O$: C, 48.04; H, 5.53; N, 8.79. Found: C, 47.85; H, 5.53, N, 8.99.

5-Acetoxy-2′,3′-*O*-isopropylidene-*O*$^{5'}$,6-methanouridine (17). The cyclonucleoside **8** (312 mg, 1 mmole) was dissolved in 5 mL of 0.2*N* sodium hydroxide solution in order to generate the 5-monoanion. Acetic anhydride (0.5 mL) was added to the rapidly stirred solution, whereupon colorless crystals of **17** appeared within a few seconds. The solid was collected after about five minutes and washed liberally with water. The yield of air-dried **17** was 319 mg (90%). Fine needle-like crystals of **17** were obtained from warm methanol, mp > 260 °C; UV (water) λ_{max} = 276nm (ε 10,900), λ_{min} = 238nm (ε 1,790); ^{1}H-NMR (200MHz) δ 11.92 (1H, s, NH), 6.35 (1H, d, H1′), 4.97 (1H, d, H7*S*), 4.78 (dd) and 4.75 (d, total 2H, H2′ and H3′), 4.51 (1H, d, H4′), 4.45 (1H, d, H7*R*), 3.93 (1H, d, H5′*R*), 3.70 (1H, dd, H5′*S*), 2.25 (3H, s, *Me*CO), 1.47 (3H, s) and 1.29 (3H, s, *Me*C*Me*), $J_{1',2'} = 1.2$, $J_{2',3'} = 6.2$, $J_{3',4'} = J_{4',5'R} \approx 0$, $J_{4',5'S} = 3.2$, $J_{5'gem} = 12.7$, $J_{7gem} = 14.8$Hz; ^{13}C-NMR, δ 169.1 (Me*C*O), 157.9 (C4), 150.1 (C2), 142.2 (C6), 124.8 (C5), 112.1 (Me*C*Me), 96.8 (C1′), 88.2 (C4′),

87.4 (C2′), 83.4 (C3′), 72.5 (C5′), 66.3 (C7), 27.0 and 25.1 (*Me*C*Me*), 20.3 (*Me*CO), $^3J_{C2,H1'}$ = 1.6, $^1J_{C1',H1'}$ = 174.3Hz.
Anal. Calcd. for $C_{15}H_{18}N_2O_8$: C, 50.85; H, 5.12; N, 7.91. Found: C, 50.98; N, 5.15, N, 7.81.

5-Hydroxy-*O*$^{5'}$,6-methanouridine (16). The cyclonucleoside **8** (230 mg, 0.74mmole) was suspended in 17 mL of 80% aqueous acetic acid (v/v) and the mixture was heated under reflux for 35 min., at which time HPLC analysis of neutralized samples indicated that the starting material had been essentially consumed.[29] The reaction mixture was evaporated to dryness and the white residue was dissolved in 4 mL of hot water. Cooling induced crystallization of hydrated **16** (142 mg, 71%, obtained in two crops), mp indistinct at about 250 °C (dec); UV (water) λ_{max} = 290nm (ϵ 9,230), λ_{min} = 249 (ϵ 2,380); UV (pH 12) λ_{max} = 319.5nm (ϵ 6,760), 224nm (ϵ 10,200) and 250sh (ϵ 4,530), λ_{min} 274nm (ϵ 1,710); ^{1}H-NMR (500MHz) δ 11.60 (1H, br s, NH), 8.83 (1H, s, 5-OH), 6.25 (1H, d, H1′), 5.27 (d, H7*S*) overlapping 5.26 (d, total 2H, 2′-OH), 5.00 (1H, d, 3′-OH), 4.34 (1H, d, H7*R*), 4.30 (1H, m, H2′, changes to t with D_2O), 4.14 (1H, br t, H4′), 3.96 (1H, m, H3′, changes to dd with D_2O), 3.75 (1H, d, H5′*R*), 3.65 (1H, dd, H5′*S*), $J_{1',2'}$ = 4.6, $J_{2',3'}$ = 4.8, $J_{3',4'}$ = 2.0, $J_{4',5'R}$ ≈ 0, $J_{4',5'S}$ = 3.2, $J_{2',2'\text{-OH}}$ = 6.5, $J_{3',3'\text{-OH}}$ = 4.5, $J_{5'gem}$ = 12.9, J_{7gem} = 13.9Hz; ^{13}C-NMR, δ 159.8 (C4), 149.4 (C2), 132.0 (C5), 129.1 (C6), 92.3 (C1′), 86.0 (C4′), 76.9 (C2′), 73.0 (C3′), 70.9 (C5′), 65.7 (C7), $^3J_{C2,H1'}$ = 1.8, $^1J_{C1',H1'}$ = 171.0Hz.

Anal. Calcd. for $C_{10}H_{12}N_2O_7 \cdot 1.25H_2O$: C, 40.75; H, 4.96, N, 9.50. Found: C, 40.55; H, 5.08; N, 9.37.

5-Trifluoromethanesulfonyloxy-2′,3′-*O*-isopropylidene - *O*$^{5'}$,6-methanouridine (14). N-Phenyltrifluoromethanesulfonimide (1.08 g, 3.02 mmoles) was added to a mixture of cyclonucleoside **8** (0.86 g, 2.75 mmoles) and potassium carbonate (0.42 g, 3.04 mmoles) in dioxane-water (4:1, 40 mL). The solution was stirred at ambient temperature for 1.5 h, at which time TLC (ethyl acetate-hexane-glacial acetic acid, 200:200:1) indicated the complete disappearance of **8** (R_f = 0.17) and the appearance of a new UV absorbing spot with R_f = 0.54. The reaction mixture was evaporated to dryness and the solid residue was partitioned between water and ethyl acetate. The organic layer was washed thoroughly with water (5-6 times) until a drop of the aqueous layer when spotted on a TLC plate did not indicate the presence of any UV absorbing compound. The now clear and colorless organic layer was dried (Na_2SO_4) and the solvent was removed. Crystallization of the residue from absolute ethanol afforded 0.99 g (81 %) of **14** as colorless needles, mp

207-210 °C (dec); UV (water) λ_{max} 209.5 and 276nm, λ_{min} 237.5; UV (pH 12)[30] λ_{max} 272.5nm, λ_{min} 241nm; ^{1}H-NMR (200MHz, 50 °C) δ12.22 (1H, br s, NH), 6.33 (1H, d, H1'), 4.97 (1H, d, H7*S*), 4.85 (1H, dd, H2'), 4.76 (1H, d, H3'), 4.69 (d, H7*R*) overlapping 4.65 (d, total 2H, H4'), 3.96 (1H, d, H5'*R*), 3.79 (1H, dd, H5'*S*), 1.47 (3H, s) and 1.28 (3H, s, *Me*C*Me*), $J_{1',2'}$ = 1.3, $J_{2',3'}$ = 6.1, $J_{3',4'} = J_{4',5'R} \approx 0$, $J_{4',5'S}$ = 3.3, $J_{5'gem}$ = 13.0, J_{7gem} = 15.0Hz.

Anal. Calcd. for $C_{14}H_{15}F_3N_2O_9S$: C, 37.84; H, 3.40; N,6.30; S,7.22. Found C, 37.66; H, 3.58; N, 6.26; S, 7.17.

2',3'-*O*-Isopropylidene-$O^{5'}$,6-methanouridine(15). A suspension of the triflate **14** (0.6 g, 1.35 mmoles) in dry THF (10 mL) was added to a slurry of LiCl (0.34 g, 8.02 mmoles) and $[(Ph)_3P]_4Pd$ (0.062 g, 0.05 mmole) in dry THF (10 mL). This was followed by the addition of tributyltin hydride (0.79 g, 2.71 mmoles), whereupon copious effervescence ensued. The mixture was heated at reflux under nitrogen, and periodic additions of tributyltin hydride (0.79 g, 2.71 mmoles) were made at the end of 2, 4 and 6 h. Also, an additional portion of $[(Ph)_3P]_4Pd$ (0.031 g, 0.03 mmole) was added after 6 h. After a total reflux period of 8.5 h, TLC (hexanes-ethyl acetate-glacial acetic acid, 200:200:1) indicated the presence of some unreacted triflate (**14**, R_f = 0.5) and the appearance of a new polar product with R_f = 0.11. The reaction mixture was evaporated to dryness and the residue was triturated several times with hexanes. It was then purified by preparative TLC, developing twice with ethyl acetate-hexanes-glacial acetic acid (100:100:1.2). The unreacted triflate **14** (0.171 g) and the product **15** (0.25 g, 86 % based on amount of triflate reacted) were extracted using CH_2Cl_2-MeOH, 85:15. An analytical sample of **15** was obtained by crystallization from absolute ethanol, mp > 250 °C; UV (water) λ_{max} = 269nm (ϵ 11,430), λ_{min} = 233 (ϵ 1,800); CD (water) $[\theta]_{max}$ (nm) 14,300 (272), 0 (247); ^{1}H-NMR (200MHz, pyridine-d_5, 60 °C) δ 13.12 (br s, NH), 6.93 (1H, d, H1'), 5.68 (1H, d, H5), 4.95 (1H, dd, H2'), 4.83 (1H, d, H3'), 4.75 and 4.71 (2H, H7*R* d overlapping H4' d), 4.59 (1H, d, H7*S*), 3.91 (1H, d, H5'*R*), 3.68 (1H, dd, H5'*S*), 1.60 and 1.36 (two 3H s, *Me*C*Me*), $J_{1',2'}$ = 1.7, $J_{2',3'}$ = 6.0, $J_{3',4'}$ < 1Hz, $J_{4',5'R} \approx 0$, $J_{4',5'S}$ = 3.2, $J_{5'gem}$ = 13.0, J_{7gem} = 13.9, $J_{5,7R}$ = 1.1 Hz; ^{13}C-NMR, δ 162.4 (C4), 151.3 (C2), 150.7 (C6), 111.7 (MeCMe), 102.7 (C5), 95.5 (C1'), 88.0 (C4'), 87.2 (C2'), 83.1 (C3'), 73.5 (C7), 72.4 (C5'), 26.7 and 24.9 (*Me*C*Me*), $^3J_{C2,H1'}$ = 1.6, $^1J_{C1',H1'}$ = 173.8Hz.

Anal. Calcd. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.81; H, 5.57; N, 9.24.

$O^{5'}$,6-Methanouridine (4). A solution of **15** (0.09 g, 0.3 mmole) in 80 % v/v AcOH (10 mL) was heated at 100-105 °C for 50 min.[29] TLC (CH_2Cl_2-MeOH, 9:1) indicated the presence of some starting material (R_f = 0.72) and the appearance of a new polar product with R_f = 0.22. The solution was evaporated to dryness under high vacuum, and ethanol was added to and evaporated from the residue in order to remove traces of acetic acid. The resulting colorless solid was crystallized twice from absolute ethanol to give **4** (0.037 g, 46 %), mp 222-225 °C; UV (water) λ_{max} = 270nm (ϵ 10,400), λ_{min} = 234nm (ϵ 1,600); CD (water) $[\theta]_{max}$ (nm) 20,500 (273), 0 (248); MS (FAB) *m/z* [MH^+] 257.1 (calcd. for $C_{10}H_{13}N_2O_6$, [MH^+] 257.07); ^{1}H-NMR (500MHz) δ11.40 (1H, br s, NH), 6.18 (1H, d, H1′), 5.64 (1H, s, H5), 5.35 (1H, d, 2′-OH), 5.07 (1H, d, 3′-OH), 4.70 (1H, dd, H7*R*), 4.55 (1H, d, H7*S*), 4.26 (1H, m, H2′, changes to t with D_2O), 4.17 (1H, t, H4′), 4.01 (1H, m, H3′, changes to dd with D_2O), 3.79 (1H, d, H5′*R*) and 3.68 (1H, dd, H5′*S*), $J_{1',2'}$ = 4.2, $J_{2',3'}$ = 4.8, $J_{3',4'}$ = 2.7, $J_{2',2'\text{-OH}}$ = 6.2, $J_{3',3'\text{-OH}}$ = 4.7, $J_{4',5'R} \approx 0$, $J_{4',5'S}$ = 3.2, *J*5,7*R* ≈ 0.8, $J_{5'gem}$ = 12.9, J_{7gem} = 13.9Hz; ^{13}C-NMR, δ162.4 (C-4), 151.2, 151.3 (C-6, C-2), 104.3 (C-5), 92.2 (C-1′), 85.9 (C-4′), 77.1 (C-2′), 73.5 (C-7), 72.3 (C-3′), 70.9 (C-5′), $^3J_{C2,H1'}$ not visible (overlap), $^1J_{C1',H1'}$ = 172.3Hz.

Anal. Calcd. for $C_{10}H_{12}N_2O_6 \cdot 0.2\ CH_3CH_2OH$: C, 47.06; H, 5.01; N, 10.55. Found: C, 46.71; H, 5.00; N, 10.70.

7(*S*)-Hydroxy-2′,3′-*O*-Isopropylidene-$O^{5'}$,6-methanouridine (20) and 2′,3′-*O*-isopropylidene-7-formyloxy-$O^{5'}$,6-methanouridine(21). A solution of **14** (0.4 g, 0.9 mmole) in dry DMF (18 mL) containing formic acid (0.083 g, 1.80 mmoles) and tributylamine (0.62 g, 3.36 mmoles) was heated under a nitrogen atmosphere at 60 °C for 1.25 hours. TLC (ethyl acetate- hexanes-glacial acetic acid, 100:100:1) indicated the complete disappearance of the triflate **14** and the appearance of two products with R_f = 0.21 and R_f = 0.04. The dark yellow solution was evaporated to dryness under high vacuum and the residue was purified by preparative TLC, developing twice with the above solvent system. The slower moving band, which contains compound **20**, was extracted with CH_2Cl_2-MeOH, 9:1. The residue obtained after removal of the solvent was subjected to three cycles of trituration with diethyl ether followed by decantation, and finally dried to give 0.11 g (38 %) of **20**. A sample crystallized from hot water showed mp 208-210 °C; UV (water) λ_{max} 205 and 264nm, λ_{min} 232nm; UV (pH 12) λ_{max} 265, λ_{min} 245nm; ^{1}H-NMR (200MHz) δ11.42 (1H, br d, NH), 7.29 (1H, d, 7-OH), 6.27 (1H, d, H1′), 5.81 (1H, dd, H5), 5.73 (1H, dd, H7), 4.73 (1H, d, H3′), 4.66 (1H, dd, H2′), 4.59 (1H, d, H4′), 3.97 (1H, d, H5′*R*), 3.86 (1H, dd, H5′*S*), 1.44 (3H, s) and 1.26 (3H, s, *MeCMe*), $J_{1',2'}$ = 1.5, $J_{2',3'}$ = 6.1, $J_{3',4'}$ = $J_{4',5'R}$ ≈ 0, $J_{4',5'S}$ = 3.4, $J_{5'gem}$ = 12.8, $J_{7,7\text{-OH}}$ = 6.4, $J_{5,NH}$ = 2.3, $J_{5,7}$ = 1.1Hz; ^{13}C-NMR (anhyd. DMSO-d_6) δ 162.3 (C4), 152.9 (C6), 151.3 (C2), 111.3 (Me*C*Me), 99.3 (C5), 96.7 (C1'), 94.4 (C7), 87.9 (C4'), 87.5 (C2'), 83.2 (C3'), 70.1 (C5'), 24.7 and 26.5 (*MeCMe*).

Anal. Calcd. for $C_{13}H_{16}N_2O_7 \cdot 0.5H_2O$: C, 48.60; H, 5.33; N, 8.72. Found: C, 48.97; H, 5.30; N, 8.77.

The zone containing the less polar product was extracted with CH_2Cl_2- MeOH, 9:1. The residue obtained after removal of solvents was triturated repeatedly with hexanes to give 0.11 g of the unstable formate ester **21**; ^{1}H-NMR (200 MHz) δ11.60 (1H, br s, NH), 8.41 (1H, s, OC*H*O, 6.79 (1H, s, H7), 6.29 (1H, s, H1'), 5.83 (1H, s, H5), 4.77 (2H, s, H2' and H3'), 4.68 (1H, d, H4'), 4.19 (1H, dd, H5'*S*)[31], 4.08 (1H, d, H5'*R*), 1.45 (3H, s) and 1.26 (3H, s, *MeCMe*), $J_{5'gem}$ = 12.8, $J_{4',5'S}$ = 3.1Hz. Resonances from a small amount of the corresponding alcohol **20** were evident in the foregoing NMR spectrum, and further purification was not attempted.

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13) A complete description of the furanose ring conformation must await a more exhaustive analysis of the vicinal coupling constants. It is noted that the sum (6.9 Hz) of $J_{1',2'}$ (4.2 Hz) and $J_{3',4'}$ (2.7 Hz) for the title compound **4** is about 3 Hz less than that generally seen for unconstrained *anti* pyrimidine-β-D-ribonucleosides, and that $J_{2',3'}$ (4.8 Hz) is slightly smaller than usual[14]. The furanose conformation of the isopropylidene compounds evidently differs from that of the deblocked compounds **4** and **16** because $J_{3',4'}$ decreases to < 1Hz, $J_{1',2'}$ decreases to an average of 1.5 Hz, and $J_{2',3'}$ increases to an average of 6.1 Hz.

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16) The coupling constant ${}^3J_{C2,H1'}$ could not be obtained for the parent compound **4** because the C2 and C6 resonances overlap in the coupled spectrum. Davies and coworkers[17] also proposed that the magnitude of the geminal coupling constant ${}^1J_{C1',H1'}$ varies in Karplus fashion as a function of the dihedral angle C2,N1,C1',H1'. The average value of 173 Hz found for compounds **4**, **8**, **15**, **16** and **17** corresponds to a dihedral angle of about 25°, a somewhat smaller value than that indicated by ${}^3J_{C2,H1'}$, but still closer to that expected for **II** than for **III**. However, the geminal method may not be entirely reliable because some of our compounds (the *syn*-nucleosides **5** and **13**) show couplings (165 Hz and 163 Hz, respectively) that are considerably smaller than the values predicted by the Karplus-type equation proposed[17]. In fact, all of these *J*/dihedral angle relationships should be used with caution, particularly in the absence of other evidence. Thus, using a set of Karplus parameters for ${}^3J_{C2,H1'}$ that preceded those of reference 15, we previously proposed[8] a conformation akin to **III** for the imidazole cyclonucleoside **9**; our subsequent NOE studies show that the basic conformation of **9** is essentially the same as that of the $O^{5'}$,6- methanouridines, namely **II**.

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25) K. Hirota, Y. Yamada, Y. Kitade, and S. Senda, *J. Chem. Soc. Perkin I*, 2943 (1981).

26) In view of the recent report that certain 1',2'-seco nucleoside tosylates unexpectedly undergo *inter-* rather than *intra*molecular cyclization[27], a reviewer has suggested that **8** might really be a symmetrical cyclic dimer formed when the 5'-hydroxyl groups of two molecules of **6** (R = H) attack each other's methylene groups. However, this possibility has been ruled out by the observation of the MH^+ peak expected for the monomeric product **8**. In addition, inspection of Dreiding models strongly suggests that such dimers would show different patterns of NOEs and $J_{4',5'(5'')}$ coupling constants than those actually observed for **8** and the compounds derived from it.

27) A. F. Cichy, R. Saibaba, H. I. El Subbagh, R. P Panzica, and E. Abushanab, *J. Org. Chem.*, 56, 4653 (1991).

28) Values given for coupling constants for **13** were checked by spectral simulations.

29) HPLC also shows that the product decomposes on longer heating in 80% acetic acid to give more polar products. These have not been investigated.

30) Triflate **14** is hydrolyzed smoothly at this pH (isosbestic points at 251 and 290nm) to give the 5-hydroxy nucleoside **8**. Under comparable conditions (ca. 2 X 10^{-4} *M* nucleoside, 7 *mM* sodium hydroxide), triflate **14** is hydrolyzed about seven times more slowly than the acetate **17**.

31) In this case, the shielding properties of the neighboring formyloxy group evidently cause H5'*S* to resonate downfield of H5'*R*.

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