MeOH/CH_3CN/H_2O). Piptocarphin F (**1f**) was separated as a colorless oil: 0.003% overall yield; ED_{50} 3.2 μg/mL; UV (MeOH) λ_{max} 284 nm (log ε 4.39); IR (KBr) ν_{max} 3500, 1755, 1520, 1630 cm^{-1}; high-resolution EI mass spectrum, *m/e* 408.180 (calcd for $C_{21}H_{28}O_8$, 408.178); CI mass spectrum, *m/e* 409 (MH^+), 391 (100%, $MH^+ - H_2O$), 373 ($MH^+ - 2\ H_2O$), 363 ($MH^+ - C_2H_6O$), 323 ($MH^+ - C_4H_6O_2$), 305 ($MH^+ - C_4H_6O_2 - H_2O$), 287 ($MH^+ - C_4H_6O_2 - 2\ H_2O$), 277 ($MH^+ - C_4H_6O_2 - C_2H_8O$), 259 ($MH^+ - C_4H_6O_2 - C_2H_6O - H_2O$); ^1H NMR ($CDCl_3$) δ 6.58 (d, br, 9.5, H-8), 6.27 (m, H-3a'), 5.82 (s, H-5), 5.66 (m, H-3b'), 4.58 (d, 12.2, H-13a), 4.30 (d, 12.2, H-13b), 4.07 (s, br, OH), 3.77 (s, br, OH), 3.57 (q, 7.0, 2 H, OCH_2CH_3), 2.0–2.75 (m, c, 6 H, 2 H-2, 2 H-3, 2 H-9), 1.93 (m, 3 H, H-4'), 1.55 (s, 3 H, H-15), 1.21 (s, 3 H, H-14), 1.21 (t, 7.0, 3 H, OCH_2CH_3); ^1H NMR (Me_2SO-d_6)[27] δ 6.19 (s, br, 2 H, H-5, H-3a'), 5.76 (m, br, 2 H, H-3', H-8), 5.30 (s, br, 2 H, OH, exchangeable with D_2O), 4.28 (d, 11.7, H-13a), 4.2–4.3 (m, impurity), 4.07 (d, 11.7, H-13b), 3.42 (q, 7.1, OCH_2CH_3), 2.5–2.0 (m, br, H-2,3,9), 1.91 (s, br, 3 H, H-4'), 1.52 (s, 3 H, H-15), 1.24 (br s, m, impurity), 1.15 (s, H-14), 1.08 (t, 7.1, OCH_2CH_3).

The ^1H NMR spectra (Tables I and III) were measured on Varian FT-80, and Nicolet NTC-360 spectrometers. Both the proton-coupled and -decoupled ^{13}C NMR spectra (Table II) were obtained on Varian FT-80. The samples were dissolved in $CDCl_3$ with $CHCl_3$ used as the internal reference unless otherwise noted. All chemical shifts are expressed in parts per million (δ) relative to Me_4Si and are described with the following abbreviations: q, quartet; t, triplet; d, doublet; s, singlet; m, multiplet; br, broad; c, complex. Low-resolution chemical-ionization mass spectra were measured on a Du Pont 21-492B spectrometer using isobutane as the ionizing source. Exact mass measurements were obtained from a CEC 21-110B mass spectrometer. Beckman IR-33 and IR-4230 spectrometers were used to record infrared spectra, and a Perkin-Elmer Coleman 124 was used for ultraviolet spectra.

Thin-layer chromatography (TLC) was performed on Brinkmann EM-F254 0.25-mm precoated silica gel plates which were eluted with acetonitrile/chloroform (1:2). Visualization was accomplished by UV fluorescence (λ = 254 nm) and by charring with 10% H_2SO_4. Column chromatography employed SilicAR CC-7 silica gel, Florisil (Fisher, 60–100 mesh), and Sephadex LH-20 (Pharmacia) as specified. Low-pressure column chromatography (LC) was performed by using reversed-phase (C-18) silica gel prepared from Whatman LF-1 silica gel 80A according to the literature procedure. The low-pressure LC column eluent was monitored continuously by a LKB Uvicord ultraviolet absorbtiometer (control unit Type 8301A, detector unit Type 8300, recorder Type 6520-3).

(27) TLC analysis of the sample after the spectrum was recorded showed a significant amount of decomposition.

Acknowledgment. The authors thank Dr. José Saenz-Renauld, Costa Rica, and the Economic Botany Laboratory, USDA, Beltsville, MD, for the collection and identification of *P. chontalensis* and Dr. Garnet E. Peck, Department of Industrial and Physical Pharmacy, Purdue University, for processing the plant material. Technical assistance was provided by Mrs. L. Sellers and Dr. Ian Jardine (CI mass spectra) and by Mr. A. Coddington (EI mass spectra). High-resolution (360 MHz) NMR spectra were recorded at the Purdue University Biological Magnetic Resonance Laboratory supported by NIH Grant RR01077 from the Division of Research Resources. In vitro testing was performed by Dr. Linda Jacobsen in the Cell Culture Laboratory, Purdue University Cancer Center. In vivo testing was performed by RALTECH, Madison, WI. This work was funded by Contract No. N01-CM-67091 with the Division of Cancer Treatment (J.M.C.), National Cancer Institute, NIH, Bethesda, MD.

Registry No. **1a**, 76248-63-0; **1b**, 76215-49-1; **1c**, 76215-50-4; **1d**, 76215-51-5; **1e**, 76215-52-6; **1f**, 76215-53-7.

Supplementary Material Available: Photographs of the Dreiding models of **1a** and **4** (2 pages). Ordering information is given on any current masthead page.

Synthesis and Reactions of Spirooxiranes in the 6,5'-Cyclopyrimidine Nucleoside Series: Preparation of 5'-Deoxy-5'-(hydroxymethyl)-6,5'-(*S*)- and -6,5'(*R*)-cyclouridines[1,2]

Isaac M. Sasson and Brian A. Otter*

Laboratory of Organic Chemistry, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received October 17, 1980

Treatment of 2',3'-*O*-isopropylidene-5'-oxo-6,5'-cyclouridine (**6**) with either dimethylsulfonium methylide or dimethylsulfoxonium methylide affords the 5'*R* oxirane **7** stereoselectively in good yield. Under more vigorous conditions (60 °C) both ketone **6** and oxirane **7** react with excess dimethylsulfoxonium methylide to give the spirooxetane **9**. Reduction of **7** with lithium triethylborohydride affords the tertiary alcohol **12** exclusively, whereas hydrogenolysis in the presence of platinum on carbon proceeds with inversion to give the 5'*R* primary alcohol **16**. Hydrogenation of **7** with Raney nickel as catalyst affords two pairs of diastereomers—the alcohols **15** and **16** and the deoxygenated 5'-methyl nucleosides **13** and **14**. The 5'-hydroxymethyl nucleosides **15** and **16**, as well as the title compounds **3** and **4**, undergo base-catalyzed epimerization at C-5' via a carbanion mechanism to give equilibrium mixtures in which the 5'*S* isomers (**3** and **15**) predominate. Ultraviolet irradiation of oxirane **7** affords the aldehyde **18** as the major product. Compound **18** exists predominantly as the (*Z*)-enol form in solution, as shown by nuclear Overhauser studies, but it can be reduced with sodium cyanoborohydride to give selectively the 5'*S*-hydroxymethyl nucleoside **15**. Small amounts of the 5'*S* oxirane **11** are also formed on irradiation of **7**.

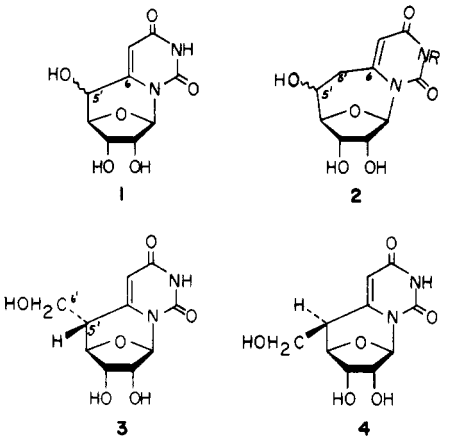
Recent investigations in this laboratory have led to the synthesis of a variety of conformationally restricted pyrimidine nucleosides—for example, the 6,5'-cyclouridines[3] **1** (Scheme I) and the ring-expanded 6,6'-cyclohexo-

(1) This investigation was supported by funds from the National Cancer Institute (Grants CA-24821 and 08748).

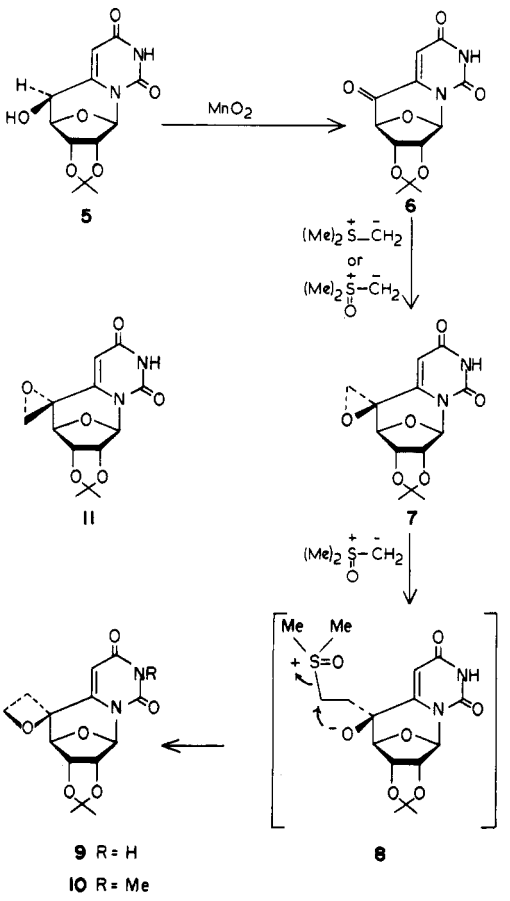
(2) This paper is the fourth of a series entitled "Conformationally Restricted Analogs of Pyrimidine Nucleosides". For part 3, see ref 4.

0022-3263/81/1946-1114$01.25/0

Scheme I



Scheme II



furanosyluracils 2 (R = Me, H).[4,5] These compounds, which resemble various anti-gauche/trans and anti-trans/gauche conformers of uridine, were prepared in connection with our studies of the relationship between substrate-inhibitor conformation and the specificities of the enzymes of nucleic acid biosynthesis. As an extension of this work, we required 5′-deoxy-5′-(hydroxymethyl)-6,5′-cyclopyrimidine nucleosides of types 3 and 4 for comparison with types 1 and 2 in enzyme-catalyzed reactions. Nucleosides 3 and 4 are also held rigidly within the anti conformational range, but the primary 6′-hydroxyl groups, while restricted to one side of the molecule by the chirality at C-5′, can adopt a variety of conformations because of free rotation about the C-5′,C-6′ bond. This situation contrasts with that of 1 and 2 where the 5′-hydroxyl groups are secondary and have fixed orientations.

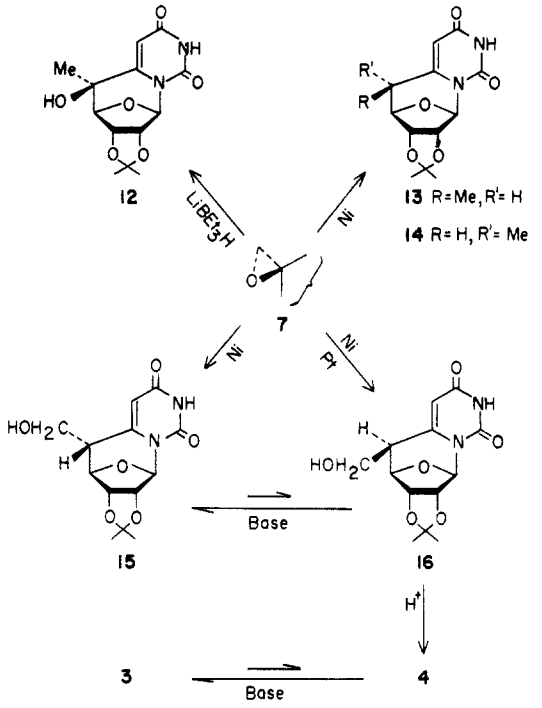
In this paper we describe the synthesis of 5′-(hydroxymethyl)-6,5′-cyclopyrimidine nucleosides via routes that involve hydrogenolytic or photochemical ring opening of oxirane 7 (Scheme II). Spirooxiranes of type 7 can be prepared in fairly good yield by treating 5′-oxo-6,5′-cyclopyrimidine nucleosides with diazomethane.[4,5] However, for uracil nucleosides such as 7 itself, the diazomethane method has the disadvantage that two extra steps—N-3 benzoylation and debenzoylation—are required to circumvent N-methylation.[5] We have therefore investigated the more direct route to 7 involving the reaction of 6 with sulfur ylides.[6] Ketone 6, which is readily available by oxidation of the alcohol[3a] 5 with manganese dioxide, affords oxirane 7 in better than 80% yield when treated with a twofold excess of dimethylsulfonium methylide in cold Me_2SO–THF. Somewhat lower yields (67%) of the same oxirane (7) were obtained by using the less reactive dimethylsulfoxonium methylide at room temperature. The 5′*R* stereochemistry depicted for 7 was assigned on the basis that nucleophilic attack on ketone 6 is known[3b] to occur selectively from the less hindered, exo side.[7] The isomeric 5′*S* oxirane 11, which became available from the photochemical studies described below, was not detected by TLC or high-pressure LC analysis of the reaction mixtures of 6 with either of the sulfur ylides.

When the reaction of ketone 6 with dimethylsulfoxonium methylide was conducted under more rigorous conditions (60 °C, fourfold excess of ylide), the product was not the oxirane 7 but rather a 10:1 mixture of the spirooxetanes 9 and 10. The structure of these compounds was evident from their NMR spectra, each of which shows two coupled methylene signals with chemical shifts (9, H-6′a,b at δ 2.86; H-7′a,b at δ 4.70) appropriate for an oxetane ring.[8] Clearly, oxirane 7 is formed initially under these conditions, but it reacts with excess ylide to generate intermediate 8. Ring closure of 8, with loss of dimethyl sulfoxide, would then afford 9. In fact, preformed 7 *does* react with a twofold excess of dimethylsulfoxonium methylide at 60 °C to afford the same 9/10 mixture that was obtained by starting from 6. Warm dimethylsulfoxonium methylide is known to N-methylate nitrogen heterocycles, including uracils,[9] and this could occur anywhere in the sequence 6 → 9 to account for the formation of 10. We are not aware of other reports of the formation of oxetanes from the reaction of ketones or oxiranes with dimethylsulfoxonium methylide;[10] however, after this work was completed, Welch and Rao[11] reported a closely related one-step oxetane synthesis that involves the reaction of cyclic ketones with the sodium salt of *S*,*S*-dimethyl-*N*-(*p*-toluenesulfonyl)sulfoximine.

Oxirane 7, featuring an allylic C5′–O bond, can be opened under appropriate conditions to give either a tertiary alcohol (C6′ attack) or a primary alcohol (C5′ attack).

(3) (a) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, 41, 3133 (1976); (b) *ibid.*, 43, 481 (1978).
(4) B. A. Otter and E. A. Falco, *Tetrahedron Lett.*, 4383 (1978).
(5) B. A. Otter and E. A. Falco, unpublished results.
(6) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 87, 1353 (1965).
(7) 5′-Exo substituents are on the same side of the molecule as the 1′,4′-oxygen bridge—that is, to the rear of C-5′ when the structures are oriented as shown in the schemes.
(8) Varian NMR Spectra Catalog, Varian Associates, Palo Alto, CA, 1963, spectrum 33.
(9) T. Kunieda and B. Witkop, *J. Am. Chem. Soc.*, 91, 7751 (1969).
(10) Certain highly substituted aziridines react with sulfur ylides to give azetidines. However, this reaction may involve prior equilibration of the aziridines with the corresponding azomethine ylides. See M. Vaultier, R. Danion-Bougot, D. Danion, J. Hamelin, and R. Carrie, *Tetrahedron Lett.*, 1923 (1973); *J. Org. Chem.*, 40, 2990 (1975).
(11) S. C. Welch and A. S. C. Rao, *J. Am. Chem. Soc.*, 101, 6135 (1979).

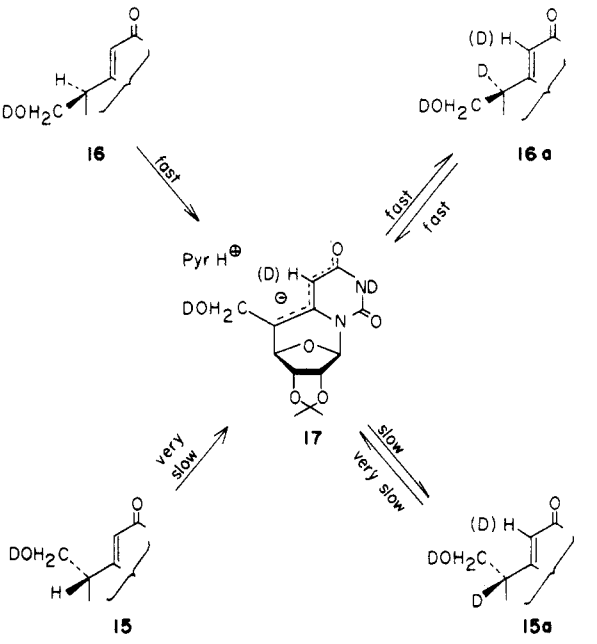
Scheme III



Thus, treatment with lithium triethylborohydride[12] affords the tertiary alcohol **12** exclusively,[13] while reduction with hydrogen in the presence of 5% platinum–carbon catalyst yields the required primary alcohol (Scheme III). Moreover, the hydrogenolysis proceeds with inversion—a phenomenon frequently noted for chiral oxiranes[14]—and the product is almost exclusively the 5′*R*-hydroxymethyl nucleoside **16**. The 5′*R* configuration of **16**, and the direction of ring opening, is established unambiguously from the NMR spectrum. In addition to the presence of the expected resonances—for example, the primary hydroxyl group (exchangeable triplet, δ 5.18), the spectrum shows a $J_{4',5'}$ value of 6.4 Hz. This value is diagnostic because molecular models indicate a 4′,5′ dihedral angle of $\sim$ 30°—and hence sizeable coupling—for the 5′*R* isomer **16**, but a $\sim$90° angle—and hence zero coupling—for the 5′*S* isomer **15**. Acid-catalyzed removal of the isopropylidene-blocking group of **16** then affords the free nucleoside **4**.

Unlike the smooth reduction of **7** with H_2–Pt/C, reduction with hydrogen and Raney nickel affords two epimeric pairs of products[15]—the 5′-hydroxymethyl nucleosides **15** and **16** and the deoxygenated 5′-methyl nucleosides **13** and **14**. These products were obtained in the approximate ratio of 1:1.5:3.75:1, respectively, and the assignments are again based on the values of $J_{4',5'}$. Hydrogenolysis with and without inversion, and the formation

Scheme IV



of deoxygenated products, has been observed previously for Raney nickel reduction of oxiranes.[14] In our case, however, it seemed possible that the formation of the epimer pairs might result in part from subsequent 5′-epimerization reactions as well as from the reduction itself. This follows from our previous findings[3a] that 5′-*O*-substituted-6,5′-cyclopyrimidine nucleosides readily epimerize at C-5′ in base and from the fact that Raney nickel frequently contains traces of alkali left over from its preparation. As suspected, stirring pure 5′*R* nucleoside **16** in a suspension of Raney nickel in ethanol results in the gradual appearance of the 5′*S* isomer **15**, as evidenced by high-pressure LC and NMR analyses. In fact, **15** proved to be the more stable isomer when equilibrium was established under more alkaline conditions.[16] The following NMR studies show that the isomerization proceeds via a carbanion mechanism (Scheme IV).

The NMR spectrum of **16** in pyridine-d_5 containing 5% D_2O initially shows tightly coupled multiplets for H-6′ and H-5′ (δ 4.23 and 3.78) and doublets for H-4′ (δ 5.08) and H-5 (δ 6.15, allylic coupling to H-5′). On standing at the probe temperature (22 °C), H-5′ is gradually exchanged for deuterium, as shown by the collapse of the H-6′ signal to an AB system and collapse of the H-4′ and H-5 doublets to singlets. No spectral shifts occur, indicating that the exchange proceeds with retention of configuration. In addition, H-5 exchanges, but at a slower rate than H-5′. At 2.5 h, when H-5′ had exchanged completely, H-5 had exchanged to the extent of $\sim$50%. Exchange of H-5 is completed when the solution is heated at 55 °C but under these conditions **16a** equilibrates with its 5′*S* isomer **15a**, with a final *S*:*R* ratio of 6.5:1 being reached at 72 h. When the pure 5′*S* isomer **15** was treated with pyridine-d_5 and D_2O, *no* exchange of H-5′ could be detected at 22 °C. Heating this solution at 55 °C results in the gradual appearance of **16a**, and the same 6.5:1 *S*:*R* ratio is reached within 72 h. In this case the 5′*S* component of the mixture is composed of the deuterated **15a** together with unchanged **15**. These results indicate that the isomerization

(12) H. C. Brown, S. C. Kim, and S. Krishnamurthy, *J. Org. Chem.*, **45**, 1 (1980).

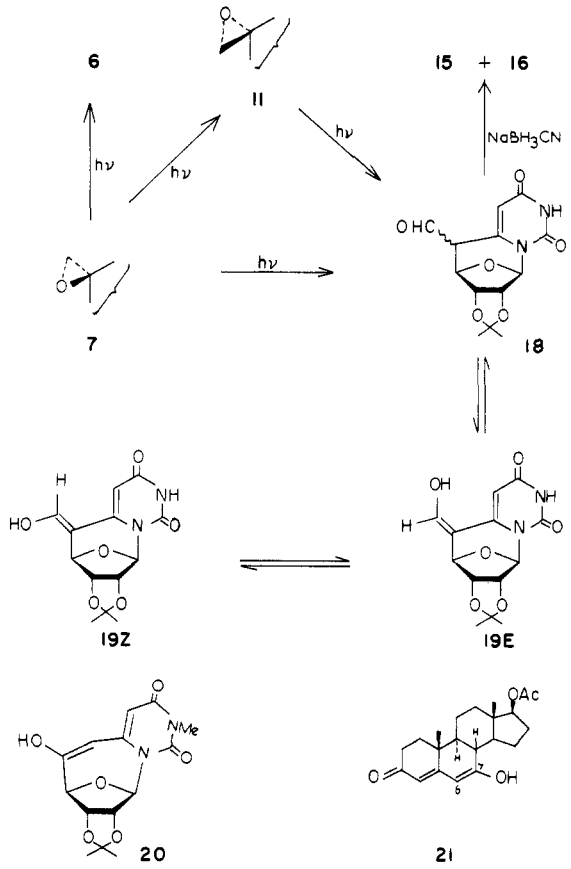
(13) We have also found that sodium hydride opens the oxirane ring to give a tertiary alcohol. This was noted when a large excess of sodium hydride was used inadvertently in the reaction of ketone **6** with a twofold excess of dimethylsulfonium methylide. The ylide also attacks the pyrimidine 5,6 double bond under these conditions, so the product obtained is the 5,6-methylene (presumably exo) derivative of **12**. 5,6-Methylenepyrimidine nucleosides have been prepared by using dimethylsulfoxonium methylide in refluxing THF. See T. Kunieda and B. Witkop, *J. Am. Chem. Soc.*, **93**, 3478 (1971).

(14) See P. N. Rynlander, "Catalytic Hydrogenation in Organic Syntheses", Academic Press, New York, 1979.

(15) Hydrogenolysis of a similar spirooxirane in the 8,5′-cyclopurine nucleoside series with Raney nickel also leads to diastereomeric pairs of 5′-hydroxymethyl and 5′-methyl products. See A. Matsuda, K. Niizuma, and T. Ueda, *Chem. Pharm. Bull.*, **28**, 876 (1980).

(16) In the case of 5′-*O*-substituted-6,5′-cyclopyrimidine nucleosides, the relative stability of the 5′-epimers is opposite to that found for the 5′-deoxy nucleosides **15** and **16**—for example, the 5′-acetate of **5** (endo) is more stable than its exo isomer.[3a]

Scheme V



proceeds via the resonance-stabilized carbanion **17**, which is formed at a much greater rate from the 5′*R* isomers **16** and **16a** than from the 5′*S* isomers **15** and **15a**, presumably because of steric effects. Further, deuteration of anion **17** occurs more readily from the exo side than from the endo side, as shown by the formation of the kinetically controlled product **16a** from **17** at 22 °C.

Similar results were obtained when the interconversions of **15** and **16** were carried out in 0.06 N NaOD in D_2O. In this case, however, a final *S*:*R* (**15**:**16**) ratio exceeding 10:1 was reached at ~2.5 h at probe temperature.[17] The favorable *S*:*R* ratio obtained in aqueous sodium hydroxide facilitates the synthesis of the unblocked 5′-hydroxymethyl nucleoside **3**. Thus, removal of the isopropylidene group of **16** with hot 80% acetic acid, followed by treatment with dilute sodium hydroxide affords predominantly **3**, which can be isolated without recourse to chromatography. Alternatively, isomerization of **4** in aqueous triethylamine leads to a 12:1 ratio in favor of **3**.

During our investigations of the chemistry of oxirane **7**, it became apparent that this compound is extraordinarily sensitive to UV light. Even brief irradiation of **7** as a spot on a TLC plate was sufficient to cause a considerable amount of photoreaction, as shown by the separation of new spots on subsequent redevelopment of the plate. Irradiation of ~2×10^{-4} M solutions of **7** in ethanol with 2537-Å light results in a shift of the original 273-nm absorption to 255 and 320 nm, a process that is complete within 5 min. On addition of very dilute sodium hydroxide solution, the product(s) spectrum shows an intense peak at 358 nm. This spectral pattern is reminiscent of the enolized ketone[4] **20** (Scheme V), suggesting that **7** was being converted into the aldehyde **18**, which, in the enol form **19**, would contain a chromophore closely similar to that of **20**. A precedent for this sort of photorearrangement is found in the formation of the enolic androstene derivative **21** on irradiation of the corresponding 6,7α epoxide.[18] Irradiation of **7** on a preparative scale, followed by concentration of the solution, afforded the major photoproduct in crystalline form. Reduction of this material with sodium cyanoborohydride in aqueous acetic acid–methanol affords a 13:1 mixture of the 5′-hydroxymethyl nucleosides **15** and **16**, respectively, in essentially quantitative yield, thereby confirming that the photoproduct was indeed the aldehyde **18**. Since **15** and **16** do not equilibrate under these acidic conditions, the preponderance of **15** indicates that the exo aldehyde is more stable than the endo isomer.[19] It is not clear from the infrared spectrum whether **18** crystallizes in the aldehyde or in the enol form, but the compound exists entirely in Me_2SO-d_6 solution as a 1:1.33 mixture of the two enols **19E** and **19Z**. This follows from the appearance in the NMR spectrum of two well-resolved vinylic signals (H-6′) and the absence of any resonances assignable to H-5′ or aldehydic protons. The relative shielding of the two H-6′ signals (larger δ 7.75, smaller δ 7.31) would argue for a preponderance of the *Z* isomer, and this is confirmed by a nuclear Overhauser experiment. Thus, irradiation of the larger of the two H-5 signals results in a 25% enhancement in the integrated area of the larger of the two H-6′ signals. Addition of D_2O to the **19E**–**19Z** mixture in Me_2SO-d_6 results in the very rapid exchange of H-5 in both isomers, a result which is consistent with extensive delocalization in the enolate formed from **19**.

A number of other products are formed in addition to **18** (**19E**/**Z**, 36% yield) during photolysis of oxirane **7**. Most of these are polar, unidentified decomposition products, but small amounts of three less polar materials were isolated by preparative TLC. These were identified as unchanged starting 5′*R* oxirane **7**, the 5′-oxo nucleoside **6** and the 5′*S* oxirane **11**. The structure of **11** was assigned on the basis of the similarity of its NMR spectrum to that of **7**, in particular the appearance of a two-proton signal (AB system δ 3.45, 3.35) with the small geminal coupling constant (4.6 Hz) characteristic of oxiranes. Moreover, irradiation of **11** in ethanol results in the appearance of a new UV spectrum indistinguishable from that obtained by irradiation of **7**. Oxirane **11** is presumably formed by rotation and recombination of a planar diradical generated during photolysis of **7**.[20]

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra was measured on Cary Model 15 and Unicam SP-800 spectrophotometers. Thin-layer chromatography

(17) Although both H-5′ and H-5 of **16** exchange in pyridine–5% D_2O, only H-5′ exchanges in 0.06 N NaOD under the conditions used. This result probably reflects the extent of ionization of N-3. The N-3 proton of **16** will certainly be dissociated in 0.06 N NaOD and exchange of H-5 in the resulting dianion is presumably inhibited because of reduced delocalization of the 5′-carbanion system relative to monoanion **17**. The extent of N-3 ionization in pyridine–D_2O is not so clear. If N-3 is in fact not ionized, then the observed deuterium exchanges could proceed via monanion **17**. If, however, dianion formation occurs extensively in pyridine–D_2O, small differences in solvation or type of ion pairing relative to the dianion formed in NaOD may account for the observed results.

(18) J. A. Saboz, T. Iizuka, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **51**, 1362 (1968).

(19) Preliminary attempts to prepare aldehyde **18** by other procedures were not successful. Oxirane **7** was recovered unchanged after treatment with BF_3 etherate or other Lewis acids. Treatment of the alcohol **16** with Me_2SO–DCC appears to lead to elimination rather than oxidation. This and other aspects of the chemistry of **16** will be described in a forthcoming paper.

(20) For an example of oxirane photoisomerization, see C. K. Johnson, B. Dominy, and W. Reusch, *J. Am. Chem. Soc.*, **85**, 3894 (1963).

Table I. Proton Chemical Shifts (δ) at 100 MHz[a]

compd no.	solvent	NH	H5	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′	Ip methyls	other
7	D	11.48	5.39 br	6.02	4.86 d	4.94 d	4.34		3.40 d, 3.25 d	1.40, 1.28	
11	D	11.54	5.54 br	6.01	4.86 d	4.95 d	4.16		3.35 d, 3.45 d	1.40, 1.27	
9	C	8.34	6.30 d	6.14	4.56 d	4.78 d	4.78		2.96 t (2 H)	1.52, 1.32	H-7′, ~4.70 m (2 H)
9	D	11.44	6.15 d	5.89	[b]		4.93		2.86 m (2 H)	1.41, 1.25	H-7′, ~4.70 m (2 H)
10	D		6.30	5.95	4.62 d	4.77 d	4.97		2.91 m (2 H)	1.42, 1.25	H-7′, ~4.68 m (2 H); MCH_3, 3.13
12	D	11.36	5.74 b	5.90	4.70 d	5.00 d	4.14		1.54 (3 H)	1.39, 1.26	5′-OH, 6.28
13	A	n.o.	5.55 d	6.01	4.77 d	4.95 d	4.46 d	3.30 m	1.34 d (3 H)	1.43, 1.30	
14[c]	A	ex	5.56 d	6.02	4.79		4.28	2.90 m	1.47 d (3 H)	1.43, 1.30	
15	D	11.34	5.55 nm	5.89	4.74		4.55	2.74 t	3.59 d (2 H)	1.40, 1.25	6′-OH, 5.31
16	D	11.36	5.66 dd	5.88	4.66 d	4.91 d	4.57 d	3.35 m	3.75 m (2 H)	1.39, 1.25	6′-OH, 5.18
15	B	ex	6.02 d	6.51	4.82 d	4.91 d	5.19	3.12 t	4.13 d (2 H)	1.56, 1.38	
16	B	ex	6.15 d	6.45	4.82 d	5.42 d	5.08 d	3.78 m	4.23 m (2 H)	1.60, 1.39	
3	D	11.22	5.50 br	5.76	4.07		4.40	2.69 t	3.53 d (2 H)		2′,3′,6′-OH, ~5.3 m
4	D	11.27	5.60 br	5.77	4.02 dd	4.31 dd	4.40 d	3.27 m	3.72 m (2 H)		2′-OH, 5.33 d; 3′-OH, ~5.13 d; 6′-OH, 5.10 t
19Z 19E	D[d]	11.11	5.90 d 6.28 d	5.93 5.91	~4.53 d ~4.58 d	4.74 d	5.13 4.89		7.75 7.31 (1 H)	1.39, 1.25	6′-OH, 11.54

[a] Spectra were obtained on a JEOL PFT-100 spectrometer. Chemical shift values are first order and were obtained at 1250 Hz width with 8K data points, giving a digital resolution of 0.3 Hz. Me_4Si was used as an internal standard. Solvents are abbreviated as follows: acetone-d_6 (A); pyridine-d_5 + 5% D_2O (B); $CDCl_3$ (C); Me_2SO-d_6 (D). Peaks are singlets unless designated d (doublet), t (triplet or overlapping double doublets), m (complex multiplet). Other abbreviations: n (narrow), ex (exchanged), n.o. (not observed), br (broad). The assignments of H-2′ and H-3′ can be interchanged because the zero coupling constants $J_{1',2'}$ and $J_{3',4'}$ preclude unambiguous assignment. [b] In the range δ 4.60–4.77; obscured by H-7′ methylene protons. [c] D_2O added to remove H_2O–H-5′ overlap. [d] Solution was degassed by the freeze–pump–thaw method (five cycles) and sealed under vacuum. Irradiation of the H-5 signal (0.6 H) at δ 5.90 caused a 25% increase in the integrated area of the H-6′ at δ 7.75. Off-resonance controls gave no enhancement. On addition of D_2O and 1 N DCl, H-2′ and H-3′ were resolved for each isomer, appearing at δ 4.76 and 4.55 (*Z*) and 4.74 and 4.59 (*E*).

(TLC) was performed on 250-μm silica gel GF_{254} plates (2.8 × 8 cm, Analtech, Inc.); preparative separations were effected on 500-μm (20 × 20 cm) plates. Separated materials were detected with ultraviolet light and/or by spraying with sulfuric acid in ethanol (10% v/v) followed by charring. High-pressure liquid chromatography (LC) analyses were perfomed on a Waters Associates Model 6000A equipped with two Partisil PXS 10/25D (Whatman) columns connected in series (except where noted); ethyl acetate and ethyl acetate–*n*-hexane mixtures were used as solvents. All evaporations were carried out in vacuo. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, and by Galbraith Laboratories, Inc., Knoxville, TN.

Proton chemical shifts and first-order coupling constants are given in Tables I and II.

2′,3′-*O*-Isopropylidene-5′-oxo-6,5′-cyclouridine[21] (6). Activated manganese dioxide (5.5 g, Sterling-Winthrop) was added to a solution of 2′,3′-*O*-isopropylidene-6,5′(*S*)-cyclouridine[3a] (5, 1.1 g) in methanol (165 mL), and the mixture was stirred vigorously at room temperature. After 22 h, TLC (EtOAc) indicated that the reaction was complete. The solution was filtered, the residue was washed liberally with methanol, and the filtrate was passed through a short column (3 × 6 cm) of methanol-washed Dowex 50 (H^+). Removal of solvent afforded a colorless solid (1.01 g, 93%) which was sufficiently pure for the next step. A sample recrystallized from ethyl acetate showed physical properties (melting point, TLC, UV, NMR) identical with those of 6 prepared by alternative procedures.[3b]

The following preparations involving the use of sulfur ylides[6] were carried out under argon in flasks equipped with serum caps. Solutions were added to the reaction mixtures via a syringe.

1-(5′,6′-Anhydro-2′,3′-*O*-isopropylidene)-6,5′-cyclo-β-D-*allo*-furanosyluracil (5′*R* Spirooxirane 7). Method A. Dry Me_2SO (45 mL) was added to 8.0 mmol of NaH (324 mg of 59.3% oil dispersion that had been washed with hexane), and the solution was heated at 70 °C for 1 h. The solution was cooled to room temperature, diluted with dry THF (75 mL, to prevent freezing), and cooled to −10 °C. Trimethylsulfonium iodide (1.640 g, 8.05 mmol) was added rapidly, with stirring, to generate dimethylsulfonium methylide. A solution of ketone 6 (1.008 g, 3.6 mmol) in dry THF (5 mL) was added immediately. The cooling bath was removed after 5 min and stirring was continued for an additional 0.5 h, at which time TLC (EtOAc–*n*-hexane, 4:1 v/v) showed the absence of starting material. The reaction mixture was poured into cold water (500 mL) containing acetic acid (1 mL). The solution was extracted with ethyl acetate, and the organic layer was washed (brine), dried (Na_2SO_4), and concentrated to dryness. Crystallization of the residue from ethyl acetate afforded pure 7 (830 mg, 80%). High-pressure LC analysis showed that the mother liquor contained predominantly 7: mp 234–236 °C dec; UV (EtOH) λ_{max} 273, λ_{min} 250.5 nm.

(21) 6,5′-Cyclopyrimidine nucleosides are more properly described as derivatives of 6,9-epoxypyrimido[1,6-*a*]azepine, but for ease of comparison with ordinary nucleosides we prefer the trivial names and conventional nucleoside numbering used in this paper.

Table II. First-Order Coupling Constants (Hz)[a]

compd. no.	solvent	$J_{2',3'}$	$J_{4',5'}$	$J_{5,5'}$	$J_{5',NH}$	$J_{5',6'}$	other
7	D	5.8			n.r.		$J_{6'a,6'b}$ = 5.8
11	D	5.8			n.r.		$J_{6'a,6'b}$ = 4.6
9	C	5.8			1.5		H-6' splitting = 7.8
9	D	n.r.			1.5		
10	D	5.5					
12	D	5.8			n.r.		
13	A	5.5	6.2	1.8	ex	7.3	
14	A	equiv	0	0.8	n.r.	7.0	
15[b]	D	5.8	0	0.8	~1.5	7.6	$J_{6',OH}$ = 5.8
16	D	5.8	6.4	1.5	1.5	n.r.	$J_{6',OH}$ = 4.3
15	B	5.8	0	0.9	ex	7.6	
16[c]	B	5.5	6.1	1.5	ex	n.r.	$J_{6',6'}$ = 11.6
3	D	equiv	0	~0.5	n.r.	7.3	
4	D	5.8	5.8	1.5	n.r.	n.r.	$J_{2',OH} = J_{3',OH}$ = 5.8, $J_{6',OH}$ = 4.6
19Z[d]	D	5.5			n.r.		$J_{4',6'}$ = 1.2, $J_{1',4'}$ = 0.6
19E[d]	D	5.5			1.8		$J_{4',6'}$ = 0.6, $J_{1',4'}$ = 0.6

[a] In all cases, $J_{1',2'} = J_{3',4'}$ = 0 Hz. Values of $J_{5',5}$ were obtained after removal of $J_{5',NH}$ by D_2O addition. $J_{5,NH}$ was not always resolved, but D_2O addition, or decoupling in the case of 19E,Z, sharpens the H-5 signals. Values of small coupling constants were obtained at decreased spectral widths and/or increased data points to improve the digital resolution. Abbreviation n.r. = not resolved; ex = exchanged; equiv = equivalence of H-2' and H-3' gives no observable coupling. [b] $J_{6',6'}$ value obtained from deuterated 16b. [c] $J_{2',3'}$ obtained after D_2O addition, when H-2' and H-3' are no longer equivalent. [d] Four-bond couplings were confirmed by decoupling experiments.

Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.10; H, 5.00; N, 9.20.

Method B. Dimethylsulfoxonium methylide was generated by adding trimethylsulfoxonium iodide (990 mg, 4.5 mmol, recrystallized from water and dried) to a stirred solution of sodium hydride (4.4 mmol, 180 mg of 59.3% oil dispersion, hexane washed) in dry Me_2SO (10 mL). After 30 min, a solution of ketone 6 (600 mg, 2.14 mmol) in dry THF (5 mL) was added dropwise (2 min) and stirring was continued for an additional 30 min. The reaction mixture was poured into water (500 mL) and processed as described above to afford pure 7 (420 mg, 67%) indistinguishable (NMR, high-pressure LC) from oxirane prepared by using dimethylsulfonium methylide.

1-(5',7'-Anhydro-6'-deoxy-2',3'-*O*-isopropylidene)-6,5'-cyclo-β-D-*allo*-heptofuranosyluracil (9) and the *N*-Methyl Derivative (10). Dimethylsulfoxonium methylide in Me_2SO (8 mL) was prepared on one-half the scale described in method B above, and a solution of ketone 6 (150 mg, 0.54 mmol) in Me_2SO (2 mL) was added. The reaction mixture was kept for 5 min at room temperature and then heated at 60 °C for 0.5 h. The cooled reaction mixture was poured into water, and the products were isolated by extraction with ethyl acetate. A 10:1 mixture of 9 and 10 (R_f 0.53 and 0.64, respectively, in EtOAc–hexane, 4:1 v/v) was obtained in quantitative yield on evaporation of the ethyl acetate solution. Separation by preparative TLC afforded pure 10, mp 176–179 °C (from ether), characterized by its NMR spectrum, and pure 9: mp 146–148 °C (shrinks at 125 °C, from ether); UV (EtOH) λ_{max} 270, λ_{min} 235 nm.

Anal. Calcd for $C_{14}H_{16}N_2O_6 \cdot 0.5H_2O$: C, 53.00; H, 5.40; N, 8.83. Found: C, 52.99; H, 5.46; N, 8.76.

A similar mixture of 9 and 10 was obtained by treating oxirane 7 with 2 equiv of dimethylsulfoxonium methylide at 60 °C for 0.5 h.

2',3'-*O*-Isopropylidene-5'-*C*-methyl-6,5'(*S*)-cyclouridine (12). Lithium triethylborohydride (3 mL of 1 M solution in THF, Aldrich) was added dropwise via a syringe to a cold (0 °C), stirred solution of 7 (116 mg, 0.4 mmol) in THF (25 mL) under argon. After 15 min, the reaction mixture was poured into cold water (200 mL) and extracted with ethyl acetate. Evaporation of the washed and dried ethyl acetate extracts afforded 128 mg of crude product which contained (TLC) mostly 12, together with traces of starting material. Separation by high-pressure LC, using two 7.8 mm × 60 cm columns packed with LiChrosorb SI 60 (EM Reagents, connected in series) and elution with ethyl acetate, afforded 80 mg (67%) of pure 12. The analytical sample was crystallized from ether: mp 144–145 °C; UV (EtOH) λ_{max} 266, λ_{min} 234 nm; UV (pH 10) λ_{max} 267, λ_{min} 242 nm. Crystalline 12 contained very tightly bound ether that could not be removed, even by heating in vacuo over boiling ethanol for 6 days. The identity and amount of diethyl ether was confirmed by the NMR spectrum in Me_2SO-d_6.

Anal. Calcd for $C_{13}H_{16}N_2O_6 \cdot 0.2Et_2O$: C, 53.28; H, 5.83; N, 9.00. Found: C, 52.98; H, 6.08; N, 8.59.

Hydrogenolysis of Oxirane 7. A. With Platinum on Carbon Catalyst. Five percent platinum–carbon catalyst (1.0 g) was added to a solution of 7 (1.0 g) in ethyl acetate–ethanol (350 mL, 1:1 v/v), and the mixture was shaken under hydrogen (2–3 atm) on a Parr apparatus for 24 h. The catalyst was removed, and the filtrate was evaporated to dryness. The residue was dissolved in warm ethanol, and the solution was filtered to remove traces of carbon. Crystallization of 5'-deoxy-2',3'-*O*-isopropylidene-5'-(hydroxymethyl)-6,5'(*R*)-cyclouridine (16, 700 mg) occured when the solution was stored at room temperature; a further crop (140 mg, total yield 84%) of 16 was obtained by concentrating and cooling the filtrate. TLC and high-pressure LC indicated the presence of traces of 7 and the 5'*S*-hydroxymethyl nucleoside 15 in the mother liquor. Compound 16, which contained tightly bound ethanol, showed the following: mp 199–201 °C; UV (H_2O) λ_{max} 269, λ_{min} 233 nm; UV (pH 10) λ_{max} 267.5, λ_{min} 243.5 nm. The identity and amount of ethanol of crystallization was established from the NMR spectrum in Me_2SO-d_6.

Anal. Calcd for $C_{13}H_{16}N_2O_6 \cdot 0.25EtOH$: C, 52.68; H, 5.73; N, 9.10. Found: C, 52.29; H, 5.59; N, 9.12.

B. With Raney Nickel. A solution of 7 (50 mg) in ethyl acetate (10 mL) was shaken with excess Raney nickel and hydrogen (2–3 atm) on a Parr apparatus. After 18 h, when TLC showed the absence of starting material, the solution was filtered and evaporated to dryness. Three fractions were isolated by preparative TLC (ethyl acetate–hexane, 4:1 v/v): (a) R_f 0.16, 6 mg, identified by NMR as a 3:2 mixture of 5'-deoxy-2',3'-*O*-isopropylidene-5'-(hydroxymethyl)-6,5'(*R*)-cyclouridine (16) and its 5'*S* isomer 15, respectively; (b) R_f 0.30, 2.5 mg, identified by NMR as 5'-deoxy-2',3'-*O*-isopropylidene-5'-methyl-6,5'(*R*)-cyclouridine (13); (c) R_f 0.39, 9.0 mg, identified by NMR as 5'-deoxy-2',3'-*O*-isopropylidene-5'-methyl-6,5'(*S*)-cyclouridine (14).

Photolysis of Oxirane 7. A quartz flask containing a solution of 7 (50 mg) in ethanol (250 mL) was placed at the center of a circular array of eight RPR 2537A tubes (Rayonet photochemical reactor), and the solution was irradiated for 1 h. The cooled solution was evaporated to dryness, and the residue was dissolved in ~1 mL of hot water. Slow cooling induced crystallization of 5'-deoxy-2',3'-*O*-isopropylidene-5'-formyl-6,5'(*RS*)-cyclouridine (18, 17 mg, 36%, corrected for recovered starting material): mp 272–275 °C dec (darkens above 250 °C); UV of neutral species (0.1 N HCl) λ_{max} (ε) 340 (sh, 4000), 320 (6250), 285 (sh, 5200), 260 (9200), λ_{min} 293 (4000), 233 (4300) nm; UV of monoanion (pH 8 phosphate buffer) λ_{max} 367 (sh, 26 500), 358 (29 500), 258 (11 900),

λ_{min} 295 (1000), 235 (5400) nm; UV of dianion (0.1 N NaOH) λ_{max} 344 (21 500), 260 (sh, 9100), 253 (10 500), λ_{min} 285 (1800), 232 nm (7000).

Anal. Calcd for $C_{13}H_{14}N_2O_6 \cdot 0.5H_2O$: C, 51.49; H, 5.00; N, 9.24. Found: C, 51.58; H, 4.83; N, 9.02.

The filtrate remaining after the removal of 18 was evaporated to dryness, and the residue was dried by adding and evaporating several batches of ethanol. A solution of the residue in acetone was fractionated by preparative TLC (ethyl acetate–hexane, 2:1 v/v). The following materials were located by viewing only the edges of the plate under UV light (to avoid further photoreaction of the oxirane products) and extracted with ethyl acetate or ethyl acetate–methanol for the more polar products: (a) R_f 0.67, 1.4 mg, identified (TLC, NMR) as the 5′-ketone **6**; (b) R_f 0.58, 3.7 mg, identified (TLC, NMR) as the starting 5′*R* oxirane **7**; (c) R_f 0.43, 4.3 mg, unidentified, intense blue fluorescence under UV light; (d) R_f 0.24, 2.0 mg, identified (NMR) as 1-(5′,6′-anhydro-2′,3′-*O*-isopropylidene)-6,5′-cyclo-α-L-*talo*-furanosyluracil (5′*S* spirooxirane **11**), UV (EtOH) λ_{max} 275, λ_{min} 251 nm; (e) R_f 0.03–0.2, 19.7 mg, unidentified products, but includes additional aldehyde **18**.

5′-Deoxy-2′,3′-*O*-isopropylidene-5′-(hydroxymethyl)-6,5′-(*S*)-cyclouridine (15). Sodium cyanoborohydride (4 mg, 0.064 mmol) was added to a solution of aldehyde **18** (10 mg, 0.033 mmol) in a mixture of water, methanol, and acetic acid (2 mL; 1:1:1 v/v/v). The solution was stirred at room temperature for 4 h, at which time the ultraviolet spectra (pH 9) of aliquots showed the absence of the 358-nm absorption characteristic of the enol form of aldehyde **18**. Dowex 50 (H^+) was added to remove sodium ions, and the filtrate was evaporated to dryness. Several portions of methanol were distilled from the residue. The NMR spectrum of the syrup (10 mg, 99%) revealed a 13:1 mixture of **15** and **16**, respectively. Pure **15** was obtained by crystallizing the syrup from ethyl acetate: mp 194–196 °C d; UV (H_2O) λ_{max} 270, λ_{min} 234 nm; UV (pH 10) λ_{max} 268.5, λ_{min} 242 nm.

Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.61; H, 5.51; N, 9.41.

The base-catalyzed (pyridine-d_6 + D_2O; NaOD) formation of **15** from **16** described in the text was carried out with ~0.02 M solutions in NMR tubes. Obviously, these methods could be adapted to afford **15** efficiently on a preparative scale.

5′-Deoxy-5′-(hydroxymethyl)-6,5′(*R*)-cyclouridine (4). A solution of **16** (200 mg, 0.675 mmol) in methanol (8 mL)–1 N HCl (8 mL) was heated at 60 °C for 18 h, at which time TLC (CH_2Cl_2–MeOH, 5:1 v/v) indicated complete reaction. After the mixture cooled, the solvent was removed to afford 168 mg (97%) of product containing 95% **4** along with 5% of the exocyclic olefin formed by dehydration. The structure of the olefin was deduced (UV, NMR) from a pure sample obtained by reverse-phase high-pressure LC. An analytical sample of **4** was obtained by crystallization from 7.5:1 v/v ethanol–water: mp 258–260 °C dec; UV (H_2O) λ_{max} 270.5, λ_{min} 234 nm; UV (pH 10) λ_{max} 269, λ_{min} 240 nm.

Anal. Calcd for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93. Found: C, 46.81; H, 4.79; N, 10.63.

5′-Deoxy-5′-(hydroxymethyl)-6,5′(*S*)-cyclouridine (3). A solution of **16** (100 mg) in 80% acetic acid (10 mL) was heated at reflux for 4 h and then stirred for 18 h at room temperature. TLC (CH_2Cl_2–MeOH, 5:1 v/v) showed the absence of starting material **16** (R_f 0.67) and the presence of **4** (R_f 0.26) together with material (R_f 0.53) that probably is partially acetylated. After removal of solvent, methanol (5 mL) and aqueous NaOH (2 mL of 20% solution) were added to effect deesterification and 5′-isomerization. The solution was stirred for 10 min, deionized by passage through excess Dowex 50 (H^+), and concentrated to dryness. Pure **3** was obtained as the hemihydrate by crystallization from aqueous ethanol: mp 238–240 °C dec; UV (H_2O) λ_{max} 271.5, λ_{min} 235 nm; UV (pH 10) λ_{max} 270, λ_{min} 242 nm.

Anal. Calcd for $C_{10}H_{12}N_2O_6 \cdot 0.5H_2O$: C, 45.28; H, 4.93; N, 10.56. Found: C, 45.06; H, 4.82; N, 10.34.

Base-Catalyzed Isomerization of 5′-Deoxy-5′-(hydroxymethyl)-6,5′(*S*)- (3) and -6,5′(*R*)-cyclouridines (4). Heating either **4** (5 mg) or **3** (5 mg) in water (0.5 mL) containing triethylamine (5 μL) for 90 min at 50 °C or for 60 min at 60 °C affords an equilibrium mixture with a ~12:1 ratio in favor of the 5′-*S* isomer **3**. These isomerizations were monitored by high-pressure LC on a C-18 μBondapack reverse-phase column (Waters Assoc., 3.9 mm × 30 cm), using 0.01 M $NH_4H_2PO_4$ buffer (adjusted to pH 5.5 with aqueous ammonia) for elution. With a flow rate of 2.0 mL/min, the 5′-*R* isomer (**4**) was eluted at 10.8 min and the 5′*S* isomer (**3**) at 6.2 min. The *S*:*R* ratio was estimated by measuring the area of the peaks in the UV-elution profile.

Acknowledgment. We are indebted to Dr. J. J. Fox for his continued interest and to Drs. R. S. Klein and A. Matsuda for helpful discussions. In addition, the valuable contributions of Elvira A. Falco made during the early stages of this investigation are gratefully acknowledged.

Registry No. **3**, 76207-41-5; **4**, 76248-58-3; **5**, 59686-58-7; **6**, 64200-82-4; **7**, 76207-42-6; **9**, 76207-43-7; **10**, 76207-44-8; **11**, 76248-20-9; **12**, 76207-45-9; **13**, 76207-46-0; **14**, 76248-21-0; **15**, 76207-47-1; **16**, 76248-22-1; **18**, 76207-48-2; **19Z**, 76207-49-3; **19E**, 76248-23-2.