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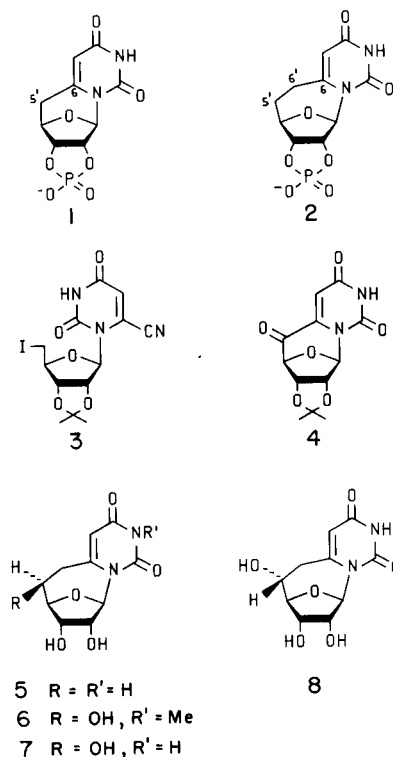
The protected 5'-oxo-6,5'-cyclo-uridine **13** reacts with diazomethane to afford mostly the spiro-epoxide **18** (79%), but it also undergoes ring-expansion to give the corresponding 5'-oxo-6,6'-cyclo-nucleoside **16**. Under the conditions of the reaction, ketone **16** reacts further with diazomethane to give the enol ether **20** (12% overall), the isomeric 4-methoxy nucleoside **15** (2%), and the spiro-epoxide **19** (4.4%). Acid hydrolysis of the enol ether **20**, followed by reduction of the resulting ketone with sodium borohydride, affords a separable mixture of the 5'S (L-talo) and 5'R (D-allo) methylene-bridged cyclonucleosides **7** and **8**, respectively. From proton nmr measurements, it appears that the 6'-methylene groups of these cyclonucleosides project towards the 2',3'-edge of the furanose ring.

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Cyclonucleotides in which a carbon bridge restricts the glycosyl torsion angle to a particular range are useful for probing the conformational aspects of nucleotide-enzyme interactions. For example, recent studies of the rates at which pancreatic ribonuclease cleaves the cyclic compounds **1** and **2** (Scheme 1) led to the conclusion that normal substrates also adopt the anti-conformation when bound to the enzyme [2]. Of these two types of cyclonucleosides, those containing a 6,5'-linkage as in structure **1** are now well known, and effective methods are available for preparing compounds with [3] and without [4] substituents at the 5'-position. On the other hand, only two approaches have been described for the synthesis of the pyrimidine 6,6'-cyclo system contained in compound **2**. In a recently reported method, Ueda and coworkers [5] constructed the 6,6'-cyclo linkage *via* an intramolecular radical cyclization of the highly functionalized uridine derivative **3**. The initially formed 6'-imino-6,6'-cyclonucleoside was then converted into the 5',6'-unsubstituted product **5** by an additional series of reactions. In a different approach, we reported some time ago that the 5'-oxo-6,5'-cyclonucleoside **4** undergoes expansion to the 6,6'-cyclo system when treated with diazomethane [6]. Although the yields of ring-expanded products are rather modest, the method does offer the advantage of providing a route to 5'-substituted compounds, such as **6**, where the orientation of the 5'-substituent simulates a particular 4',5'-rotamer of unrestricted nucleosides. We have now examined the diazomethane approach in greater detail, and we report in the present paper a number of modifications that allow the synthesis of both the 5'R and 5'S isomers of 6,6'-cyclo-6'-deoxyhexofuranosyluracil, namely, the cyclonucleosides **7** and **8**.

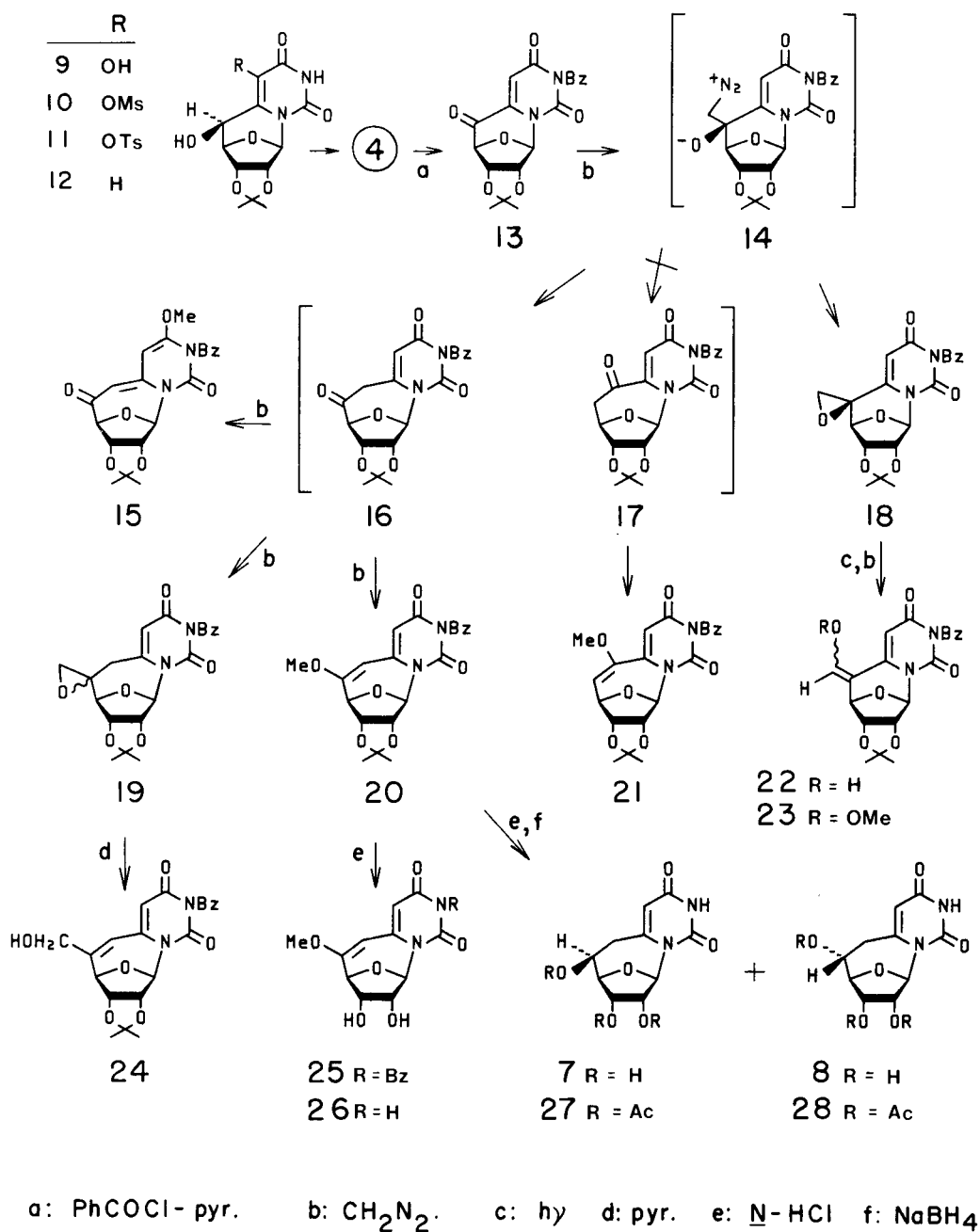
The starting ketone **4** (Scheme 2) is readily available from the corresponding alcohol **12** *via* manganese dioxide

Scheme 1



oxidation [3c,7]. In order to avoid *N*-methylation of **4** during the diazomethane step, the compound was converted into its benzoyl derivative **13**. The conclusion that benzylation occurs at N-3 rather than O-4 follows from the lack of any marked differences in the chemical shifts of the pyrimidine carbon atoms of **13** and **4** [8].

Scheme 2



Since ketone **4** reacts with diazomethane to give predominantly a 5'-spiro-epoxide [6], it was not surprising to find that the protected ketone **13** follows a similar course. In the present case, epoxide **18** was isolated in 79% yield. The configuration at C-5' of **18** has not been established rigorously, but diazomethane probably approaches the carbonyl group of **13** from the less-hindered, rear side. The resulting intermediate (possibly but not necessarily **14**) [9] would then undergo ring-closure to give **18** with the

illustrated 5'-stereochemistry. Other reagents, such as sodium cyanoborohydride, are known [3d] to attack the 5'-position of **4** exclusively from the rear side.

Although epoxide **18** is by far the most abundant product formed from **13** and diazomethane, a moderate amount of ring expansion does take place. Three such products were isolated in a combined yield of 18%. Of these, the 5'-enol ether **20** was obtained in the largest amounts (12%), which is fortunate because this compound serves as

a precursor of the desired 6,6'-cyclonucleosides **7** and **8**. These transformations, which are described below, establish the structure of **20**.

The second ring-expanded product, obtained in 4.4% yield, has been assigned structure **19** on the basis of its nmr spectrum. Compound **19** was isolated as a single 5'-epimer of undetermined stereochemistry. The proposed structure receives strong support from the observation that addition of pyridine-*d*<sub>5</sub> to a solution of **19** in DMSO-*d*<sub>6</sub> results in the smooth formation of a new product with an nmr spectrum consistent with the hydroxymethyl alkene **24**.

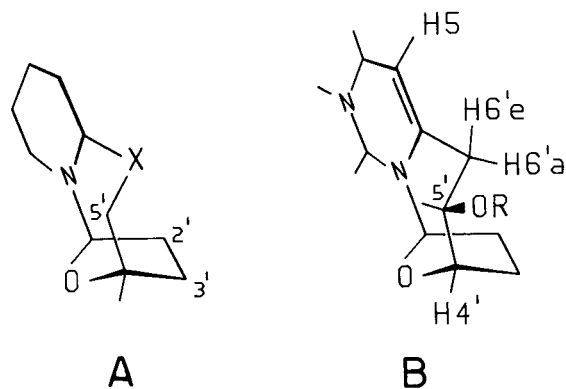
The third ring-expanded product was obtained in only 2% yield. The substance is clearly a positional isomer of **20** from its uv and nmr characteristics, and it appears to be the somewhat unusual 4-methoxypyrimidine **15**. This structure, which would be formed by methylation of the appropriate tautomer of ketone **16**, confirms that N-3 is the site of benzylation of the starting ketone **13**. Two additional candidates for the structure of **15** have been eliminated. For example, the compound is not the 6'-enol ether **21** because the 1.2 Hz coupling observed between H-4' and the vinyl proton is too small to be accommodated by that structure. In similar bicyclic systems, vicinal coupling constants between protons at bridgehead positions and vinylic protons generally lie in the range of 4-8 Hz [11]. On the other hand, the observed 1.2 Hz coupling constant is appropriate for the four-bond, planar W-relationship between H4' and H6' in structure **15**. Similarly, the possibility that the product assigned structure **15** is really the exocyclic enol ether **23** has also been counted out. Enol **23** might have been formed by methylation of the aldehyde **22**, which is the expected photolysis product of epoxide **18**. We had already found [3c] that spiro-epoxides of type **18** undergo such photolysis with extraordinary ease. Since the diazomethane reaction was not conducted in the dark, it was not out of the question that **22**, and hence **23**, could be formed to a small extent. Deliberate photolysis of **18** followed by methylation *does*, in fact, afford an *E/Z* mixture of enols **23**. However, it was clear from the nmr spectra of the mixed isomers that neither the *E* nor the *Z* form of **23** corresponds to the material assigned structure **15**.

It will be noted that the ring-expanded products **15**, **19**, and **20** are each derived by methylation or epoxidation of a common intermediate, namely the 5'-ketone **16**. This intermediate would be formed by migration of the 5',6-bond of **14** during the ring expansion reaction. The alternative migration of the 4',5'-bond of **14**, which would lead to the 6'-ketone **17**, has not been observed. The preference for 5',6-migration in **14** is consistent with the migratory aptitudes noted in previous studies [10a] of the reactions between diazoalkanes and  $\alpha,\beta$  unsaturated ketones, which undergo ring-expansion to form  $\beta,\gamma$  unsaturated ketones.

However, unlike these earlier examples, the ring-expansion of **13** does not require Lewis-acid catalysis. In fact, conducting the reaction of **13** with diazomethane in the presence of boron trifluoride appears to decrease the extent of ring expansion relative to epoxide formation.

As an enol ether, compound **20** is susceptible to acid hydrolysis, although fairly vigorous conditions are required. Thus, conversion of **20** into the de-isopropylidened version of ketone **16** requires warming in 1*N* hydrochloric acid at 65-70° for at least an overnight period, and even then some 10% of the 2',3'-*O*-unsubstituted 5'-enol ether **25** was obtained as a by-product. The 5'-oxo group of the major product was reduced *in situ* on the addition of a large excess of sodium borohydride. These alkaline conditions also serve to remove the N-3 benzoyl protecting group. In contrast to our previous finding that similar reduction of ketone **4** leads exclusively to the 5'(*S*)-alcohol, reduction of the 5'-oxo-6,6'-cyclo nucleoside providentially affords an approximately 1:1 mixture of both isomers, that is, the L-talo and D-allo nucleosides **7** and **8**, respectively [12]. After separation on a reverse-phase hplc column, cyclonucleosides **7** and **8** were each obtained in about 25% overall yield from **20**. These compounds have also been characterized as their 2',3',5'-tri-*O*-acetyl esters **27** and **28**.

Pyrimidine cyclonucleosides in which a heteroatom links C-5' to either C-2 or C-6 of the base generally adopt a conformation where the bridging group projects towards the C2',C3'-edge of the furanose ring rather than towards the ring oxygen atom. For example, X-ray diffraction studies [13a,b] and nmr analysis [13a] indicate that isopropylidene-2,5'-anhydrouridine adopts such a conformation (**A**) in the crystalline state as well as in solution. The nmr spectra of pyrimidine 6,5'-*O*, 6,5'-*S*, and 6,5'-NH-cyclonucleosides are also consistent with type **A** conformations for



these compounds [13c,d]. With an increased number of ring protons, the methylene-bridged compounds **7** and **8**, and the acetates **27** and **28**, exhibit some long-range coupling interactions that are not found in hetero-bridged cy-

clonucleosides. Analysis of these couplings provides an independent method for determining the orientation of the methylene bridge, and it is clear that a similar conformational pattern prevails. The presence of a four-bond coupling (1-1.3 Hz) between H-4' and the downfield H-6' proton for compounds **7**, **8**, **27** and **28** is particularly diagnostic because it establishes a near-planar, W-relationship between these two groups. This orientation, which is possible only for the chair conformation shown schematically as **B**, places the H-6' proton to which H-4' is coupled in an equatorial position close to the plane of the pyrimidine 5,6-double bond. In agreement with this, H-5 exhibits allylic coupling (~1 Hz) only with the upfield H-6' proton, which is therefore in an axial position. It follows that the glycosyl torsion angle  $\chi$  (O4'-C1'-N1-O2) is close to 240°.

With the orientation of the methylene bridge known, the values of the coupling constants  $J_{5,6'a}$  serve to differentiate the various 5'-epimers. For example, the trans-diaxial relationship between H-5' and H-6'a in the L-talo (5'S) compounds **7** and **27** (which corresponds to the 5' configuration shown in **B**) is reflected in the 11.5 Hz coupling constant between these protons. Conversely, the D-allo (5'R) isomers **8** and **28** exhibit  $J_{5,6'a}$  values in the range 2.3-2.5 Hz. It is also of interest that the 5'-acetyl group in the 5'(S) isomer **27** causes a deshielding effect such that H-3' resonates downfield of H-2'. In the 5'(R) isomer **28**, H-3' resonates upfield of H-2'.

## EXPERIMENTAL

### General Procedures.

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were measured with a Unicam SP-800 spectrophotometer. Thin-layer chromatography was performed on 250  $\mu$ m GF254 plates (2.8  $\times$  8 cm, Analtech, Inc), and separated materials were detected with ultraviolet light and/or by spraying with sulphuric acid in ethanol (10% v/v) followed by charring. Preparative separations were effected on 500  $\mu$ m (20  $\times$  20 cm) plates. Silica gel 60 (Merck) was used for flash column chromatography. Nuclear magnetic resonance spectra were determined with JEOL FX90Q or PFT-100 instruments; chemical shifts were measured relative to internal tetramethylsilane (TMS) for organic solvents, and 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) for deuterium oxide. Microanalyses were performed by MHW Laboratories, Phoenix, Arizona, and by Galbraith Laboratories, Inc., Knoxville, Tennessee. All evaporations were carried out *in vacuo*.

### 2',3'-O-Isopropylidene-5-(*p*-toluenesulphonyloxy)-6,5'(S)-cyclouridine (**11**).

Solid *p*-toluenesulphonyl chloride (702 mg, 3.68 mmoles) was added in one portion to a cold (0°) solution of the 5-hydroxy cyclonucleoside **9** [3b] (1.00 g, 3.36 mmoles) in dry pyridine (10 ml), and the reaction mixture was stirred for 3 hours. After concentration to ~2 ml, 50% ethanol (50 ml) was added to induce crystallization of **11**. The resulting solid was collected and washed thoroughly with ethanol. Recrystallization of this material from 75 ml of boiling ethanol afforded 1.3 g (86%) of **11** in two crops, as well-formed needles, mp 255-256°; <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>):  $\delta$  11.83 (1H, s, NH), 7.87 and 7.45 (2H each, two d, aromatic), 6.34 (1H, d, 5'-OH), 5.87 (1H, s, H-1'), 5.07 and 4.98 (2H, d overlapping dd, H-2' and H-5'), 4.76 (1H, d, H-3'), 4.48 (1H, d, H-4'), 2.45 (3H, s overlapping solvent signal, *p*-Me), 1.40 and 1.26 (3H each, two s, isopropylidene methyls),  $J_{2,3'} = 5.7$  Hz,  $J_{4,5'} = 7.4$  Hz,  $J_{5',OH} = 6.7$  Hz,  $J$  (vicinal aromatic) = 8 Hz.

*Anal.* Calcd. for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>9</sub>S: C, 50.44; H, 4.46; N, 6.19; S, 7.09. Found: C, 50.52; H, 4.58; N, 6.07; S, 7.11.

### 2',3'-O-Isopropylidene-6,5'(S)-cyclouridine (**12**).

Triethylamine (0.6 ml) and 5% platinum-on-carbon catalyst (3 g) were added to a solution of **11** (1.5 g) in ethanol (150 ml)-ethyl acetate (100 ml), and the mixture was subjected to hydrogenation in a Parr apparatus for 6 hours. After removal of the catalyst, the filtrate was added to the combined filtrates from three similar runs, and the solution was evaporated to dryness. The residue was suspended in a 1:1 mixture of ethyl acetate and acetonitrile (100 ml), the flask was heated for 2 minutes on a steam bath, and the insoluble material was removed by filtration through a pad of Celite. The filtrate and ethyl acetate washings were then concentrated to afford a syrupy residue that crystallized from 50 ml of 95% ethanol, affording 3.4 g (91%) of **12** in two crops. The hplc analysis (C-18 reverse phase, 30% methanol, refractive index detector) indicated that while the mother liquor contained **12** and some of the corresponding 5,6-dihydro nucleoside [3b], the crystalline product contained **12** of better than 97% purity. The uv and nmr spectra of **12** prepared from **8**, as well as the melting point and hplc retention time, are identical with authentic material [3b].

### N<sup>3</sup>-Benzoyl-2',3'-O-isopropylidene-5'-oxo-6,5'-cyclouridine (**13**).

An excess of benzoyl chloride (1 ml, 8.6 mmoles) was added dropwise to a solution of **4** (830 mg, 3 mmoles) [3c] in dry pyridine (25 ml), and the solution was stirred at room temperature for 16 hours. Water was added to hydrolyze the remaining benzoyl chloride and the reaction mixture was evaporated to dryness. The syrupy residue was partitioned between water and chloroform (2  $\times$  50 ml), and the combined organic layers were treated with an aqueous solution of cadmium chloride in order to remove residual pyridine. After filtration, the chloroform layer was washed with water and then dried over sodium sulphate. Although reasonably pure **13** can be obtained in ~50% yield simply by removing the chloroform and crystallizing the residue from ethyl acetate/petroleum ether, the product is more efficiently isolated by flash chromatography on silica gel using ethyl acetate-ether (1:1, v/v) as the eluant. Pure **13** (950 mg, 83%) was obtained in this way as a white powder that was subsequently crystallized from ethanol, mp 204-205°; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  7.97-7.87 and 7.77-7.41 (2H and 3H m, benzoyl), 6.50 (1H, s, H-1'), 6.31 (1H, s, H-5), 4.90 (2H, s, H-2',3'), 4.87 (1H, s, H-4'), 1.54 and 1.35 (3H each, two s, isopropylidene methyls); <sup>13</sup>C-nmr (DMSO-*d*<sub>6</sub>):  $\delta$  184.5 (C-5'), 141.5 (C-6), 102.5 (C-5), 161.2 (C-4), 147.2 (C-2). For comparison, the analogous carbon resonances of ketone **4** appear in DMSO-*d*<sub>6</sub> at 185.1, 141.0, 102.6, 162.3 and 148.6 ppm, respectively.

*Anal.* Calcd. for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>7</sub>: C, 59.37; H, 4.20; N, 7.29. Found: C, 59.54; H, 4.32; N, 7.13.

### Reaction of Ketone **13** with Diazomethane.

A mixture of dichloromethane (100 ml) and 40% potassium hydroxide solution (20 ml) contained in an open beaker was cooled to -10° in an acetone-dry ice bath. Finely divided *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (**6** g) was added in small portions to the vigorously stirred mixture. At the end of the addition (about 30 minutes), the contents of the beaker were transferred *via* a glass funnel with a fire-polished outlet tube to a separatory funnel equipped with a teflon stopcock and clear-seal joints. Following separation of the layers, the solution of diazomethane in dichloromethane was washed by gentle swirling with cold water. The washing was repeated in order to remove traces of alkali that would not be compatible with the presence of an *N*-benzoyl group in the following reaction.

The *N*-benzoyl ketone **13** (580 mg) was dissolved in a mixture of methanol (25 ml) and dichloromethane (5 ml), the solution was cooled to -10°, and the above preparation of diazomethane was added dropwise over a twenty minute period. Stirring was continued for a further 1 hour period at -10°, at which time tlc (ethyl acetate-hexane 1:1, v/v) indicated the absence of starting material (**13**). The excess diazomethane was destroyed by the addition of a few drops of acetic acid, and the reaction mixture was evaporated to dryness. A solution of the syrupy residue in

the minimum volume of ethylacetate-hexane (1:1) was applied to a column (2.6 × 25 cm) of silica gel packed in hexane. Elution with ethyl acetate-hexane (2:3, v/v) (800 ml) then afforded the following materials, where Rf values refer to tlc using ethyl acetate-hexane 1:1 v/v.

i) 1-(5,6-Anhydro-2,3-O-isopropylidene)-3-benzoyl-6,5'-cyclo-D-allofuranosyluracil (**18**).

This compound was obtained as a crystalline solid (470 mg) in 79% yield, Rf = 0.71, mp 213-215°, <sup>1</sup>H-nmr (deuteriochloroform): δ 7.97-7.76 and 7.68-7.41 (2H and 3H m, benzoyl), 6.28 (1H, s, H-1'), 5.61 (1H, s, H-5), 5.02 and 4.81 (2H, two d, H-2' and H-3'), 4.17 (1H, s, H-4'), 3.20 (2H, ABq, H-6'a and H-6'b), 1.51 and 1.35 (3H each, two s, isopropylidene methyls), J<sub>2',3'</sub> = 5.8 Hz, J<sub>6'gem</sub> = 5.5 Hz.

Anal. Calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>7</sub>: C, 60.30; H, 4.55; N, 7.03. Found: C, 60.34; H, 4.56; N, 7.05.

ii) Spiro-epoxy-6,6'-cyclonucleoside **19**.

This compound was obtained in 4.4% yield (27 mg) after crystallization from ethyl acetate-ether, Rf = 0.29, mp 160-162° dec; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): (with T<sub>1</sub> pulse sequence to remove solvent resonance): δ 8.05-7.89 and 7.81-7.52 (2H and 3H m, benzoyl), 6.42 (1H, s, H-1'), 6.00 (1H, s, H-5), 5.32 and 5.20 (2H, AB system, H-2' and H-3'), J = 5.6 Hz), 4.04 (1H, nd, H-4'), J<sub>4',6'e</sub> ~ 0.6 Hz), 2.98 and 2.92 (2H, AB system, epoxide methylene J<sub>gem</sub> = 5 Hz), 3.38 and 2.58 (1H each, two broadened d, H-6'a and H-6'e, J<sub>gem</sub> = 15.6 Hz), 1.43 and 1.34 (3H each, two s, isopropylidene methyls).

Anal. Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>: C, 61.16; H, 4.88; N, 6.79. Found: C, 61.10; H, 4.88; N, 6.79.

iii) 5'-Enol ether **20**.

Following removal of **19** from the column, elution with ethyl acetate-hexane 2:1 v/v (600 ml) afforded the 5'-enol ether **20** (75 mg, 12%), Rf = 0.21, mp 243-245°; uv (water): λ max 255 and 315, λ min 278 nm; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 7.5-8.1 (2H and 3H m, benzoyl), 6.37 (1H, s, H-1'), 5.96 (1H, s, H-5), 5.78 (1H, s, H-6'), J<sub>4',6'</sub> < 0.6 Hz), 5.13 and 4.93 (1H each, two d, H-2' and H-3'), J<sub>2',3'</sub> = 5.8 Hz), 4.84 (1H, s, H-4'), 3.77 (3H, s, OMe), 1.43 and 1.27 (3H each, two s, isopropylidene methyls).

Anal. Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>: C, 61.16; H, 4.88; N, 6.79. Found: C, 61.02; H, 5.09; N, 6.82.

iv) 4-Methoxy-5'-oxo Nucleoside **15**.

After **20** had been removed from the column, elution with ethyl acetate afforded the 4-methoxy-5'-oxo nucleoside **15**, which crystallized from 95% ethanol as colorless needles (120 mg, 2%), mp 145-146°, Rf 0.1, uv (acetonitrile): λ max 342, λ min 280 nm; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 7.5-8.1 (2H and 3H m, benzoyl), 6.40 (1H, s, H-1'), 5.77 (1H, s, H-5), 5.19 (1H, d, H-6'), J<sub>4',6'</sub> = 1.2 Hz), 5.10 and 4.85 (1H each, two d, H-2' and H-3'), J<sub>2',3'</sub> = 5.8 Hz), 4.58 (1H, bd, H-4'), 3.78 (3H, s, OMe), 1.43 and 1.26 (3H each, two s, isopropylidene methyls).

Anal. Calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>: C, 61.16; H, 4.88; N, 6.79. Found: C, 60.97; H, 5.07; N, 6.66.

2',3'-O-Isopropylidene-5',6'-dideoxy-5',6'-didehydro-5'-hydroxymethyl-6,6'-cyclo-1-(β-D-ribohexofuranosyl)uracil (**24**).

This compound was generated *in situ* when the DMSO-d<sub>6</sub> solution of epoxide **19** was diluted with about 10% pyridine-d<sub>5</sub>. After 30 minutes at 25°, the signals of **19** had been completely replaced by the following spectrum: δ 8.13-8.22 and 7.81-7.58 (2H and 3H m, plus solvent peak, benzoyl), 6.62 (1H, s, H-1'), 6.51 (1H, s, H-6'), 6.23 (1H, s, H-5), 5.20 and 5.04 (two d, H-2' and H-3'), J<sub>2',3'</sub> = 5.8 Hz) overlapped by 5.13 (s, total 3H, H-4'), 4.42 (2H, bs, methylene), 1.50 and 1.34 (3H each, two s, isopropylidene methyls).

6'-Deoxy-6,6'-cyclo-1-(α-L-talofuranosyl)uracil (**7**) and 6'-Deoxy-6,6'-cyclo-1-(β-D-allofuranosyl)uracil (**8**).

The 5'-enol ether **20** (150 mg, 0.36 mmole) was dissolved in a mixture of *N* hydrochloric acid (20 ml) and ethanol (5 ml), and the solution was heated at 65-70° for 18 hours. After cooling, the solution was extracted

with chloroform in order to remove a small amount of **25**. Evaporation of the chloroform solution and crystallization of the residue from ethanol (4 ml) afforded colorless crystals of **25** (14 mg, 10%), mp 210-211° dec, Rf (ethyl acetate-hexane, 4:1 v/v) 0.24; uv (acetonitrile): λ max 315, λ min 277 nm; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 7.5-8.1 (2H and 3H m, benzoyl), 6.34 (1H, d, H-1'), J<sub>1',2'</sub> = 3 Hz), 5.96 (1H, s, H-5), 5.74 (1H, s, H-6'), 5.64 (1H, d, 3'-OH, J<sub>3'OH</sub> = 5 Hz), 5.47 (1H, d, 2'-OH, J<sub>2'OH</sub> = 8 Hz), 4.59 (s, H-4') overlapping 4.50 (m, H-2'), total 2H), 4.18 (1H, m, H-3'), J<sub>2',3'</sub> = 5.5 Hz), 3.75 (3H, s, OMe).

Anal. Calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>7</sub>: C, 58.31; H, 3.81; N, 7.56. Found: C, 58.21; H, 4.02; N, 7.53.

The aqueous layer from the above extraction, containing largely the de-isopropylidened 5'-keto nucleoside derived from **16** [uv (pH 7): λ max 315; (pH 10): λ max 355] was evaporated to dryness and the residue was dissolved in 50 ml of 80% ethanol. Sodium borohydride 1*N* solution (4.4 ml, ~12 equivalents) was added dropwise to the reaction mixture over a 45 minute period, during which time the uv absorption maximum at 355 nm essentially disappeared. The reaction mixture was neutralized by the cautious addition of washed Dowex 50(H<sup>+</sup>), the resin was removed, and the filtrate and washings were reduced in volume. After extraction with ether, the aqueous layer was evaporated to dryness and several portions of methanol were evaporated from the residue. The D-allo isomer **8** can be obtained at this stage by fractional crystallization from ethanol, but the separation was carried out more efficiently by using preparative hplc on a Waters Associates μBondapak C-18 reverse phase column (7.8 × 30 cm). Using water-methanol, 99:1 v/v (containing 1 ml of acetic acid per 4 liters) as the solvent, and a flow rate of 2 ml/minute, the D-allo isomer **8** was eluted at 8.4 minutes, and the L-talo isomer **7** at 16 minutes. A minor product eluting at 11.5 minutes was not characterized. Following evaporation of the appropriate fraction and crystallization from ethanol, the following compounds were obtained.

6'-Deoxy-6,6'-cyclo-1-(β-D-allofuranosyl)uracil (**8**).

This compound was obtained as colorless needles (21 mg, 23%), mp > 290°, Rf = 0.15 (dichloromethane-methanol, 5:1); uv (water): λ max 265, λ min 232; uv (pH 10): λ max 266, λ min 244 nm; <sup>1</sup>H-nmr: (deuterium oxide): (with T<sub>1</sub> pulse sequence to remove the solvent resonance) δ 6.49 (1H, d, H-1'), 5.77 (1H, bs, H-5), 4.78 (1H, dd, H-2'), 4.40 (1H, bd, H-4'), 4.33 (1H, d, H-3'), 4.14 (1H, ddd, H-5'), 2.89 and 2.86 (2H, m, H-6'e and H-6'a), J<sub>1',2'</sub> = 1.8, J<sub>2',3'</sub> = 6.1, J<sub>3',4'</sub> = 0, J<sub>4',6'e</sub> = 1.0, J<sub>5,6'e</sub> < 0.5, J<sub>5,6'a</sub> = 1.2, J<sub>4',5'</sub> = 2.75, J<sub>5',6'a</sub> = 2.5, J<sub>5',6'e</sub> = 5.2, J<sub>6'a,6'e</sub> = 16.0 Hz [14].

Anal. Calcd. for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>: C, 46.88; H, 4.72; N, 10.93. Found: C, 46.84; H, 4.81; N, 10.76.

6'-Deoxy-6,6'-cyclo-1-(α-L-talofuranosyl)uracil (**7**).

This compound was obtained similarly from ethanol as colorless needles (24 mg, 26%), mp > 290°, Rf = 0.25 (dichloromethane-methanol 5:1); uv (water): λ max 266, λ min 232.5; uv (pH 10): λ max 267, λ min 244 nm; <sup>1</sup>H-nmr (deuterium oxide): (with T<sub>1</sub> pulse sequence to remove solvent resonance) δ 6.38 (1H, d, H-1'), 5.73 (1H, bs, H-5), 4.61 (1H, dd, H-2'), 4.44 (1H, d, H-3'), 4.35 (1H, bd, H-4'), 3.91 (1H, ddd, H-5'), 2.83 and 2.58 (2H, two 8-line m, H-6'e and H-6'a), J<sub>1',2'</sub> = 1.8, J<sub>2',3'</sub> = 6.5, J<sub>3',4'</sub> = 0, J<sub>4',6'e</sub> = 1.2, J<sub>5,6'e</sub> < 0.5, J<sub>5,6'a</sub> = 1.3, J<sub>4',5'</sub> = 4.3, J<sub>5',6'a</sub> = 11.5, J<sub>5',6'e</sub> = 4.2, J<sub>6'a,6'e</sub> = 16.4 Hz [14].

Anal. Calcd. for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>6</sub>: C, 46.88; H, 4.72; N, 10.93. Found: C, 46.96; H, 4.58; N, 10.76.

Following collection of **7**, the column was eluted with methanol in order to remove some less polar products (20 mg). This mixture was rechromatographed on the above hplc column. Using 30% aqueous methanol at 2 ml/minute, the major component eluted at 10.5 minutes. Evaporation of the solvent and crystallization of the residue from ethanol-2-propanol then afforded 5 mg (5%) of the enol ether **26**, mp 228-230°, Rf = 0.42 (dichloromethane-methanol, 5:1), uv (methanol): λ max 313, λ min 275 nm; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 11.3 (1H, bs, NH), 6.37 (1H, d, H-1'), J<sub>1',2'</sub> = 3 Hz), 5.69 (1H, s, H-5), 5.59 (1H, s, H-6'), 4.49 (1H, s, H-4'), 4.35 (1H, dd, H-2'), J<sub>2',3'</sub> = 5.2 Hz), 4.11 (1H, d, H-3'), 3.70 (3H, s, OMe).

2',3',5'-Tri-*O*-acetyl-6'-deoxy-6,6'-cyclo-1-( $\alpha$ -L-talofuranosyl)uracil (**27**) and 2',3',5'-Tri-*O*-acetyl-6'-deoxy-6,6'-cyclo-1-( $\beta$ -D-allofuranosyl)uracil (**28**).

The crude residue containing the un-separated isomers **7** and **8** obtained as above was dissolved in a mixture of pyridine and acetic anhydride. Following a conventional work-up, the isomers were separated on the above reverse-phase hplc column using water-methanol-acetonitrile (75/22/3) as solvent at 2 ml/minute. The 5'*R* isomer **28** and the 5'*S* isomer **27** eluted as sharp peaks at 31 and 46 minutes, respectively. Evaporation of the appropriate fractions and crystallization of the residue from ethyl acetate-ether afforded **27** as colorless crystals in 25% yield from **20**, mp 180-181° dec; uv (water):  $\lambda$  max 263,  $\lambda$  min 226 nm; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  9.10 (1H, bs, NH), 6.78 (1H, d, H-1'), 5.70 (1H, s, H-5), 5.61 (1H, d, H-3'), 5.54 (1H, dd, H-2'), 5.05 (1H, ddd, H-5'), 4.62 (1H, bd, H-4'), 2.96 and 2.77 (2H, m, H-6'e and H-6'a), 2.15, 2.14 and 2.13 (9H, three s, acetyls),  $J_{1',2'} = 1.85$ ,  $J_{2',3'} = 6.6$ ,  $J_{3',4'} = 0$ ,  $J_{4',5'} = 4.5$ ,  $J_{4',6'e} = 1$ ,  $J_{5,6'e} < 0.5$ ,  $J_{5,6'a} = 1$ ,  $J_{5',6'a} = 11.5$ ,  $J_{5',6'e} = 3.9$ ,  $J_{6'a,6'e} = 16.3$  Hz, [14].

Anal. Calcd. for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>: C, 50.27; H, 4.74; N, 7.33. Found: C, 50.34; H, 4.75; N, 7.25.

The 5'*R* isomer **28** was also obtained in 25% yield following crystallization from ethyl acetate-ether, mp 194-195° dec; uv (water):  $\lambda$  max 262,  $\lambda$  min 226 nm; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  9.29 (1H, bs, NH), 6.82 (1H, d, H-1'), 5.62 (s, H-5) overlapping left part of 5.63 (dd, H-2', total 2H), 5.41 (1H, d, H-3'), 5.14 (1H, ddd, H-5'), 4.61 (1H, nm, H-4'), 3.06 and 2.82 (2H, m, H-6'e and H-6'a), 2.14 and 2.12 (6H and 3H, two s, acetyls),  $J_{1',2'} = 2.0$ ,  $J_{2',3'} = 6.5$ ,  $J_{3',4'} = 0$ ,  $J_{4',5'} = 2.3$ ,  $J_{4',6'e} = 1.2$ ,  $J_{5,6'e} < 0.5$ ,  $J_{5,6'a} = 1.2$ ,  $J_{5',6'a} = 2.3$ ,  $J_{5',6'e} = 4.9$ ,  $J_{6'a,6'e} = 16.5$  Hz [14].

Anal. Calcd. for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>: C, 50.27; H, 4.74; N, 7.33. Found: C, 50.29; H, 4.81; N, 7.23.

#### Photolysis of Epoxide **18**.

A quartz flask containing a solution of **18** (50 mg) in ethanol (100 ml) was placed in the center of a circular array of sixteen RPR 2537A tubes in a Rayonet photochemical reactor, and the solution was irradiated for 30 minutes. During this time, the original uv-absorption shifts smoothly to 327 nm, reflecting the formation of the enol **22**. The reaction mixture was evaporated to dryness and an excess of diazomethane in ether was added in order to generate **23**. The mixture of the *E* and *Z* isomers of **23** obtained as the major product after preparative tlc (ethyl acetate-hexane, 2:1, v/v) shows the following; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  7.98-7.48 (2H and 3H m, benzoyl), 7.05 and 6.67 (two s, 1H, H-6'*Z* and H-6'*E*), 6.21 (1H, s, H-1'), 5.78 and 5.30 (two s, 1H, H-5*Z* and H-5*E*), 4.60-4.78 (3H, m, H-2', H-3' and H-4'), 3.97 and 3.94 (two s, 1H, OMe), 1.51 and 1.31 (3H each, two s, isopropylidene methyls).

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