Synthesis of 6,6′-Cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)cytosine and Related Nucleosides (Nucleosides and Nucleotides. LXXXVIII)[1]

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A new synthetic route to 6,6′-cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)-uracil, -cytosine, and -4-thiouracil is described. The method involves a base-catalyzed condensation of 2,4-dimethoxy-6-methylpyrimidine and 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribopentofuranosyldialdehyde, followed by an intramolecular glycosylation, and derivatization of the base moiety. The relationship of the sign of the circular dichroism (CD) spectra of carbon-bridged cyclopyrimidine nucleosides to the glycosyl torsion angle is discussed.

Keywords 6,6′-cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)cytosine; carbon-bridged cyclonucleoside; nucleoside conformation; ceric chloride; Peterson olefination; CD spectra; NMR

Carbon-bridged cyclonucleosides (C-cyclonucleosides) have served as conformational probes for stereochemical investigation of nucleosides and nucleotides.[2] We have been focusing on the synthesis of C-cyclonucleosides starting from naturally occurring nucleosides. However, other access to C-cyclonucleosides is needed, especially for large-scale preparation. We have recently reported the synthesis of 6,3′-methano derivatives of uridine, cytidine, 2′-deoxycytidine,[3] and thymidine[4] by condensation of a 3-pentulofuranose and a 6-methylpyrimidine followed by an intramolecular glycosylation as the key step.

We describe here a new route to the synthesis of 6,6′-cyclo-5′,6′-dideoxyhexofuranosyluracil[5] and related nucleosides[6] starting from a ribose-5-aldehyde and a 6-methylpyrimidine. We also summarize the discussion on the relationship of the circular dichroism (CD) spectral pattern and the glycosyl torsion angle (χ) of C-cyclopyrimidine nucleosides.[7]

Treatment of the lithio derivative of 6-methyl-2,4-dimethoxypyrimidine (**1**)[3] with methyl 2,3-*O*-isopropylidene-β-D-ribopentodialdo-1,4-furanoside[8] (**2**) at −40 °C gave the adduct (**3**) in 65% yield as a diastereomeric mixture. The 5-hydroxy group of **3** was removed by way of conversion to the 5-imidazolylthiocarbonate and successive reduction with tributyltin hydride to give **4** in 59% yield. The removal of the 5-hydroxy group of **3** was found to be necessary; with this hydroxy group (or protected hydroxy group) present, the dehydration took place in a later step involving the intramolecular glycosylation (data not shown). Since this was the case, another route to the preparation of **4** was to perform the Peterson reaction[9] with **1** and **2** followed by hydrogenation of the olefinic bond.

Thus, **1** was converted to the 6-trimethylsilylmethylpyrimidine (**5**), which was condensed with **2** in the presence of lithium diisopropylamide (LDA) and ceric chloride.[9c,d] The product was a mixture of **6** and the silanol (**6A**) as judged by nuclear magnetic resonance (NMR) measurement. The mixture was then treated with potassium hydride in tetrahydrofuran (THF) to ensure dehydration. However, the product, isolated in crystalline form, turned out to be a condensed pyrimidopyridine derivative (**7**). The structure of **7** was confirmed by NMR and mass spectrum (MS) measurement as well as by elemental analysis (see

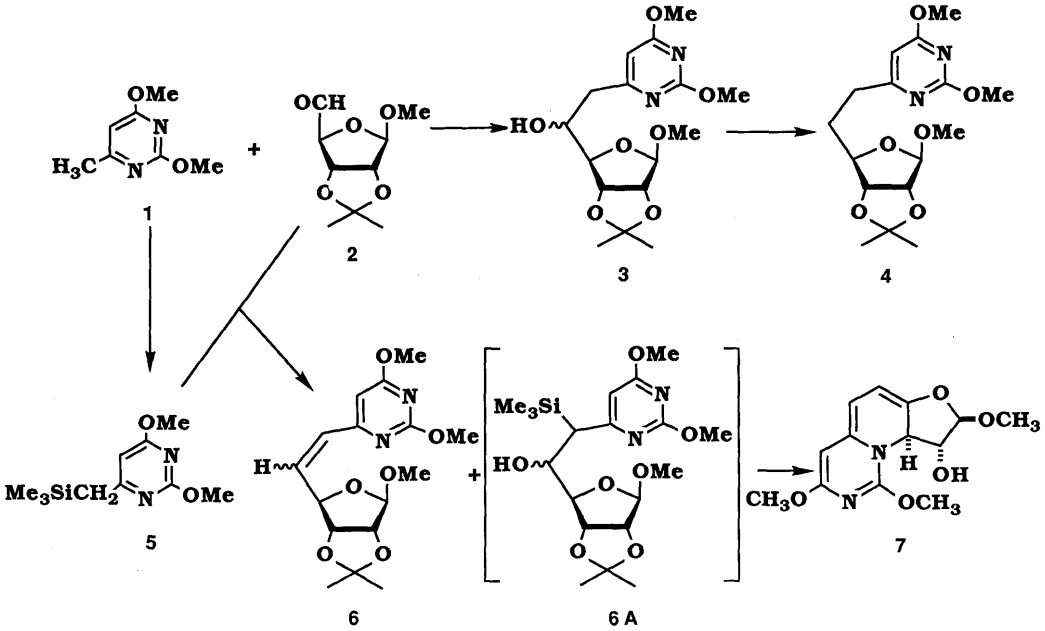

Chart 1

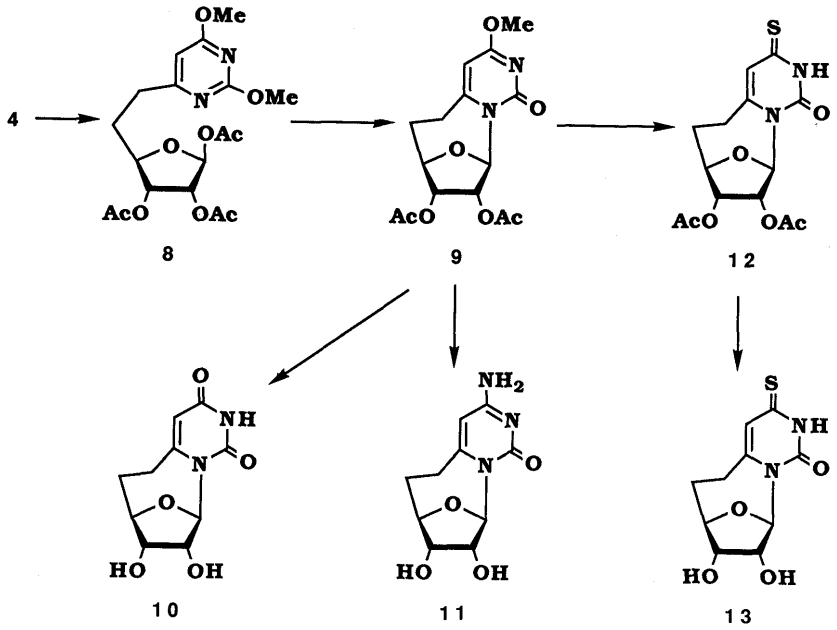

Chart 2

Experimental). The dissociation of the H-4 of **6** by the strong base must have initiated the nucleophilic attack of N-1 on C-3.

Therefore, the elimination of the silanol (**6A**) was promoted by acetylation of the hydroxy group of **6A** in the mixture with **6** by treatment with acetyl chloride and diisopropylethylamine, followed by treatment with tetrabutylammonium fluoride to furnish the olefin (**6**) as an *E,Z* mixture (74% yield, 2.2 : 1). Compound **6** could be separated by chromatography to give **6**-*E* and **6**-*Z*, the structure of each being confirmed by NMR and mass (MS) spectral analyses. Compound **6** was hydrogenated over Pd–carbon to give **4** (86% yield) as a foam. The physical properties of the product (**4**) were identical with those of the product obtained by the aforementioned route. This approach is superior to the other in that it eliminates a somewhat laborious separation of tributyltin compounds formed in the deoxygenation step of the former procedure.

Compound **4** was next subjected to acid hydrolysis to remove the sugar-protecting group by treatment with trifluoroacetic acid, then the hydrolyzate was acetylated to give the tri-*O*-acetate (**8**). Intramolecular glycosylation of **8** by treatment with stannic chloride[10] in acetonitrile at room temperature gave the product (**9**) as a foam. The ultraviolet (UV), MS and NMR data were consistent with the structure **9**. The "*endo*"-puckering of the carbon bridge (*i.e.*, *gauche–gauche* conformation at C-5′) of **9** was confirmed by an nuclear Overhauser effect (NOE) experiment showing NOE between H-3′ and H-6′ (3.6%), and H-3′ and H-5′ (2.7%), respectively. Compound **9** was converted to the uridine, cytidine and 4-thiouridine counterparts by the following procedures.

Deprotection of **9** by treatment with aqueous sodium hydroxide in dioxane afforded the cyclouridine (**10**) as a foam; the physical data were identical with those of an authentic sample.[5] Treatment of **9** with methanolic ammonia in a stainless steel tube at 100 °C overnight afforded the cyclocytidine (**11**) which was crystallized as the hydrochloride salt. Treatment of **9** with liquid hydrogen sulfide in pyridine[11] for 3 d at 60 °C was effective to convert the 4-methoxy group to the 4-thio group, to give the di-*O*-acetate of the cyclo-4-thiouridine (**12**) in crystalline form. Deacetylation of **12** with methanolic triethylamine at room temperature furnished the cyclo-4-thiouridine (**13**).

The procedure described here seems to be a versatile alternative method for the synthesis of pyrimidine nucleosides fixed in an *anti* form by one methylene bridge between the 5′- and 6-positions.

We shall next consider the features of the CD spectra of 6,6′-cyclopyrimidine nucleosides in relation to those of other cyclouridines. As we have discussed in previous papers,[3,12] the sign and magnitude of the CD spectra of C-cyclouridines are a function of their glycosyl torsion angle [χ, for O1′–C1′–N1–C6]. Whereas the cyclouridines fixed by a 6,5′-bridge[2,13] exhibited strong positive CD bands (θ, +10000—+19000) around their main absorption regions, the cyclouridines bridged by 6,3′-methano,[3,4,14] 6,2′-methano,[15] and 6,2′-ethano[12] linkages showed strong negative bands (θ, −18000—−20000). The CD spectra of 6,6′-cyclouridine[5] (**10**) showed an intermediate pattern having a negative band (θ at 240 nm, −10300) at a shorter wavelength region than the main absorption region (UV λ_{max}, 266 nm). Moreover, in the case of the 2′,3′-*O*-isopropylidene derivative of **9**, a weak positive band at 275 nm (θ, +2900) was observed along with the negative band at 245 nm (θ, −13000).[5]

It is evident that the glycosyl torsion angle of **10** is intermediate between of that of 6,5′-cyclo and 6,3′-methano derivatives, since the stable conformation of **10** at the 5′-position is expected to be *gauche–gauche*, as depicted in Fig. 1, on the basis of the NOE experiment of **9** as well as the X-ray analysis of **10**.[16] As the conformation at the 4′-5′-6′-6 linkage of **10** (that reflects the χ-value) is expected to be more flexible than in the rest of the cyclonucleosides, the difference between the θ values of **10** and its isopropylidene derivative may be due to a slight change of the glycosyl torsion angle.

It is therefore of interest to measure the CD spectra of

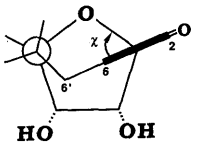

Fig. 1. Conformation of 6,6′-Cyclopyrimidine Nucleosides

other 6,6′-cyclopyrimidine nucleosides in addition to **10**. The cyclocytidine (**11**) in neutral solution showed no extreme of the CD band around the main absorption region (275 nm) and showed negative ellipticity at the shorter wavelength region around 218 nm ($\theta = -29000$). By contrast, the protonated form of **11** showed a weak positive band at 275 nm ($\theta = +3000$). The cyclo-4-thiouridine (**13**) exhibited a weak negative band at the main absorption region ($\theta = -1600$ at 330 nm). Thus, all the 6,6′-cyclopyrimidine nucleosides showed very weak CD bands at their main absorption regions with either positive or negative sign, probably because their χ-values are very close to the transitional angle for the reversal of the sign of the CD bands.

Therefore, it can be stated, in general, that the usual pyrimidine nucleosides of *anti* conformation show positive CD bands like 6,5′-cyclouridine ($\chi = 38°$[16]), and have the average glycosyl torsion angle smaller than 63° (which is the measured value of **10** by the X-ray analysis[16]). Pyrimidine nucleosides of *anti* conformation having the glycosyl torsion angle greater than that will show negative CD bands like 6,3′-methanouridine ($\chi = 88.1°$[16]) and 2′-deoxy-6,2′-ethanouridine ($\chi = 88.1°$[16]). Therefore, the transitional glycosyl torsion angle will be around 60°. If the pyrimidine nucleosides adopt *syn*-conformation, there will be another set of torsion angle region showing positive and negative CD bands.

Experimental

Melting points were determined on a Yanagimoto Mp-3 micro melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL FX-100FT or FX-200FT spectrometer in $CDCl_3$, D_2O, or DMSO-d_6 as the solvent with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ), and signals are described as s (singlet), d (doublet), t (triplet), m (multiplet) or br (broad). All exchangeable protons were confirmed by addition of D_2O. UV spectra were recorded with a Shimadzu UV-240 spectrophotometer. MS were measured on a JEOL D-300 spectrometer. CD spectra were recorded on a JASCO J-500A spectropolarimeter at room temperature. Thin layer chromatography (TLC) was carried out on Merck pre-coated plates $60F_{254}$. Silica gel for column chromatography was SIL-60A 230/70 mesh.

Methyl 5-(2,4-Dimethoxypyrimidin-6-yl)methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (3) 2,4-Dimethoxy-6-methylpyrimidine[3] (**1**, 2.48 g, 16.1 mmol) was dissolved in THF (100 ml) and the solution was cooled to −48 °C. BuLi (11.5 ml of 1.54 M solution in hexane, 1.1 eq) was then added dropwise, and the solution was kept for 30 min with stirring in an Ar atmosphere. Compound **2** (3.26 g, 16.1 mmol) in THF (20 ml) was slowly added to the above solution through a syringe and the whole was stirred for 2 h at −43 °C. After neutralization by addition of AcOH, the solution was brought to room temperature and the solvent was removed *in vacuo*. The residue was partitioned between AcOEt and H_2O, the organic layer was separated, dried over Na_2SO_4, and filtered, and the filtrate was concentrated. This was applied to a column of silica gel (6.6 × 12 cm) and the column was eluted with 10—20—40% AcOEt in hexane. The eluate containing the product was concentrated to leave **3** as a syrup (3.7 g, 65%). UV λ_{max}^{MeOH} nm: 260. MS *m/z*: 356 (M^+), 341, 325, 183, 154. ^{1}H-NMR ($CDCl_3$): 6.29 (1H, s, H-5), 4.97 (2H, m, H-1′ and H-2′), 4.59 (1H, d, H-3′, $J_{2',3'} = 6.2$ Hz), 4.11 (1H, d, H-4′, $J_{4',5'} = 6.6$ Hz), 4.05—3.97 (1H, m, H-5′), 3.97, 3.96 (3H each, s, MeO-2 and 4), 3.29 (3H, s, MeO-1′), 2.94 (1H, dd, H-6′a, $J_{6'a,b} = 14.7$ Hz, $J_{5',6'a} = 3.7$ Hz), 2.77 (1H, dd, H-6′b, $J_{5',6'b} = 7.7$ Hz), 1.48, 1.33 (3H each, s, Me_2C).

Methyl 5-Deoxy-5-(2,4-dimethoxypyrimidin-6-yl)methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (4) Method A) A mixture of **3** (0.7 g, 1.97 mmol) and thiocarbonyldiimidazole (1.17 g, 5.9 mmol) in *N,N*-dimethylformamide (DMF) (5 ml) was stirred at room temperature for 2 d. The solvent was removed and the residue was dissolved in AcOEt. This solution was washed five times with H_2O and the organic layer was dried over Na_2SO_4. The solvent was removed *in vacuo*, the residue was taken up in toluene (15 ml), Bu_3SnH (2.65 ml, 9.85 mmol) and azobisisobutyronitrile (AIBN, 10 mg) were added, and the whole was stirred at 100 °C for 1 h under an Ar atmosphere. After evaporation of the solvent, the residue was chromatographed on silica gel (2.3 × 21 cm, eluted with 5—10—20% AcOEt in hexane). Evaporation of the solvent of appropriate combined fractions left **4** (464 mg, 69.4%) as a syrup.

Method B) from **6**. Compound **6**-*E,Z* (2.50 g, 7.4 mmol) was hydrogenated over 10% Pd–C (300 mg) in AcOEt (40 ml) at room temperature overnight under atmospheric pressure. Pd–C was filtered off, the filtrate was concentrated, and the residue was applied to a column of silica gel (2.8 × 16 cm). The eluate with 10—20% AcOEt in hexane was concentrated to leave **4** (2.17 g, 86%). UV λ_{max}^{MeOH} nm: 258. MS *m/z*: 340 (M^+), 325, 251, 193, 154. ^{1}H-NMR ($CDCl_3$): 6.23 (1H, s, H-5), 4.97 (1H, s, H-1′), 4.62 (1H, d, H-2′, $J_{2',3'} = 5.9$ Hz), 4.56 (1H, d, H-3′), 4.17 (1H, t, H-4′, $J_{4',5'} = 7.7$ Hz), 2.75 (1H, ddd, H-6′a, $J_{5'a,6'a} = 6.6$ Hz), 2.70 (1H, ddd, H-6′b, $J_{5',6'b} = 6.6$ Hz, $J_{6'a,b} = 13.5$ Hz). 1.96 (2H, q, H-5′), 1.48, 1.31 (3H each, s, Me_2C).

Pyrimidopyridoxolane Derivative (7) Compound **5** was prepared by the procedure reported for the synthesis of 2-(trimethylsilylmethyl)pyridine.[17] BuLi (3.1 ml of 1.6 M in hexane, 5.0 mmol) was added dropwise to a solution of **1** (770 mg, 5 mmol) in THF (40 ml) at −35 °C. After stirring for 30 min, the whole was cooled down to −80 °C. Chlorotrimethylsilane (0.67 ml, 5.28 mmol in 10 ml of THF) was slowly added to the solution at −80 °C with stirring. After 1.5 h, 1 N NH_4Cl in H_2O (50 ml) was added and the whole was brought to room temperature, then ether (100 ml) was added and the organic layer was separated. The aqueous layer was extracted with ether three times and the combined organic layer was washed with saturated NaCl solution, then dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue containing **5** was immediately used for the next step without further purification.

Compound **5** thus obtained (estimated as 5 mmol) was dissolved in THF (10 ml), cooled to −35 °C and added dropwise to a solution of LDA (5.0 mmol in 40 ml of THF, −35 °C) under an Ar atmosphere, then the whole was cooled down to −70 °C. A suspension of $CeCl_3$ (prepared from 1.94 g of $CeCl_3 \cdot 7H_2O$, 5.2 mmol) in THF[9c] (15 ml) was added to the solution and the whole was kept stirring for 30 min at −70 °C. Compound **2** (1.03 g, 5.0 mmol) in THF (10 ml) was slowly added to the solution at that temperature and the mixture was kept stirring overnight. The reaction mixture was brought to room temperature and saturated $NaHCO_3$ solution was added with vigorous stirring for 5 min. The precipitate was removed by filtration through a celite bed, and the filtrate was extracted four times with ether. The combined extract was dried over Na_2SO_4, then concentrated, and the residue was chromatographed on silica gel (3.7 × 14 cm, eluted with 5—10% AcOEt in hexane). The eluate was concentrated to leave a mixture of **6** and **6A** as a syrup (1.42 g). This was dissolved in THF (30 ml), KH (80 mg, 2.0 mmol in 10 ml of THF) was added to the solution on an ice water-bath, and the mixture was kept stirring for 1 h then another 1 h at room temperature. The solution was mixed with 1 N NH_4Cl and extracted with ether four times. The combined extract was washed with saturated NaCl, then dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (5.1 × 7 cm, eluted with 20—40% AcOEt in hexane). The eluate was concentrated to leave **7** (710 mg, 50.7%). Analytically pure **7** was obtained by crystallization from EtOH–hexane, mp 124—124.5 °C. UV λ_{max}^{MeOH} nm: 313, $\lambda_{max}^{1\,N\,HCl}$ nm: 330. MS *m/z*: 280 (M^+), 262, 220, 191. ^{1}H-NMR ($CDCl_3$): 7.32 (1H, d, H-5′, $J_{5',6'} = 15.4$ Hz), 6.82 (1H, d, H-6′), 6.29 (1H, s, H-5), 5.42 (1H, d, H-3′, $J_{2',3'} = 2.9$ Hz), 5.26 (1H, d, H-1′), 4.69 (1H, br s, H-2′), 4.02, 3.97 (3H each, s, MeO of base), 3.55 (3H, s, MeO-1′), 1.83 (1H, br d, HO-2′). *Anal.* Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00. Found: C, 55.81; H, 5.97; N, 9.78.

Methyl (5-*E,Z*)-5-Deoxy-5-(2,4-dimethoxypyrimidin-6-yl)methylene-2,3-*O*-isopropylidene-β-D-ribofuranoside (6) Compound **5** (10 mmol), prepared by the method described above, in THF (7 ml) was added dropwise to a solution of LDA in THF (10 mmol, 50 ml) at −35 °C and the mixture was stirred for 40 min. The whole was cooled to −70 °C and a suspension of anhydrous $CeCl_3$ (prepared from 3.91 g of the heptahydrate, 10.5 mmol) in THF (20 ml) was added. After 30 min at −70 °C, **2** (2.19 g, 10.8 mmol) in 10 ml of THF was added and the solution was kept stirring

for 2.5 h. The mixture was taken from the cool bath, and mixed with saturated $NaHCO_3$ solution. The precipitate was filtered off through a celite bed, and the filtrate was extracted with ether three times. The combined ether solution was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (80 ml), diisopropylethylamine (2 ml, 11 mmol) and acetyl chloride (0.71 ml, 10 mmol) were added, and the whole was stirred overnight at room temperature. Saturated $NaHCO_3$ solution was added and the mixture was extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was dissolved in THF (50 ml), Bu_4NF (7 ml of 1 M in THF) was added and the whole was stirred for 20 min at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ether. The ether solution was washed twice with H_2O and saturated NaCl, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (4.9 × 13.5 cm, eluted with 10—20% AcOEt in hexane). The eluate was concentrated to leave **6** (2.50 g, 74%, *E*:*Z* = 2.2:1), contaminated with a trace of **1**. A portion of **6** was rechromatographed on silica gel with 5% AcOEt in hexane to separate **6**-*Z* as a less polar component and **6**-*E* as a more polar component.

Physical Properties of **6**-*Z*: UV λ_{max}^{MeOH} nm: 285. MS *m/z*: 338 (M^+), 323, 210, 195. Exact MS: Calcd for 338.14786. Found: 338.14837. ^{1}H-NMR ($CDCl_3$): 6.29 (1H, s, H-5), 6.22 (1H, dd, H-6′, $J_{5',6'}$ = 11.7 Hz, $J_{3',6'}$ = 1.1 Hz), 6.13 (1H, d, H-4′), 6.04 (1H, dd, H-5′, $J_{4',5'}$ = 8.1 Hz), 5.04 (1H, d, H-2′), 4.68 (1H, d, H-3′, $J_{2',3'}$ = 5.9 Hz), 4.06, 3.96 (3H each, s, MeO-2 and 4), 3.41 (3H, s, MeO-1′), 1.48, 1.29 (3H each, s, Me_2C).

Physical Properties of **6**-*E*: UV λ_{max}^{MeOH} nm: 286. MS *m/z*: 338 (M^+), 323, 220, 195, 179. Exact MS: Calcd for 338.14786. Found: 338.14826. ^{1}H-NMR ($CDCl_3$): 6.98 (1H, dd, H-5′, $J_{5',6'}$ = 15.6 Hz, $J_{4',5'}$ = 7.7 Hz), 6.46 (1H, dd, H-6′, $J_{3',6'}$ = 1.1 Hz), 6.24 (1H, s, H-5), 5.05 (1H, s, H-1′), 4.83 (1H, d, H-4′), 4.73 (1H, dd, H-3′, $J_{2',3'}$ = 5.9 Hz), 4.66 (1H, d, H-2′), 4.00, 3.96 (3H each, d, MeO-2 and 4), 3.38 (3H, s, MeO-1′), 1.52, 1.33 (3H each, s, Me_2C).

5-Deoxy-5-(2,4-dimethoxypyrimidin-6-yl)methyl-1,2,3-tri-*O*-acetyl-β-D-ribofuranose (8) Compound **4** (1.28 g, 3.76 mmol) was dissolved in trifluoroacetic acid (70%, 10 ml) and the mixture was stirred for 4 h. The solvent was removed *in vacuo* and the residual acid was removed by co-distillation with toluene three times. The residue was taken up in acetonitrile and to this solution, Ac_2O (3 ml) and Et_3N (12 ml) were added. The mixture was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between AcOEt and H_2O. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was chromatographed on silica gel (2.8 × 16 cm, eluted with 20—30% AcOEt in hexane). The eluate was concentrated to leave **8** (1.11 g, 72%) as a foam. MS *m/z*: 412 (M^+), 293, 251, 233, 154. ^{1}H-NMR ($CHCl_3$): 6.22 (1H, s, H-5), 6.14 (1H, d, H-1′, $J_{1',2'}$ = 1.0 Hz), 5.34 (1H, dd, H-2′, $J_{2',3'}$ = 4.6 Hz), 5.22 (1H, dd, H-3′, $J_{3',4'}$ = 11.2 Hz), 4.29—4.01 (1H, m, H-4′), 3.97, 3.95 (3H each, s, MeO-2 and 4), 2.82—2.63 (2H, m, H-5′), 2.29—1.86 (2H, m, H-6′), 2.11, 2.10, 2.04 (3H each, s, AcO).

2′,3′-Di-*O*-acetyl-6,6′-cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)-4-methoxypyrimidin-2-one (9) Compound **8** (1.11 g, 2.69 mmol) in acetonitrile (10 ml) was added to a solution of $SnCl_4$ (0.38 ml, 3.23 mmol) in acetonitrile (30 ml) in an ice-water bath. The mixture was stirred at room temperature for 2.5 h. After removal of the solvent *in vacuo*, the residue was taken up in $CHCl_3$, then saturated $NaHCO_3$ solution (50 ml) was added, and the mixture was stirred vigorously. The precipitate was filtered off through a celite bed and the organic layer was separated. The aqueous layer was neutralized by addition of 2 N HCl, then extracted with $CHCl_3$ several times. The combined organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (2.4 × 15 cm, eluted with 1% EtOH in $CHCl_3$) to give **9** (600 mg, 66%) as a foam. UV λ_{max}^{MeOH} nm: 280. MS *m/z*: 338 (M^+), 279, 166, 140. Exact MS: Calcd for 338.1144. Found: 338.1127. ^{1}H-NMR ($CDCl_3$): 7.04 (1H, d, H-2′, $J_{1',2'}$ = 1.8 Hz), 5.77 (1H, s, H-5), 5.49 (1H, dd, H-2′, $J_{2',3'}$ = 6.2 Hz), 5.36 (1H, d, H-3′), 4.56 (1H, t, H-4′, $J_{4',5'}$ = 3.7 Hz), 3.94 (3H, s, MeO-4), 2.89 (1H, ddd, H-6′a, $J_{6'a,b}$ = 16.1 Hz), $J_{5',6'a}$ = 4.0, 4.8 Hz), 2.69 (1H, ddd, H-6′b, $J_{5',6'b}$ = 4.8, 11.4 Hz), 2.17—2.01 (2H, m, H-5′), 2.14, 2.13 (3H each, s, AcO-2′ and 3′).

6,6′-Cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)uracil (10) A solution of **9** (300 mg, 0.89 mmol) in dioxane (4 ml) and 2 N NaOH (4 ml) was heated at 100 °C for 20 min. After cooling, the solution was neutralized by addition of Dowex 50W-X8 (H^+ form). The resin was filtered off and the filtrate was concentrated. The residue was dissolved in a small volume of EtOH and this solution was adsorbed on silica gel (10 g). The gel was dried and placed on top of a column of silica gel (2.4 × 8 cm). The column was eluted with 30% EtOH in $CHCl_3$. The eluate was concentrated to leave **10** (140 mg, 66%) as a solid. The physical properties were identical with those of an authentic sample.[5] ^{1}H-NMR (DMSO-d_6): 11.29 (1H, br s, HN-3), 6.33 (1H, d, H-1′, $J_{1',2'}$ = 1.7 Hz), 5.62 (1H, br s, H-5), 5.37 (1H, d, HO-2′, *J* = 7.2 Hz), 5.15 (1H, d, HO-3′, *J* = 4.9 Hz), 4.52—4.48 (1H, m, H-2′, $J_{2',3'}$ = 6.0 Hz), 4.31 (1H, br s, H-4′), 4.14—4.10 (1H, m, H-3′), 2.75—2.53 (2H, m, H-6′), 1.91—1.70 (2H, m, H-5′).

6,6′-Cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)cytosine (11) Hydrochloride A solution of **9** (300 mg, 0.89 mmol) in MeOH saturated with ammonia (30 ml) was heated at 100 °C for 22 h in a sealed tube. The solvent was removed *in vacuo* and the residue was dissolved in H_2O. This solution was applied to a column of Dowex 50W × 8 (H^+ form, 1.7 × 11.5 cm). The column was eluted with 1 N NH_4OH and the eluate was concentrated *in vacuo* to leave **11** (200 mg, 94%). A small portion of **11** was dissolved in 1 N HCl, then evaporated, and the residue was crystallized from MeOH to give the HCl salt of **11**, mp 210 °C (dec.). UV $\lambda_{max}^{H_2O}$ nm (ε): 276, (9700); $\lambda_{max}^{0.1\,N\,HCl}$ nm (ε): 283, (14000). CD (H_2O) [θ] (nm): 0 (275), −29000 (218); (0.1 N HCl) nm: 3000 (275). MS for **11** *m/z*: 239 (M^+), 210, 125. ^{1}H-NMR (DMSO-d_6) for **11**: 7.03 (2H, br d, H_2N-4), 6.51 (1H, d, H-1′, $J_{1',2'}$ = 1.5 Hz), 5.59 (1H, s, H-5), 5.27 (2H, br s, HO-2′ and 3′), 4.40 (1H, dd, H-2′, $J_{1',2'}$ = 1.5 Hz, $J_{2',3'}$ = 5.9 Hz), 4.27 (1H, t, H-4′, $J_{4',5'}$ = 2.6 Hz), 4.09 (1H, d, H-3′, $J_{2',3'}$ = 5.9 Hz), 2.61—2.56 (2H, m, H-6′), 1.87—1.64 (2H, m, H-5′). *Anal.* Calcd for $C_{10}H_{14}ClN_3O_4$: C, 43.57; H, 5.12; Cl, 12.86; N, 15.24. Found: C, 43.49; H, 5.16; Cl, 12.73; N, 15.16.

2′,3′-Di-*O*-acetyl-6,6′-cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)-4-thiouracil (12) Compound **9** (160 mg, 0.473 mmol) in pyridine (4 ml) was mixed with liquid H_2S in pyridine (13 ml in 5 ml) in a steel tube[11] and the whole was kept at 60 °C for 3 d. The tube was opened and flushed with N_2 gas. The solvent was removed *in vacuo*, then the residue was taken up in toluene and evaporated twice from toluene. The final residue was chromatographed on silica gel (1.7 × 7 cm, eluted with 30—60% AcOEt in hexane). The eluate was concentrated and the residue was crystallized from EtOH to give **12** (126 mg, 87%), mp > 200 °C (sublimed). UV λ_{max}^{MeOH} nm: 332. MS *m/z*: 340 (M^+), 298, 209, 167, 142. ^{1}H-NMR ($CDCl_3$): 9.24 (1H, br s, HN-3), 6.73 (1H, d, H-1′, $J_{1',2'}$ = 1.8 Hz), 6.35 (1H, s, H-5), 5.51 (1H, dd, H-2′, $J_{2',3'}$ = 6.2 Hz), 5.37 (1H, d, H-3′), 4.61 (1H, m, H-4′), 2.80—2.58 (2H, m, H-6′), 2.14 (6H, s, AcO-2′ and 3′), 2.14—2.05 (2H, m, H-5′). *Anal.* Calcd for $C_{14}H_{16}N_2O_6S$: C, 49.14; H, 4.74; N, 8.23; S, 9.42. Found: C, 49.53; H, 4.67; N, 8.07; S, 9.32.

6,6′-Cyclo-5′,6′-dideoxy-1-(β-D-allofuranosyl)-4-thiouracil (13) A solution of **12** (102 mg, 0.300 mmol in MeOH (10 ml) containing 0.5 ml of Et_3N was stirred for 18 h at room temperature. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (1.7 × 5.5 cm, eluted with 4—8% MeOH in $CHCl_3$). The eluate was concentrated and the residue was crystallized from EtOH–H_2O to give **13** (59 mg, 77%), mp 185—186 °C. UV $\lambda_{max}^{H_2O}$ nm (ε): 335 (23700). CD (H_2O) [θ] nm: −1600 (330). MS *m/z*: 256 (M^+), 167, 142, 124. ^{1}H-NMR (DMSO-d_6): 12.65 (1H, br s, HN-3), 6.38 (1H, s, H-5), 6.30 (1H, d, H-1′, $J_{1',2'}$ = 1.1 Hz), 5.41 (1H, d, HO-2′, *J* = 7.7 Hz), 5.20 (1H, d, HO-3′, *J* = 4.4 Hz), 4.58—4.54 (1H, m, H-2′, $J_{2',3'}$ = 6.0 Hz), 4.34 (1H, br s, H-4′), 4.15—4.11 (1H, m, H-3′), 2.76—2.53 (2H, m, H-6′), 1.92—1.68 (2H, m, H-5′). *Anal.* Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.87; H, 4.72; N, 10.93; S, 12.51. Found: C, 46.92; H, 4.76; N, 10.95; S, 12.48.

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References and Notes

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