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Alternative Synthesis of 2′-Deoxy-6,2′-methano-pyrimidine Nucleosides (Nucleosides and Nucleotides. XC[1])

Yuichi YOSHIMURA, Akira MATSUDA, and Tohru UEDA*

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan. *Received August 19, 1989*

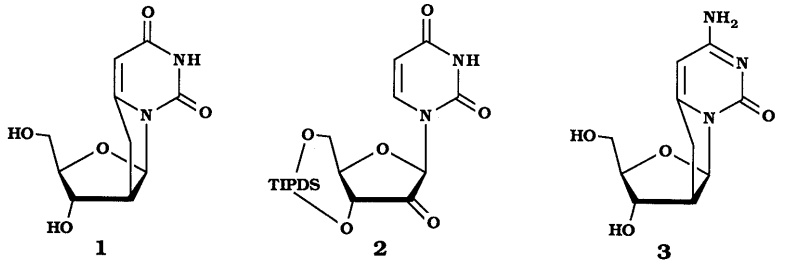
An alternative method for the synthesis of 2′-deoxy-6,2′-methanouridine (1), -cytidine (3) and -4-thiouridine (13) is described which involves a condensation of an isopropyl β-D-2-pentuloside (5) and a carbanion formed from 6-trimethylsilylmethylpyrimidine (6), followed by intramolecular glycosylation.

Keywords carbon-bridged cyclonucleoside; 2′-deoxy-6,2′-methanouridine; 2′-deoxy-6,2′-methanocytidine; 2′-deoxy-6,2′-methano-4-thiouridine; Peterson olefination; intramolecular glycosylation; ketosugar; nucleoside conformation

The *syn–anti* conformation of nucleosides around the glycosyl linkages is important in exhibiting biological activities, *e.g.*, for a substrate or inhibitor of enzymes utilizing nucleosides or nucleotides. For stereochemical studies of the interaction of nucleosides and nucleotides with enzymes utilizing them, nucleosides with glycosyl torsion angles fixed at various values would be useful. Such fixation would be realized in cyclonucleosides. We have prepared a variety of such nucleosides having a carbon bridge between the base and sugar portions, the *C*-cyclonucleosides.[2] For example, 2′-deoxy-6,2′-methanouridine (**1**) can be regarded as a conformer of 2′-deoxyuridine fixed in a high-*anti* conformation. This compound has been prepared[3] from a 2′-ketouridine (**2**) by a multistep conversion involving carbonbridge formation in the final step.

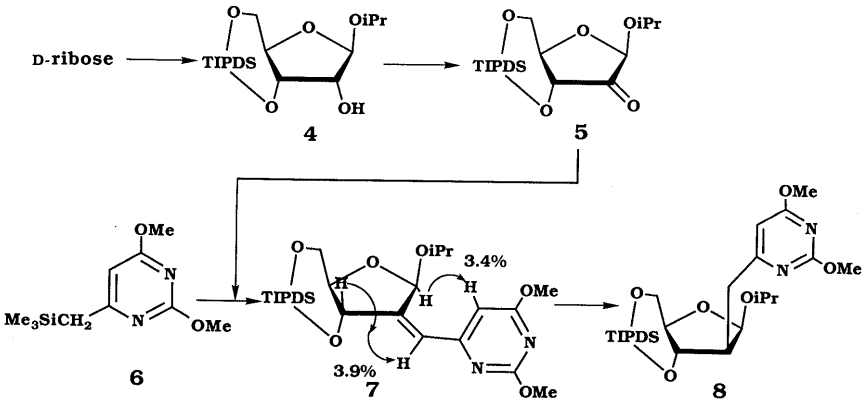
We have recently reported[4] a new route to the *C*-cyclonucleosides starting from a keto sugar and a suitable pyrimidine, constructing a carbon–carbon linkage at first followed by an intramolecular glycosylation in a later step. By this procedure, 6,3′-methanouridines[4] and 6,5′-methanouridines[5] have been readily prepared. This paper describes an alternative synthesis of 2′-deoxy-6,2′-methano-pyrimidine nucleosides including 2′-deoxy-6,2′-methanocytidine (**3**, Chart 1). A preliminary account of this work has appeared.[6]

The strategy to construct a *C*-cyclopyrimidine nucleoside with a 6,2′-methano bridge is to condense a suitable 2-ketoribose with a 6-methylpyrimidine derivative, followed by an intramolecular glycosyl bond formation. For this purpose we employed an isopropyl β-D-*erythro*-2-pentulofuranoside as a starting sugar part. Thus, D-ribose was converted to isopropyl β-D-ribofuranoside, which was 3′,5′-bis-silyl protected to give **4** (Chart 2) in a crystalline form by treatment with 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-disiloxane. The choice of the β-isopropyl ribofuranoside was to assure a stereospecific hydrogenation as well as a ready deprotection



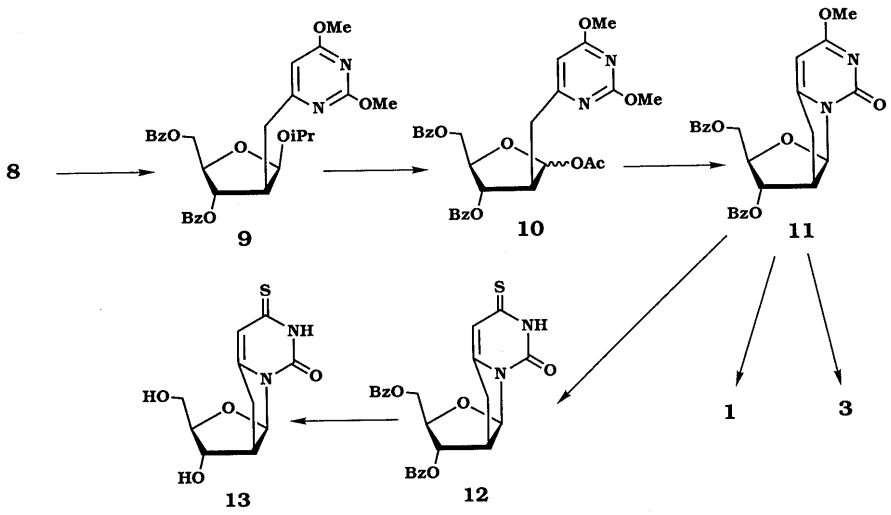
TIPDS = 1,1,3,3-tetraisopropyldisiloxan-1,3-diyl

Chart 1



iPr = isopropyl

Chart 2



Bz = benzoyl

Chart 3

in later steps. Compound **4** was oxidized by chromium trioxide–pyridine complex[7] to give the 2-pentuloside (**5**).

Condensation of **5** with 2,4-dimethoxy-6-trimethylsilylmethylpyrimidine[5] (**6**) in the presence of butyllithium at −60 °C proceeded to afford a Peterson olefination[8] product, the 2-pyrimidinylmethylene compound (**7**), in good yield. The (*Z*)-geometry of the olefin **7** was confirmed by proton nuclear magnetic resonance (^{1}H-NMR) analysis showing nuclear Overhauser effect (NOE) between H-3′ and H-2″ (3.9%), and between H-6 and H-1′ (3.4%) of **7**. The red shift in the ultraviolet (UV) absorbance of **7** also supports the conjugation of the pyrimidine nucleus with an olefin. Catalytic hydrogenation of **7** with Pd–charcoal in ethyl acetate overnight afforded the 2*C*-pyrimidinylmethyl-*arabino*-furanoside (**8**) in high yield. The analysis of the crude reaction product by ^{1}H-NMR showed the presence of the 2-α-product in a β/α ratio of *ca.* 9 : 1. The β-product **8** was isolated after chromatographic separation. The stereochemistry at the 2-position of **8** was fully elucidated by the X-ray analysis of one of the final cyclonucleosides. When the methyl β-pentofuranoside corresponding to **7** was hydrogenated in a similar manner, no stereoselective hydrogenation occurred (data not shown), indicating an important role of the bulkier protection (such as isopropyl) at the 1-β-position of the sugar to assure hydrogenation from the α side of the sugar ring of **7**.

The silyl protecting group of **8** was removed by treatment with tetrabutylammonium fluoride and then the product was benzoylated with benzoic anhydride to give the 3′,5′-di-*O*-benzoate (**9**) (Chart 3). Several attempts at the direct intramolecular glycosylation of **9** met with little success, then the isopropoxy group of **9** was converted to the acetoxy group by treatment with trifluoroacetic acid for 65 h at room temperature, followed by acetic anhydride, leading to an anomeric mixture of the 1-*O*-acetate (**10**). The removal of the isopropoxy group of **9** under acidic conditions proceeded well as compared to the methoxy counterpart. In the latter case, the benzoyl groups were also removed and, hence, furanosyl to pyranosyl isomerization took place (data not shown).

The intramolecular glycosylation was carried out by treatment of **10** with stannic chloride in acetonitrile at room temperature for 3 h, giving the 4-*O*-methyl-6,2′-methanouridine derivative (**11**) in good yield. Having obtained the 4-*O*-methyl derivative, this was readily converted to a series of pyrimidine nucleosides. Treatment of **11** with sodium hydroxide in aqueous dioxane afforded 2′-deoxy-6,2′-methanouridine (**1**). The physical constants of **1** were in good agreement with those of the compound previously prepared by another route.[3] The X-ray analysis of **1** clearly showed that the compound had the β-configuration.[9] Treatment of **11** with methanolic ammonia in a sealed tube at 100 °C for 22 h gave 2′-deoxy-6,2′-methanocytidine (**3**) in a crystalline form. The sulfhydrolysis[5,10] of **11** with liquid H_2S–pyridine at 60 °C for 3 d gave the crystalline 4-thio derivative (**12**) in high yield. The red shift of the UV absorption maximum (331 nm) of **12** is characteristic of a 4-thiouridine compound. The deprotection of **12** with sodium methoxide in methanol gave 2′-deoxy-6,2′-methano-4-thiouridine (**13**).

In conclusion, the present result provides a further example of a versatile route for the synthesis of *C*-cyclonucleosides. The 6,2′-methano-pyrimidine nucleosides described here will be useful for further conformational analysis of nucleosides. The nature of the circular dichroism (CD) spectrum of these *C*-cyclonucleosides has been reported in previous papers.[3,5]

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-270FT spectrometer 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 measured with a Shimadzu UV-240 spectrophotometer. CD spectra were recorded on a JASCO J-500A spectropolarimeter at room temperature. Mass spectra (MS) were measured on a JEOL D-300 spectrometer. Thin layer chromatography (TLC) was carried out on Merck pre-coated plates $60F_{254}$. The extent of reaction was monitored by TLC of portions of the reaction mixture. Silica gel used for column chromatography was SIL-60A 230/70 mesh.

Isopropyl 3,5-Di-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β-D-ribofuranoside (4) A suspension of D-ribose (5.0 g, 33.3 mmol) in 1% HCl–iso-PrOH (150 ml) was stirred for 2.5 h at room temperature. Et_3N (3 ml) was added to neutralize the solution, then the solvent was removed *in vacuo*. The residue was dried by co-distillation with benzene several times.

The syrup was dissolved in pyridine (100 ml), 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (10.5 ml, 33.3 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*, then the residue was taken up in AcOEt, and washed with H_2O twice. The organic layer was dried over Na_2SO_4, the salt was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in hexane and applied to a column of silica gel (6.4 × 20 cm). The eluate with 10—20% Et_2O in hexane was collected and the solvent was removed *in vacuo* to leave **4** (8.49 g, 58%) as colorless crystals, mp 43.5—45 °C. ^{1}H-NMR ($CDCl_3$): 5.03 (1H, s, H-1), 4.53 (1H, br t, H-3, J=5.13, 5.49 Hz), 4.05—3.79 (5H, m, H-2, 3, 4 and Me_2CH), 2.98 (1H, br d, HO-2, J=0.73 Hz), 1.15—0.99 (34H, m, Me_2C). MS *m/z*: 391 (M−iso-Pr). *Anal.* Calcd for $C_{20}H_{42}O_6Si_2$: C, 55.26; H, 9.74. Found: C, 55.14; H, 9.74.

Isopropyl 3,5-Di-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β-D-*erythro*-2-pentulofuranoside (5) Compound **4** (8.26 g, 19 mmol) in CH_2Cl_2 (130 ml) was treated with CrO_3–pyridine complex[7] [CrO_3 (5.7 g, 57 mmol), pyridine (9.5 ml, 117 mmol), Ac_2O (5.7 ml, 60 mmol)] at room temperature for 3 h. The same amount of CrO_3–pyridine complex was added and the solution was stirred for 1 h. The mixture was added dropwise into hexane–AcOEt (1 : 1, 1.5 l). The precipitate was filtered off through a Celite bed and the filtrate was concentrated. The residue was taken up in hexane and applied to a column of silica gel (7.7 × 11 cm). The eluate with 20% Et_2O in hexane was collected and the solvent was removed *in vacuo* to leave **5** (6.36 g, 77%) as a colorless oil. ^{1}H-NMR ($CDCl_3$): 4.83 (1H, d, H-1, J=0.7 Hz), 4.58 (1H, dd, H-3, $J_{3,4}$=8.4 Hz), 4.15—4.03 (2H, m, H-5), 3.98 (1H, q, Me_2CH, J=6.2 Hz), 3.89—3.83 (1H, m, H-4), 1.22 (6H, dd, Me_2C), 1.19—0.96 (28H, m, iso-Pr). MS *m/z*: 389 (M−iso-Pr), 347, 273.

Isopropyl (*Z*)-2-Deoxy-2*C*-[(2,4-dimethoxypyrimidin-6-yl)methylene]-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β-D-*erythro*-pentofuranoside (7) BuLi (1.55 M in hexane 9.5 ml, 14.7 mmol) was added to a stirred solution of compound **6**, which was prepared from 2,4-dimethoxy-6-methylpyrimidine[5] (2.26 g, 14.7 mmol), in tetrahydrofuran (THF) (100 ml) at −40 °C under an Ar atmosphere, and the whole was stirred for 30 min. After cooling the mixture to −60 °C, **5** (6.36 g, 14.7 mmol) in THF (20 ml) was added dropwise and the whole was kept for 1 h at −60 °C. The bath temperature was raised to room temperature over a period of 1.5 h and H_2O (30 ml) was added. The mixture was extracted with Et_2O three times and the combined ether layer was dried over Na_2SO_4, filtered and concentrated to leave a syrup. This was taken up in hexane and chromatographed on silica gel (5.3 × 18 cm). The eluate with 5—10% Et_2O in hexane was collected and the solvent was removed *in vacuo* to leave **7** (6.35 g, 76%) as a syrup. ^{1}H-NMR ($CDCl_3$): 6.42 (1H, s, H-5), 6.38 (1H, d, vinylic H at C-2′, $J_{2',3'}$=1.5 Hz), 6.23 (1H, s, H-1′), 5.06 (1H, dd, H-3′, $J_{3',4'}$=6.6 Hz), 4.12—3.93 (3H, m, H-5′, Me_2CH), 4.00, 3.97 (3H each, s, MeO), 3.80—3.74 (1H, m, H-4′), 1.23 (6H, d, Me_2C, J=6.2 Hz), 1.10—1.06 (28H, m, iso-Pr). MS *m/z*: 568 (M), 525 (M−iso-Pr). HR-MS Calcd for $C_{27}H_{48}N_2O_7Si_2$: 568.2998. Found: 568.2994. UV λ_{max}^{MeOH} nm: 284, 242 (sh); $\lambda_{max}^{H^+}$ nm: 311 (sh), 299, 290 (sh).

Isopropyl 2-Deoxy-2*C*-[(2,4-dimethoxypyrimidin-6-yl)methyl]-3,5-di-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β-D-*arabino*-pentofuranoside (8) Compound **7** (6.12 g, 10.8 mmol) in AcOEt (150 ml) was hydrogenated over 10% Pd–C (3 g) overnight under atmospheric pressure. Pd–C was removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was taken up in hexane and chromatographed on silica gel (6.3 × 13.5 cm). The eluate with 10% Et_2O in hexane was collected and the solvent was removed *in vacuo* to leave **8** (5.04 g, 82%). ^{1}H-NMR ($CDCl_3$): 6.24 (1H, s, H-5), 4.90 (1H, d, H-1′, J=3.3 Hz), 4.32 (1H, dd, H-3′, J=5.1, 8.1 Hz), 4.02—3.77 (3H, m, H-4′, 5′), 3.98, 3.94 (3H each, s, MeO), 3.72 (1H, dq, Me_2CH, J=6.2 Hz), 2.87—2.79 (3H, m, H-2′, H-2″), 1.12—1.10 (31H, m, Me_2CHO, iso-Pr), 0.91 (3H, d, Me_2C). MS *m/z*: 570 (M), 543 (M−iso-Pr). HR-MS Calcd for $C_{27}H_{50}N_2O_7Si_2$: 570.3156. Found: 570.3140. UV λ_{max}^{MeOH} nm: 256.

Isopropyl 2-Deoxy-3,5-di-*O*-benzoyl-2*C*-[2,4-dimethoxypyrimidin-6-yl)-methyl]-β-D-*arabino*-pentofuranoside (9) Compound **8** (5.04 g, 8.83 mmol) in THF (50 ml) was treated with Bu_4NF (1 M in THF, 17.7 ml, 2 eq) at room temperature for 10 min under stirring. The solvent was removed *in vacuo*, and the residue was dissolved in CH_3CN (50 ml). Bz_2O (5.99 g, 26.5 mmol), 4-dimethylaminopyridine (DMAP, 25 mg), and Et_3N (3.7 ml, 26.5 mmol) were added to the solution and the whole was stirred overnight at room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in AcOEt (200 ml), and washed successively with H_2O, aqueous $NaHCO_3$ (twice), and saturated NaCl solution. The organic layer was dried over Na_2SO_4, the salt was filtered off, and the solvent was removed *in vacuo*. The residue was dissolved in a small volume of AcOEt which was absorbed on a small amount of silica gel. This was dried and then applied on the top of a column of silica gel (6.4 × 95 cm) and chromatographed. The eluate with 10—20% AcOEt in hexane was collected and the solvent was removed *in vacuo* to leave **9** (4.19 g, 88%). ^{1}H-NMR ($CDCl_3$): 8.04—7.89 (4H, m, H-*o*-Bz), 7.58—7.33 (6H, m, H-*m*, *p*-Bz), 6.22 (1H, s, H-5), 5.58 (1H, dd, H-3′, J=5.5, 9.2 Hz), 5.21 (1H, d, H-1′, J=5.1 Hz), 4.66 (1H, dd, H-5′a, $J_{5'a,b}$=11.4 Hz, $J_{4',5'a}$=4.8 Hz), 4.54 (1H, dd, H-5′b, $J_{4',5'b}$=7.3 Hz), 4.43—4.36 (1H, m, H-4′), 3.93—3.81 (1H, m, Me_2CH), 3.93, 3.81 (3H each, s, MeO), 3.25—3.16 (1H, m, H-2′), 2.99 (1H, dd, H-2″a, $J_{2'',a,b}$=14.3 Hz, $J_{2',2''a}$=8.4 Hz), 2.87 (1H, dd, H-2″b, $J_{2',2''b}$=6.6 Hz), 1.14 (6H, d, Me_2C, J=6.2 Hz). MS *m/z*: 536 (M), 493 (M−iso-Pr). HR-MS Calcd for $C_{29}H_{32}N_2O_8$: 536.2159. Found: 536.2147.

1-*O*-Acetyl-2-deoxy-3,5-di-*O*-benzoyl-2*C*-[(2,4-dimethoxypyrimidin-6-yl)methyl]-α,β-D-arabino-pentofuranose (10) Compound **9** (4.07 g, 7.58 mmol) was dissolved in CF_3CO_2H (160 ml) and the solution was kept for 65 h under stirring at room temperature. The solvent was removed *in vacuo* and the residual acid was removed by codistillation with toluene. The residue was taken up in $CHCl_3$ and this solution was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was dissolved in pyridine (80 ml), Ac_2O (1.45 ml, 15.4 mmol) and DMAP (20 mg) were added, and the whole was stirred for 2 h at room temperature. EtOH (5 ml) was added to the mixture, the solvent was removed *in vacuo*, the residue was codistilled twice with toluene, and the final residue was dissolved in AcOEt. This was washed with H_2O and the organic layer was dried over Na_2SO_4. The solvent was removed and the residue taken up in AcOEt was absorbed on a small amount of silica gel, which was then dried. This was applied on top of a column of silica gel (6.4 × 7 cm) and chromatographed. The eluate with 20—40% AcOEt in hexane was collected and the solvent was removed to leave **10** (2.30 g, 57%). ^{1}H-NMR ($CDCl_3$): 8.09—7.87 (4H, m, H-*o*-Bz), 7.63—7.35 (6H, m, H-*m*,*p*-Bz), 6.46 (0.4H, d, H-1′β, J=4.8 Hz), 6.32 (0.6H, s, H-1′α), 6.19 (0.6H, s, H-5α), 6.17 (0.4H, s, H-5β), 5.68 (0.4H, dd, H-3′β, J=6.2, 9.5 Hz), 5.35—5.33 (0.6H, m, H-3′α), 4.75—4.45 (3H, m, H-4′, 5′), 3.91, 3.90, 3.89, 3.80 (6H, total, s, MeO), 3.39—3.36 (0.4H, m, H-2′β), 3.13—3.02 (0.6H, m, H-2′α), 2.97—2.90 (2H, m, H-2″), 2.10 (1.8H, s, AcO-α), 1.99 (1.2H, s, AcO-β). MS *m/z*: 536 (M), 493 (M−iso-Pr), 477, 154. HR-MS Calcd for $C_{28}H_{28}N_2O_9$: 536.1795. Found: 536.1781.

2′-Deoxy-3′,5′-di-*O*-benzoyl-4-*O*-methyl-6,2′-methanouridine (11) Compound **10** (2.30 g, 4.29 mmol) was dissolved in CH_3CN (30 ml) and $SnCl_4$ (0.5 ml, 4.27 mmol in 50 ml of CH_3CN) was added to the solution under cooling in an ice bath. The mixture was stirred for 3 h at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in $CHCl_3$ and vigorously mixed with saturated aqueous $NaHCO_3$. The precipitate was filtered off through a Celite bed. The organic layer was separated, the aqueous layer was extracted with $CHCl_3$, and the combined organic layer was dried over Na_2SO_4. The filtrate was concentrated and the residue was taken up in $CHCl_3$ and chromatographed on silica gel (2.8 × 27 cm). The eluate with $CHCl_3$ was concentrated to leave **11** (1.55 g, 78%) as a pale yellow foam. ^{1}H-NMR ($CDCl_3$): 8.03—7.93 (4H, m, H-*o*-Bz), 7.64—7.36 (6H, m, H-*m*,*p*-Bz), 6.47 (1H, d, H-1′, J=6.2 Hz), 5.74 (1H, s, H-5), 5.29 (1H, dd, H-3′, J=2.4, 4.2 Hz), 4.73—4.67 (1H, m, H-4′), 4.51 (2H, d, H-5′, J=5.1 Hz), 3.95 (3H, s, MeO), 3.43—3.39 (2H, m, H-2″), 3.33—3.25 (1H, m, H-2′). MS *m/z*: 462 (M), 357, 340. HR-MS Calcd for $C_{25}H_{22}N_2O_7$: 462.1427. Found: 462.1410. UV λ_{max}^{MeOH} nm: 272, 228.

2′-Deoxy-6,2′-methanouridine (1) Compound **11** (100 mg, 0.216 mmol) was dissolved in dioxane (2 ml) and 2 N NaOH (2 ml) was added to the solution. The whole was kept at 100 °C for 40 min. After cooling, the solution was neutralized by addition of Dowex 50W-X8 (H^+-form) resin. The resin was filtered off, and washed with MeOH, and the filtrate was concentrated to a small volume. Water was added and the mixture was washed with ether. The aqueous layer was concentrated and the residue was dissolved in a small volume of MeOH, which was absorbed on a small amount of silica gel. This was dried, applied on top of a column of silica gel (1.7 × 4.5 cm) and chromatographed. The appropriate eluate fraction with 4—6—8% MeOH in $CHCl_3$ was collected and the solvent was removed to leave **1** (42 mg, 81%). A pure sample was obtained by crystallization from aqueous MeOH, mp 196—198 °C. ^{1}H-NMR (DMSO-d_6): 11.02 (1H, br s, HN-3), 6.01 (1H, d, H-1′, J=6.1 Hz), 5.40 (1H, s, H-5), 5.38 (1H, br d, HO-3′), 4.86 (1H, br t, HO-5′), 3.96 (1H, br s, H-3′), 3.89—3.85 (1H, m, H-4′), 3.36 (2H, br d, H-5′, J=4.4 Hz), 3.20—3.05 (1H, m, H-2″a), 2.97 (2H, m, H-2′, 2″b). MS *m/z*: 240 (M). These data as well as other physical constants were indistinguishable from those of compound **1** prepared by the previously described routes.[3] The crystal data of **1** were as follows. $C_{10}H_{12}N_2O_5$. M_r 240.22. Orthrombic, $P2_12_12_1$. a=9.368 (1), b=13.859 (1), c=7.979 (1) Å. V=1035.8 Å^3. D_x=1.540 g/cm^3. X-Ray

analysis of **1** showed that the anomeric configuration was β, and the glycosyl torsion angle (C6–N1–C1′–O4′) was 111.03 deg. The 5′-substituent was in *g,g*-conformation.[9]

2′-Deoxy-6,2′-methanocytidine (3) Compound **11** (320 mg, 0.692 mmol) dissolved in MeOH (10 ml) was added to methanol saturated with ammonia (20 ml) in a sealed tube and this was kept at 100 °C for 22 h. The solvent was removed *in vacuo* and the residue was crystallized from EtOH to give **3** (84 mg). From the mother liquor, an additional 32 mg (total 70%) of **3** was obtained. An analytically pure sample of **3** was obtained by recrystallization from EtOH–H_2O. mp >250 °C (dec.). ^{1}H-NMR (DMSO-d_6): 6.99 (2H, br d, H_2N-4), 5.98 (1H, d, H-1′, J=6.2 Hz), 5.49 (1H, s, H-5), 5.32 (1H, d, HO-3′, J=4.8 Hz), 4.81 (1H, t, HO-5′, J=5.49, 5.87 Hz), 3.94—3.91 (1H, m, H-3′), 3.84—3.79 (1H, m, H-4′), 3.30—3.25 (2H, m, H-5′), 3.14 (1H, dd, H-2′′a, J=9.52, 17.6 Hz), 2.93—2.77 (2H, m, H-2′ and H-2′′b). FAB-MS *m/z*: 957 (4M+1), 718 (3M+1), 479 (2M+1), 240 (M+1). UV $\lambda_{max}^{H_2O}$ nm (ε): 267 (9640); $\lambda_{max}^{0.1\,N\,HCl}$: 276 (13300). CD ($H_2O$) θ (nm): −25700 (267), (0.1 N HCl) θ: −23400 (275). *Anal.* Calcd for $C_{10}H_{13}N_3O_4 \cdot H_2O$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.63; H, 5.94; N, 16.22.

2′-Deoxy-3′,5′-di-*O*-benzoyl-6,2′-methano-4-thiouridine (12) Compound **11** (500 mg, 1.08 mmol) dissolved in pyridine (4 ml) was mixed with liquid H_2S–pyridine (H_2S was absorbed in 5 ml of pyridine in a dry ice-acetone bath to a volume of 18 ml) in a steel tube. The tube was sealed and kept for 3 d at 60 °C. The H_2S was released and the solvent was removed *in vacuo*. The residue was co-distilled with toluene several times to remove traces of pyridine and the final residue was dissolved in AcOEt then absorbed on a small amount of silica gel, and dried. This was applied on top of a column of silica gel (2.3×8.5 cm) and chromatographed. The appropriate eluate fraction with 25—30—50% AcOEt in hexane was collected and the solvent was removed to leave **12** (450 mg, 90%) as a solid. An analytically pure sample was obtained by crystallization from $CHCl_3$–95% MeOH; mp 115.5—117.3 °C. ^{1}H-NMR ($CDCl_3$): 9.27 (1H, br s, HN-3), 8.04—7.94 (4H, m, H-*o*-Bz), 7.65—7.41 (6H, m, H-*m*,*p*-Bz), 6.36—6.34 (1H, m, H-1′), 6.28 (1H, s, H-5), 5.31 (1H, d, H-3′, J=3.7 Hz), 4.72 (1H, q, H-4′, J=4.4 Hz), 4.57 (2H, d, H-5′, J=4.8 Hz), 3.35—3.25 (3H, m, H-2′, 2′′), 1.60 (2H, br s, H_2O). MS *m/z*: 464 (M). UV λ_{max}^{MeOH} nm: 331. *Anal.* Calcd for $C_{24}H_{20}N_2O_6S \cdot H_2O$: C, 59.74; H, 4.60; N, 5.81; S, 6.64. Found: C, 59.99; H, 4.79; N, 5.90; S, 6.61.

2′-Deoxy-6,2′-methano-4-thiouridine (13) Compound **12** (350 mg, 0.754 mmol) was suspended in MeOH (10 ml), and 0.1 N NaOMe (1 ml) was added. After stirring at room temperature for 13 h the solution was neutralized by addition of AcOH and the precipitate was collected by filtration to give **13** (83 mg). The filtrate was concentrated and the residue was chromatographed on silica gel (1.7×7.5 cm). The eluate with 4—8% MeOH in $CHCl_3$ was concentrated to give a further 68 mg (total 78%) of **13**. An analytically pure sample was obtained by crystallization from MeOH, mp >225 °C (dec.). ^{1}H-NMR (DMSO-d_6): 12.40 (1H, br s, HN-3), 6.20 (1H, s, H-5), 6.06 (1H, d, H-1′, J=6.6 Hz), 3.99 (1H, t, H-3′, J=2.2 Hz), 3.93—3.89 (1H, m, H-4′), 3.34 (2H, d, H-5′, J=4.4 Hz), 4.9—3.8 (2H, br s, HO-5′ and HO-3′), 3.14 (1H, dd, H-2′′a, J=11.5, 19.8 Hz), 3.00—2.91 (2H, m, H-2′, 2′′b). MS *m/z*: 256 (M). UV $\lambda_{max}^{H_2O}$ nm (ε): 330 (23000). CD (H_2O) θ (nm): −12600 (333), −7700 (266), +4900 (235). *Anal.* Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.87; H, 4.72; N, 10.93; S, 12.51. Found: C, 46.87; H, 4.77; N, 10.79; S, 12.42.

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