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Synthesis of 6,3'-Methanocytidine, 6,3'-Methanouridine, and Their 2'-Deoxyribonucleosides (Nucleosides and Nucleotides. LXXVII¹⁾)

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Condensation of 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene- α -D-erythro-3-pentulofuranose (**4**) with 2,4-dimethoxypyrimidin-6-ylmethylithium (**5**) afforded a 3-pyrimidinylmethyl-ribose derivative (**6**). The protecting groups of **6** were changed to give the 5-*O*-benzoyl-1,2-di-*O*-acetyl derivative (**8**). The intramolecular glycosylation of **8** by treatment with stannic chloride furnished the 6,3'-methanol-*O*⁴-methyluridine derivative (**9**), which was further converted to 6,3'-methanouridine (**10**) and 6,3'-methanocytidine (**11**). The 2'-deoxygenation of **9** by way of the 2'-imidazolylthiocarbonyl derivative gave, after appropriate derivatization, 2'-deoxy-6,3'-methanocytidine (**16**) and -uridine (**17**).

Keywords—C-cyclonucleoside; 6,3'-methanocytidine; 6,3'-methanouridine; 2'-deoxy-6,3'-methanocytidine; deoxygenation; intramolecular glycosylation; 3-ketoribose; nucleophilic addition; NMR

We have reported the synthesis of a number of carbon-bridged cyclonucleosides for stereochemical studies of nucleosides and nucleotides.²⁾ Among them, the 6,3'-carbon bridged nucleosides seem to be interesting. The glycosyl torsion angle ($\chi_{CN} = 265.3^\circ$) of 5'-*O*-acetyl-2',3'-dideoxy-6,3'-methanouridine (**1**) as determined by X-ray analysis³⁾ was close to those of usual pyrimidine nucleosides in the anti-conformations.⁴⁾ Therefore, an efficient synthesis of 6,3'-methanopyrimidine nucleosides is desirable for further studies of their biological properties, since the previous procedure for the synthesis of 6,3'-methanouridine derivative (**1**) required a multi-step conversion of uridine.⁵⁾ This paper describes a versatile synthesis of 6,3'-methanopyrimidine nucleosides and their 2'-deoxy derivatives from a 3-ketosugar and a pyrimidine. A preliminary account of the present study has appeared.⁶⁾

The present synthetic strategy is to provide the ribose derivative with the pyrimidine moiety already attached at the 3-position and then to glycosylate intramolecularly to furnish the 6,3'-methanopyrimidine nucleoside.

1,2-*O*-Isopropylidene- α -D-xylofuranose⁷⁾ (**2**) was treated with *tert*-butyldimethylchlorosilane to give the 5-*O*-silyl derivative (**3**). Compound **3** was then oxidized by chromium trioxide to give the 3-ulose (**4**) in a crystalline form. Treatment of **4** with 2,4-dimethoxypyrimidin-6-ylmethylithium (**5**), prepared from 2,4-dimethoxy-6-methylpyrimidine⁸⁾ and *n*-butyllithium, in tetrahydrofuran (THF) afforded 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-3(*R*)-(2,4-dimethoxypyrimidin-6-yl)methylribose (**6**), which was crystallized from *n*-hexane. It is expected that the carbanion should attack from the β -side of **4** due to the steric hindrance of the 1,2-*O*-isopropylidene group to α -attack. The 5-*O*-*tert*-butyldimethylsilyl group of **6** was removed, and then benzylation gave the 5-*O*-benzoate (**7**). Acid hydrolysis of **7** with 90% trifluoroacetic acid followed by acetylation with acetic anhydride and triethylamine in methylene chloride gave an anomeric mixture of the 1,2-di-*O*-acetate (**8**) as a foam. An attempt at the direct acetolysis of **6** to obtain the 1,2-di-*O*-acetate

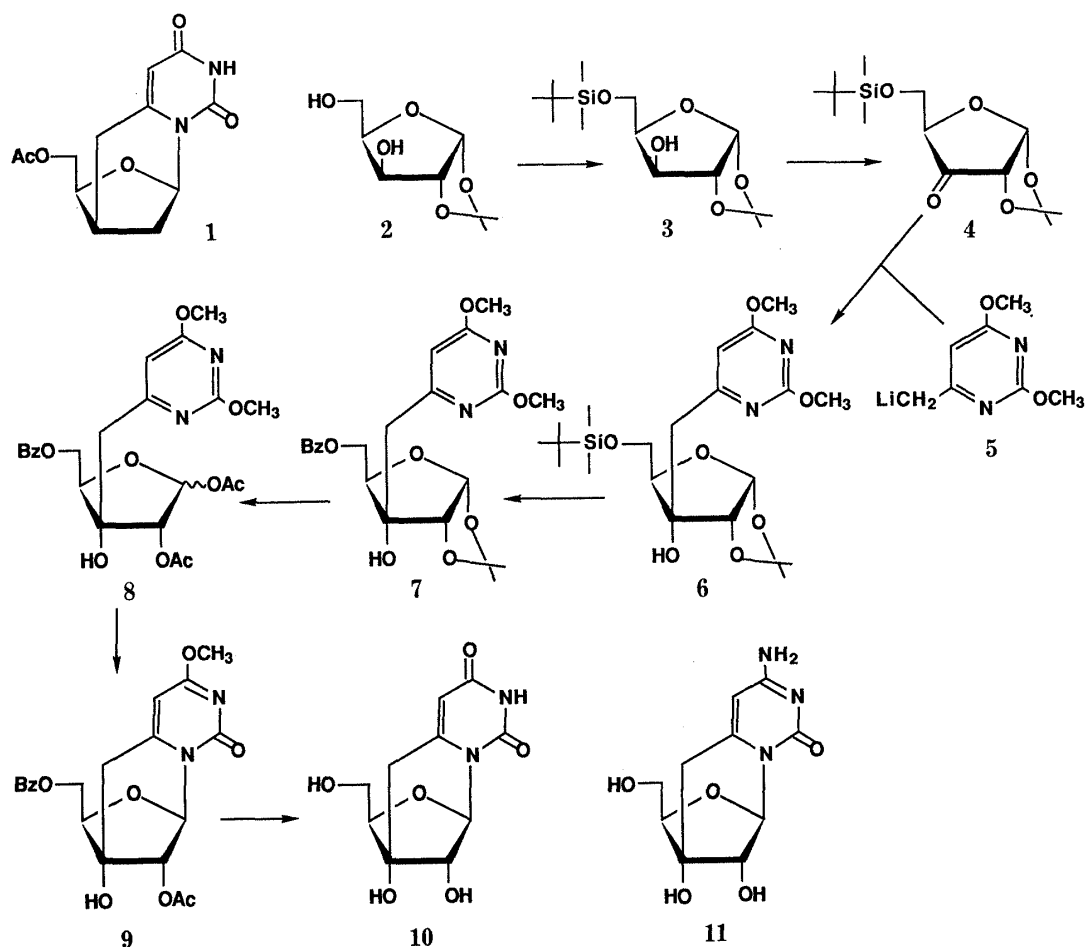


Chart 1

resulted in the 5-*O*-desilylation of **6** followed by a furanose-to-pyranose isomerization. Therefore, the prior conversion of *tert*-butyldimethylsilyl to benzoyl at the 5-position was important.

Treatment of **8** with stannic chloride in acetonitrile at room temperature afforded the 6,3'-methano-*O*⁴-methyluridine derivative (**9**) as a foam. Treatment of **9** with 1 *N* sodium hydroxide under reflux caused complete deprotection to furnish 6,3'-methanouridine (**10**) in a crystalline form. The nuclear magnetic resonance (NMR) spectrum of **10** was consistent with the proposed structure. Thus, in the spectrum of **10**, both H-1' (δ 5.82) and H-2' (δ 3.83) appeared as a singlet, since the dihedral angle of H₁-C₁'-C₂'-H₂' is fixed at *ca.* 90° due to the 6,3'-methano-bridge. The 6,3'-methylene protons (δ 3.06 and 2.83) appeared as a pair of doublets due to the geminal coupling (J = 18.6 Hz). It is worthy of note that the signals of the 5'-protons also showed geminal coupling, probably as a result of hindered rotation of the C₄'-C₅' bond owing to the presence of the 6,3'-methano-bridge. The X-ray diffraction analysis of **10** also confirmed the structure.⁹⁾ The circular dichroism (CD) spectrum of **10** showed a strong negative band at the main absorption region, as was predicted from the previously accumulated results.¹⁰⁾

Treatment of **9** with methanolic ammonia at 100 °C for 20 h afforded 6,3'-methanocytidine (**11**). The NMR spectra and other physical data of **11** showed characteristic features similar to those found for **10**.

While compounds **10** and **11** are regarded as pyrimidine ribonucleosides fixed in the anti-conformation range, their 2'-deoxyribonucleosides may be more useful for the study of

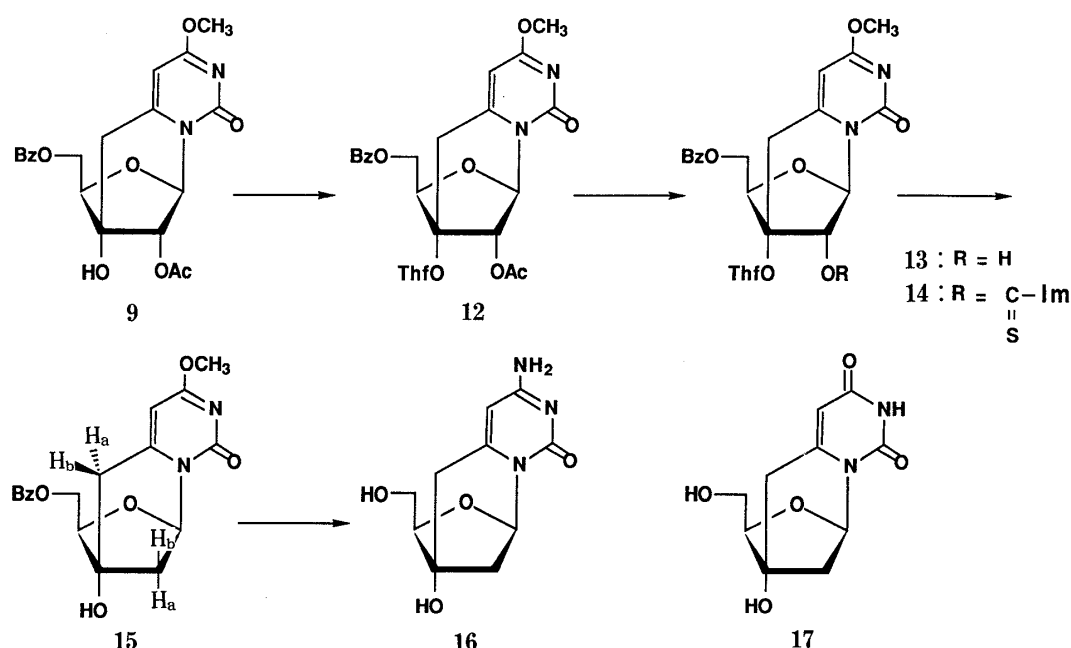


Chart 2

enzymes related to deoxyribonucleic acid (DNA) biosynthesis. The synthesis of the 2'-deoxy derivatives was therefore attempted. Several attempts at the selective 2'-deoxygenation of **10** or **11** by well-documented methods for the conversion of ribonucleosides to 2'-deoxyribonucleosides¹¹⁾ met with little success, *e.g.*, the 2'-imidazolylthiocarbonylation of **10** and radical deoxygenation, or the 3',5'-bis-protection of **10** with 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-disiloxane and further derivatization of the 2'-hydroxyl group, or the conversion of the 2'-hydroxyl group of **10** to the halogeno groups. Similar difficulties in the 2'-derivatization of C-cyclonucleosides have been encountered, for example, in the 2'-deoxygenation of 6,5'-cyclo-5'-deoxyuridine.¹²⁾

Therefore, an other route was developed starting from **9**. Treatment of **9** with 2,3-dihydrofuran in the presence of *p*-toluenesulfonic acid in dioxane afforded the 3'-tetrahydrofuranyl derivative (**12**) as a foam. The selective 2'-de-O-acylation of **12** was achieved by treatment with methanolic triethylamine at room temperature for 3 h to give the 2'-alcohol (**13**). The imidazolylthiocarbonylation¹³⁾ of **13** by treatment with *N,N'*-thiocarbonyldiimidazole gave a crude product (**14**), which was subjected to the radical deoxygenation by treatment with tributyltin hydride and azobisisobutyronitrile (AIBN) to give the 2'-deoxy compound, which was subsequently treated with trifluoroacetic acid to furnish crystalline 5'-*O*-benzoyl-2'-deoxy-*O*⁴-methyl-6,3'-methanouridine (**15**). The ¹H-NMR spectrum of pure **15** exhibited a doublet due to H-1' (δ 6.61), a doublet due to H-2'b, and three sets of doublets due to H-2'a split by H-1', H-2'b, and by one proton (H-6'a) at the 6,3'-methano-bridge situated in the W-type conformation. This result showed that the 2'-deoxygenation of **9** had proceeded to give **15**. Treatment of **15** with methanolic ammonia at 100 °C for 22 h furnished 2'-deoxy-6,3'-methanocytidine (**16**). Alkaline hydrolysis of **15** afforded 2'-deoxy-6,3'-methanouridine (**17**), as expected.

In conclusion, the present synthetic route will be useful to provide the 6,3'-methanopyrimidine nucleosides in quantities for use in biochemical studies of these conformationally fixed nucleosides. Furthermore, the present method may be adaptable not only for the synthesis of 6,3'-cyclopyrimidine nucleosides but also for various types of carbon-bridged pyrimidine and purine cyclonucleosides.

Experimental

Melting points were determined on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The ^1H -NMR spectra were recorded on a JEOL FX-100FT or FX-270FT spectrometer in an appropriate 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 . Ultraviolet absorption spectra (UV) were recorded on a Shimadzu UV-260 spectrophotometer. Mass spectra (MS) were measured on a JEOL D-300 spectrometer. CD spectra were recorded on a JASCO J-500A spectropolarimeter at room temperature. Silica gel used for column chromatography was Merck Kieselgel 60 (70—200 mesh). Thin-layer chromatography (TLC) was carried out on Merck pre-coated 60F_{254} plates.

5-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene- α -D-xylose (3)—A mixture of **2**⁷⁾ (19 g, 10 mmol) and *tert*-butyldimethylchlorosilane (18.1 g, 12 mmol) in pyridine (200 ml) was stirred at room temperature for 1.5 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc, washed with H_2O twice, dried over Na_2SO_4 , and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (7.5 \times 11 cm) with 0—5% MeOH in CHCl_3 . The eluate was concentrated to leave **3** (30.5 g, 100%) as a foam. MS m/z : 304 (M^+), 289 ($\text{M}^+ - \text{Me}$). ^1H -NMR (CDCl_3): 5.92 (1H, d, H-1, $J = 3.66$ Hz), 4.46 (1H, d, H-2), 4.08 (3H, br s, H-4, 5), 1.45, 1.28 (3H each, s, *iso*-Pr), 0.86 (9H, s, *tert*-Bu), 0.07 (6H, s, Me).

5-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene- α -D-erythro-3-pentulofuranose (4)—A solution of **3** (15.74 g, 51.8 mmol) in CH_2Cl_2 (50 ml) was added to the previously prepared CH_2Cl_2 solution (250 ml) containing CrO_3 —pyridine— Ac_2O (15.5 g, 3 eq: 26 ml: 5 ml). The mixture was stirred for 1.5 h at room temperature and then added dropwise to EtOAc (1000 ml) under stirring. The precipitate was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (6.6 \times 17.5 cm) with 5% EtOAc in *n*-hexane. The eluate was concentrated and the residue was crystallized from *n*-hexane to give **4** (12.1 g, 77%), mp 40—43 °C. MS m/z : 287 ($\text{M}^+ - \text{Me}$), 245 ($\text{M}^+ - \text{tert-Bu}$). ^1H -NMR (CDCl_3): 6.13 (1H, d, H-1, $J = 4.4$ Hz), 4.37 (1H, m, H-4), 4.28 (1H, dd, H-2, $J_{2,4} = 1.1$ Hz), 3.85 (2H, m, H-5), 1.45 (6H, s, *iso*-Pr), 0.86 (9H, s, *tert*-Bu), 0.056, 0.031 (3H each, s, Me). *Anal.* Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_5\text{Si}$: C, 55.59; H, 8.67. Found: C, 55.55; H, 8.69.

5-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-3(*R*)-(2,4-dimethoxypyrimidin-6-yl)methyl- α -D-ribofuranose (6)—2,4-Dimethoxy-6-methylpyrimidine (3.08 g, 20 mmol) was suspended in THF (100 ml) at -70 °C. *n*-BuLi (1.58 m in *n*-hexane, 12.7 ml, 1 eq) was slowly added to the suspension, the temperature was raised to -35 °C, and the whole was stirred for 1 h to prepare **5**. A solution of **4** (6.30 g, 1.04 eq) in THF (20 ml) was added dropwise to the above suspension, then the whole was stirred for 1 h at -35 °C. The solution was neutralized by addition of AcOH and the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and H_2O , the organic layer was dried over Na_2SO_4 , then the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (7.4 \times 15 cm) with 10—20% EtOAc in *n*-hexane. The eluate was concentrated to leave **6** (6.87 g, 75%). Crystallization from *n*-hexane gave a pure sample for analysis, mp 79—81 °C. MS m/z : 456 (M^+), 441 ($\text{M}^+ - \text{Me}$), 399 ($\text{M}^+ - \text{tert-Bu}$). ^1H -NMR (CDCl_3): 6.33 (1H, s, H-5), 5.79 (1H, d, H-1', $J = 3.9$ Hz), 4.79 (1H, s, HO-3'), 4.28 (1H, d, H-2'), 4.06—3.84 (3H, m, H-4', 5'), 3.97 (6H, s, MeO), 2.99 (1H, d, H-6'a, $J_{a,b} = 14.6$ Hz), 2.62 (1H, d, H-6'b), 1.58, 1.49 (3H each, s, *iso*-Pr), 0.90 (9H, s, *tert*-Bu), 0.09 (6H, s, Me). *Anal.* Calcd for $\text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_7\text{Si}$: C, 55.24; H, 7.95; N, 6.14. Found: C, 55.42; H, 7.98; N, 6.19.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-3(*R*)-(2,4-dimethoxypyrimidin-6-yl)methyl- α -D-ribofuranose (7)—A mixture of **6** (6.25 g, 13.9 mmol) in THF (50 ml) and tetrabutylammonium fluoride (1 M in THF, 14 ml) was stirred for 10 min at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in pyridine (70 ml). Benzoyl chloride (4 ml) was added to the solution in an ice-bath and the solution was stirred overnight at room temperature. The solvent was removed *in vacuo*, the residual pyridine was removed by co-evaporation with toluene three times, and the residue was dissolved in CHCl_3 . The solution was washed with H_2O , saturated NaHCO_3 in H_2O , and H_2O , then the organic layer was dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (7.7 \times 16.5 cm) with 20—40% EtOAc in *n*-hexane. The eluate was concentrated to leave **7** (5.67 g, 91%). Crystallization from *iso*-PrOH gave a pure sample, mp 132—134 °C. MS m/z : 446 (M^+), 431 ($\text{M}^+ - \text{Me}$), 388 ($\text{M}^+ - 58$). ^1H -NMR (CDCl_3): 8.1—8.0 (2H, m, Bz), 7.6—7.3 (3H, m, Bz), 6.36 (1H, s, H-5), 5.84 (1H, d, H-1', $J = 3.9$ Hz), 5.18 (1H, s, HO-3'), 4.72—4.42 (2H, m, H-5'), 4.39 (1H, m, H-4'), 4.30 (1H, d, H-2'), 3.98 (6H, s, MeO), 3.01 (1H, d, H-6'a, $J_{a,b} = 14.4$ Hz), 2.68 (1H, d, H-6'b), 1.62, 1.32 (3H each, s, *iso*-Pr). *Anal.* Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_8$: C, 59.18; H, 5.87; N, 6.28. Found: C, 58.93; H, 5.89; N, 6.35.

1,2-Di-*O*-acetyl-5-*O*-benzoyl-3(*R*)-(2,4-dimethoxypyrimidin-6-yl)methyl-D-ribofuranose (8)—A solution of **7** (5.67 g, 12.7 mmol) in 90% trifluoroacetic acid (50 ml) was stirred at room temperature for 1.5 h. The solvent was removed *in vacuo* and the residual acid was co-distilled with *iso*-PrOH three times. The residue was dissolved in CH_2Cl_2 — Et_3N (5:1, 50 ml) and Ac_2O (5 ml) was added. The mixture was stirred for 2 h, then MeOH was added. The whole was diluted with CHCl_3 , washed with saturated NaHCO_3 in H_2O three times, then dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (5.3 \times 24 cm) with 40% EtOAc in *n*-hexane. The eluate was concentrated to leave **8** (5.71 g, 92%) as a foam. MS m/z : 490 (M^+), 447 ($\text{M}^+ - \text{Ac}$), 431 ($\text{M}^+ - \text{AcO}$). ^1H -NMR (CDCl_3): 8.15—8.01 (2H, m, Bz), 7.53—7.30 (3H, m, Bz), 6.43 (0.3H, d, $J = 5.00$ Hz), 6.27—

6.19 (1H, m, H-1', 5), 5.22, 5.04 (1H total, d, H-2', $J = 1.71$ Hz), 4.65—4.08 (3H, m, H-4', 5'), 3.97, 3.96 (3H each, s, MeO), 3.09, 2.99 (2H, brs, H-6'), 2.13, 2.09, 2.05, 2.04 (6H total, s, Ac).

2'-O-Acetyl-5'-O-benzoyl-O⁴-methyl-6,3'-methanouridine (9)—Stannic chloride (0.45 ml in 5 ml of acetonitrile, 3.69 mmol) was added to a solution of **8** (900 mg, 1.84 mmol) in acetonitrile (15 ml) under cooling in an ice-bath. The solution was stirred for 3 h at room temperature and the solvent was removed *in vacuo*. The residue was taken up in CHCl_3 and washed with saturated NaHCO_3 in H_2O . The precipitate was filtered off through a celite bed, and the organic layer was separated. The aqueous layer was extracted with CHCl_3 and the combined CHCl_3 layer was dried over Na_2SO_4 . The solvent was evaporated off and the residue was chromatographed on silica gel (2.3×23 cm) with 1% MeOH in CHCl_3 . The eluate was concentrated to leave **9** (630 mg, 82%) as a foam. MS m/z : 416 (M^+), 373 ($\text{M}^+ - \text{Ac}$). UV $\lambda_{\text{max}}^{\text{MeOH}}$: 281 nm. $^1\text{H-NMR}$ (CDCl_3): 8.00—7.90 (2H, m, Bz), 7.67—7.28 (3H, m, Bz), 6.50 (1H, s, H-1'), 5.72 (1H, s, H-5), 5.11 (1H, s, H-2'), 4.69—4.30 (3H, m, H-4', 5'), 3.88 (3H, s, MeO), 3.65 (1H, s, HO-3'), 3.36 (2H, dd, H-6'), 2.21 (3H, s, Ac).

6,3'-Methanouridine (10)—Compound **9** (2.0 g, 4.80 mmol) was dissolved in dioxane (20 ml) and 2 N NaOH (20 ml) was added to the solution. The mixture was heated at 100 °C for 20 min. The solution was neutralized by addition of Dowex 50 (H^+). The resin was filtered off and the filtrate was extracted with EtOEt to remove benzoic acid. The aqueous layer was concentrated and the residue was crystallized from H_2O to give **10** (0.66 g, 53%), mp > 300 °C. MS m/z : 256 (M^+), 238 ($\text{M}^+ - \text{H}_2\text{O}$). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$: 266 nm (ϵ , 10900). CD (H_2O) $[\theta]$ (nm): -19600 (260). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): 11.22 (1H, brs, HN-3), 5.82 (1H, s, H-1'), 5.48 (1H, s, H-5), 3.97 (1H, dd, H-4', $J_{4',5'} = 2.7$, 7.1 Hz), 3.83 (1H, s, H-2'), 3.63 (1H, dd, H-5'a, $J_{a,b} = 12.0$ Hz), 3.36 (1H, dd, H-5'b), 3.06 (1H, d, H-6'a, $J_{a,b} = 18.6$ Hz), 2.83 (1H, d, H-6'b). The signals of the hydroxyl protons were not detected. Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_6 \cdot \text{C}$, 46.87; H, 4.72; N, 10.94. Found: C, 46.82; H, 4.74; N, 10.73.

6,3'-Methanocytidine (11)—Compound **9** (3.01 g, 7.23 mmol) was heated in MeOH saturated with NH_3 (30 ml) at 100 °C for 20 h in a sealed tube. After cooling, the separated crystals were collected by filtration to give **11** (1.14 g, 62%), mp 310 °C. MS m/z : 255 (M^+). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$: 275 nm; $\lambda_{\text{max}}^{0.1\text{N HCl}}$: 282 nm. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): 7.07 (2H, br, H_2N), 5.95 (1H, s, H-1'), 5.80 (1H, d, HO-2', $J = 3.4$ Hz), 5.50 (1H, s, H-5), 5.45 (1H, s, HO-3'), 4.74 (1H, t, HO-5', $J = 5.4$ Hz), 3.95 (1H, dd, H-4'), 3.75 (1H, d, H-2'), 3.55 (1H, m, H-5'a), 3.2 (1H, m, H-5'b), 2.97 (1H, d, H-6'a, $J_{a,b} = 17.8$ Hz), 2.85 (1H, d, H-6'b). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_5 \cdot \text{H}_2\text{O}$: C, 43.95; H, 5.53; N, 15.38. Found: C, 43.92; H, 5.56; N, 15.65.

2'-O-Acetyl-5'-O-benzoyl-3'-O-tetrahydrofuranyl-O⁴-methyl-6,3'-methanouridine (12)—A mixture of **9** (2.19 g, 5.26 mmol), 2,3-dihydrofuran (0.8 ml, 10.5 mmol) and *p*-toluenesulfonic acid (60 mg) in dioxane (40 ml) was stirred overnight at room temperature. The solution was neutralized by addition of anhydrous K_2CO_3 . The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in EtOAc, the solution was washed with H_2O , and the organic layer was dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (3.6×17 cm) with CHCl_3 . The solvent was removed *in vacuo* to leave **12** (2.09 g, 82%) as a foam. MS m/z : 486 (M^+), 416 ($\text{M}^+ - \text{Thf}$). $^1\text{H-NMR}$ (CDCl_3): 8.00—7.95 (2H, m, Bz), 7.56—7.37 (3H, m, Bz), 6.53, 6.45 (1H, s, H-1'), 5.72, 5.69 (1H, s, H-5), 5.50, 5.36 (1H, m, H-2 of Thf), 5.39—5.31 (1H, s, H-2'), 4.65—4.32 (3H, m, H-4', 5'), 3.91 (3H, s, MeO), 3.90—3.82 (2H, m, H-5 of Thf), 3.62—3.30 (2H, m, H-6'), 2.20, 2.19 (3H, s, Ac), 1.95—1.80 (4H, s, H-3,4 of Thf).

5'-O-Benzoyl-3'-O-tetrahydrofuranyl-O⁴-methyl-6,3'-methanouridine (13)—Compound **12** (2.09 g, 4.27 mmol) was dissolved in MeOH-Et₃N (10:1, 44 ml). After 3 h at room temperature, the solvent was removed *in vacuo* and the residue was chromatographed (3.2×16 cm) with 0—1% MeOH in CHCl_3 . The eluate was concentrated to leave **13** (1.51 g, 80%) as a foam. MS m/z : 444 (M^+), 374 ($\text{M}^+ - \text{Thf}$). $^1\text{H-NMR}$ (CDCl_3): 7.99—7.94 (2H, m, Bz), 7.56—7.37 (3H, m, Bz), 6.55, 6.47 (1H, s, H-1'), 5.68 (1H, brs, H-5), 5.62, 5.50 (1H, br d, H-2 of Thf), 4.63—4.29 (3H, m, H-4', 5'), 4.23, 4.18 (1H, brs, H-2'), 3.91 (3H, s, MeO), 4.11—3.89 (2H, m, H-5 of Thf), 3.30—3.20 (2H, br dd, H-6'), 2.04—1.86 (4H, m, H-3,4 of Thf).

5'-O-Benzoyl-3'-O-tetrahydrofuranyl-2'-O-imidazolylthiocarbonyl-O⁴-methyl-6,3'-methanouridine (14)—A solution of **13** (1.5 g, 3.38 mmol) and *N,N'*-thiocarbonyldiimidazole (1.3 g, 6.76 mmol) in dimethylformamide (15 ml) was stirred overnight at room temperature. The solvent was removed *in vacuo*, the residue was dissolved in EtOAc, this solution was washed with H_2O three times, and the organic layer was dried over Na_2SO_4 . The solution was concentrated and the residue was chromatographed on silica gel (3.2×16 cm) with CHCl_3 to give **14** (1.36 g, 72%) as a foam. $^1\text{H-NMR}$ (CDCl_3): 8.41, 8.39 (1H, s, H-2 of imidazolyl), 8.06, 7.98 (2H, m, Bz), 7.69, 7.67 (1H, brs, H-5 of imidazolyl), 7.66—7.40 (3H, m, Bz), 7.11 (1H, brs, H-4 of imidazolyl), 6.78, 6.74 (1H, s, H-1'), 6.02, 5.87 (1H, s, H-2'), 5.74, 5.75 (1H, s, H-5), 5.49, 5.36 (1H, br d, H-2 of Thf), 4.67—4.41 (3H, m, H-4', 5'), 3.93 (3H, s, MeO), 3.93—3.69 (3H, m, H-6'a, H-5 of Thf), 3.45—3.32 (1H, d, H-6'b, $J_{a,b} = 18.68$, 17.95 Hz), 1.93—1.77 (4H, m, H-3,4 of Thf).

5'-O-Benzoyl-2'-deoxy-O⁴-methyl-6,3'-methanouridine (15)—A mixture of **14** (1.35 g, 2.44 mmol), Bu_3SnH (2 ml, 7.32 mmol) and AIBN (20 mg) in toluene (40 ml) was heated at 110 °C for 1.5 h. After cooling, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel (3.9×30 cm) with 0—1% MeOH in CHCl_3 . From the less polar fractions, the 2'-deoxy compound (450 mg, 43%) was obtained. From the second fraction, **13** (550 mg, 51%) was recovered. The 2'-deoxy compound (450 mg, 1.05 mmol) was dissolved in 90% trifluoroacetic acid (5 ml) and the solution was stirred for 10 min at room temperature. The solvent was removed *in vacuo* and residual

acid was co-distilled with iso-PrOH three times. The residue was dissolved in CHCl_3 and washed with H_2O , then the organic layer was dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residue was triturated in EtOEt-*n*-hexane to give a solid, which was crystallized from EtOH to give **15** (260 mg, 73%), mp 192–193 °C. MS m/z : 358 (M^+), 237 ($\text{M}^+ - \text{BzO}$). $^1\text{H-NMR}$ (CDCl_3): 7.99–7.95 (2H, m, Bz), 7.61–7.40 (3H, m, Bz), 6.68 (1H, d, H-1', $J = 5.13$ Hz), 5.71 (1H, s, H-5), 4.53 (1H, dd, H-5'a, $J_{4',5'a} = 5.50$ Hz, $J_{5'a,b} = 11.72$ Hz), 4.34 (1H, dd, H-5'b, $J_{4',5'b} = 5.13$ Hz), 4.24 (1H, m, H-4'), 3.91 (3H, s, MeO), 3.34 (1H, dd, H-6'a, $J_{6'a,b} = 18.32$ Hz, $J_{6'a,2'a} = 2.56$ Hz), 3.22 (1H, d, H-6'b), 2.69 (1H, ddd, H-2'a, $J_{2'a,b} = 11.36$ Hz), 2.14 (1H, d, H-2'b). *Anal.* Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.36; H, 5.04; N, 7.73.

2'-Deoxy-6,3'-methanocytidine (16)—Compound **15** (100 mg, 0.279 mmol) in MeOH saturated with NH_3 (4 ml) was heated at 100 °C for 22 h in a sealed tube. The solvent was removed *in vacuo* and the residue was chromatographed on Dowex 50W-X8 (1.2 × 9.3 cm) with 1 N ammonia. The eluate was concentrated and the residue was crystallized from MeOH-EtOAc to give **16** (64 mg, 91%), mp 275–278 °C (dec.). MS m/z : 239 (M^+). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm (ϵ): 276 (9500); $\lambda_{\text{max}}^{0.1 \text{ N HCl}}$: 283 (13500). CD H_2O $[\theta]$ (nm): –17600 (275); 0.1 N HCl: –23600 (283). $^1\text{H-NMR}$ (D_2O , sodium trimethylsilylpropanesulfonate (TSPS) as the internal standard): 6.42 (1H, d, H-1', $J_{1',2'a} = 4.40$ Hz), 3.98 (1H, dd, H-4', $J_{4',5'a} = 3.48$ Hz, $J_{4',5'b} = 6.51$ Hz), 3.82 (1H, dd, H-5'a, $J_{5'a,b} = 12.2$ Hz), 3.61 (1H, dd, H-5'b), 3.20 (2H, brs, H-6'), 2.62 (1H, br dd, H-2'a, $J_{2'a,b} = 11.34$ Hz), 2.19 (1H, d, H-2'b). *Anal.* Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_4 \cdot 1/4 \text{H}_2\text{O}$: C, 49.27; H, 5.48; N, 17.24. Found: C, 49.52; H, 5.64; N, 16.90.

2'-Deoxy-6,3'-methanouridine (17)—Compound **15** (50 mg, 0.14 mmol) was dissolved in 2 N NaOH-dioxane (1 : 1, 2 ml) and the solution was stirred at 100 °C for 30 min. The solution was neutralized by addition of Dowex 50W-X8 (H^+) and the resin was filtered off. The filtrate was concentrated and the residue was subjected to preparative TLC developed twice with MeOH- CHCl_3 (1 : 8). From the appropriate band, **17** (31 mg, 91%) was obtained as a solid, which was crystallized from EtOH, mp 192.0–192.5 °C. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm (ϵ): 268 (10400). CD H_2O $[\theta]$ (nm): –18000 (265). MS m/z : 240 (M^+), 222 ($\text{M}^+ - \text{H}_2\text{O}$). $^1\text{H-NMR}$ (D_2O , TSPS as the internal standard): 6.40 (1H, d, H-1', $J_{1',2'a} = 4.76$ Hz), 5.74 (1H, s, H-5), 4.00 (1H, m, H-4', $J_{4',5'a} = 3.66$ Hz, $J_{4',5'b} = 6.59$ Hz), 3.84 (1H, ddd, H-2'a, $J_{2'a,b} = 11.35$ Hz), 2.19 (1H, d, H-2'b). *Anal.* Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_5 \cdot \text{H}_2\text{O}$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.34; H, 5.44; N, 10.79.

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