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A FACILE SYNTHESIS OF 6,3'-METHANO-URIDINE AND-CYTIDINE
FROM A 3-KETOSUGAR (NUCLEOSIDES AND NUCLEOTIDES LXVIII)¹⁾

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The synthesis of 6,3'-methanouridine was achieved by condensation of 2,4-dimethoxy-6-lithiomethylpyrimidine with 5-O-(tert-butyldimethyl)silyl-1,2-O-isopropylidene-3-ketoxylucose, followed by intramolecular glycosylation and deprotection. 6,3'-Methanocytidine was also prepared from the 4-O-methyl intermediate. The title compounds are the first example of uridine and cytidine fixed between C-6 and the 3'-position of pyrimidine nucleosides by a methylene group.

KEYWORDS — 6,3'-methanouridine; 6,3'-methanocytidine; C-cyclonucleoside; 3-ketoxylucose; 2,4-dimethoxy-6-methylpyrimidine; intramolecular glycosylation; SnCl₄; NMR; CD

We have reported several methods of synthesizing various carbon-bridged cyclonucleosides for the conformational study of nucleosides and nucleotides around their glycosyl linkages.²⁾ The cyclonucleosides provide information on the nucleotide conformation at the binding to nucleotide-utilizing enzymes,^{2c)} and on the sign and magnitude of the circular dichroism spectra as a function of glycosyl torsion angles.^{1,2h)} All C-cyclonucleosides have been prepared from natural nucleosides from which the necessary extra carbon chain was introduced either at the base or sugar portion, and finally cyclized. These synthetic routes generally require several steps and the overall yields are sometimes quite low, especially in the synthesis of 2',3'-dideoxy-6,3'-methanouridine from uridine.³ For the investigation of the biological and pharmacological properties of C-cyclonucleosides, a practical procedure has been needed to provide them in quantities.

We report here a new synthetic method of C-cyclopyrimidine nucleosides to meet this purpose. The method involves a condensation of a ketosugar and a 6-methylpyrimidine followed by an intramolecular glycosylation.

1,2-O-Isopropylidene- α -D-xylose (**1**)⁴⁾ was treated with t-butyldimethylchlorosilane to give the 5-O-silyl derivative, which was oxidized by chromium trioxide to furnish 5-O-t-butyldimethylsilyl-1,2-O-isopropylidene- α -D-erythro-pentofuranos-3-ulose (**2**, 92%, mp 40-43°C. MS m/z: 287 (M-15), 245 (M-tBu), 187 (M-t-butyldimethylsilyl). NMR δ (CDCl₃): 6.12 (1H, d, H-1, J_{1,2} = 4.6 Hz), 4.35 (1H, m, H-4), 4.27 (1H, dd, H-2, J_{2,4} = 1 Hz), 3.84 (2H, m, H-5), 1.44 (6H, br s, Me₂C), 0.85 (9H, s, t-Bu), 0.05 and 0.04 (3H each, s, Me₂Si). Anal. Calcd for C₁₄H₂₆O₅Si: C, 55.59; H, 8.67. Found: C, 55.55; H, 8.69]. 2,4-Dimethoxy-6-methylpyrimidine⁵⁾ was lithiated at the 6-methyl group to give **3**, which was condensed with **2** in tetrahydrofuran (THF) to give the 3-pyrimidinylmethylribose (**4**, R=TBD) in 63% yield [mp 79-80°C. MS m/z: 456 (M), 441 (M-15), 399 (M-tBu). NMR (CDCl₃, the numbering was as that of nucleosides): 6.34 (1H, s, H-5), 5.80 (1H, d, H-1', J_{1',2'} = 3.9 Hz), 4.80 (1H, s, HO-3'), 4.28 (1H, d, H-2'), 4.1 (1H, dd, H-4'), 3.98 (6H, s, MeO-2 and 4), 3.90 (2H, m, H-5'), 2.99 (1H, d, H-3''a), 2.62 (1H, d, H-3''b, J_{a,b} = 14.7 Hz), Anal. Calcd for C₂₁H₃₆N₂O₇Si: C, 55.24; H, 7.95; N, 6.14. Found: C, 55.42; H, 7.98; N, 6.19].

This addition reaction occurred stereoselectively, as expected, because of the steric hindrance of the 1,2-O-isopropylidene group of **2** for the attack from

the side. The 5-O-t-butyldimethylsilyl group of **4** was then removed and benzoylated to give the 5-O-benzoate (**5**, R=Bz) in 70 % yield. Acid hydrolysis of **5** with 90% trifluoroacetic acid followed by acetylation of the product in dichloromethane gave the 1,2-di-O-acetates (**6**) in over 90% yield.

Intramolecular glycosylation of **6** with SnCl₄ in acetonitrile at room temperature gave 2'-O-acetyl-5'-O-benzoyl-4-O-methyl-6,3'-methanouridine (**7**) in almost quantitative yield [m/z: 416 (M), 373 (M-Ac), UV λ_{max} MeOH: 281 nm, NMR (CDCl₃): 8.0-7.3 (5H, m, Bz), 6.52 (1H, s, H-1'), 5.72 (1H, s, H-5), 5.09 (1H, s, H-2'), 4.7-4.3 (3H, m, H-4',5'), 3.90 (3H, s, MeO), 3.35 (2H, dd, H-3''), 3.38 (1H, s, HO-3'), 2.23 (3H, s, AcO)]. Treatment of **7** with 1 N sodium hydroxide under reflux caused complete deprotection to furnish 6,3'-methanouridine (**8**) in 56% yield [mp >310°C. UV λ_{max} H₂O: 266nm (ε, 10900). CD in H₂O (θ): 260nm (-19600). MS m/z: 256 (M), 238 (M-H₂O). NMR (DMSO-d₆): 11.22 (1H, bs, 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 and 7.1 Hz), 3.83 (1H, s, H-2'), 3.63 (1H, dd, H-5'a, J_{5'a,b} = 12.0 Hz), 3.36 (1H, dd, H-5'b), 3.06 (1H, d, H-3''a, J_{3''a,b} = 18.6 Hz), 2.83 (1H, d, H-3''b). Anal. Calcd for C₁₀H₁₂N₂O₆: C, 46.87; H, 4.72; N, 10.94. Found: C, 46.82; H, 4.74; N, 10.73].

Treatment of **7** with methanolic ammonia at 100°C for 20 h afforded 6,3'-methanocytidine (**9**) in 62% yield [mp >300°C. UV λ_{max} H₂O: 275nm. λ_{max} 1 N HCl; 282nm. MS m/z: 255 (M). NMR (DMSO-d₆): 7.07 (2H, bd, H₂N-4), 5.95 (1H, s, H-1'), 5.80 (1H, d, HO-2'), 5.50 (1H, s, H-5), 5.45 (1H, s, HO-3'), 4.74 (1H, t, HO-5'), 3.95 (1H, dd, H-4'), 3.75 (1H, d, H-2'), 3.55 (1H, dd, H-5'a), 3.2 (1H, dd, H-5'b), 2.97 (1H, d, H-3''a), 2.85 (1H, d, H-3''b). Anal. Calcd for C₁₀H₁₃N₃O₅. H₂O: C, 43.95; H, 5.53; N, 15.38. Found: C, 43.92; H, 5.56; N, 15.65].

The structure of **8** was also confirmed by X-ray diffraction analysis.⁶⁾ We believe that the present method is quite effective for the large scale preparation of 6,3'-methanouridine and related compounds of biochemical interest.

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