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SYNTHESIS OF 2'-METHYLATED PYRIMIDINE C-NUCLEOSIDES[1]

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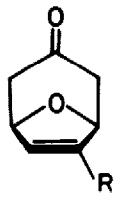
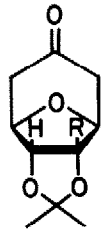
Summary: The title C-nucleosides have been prepared in a direct and stereocontrolled manner through the polybromo ketone/furan cyclocoupling approach.

Introduction of methyl group to the C-2' or C-3' position of certain nucleosides is known to retard the enzymatic destruction, thereby increasing the biological activities markedly.[2] In addition, 2'-methylated nucleosides might be expected to mimic 2'-deoxy nucleosides either by lowering the chemical activity of the 2'-hydroxyl function[3] or by changing conformation of normal ribofuranosyl skeleton. However, only limited number of reports[2,4] are present for the synthesis of such analogues mainly because of difficulty in preparation of branched-chain sugar moieties.[5] Described herein is the first, general synthesis of 2'-methylated pyrimidine C-nucleosides, which is based on the efficiency of the [3 + 4] reductive cyclocoupling reaction of polybromo ketones and furans.[6]

The oxabicyclic ketone I was obtained in 86% yield by the reductive cyclocoupling of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and 3-methylfuran using Zn/Ag couple[7] (3:1:2 ratio, THF, 20 °C, 14 h), followed by removal of bromine atoms from the [3 + 4] adduct (Zn/Cu couple, CH_3OH saturated with NH_4Cl, 20 °C, 1 h). The unsaturated ketone I was then converted specifically to the acetonide II[8] in 78% yield (1.8 equiv of N-methylmorpholine-N-oxide, 1 mol % of OsO_4, $(CH_3)_2CO-H_2O-t\text{-}C_4H_9OH$;[9] then acetone—anhyd $CuSO_4$—p-TsOH). The α configuration was substantiated by occurrence of the NMR signal for the C-3' hydrogen (pseudouridine numbering; indicated as H in formula II) as a singlet at δ 4.15.[10] In the subsequent Baeyer–Villiger oxidation with CF_3CO_3H, presence of the methyl substituent at C-2' gave a bias toward the production of III as the major regioisomer (52% yield[11] or 84% yield based on consumed II, III[12]/IV[13] = 67:33). Then introduction of a one-carbon unit to III at position α to the carbonyl group was effected with t-butoxybis(dimethylamino)methane (excess, DMF, 70 °C, 1 h) to afford V in 63% yield. This compound serves as a versatile intermediate for the synthesis of various pyrimidine C-nucleosides. For example, base-catalyzed reaction of V and urea (7 equiv, 1 M C_2H_5ONa in C_2H_5OH, reflux, 3 h), giving VI[14] (32%), followed by removal of the isopropylidene blocking group (10% HCl in CH_3OH, 25 °C, 60 min, 96%) gave



I



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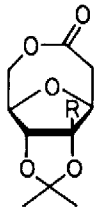

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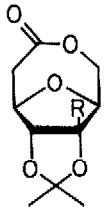

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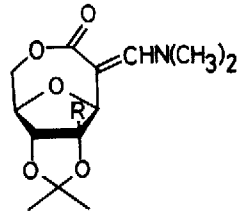
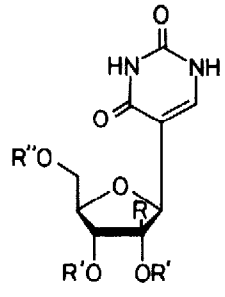


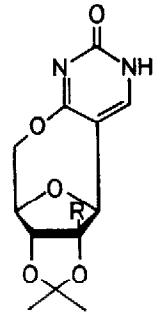
V



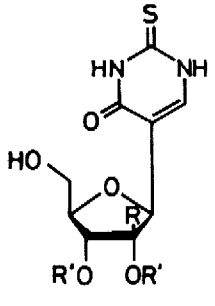
VI, R'—R' = $C(CH_3)_2$; R" = H

VII, R' = R" = H

VIII, R'—R' = $C(CH_3)_2$; R" = SO_2CH_3

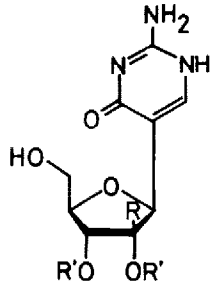


IX



X, R'—R' = $C(CH_3)_2$

XI, R' = H



XII, R'—R' = $C(CH_3)_2$

XIII, R' = H (HCl salt)

All R substituents in the formulas are CH_3 group.

5-(2-methyl-β-ribofuranosyl)uracil (2'-methylpseudouridine) (VII).[15,16] The β stereochemistry at the anomeric, C-1' position was established chemically by converting VI to the cyclo-C-nucleoside IX; the mesylate VIII derived from VI (CH_3SO_2Cl, pyridine, 20 °C, 14 h, 83%) was cyclized by 1,5-diazabicyclo[5.4.0]undec-5-ene (CH_3CN, 80 °C, 3 h)[17] to form IX in 81% yield. When UV spectrum of IX in CH_3OH (λ_{max} 293 nm, ε 3080) was compared with that of the corresponding open form VI (λ_{max} 265 nm, ε 7430), a well-known, characteristic bathochromic shift[18] was observed.

Elaboration of a heterocycle onto the lactone V by use of thiourea (7 equiv, 1 M C_2H_5ONa in C_2H_5OH, reflux, 3 h) and deprotection of the resulting X (10% HCl in CH_3OH) provided 5-(2-methyl-β-ribofuranosyl)-2-thiouracil (XI)[15] in 68% yield. Similarly, condensation of V and guanidine, giving XII, and subsequent acid deblocking under standard conditions led to 5-(2-methyl-β-ribofuranosyl)isocytosine (XIII) as HCl salt[15,19] in 61% yield.

Thus we could open a stereocontrolled, general way to a variety of C-2' alkylated pyrimidine C-nucleosides starting from nonsugar materials.

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5. For synthesis of branched-chain sugars, see H. Grisebach and R. Schmid, Angew. Chem., Int. Ed. Engl., 11, 159 (1972); H. Paulsen, Pure Appl. Chem., 49, 1169 (1977); P.-T. Ho, Tetrahedron Lett., 1623 (1978); P.-T. Ho, Can. J. Chem., 57, 381, 384 (1979).
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7. T. Sato and R. Noyori, Bull. Chem. Soc. Jpn., 51, 2745 (1978).
8. Mp 72.0—73.0 °C. IR ($CHCl_3$) 1720 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.41 (s, CH_3), 1.41 and 1.50 (s, isopropylidene CH_3), 2.2—2.9 (m, H_5 and $H_{5'}$), 4.15 (s, $H_{3'}$), 4.45 (t-like,

J = 5.0 Hz, $H_{1'}$ and $H_{4'}$).

9. V. VanRheenen, R. C. Kelly, and D. Y. Cha, Tetrahedron Lett., 1973 (1976); V. VanRheenen, D. Y. Cha, and W. M. Hartley, Org. Synth., 58, 43 (1978).
10. R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 100, 2561 (1978).
11. The presence of the methyl group retards the oxidation considerably. A competition experiment revealed that II (R = CH_3) reacts four times slower than the parent ketone (II, R = H).
12. Mp 132–133 °C. IR ($CHCl_3$) 1731 cm^{-1} (C=O). ^1H NMR (C_6D_6) δ 1.28 (s, CH_3), 1.28 and 1.48 (s, isopropylidene CH_3), 2.26 (dd, J = 3.2, 17.0 Hz, H_{5a}), 2.52 (dd, J = 4.2, 17.0 Hz, H_{5b}), 3.38 (dd, J = 3.3, 14.6 Hz, $H_{5'a}$), 3.58 (d, J = 14.6 Hz, $H_{5'b}$), 3.82 (m, $H_{1'}$ and $H_{4'}$), 4.34 (s, $H_{3'}$).
13. Mp 129.5–130 °C. IR ($CHCl_3$) 1736 cm^{-1} (C=O). ^1H NMR (C_6D_6) δ 1.32 (s, CH_3), 1.34 and 1.48 (s, isopropylidene CH_3), 2.24 (dd, J = 3.0, 16.0 Hz, H_{5a}), 2.52 (dd, J = 4.8, 16.0 Hz, H_{5b}), 3.38 (dd, J = 3.2, 14.0 Hz, $H_{5'a}$), 3.62 (d, J = 14.0 Hz, $H_{5'b}$), 3.78 (m, $H_{1'}$ and $H_{4'}$), 4.14 (s, $H_{2'}$).
14. Mp 126–128 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 1.12 (s, CH_3), 1.32 and 1.51 (s, isopropylidene CH_3), 3.52 (d-like, J = 4.0 Hz, $H_{5'}$), 3.92 (m, $H_{4'}$), 4.30 (d, J = 3.0 Hz, $H_{3'}$), 4.80 (s, $H_{1'}$), 7.34 (s, H_6).
15. All compounds described here are racemic mixtures.
16. Mp 138–142 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 0.99 (s, CH_3), 3.60 (m, $H_{3'}$, $H_{4'}$, and $H_{5'}$), 4.00 (br, OH), 4.68 (s, $H_{1'}$), 7.60 (d, J = 5.0 Hz, H_6), 10.78 (d, J = 5.0 Hz, H_1), 10.99 (br, H_3). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 20.95 (CH_3), 60.31 ($C_{5'}$), 73.57, 77.99, 81.31, 81.53 ($C_{1'}$–$C_{4'}$ of ribose), 112.13, 138.92, 150. 90, 163.68.
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18. A. M. Michelson and W. E. Cohn, Biochem., 1, 490 (1962).
19. Mp 222–225 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 1.02 (s, CH_3), 3.62 (m, $H_{3'}$, $H_{4'}$, and $H_{5'}$), 4.70 (s, $H_{1'}$), 7.88 (s, H_6), 8.48 (br, NH_2). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 20.84 (CH_3), 60.20 ($C_{5'}$), 73.35, 78.28, 80.97, 81.64 ($C_{1'}$–$C_{4'}$ of ribose), 117.18, 138.33, 152.50, 159.53. UV λ_{max} (CH_3OH) 224 nm (ε 10700), 265 (6890), λ_{max} (0.1N HCl) 222 nm (ε 5800), 264 (4250), λ_{max} (0.1N NaOH) 233 nm (ε 9010), 280 (6750).

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