CHEMISTRY LETTERS, pp. 679-682, 1980.

STEREOCONTROLLED SYNTHESIS OF 1',4'-DIALKYLATED PYRIMIDINE RIBO-C-NUCLEOSIDES[1]

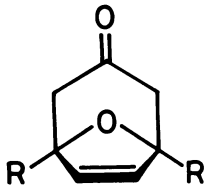
Tsuneo SATO, Makoto WATANABE, and Ryoji NOYORI*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464

The first, stereocontrolled entry to 1',4'-dialkylated pyrimidine C-nucleosides is outlined.

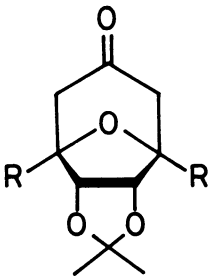
The recent development of the efficiently stereocontrolled entry to ribo-C-nucleosides starting from non-carbohydrate materials[2] prompted us to synthesize various analogues substituted at the ribofuranosyl skeleton. As a part of the program to prepare such analogues, we have synthesized hitherto unknown 1',4'-disubstituted ribo-C-nucleosides.

The oxabicyclic ketone Ia was obtained in 66% yield by the [3 + 4] annulation[3] reaction using $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone, 2,5-dimethylfuran, and Zn/Ag couple[4] (3:1:2 mol ratio, THF, 20 °C, 12 h) followed by treatment of the product with Zn/Cu couple (excess, NH_4Cl–CH_3OH, 0 °C for 2 h and then 20 °C for 1 h). Reaction of Ia with 30% H_2O_2 (3 equiv) and a catalytic amount of OsO_4 (10:1:1 acetone–t-C_4H_9OH–ether, 19 °C, 27 h) and then with excess of $CuSO_4$ and p-TsOH (20 °C, 12 h) led to a single acetonide IIa.[5] The stereochemical assignment was made on the basis the ^1H NMR spectrum exhibiting the $H_{2'}$ and $H_{3'}$ signal (nucleoside numbering) as a singlet at δ 4.30.[6] When IIa was exposed to CF_3CO_3H (2 equiv, CH_2Cl_2, 20 °C, 13 h), the Baeyer–Villiger product IIIa[7] was obtained in 77% yield. Subsequent condensation with tris(dimethylamino)methane[8] (neat, 90 °C, 8 h) afforded the (Z)-dimethylaminomethylene lactone IVa in 38% yield (88% yield based on consumed IIIa). This compound serves as a versatile intermediate for the synthesis of various C-nucleosides. For instance, condensation of IVa with urea (5 equiv, 1 N ethanolic C_2H_5ONa, reflux, 24 h) resulted in the production of Va[9] (28%), which was deprotected with 10% HCl in CH_3OH (20 °C, 1 h) to give quantitatively 5-(1,4-dimethyl-β-ribofuranosyl)uracil (1',4'-dimethylpseudouridine) (VIa).[10] There exists little chance for epimerization at the C-1' position throughout the overall synthetic sequence involving the rigid cyclic intermediates. The β stereochemistry assigned for Va was consistent with the ^1H NMR spectrum (dimethyl-d_6 sulfoxide) giving isopropylidene methyl signals at δ 1.28 and 1.50 ($\Delta\delta$ 0.22 ppm).[11] When thiourea in the cyclization in place of urea, the 2-thiouracil derivative VIIa, leading to VIIIa[12] after acidic deblocking, was obtained in 60% yield. Use of guanidine in the heterocycle formation gave rise to Xa[13] (HCl salt) via IXa (75% yield).

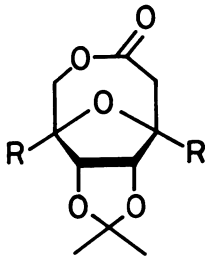
In a similar manner, the 1',4'-dipentyl analogues, VIb,[14] VIIIb, and Xb,[15] have been prepared starting from Ib.[16]



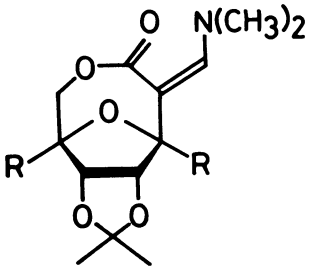
I



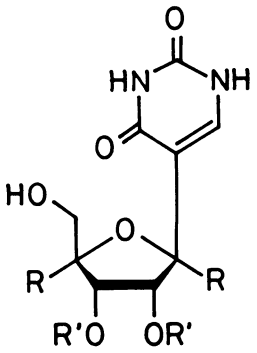
II



III

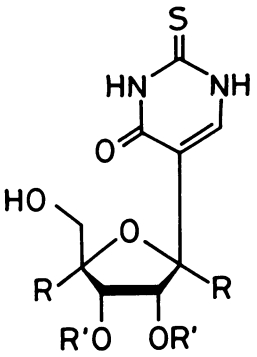


IV



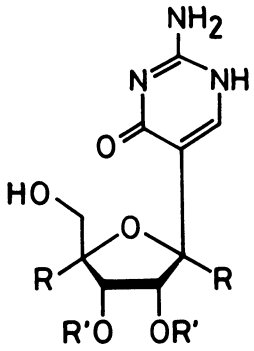
V, R'—R' = $C(CH_3)_3$

VI, R' = H



VII, R'—R' = $C(CH_3)_3$

VIII, R' = H



IX, R'—R' = $C(CH_3)_2$

X, R' = H (HCl salt)

a: R = CH_3, b: R = $\underline{n}$-C_5H_{11}

Thus the present methodology appears to provide a facile, general way to 1',4'-disubstituted C-nucleosides which are not available by the conventional approaches reported to date.

Acknowledgment. This work was partially supported by the Yamada Science Foundation and the Ministry of Education, Japanese Government (Grand-in-aid, 484026).

REFERENCES AND NOTES

1. C-Nucleoside Synthesis. 12. Part 11: T. Sato, M. Watanabe, and R. Noyori, Heterocycles, in press.

2. R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 100, 2561 (1978).

3. R. Noyori, Acc. Chem. Res., 12, 61 (1979).

4. T. Sato and R. Noyori, Bull. Chem. Soc. Jpn., 51, 2745 (1978).

5. Mp 67—68 °C. IR ($CHCl_3$) 1720 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.30 and 1.52 (s, $C(CH_3)_2$), 1.41 (s, CH_3), 2.28 (d, J = 15.0 Hz, H_{5a} and $H_{5'a}$), 2.50 (d, J = 15.0 Hz, H_{5b} and $H_{5'b}$), 4.30 (s, $H_{2'}$ and $H_{3'}$).

6. Typical $H_{2'}$ and $H_{3'}$ chemical shifts ($CDCl_3$, δ) were: II (R = H), 4.53; II (R = H and CH_3), 4.30 and 4.51; II (R = H and n-C_5H_{11}), 4.33 and 4.49; II (R = n-C_5H_{11} and n-C_5H_{11}), 4.30.

7. Mp 123—124 °C. IR ($CHCl_3$) 1735 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.27 and 1.35 (s, CH_3), 1.35 and 1.51 (s, $C(CH_3)_2$), 2.83 (d, J = 16.0 Hz, H_{5a}), 3.07 (d, J = 16.0 Hz, H_{5b}), 4.11 (d, J = 13.5 Hz, $H_{5'a}$), 4.33 (d, J = 13.5 Hz, $H_{5'b}$), 4.56 (d, J = 6.0 Hz, $H_{2'}$), 4.82 (d, J = 6.0 Hz, $H_{3'}$).

8. H. Bredereck, F. Effenberger, and T. Brendle, Angew. Chem., Int. Ed. Engl., 5, 132 (1966); H. H. Wasserman and J. L. Ives, J. Org. Chem., 43, 3238 (1978).

9. Mp 126—134 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 1.18 and 1.28 (s, CH_3), 1.28 and 1.50 (s, $C(CH_3)_2$), 3.19 (m, $H_{5'}$), 4.45 (d, J = 6.2 Hz, $H_{2'}$), 4.48 (d, J = 6.2 Hz, $H_{3'}$), 4.95 (br, OH), 7.47 (s, H_6), 10.80 (br, NH). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 19.65 and 24.94 (CH_3), 24.41 and 25.59 ($C(CH_3)_2$), 66.30 ($C_{5'}$), 82.95, 83.12, 84.71, 85.18 ($C_{1'}$—$C_{4'}$ of ribose), 111.36 ($C(CH_3)_2$), 117.30, 138.01, 151.48, 163.18.

10. Mp 134—138 °C. ^1H NMR (C_5D_5N) δ 1.78 and 2.14 (s, CH_3), 3.96 (s, $H_{5'}$), 4.87 (d, J = 5.5 Hz, $H_{2'}$), 5.05 (d, J = 5.5 Hz, $H_{3'}$), 6.24 (br, OH), 8.48 (br s, H_6), 12.50 (br, H_1), 13.04 (br, H_3). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 19.74 and 23.46 (CH_3), 67.24 ($C_{5'}$), 72.11, 75.80, 82.23, 84.53 ($C_{1'}$—$C_{4'}$ of ribose), 117.80, 139.04, 151.60, 164.15. UV λ_{max} (CH_3OH) 265 nm (ε 6190), λ_{max} (0.1 N NaOH) 287 nm (ε 4760).

11. In the ^1H NMR spectrum of 5'-O-trityl derivative of V (R = H) in $CDCl_3$, the isopropylidene methyls exhibited singlets at δ 1.32 and 1.56 ($\Delta\delta$ 0.24 ppm). Its α isomer afforded the methyl signals at δ 1.27 and 1.39 ($\Delta\delta$ 0.12 ppm). See C. K. Chu, I. Wempen, K. A. Watanabe, and J. J. Fox, J. Org. Chem., 41, 2793 (1976).

12. Mp 182—186 °C. ^1H NMR (C_5D_5N) δ 1.75 and 2.13 (s, CH_3), 3.98 (s, $H_{5'}$), 4.86 (d, J = 5.2 Hz, $H_{2'}$), 4.97 (d, J = 5.2 Hz, $H_{3'}$), 6.50 (br, OH), 8.65 (s, H_6). ^{13}C NMR (dimethyl-d_6

sulfoxide) δ 19.59 and 22.88 (CH_3), 66.42 ($C_{5'}$), 71.24, 75.06, 81.95, 84.30 ($C_{1'}$–$C_{4'}$ of ribose), 123.01, 138.83, 160.89, 175.01.

13. Mp 215–220 °C. ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 1.12 and 1.39 (s, CH_3), 3.29 (s, $H_{5'}$), 3.90 (d, J = 5.7 Hz, $H_{2'}$), 4.11 (d, J = 5.7 Hz, $H_{3'}$), 7.94 (s, H_6), 8.37 (br, NH_2). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 19.47 and 22.77 (CH_3), 66.07 ($C_{5'}$), 70.95, 74.83, 81.77, 84.24 ($C_{1'}$–$C_{4'}$ of ribose), 122.18, 137.78, 152.54, 159.42.

14. Mp 232–236 °C. ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 0.86 (m, CH_3), 1.0–2.1 (m, CH_2), 3.51 (br s, $H_{5'}$), 4.03 (m, $H_{2'}$ and $H_{3'}$), 4.81 (br, OH), 7.51 (m, H_6), 10.88 (br, H_1), 11.00 (br s, H_3). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 13.73, 21.98, 22.40, 22.58, 31.62, 31.77, 32.35, 32.77 (n-C_5H_{11}), 63.93 ($C_{5'}$), 72.11, 76.65, 83.80, 85.65 ($C_{1'}$–$C_{4'}$ of ribose), 115.67, 138.98, 151.07, 163.94. UV λ_{max} (CH_3OH) 265 nm (ε 7240), λ_{max} (0.1 N NaOH) 290 nm (ε 7200), λ_{max} (0.1 N HCl) 265 nm (ε 2300).

15. Mp 245–250 °C. ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 0.87 (m, CH_3), 1.0–2.0 (m, CH_2), 3.19 (d, J = 7.1 Hz, $H_{5'a}$), 3.33 (d, J = 7.1 Hz, $H_{5'b}$), 4.04 (m, $H_{2'}$ and $H_{3'}$), 4.0–5.2 (br, OH), 7.82 (s, H_6), 8.30 (br, NH_2). ^{13}C NMR (dimethyl-d_6 sulfoxide) δ 14.02, 22.28, 22.59, 32.20, 32.64 (n-C_5H_{11}), 63.95 ($C_{5'}$), 72.06, 76.55, 84.14, 86.08 ($C_{1'}$–$C_{4'}$ of ribose), 120.55, 139.68, 153.32, 160.33. UV λ_{max} (CH_3OH) 263 nm (ε 5230), λ_{max} (0.1 N NaOH) 230 nm (ε 6780), 278 (3920), λ_{max} (0.1 N HCl) 265 nm (ε 3720).

16. All compounds described herein are racemic.

(Received March 10, 1980)