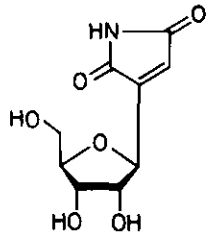
SYNTHESIS OF HOMOSHOWDOMYCIN AND HOMOPYRAZOMYCIN[1]

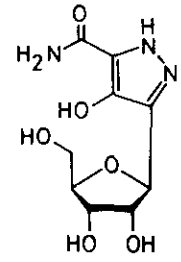
T. Sato and R. Noyori*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

Abstract — An efficiently stereocontrolled entry to the title homo-C-nucleosides is described.

Showdomycin (I)[2] and pyrazomycin (II)[3] are C-nucleosides that possess marked antibacterial and antitumor activities.[4] Disclosed herein is the synthesis of homoshowdomycin (VII) and homopyrazomycin (XII), the analogues in which the ribofuranosyl group and nitrogen heterocycle are linked by a methylene unit. The synthesis starting from the readily available chiral lactone III[2e, 2f] has been accomplished in a stereospecific manner.



I



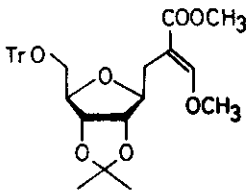
II

The lactone III can be converted to IV easily as reported earlier.[1] Ozonolysis of IV in ethyl acetate at -78 °C followed by workup with dimethyl sulfide[5] produces the keto ester V, which without purification was subjected to the Wittig condensation with carbamoylmethylenetriphenylphosphorane[2b, 2d, 6] (1.3 equiv, $CHCl_3$, 25 °C, 30 min) to give a 23:77 mixture of the maleimide derivative VI[7] and uncyclized VIII[8] having an E double bond (66% yield based on IV). The reaction conditions were mild enough to maintain the C-β-glycoside structure throughout such transformation. In the NMR spectra of VI ($CDCl_3$), the isopropylidene methyls exhibited ^1H signals at δ 1.34 and 1.54 (Δδ 0.20 ppm)[9] and ^{13}C signals at δ 25.53 and 27.44 (Δδ 1.91 ppm),[10] in accord with the assigned configuration. A direct method for converting VIII to VI has not yet been found, but VIII could be subjected to recycle use, since upon ozonolysis it reverted to the keto ester V. Finally treatment of VI with 9:1 trifluoroacetic acid—water (25 °C, 45 min) afforded 2-(β-D-ribofuranosyl)methylmaleimide (homoshowdomycin) (VII)[11] in 90% yield.

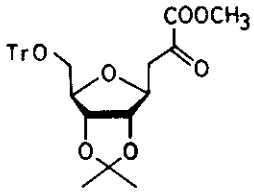
When the keto ester V was treated with ethyl hydrazinoacetate hydrochloride and sodium acetate (2 equiv each, CH_3OH—THF—H_2O, 25 °C, 12 h), the hydrazone IX was obtained (47% yield based on IV). Cyclization was then effected by 0.29 N methanolic sodium methoxide

(reflux, 4.5 h)[12] to form X.[13] Ammonolysis of X (NH_3/CH_3OH, 25 °C, 4 days, 75%), giving XI,[14] followed by removal of the protective groups in 90% aqueous trifluoroacetic acid (25 °C, 20 min, 87%) completed the synthesis of 3-(β-D-ribofuranosyl)methyl-4-hydroxypyrazole-5-carboxamide (homopyrazomycin) (XII).[15]

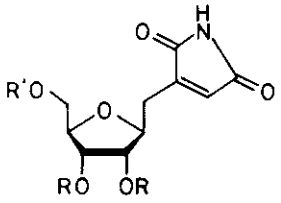
III



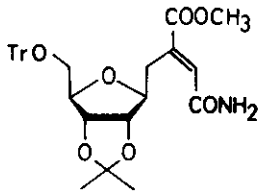
IV



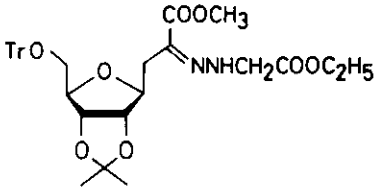
V



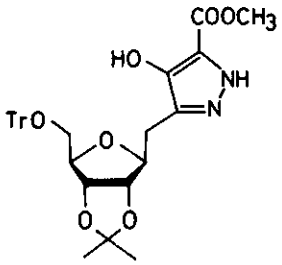
VI, R—R = $C(CH_3)_2$, R' = Tr
VII, R = R' = H



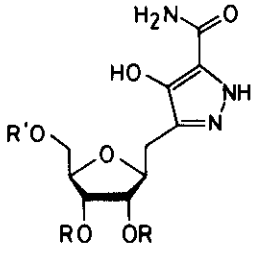
VIII



IX



X



XI, R—R = $C(CH_3)_2$, R' = Tr
XII, R = R' = H

Acknowledgement. This work was partially supported by grants from the Yamada Science Foundation and the Ministry of Education, Japanese Government (Grant-in-aid, No. 401538).

REFERENCES AND NOTES

1. C-Nucleoside Synthesis. VIII. Part VII: T. Sato, K. Marunouchi, and R. Noyori, Tetrahedron Lett., in press.
2. Synthesis: (a) L. Kalvoda, J. Farkas, and F. Sorm, Tetrahedron Lett., 1970, 2297; (b) G. Trummlitz and J. G. Moffatt, J. Org. Chem., 1973, 38, 1841; (c) L. Kalvoda, J. Carbohydr., Nucleosides Nucleotides, 1976, 3, 47; (d) H. Minato, Y. Katsuyama, T. Nagasaki, J. Irisawa, and K. Igarashi, J. Labelled Compd. Radiopharm., 1978, 14, 455; (e) R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 1978, 100, 2561; (f) T. Sato, R. Ito, Y. Hayakawa, and R. Noyori, Tetrahedron Lett., 1978, 1829; (g) J. G. Buchanan, A. R. Edger, M. J. Power, and C. T. Shanks, J. Chem. Soc., Perkin Trans.1, 1979, 225.
3. Synthesis: (a) J. Farkas, Z. Flegelova, and F. Sorm, Tetrahedron Lett., 1972, 2279; (b) S. D. Bernardo and M. Weigele, J. Org. Chem., 1976, 41, 287.
4. Review: R. J. Suhadolnik, ' Nucleoside Antibiotics ', Wiley-Interscience, New York, N.Y., 1970, pp. 390—403.
5. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, Tetrahedron Lett., 1966, 4273.
6. (a) S. Trippett and D. M. Walker, J. Chem. Soc., 1959, 3874; (b) G. Just and S. Kim, Tetrahedron Lett., 1976, 1063; (c) G. Just and M.-I. Lim, Can. J. Chem., 1977, 55, 2993; (d) G. Just and G. P. Donnini, ibid., 1977, 55, 2998.
7. Foam. IR ($CHCl_3$) 3440 (NH), 1781 and 1728 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.34 and 1.54 (s, isopropylidene CH_3), 2.79 (m, CH_2-maleimide), 3.20 (dd, J = 4.8, 10.5 Hz, $H_{5'a}$), 3.35 (dd, J = 4.0, 10.5 Hz, $H_{5'b}$), 4.18 (m, $H_{1'}$ and $H_{4'}$), 4.45 (dd, J = 4.9, 6.1 Hz, $H_{2'}$), 4.67 (dd, J = 3.5, 6.1 Hz, $H_{3'}$), 6.51 (m, H_3), 7.30 (m, Tr), 7.94 (br, NH). UV λ_{max} (CH_3OH) 221 nm (sh, ε 13500).
8. Foam. IR ($CHCl_3$) 3470 and 3310 (NH), 1708 and 1668 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.32 and 1.52 (s, isopropylidene CH_3), 2.87 (dd, J = 9.1, 13.1 Hz, H_aH_bC=), 3.11 (dd, J = 5.0, 13.1 Hz, H_aH_bC=), 3.24 (dd, J = 3.6, 12.8 Hz, $H_{5'a}$), 3.38 (dd, J = 4.2, 12.8 Hz, $H_{5'b}$), 3.74 (s, OCH_3), 4.07 (m, $H_{1'}$ and $H_{4'}$), 4.45 (dd, J = 5.0, 6.2 Hz, $H_{2'}$), 4.64 (dd, J = 4.8, 5.0 Hz, $H_{3'}$), 6.44 (br, NH_2), 6.97 (s, =$CHCONH_2$), 7.30 (m, Tr).
9. J.-L. Imbach, Ann. N.Y. Acad. Sci., 1975, 255, 177.
10. (a) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, J. Am. Chem. Soc., 1975, 97, 4602; (b) J. A. Secrist III, J. Org. Chem., 1978, 43, 2925.
11. Mp 150—154 °C. $[\alpha]^{20}_D$ -24° (c 0.20, CH_3OH). ^1H NMR (acetone-d_6) δ 2.70 (m, CH_2-maleimide), 3.66 (m, $H_{5'}$), 3.82 (m, $H_{1'}$ and $H_{4'}$), 4.16 (m, $H_{2'}$ and $H_{3'}$), 4.0—5.0 (br, OH), 6.56 (m, H_3), 9.52 (br, NH). ^{13}C NMR (acetone-d_6) δ 61.36 ($C_{5'}$), 70.68, 74.39, 80.10,

84.30 ($C_{1'}$–$C_{4'}$ of ribose), 146.41, 173.32, CH_2-maleimide obscured by acetone peaks. UV λ_{max} (CH_3OH) 222 nm (ε 10200).

12. The cyclization was carried out according to the method of G. Just and S. Kim, Can. J. Chem., 1977, 55, 427.

13. Foam. IR ($CHCl_3$) 3580–3200 (NH and OH), 1698 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.35 and 1.54 (s, isopropylidene CH_3), 2.92 (dd, J = 7.3, 15.9 Hz, CH_aH_b-pyrazole), 3.15 (dd, J = 4.6, 15.9 Hz, CH_aH_b-pyrazole), 3.25 (dd, J = 5.0, 10.5 Hz, $H_{5'a}$), 3.41 (dd, J = 4.0, 10.5 Hz, $H_{5'b}$), 3.95 (s, OCH_3), 4.12 (m, $H_{1'}$ and $H_{4'}$), 4.56 (m, $H_{2'}$ and $H_{3'}$), 7.32 (m, Tr). UV λ_{max} (CH_3OH) 228 nm (sh, ε 14200), 268 (4830).

14. Foam. IR ($CHCl_3$) 3580–3200 (NH and OH), 1675 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.30 and 1.50 (s, isopropylidene CH_3), 2.87 (dd, J = 7.9, 15.1 Hz, CH_aH_b-pyrazole), 3.19 (dd, J = 3.5, 15.1 Hz, CH_aH_b-pyrazole), 3.21 (dd, J = 5.5, 10.3 Hz, $H_{5'a}$), 3.46 (dd, J = 3.2, 10.3 Hz, $H_{5'b}$), 4.22 (m, $H_{1'}$ and $H_{4'}$), 4.49 (m, $H_{2'}$ and $H_{3'}$), 5.97 and 6.67 (br, NH_2), 7.30 (m, Tr), 8.03 (br, NH and OH). UV λ_{max} (CH_3OH) 227 nm (sh, ε 14300), 268 (5100).

15. Mp 109–113 °C. $[\alpha]_D^{21}$ -22° (c 0.23, CH_3OH). ^1H NMR (D_2O) δ 3.01 (m, CH_2-pyrazole), 3.73 (m, $H_{5'}$), 3.90–4.30 (m, $H_{1'}$, $H_{2'}$, $H_{3'}$, $H_{4'}$). ^{13}C NMR (D_2O) δ 30.38 (CH_2-pyrazole), 64.82 ($C_{5'}$), 74.25, 77.20, 84.80, 86.78 ($C_{1'}$–$C_{4'}$ of ribose), 132.31, 169.21. UV λ_{max} (H_2O) 223 nm (ε 8630), 266 (5150), λ_{max} (0.1 N NaOH) 235 nm (ε 4330), 311 (5460).

Received, 27th August, 1979