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TOTAL SYNTHESIS AND THE ABSOLUTE CONFIGURATION OF AUROVERTIN B

Shigeru Nishiyama, Hiroaki Toshima, Hiroki Kanai, and Shosuke Yamamura*
Department of Chemistry, Faculty of Science and Technology, Keio University,
Hiyoshi, Yokohama, Japan

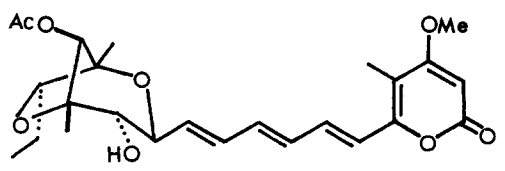
Summary: Aurovertin B, a metabolite of Calcarisporium arbuscula, has been synthesized starting from D-glucose, in connection with which, its absolute configuration has been unambiguously determined.

In connection with citreoviridin, citreoviridinol and related mycotoxins,[1] we herein describe a total synthesis of aurovertin B (1),[2] a potent inhibitor of ATP-synthesis and ATP-hydrolysis catalyzed by mitochondrial enzyme system, starting from D-glucose. In addition, the absolute configuration of aurovertin B has been unambiguously established as 1.

The known diketal (2),[3] which was derived from D-glucose, was readily converted into the corresponding monoketal (3)[4] in 5 steps [1) BnBr - NaH in DMF (0 °C - room temp., 1.5 h), 2) 1% aq.H_2SO_4 in MeOH (room temp., 2 days), 3) MsCl - pyridine in CH_2Cl_2 (0 °C - room temp., 6 h), 4) NaI in MeCOEt (refluxing temp., 18 h), 5) H_2/10% Pd-C in MeOH (room temp., 18 h), 90% overall yield from 2]. This ketal (3) was further converted into an α,β-unsaturated ester (4),[4] in 4 steps [1) 80% aq.AcOH (80 °C, 20 h), 2) $NaIO_4$ (1.5 equiv.) in MeOH - H_2O (1 : 1) (room temp., 1 h), 3) Ph_3P=C(Me)COOMe in benzene (refluxing temp., 20 h), 4) K_2CO_3 (1 equiv.) in MeOH (room temp., 30 min), 81% overall yield from 3], which was treated with $CH_2(OMe)_2$ - P_2O_5 in $CHCl_3$ (room temp., 1 h) and then with diisobutylaluminium hydride (4.5 equiv.) in THF (-78 °C, 1.5 h) to afford an allyl alcohol (5),[4,5] in 93% yield. On treatment with m-chloroperbenzoic acid (1.2 equiv.) in CH_2Cl_2 (-35 - -20 °C, 25 h), 5 was stereoselectively[6] converted into a desired epoxide (6),[4] in 90% yield, which was further subjected to Swern oxidation [$(COCl)_2$ (1.5 equiv.) - DMSO (3.0 equiv.) - Et_3N (5 equiv.) in CH_2Cl_2 (-50 °C, 15 min)] followed by Wittig reaction [Ph_3P=CHCOOEt in benzene (room temp., 2 h)] to afford an α,β-unsaturated ester (7),[4] in 93% yield. Then, stereospecific cyclization of 7 was carried out using CF_3COOH in $CHCl_3$ (room temp., 10 min) to give rise to a desired tetrahydrofuran (8)[4] in 94% yield.

In the next step, a 2,6-dioxabicyclo[3.2.1]octane (9) accommodated in the structure of aurovertin B (1) was synthesized in regio- and stereospecific manner, as follows.

The tetrahydrofuran (8) so far obtained was readily converted into an allyl alcohol (10)[4] in 4 steps [1) DIBAL-H in THF (-78 °C, 1 h), 2) Trityl chloride - pyridine in CH_2Cl_2 (room temp., 22 h), 3) Ac_2O in pyridine (room temp., 2.5 h), 4) p-TsOH in MeOH (room temp., 1 h), 87% overall yield from 8]. On treatment of 10 with m-chloroperbenzoic acid (1.2 equiv.) in CH_2Cl_2 (0 °C - room temp., 1 day), an undesired epoxide (11)[4,7] was obtained in 91% yield. As expected, however, epoxidation of 10 was carried out under Sharpless condition [$Ti(OPr^i)_4$ (1.4 equiv.) - D-(-)-DET (1.4 equiv.) - TBHP (3.3 equiv.) in CH_2Cl_2 (-20 °C, 12 h)][8] to afford



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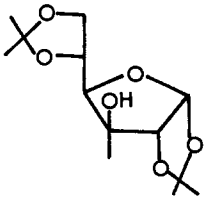

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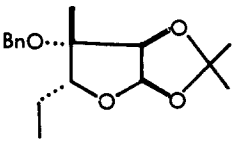

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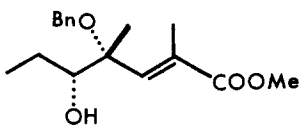

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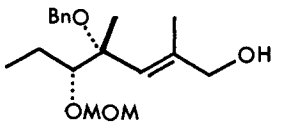

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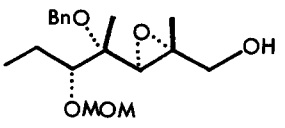

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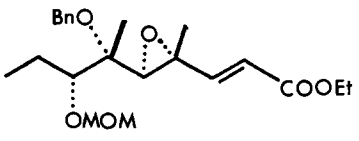

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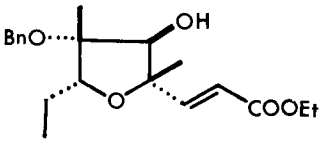

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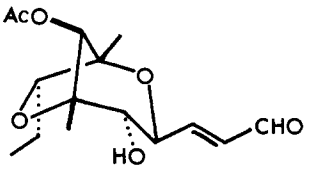

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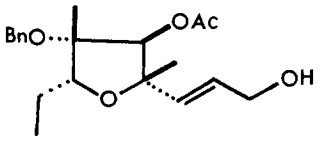

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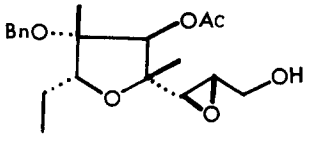

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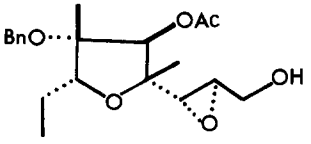

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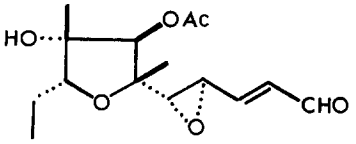

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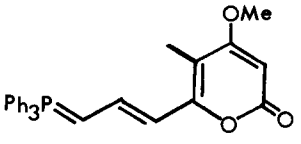

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a desired epoxide (12)[4,7] in 99% yield. Furthermore, this epoxide (12) was subjected to catalytic hydrogenation [H_2/Pd black in MeOH (room temp., 30 min)] followed successively by Swern oxidation [$(COCl)_2$ (1.5 equiv.) - DMSO (3.0 equiv.) - Et_3N (5.0 equiv.) in CH_2Cl_2 (-50 °C, 15 min)], Wittig reaction [Ph_3P=CHCHO in benzene (room temp., 1.5 h)] giving an α,β-unsaturated aldehyde (13),[4] and then stereospecific cyclization using camphorsulfonic acid in CH_2Cl_2 (room temp., 3 h) to afford a desired 2,6-dioxabicyclo[3.2.1]octane (9),[4] in 50% overall yield from 12.

Finally, when treated with a triphenylphosphorane (14)[9] in THF (0 °C - refluxing temp., 45 h),[10] the α,β-unsaturated aldehyde (9) was successfully converted into the corresponding condensation product, in 22% yield, which was identical with natural aurovertin B (1) in all respects of spectral data.[1] Particularly, the optical rotation of the synthetic sample ($[\alpha]_D^{27}$ -57.9° (c 0.125, EtOH)) is in a good agreement with that of natural aurovertin B (1) ($[\alpha]_D^{20}$ -50.6° (EtOH)),[1] indicating that the absolute configuration of aurovertin B is the same as that of citreoviridin which has been already synthesized from D-glucose.[9]

This research has been supported in part by grants from the Ministry of Education, Science and Culture, to which grateful acknowledgment is made.

References and Notes

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3. M. Funabashi, H. Sato, and J. Yoshimura, Bull. Chem. Soc. Jpn., 49, 788 (1976).
4. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: 3: $C_{17}H_{24}O_4$ [m/z 277.1438(M^+ - Me)]; δ($CDCl_3$) 1.05(3H, t, J= 7.5Hz), 1.70(2H, m), 4.55(2H, s), and 7.31(5H, br.s). 4: $C_{17}H_{24}O_4$ [m/z 293.1725 (M^+ + 1)]; IR (film) 3500, 1710, and 1640 cm^{-1}; δ($CDCl_3$) 1.02(3H, t, J= 7.5Hz), 1.40 (2H, m), 1.42(3H, s), 2.05(3H, d, J= 1Hz), 3.66(1H, m), 3.78(3H, s), 4.30(1H, d, J= 11Hz), 4.43(1H, d, J= 11Hz), 5.59(1H, q, J= 1Hz), and 7.33(5H, br.s). 5: $C_{18}H_{28}O_4$ [m/z 277.1802 (M^+ - OMe)]; IR (film) 3450 cm^{-1}; δ($CDCl_3$) 1.82(3H, s), 3.98(2H, br.s), and 5.31(1H, br.s). 6: $C_{18}H_{28}O_5$ [m/z 325.1982(M^+ + 1)]; δ($CDCl_3$) 1.29(3H, s) and 3.25(1H, s). 7: $C_{22}H_{32}O_6$ [m/z 347.1857(M^+ - OEt)]; IR (film) 1720 and 1650 cm^{-1}; δ($CDCl_3$) 1.28(3H, t, J= 7.5Hz), 4.18(2H, q, J= 7.5Hz), 6.01(1H, d, J= 16Hz), and 6.80(1H, d, J= 16Hz). 8: $C_{20}H_{28}O_5$ [m/z 348.1935(M^+)]; IR (film) 3460 and 1710 cm^{-1}; δ($CDCl_3$) 3.73(1H, d, J= 4.5, 7.5Hz), 4.08(2H, q, J= 7.5Hz), and ca. 4.1(1H, overlapped with the quartet at δ4.08). 9: mp 138 - 140 °C; $C_{15}H_{22}O_6$ [m/z 298.1425(M^+)]; $[\alpha]_D^{26}$ -45.8° (c 1.06, $CHCl_3$); IR (film) 3450, 1740, and 1690 cm^{-1}; δ($CDCl_3$) 1.07(3H, t, J= 7.5Hz), 1.19(3H, s), 1.26(3H, s), 1.62(2H, m), 2.16(3H, s), 3.33(1H, dd, J= 8, 11Hz), 3.93(1H, t, J= 7Hz), 4.32(1H, m), 4.76(1H, s), 6.40(1H, ddd, J= 1.5, 8, 15.5Hz), 6.97(1H, dd, J= 4, 15.5Hz), and 9.60(1H, d, J= 8Hz). 10: $C_{20}H_{28}O_5$ [m/z 348.1915(M^+)]; IR (film) 3450 and 1740 cm^{-1}; δ($CDCl_3$) 2.14(3H, s) and 5.34(1H, s). 11: $C_{20}H_{28}O_6$ [m/z 364.1846(M^+)]; δ($CDCl_3$) 3.00(1H, m), 3.20(1H, d, J= 2Hz), and 3.3 - 3.8(3H, complex). 12: $C_{20}H_{28}O_6$ [m/z 364.1867(M^+)]; IR (film) 3450 and 1740 cm^{-1}; δ($CDCl_3$) 3.09(1H, d, J= 2Hz), 3.25(2H, m), and 3.4 - 3.7(2H, complex). The compound (13) has not yet been obtained in completely pure state, but its structure is supported by the following ^1H NMR spectral data: δ($CDCl_3$) 1.01(3H, t, J= 7.5Hz), 1.17(3H, s), 1.20(3H, s), 1.40 - 1.75(2H, complex), 2.13(3H, s), 3.19(1H, d, J= 2.5Hz), 3.53(1H, dd, J= 6, 8Hz), 3.89(1H, dd, J= 2.5, 6Hz), 4.74(1H, s), 6.39(1H, dd, J= 6, 16.5Hz), 6.60(1H, dd, J= 6, 16.5Hz), and 9.60(1H, d, J= 6Hz).
5. This compound (5) can be produced from methyl cis-2-methyl-2-pentenoate according to essentially the same procedure as that of citreoviral: Y. Shizuri, S. Nishiyama, H. Shigemori, and S. Yamamura, 50th Annual Meeting of the Chemical Society of Japan, Tokyo, April

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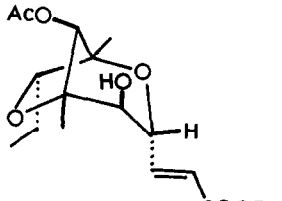
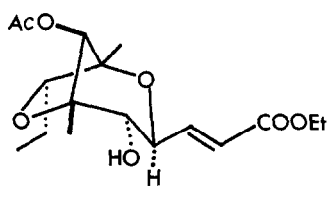
6. M. R. Johnson and Y. Kishi, Tetrahedron Lett., 1979, 4347; S. Hatakeyama, Y. Matsui, M. Suzuki, K. Sakurai, and S. Takano, ibid., 26, 6485 (1985).
7. Both epoxides (11 and 12) have been readily converted into the corresponding 2,6-dioxabicyclo[3.2.1]octanes [A] and [B], respectively, in regio- and stereospecific manner [1) H_2/Pd black in MeOH, 2) Swern oxidation, 3) Wittig reaction using Ph_3P=CHCOOEt, 4) p-TsOH in benzene]. Their structures have been supported by the following spectral data: [A]: $C_{17}H_{26}O_7$ [m/z 342.1654(M^+)]; IR (film) 3500, 1740, 1720, and 1640 cm^{-1}; $\delta(CDCl_3)$ 0.98(3H, t, J= 7.5Hz), 1.18(3H, s), 1.23(3H, s), 1.27(3H, t, J= 7.5Hz), 1.53(2H, m), 2.14 (3H, s), 3.60(2H, complex), 4.19(2H, q, J= 7.5Hz), 4.22(1H, m), 5.50(1H, s), 6.10(1H, dd, J= 2, 17Hz), and 6.98(1H, dd, J= 5, 17Hz). [B]: $C_{17}H_{26}O_7$ [m/z 342.1661(M^+)]; IR (film) 3500, 1740, 1720, and 1640 cm^{-1}; $\delta(CDCl_3)$ 1.05(3H, t, J= 7.5Hz), 1.17(3H, s), 1.24(3H, s), 1.27(3H, t, J= 7.5Hz), 1.61(2H, m), 2.15(3H, s), 3.28(1H, dd, J= 8.5, 10Hz), 3.92 (1H, t, J= 6.5Hz), 4.19(2H, q, J= 7.5Hz), 4.20(1H, m), 4.74(1H, s), 6.13(1H, dd, J= 2, 16Hz), and 7.07(1H, dd, J= 4.5, 16Hz).



[A]



[B]

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10. The reaction condition for this Wittig reaction is not always optimum.

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