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TOTAL SYNTHESIS AND THE ABSOLUTE CONFIGURATION OF CITREOVIRAL AND CITREOVIRIDIN

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Summary: Both citreoviral and citreoviridin, metabolites of Penicillium citreo-viride B., have been synthesized starting from D-glucose, in connection with which their absolute configuration has also been established.

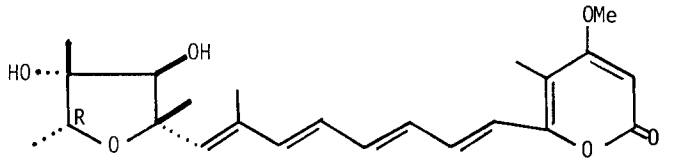
In connection with citreoviridin (1), a potent inhibitor of ATP-synthesis and ATP-hydrolysis catalyzed by mitochondrial enzyme system,[1] we have isolated more than 10 novel metabolites of Penicillium citreo-viride B. (IFO 6050 and 6200), including citreoviral (2).[2] Recent publications of synthetic studies on citreoviridin[3] and asteltoxin[4] prompted us to describe the total synthesis of citreoviral and citreoviridin, starting from D-glucose. In connection with D-glucose, furthermore, we could determine the absolute configuration of these two metabolites (1 and 2), which remained unsettled, as described herein.

The known dibenzyl ether (3), which was derived from D-glucose,[5] was readily converted into the corresponding hexanol (4)[6] in 4 steps [1) Ac_2O - BF_3·etherate (0 °C, 1 h), 2) 0.4M NaOMe in MeOH (room temp., overnight), 3) excess $NaBH_4$ in H_2O - MeOH (1 : 2) (room temp., 5 h), 4) p-TsOH - Drierite in acetone (room temp., 1 h)], in 40% overall yield from 3. Catalytic hydrogenation of 4 over Pd - C in MeOH (room temp., 24 h) afforded a triol (5),[7] in quantitative yield, which was then treated with $NaIO_4$ (2.1 equiv.) in MeOH - H_2O (1 : 1) (room temp., 2.5 h) followed by Wittig reaction [Ph_3P=C(Me)COOMe in benzene (room temp., 11 h and then 70 °C, 1 h)] to give an $\alpha\beta$-unsaturated ester (6)[8] in 64% yield. In 3 steps [1) DIBAL-H in toluene (-78 °C, 2 h), 2) PDC in DMF (0 °C, 1.5 h), 3) Ph_3P=C(Me)COOMe in benzene (refluxing temp., 4 h)], furthermore, the ester (6) was converted into an $\alpha\beta,\gamma\delta$-unsaturated ester (7),[9] in 79% overall yield from 6, which was treated with Amberlite IR - 120 (H^+) in MeOH - H_2O (2 : 1) at room temperature for 2 h to give a diol (8)[10] in 77% yield. In the next step, the desirable tetrahydrofuran ring corresponding to both citreoviridin (1) and citreoviral (2) was constructed in 2 steps from 8, as follows.

On epoxidation[11] with m-chloroperbenzoic acid (1.5 equiv.) in CH_2Cl_2 (0 °C, 3 h) followed by stereospecific cyclization [CsOH in CH_2Cl_2 (room temp., 1.5 h)], the diol (8) was readily converted into two cyclization products (9 and 10)[12] in 72% yield (9/10 = 3/4). As monitored by analytical TLC, the latter (10) was formed in the process of epoxidation followed by simultaneous intramolecular cyclization, while the epoxide corresponding to 9 was rather stable and its stereospecific cyclization took place on treatment with CsOH giving rise to 9.

Finally, the compound (9) was reduced with DIBAL-H (5 equiv.) in THF (-78 °C, 1 h) and then treated with active MnO_2 in CH_2Cl_2 (room temp., 4 h) to afford an aldehyde, in 57%

yield, which was completely identical with natural citreoviral (2) in all respects of their spectral data. Particularly, the optical rotation of the synthetic aldehyde ($[\alpha]_D^{30}$ +21.1° (c 2.5, $CHCl_3$)) is identical with that of the natural one ($[\alpha]_D^{30}$ +19.9° (c 1.8, $CHCl_3$)),[2,13] indicating that the absolute stereostructures of both citreoviridin and citreoviral are depicted as 1 and 2, respectively.



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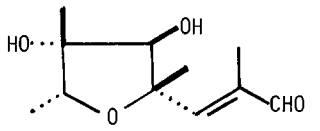

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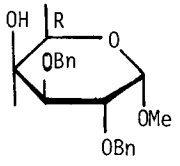

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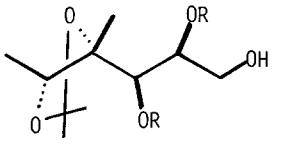
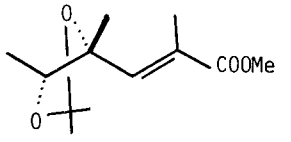


4 R = Bn
5 R = H



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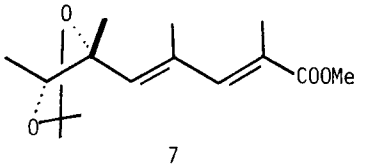

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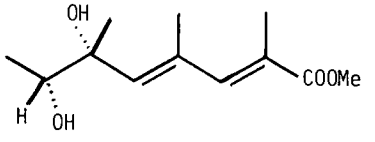

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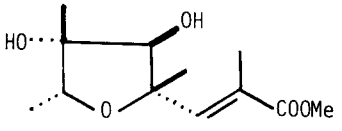

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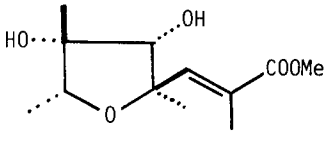

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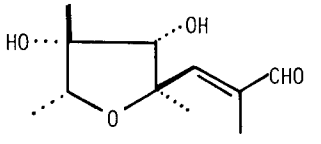

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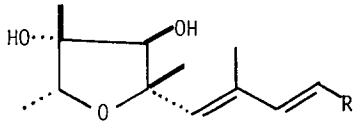
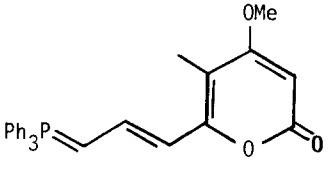
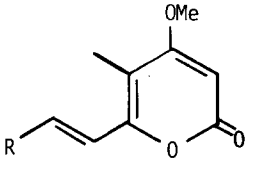


12 R = CH_2OH
13 R = CHO



14



15 R = CHO
16 R = CH_2OH
17 R = CH_2OMs
18 R = CH_2Cl

According to essentially the same procedure as described in 9 [1) DIBAL-H (5 equiv.) in THF (-78 °C, 1 h), 2) excess MnO_2 in CH_2Cl_2 (room temp., 13 h)], 10 was readily converted into the corresponding aldehyde (11),[14] in 42% yield, whose optical rotation ($[\alpha]_D^{30}$ -22.9° (c 1.2, $CHCl_3$)) is negative in contrast to that of citreoviral (2).

Finally, citreoviridin (1) was synthesized from citreoviral (2), as follows. Citreoviral (2) was subjected to Wittig reaction [Ph_3P=CHCOOEt in benzene (room temp., overnight)] followed by reduction with DIBAL-H (5 equiv.) in THF (-78 °C, 1.5 h) to give a triol (12),[15] in 64% overall yield from 2, which was further oxidized with active MnO_2 in CH_2Cl_2 (room temp., 4 h) to afford a desirable $\alpha\beta,\gamma\delta$-unsaturated aldehyde (13),[16] in 57% yield. When treated with a triphenylphosphorane (14) in benzene (0 °C, 1 h), 13 was successfully converted into a desirable condensation product, in ca. 10% yield,[17] which was completely identical with natural citreoviridin (1) in all respects of spectral data and chromatographic behavior (TLC and HPLC). In the above reaction, the triphenylphosphorane (14) was readily produced from secocitreoviridin (15), which had been already synthesized by Suzuki et al.,[18] in 4 steps: 15 was quantitatively reduced with DIBAL-H (1 equiv.) in THF (-78 °C, 3 h) giving a hydroxy compound (16)[19] and then treated with mesyl chloride - pyridine in CH_2Cl_2 (0 °C, 2 h) to afford a mixture of a mesylate (17) and a chloride (18),[20] in almost quantitative yield, which was directly treated with triphenylphosphine in benzene (refluxing temp., 2 days) and then with NaH in THF (0 °C, 1 h) to give the triphenylphosphorane (14).

This is the first synthesis of citreoviridin (1). In addition, it should be noted that the absolute configuration of both citreoviridin (1) and citreoviral (2) was established in connection with D-glucose. Furthermore, many mycotoxins related to citreoviridin (1) are expected to have the same absolute configuration as that of 1.

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

1. M. Niwa, S. Ogiso, T. Endo, H. Furukawa, and S. Yamamura, Tetrahedron Lett., 21, 4481 (1980); M. Niwa, T. Endo, S. Ogiso, H. Furukawa, and S. Yamamura, Chem. Lett., 1981, 1285; Y. Shizuri, M. Niwa, H. Furukawa, and S. Yamamura, Tetrahedron Lett., 24, 1053 (1983); Y. Shizuri, S. Kosemura, S. Yamamura, H. Furukawa, K. Kawai, and N. Okada, ibid., 25, 1583 (1984).

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3. C. S. Wilcox, G. W. Long, and H. Suh, Tetrahedron Lett., 25, 395 (1984).

4. S. L. Schreiber and K. Satake, J. Am. Chem. Soc., 105, 6723 (1983).

5. M. Matsuzawa, K. Sato, T. Yasumori, and J. Yoshimura, Bull. Chem. Soc. Jpn., 54, 3505 (1981).

6. 4 as an oil; $C_{24}H_{32}O_5$ [m/z 401.2314(M^+ + 1)]; $[\alpha]_D^{26}$ -10.0° (c 2.4, $CHCl_3$); IR (film) 3550 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.18(3H, s), 1.23(3H, d, J= 6Hz), 1.35(3H, s), 1.43(3H, s), 2.95(1H, br.s), 3.50 - 3.90(4H, complex), 4.00(1H, q, J= 6Hz), 4.58(1H, d, J= 10.5Hz), 4.68(2H, s), 4.99(1H, d, J= 10.5Hz), and 7.35(10H, br.s).

7. 5 as an oil; $C_{10}H_{20}O_5$ [m/z 205.1070(M^+ - 15)]; $[\alpha]_D^{30}$ -15.0° (c 0.68, $CHCl_3$); IR (film) 3450 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.18(3H, s), 1.30(3H, d, J= 6Hz), 1.38(3H, s), 1.45(3H, s), 3.50(5H, complex), 3.75(2H, complex), and 4.17(1H, q, J= 6Hz).

8. 6 as an oil: $C_{12}H_{20}O_4$ [m/z 213.1123(M^+ - 15)]; $[\alpha]_D^{30}$ -25.3° (c 2.0, $CHCl_3$); IR (film) 1720 and 1655 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.23(3H, s), 1.28(3H, d, J= 6Hz), 1.35(3H, s), 1.47 (3H, s), 2.08(3H, d, J= 1Hz), 3.77(3H, s), 4.05(1H, q, J= 6Hz), and 6.62(1H, q, J= 1Hz).

9. 7 as an oil: $C_{15}H_{24}O_4$ [m/z 253.1434(M^+ - 15)]; $[\alpha]_D^{27}$ -28.4° (c 8.0, $CHCl_3$); IR (film) 1715 and 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.20(3H, d, J= 6Hz), 1.22(3H, s), 1.33(3H, s), 1.43 (3H, s), 1.95(3H, d, J= 1Hz), 2.00(3H, d, J= 1Hz), 3.77(3H, s), 4.02(1H, q, J= 6Hz), 5.40 (1H, br.s), and 7.10(1H, br.s).

10. 8 as an oil: $C_{12}H_{20}O_4$ [m/z 229.1443(M^+ + 1)]; $[\alpha]_D^{27}$ -15.9° (c 1.9, $CHCl_3$); IR (film) 3470, 1705, 1620 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.19(3H, d, J= 6Hz), 1.35(3H, s), 1.98(3H, d, J= 1Hz), 2.08(3H, d, J= 1Hz), 2.30(2H, br.s), 3.80(3H, s), 3.83(1H, q, J= 6Hz), 5.55(1H, br.s), and 7.10(1H, br.s).

11. The oxidation condition for epoxidation is not always optimum. Further study of stereospecific epoxidation of 8 giving 9 is is progress, using other reagents.

12. 9 as an oil: $C_{12}H_{20}O_5$ [m/z 226.1207(M^+ - 18)]; $[\alpha]_D^{26}$ +3.3° (c 3.7, $CHCl_3$); IR (film) 3470, 1700, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.20(3H, d, J= 6Hz), 1.23(3H, s), 1.35(3H, s), 1.97(3H, d, J= 1Hz), 1.97(2H, overlapped with Me doublet, OH), 3.75(3H, s), 3.83 (1H, q, J= 6Hz), 3.97(1H, br.s), and 7.02(1H, q, J= 1Hz).
10 as an oil: $C_{12}H_{20}O_5$ [m/z 226.1201(M^+ - 18)]; $[\alpha]_D^{25}$ -4.3° (c 4.5, $CHCl_3$); IR (film) 3500, 1710, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.22(3H, s), 1.25(3H, d, J= 6Hz), 1.30(3H, s), 1.88(1H, br.s), 1.98(3H, d, J= 1Hz), 2.93(1H, d, J= 10.5Hz), 3.58(1H, q, J= 6Hz), 3.77 (3H, s), 3.84(1H, d, J= 10.5Hz), and 6.95(1H, q, J= 1Hz).

13. The value of optical rotation cited in the previous paper (see ref. 2) should be corrected.

14. 11 as an oil: $C_{11}H_{18}O_4$ [m/z 214.1231(M^+)]; IR (film) 3450, 1690, and 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.30(3H, d, J= 6Hz), 1.30(3H, s), 1.43(3H, s), 1.97(3H, d, J= 1Hz), 1.97(1H, overlapped with Me doublet), 3.12(1H, d, J= 9Hz), 3.67(1H, q, J= 6Hz), 3.92(1H, d, J= 9Hz), 6.67(1H, q, J= 1Hz), and 9.45(1H, s).

15. 12 as an oil; $C_{13}H_{22}O_4$ [m/z 242.1494(M^+)]; $[\alpha]_D^{26}$ -20.1° (c 2.1, $CHCl_3$); IR (film) 3400 and 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.17(3H, d, J= 6Hz), 1.23(3H, s), 1.38(3H, s), 1.93(3H, br.s), 1.97(2H, br.s), 2.58(1H, d, J= 6Hz), 3.80(1H, q, J= 6Hz), 3.93(1H, d, J= 6Hz), 4.18 (2H, d, J= 6Hz), 5.78(1H, br.s), 5.82(1H, dt, J= 15, 6Hz), and 6.25(1H, d, J= 15Hz).

16. 13 as an oil: $C_{13}H_{20}O_4$ [m/z 240.1359(M^+)]; $[\alpha]_D^{27}$ -27.6° (c 0.98, $CHCl_3$); IR (film) 3450, 1675, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.22(3H, d, J= 6Hz), 1.28(3H, s), 1.43(3H, s), 2.00 (3H, br.s), 2.00(2H, overlapped with Me signal), 3.87(1H, q, J= 6Hz), 4.00(1H, br.s), 6.20(1H, dd, J= 15, 9Hz), 6.33(1H, br.s), 7.15(1H, d, J= 15Hz), and 9.65(1H, d, J= 9Hz).

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

18. E. Suzuki, B. Katsuragawa, and S. Inoue, J. Chem. Research (S), 1982, 224. This pyrone has also been synthesized by G. Pattenden (University of Nottingham) (private communication from Prof. Pattenden).

19. 16: mp 158 - 160 °C; $C_{10}H_{12}O_4$ [m/z 196.0732(M^+)]; IR (Nujol) 3480, 1735, 1700, 1665, 1630, and 1570 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.98(3H, s), 3.87(3H, s), 4.38(2H, d, J= 4.5Hz), 5.50(1H, s), 6.55(1H, d, J= 16.5Hz), and 6.85(1H, dt, 16.5, 4.5Hz).

20. This mixture was directly used for the next experiment without separation. Clearly, this mixture includes the two compounds (16 and 17), as judged from its ^1H NMR spectrum ($CDCl_3$): δ1.95(3H, s), 3.02(2H, s; $MeSO_3$), 3.87(3H, s), 4.23(2/3H, d, J= 6Hz; $ClCH_2$), 4.90(4/3H, d, J= 6Hz; $MeSO_3CH_2$), 5.51(1H, s), and 6.70(2H, complex).

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