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Isolation, Structural Elucidation, and Total Synthesis of Epiisocitreoviridinol

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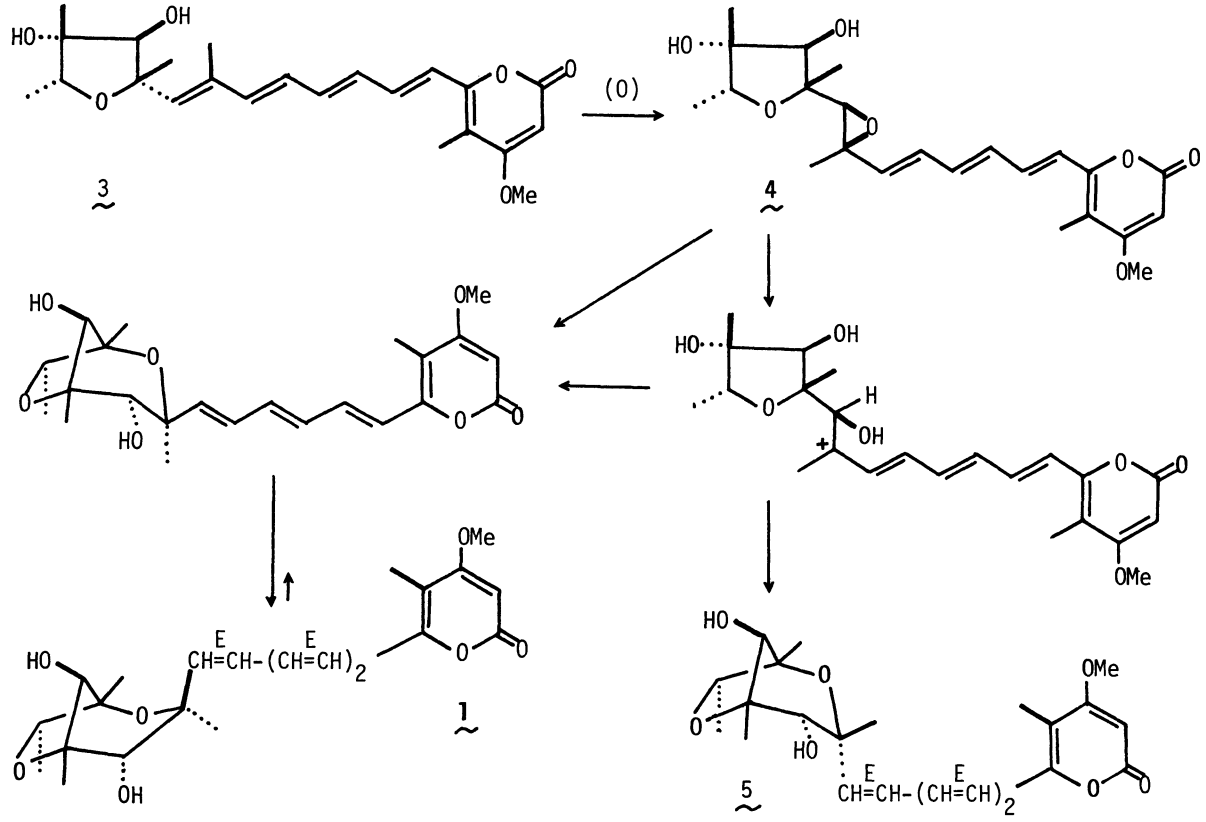
Epiisocitreoviridinol, biogenetically relevant to citreoviridinol, has been isolated as a new metabolite of Penicillium citreo-viride B. (IFO 6049). Its stereostructure including the absolute configuration has been determined unambiguously by its total synthesis in optically active form.

In connection with citreoviridin, a potent inhibitor of ATP-synthesis and ATP-hydrolysis catalyzed by mitochondrial enzyme system, we have isolated citreoviridinol and isocitreoviridinol, metabolites of Penicillium citreo-viride B. (IFO 6050),[1] both of which have a 2,6-dioxabicyclo[3.2.1]octane skeleton. In the light of recent studies on biosyntheses of citreoviridin[2] and aurovertin B,[3] both of which have the same absolute configuration in their non-chromophore moiety,[4] the metabolite (1) corresponding to aurovertin B (2)[3,5] must be formed from citreoviridin (3) through a plausible epoxide (4), as shown in Scheme 1, wherein the epoxide ring may be cleaved very easily at the fully substituted allylic position giving rise to 1 and citreoviridinol (5).[1] In this case, it is possible that the former (1) is directly formed from the epoxide (4) in concerted manner. Thus, further careful examination of toxic compounds produced by Penicillium citreo-viride B. (IFO 6049) resulted in the isolation of epiisocitreoviridinol (1), an isomer of citreoviridinol (5) and isocitreoviridinol (6).[1] We describe herein structural determination of the newly isolated toxin (1) by means of its total synthesis.

According to essentially the same procedure as described in the previous paper,[1] the ethyl acetate extract of the yellow rice was chromatographed on silica gel (Katayama Chemicals Type 60) using a gradient solvent of MeOH - $CHCl_3$. The fraction eluted with 5% MeOH - $CHCl_3$, containing citreoviridin (3) as a main component, was further separated by repeating preparative TLC (Kieselgel PF_{254}) using successively $CHCl_3$ - MeOH (15 : 1), hexane - acetone (3 : 2), hexane - EtOAc (1 : 3), and then $CHCl_3$ - MeOH (15 : 1) to afford epiisocitreoviridinol (1) in 0.041% yield[6] as a pale yellow oil: $C_{23}H_{30}O_7$ [m/z 418.1982 (M^+)]; IR (film) 3420, 1685, 1610, 1560, and 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20(3H, d, J =

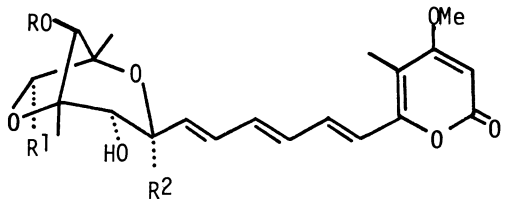
6 Hz), 1.28(3H, s), 1.34(3H, s), 1.37(3H, s), 1.80(1H, d, J = 6 Hz), 1.97(3H, s), 3.29(1H, d, J = 11 Hz), 3.59(1H, d, J = 11 Hz), 3.84(3H, s), 4.09(1H, q, J = 6 Hz), 4.26(1H, d, J = 5 Hz), 5.51(1H, s), 5.96(1H, d, J = 15 Hz), 6.3 - 6.5(4H, complex), and 7.19(1H, dd, J = 11, 15 Hz).



Scheme 1. Biogenesis of epiisocitreoviridinol (1) and citreoviridinol (5).

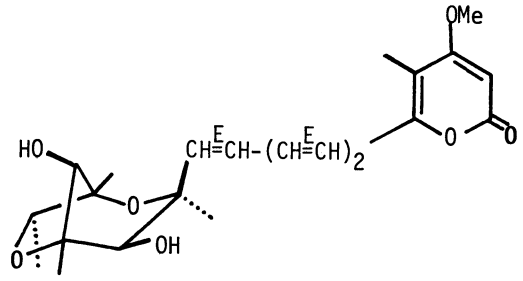
In the ^{1}H NMR spectrum of 1, some characteristic signals such as methyl signals and conjugated olefinic pattern indicated that 1 has a citreoviridinol-type structure possessing a 2,6-dioxabicyclo[3.2.1]octane attached to a pyrone via conjugated olefinic chain. Further detailed comparison of the ^{1}H NMR frequences in these three metabolites (1, 5, and 6) strongly suggested that epiisocitreoviridinol has 12S and 13S stereochemistries, as depicted in 1. Finally, the stereostructure of epiisocitreoviridinol was determined unambiguously by its synthesis, as follows.

In the course of our structural studies on citreoviridinol (5) and isocitreoviridinol (6), we have already synthesized the optically active α,β-unsaturated ester (7) from the synthetic citreoviral in 4 steps.[1] This ester (7) was successfully converted into the corresponding aldehyde (8)[7] in 2 steps [1) DIBAL-H in THF (-78 °C, 2 h), 70% yield; 2) MnO_2 in CH_2Cl_2 (4 °C, overnight), 100% yield]. Further condensation of the aldehyde (8) with the known



1 R = H, R^1 = R^2 = Me

2 R = Ac, R^1 = Et, R^2 = H



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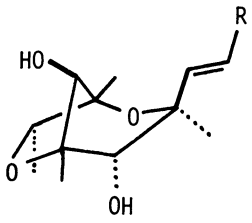
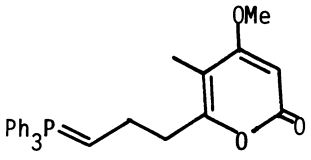


7 R = COOEt

8 R = CHO



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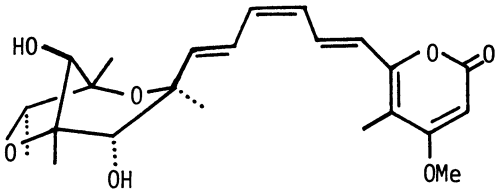

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triphenylphosphorane (9)[8] in refluxing THF for 4 h afforded a desired product (1) as well as its cis isomer (10)[9] in 49 and 45% yields, respectively. The synthetic compound (1) was completely identical with an authentic sample of epiisocitreoviridinol in all respects of spectral (^{1}H NMR, IR, and Mass) and chromatographycal (TLC) data. Particularly, an optical rotation of the synthetic compound ($[\alpha]_D^{31}$ +16.1° (c 0.18, $CHCl_3$)) was nicely fitted to that of natural epiisocitreoviridinol (1) ($[\alpha]_D^{28}$ +17.4° (c 0.23, $CHCl_3$)).

From a biogenetic point of view, isocitreoviridinol (6) seems to be formed on enzymatic epoxidation which takes place at the opposite side as compared with the epoxide (4). As seen in Scheme 1, probably, 4 is converted into both epiisocitreoviridinol (1) and citreoviridinol (5).

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References

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5) L. J. Mulheirn, R. B. Beechey, and D. P. Leworthy, J. Chem. Soc., Chem. Commun., 1974, 874.

6) Based on the weight of the AcOEt extract.

7) The aldehyde (8) as needles (hexane - AcOEt): mp 126 - 128 °C; $C_{13}H_{20}O_5$ [m/z 256.1302 (M^+)]; $[\alpha]_D^{31}$ -23.8° (c 0.8, $CHCl_3$); IR (film) 3400, 1670, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.20(3H, d, J = 6.3 Hz), 1.33(6H, s). 1.37(3H, s), 3.34(1H, d, J = 10.7 Hz), 3.66(1H, d, J = 10.7 Hz), 3.95(1H, s), 4.11(1H, q, J = 6.3 Hz), 6.30(1H, dd, J = 7.8, 15.6 Hz), 6.91(1H, d, J = 15.6 Hz), and 9.57(1H, d, J = 7.8 Hz).

8) S. Nishiyama, H. Toshima, and S. Yamamura, Chem. Lett., 1986, 1973.

9) The structure of 10 could be confirmed by the following data: $C_{23}H_{30}O_7$ [m/z 418.1999 (M^+)]; IR (film) 3400, 1720 (sh), 1700 (sh), 1690, 1610, and 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.19(3H, d, J = 6.4 Hz), 1.30(3H, s), 1.39(3H, s), 1.40(3H, s), 1.93(3H, s), 3.33(1H, d, J = 10.5 Hz), 3.62(1H, d, J = 10.5 Hz), 3.85(3H, s), 4.14(1H, q, J = 6.4 Hz), 4.31(1H, d, J = 3.5 Hz), 5.51(1H, s), 5.98(1H, d, J = 15.4 Hz), 6.19(1H, t, J = 9.8 Hz), 6.35 - 6.44(2H, complex), 6.72(1H, dd, J = 15.4, 9.8 Hz), and 7.57(1H, dd, J = 15.4, 9.8 Hz).

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