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Total Syntheses of Citreoviridinol and Neocitreoviridinol

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Both citreoviridinol and neocitreoviridinol, metabolites of Penicillium citreo-viride B., have been synthesized from the known synthetic intermediate of citreoviridin, in regio- and stereoselective manner.

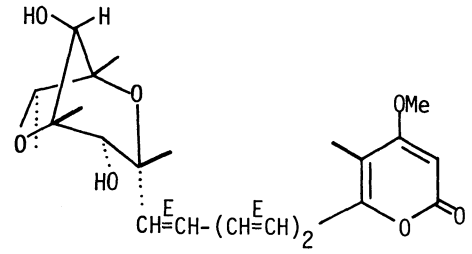
In connection with citreoviridin, a potent inhibitor of ATP-synthesis and ATP-hydrolysis catalyzed by mitochondrial enzyme system, we have isolated a number of novel metabolites of Penicillium citreo-viride B., of which the representative ones, citreoviridinol (1)[1] and neocitreoviridinol (2),[2] have a 2,6-dioxabicyclo[3.2.1]octane and a 2,5-dioxabicyclo[2.2.1]heptane, respectively, as a non-chromophore moiety in their structures. The recent publication[3] of synthetic study on citreoviridinol (1) and related compounds prompted us to describe total syntheses of citreoviridinol (1) and neocitreoviridinol (2), as follows.

In the course of our structural studies on these two metabolites (1 and 2), we have already synthesized the two promising synthetic intermediates (3 and 4) for them,[1,2] wherein both 3 and 4 have been regio- and stereoselectively obtained from the common epoxide (5) which has been derived from the known synthetic intermediate of citreoviridin.[4]

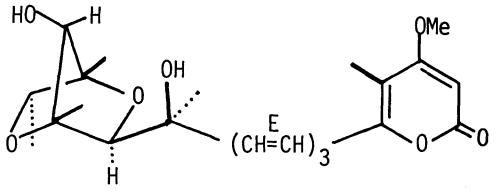
The compound (3) was further converted into an inseparable mixture of the desired two diastereoisomers (6a and 6b)[5] in 3 steps [1) CH_2=CH(OEt) - p-TsOH in THF (room temp, 30 min); 2) DIBAL-H (7 equiv.) in THF (-70 °C, 2 h); 3) MnO_2 (15 equiv.) in CH_2Cl_2 (room temp, 1 h); 89% overall yield]. This mixture was further subjected to Wittig reaction using the known triphenylphosphorane (7)[4,6] in THF (refluxing temp, 17 h) followed successively by acetylation with Ac_2O in pyridine (room temp, overnight), deacetalization with 0.5M HCl in THF (0 °C, 5 h), oxidation with DMSO - DCC in benzene containing pyridine and TFA (0 °C, overnight), reduction with $NaBH_4$ in EtOH (0 °C, 1 h),[1] and then deacetylation with excess K_2CO_3 in MeOH (0 °C, 2 h) to give rise to a desired condensation product (1) and its geometrical isomer (8)[7] in 20 and 8.4% overall yields, respectively.[8] The former ($[\alpha]_D^{31}$ -32.6° (c 0.12, $CHCl_3$)) was completely identical with an authentic sample of citreoviridinol (1)[1] in all respects of spectral data (IR and ^{1}H NMR) and chromatographic behavior (TLC) using a variety of solvent systems.

As mentioned earlier,[2] the known α,β-unsaturated ester (4) was also treated

with DIBAL-H (8 equiv.) in THF (-70 °C, 2 h) to afford an allyl alcohol, in ca. 55% yield, which was further oxidized with MnO_2 (10 equiv.) in CH_2Cl_2 (room temp, 100 min) to give rise to a desired aldehyde (9)[9] in ca. 75% yield. Finally, this aldehyde (9) was treated with the known triphenylphosphorane (7)[4,10] in THF (refluxing temp, 24 h) to afford a desired condensation product (2) and its geometrical isomer (10)[11] in 44 and 11.5% yields, respectively. The former ($[\alpha]_D^{27}$ -25.6° (c 0.29, $CHCl_3$)) was completely identical with an authentic sample



1



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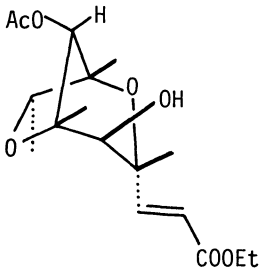

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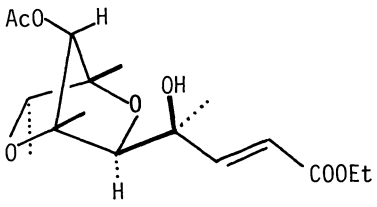

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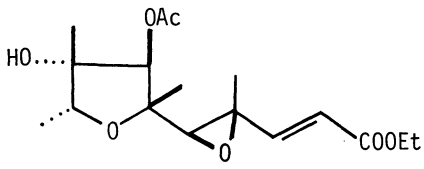

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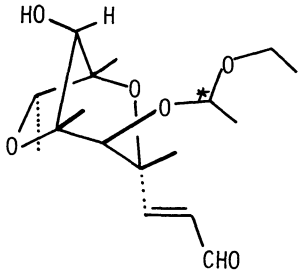
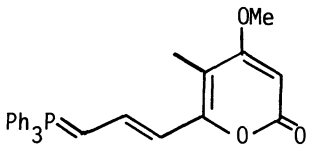


6a,b



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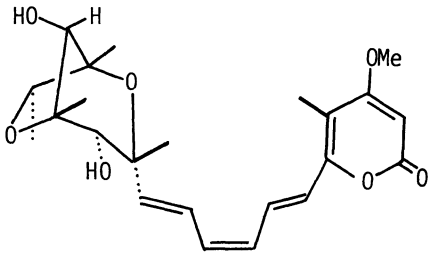

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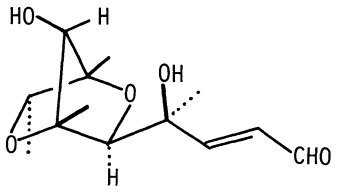

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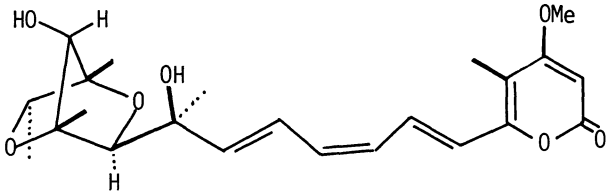

10

of neocitreoviridinol (2)[2] in all respects of spectral data (IR and ^{1}H NMR) and chromatographic behavior (TLC). In the present experiment, our synthetic neocitreoviridinol was obtained as pale yellow crystals (mp 216 - 218 °C from benzene - $CHCl_3$), although the natural one was reported as a syrup.[2,12] The structure of the isomer (10) was also confirmed by its spectral data: particularly, the ^{1}H NMR signals at δ 6.12 and 6.20 indicate the presence of one cis double bond.

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References

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2) S. Nishiyama, Y. Shizuri, S. Yamamura, Y. Terada, K. Kawai, and H. Furukawa, Tetrahedron Lett., 26, 6239 (1985).

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4) S. Nishiyama, Y. Shizuri, and S. Yamamura, Tetrahedron Lett., 26, 231 (1985).

5) These two diastereoisomers (6a and 6b) were obtained as an inseparable mixture. However, their structures are supported by the following spectral data: $C_{17}H_{28}O_6$ [m/z 283.1538(M^+ - OEt)]; IR (film) 3430, 1685, and 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.1 - 1.4(18H, complex), 3.3 - 3.7(2.5H, complex), 3.8 - 4.1(2.5H, complex), 4.55(1H, complex), 6.03 and 6.25(total 1H, dd, J = 7.5, 15 Hz), 7.12 and 7.15(total 1H, d, J = 15 Hz), and 9.53(1H, d, J = 7.5 Hz).

6) The reaction procedure cited in the reference 4 has been improved, resulting in almost quantitative yields of the condensation products containing diastereo- and geometrical isomers: to a solution of the mixture (6a and 6b) in THF was added a solution of the triphenylphosphorane (7) generated from the corresponding bromide and NaH in THF (room temp, 1 h), and then the solution was stirred at refluxing temperature for 17 h.

7) The structure of the isomer (8) is supported by its spectral data: $C_{23}H_{30}O_7$ [m/z 418.1988(M^+)]; IR (film) 3400, 1685, 1610, 1560 (sh), and 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.23(3H, d, J = 6.8 Hz), 1.33(3H, s), 1.39(3H, s), 1.49 (3H, s), 1.98(3H, s), 2.81(1H, d, J = 11 Hz), 3.55(1H, d, J = 11 Hz), 3.84(3H, s), 4.08(1H, d, J = 5 Hz), 4.14(1H, q, J = 6.8Hz), 5.51(1H, s), 6.1 - 6.5(4H, complex), 6.89(1H, dd, J = 12, 15 Hz), and 7.56(1H, dd, J = 12, 15 Hz).

8) In this case, we also obtained, in ca. 18% yield, a structurally undetermined compound with the same molecular formula as those of 1 and 8.

9) 9 as a colorless oil: $C_{13}H_{20}O_5$ [m/z 239.1296(M^+ - OH)]; $[\alpha]_D^{25}$ -80.5° (c 0.10, $CHCl_3$); IR (film) 3400, 1670, and 1630 (sh) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.20 (3H, s), 1.25(3H, d, J = 6.4 Hz), 1.29(3H, s), 1.40(3H, s), 1.76(1H, d, J = 8

Hz), 3.78(1H, s), 3.91(1H, d, J = 8 Hz), 4.08(1H, q, J = 6.4 Hz), 6.39(1H, dd, J = 7.8, 15.6 Hz), 6.81(1H, d, J = 15.6 Hz), and 9.60(1H, d, J = 7.8 Hz).

10) According to essentially the same procedure as cited in the reference 6, this condensation reaction was carried out.

11) 10 as a syrup: $C_{23}H_{30}O_7$ [m/z 418.1983(M^+)]; IR (film) 3400, 1690, 1615, 1560 (sh), and 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.23(3H, s), 1.25(3H, d, J = 6.3 Hz), 1.29(3H, s), 1.36(3H, s), 1.98(3H, s), 3.72(1H, s), 3.84(3H, s), 3.96(1H, d, J = 8 Hz), 4.07(1H, q, J = 6.3 Hz), 5.52(1H, s), 5.85(1H, d, J = 15 Hz), 6.12(1H, t, J = 11 Hz), 6.20(1H, t, J = 11 Hz), 6.38(1H, d, J = 15 Hz), 6.90(1H, dd, J = 11, 15 Hz), and 7.58(1H, dd, J = 11, 15Hz).

12) On treatment with Ac_2O in pyridine (room temp, overnight), the secondary hydroxyl group of the synthetic neocitreoviridinol was readily acetylated to give the corresponding monoacetate, which was completely identical with acetylneocitreoviridinol[2] in all respects of spectral data (MS, IR, and ^1H NMR) and chromatographic behavior (TLC). Particularly, the optical rotation of the synthetic sample ($[\alpha]_D^{28}$ +57.5° (c 0.15, $CHCl_3$)) is roughly compatible with that of the latter ($[\alpha]_D^{30}$ +49° (c 0.11, $CHCl_3$)).

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