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NATURAL POLYENE PYRONES. SYNTHESIS OF THE 2,6-DIOXABICYCLO[3.2.1]OCTANE UNIT OF CITREOVIRIDINOL

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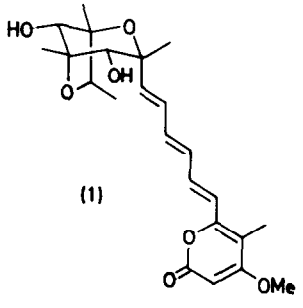
Summary: The 2,6-dioxabicyclo[3.2.1]octane unit, viz 10, present in citreoviridinol (1) has been produced in a stereoselective manner by treatment of the epoxide (8) derived from citreoviral (6), via (7), with p-toluenesulphonic acid.

Citreoviridinol (1), citreoviridin (2) and citreomontanin (3) are members of a biogenetically connected group of polyene pyrone metabolites isolated from Penicillium sp.[1] Citreoviridinol is structurally related to the aurovertins, e.g. aurovertin B (4), produced by Calcarisporium arbuscula.[2] Both citreoviridin and aurovertin B have been found to be potent inhibitors of ATP synthesis and ATP hydrolysis catalysed by mitochondrial enzyme systems. It seems highly probable that citreoviridinol (1) is derived in Nature, via citreoviridin (2), by successive epoxidations (perhaps accompanied by 1,2-diol formation) of the trisubstituted double bonds associated with the terminal triene segment of citreomontanin (3).† In the accompanying papers[4,5] we have



(1)

described total syntheses of all-E-citreomontanin (3) and of citreoviral (6) which is a co-metabolite of citreoviridin in P.citreoviride.[6] The synthesis of citreoviral (6) was achieved via the intermediate epoxy-diol (5), thus

† At the outset of this work, the full stereochemistry of naturally derived citreoviridinol (1) was not known with certainty; see ref.3.

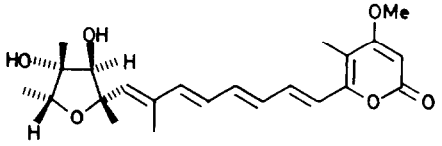
providing some evidence for the biogenetic speculation mentioned above. In this Letter, we describe the elaboration of synthetic citreoviral (6) to the 2,6-dioxabicyclo[3.2.1]octane unit (10) via the epoxide (8), which paints in a further part of the picture of the probable biosynthetic interrelationships between (1), (2) and (3).

Synthetic (±)-citreoviral (6)[5] was first treated with methoxycarbonylmethylenetriphenylphosphorane (C_6H_6, 25°C; 3 days) to provide the E,E-dienoate (7; 70%)[7] as an oil, which showed ν_{max} 3560, 3420, 1700, 1625 $cm.^{-1}$, δ7.26 (d, J 15, :CH), 6.14 (br, :CH), 5.86 (d, J 15, :CH), 3.95 (br, CH), 3.82 (q, J 6, CHMe), 3.74 (OMe), 1.94 (d, J 1, :CMe), 1.36 (Me), 1.21 (Me), 1.15 (d, J 6, CHMe) p.p.m.

Reaction between the E,E-dienoate (7) and meta-chloroperbenzoic acid (1.5 equiv. in CH_2Cl_2, 25°C; 24 h) then led to a clean 2:1 mixture of monoepoxides which was separated by chromatography [silica G; 3:1 diethyl ether-light petroleum (b.p. 40-60°C)]. The major epoxide showed spectral data, ν_{max} 3440, 1710, 1645 $cm.^{-1}$, δ6.76 (d, J 15, :CH), 6.03 (d, J 15, :CH), 3.97 [br, CH(OH)], 3.84 (q, J 6, CHMe), 3.75 (OMe), 2.83 (CH.O), 1.74 (MeC.O), 1.31 (Me), 1.19 (Me), 1.13 (d, J 6, CHMe) consonant with the α-oriented isomer (8), whereas the minor epoxide was assigned the β-configuration (9), δ6.77 (d, J 15, :CH), 6.01 (d, J 15, :CH), 4.0 [br, CH(OH)], 3.74 (q, J 6, CHMe), 3.74 (OMe), 3.12 (CH.O), 1.52 (MeC.O), 1.3 (Me), 1.21 (Me) 1.19 (d, J 6, CHMe) p.p.m.

Treatment of the α-epoxide (8) with catalytic p-toluenesulphonic acid (dry C_6H_6, 25°C; 3 h) resulted in its smooth stereoselective transformation to a single 2,6-dioxabicyclo[3.2.1]octane. The dioxabicyclooctane was assigned the relative stereochemistry (10) on the basis of its method of formation, and by comparison of its p.m.r. shift data, δ7.2 (d, J 15, :CH), 5.87 (d, J 15, :CH), 4.12 (d, J 5, CHOH), 4.04 (q, J 6, CHMe), 3.87 (d, J 5, CHOH), 3.74 (OMe), 2.16 (d, J 5, CHOH), 1.82 (d, J 5, CHOH), 1.37 (Me), 1.34 (Me), 1.23 (Me), 1.17 (d, J 6, CHMe) p.p.m. with those of natural citreoviridinol and its degradation products.[8] The 2,6-dioxabicyclo[3.2.1]octane derivative (10) correlates with natural citreoviridinol (1), except that the secondary OH group in (10) is in an axial configuration.[8] In a similar manner, treatment of the β-epoxide (9) with p-toluenesulphonic acid resulted in facile cyclisation to the corresponding isomeric 2,6-dioxabicyclo[3.2.1]octane (11)[9], δ7.06 (d, J 15, :CH), 6.05 (d, J 15, :CH), 4.09 (q, J 6, CHMe), 4.06 (br, CHOH), 3.76(OMe), 3.62 (d, J 10, CHOH), 3.3 (d, J 10, CHOH), 1.84 (OH), 1.35 (Me), 1.32 (Me), 1.28 (Me), 1.19 (d, J 6, CHMe) p.p.m. which correlates with natural iso-citreoviridinol (12) except that the secondary OH group in (11) is in an equatorial configuration.[8]

Further work is now in progress to produce citreoviridinol using intermediates produced in this work and in the accompanying papers.[4,5]



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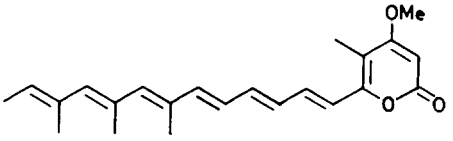

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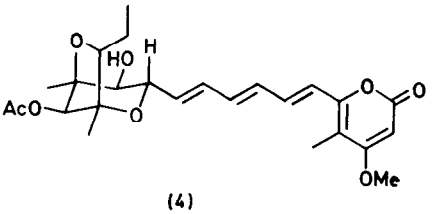

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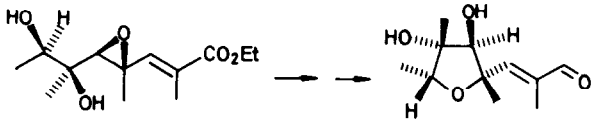

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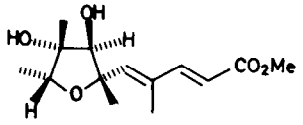

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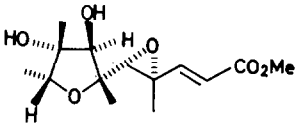

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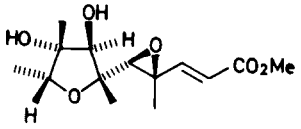

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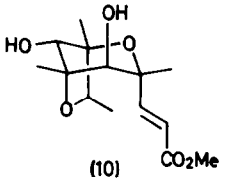

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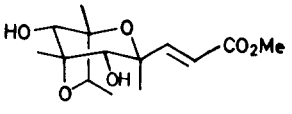

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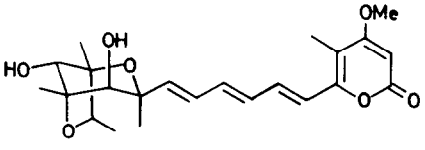

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6. Y. Shizuri, S. Nishiyama, D. Imai, S. Yamamura, H. Furukawa, K. Kawai and N. Okada, Tetrahedron Letters, 1984, 25, 4771.
7. All new compounds showed satisfactory spectral data and microanalytical or mass spectral data.
8. cf. Yamamura et al., refs 1 and 3.

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