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NATURAL POLYENE α-PYRONES. SYNTHESIS OF (±)-CITREOVIRAL

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Summary: The total synthesis of (±)-citreoviral(2) and also of iso-citreoviral(21), using two conceptually distinct approaches starting from methyl tiglate, are described.

The polyene pyrone citreoviridin(1), found in Penicillium citreoviride, is a potent neurotoxic mycotoxin, acting as an inhibitor of ATP synthesis and hydrolysis catalysed by mitochondrial enzyme systems.[1] Recently, Yamamura et al.[2] have reported the isolation of the closely related metabolites citreoviral(2) and citreodiol(3) from P.citreoviride. In the previous Letter, we presented a total synthesis of the polyene pyrone citreomontanin(4), found in P.pedomontanum[3], which could have a biogenetic link with citreoviridin. In this Letter, we describe a total synthesis of (±)-citreoviral(2), and also of one of its isomers(21), using two conceptually distinct approaches starting from methyl tiglate(5).

Thus, in the first approach, conversion of methyl tiglate to the corresponding acetonide(6) [OsO_4, NMMO; then $(MeO)_2CMe_2$, p-TSA] followed by sequential reduction ($LiAlH_4$) and oxidation (PCC-celite), first led to the aldehyde (7). A Wittig condensation between (7) and ethoxycarbonylethylidene triphenylphosphorane (CH_2Cl_2, reflux) then gave rise to the E-ester (8)(88%) exclusively[4], which by successive reduction ($LiAlH_4$), oxidation (MnO_2, CH_2Cl_2, 93%) and a further Wittig condensation ($Ph_3P{:}C.Me.CO_2Et$) provided the E,E-dienoate (9). After conversion of (9) to the 1,2-diol (10) (Amberlight H^+ 120), δ 7.07, 5.51, 3.83 [q, J 6.5, MeCH(OH)], 2.07 (d, J 1, :CMe), 1.98 (d, J 1.5, :CMe), 1.31 (Me), 1.18 (d, J 6.5, CHMe) [cf. natural citreodiol (3)], reaction with meta-chloroperbenzoic acid produced largely the diastereoisomeric epoxide (11)(54%).[5] Treatment of the diol epoxide (11) with p-toluenesulphonic acid (CH_2Cl_2, 25°C) then provided the substituted tetrahydrofuran (12). Finally, reduction of (12) using lithium aluminium hydride, followed by oxidation of the resulting carbinol (MnO_2, CH_2Cl_2) led to (±)-citreoviral, which showed identical spectral data to those reported for naturally derived material.[6]

In a conceptually distinct approach to citreoviral, the epoxy-aldehyde (13) derived from methyl tiglate (5) [$LiAlH_4$; m-CPBA; Collins] was first reacted with the anion derived from trimethyl 2-phosphonopropionate (NaH, THF; -78°C) to give largely (9:1, Z:E; 90%) the epoxy-ester (14). Treatment of (14) with hot 60% perchloric acid (Me_2CO, reflux 20 h)[7] then provided the butenolide (15), b.p. 120°C at 0.1 mm, as a colourless oil. Reaction between (15) and osmium tetraoxide in the presence of N-methylmorpholine oxide, gave rise to a single diastereoisomer of the corresponding triol, white flakes, m.p. 130-140°C (ether)(51%) which was shown to have the relative stereochemistry shown in (16) by a single crystal X-ray determination.[8] Subsequent to this observation, both Kishi and Stork and their collaborators published details[9] of their extensive investigations of the stereoselectivity of osmium tetraoxide oxidations of allylic alcohol and γ-hydroxy-α,β-unsaturated ester systems.

Conversion of the triol (16) into the corresponding benzylidene acetal (17) (PhCHO, p-TSA)(95%), followed by reaction with N-bromosuccinimide in dry chloroform[10], then led (73%) to the bicyclic ether-lactone (18), which smoothly underwent ester interchange in aqueous methanol in the presence of triethylamine, leading to the substituted tetrahydrofuran (19)(88%), ν_{max} 3400, 1720 cm^{-1}, δ 4.1 (q, J 6.5, CHMe), 3.79(Me), 3.6(1H), 2.76(OH), 1.8(OH), 1.55(Me), 1.23(Me), 1.21 (d, J 6.5, CHMe). After conversion to the corresponding acetonide [$(MeO)_2CMe_2$, p-TSA; 86%], reduction with di-isobutylaluminium hydride led to the aldehyde (20). A Wittig reaction between (20) and $Ph_3P{:}C(Me).CO_2Et$ then gave the corresponding E-ester which, after removal of the acetonide, followed by reduction ($LiAlH_4$) and oxidation provided the iso-citreoviral (21), δ 9.42(CHO), 6.68(q, J 1.5, :CH), 3.75(q, J 6.5, CH_3CH), 3.54(CHOH), 1.95(d, J 1.5, :CMe), 1.47(Me), 1.28(Me), 1.22(d, J 6.5, CHMe) p.p.m.[11] Further work is now in progress to produce (+)-citreoviral and hence natural citreoviridin using the above strategy, starting from methyl angelate.

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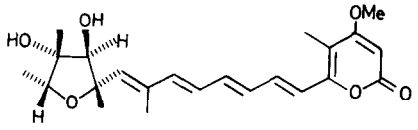
3. P. Patel and G. Pattenden, Tetrahedron Letters, 1985, 26, immediately preceding.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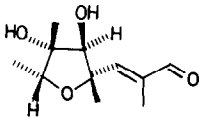
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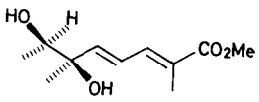
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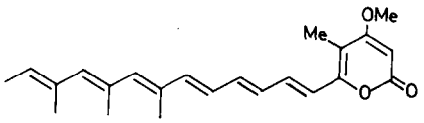
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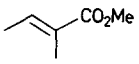
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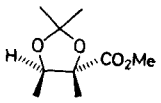
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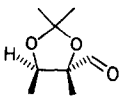
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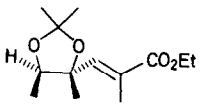
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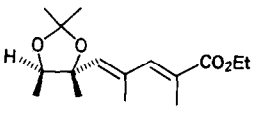
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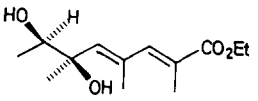
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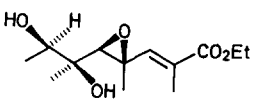
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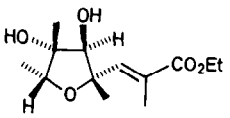
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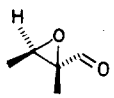
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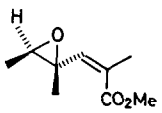
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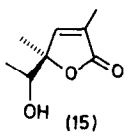
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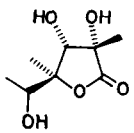
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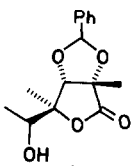
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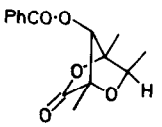
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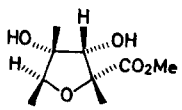
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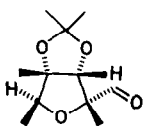
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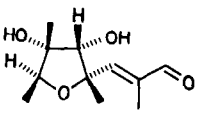
(21)

4. All new compounds showed satisfactory spectral data and microanalytical or mass spectral data.

5. The corresponding (α-) diastereoisomeric epoxide largely underwent *in situ* cyclisation to the isomeric tetrahydrofuran [*cf.* (12)] during attempted separation by chromatography; the combined yield of isomeric epoxides was 90%.

6. In contemporaneous studies, Yamamura *et al.*, have described a closely similar route to (+)-citreoviral starting from D-glucose, see: S. Nishiyama, Y. Shizuri and S. Yamamura, Tetrahedron Letters, 1985, 26, 231. For two very recent alternative syntheses of (±)-citreoviral, see: Y. Shizuri, S. Nishiyama, H. Shigemori and S. Yamamura, J.Chem.Soc., Chem.Commun., 1985, 292; D.R. Williams and F.H. White, Tetrahedron Letters, 1985, 26, 2529.

7. *cf.* J. Cardellach, C. Estopa, J. Font, M. Moreno-Manas, R.M. Ortuno, F. Sanchez-Ferrando, S. Valle and L. Vilamajo, Tetrahedron, 1982, 38, 2377.

8. We have to thank Dr. M.J. Begley of this Department for this information.

9. See: J.K. Cha, W.J. Christ and Y. Kishi, Tetrahedron Letters, 1983, 24, 3943; G. Stork and M. Khan, *ibid.*, 1983, 24, 3951.

10. *cf.* D.R. Williams, Y. Harigaya, J.L. Moore and A. D'Sa, J.Am.Chem.Soc., 1984, 106, 2641.

11. A substantial amount (*ca* 30%) of the alternative isomer of (21) was produced during its preparation and purification by chromatography.

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