

NATURAL POLYENE α -PYRONES. TOTAL SYNTHESIS OF
CITREOMONTANIN FROM PENICILLIUM PEDOMONTANUM.

Prakash Patel and Gerald Pattenden*

Department of Chemistry, The University,
Nottingham, NG7 2RD.

Summary: A total synthesis of all-E-citreomontanin (7), a novel polyene α -pyrone produced by Penicillium pedomontanum, is described.

Citreoviridin (1)^{1,2} and citreomontanin (2a)³ are members of a family of biologically active polyene α -pyrones isolated from Penicillium sp. The molecules (1) and (2a) are related to each other biogenetically, and also to aurovertin (2b)⁴ and asteltoxin (2c)⁵ found in Calcarisporium arbuscula and Aspergillus stellatus respectively. Citreoviridin and aurovertin B are potent neurotoxic mycotoxins, acting as inhibitors of ATP synthesis and hydrolysis, catalysed by mitochondrial enzyme systems. The toxicity of citreoviridin which is comparable to that of the aflatoxins, has been responsible for the occurrence of cardiac beriberi in E. Asia. In this Letter we describe a total synthesis of citreomontanin (2a) found in P.pedomontanum, and in the accompanying communication we outline a stereocontrolled synthesis of the novel tetrahydrofuran ring portion present in citreoviridin (1).

Treatment of 5,6-dimethyl-4-hydroxy-2-pyrone (3a)⁶ with dimethyl sulphate in the presence of potassium carbonate first led to the corresponding 4-methoxy pyrone (3b, 84%), m.p. 100-02°C, δ (DMSO/CDCl₃), 1.84 (5-Me), 2.16 (6-Me), 3.8 (OMe), 5.44 (:CH); δ_{carbon} 170.5, 163.0, 157.5, 106.1, 87.2d, 56.5q (OMe), 16.2q (C-6-Me), 9.1q (C-5-Me) p.p.m. Regioselective oxidation of the C-6-Me group in (3b) was then smoothly accomplished using selenium dioxide in hot dioxan (sealed tube, 140°C).⁷ producing the 6-formyl pyrone (4) (75%), m.p. 134-6°C, ν_{max} (KBr) 1740, 1710, 1610 cm⁻¹, δ 2.25 (C-5-Me), 3.95 (OMe), 5.0 (:CH), and 9.95 (CHO); δ_{carbon} 183.8 (CHO), 168.9 (C-4), 160.7 (C-2), 148.4 (C-6), 120.3 (C-5), 94.2 (C-3), 57.3 (OMe), and 7.4 (C-5-Me) p.p.m. The structure assigned to (4) followed from a nuclear Overhauser difference spectrum and by analysis of its mass fragmentation.⁸

Condensation between the 6-formyl pyrone (4) and the vinyl lithium reagent produced from the vinylstannane (5)⁹, followed by in situ hydrolysis-dehydration (p-TSA; 14 h) of the intermediate sec-alcohol, then gave the vinyllogous all-E-aldehyde (6a) (33% overall)¹⁰ as yellow crystals, m.p. 186-8°C (MeOH),

λ_{\max} (EtOH) 357, 265 nm.¹¹ Reduction of (6a) using sodium borohydride gave rise to the carbinol (6b) (84%), m.p. 170-5°C (MeOH), δ (CD₃OD), 2.0 (Me), 3.29 (OMe), 4.2 (d, \underline{J} 4, CH₂OH), 5.6 (C-3-H), and 6.0-7.5 (m, 4H) which was converted into the corresponding phosphonium salt (6c) (glassy solid) (CBr₄, PPh₃ 25°, 0.5 h; then PPh₃ in CH₂Cl₂. 25°, 14 h).

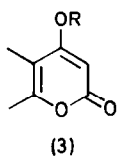
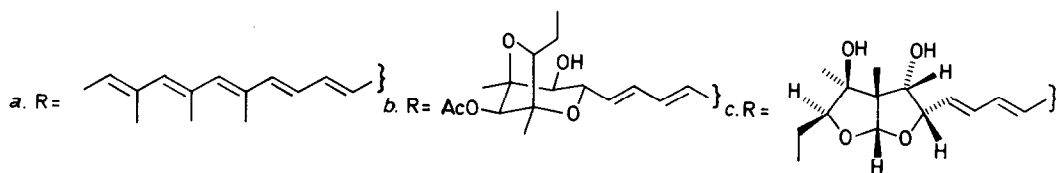
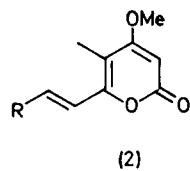
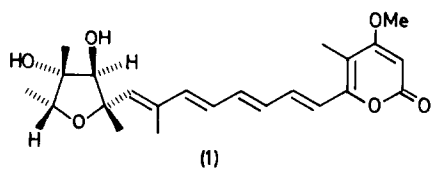
Treatment of the phosphonium salt (6c) in tetrahydrofuran with *n*-butyl lithium, followed by reaction between the resulting ylide and the all-*E*-trienal (12) then gave a mixture of the all-*E*- (major) and *Z*-11- (minor) isomers of the polyene (7) in a combined yield of 35%. Chromatography (silica, diethyl ether) and crystallisation from ether provided the all-*E*-polyene m.p. 158-61°C (sealed tube, in vacuo), λ_{\max} (EtOH) 416 (ϵ 29,600) nm., whose p.m.r. spectrum was superimposable on that of natural citreomontanin from *P. pedomontanum*¹².

The all-*E*-trienal (12) was produced from tiglinlaldehyde (8) by two successive stereoselective Wittig reactions. Thus, condensation between tiglinlaldehyde and α -methoxycarbonylethylidenetriphenylphosphorane (CH₂Cl₂, reflux 48 h) first gave the *E,E*-diene (9) (94%) which was homogeneous by g.l.c. (OV-17; 170°C) and n.m.r. spectroscopic analysis, δ 1.76 (d, \underline{J} 7, :CHMe), 1.86 (C-4-Me), 2.04 (C-2-Me), 3.8 (OMe), 5.76 (q, \underline{J} 7, :CHMe), and 7.12 (:CH), δ_{carbon} 169.8, 143.3, 130.9 (C-3/C-5), 133.1, 124.7 (C-2/C-4), 51.8 (OMe), 16.0 (C-2-Me), 14.0 (C-4 and C-5-Me) p.p.m. The *E,E*-diene (9) was then converted into the *E,E*-dienal (10) via the corresponding carbinol (LiAlH₄, then MnO₂) which in a second stereoselective Wittig reaction with α -ethoxycarbonylethylidenetriphenylphosphorane led to the all-*E*-polyene ester (11) (57%). Reduction of (11) using lithium aluminium hydride followed by oxidation (MnO₂, CH₂Cl₂) of the resulting carbinol then produced the all-*E*-trienal (12)¹³ as a colourless liquid, λ_{\max} (EtOH) 282 nm, ν_{\max} (film) 2970, 2930, 1690, 1605 cm⁻¹, δ 1.7-1.9 (C-6 and C-7 Me), 2.14 (C-2-Me), 5.68 (q, \underline{J} 8, :CHMe), 6.3 (C-5-H), 6.8 (C-3-H), and 9.45 (CHO) p.p.m.

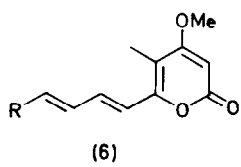
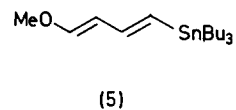
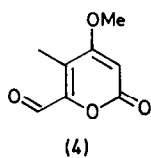
We thank Professor Rebuffat who kindly provided a sample and spectral data of natural citreomontanin, and Dr. G. Kneen (Wellcome Research Laboratories) for his interest. We also thank the S.E.R.C for a studentship (to P.P.) and Wellcome Research Laboratories for financial support (C.A.S.E. award to P.P.)

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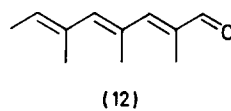
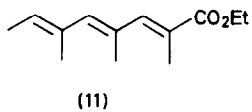
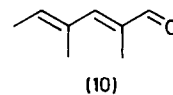
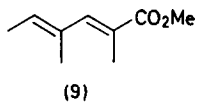
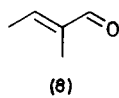
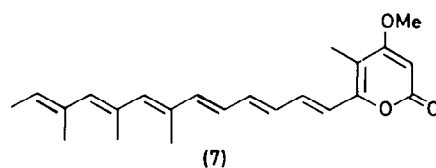
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a. R = H; b. R = Me



a. R = CHO; b. R = CH₂OH;
c. R = CH₂P⁺Ph₃Br⁻



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10. All new compounds showed satisfactory spectral data, and microanalytical or mass spectral data.
11. Condensation between (4) and formylallylidenetriphenylphosphorane led to a low yield (> 20%) of a 1:1 mixture of E-E- and Z,E- isomers of the pyrone aldehyde (6a). A similar Wittig reaction between (4) and formylmethylene-triphenylphosphorane produced the aldehyde (2, R=CHO), also known as seco-citreoviridin, a product of oxidation of citreoviridin; cf. E. Suzuki, B. Katsuragawa and S. Inoue, J.Chem.Research (S), 1982, 224. We thank Professor S. Yamamura (Keino University) for forwarding a sample of seco-citreoviridin for comparison.
12. Natural citreomontanin shows m.p. 165-6°C, λ_{\max} 415 (ϵ 31,300). The polyene was also produced in much lower overall yields, by alternative Wittig reactions, e.g. between (6a) and the triphenylphosphonium salt corresponding to (12)(2%). Details will be provided in the full publication.
13. 2,4-Dinitrophenylhydrazone, m.p. 157-8°C (EtOH).

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