Tetrahedron Letters,Vol.29,No.6,pp 711-714,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

TOTAL SYNTHESIS OF (±)-CITREOVIRAL

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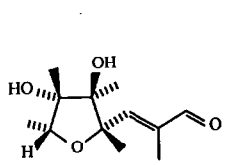
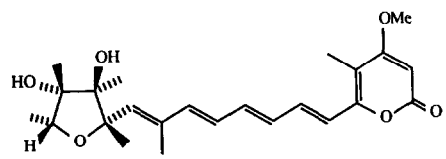
Summary: A total synthesis of (±)-citreoviral (1) found in Penicillium citreoviride, which uses the bicyclic lactone (5) as a key intermediate, is described.

Citreoviral (1)[1], together with citreoviridin (2)[2] and the citreoviridinols (3) and (4)[3,4] are complex, substituted tetrahydrofuran metabolites produced by Penicillium citreoviride. Citreoviridin (2) is a potent neurotoxic mycotoxin, acting as an inhibitor of ATP synthesis and hydrolysis catalysed by mitochondrial enzyme systems. The synthesis of members of the 'citreoviridinoids' has been the subject of considerable recent research.[3,4,5] In this Letter we describe a new synthesis of (±)-citreoviral (1), which uses a strategy whereby three of the four stereocentres in the natural product are locked in the key bicyclic lactone intermediate (5), produced from angelic acid via the epoxy-ester (7) and the substituted butyrolactone (6) (Scheme).



(1)



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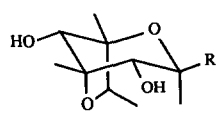

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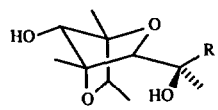

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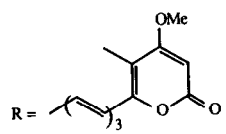
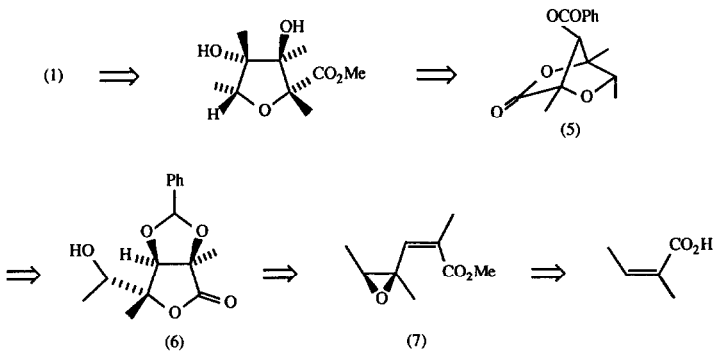


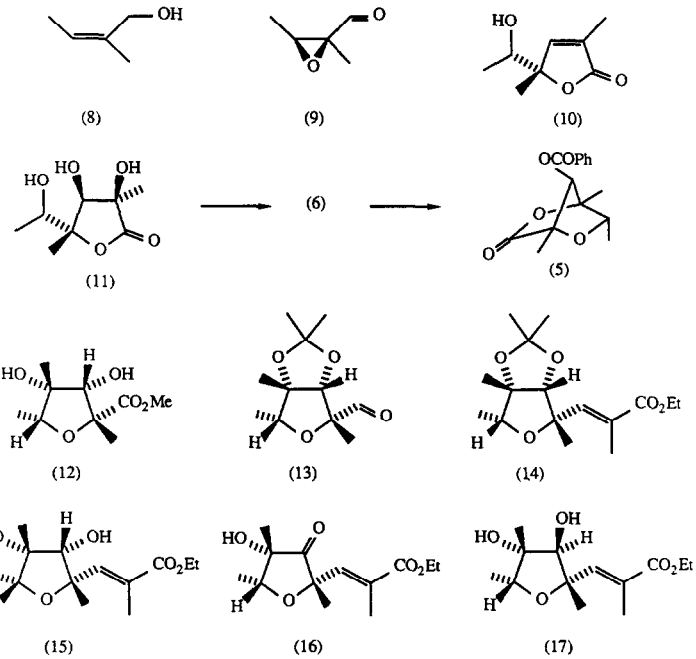
Thus, reduction ($LiAlH_4$, Et_2O reflux) of angelic acid[6] to the carbinol (8), followed by epoxidation (m-CPBA, CH_2Cl_2, 25 °C) and oxidation (Collins) first led to the epoxy-aldehyde (9)[7]. A Wadsworth-Emmons reaction between (9) and

trimethyl 2-phosphonopropionate (NaH, THF, -70 °C) then gave (78%) the Z-alkene (7) (δ 6.03, :CH) containing less than 10% of the corresponding E-geometrical isomer (δ 6.6, :CH). Treatment of the Z-epoxy ester (7) with hot 60% perchloric acid in dioxan for 0.5 h, next produced the butenolide (10, 83%), which underwent stereospecific vicinal bis-hydroxylation from the least hindered face of the C - C double bond (OsO_4, NMMO, tBuOH-H_2O) leading to the triol (11, 57%).[8] Conversion of the triol (11) to the crystalline benzylidene acetal (6) m.p. 118-118.5°C, followed by reaction with N-bromosuccinimide in dry chloroform[9] then led (76%) to the key bicyclic lactone intermediate (5) (white needles m.p. 79-80°C) containing three of the four stereocentres in citreoviral (1) in the correct relative configuration.



Scheme

Treatment of the key bicyclic lactone intermediate (5) with triethylamine in methanol-water resulted in smooth hydrolysis and ester exchange producing the substituted tetrahydrofuran (12) (80%), m.p. 89-91°C. After conversion into the corresponding acetonide, reduction ($LiAlH_4$) followed by oxidation (PCC) next led to the aldehyde (13). A Wittig condensation between the aldehyde (13) and ethoxycarbonylethyidenetriphenylphosphorane gave an excellent 82% yield of the E-unsaturated ester (14), an oil, which was then converted into the crystalline diol (15), m.p. 70-71°C, by treatment with Amberlyst acidic resin.



The secondary hydroxyl-substituted centre in (15) was inverted to the correct stereochemistry, i.e. (17), found in natural citreoviral following Moffatt oxidation (DMSO-DCC-TFA) to the ketone (16) (57%) and reduction using sodium borohydride ($NaBH_4$, THF, -60°C). The synthesis of citreoviral (1) from (17) was then completed by straightforward reduction to the corresponding carbinol ($LiAlH_4$) and oxidation of the latter in the presence of manganese dioxide. The (±)-citreoviral, thus obtained, showed identical spectroscopic data to those reported for naturally derived material.

We thank Dr W.P. Jackson (Wellcome Research Laboratories) for his interest in this work. We also thank the S.E.R.C. and Wellcome Research Laboratories for financial support (C.A.S.E. award to M.C.B.).

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6. Prepared by halogen-lithium exchange of 2-bromo-Z-2-butene, followed by carboxylation of the resulting vinyl lithium species. We thank Dr. W.P. Jackson for assistance with this preparation.
7. Satisfactory spectroscopic data together with microanalytical and mass spectroscopic data were obtained for all new compounds.
8. cf. J.K. Cha, W. J. Christ and Y. Kishi, Tetrahedron Lett., 1983, 24, 3943; G. Stork and M. Khan, ibid, 1983, 24, 3951.
9. cf. D.R. Williams, Y. Harigaya, J.L. Moore and A. D'Sa, J. Am. Chem.Soc., 1984, 106, 2641.

(Received in UK 14 December 1987)