

SYNTHESIS OF PUKELEIMIDE A

Gwyn D. James and Gerald Pattenden*

Department of Chemistry, The University, Nottingham NG7 2RD

Stuart D. Mills

ICI Pharmaceuticals Division, Mereside Alderley Park,

Macclesfield SK10 4TG

Summary: A total synthesis of the 5-ylidenepyrrole-2-one pukeleimide A (3), a constituent of the marine blue-green alga Lyngbya majuscula, is described.

Certain strains of the marine blue-green alga Lyngbya majuscula are well known to be responsible for the contact dermatitis called 'swimmer's itch,' and two known irritants found in different samples of L. majuscula are the indole alkaloid lyngbyotoxin (1) and the spiroketal debromoaplysiatoxin (2).^{1,2} Samples of Lyngbya majuscula that contain lyngbyotoxin have also provided minor amounts of the interesting and rare class of natural 5-ylidenepyrrole-2-ones known as 'pukeleimides', exemplified by pukeleimide A (3), pukeleimide C (4), and pukeleimide E (5).³ In this Letter we report the first synthetic entry into this class of compound by describing a total synthesis of pukeleimide A (3).

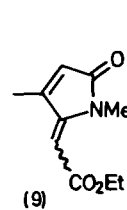
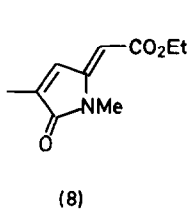
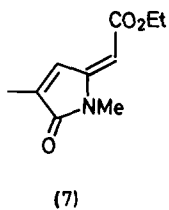
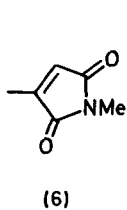
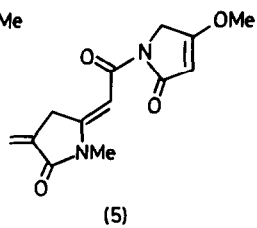
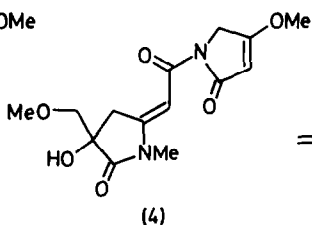
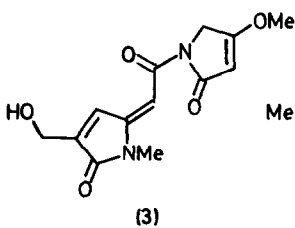
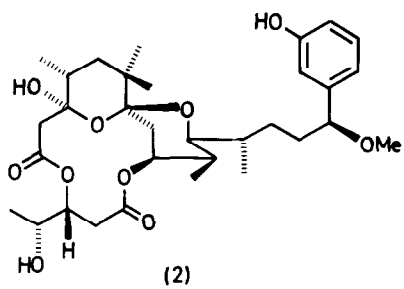
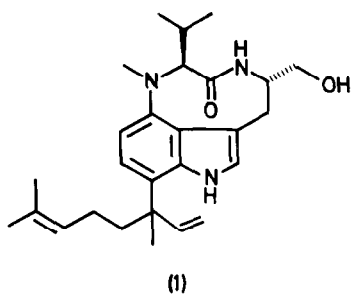
Refluxing a solution of 2-methylmaleic anhydride in glacial acetic acid in the presence of freshly prepared methylamine acetate for 3h produced 1,3-dimethyl (1H)-pyrrole-2,5-dione (6), b.p. 82-3° at 10mm Hg, in 83% yield.⁴ Interaction of the pyrrole-2,5-dione (6) with carboethoxymethylenetriphenylphosphorane (5 equivs) (toluene, reflux, 36h) proved to be largely regio- and stereo-selective and gave the E-ylidenepyrrolone (7) (31%), as almost colourless crystals,

m.p. 93-4°C (benzene), λ_{\max} (EtOH) 280 (18,500) 322 (5,800) nm., ν_{\max} (CHCl₃) 1710, 1670, 1640 cm.⁻¹, δ 2.02 (:CMe), 3.1 (NMe), 5.51 (:CH.CO₂Et), 7.82 (:CH).⁵

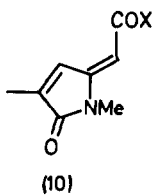
By chromatography it was also possible to separate small amounts (ca 2%) of the geometric isomer (8) [δ 2.0 (:CMe), 3.44 (NMe), 5.34 (:CH.CO₂Et), 6.61 (:CH)] of (7), and also the two geometrical isomers (9a) [δ 2.39 (:CMe), 3.1 (NMe), 5.6 (:CH.CO₂Et) 6.15 (:CH)] and 9b [δ 2.14 (:CMe), 3.37 (NMe), 5.5 (:CH.CO₂Et), 6.09 (:CH)] of the corresponding isomeric 1,4-dimethyl-5-ylidenepyrrolone.⁶ The structures and stereochemistries of the isomeric ylidenepyrrolones (7), (8), (9a) and (9b) followed conclusively from inspection and comparison of the p.m.r. chemical shift data with those of the corresponding ylidenebutenolides which we and others have published previously.⁷

Saponification of the unsaturated ester group in (7), using aqueous potassium hydroxide in tetrahydrofuran (reflux 3h), was accomplished without stereomutation about the carbon-to-carbon double bond, and the resulting acid (10a), ν_{\max} 1700, 1640 cm.⁻¹, δ 1.98 (:CMe), 3.08 (NMe), 5.62 (:CH.CO₂H), 7.82 (:CH), was then converted to the corresponding acid chloride (10b) (SOCl₂; benzene, reflux 1h). Without purification the acid chloride (10b) in tetrahydrofuran was added to a stirred solution of the anion produced from the pyrrolinone (11) (n-BuLi, THF, 0-5°C) to give the desoxypukeleimide (12) (25%) accompanied by varying amounts of the carboxylic acid anhydride corresponding to (10a). The pyrrolinone (11) was most conveniently obtained starting from the bromide (13) derived from ethyl acetoacetate [HC(OMe)₃, H₂SO₄; then NBS, CCl₄] by reaction with aqueous ammonia (67%),⁸ or alternatively by reaction with sodium azide (to 14) followed by reduction to the corresponding amine and cyclisation.

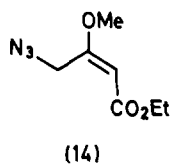
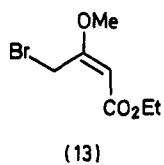
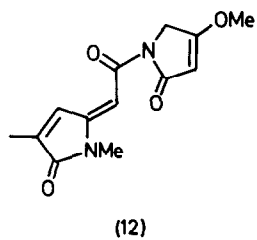
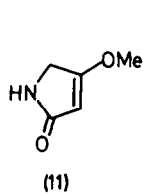
The synthesis of (3) was completed by reaction of the desoxy compound (12) with selenium dioxide in glacial acetic acid (reflux, 1h) followed by chromatography, which gave pukeleimide A(3) (60%)



a, Z- isomer
b, E- isomer



a, X=OH; b, X=Cl



showing spectral data (i.r., uv., p.m.r., m.s.) identical with those published for the natural product.³

We thank the S.E.R.C. for a studentship (C.A.S.E. award to G.D.J.) and ICI Pharmaceuticals Division for financial support.

References

1. J.H. Cardellina, II, F.J. Marner and R.E. Moore, Science, 1979, 204, 193.
2. J.S. Mynderse, R.E. Moore, M. Kashiwagi and T.R. Norton, Science, 1977, 196, 538.
3. C.J. Simmons, F.-J. Marner, J.H. Cardellina II, R.E. Moore, and K. Seff, Tetrahedron Lett., 1979, 2003; J.H. Cardellina II, and R.E. Moore, ibid, 1979, 2007.
4. See T.V. Sheremeteva and T.A. Trushkova, Doklady Akad Nauk S.S.S.R., 1958, 122, 828 (Chem. Abs., 1959, 53, 4127h).
5. Satisfactory analytical and spectroscopic data were obtained for all new compounds.
6. The Wittig-type reactions between pyrrole-2,5-diones and phosphorus based ylides, of α -metallated organosilanes, provides an expeditious synthesis or a range of substituted ylidene-pyrrolones, and details will be published in a separate communication.
7. D.W. Knight and G. Pattenden, J.Chem.Soc., Perkin Trans I, 1979, 62.
8. cf K.S. Kochhar and H.W. Pinnick, J. Org. Chem., 1984, 49, 3222.

(Received in UK 29 April 1985)