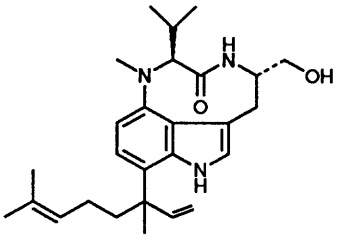
Total Synthesis of Pukeleimide A, a 5-Ylidenepyrrol-2(5*H*)-one from Blue Green Algae

Gwyn D. James,[a] Stuart D. Mills[b] and Gerald Pattenden*[,a]
[a] *Department of Chemistry, The University, Nottingham, NG7 2RD, UK*
[b] *ICI Pharmaceuticals Division, Mereside Alderley Park, Macclesfield, SK10 4TG, UK*
(ICI Pharmaceuticals is part of Zeneca Pharmaceuticals Ltd. in the UK)

A total synthesis of pukeleimide A **5**, a member of a rare family of naturally occurring 5-ylidenepyrrol-2(5*H*)-ones produced by the marine blue alga *Lyngbya majuscula*, is described. The synthesis is based on elaboration of the ylidenepyrrolone **11a** from the maleimide **13a** by a regio- and stereo-selective Wittig reaction with ethoxycarbonylmethylene(triphenyl)phosphorane, followed by conversion of **11a** into the amide **25**, and oxidation of **25** with selenium dioxide.

Certain strains of the marine blue-green alga *Lyngbya majuscula* are well known to be responsible for the contact dermatitis called 'swimmer's itch'. Two known irritants found in different samples of the algae are the indole alkaloid lyngbyotoxin **1** and the spiroketal debromoaphysiatoxin **2**.[1,2] The toxic, shallow-water variety of *L. majuscula* produces malyngamide A **3**,[3] an unusual chlorine-containing substituted 4-methoxypyrrol-2(5*H*)-one which bears a strong structural resemblance to the sponge metabolite dysidin **4**.[4] Samples of *L. majuscula* that contain lyngbyotoxin **1** have also provided minor amounts of an interesting and rare class of 5-ylidenepyrrol-2(5*H*)-ones known as pukeleimides, exemplified by pukeleimide A **5**, C **6**, and E **7**.[5] In the accompanying paper we described our investigations of the use of substituted maleimides **8** and of pyrrolinones **10** in the elaboration of 5-ylidenepyrrol-2(5*H*)-ones **9** by appropriate carbanion reactions.[6] In this paper, we describe the development of this chemistry and report a total synthesis of natural pukeleimide A **5**.[7]



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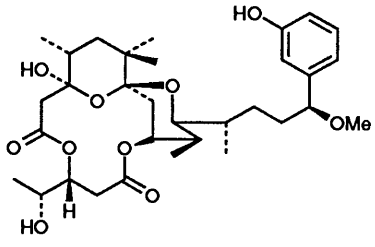

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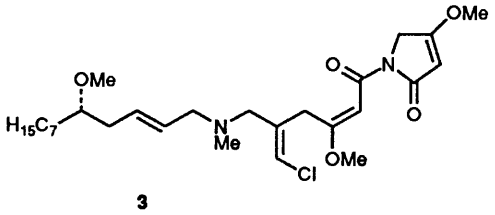

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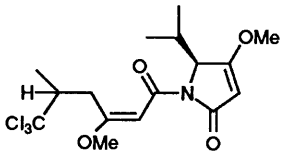

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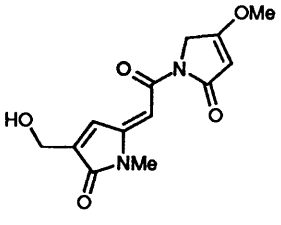

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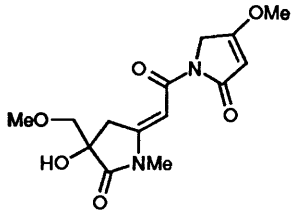

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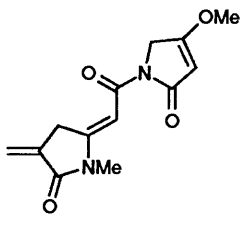

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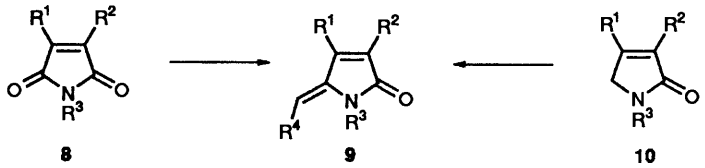
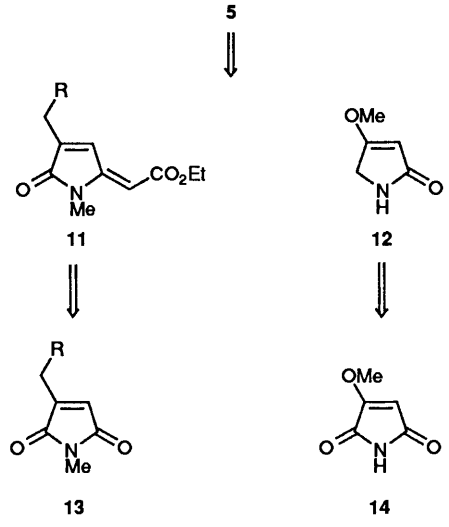


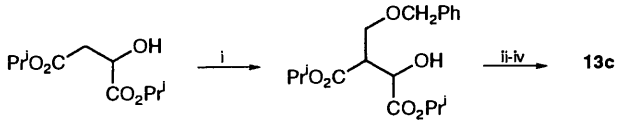
8 **9** **10**

Our overall strategy for a synthesis of pukeleimide A, was to use the substituted maleimides **13** and **14** as key intermediates and to exploit the fundamental chemistry developed earlier for these molecules,[6] *i.e.* Wittig olefination of **13** with ethoxycarbonylmethylene(triphenyl)phosphorane was expected to be regio- and stereo-selective producing **11**, and reduction of **14** should also be regioselective leading to **12** (Scheme 1).



Scheme 1

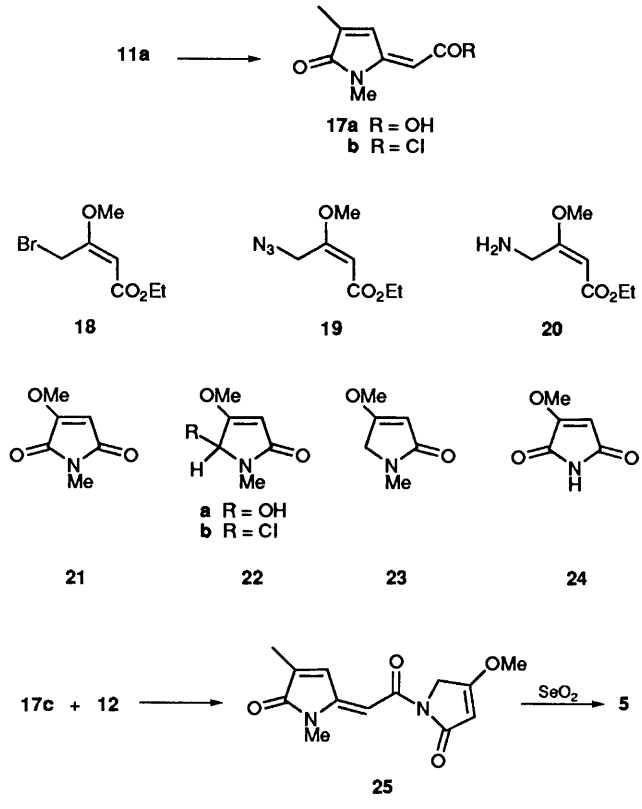
We first examined a synthesis of the 3-hydroxymethyl substituted maleimide **13b**. Thus, reaction between citraconic anhydride and methylammonium acetate in hot glacial acetic acid first produced the maleimide **13a** which could then be converted into **13b**, albeit in low yield, by treatment with selenium dioxide in hot dioxane. Attempts to induce reaction of the maleimide **13b** with ethoxycarbonylmethylene(triphenyl)-phosphorane (CMTP), however, were unsuccessful, and none of the required 5-ylidenepyrrol-2(5*H*)-one **11b** was produced. We also prepared the corresponding 3-benzyloxymethylmaleimide **13c** as outlined in Scheme 2, but this maleimide also failed to react to any appreciable extent with CMTP under a variety of conditions.



Scheme 2 *Reagents:* i, LDA–DMPU, $PhCHH_2OCH_2Cl$; ii, aq. KOH–dioxane; iii, TFAA; iv, $Me^+NH_3{}^-OAc$

At this point we decided to modify our original strategy to pukeleimide A **5** (Scheme 1), and instead synthesise the deoxypukeleimide **25** starting from the 3-methylmaleimide **13a**, and then introduce the hydroxymethyl substituent in **25** as a final step. Hence, a Wittig reaction between the 3-methylmaleimide **13a** and CMTP, as shown earlier,[6] was found to be regio- and stereo-selective and produced the (*E*)-5-ylidenepyrrol-2(5*H*)-one **11a** as needles (m.p. 93–94 °C). The structure and stereochemistry of **11a** followed from inspection and comparison of ^1H NMR chemical-shift data with related compounds, and from results of NOE signal enhancements from double-irradiation experiments. Saponification of the unsaturated ester group in **11a**, using aqueous potassium hydroxide in refluxing tetrahydrofuran was accomplished without stereomutation about the carbon-to-carbon double bond and the resulting carboxylic acid **17a** was then converted into the corresponding acid chloride **17b**, using thionyl chloride in benzene, in readiness for conversion into the amide **25** by reaction with the pyrrolone **12**.

A number of routes were investigated for the synthesis of the pyrrolone **12**. It was most conveniently obtained starting from the bromide **18**, derived from ethyl acetoacetate, by reaction with ammonia,[8,9] or alternatively by reaction with sodium azide, leading to **19**, followed by reduction to the corresponding amine **20** and cyclisation. In model studies with the *N*-methylmaleimide **21**, we found that its reduction with lithium aluminium hydride or sodium borohydride produced only the carbinol **22a** in low yields. Although the carbinol **22a** could be converted into the pyrrolinone **23**, following chlorination and reduction of the resulting chloride **22b** with tributyltin hydride, we were not attracted to this lengthy procedure as a method for the synthesis of **12** from reduction of the corresponding 3-methoxymaleimide **24**.



With a satisfactory synthesis of the pyrrolone **12** and of the acid chloride **17b** we were now in a position to complete the synthesis of pukeleimide A **5**. When the latter was added to a solution of the anion produced from the pyrrolone **12**, using butyllithium, the deoxypukeleimide **25** was produced as yellow needles in a satisfying 71% yield. The synthesis of pukeleimide A was then achieved by reaction of the deoxy compound **25** with selenium dioxide in glacial acetic acid which gave the natural product as a solid (m.p. 192–193 °C). The synthetic pukeleimide A **5** showed spectroscopic data identical with those published for the natural metabolite isolated from *L. majuscula*.

Experimental

For general experimental details see ref. 6.

3-Hydroxymethyl-1-methyl-1H-pyrrole-2,5-dione **13b**.—A solution of 1,3-dimethylmaleimide (1 g)[6] in glacial acetic acid (20 cm^3) was heated in the presence of selenium dioxide (0.89 g)

for 3 h, and then concentrated under reduced pressure. The residue was purified by chromatography (ether–hexane, 3:1) to give the *hydroxymethylmaleimide* **13b** (0.14 g, 25% based on recovered starting material) as colourless crystals, m.p. 52–53 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3350, 1770, 1710 and 1630 cm^{-1}; δ_H 6.67 (t, *J* 2, =CH), 4.65 (d, *J*2, CH_2OH), 3.32 (OH) and 3.05 (NMe) (Found: C, 51.1; H, 5.0; N, 9.9%; M, 141.0430. $C_6H_7NO_3$ requires C, 51.5; H, 5.0; N, 9.9%; *M*, 141.0425).

3-*Benzyloxymethyl*-1-*methyl*-1H-*pyrrole*-2,5-*dione* **13c**.—A solution of diisopropyl malate **15** (6.5 g) and dry 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (3.84 g) in dry THF (10 cm^3) was added dropwise over 0.5 h to a stirred solution of LDA (2.05 equiv.) at −78 °C. The solution was warmed to −20 °C over a 45 min period and then recooled to −78 °C. Benzyl chloromethyl ether (4.77 g) was added slowly over 0.5 h to the solution which was then allowed to warm up to room temperature. The THF was evaporated under reduced pressure and 10% aqueous citric acid solution was then added to the residue until the pH was just acidic. The mixture was then extracted with ethyl acetate (4 × 50 cm^3) to leave the impure alkylated malate diester **16** (5.1 g) as an orange oil. This (5.1 g) was dissolved in water and dioxane (1:1; 100 cm^3) and 20% aqueous potassium hydroxide (20 cm^3) was then added to it. The solution was heated under reflux for 16 h and then cooled when its pH was adjusted to 1.0 with 2 mol dm^{-3} hydrochloric acid. The mixture was evaporated under reduced pressure and the residue was then dissolved in trifluoroacetic anhydride (20 cm^3) and heated under reflux for 30 min. The mixture was concentrated under reduced pressure and glacial acetic acid (20 cm^3) and methylammonium acetate (1.19 g) were then added to the residue. The solution was heated under reflux for 2 h and then cooled, diluted with water and extracted with ether (3 × 25 cm^3). The combined extracts were dried and evaporated to leave a residue which was purified by chromatography using (hexane–ether, 1:1) as eluent, to give the *benzyloxymethylmaleimide* **13c** (0.4 g, 6%) as an off-white solid. Recrystallisation of this from hexane gave fine white needles, m.p. 84–86 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1760, 1700 and 1660; δ_H 7.33 (m, 5 × ArCH), 6.56 (t, *J* 1.5, =CH), 4.60 (OCH_2Ph), 4.36 (d, *J* 1.5, CH_2OCH_2Ph) and 2.97 (NMe) (Found: C, 67.8; H, 5.7; N, 6.2%; M, 125.0504. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.7; N, 6.1%; *M* 125.0477).

(E)-5-*Carboxymethylene*-1,3-*dimethylpyrrol*-2(5H)-*one* **17a**.—A solution of 5-ethoxycarbonylmethylene-1,3-dimethylpyrrol-2(5*H*)-one (663 mg)[6] and potassium hydroxide (286 mg, 1.5 equiv.) in THF–water (1:1; 50 cm^3) was heated under reflux for 3 h. The pH was adjusted to 1.0 by the addition of 2 mol dm^{-3} hydrochloric acid, after which the mixture was extracted thoroughly with ethyl acetate (6 × 10 cm^3). The combined extracts were dried and concentrated under reduced pressure to leave a white solid (567 mg, 100%). Recrystallisation of this from chloroform gave the *carboxylic acid* **17a** as colourless prisms, m.p. 195–196 °C; λ_{max}(EtOH)/nm 276; ν_{max}(KBr)/cm^{-1} 3300–2500, 1700 and 1640; δ_H([$^2H_6$]acetone) 7.90 (=CH), 5.62 (=C*H*CO_2H), 3.12 (NMe) and 1.98 (=CMe) (Found: C, 51.6; H, 5.4; N, 8.4%; M, 167.0587. $C_8H_9NO_3$ requires C, 51.5; H, 5.5; N, 8.4%; *M*, 167.0582).

4-*Methoxypyrrol*-2(5H)-*one* **12**.—*Method* (a) A mixture of ethyl 4-bromo-3-methoxybut-2-enoate (46 g) and sodium azide (13.4 g) in dimethylformamide (250 cm^3) was stirred at room temperature for 4 h and then poured into water (200 cm^3) and extracted with ether (4 × 70 cm^3). The combined extracts were washed successively with water (5 × 50 cm^3) and saturated brine (50 cm^3), and then dried and evaporated under reduced pressure to leave the *azide* **19** (36.1 g, 98%) as an orange oil. Purification of a small sample by Kugelröhr distillation gave a colourless oil, b.p. 68 °C/0.4 Torr; ν_{max}(film)/cm^{-1} 2120 and 1705 cm^{-1}; δ_H 5.14 (=CH), 4.38 (CH_2N_3), 4.14 (q, *J* 7, $CO_2CH_2CH_3$), 3.71 (OMe) and 1.28 (t, *J*7, $CO_2CH_2CH_3$) (Found: C, 45.2; H, 6.1; N, 22.7%. $C_7H_{11}N_3O_3$ requires C 45.4; H, 6.0; N, 22.7%).

Hydrogen gas was passed through a solution of the undistilled azide (2.9 g) in methanol (50 cm^3) in the presence of 10% palladium on charcoal (0.3 g) for 6 h. The mixture was concentrated under reduced pressure to leave a brown oil which was then heated at 120 °C for 1 h. The cooled residue was purified by chromatography (chloroform–methanol, 93:7) to give the 4-methoxypyrrolone **12** (423 mg, 21%) which recrystallised from benzene as colourless needles, m.p. 128–129 °C (lit.,[9] m.p. 129–131.4 °C); λ_{max}(EtOH)/nm 276 and 215 nm; ν_{max}(KBr)/cm^{-1} 3460, 1670 and 1620; δ_H 7.4 (NH), 5.13 (=CH), 3.97 (CH_2N) and 3.88 (OMe); δ_C 176.2, 176.1, 94.3 (CH), 58.3 (CH_2) and 47.0 (CH_2) (Found: C, 53.0; H, 6.5; N, 12.2%; M, 113.0475. Calc. for $C_5H_7NO_2$: C, 53.1; H, 6.2; N, 12.4%; *M*, 113.0475).

Method (b). According to the method of Kochlar and Pinnick,[8] a solution of ethyl 4-bromo-3-methoxybut-2-enoate (5 g) in aqueous ammonia (30 cm^3) was stirred at room temperature for 24 h. The solution was extracted thoroughly with ether (2 × 30 cm^3) and chloroform (4 × 25 cm^3) and the combined extracts were then dried and evaporated to leave a residue which recrystallised from benzene to give the pyrrolone **12** (1.58 g, 67%) as a white solid, m.p. 128–129 °C. The pyrrolone showed spectroscopic data identical with those described under method (a).

5-*Hydroxy*-4-*methoxypyrrol*-2(5H)-*one* **22a**.—Lithium aluminium hydride (19 mg, 0.5 equiv.) was added in one portion to a stirred solution of 3-methoxy-1-methylmaleimide (128 mg)[6,10] in THF (12 cm^3) at 0–5 °C for 30 min and then allowed to warm to room temperature over a 4 h period. Water (20 cm^3) was added to the mixture which was then extracted with ethyl acetate (3 × 20 cm^3). The separated aqueous phase was extracted continually with ethyl acetate (30 cm^3) for a further 24 h. The combined extracts were dried and then concentrated under reduced pressure to leave a brown oil (87 g). Recrystallisation from ethyl acetate gave the pure *hydroxypyrrolone* **22a** (68 mg, 43%) as white needles, m.p. 140–141 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3350, 1685 and 1640; δ_H 5.22 (=CH), 5.02 (C*H*OH), 3.89 (OMe) and 2.93 (NMe) (Found: C, 50.2; H, 6.4; N, 9.6%; M, 143.0587. $C_6H_9NO_3$ requires C, 50.4; H, 6.3; N, 9.8%; *M*, 143.0582).

5-*Chloro*-4-*methoxy*-1-*methylpyrrol*-2(5H)-*one* **22b**.—A solution of the hydroxypyrrolone **22a** (0.78 g) and thionyl chloride (2 cm^3) in dry benzene (15 cm^3) was heated under reflux for 2 h. The solution was concentrated under reduced pressure and the residue was then purified by chromatography (chloroform) to give the *chloropyrrolone* **22b** (0.74 g, 84%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1680 and 1630; δ_H 5.11 (m, CHCl plus =CH), 3.83 (OMe) and 2.88 (NMe) (Found: M–Cl, 126.0558. $C_6H_8NO_2$ requires *M*–Cl, 126.0555).

4-*Methoxy*-1-*methylpyrrol*-2(5H)-*one* **23**.—A solution of 5-chloro-4-methoxy-1-methylpyrrolone **22b** (0.34 g), tributyltin hydride (2 equiv.) and azoisobutyronitrile (0.2 g) in dry benzene (30 cm^3) was heated under reflux for 56 h. The cooled solution was concentrated under reduced pressure and the residue was purified by chromatography (chloroform–methanol, 97:3) to give the *pyrrolone* **23** (0.2 g, 74%) which crystallised from benzene–hexane as prisms, m.p. 86–87 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1670 and 1635; δ_H 5.19 (=CH), 3.88 (OMe) and 2.98 (NMe); δ_C 173.2, 172.4, 94.4 (CH), 58.1 (CH_3), 52.5 (CH_2) and 28.5 (CH_3) (Found: C, 56.6; H, 7.4; N, 11.1%; M, 127.0626. $C_6H_9NO_2$ requires C, 56.7; H, 7.1; N, 11.0%; *M*, 127.0619).

1-[(1,5-*Dihydro*-1,4-*dimethyl*-5-*oxo*-2H-*pyrrol*-2-*ylidene*)-*acetyl*]-1,5-*dihydro*-4-*methoxypyrrole*-2-*one* (*Deoxypukeleimide*) **25**.—A solution of (*E*)-5-carboxymethylene-1,3-dimethylpyrrol-2(5*H*)-one **17a** (404 mg) in thionyl chloride (10 cm^3) was heated under reflux for 2 h. The solution was concentrated to afford the corresponding acid chloride **17b** as a yellow solid. This solid was dissolved in dry THF (5 cm^3) and the solution added dropwise to a previously formed, stirred solution of 1-lithio-4-methoxypyrrol-2(5*H*)-one (305 mg) prepared by adding butyllithium (1.6 mol dm^{-3} solution in hexane; 1.1 equiv.) to a solution of 4-methoxypyrrol-2-(5*H*)-one **12** (1 equiv.) in THF (10 cm^3) at 0 °C. The resulting suspension was stirred at 0 °C for 2 h and then allowed to warm to room temperature overnight. The mixture was poured into water (20 cm^3) and then extracted with ether (2 × 20 cm^3) and chloroform (2 × 20 cm^3). The combined extracts were dried and evaporated to leave an oily solid. This was purified by chromatography (chloroform–methanol, 99:1) to give E-*deoxypukeleimide* A **25** (447 mg, 71%) which recrystallised from chloroform–hexane as yellow needles, m.p. 185.5–186 °C; λ_{max}(EtOH)/nm 262infl. (8670), 294 (16500) and 325infl. (9070); $\nu_{max}(CHCl_3)/cm^{-1}$ 1715, 1670 and 1620; δ_H 7.80 (m, =CH), 7.15 (=CHCO), 5.18 (=CH), 4.36 (CH_2N), 3.94 (OMe), 3.17 (NMe) and 2.03 (d, *J* 2, =CMe); δ_C 176.1, 170.9, 169.7, 163.5, 152.2, 137.7, 130.3 (CH), 99.1 (CH), 94.8 (CH), 58.7 (CH_3), 48.6 (CH_2), 26.0 (CH_3) and 11.1 (CH_3) (Found: M, 262.0935. $C_{13}H_{14}N_2O_4$ requires *M*, 262.0951).

1-[(1,5-*Dihydro*-4-(*hydroxymethyl*)-1-*methyl*-5-*oxo*-2H-*pyrrol*-2-*ylidene*)*acetyl*]-1,5-*dihydro*-4-*methoxypyrrol*-2-*one* (*Pukeleimide A*) **5**.—A stirred suspension of deoxypukeleimide A **25** (34 mg), selenium dioxide (50 mg) and glacial acetic acid (3 cm^3) was heated under reflux for 1 h. The cooled solution was concentrated under reduced pressure to leave a green–black residue which was purified by chromatography (chloroform–methanol, 97:3) to give: (i) recovered starting material **25** (20 mg, 59%) and (ii) *pukeleimide A* **5** (9 mg, 25%) as an off-white solid, m.p. 192–193 °C (benzene); λ_{max}(EtOH)/nm 330 and 292; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1715, 1675 and 1625^{-1}; δ_H 7.91 (t, *J* 1.5, =CH), 7.21 (=CHCO), 5.16 (=CH), 4.56 (d, *J* 1.5, CH_2OH), 4.35 (CH_2N), 3.91 (OMe) and 3.17 (NMe); δ_C 176.3, 170.1, 169.8, 163.2, 151.5, 140.0, 129.9 (CH), 101.0 (CH), 94.7 (CH), 59.0 (CH_3), 57.7 (CH_2), 48.6 (CH_2) and 25.8 (CH_3) (Found: M, 278.0889. $C_{13}H_{14}N_2O_5$ requires *M*, 278.0903).

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