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A short biomimetic synthesis of marine sponge alkaloid Pyrinadine A

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ABSTRACT

The biomimetic synthesis of the marine sponge alkaloid Pyrinadine A, based on the oxidative dimerisation of hydroxylamine, is reported.

1. Introduction

Marine sponges have continued to fascinate natural product chemists due to the wide variety of natural products that are present in these relatively simple organisms. The marine sponges of the order Haplosclerida encompass genera such as Callyspogiidae, Niphatidae, Chalinidae, Phloeodictydae and Petrosiidae.[1] These organisms have shown to be a particular rich source of 3-alkylpyridine alkaloids. In 2006, the Kobayashi group in Japan reported the isolation of a novel bis-pyridine alkaloid, Pyrinadine A (**1**), from the marine sponge *Cribochalina* sp. (SS-1115) collected off Unten Port, Okinawa.[2] Subsequently a group of similar alkaloids were also isolated from the same sponge.[3]

The structure of (**1**) was elucidated by a combination of ^{1}H, ^{13}C NMR and ESI MS/MS. The most interesting structural aspect of this compound is the presence of the azoxy moiety in the natural product. This functional group is not commonly found among natural products, with macrozamine,[4] cycasin,[5] elaiomycin,[6] LL-BH872α,[7] valanimycin,[8] azoxybacillin,[9] jietacin,[10] and maniwamycins A and B[11] being the only known prior examples. Pyrinadine A (**1**) is found to be cytotoxic against L1210 murine leukaemia and KB epidermoid carcinoma cells.[2]

The biosynthesis of naturally occurring azoxy compounds is still not well understood. Recent work of Parry suggested that a nitroso compound, possibly derived from the oxidation of a hydroxylamine, might be involved in the in vivo assembly of the azoxy moiety in valanimycin, though subsequent labelling experiments ruled out hydroxylamine as the source of the oxygen atom in the azoxy group.[12] Therefore we wondered if it would be possible to synthesise Pyrinadine A (**1**), based on a biomimetic oxidative dimerization of precursor **2**, a process analogous to nitrone formation (Fig. 1).

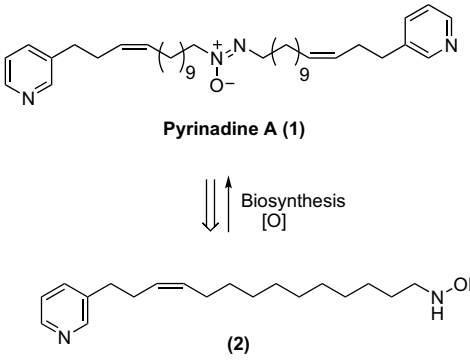

Figure 1. Pyrinadine A (**1**) and its possible biosynthetic precursor (**2**).

Conceptually it could be envisaged that a slow oxidation of hydroxylamine **2** would generate nitroso compound **3**, which would condense with a molecule of compound **2** to give dimer **4**, assuming that this condensation would be rapid compared to the tautomerization of **3** to the corresponding oxime. Elimination of a molecule of water from **4** would afford Pyrinadine A (**1**) (Scheme 1).

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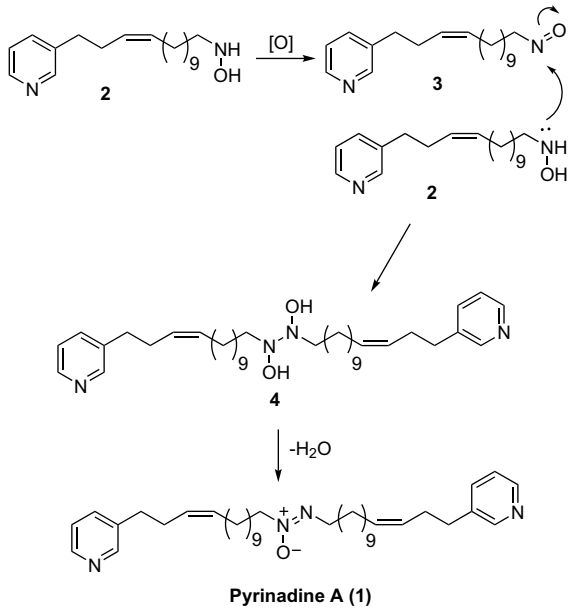
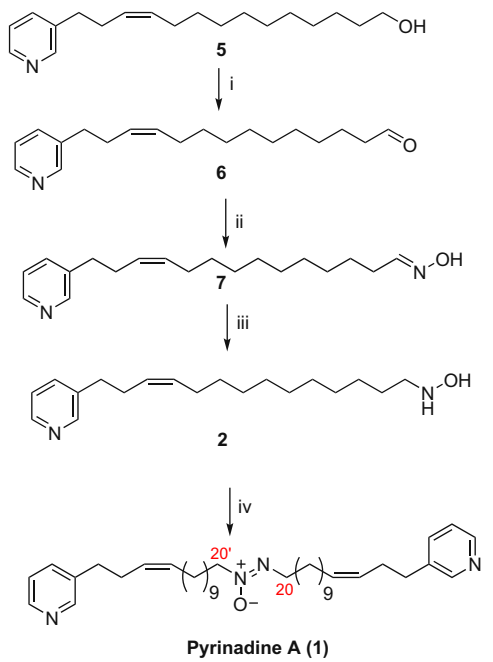


Scheme 1. Possible oxidative mechanism for the oxidative dimerization of hydroxylamine **2** to Pyrinadine A (**1**).

2. Results and discussions

The starting material for the synthesis of Pyrinadine A (**1**) was known alcohol **5**,[13] which was easily prepared from pyridine-3-propanol. A modified IBX oxidation[14] of alcohol **5** gave aldehyde **6** in 91% yield, which was converted to oxime **7** in 84% with hydroxylamine hydrochloride and sodium acetate in methanol.[15] Reduction of oxime **7** with sodium cyanoborohydride under acidic conditions[15] afforded an 88% yield of hydroxylamine **2** (Scheme 2).

The dimerization of aromatic hydroxylamines to the corresponding azoxy products has been documented in the literature.[16] However, there are only a few scattered reports on the oxidative dimerization of aliphatic hydroxylamine. Meister had previously reported the oxidation of cyclododecylhydroxylamine by oxygen and cobalt(II) salt to give a mixture of cyclododecanoxime and the corresponding azoxy dimer.[17] Stetter and Smulder had achieved the conversion of *N*-1-(adamantyl)hydroxylamine to 1,1′-azoxyadamantane by oxidation with sodium dichromate followed by base treatment.[18] The reaction probably proceeded by oxidation of the hydroxylamine to a nitroso compound followed by base catalysed condensation with the remaining hydroxylamine, similar to the mechanism outlined in Scheme 1. The only difference is the nitroso compound derived from *N*-1-(adamantyl)hydroxyamine is unable to tautomerise to an oxime as the α-carbon is tetrasubstituted. Indeed Aston and Ailman described the condensation of 2-β-hydroxylamino-2,5-dimethylhexane with the non-tautomerizable 2-nitroso-2,5-dimethylhexane with potassium hydroxide to give the corresponding azoxy product.[19] Interestingly, Nakagawa et al. observed the conversion of a hydroxylamine to an azoxy dimer by a simple aerial oxidation, although the geometry of the azoxy dimer was not determined.[20] Based on this literature precedence, a sample of hydroxylamine **2** in dichloromethane was left stirring in an open vessel for 2 days. This resulted in a clean conversion of **2** to Pyrinadine A (**1**) in 76% yield (Scheme 2).



Scheme 2. Reagents and conditions: (i) IBX, EtOAc, 80 °C, 91%; (ii) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, 84%; (iii) $NaBH_3CN$, HCl (6 M, trace), MeOH, 88%; (iv) O_2 (air), CH_2Cl_2, 76%.

The geometry of synthetic Pyrinadine A (**1**) was confirmed by NOE studies. Irradiation of H-20 caused virtually no NOE enhancement on H-20′ and vice versa. This unambiguously established the *E*-geometry of the azoxy- group. The spectroscopic data of synthetic **1** is slightly different from that reported by Kobayashi et al.[2] A close examination of the literature data revealed that only six signals that corresponded to 12 sp^2 carbons are reported in the ^{13}C NMR of natural Pyrinadine A (**1**). On the contrary for synthetic **1**, all 14 sp^2 carbons are accounted for spectroscopically by 7 ^{13}C signals. This inconsistency is likely due to a simple typological error in Ref. 2 rather than a gross mistake in the structure elucidation of Pyrinadine A (**1**).[21]

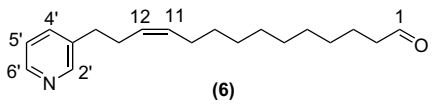
In summary, a simple and expedient synthesis of the marine sponge alkaloid Pyrinadine A is complete. In addition, our work also demonstrates that oxidative coupling of hydroxylamine is a possible scenario in the biosynthesis of the azoxy natural products.

3. Experimental

3.1. General

Infrared spectra were recorded on a Bruker Tensor 27 spectrometer. ^1H and ^{13}C NMR were recorded on either a Bruker DPX200 MHz or DPX400 MHz spectrometer. HRMS were recorded on a Micrimass GCT spectrometer. Flash chromatography was conducted with VWR silica (40–63 μm).

3.2. (*Z*)-14-(Pyridin-3-yl)tetradec-11-enal (6)



To a solution of alcohol **5** (0.224 mg, 0.78 mmol) in ethyl acetate (3 mL) was added IBX (0.65 g, 2.32 mmol). The resulting suspension was immersed in an oil bath at 80 °C and stirred vigorously open to the atmosphere. After 4 h (TLC monitoring), the reaction mixture was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with 3×2 mL of ethyl acetate, and the combined filtrates were concentrated in vacuo to yield 0.202 g (91% yield, >95% pure by ^1H NMR) of aldehyde **6** as a colourless oil.

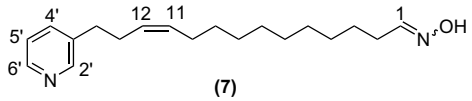
IR (neat) 2926, 2854, 1724, 1575, 1423, 1260, 1190, 1027, 901, 714 cm^{-1}.

δ_H (200 MHz, $CDCl_3$) 1.16–1.37 (12H, H-4 to H-9), 1.62 (2H, quin, *J* 7.3 Hz, H-3), 1.92 (2H, q, *J* 6.3 Hz, H-10), 2.35 (2H, q, *J* 6.7 Hz, H-13), 2.42 (2H, dt J_1 7.4 Hz, J_2 1.8 Hz, H-2), 2.67 (2H, t, *J* 7.5 Hz, H-14), 5.32–5.44 (2H, m, H-11, H-12), 7.22 (1H, dd, J_1 7.5 Hz, J_2 4.9 Hz, Py H-5′), 7.51 (1H, d, *J* 7.5 Hz, Py H-4′), 8.46 (2H, br s, Py, H-2′, H-6′), 9.76 (1H, t, *J* 1.8 Hz, H-1); δ_C (125.8 MHz, $CDCl_3$) 22.0 (1C, C-3), 27.2, 28.7, 29.1, 29.2, 29.3, 29.5, 30.0 ($9CH_2$, C-4 to C-10, and C-13 and C-14), 43.9 (1C, C-2), 123.3 (1C, Py C-5′), 127.7, 131.4 (2CH, C-11, C-12), 136.4 (1C, Py C-4′), 137.5 (1C, Py C-3′), 146.8, 149.5, 149.8 (2C, Py C-2′, C-6′), 202.9 (1C, C-1).

MS (ES): *m*/*z* (%)=$(M-H)^-$ 286.2 (100%).

HRMS: *m*/*z* $[M+H]^+$ calculated for $C_{19}H_{29}NO$: 288.2321; found 288.2322.

3.3. (11*Z*)-14-(Pyridine-3-yl)-tetradec-11-enal oxime (7)



(7)

To a stirred solution of aldehyde **6** (0.160 g, 0.56 mmol) in anhydrous methanol (4 mL) under argon were added NaOAc (0.138 g, 1.68 mmol), then $NH_2OH{\cdot}HCl$ (0.117 g, 1.68 mmol). The mixture was stirred for 4 h at room temperature. The solvent was removed in vacuo and dichloromethane (4 mL) was added, with water (4 mL) and $NaHCO_3$(s) (0.146 g, 1.74 mmol, 3.5 equiv) to neutralise the acetic acid produced. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3×20 mL). The organic phases were washed with $NaHCO_3$(aq) (satd, 20 mL), H_2O (20 mL), then with NaCl(aq) (satd, 20 mL), and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (EtOAc/petrol (30–40); 2:3) to yield oxime **7** (0.141 g, 84%) as a colourless oil.

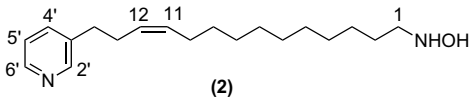
IR (neat) 2925, 2853, 1579, 1425, 1029, 932, 713 cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 1.20–138 (12H, br s, H-4 to H-9), 1.49 (2H, quin, *J* 7.1 Hz, H-3), 1.92 (2H, q, *J* 6.4 Hz, H-10), 2.20 (1H, q, *J* 7.2 Hz, H-2a), 2.30–2.46 (3H, m, H-13, H-2b), 2.66 (2H, t, *J* 7.5 Hz, H-14), 5.32–5.44 (2H, m, H-11, H-12), 6.72 (0.5H, t, *J* H-1b), 7.22 (1H, dd, J_1 7.6 Hz, J_2 4.9 Hz, Py H-5′), 7.44 (0.5H, t, *J* 6.4 Hz, H-1a), 7.52 (1H, dd, J_1 7.6 Hz, J_2 1.6 Hz, Py H-4), 8.23–8.49 (2H, m, Py H-2′, H-6′); δ_C (125.8 MHz, $CDCl_3$) 24.9, 26.1, 26.5, 27.1, 27.2, 28.8, 28.9, 29.1, 29.2, 29.3,, 29.4, 29.5, 33.1 ($11CH_2$), 123.3 (1C, Py C-5′), 127.6, 131.5 (2C, C-11, C-12), 136.3 (1C, Py C-4′), 137.5 (1C, Py C-3′), 147.0, 149.6 (2C, Py C-2′, C-6′), 152.0 (1C, C-1).

MS (ES): *m*/*z* (%)=$[M+H]^+$ 303.2 (100%).

HRMS: *m*/*z* $[M+H]^+$ calculated for $C_{19}H_{30}N_2O$: 303.2430; found 303.2431.

3.4. (*Z*)-*N*-(14-(Pyridine-3-yl)tetradec-11-enyl)hydroxylamine (2)



(2)

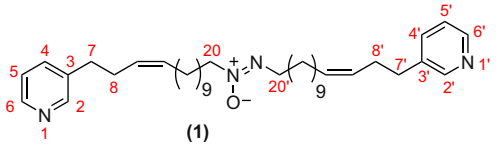
To a stirred solution of oxime **7** (0.124 g, 0.411 mmol) in MeOH (20 mL) at 0 °C were added methyl orange (indicator, 4 mg) and concd HCl (6 M) to turn the indicator red (approx. pH 3). $NaBH_3CN$ (0.103 g, 1.64 mmol) in methanol (5 mL) was added dropwise with concurrent addition of HCl to keep the mixture at pH 3. The mixture was stirred for 3 h at 0 °C and then basified with 6 N NaOH(aq), and worked up using solvents chilled to 0 °C. The mixture was washed with NaCl(aq) (satd, 25 mL) and extracted with chilled DCM (4×30 mL). The organic phases were washed with H_2O (30 mL), NaCl(aq) (satd, 20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo without heating to give hydroxylamine **2** (0.110 g, 88% yield) as a colourless oil.

IR (neat) 2925, 2853, 1575, 1423, 1319, 1027, 799, 714 cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 1.24–1.30 (14H, m, H-3 to H-9), 1.49–1.54 (2H, m, H-2), 1.89–1.97 (2H, m, H-10), 2.34 (2H, q, *J* 6.7 Hz, H-13), 2.65 (2H, t, *J* 7.6 Hz, H-14), 2.92 (2H, t, *J* 7.3 Hz, H-2), 5.31–5.44 (2H, m, H-11, H-12), 7.21 (1H, dd, J_1 7.8 Hz, J_2 4.8 Hz, Py H-5′), 7.52 (1H, d, *J* 7.8 Hz, Py H-4′), 8.42–8.49 (2H, m, Py H-2′, H-6′); δ_C (100.6 MHz, $CDCl_3$) 26.3, 26.6, 26.9, 27.1, 27.2, 27.8, 28.7, 29.0, 29.1, 29.2, 29.3, 29.5 (10CH2), 33.0 (1C, C-14), 53.9 (1C, C-1), 123.3, (1C, Py C-5), 127.6, 131.5 (2C, C-11, C-12), 136.2 (1C, Py C-4′), 137.4 (1C, Py C-3′), 147.0, 149.7 (2C, Py C-2′, C-6′), 152.0 (1C, C-1).

MS (ES): *m*/*z* (%)=$[M+H]^+$ 305.3 (100%).

3.5. Pyrinadine A (1)



(1)

A solution of hydroxylamine **2** (0.034 g, 0.112 mmol) in dichloromethane (2 mL) was stirred in open air for 2 days. The progress of autooxidation was monitored by TLC. The solvent was removed in vacuo and residue was purified by flash chromatography (EtOAc) to give pyrinadine (**1**) (0.026 g, 76% yield) as a colourless oil.

IR (neat) 2925, 2853, 1480, 1438, 1300, 1026, 764, 714, 685 cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 1.20–1.42 (28H, m, H-12 to H-18 and H12′ to H-18′), 1.70 (2H, quin, *J* 7.2 Hz, H-19′), 1.89–1.98 (6H, m, H19, H-11, H11′), 2.36 (4H, dd, J_1 14.2 Hz, J_2 6.8 Hz, H-8 and H8′), 2.66 (4H, t, *J* 7.6 Hz, H-7, and H7′), 3.39 (2H, t, *J* 7.2 Hz, H-20), 4.15 (2H, t, *J* 7.2 Hz, H20′), 5.32–5.45 (4H, m, H-9 and H-9′, H-10 and H-10′), 7.21 (2H, dd, J_1 7.8 Hz, J_2 4.8 Hz, Py H-5), 7.50 (2H, d, *J* 7.8 Hz, Py H-4), 8.41–8.47 (4H, m, Py H-2, H-6); δ_C (100.6 MHz, $CDCl_3$) 26.3, 27.1, 27.2, 27.8, 28.7, 29.2, 29.3, 29.4, 29.5, 29.6 (20C), 33.0 (2C, C-7, C7′), 53.9 (1C, C-20′), 69.7 (1C, C20), 123.2, (2C, Py C-5, C-5′), 127.7 (2C, C-9, C-9′), 131.5 (2C, C-10, C-10′), 135.9 (2C, Py C-4, C-4′), 137.3 (2C, Py C-3, C-3′), 147.3, 150.0 (4C, Py C-2, C-2′,C-6, C-6′).

MS (ES): *m*/*z* (%)$[M+H]^+$ 589.5 (38%), 303.2 (100%).

HRMS: *m*/*z* $[M+H]^+$ calculated for $C_{38}H_{60}N_4O$ 589.4839, found 589.4840.

Acknowledgements

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