Synthesis of Kalasinamide, a Putative Plant Defense Phototoxin

Michael N. Gandy and Matthew J. Piggott*

School of Biomedical, Biomolecular and Chemical Sciences, The University of Western Australia, Crawley, WA, 6009 Australia

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The first total synthesis of the azaanthracene kalasinamide (**1**) is described, and the discrepancy in the reported ^{13}C NMR data and melting points for the natural product from two different sources is resolved. Kalasinamide is prone to autosensitized photooxidation, in solution and in the solid state, to give the corresponding quinone, marcanine A (**8**). This transformation may be representative of a novel and more general step in the biosynthesis of (aza)anthraquinones. Through its ability to generate toxic singlet oxygen, kalasinamide may serve a protective role, defending the plant against predation and the invasion of microbial pathogens, following mechanical insult.

The azaanthracene kalasinamide **1** (Figure 1) was first isolated in 2000 from the acetone extract of *Polyalthia suberosa*, a shrubby tree endemic to southeast Asia and southern China.[1] The structural elucidation of the alkaloid was based on spectroscopic evidence and has been confirmed by an X-ray crystal structure.[2] More recently, **1** was obtained from the seeds of *Annona atemoya* and was named atemoine.[3,4] Although the ^1H NMR spectra of the natural product obtained from both sources were very similar, the ^{13}C NMR spectra were somewhat different (Table 1). This discrepancy and the mild anti-HIV activity of kalasinamide[5] prompted us to carry out its synthesis. In the process, we discovered some interesting photochemistry that may be biosynthetically and ecologically relevant.

The synthesis of kalasinamide **1** is outlined in Scheme 1. Attempts to nitrate 1,4-dimethoxynaphthalene **2** under standard conditions led to significant side reactions and poor yields, but with copper nitrate in acetic anhydride,[7] **3** was produced cleanly in 80% yield. Reduction gave the corresponding aniline **4**, which could be isolated in 90% yield, or reacted *in situ* with diketene **5**,[8] to give the β-ketoamide **6** in 88% yield over the two steps. Sulfuric acid-catalyzed Knorr cyclization[9] gave kalasinamide **1** but was accompanied by some ring sulfonation. This side reaction was avoided by carrying out the Knorr cyclization in 85% phosphoric acid,[10] in which case **1** was formed in 82% yield, contaminated by an additional 9% of the corresponding quinone, marcanine A (griffiazanone B) (**8**), as determined by ^1H NMR integrals. We found the two compounds to be inseparable by silica gel chromatography, and attempts to avoid the formation of **8** by carrying out the reaction under inert atmosphere and with different acids (polyphosphoric acid,[11] trifluoroacetic acid,[12] methanesulfonic acid) were unsuccessful. Ultimately, pure kalasinamide was obtained by excluding atmospheric oxygen and light during the Knorr cyclization, workup, and recrystallization.

Both the ^1H NMR and ^{13}C NMR spectra of the synthetic kalasinamide are identical to those reported by Tuchinda and coworkers[1] (Table 1). The ^1H NMR spectrum and *most* of the ^{13}C NMR signals of atemoine are also identical to those of kalasinamide. We conclude that atemoine is indeed kalasinamide and that the differences in the ^{13}C NMR data are due to impurities in the atemoine isolate. Furthermore, during our investigation, the identity of the impurity became apparent. The byproduct from the Knorr cyclization, marcanine A (**8**), was also generated during some recrystallizations. Given its facile formation from kalasinamide, we suspected it as the likely contaminant in the atemoine sample. Our suspicions were confirmed when the spurious peaks in the ^{13}C NMR spectrum of atemoine were found to be identical with some of the signals for **8** (Table 1).

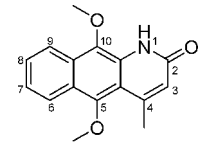

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Figure 1. IUPAC numbering of kalasinamide.[6]

Table 1. ^{13}C NMR Data for Naturally Derived **1** vs Synthetic Material

assignment in ref 1[a]	kalasinamide[1]	"atemoine"[3]	synthetic
4-CH_3	23.3	23.3	23.3
10-OCH_3	61.9	61.9 (5-OCH_3)[b]	61.9
5-OCH_3	64.0	64.1 (10-OCH_3)	64.0
4a	114.0		114.0
9	121.1	121.1 (7)	121.1
		122.7 (4a)	
3	123.1	123.0 (8)	123.1
6	123.5	123.5	123.5
5a	123.9		124.0
7	124.6	124.7 (9)	124.6
8	127.8	127.5 (5a)[c]	127.8
9a	128.1	127.9	128.1
10a	128.2		128.2
		133.7 (C8a)[c]	
10	136.0	135.8 (10a)	135.9
4	148.6	148.8 (5)	148.7
5	151.6	151.7 (10)	151.7
		152.3 (C4)[c]	
2	161.8	161.7	161.7

[a] IUPAC numbering as indicated in Figure 1 has been used here. The original assignments used non-IUPAC numbering. [b] Erroneous assignments made in ref 3 are indicated in parentheses. [c] Indicates signals that correspond with peaks in the ^{13}C NMR spectrum of marcanine A.

A subsequent experiment showed that kalasinamide (**1**), in $CDCl_3$ solution, was completely consumed within 48 h of standing in ambient light in the presence of air, the major product being marcanine A (**8**). This explains how a sample of "atemoine" that appeared pure by ^1H NMR spectroscopy subsequently became contaminated by the quinone **8** before the ^{13}C NMR spectrum was acquired. Similarly, in ambient light, solid samples of kalasinamide were completely oxidized to **8**.

A solution of kalasinamide in $CDCl_3$ was stable for at least two weeks with the exclusion of light, which suggests that the conversion into **8** is mediated by 1,4-cycloaddition of singlet oxygen[13] to give the photooxide **7** (Scheme 1). However, **7** was never observed, indicating the facile nature of the subsequent thermal or photolytic cleavage of the peroxy bridge to give the

* Corresponding author. Tel: +61 8 6488 3170. Fax: +61 8 6488 1005. E-mail: piggott@cyllene.uwa.edu.au.

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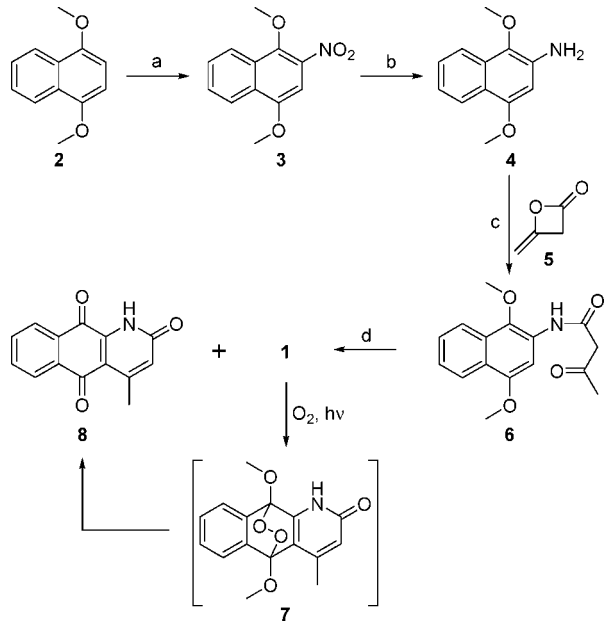
Scheme 1. [a]



[a] Reagents and conditions: (a) $Cu(NO_3)_2 \cdot 2.5H_2O$, Ac_2O, −40 °C, 80%; (b) H_2, 10% Pd/C, EtOAc, 90% (1 step); (c) **5**, PhMe, reflux, 88% (from **3**); (d) 85% H_3PO_4, 85 °C, 82%.

quinone **8**. Kalasinamide thus acts as both sensitizing agent and diene for the subsequent hetero-Diels–Alder reaction. Similar autosensitized photooxidations of 9,10-dimethoxyanthracenes are known;[14] in some cases the photooxides can be isolated, but often they are too unstable under the reaction conditions and the anthraquinones are formed directly.[13]

Marcanine A (**8**) has previously been isolated from *Goniothalamus* species[15–18] and has been shown to have antimalarial activity.[19] Given that **8** has also been isolated from *Polyalthia longifolia* var. *pendula*[20] and *Annona glabra*,[21] members of the same genera from which kalasinamide and "atemoine", respectively, were isolated, it is quite possible that kalasinamide is a biosynthetic precursor to marcanine A in these species, or the latter is an artifact. It is also possible that the anti-HIV activity of kalasinamide is actually due to marcanine A formed *in situ*; as mentioned above, the latter does exhibit reasonable antimalarial activity and is also cytotoxic to several human tumor cell lines.[18]

Alternatively, the capacity of kalasinamide to generate reactive singlet oxygen may be the source of its biological activity. Chlorophyll derivatives can be extremely phototoxic to nonphotosynthetic organisms, for the same reason.[22] Indeed, the role of light and singlet oxygen in plant defense against microbial attack and predation has recently been reviewed.[23] For example, glaucine (**9**), which, like kalasinamide and marcanine A, has previously been isolated from *Annona* species,[24,25] is rapidly oxidized to the phytoalexin[26] oxoglaucine (**10**) *in planta* upon mechanical injury, in particular by singlet oxygen (Figure 2).[23] Oxoglaucine, which has also been isolated from an *Annona* species (*pupureae*),[27] is an efficient singlet oxygen photosensitizer, and it has been speculated that its main role is to prevent the invasion of pathogens through wounds following mechanical injury.[23] It is appealing to hypothesize that kalasinamide serves a similar biological purpose: it protects the plant by generating both highly toxic singlet oxygen and the phytoalexin marcanine A at the site of injury.

A search for other naturally occurring 9,10-dimethoxyanthracenes and aza analogues revealed that annopholine (**11**) (Figure 2), which is structurally very similar to kalasinamide (**1**), co-occurs with its azaanthraquinone counterpart, cleistopholine (**12**), in *Annona hayesii*.[28] Given the facile photooxidation of kalasinamide, and the propensity of 1-azaanthracene to undergo visible light-induced

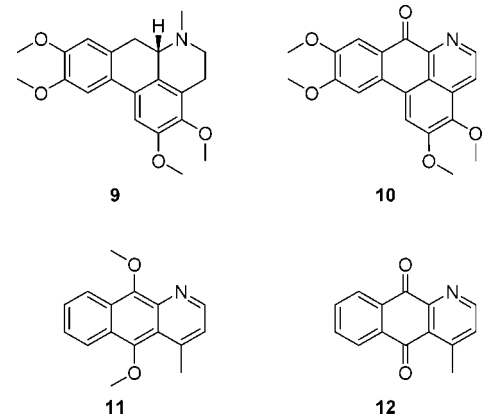


Figure 2

photooxidation,[29] it is likely that annopholine (**9**) is the biosynthetic precursor of cleistopholine (**10**). Indeed photooxidation of 9,10-dimethoxyanthracenes and their aza analogues may be a more general step in the biosynthesis of (aza)anthraquinones that has not been observed previously because of the ease with which this transformation occurs. Both the shikimate-acetate[30] and polyketide pathways[31] have previously been implicated in the biosynthesis of azaanthraquinones.

In conclusion, kalasinamide (**1**) was prepared in four steps (three pots) in an overall yield of 58%. Given the facile photooxidation of **1** to the corresponding quinone, marcanine A (**8**), the original isolation of pure kalasinamide (**1**)[1] is admirable. The photooxidation has implications for the isolation of naturally occurring 9,10-dimethoxyanthracenes and their aza analogues, and may represent a novel transformation in the biosynthesis of (aza)anthraquinones. Furthermore, the facility with which kalasinamide generates highly toxic singlet oxygen may point to a role in plant defense.

Experimental Section

General Experimental Procedures. Melting points were measured on a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were acquired using a Perkin-Elmer Spectrum One FTIR spectrometer. NMR spectra were acquired in $CDCl_3$ using Bruker Avance 500 (500 MHz, ^{1}H; 125 MHz, ^{13}C) or Varian 400 (400 MHz, ^{1}H; 100 MHz, ^{13}C) spectrometers. Chemical shift values are expressed in ppm, relative to $CHCl_3$ (1H, 7.26 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) as appropriate. Routine assignments of ^{13}C NMR spectra were made with the assistance of DEPT 135 and DEPT 90 experiments. Mass spectra were recorded on a VG Autospec instrument using a direct insertion probe and electron impact ionization (EI). Microanalysis was performed by Robertson Microlit (Parsippany, NJ). All solvents were distilled prior to use. "Hexanes" denotes the hydrocarbon fraction distilling from 64 to 67 °C. All reaction temperatures refer to bath temperatures. Organic extracts were dried over anhydrous $MgSO_4$ and then filtered. Silica gel, Merck Kieselgel 60 (40–63 μm), was used for flash chromatography. Analytical TLC was performed on Whatman flexible plates (250 μL layer, Al Sil G/UV254). Spots were visualized under UV light.

1,4-Dimethoxy-2-nitronaphthalene (3). $Cu(NO_3)_2 \cdot 2.5H_2O$ (2.53 g, 10.9 mmol) was added to Ac_2O (25 mL) under $CaCl_2$ guard. The suspension was stirred for 15 min, then cooled to −40 °C before a solution of 1,4-dimethoxynaphthalene (**2**)[32] (1.89 g, 10.0 mmol) in Ac_2O (40 mL) was added dropwise. After 1 h, H_2O (20 mL) and Et_2O (30 mL) were added and the reaction mixture was allowed to warm to room temperature. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phase was washed with H_2O (2 × 20 mL) and brine (20 mL), dried, and evaporated to give an orange residue, which was subjected to flash chromatography. Elution with hexanes−toluene (17:3) afforded **3** as a yellow, amorphous powder (1.87 g, 80%): mp 98.0–98.5 °C [lit.[33] 97–98 °C]; R_f 0.56 EtOAc−hexanes (1:9); ^{1}H NMR (500 MHz) δ 8.31–8.25 (2H, m, H-5 and H-8), 7.69–7.65 (2H, m, H-6 and H-7), 7.22 (1H, s, H-3), 4.09 (3H, s, OCH_3), 4.05 (3H, s, OCH_3); the ^{1}H NMR spectrum was similar

to that reported in d_6-acetone solution at 80 MHz;[33] ^{13}C NMR (125 MHz) δ 151.9 (Ar), 145.7 (Ar), 138.7 (Ar), 129.0 (Ar), 128.9 (ArH), 128.8 (Ar), 128.2 (ArH), 124.1 (ArH), 122.7 (ArH), 98.5 (C-3), 63.6 (OCH_3), 56.1 (OCH_3).

1,4-Dimethoxy-2-naphthylamine (4). A solution of **3** (338 mg, 1.45 mmol) in EtOAc (10 mL) was stirred overnight with 10% Pd/C (35 mg) under an atmosphere of H_2. The suspension was washed through a Celite pad with EtOAc, the filtrate was evaporated, and the residue was subjected to flash chromatography. Elution with hexanes−EtOAc (4:1) afforded **4** as a dark purple solid (265 mg, 90%): R_f 0.16 hexanes−EtOAc (9:1); ^{1}H NMR (500 MHz) δ 8.09 (1H, d, J = 8.1 Hz, ArH), 7.84 (1H, d, J = 8.2 Hz, ArH), 7.47–7.44 (1H, m, ArH), 7.25–7.22 (1H, m, ArH), 6.37 (1H, s, H-3), 4.05–3.90 (2H, br s, NH_2), 3.94 (3H, s, OCH_3), 3.85 (3H, s, OCH_3). The ^{1}H NMR spectrum was different from that reported in d_6-acetone solution at 80 MHz.[33]

***N*-(1,4-Dimethoxy-2-naphthyl)-3-oxobutanamide (6).** A solution of **3** (587 mg, 2.52 mmol) in toluene (10 mL) was stirred with 10% Pd/C (35 mg) under an atmosphere of H_2 for 3.5 h. The reaction mixture was purged of H_2 with N_2, then freshly distilled diketene (**5**) (212 μL, 2.75 mmol) was added and the mixture was heated under reflux. After 7 h more diketene (38 μL, 0.49 mmol) was added and the mixture was stirred at 70 °C overnight. The suspension was washed through a Celite pad with Et_2O (2 × 20 mL), then MeOH (2 × 20 mL), the filtrate was evaporated, and the green residue was subjected to flash chromatography. Elution with hexanes−EtOAc (9:1–3:2 gradient) afforded **6** as an orange gum (632 mg, 88%), which crystallized from MeOH as amber prisms: mp 97–97.5 °C; R_f 0.18 hexanes−EtOAc (3:2); IR (neat) ν_{max} 3274 (N−H, w br), 1712 (C═O, m), 1673 (NC═O, m) cm^{-1}; ^{1}H NMR (500 MHz)[34] δ 9.70 (br s, 1H, NH), 8.20 (1H, ddd, J = 8.4, 1.3, 0.7 Hz, H-5′), 7.99–7.96 (2H, m, H-3′ and H-8′), 7.52 (1H, ddd, J = 8.4, 6.8, 1.3 Hz, H-7′), 7.40 (1H, ddd, J = 8.4, 6.8, 1.3 Hz, H-6′), 4.00 (3H, s, 4′-OCH_3), 3.95 (3H, s, 1′-OCH_3), 3.68 (2H, s, H-2), 2.36 (3H, s, H-4); ^{13}C NMR (125 MHz)[22] δ 204.7 (C═O), 163.6 (NC═O), 152.0 (C-4′), 136.9 (C-1′), 127.53 and 127.49 (C-2′ and C-8a′), 126.8 (C-6′), 124.2 (C-7′), 123.1 (C-4a′), 122.4 (C-5′), 121.0 (C-8′), 98.5 (C-3′), 61.6 (1′-OCH_3), 55.7 (4′-OCH_3), 50.0 (CH_2), 31.1 (O═CCH_3); EIMS m/z 287 $[M]^{\bullet+}$ (15), 272 (11), 214 (13), 203 (16), 188 (100); HREIMS m/z 287.1157 (calcd for $C_{16}H_{17}NO_4$, 287.1158); *anal*. C 67.1%, H 5.8%, N 4.8%; calcd for $C_{16}H_{17}NO_4$, C 66.9%, H 6.0%; N 4.9%.

5,10-Dimethoxy-4-methylbenzo[*g*]quinolin-2(1*H*)-one (Kalasinamide) (1). *Method A:* A solution of **6** (22 mg, 0.077 mmol) in 85% phosphoric acid (2 mL) was stirred at 85 °C in a stoppered vial for 3 h. The resulting solution was poured onto ice and extracted with EtOAc (3 × 10 mL). The extract was washed with H_2O (10 mL) and brine (10 mL), dried, and evaporated to yield a yellow residue (20 mg) comprising kalasinamide (**6**) (17 mg, 82%) and marcanine A (**8**) (1.7 mg, 9%).[35]

Method B: All solvents used were deoxygenated by bubbling through Ar for at least 1.5 h, and all manipulations were carried out in the minimum light practicable. Phosphoric acid (85%, 1 mL) was added to **6** (87 mg, 0.32 mmol), and the resulting solution was stirred vigorously in the dark for 15 min. The solution was then heated at 80 °C for 2 h. The reaction mixture was poured onto cold H_2O (10 mL), basified with saturated Na_2CO_3 solution (10 mL), and extracted with EtOAc (3 × 10 mL). The extract was washed with brine (2 × 10 mL), dried, and evaporated under a stream of dry N_2, giving a yellow residue. Recrystallization (EtOH−DCM) and filtration under a flow of Ar afforded **6** as green prisms: mp 240–242 °C [lit.[1] 234–235.5 °C]; R_f 0.13 hexanes−EtOAc (3:2); ^{1}H NMR (400 MHz) δ 8.96 (1H, br s, NH), 8.18 (1H, ddd, J = 8.6, 1.2, 0.8 Hz, ArH), 8.05 (1H, ddd, J = 8.6, 1.2, 0.8 Hz, ArH), 7.58 (1H, ddd, J = 8.6, 6.7, 1.2 Hz, ArH), 7.47 (1H, ddd, J = 8.6, 6.7, 1.2 Hz, ArH), 6.46 (1H, dq, J = 2.4, 1.3 Hz, H-3), 3.99 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 2.79 (3H, d, J = 1.3 Hz, 4-CH_3). Refer to Table 1 for ^{13}C NMR data.

4-Methylbenzo[*g*]quinoline-2,5,10(1*H*)-trione (Marcanine A) (8). The quinone was obtained from kalasinamide solid samples that had completely oxidized upon standing in ambient light. Recrystallization from MeOH gave **8** as orange needles: mp 295 °C dec [lit.[36] >300 °C; lit.[21] 249–251 °C]; R_f 0.20 DCM−MeOH (99:1); ^{1}H NMR (400 MHz) δ 9.80 (1H, br s, NH), 8.24 (1H, ddd, J = 7.7, 1.3, 0.6 Hz, ArH), 8.19 (1H, ddd, J = 7.7, 1.4, 0.6 Hz, ArH), 7.87 (1H, ddd, J = 7.7, 7.6, 1.4 Hz, ArH), 7.78 (1H, ddd, J = 7.7, 7.6, 1.3 Hz, ArH), 6.69 (1H, q, J = 1.2 Hz, H-3), 2.71 (3H, d, J = 1.2 Hz, 4-CH_3). The ^{1}H NMR spectrum was similar to that reported at 500 MHz.[18]

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