New Alkaloids from *Pandanus amaryllifolius*

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Three new alkaloids, the two pyrrolidine type alkaloids (**1** and **2**) and *6E*-pandanamine (**3**), together with five known alkaloids (**4**−**8**), were isolated from the leaves of *Pandanus amaryllifolius* collected in West Java, Indonesia. All the new alkaloids have two α-methyl α,*β*-unsaturated *γ*-lactone moieties, while compound **2** also has an additional seven-membered ring, which has not been encountered before in *Pandanus* alkaloids. Two different extraction methods, namely, a solvent partitioning extraction and acid−base treatment, were tested, giving secondary and tertiary amines, respectively. Spectroscopic and chemical studies showed that the tertiary amines isolated from the acid−base treatment were artifacts formed during the extraction process. This finding suggests that the use of conventional acid−base treatment in isolating *Pandanus* alkaloids should be reviewed since it can introduce artifacts.

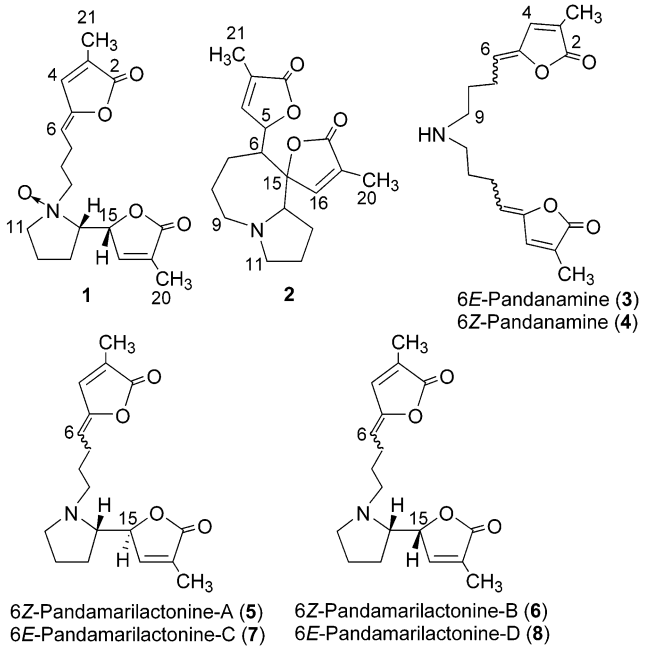
Pandanus amaryllifolius Roxb. (Pandanaceae) grows in Southeast Asia and is the only reported pandanus species with scented leaves.[1] This plant is also known as fragrant screw pine, toei hom (Thailand), pandan mabango (Philippines), pandan wangi (Malay), and daun pandan (Indonesia). The leaves are used as a food flavoring and in traditional medicine in the Philippines, Thailand, and Indonesia. Hot water extracts of the root of this plant (reported as *P. odorus* Ridl.) show hypoglycemic activity, and 4-hydroxybenzoic acid has been isolated as the active principle.[2,3]

There is biogeographic variation in the alkaloids isolated from *P. amaryllifolius* plants collected in the Philippines, Thailand, and Indonesia. Piperidine type alkaloids with lactam[4] or lactone[5] moieties have been isolated from Filipinos samples. Pyrrolidinone[6] and pyrrolidine[7−9] type alkaloids have been isolated from plant samples collected in Indonesia and Thailand, respectively. The majority of *P. amaryllifolius* alkaloids have at least one α,*β*-unsaturated *γ*-lactone ring and have been suggested to derive from the same common precursor,[8] a symmetrical secondary amine called pandanamine (**4**), which has also been isolated from the plant.[10]

Pandanus amaryllifolius from West Java, Indonesia, has not been studied previously. In this paper we report the isolation and structural identification of three new alkaloids from the plants collected in Java. A type of extraction different from the acid−base treatment normally used, namely, a solvent partitioning extraction, was also undertaken in order to compare the type of alkaloids obtained by different extraction methods.

Results and Discussion

Alkaloids **1** and **2** were isolated from the first batch of dried pandanus leaves using conventional acid−base extraction methods. The EtOH extract of the leaves was partitioned between Et_2O and HCl, then basified with NaOH and extracted into $CHCl_3$ to give the crude alkaloidal extract. This extract was further purified by RP-HPLC (H_2O/CH_3CN/TFA). The alkaloid structures were solved using several 2D NMR techniques.



Compound **1** was isolated as a colorless amorphous solid with a molecular formula of $C_{18}H_{23}NO_5$ (HRESIMS). The characteristic ^1H and ^{13}C NMR signals [*δ* 7.04 (1H, d, *J* = 1.3 Hz, H-4), 5.20 (1H, dd, *J* = 7.8, 7.8 Hz, H-6), 2.00 (3H, br s, H_3-21); *δ* 170.9 (C-2), 130.0 (C-3), 137.7 (C-4), 149.5 (C-5), 110.5 (C-6), 10.5 (C-21)] indicated the presence of a *γ*-alkylidene-α-methyl-α,*β*-unsaturated *γ*-lactone moiety. The presence of a second α-methyl-α,*β*-unsaturated *γ*-lactone ring was established from characteristic signals at *δ* 7.07 (1H, br s, H-16), 1.95 (3H, br s., H_3-20); *δ* 172.1 (C-18), 144.4 (C-16), 132.9 (C-17), 10.8 (C-20). A pyrrolidine ring was constructed from the remainder of the signals. HMBC and DQF-COSY data established that the structure of **1** was similar to that of pandamarilactonines-A and -B (**5**, **6**); however, the ^1H and ^{13}C NMR data for **1** did not match that for these two isomers. There were significant differences at *δ* 3.78 (H-9a), 2.93 (H-9b), 4.01 (H-11a), 3.03 (H-11b), 3.08 (H-14), and 5.86 (H-15), where the chemical shifts were approximately 1 ppm lower than the published values for **5** and **6**. These NMR data indicated that the nitrogen in **1** was positively charged. Compound **1** also had an extra oxygen compared to **5** and **6**; thus **1** was deter-

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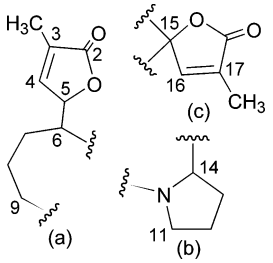


Figure 1. Structural elucidation of compound **2.** Substructures (a), (b), and (c) show the molecular fragments from C-1 to C-9, N-10 to C-14, and C-15 to C-20, respectively, as derived from a combination of HMBC and DQF-COSY data.

mined to be an N_b-oxide. Complete HMBC and DQF-COSY data are given in Supporting Information Table S1.

Compound **2** was isolated as a colorless amorphous solid with molecular formula $C_{18}H_{23}NO_4$ (HRESIMS). The ^{13}C and DEPT data indicated the presence of five quaternary carbons (including two carbonyl carbons), five methines, six methylenes, and two methyl carbons. Characteristic ^1H and ^{13}C NMR signals [δ 7.03 (1H, dd, J = 3.3, 1.6 Hz, H-4), 1.91 (3H, d, J = 1.6 Hz, H_3-21); δ 173.2 (C-2), 132.6 (C-3), 147.0 (C-4), 10.7 (C-21)] indicated the presence of an α-methyl α,β-unsaturated lactone moiety. This was supported by HMBC data that showed a correlation between a proton at δ 4.67 and C-4 and allowed the assignment of H-5. The signal at δ 79.2 (C-5) is characteristic of a methine next to an oxygen atom, hence confirming the presence of a γ-lactone residue. DQF-COSY data showed that H-5 was scalar coupled to another methine proton at δ 3.27 (H-6), which in turn, was coupled to signals at δ 1.64 (H-7a) and 1.59 (H-7b). DQF-COSY data also established the assignment of a three-methylene carbon chain, C-7 to C-9. Interpretation of these data elucidated the substructure (a) shown in Figure 1. The remainder of the methylene proton signals and one methine signal at δ 3.92 were correlated in a DQF-COSY spectrum and established the C-11 to C-14 carbon chain. The ^{13}C shift at δ 59.0 (C-11) and 69.7 (C-14) are characteristic of a methylene and a methine next to a nitrogen atom, respectively. On the basis of this information and on HMBC data, a pyrrolidine ring was constructed, and hence substructure (b) shown in Figure 1 was elucidated. From the remainder of the signals [δ 8.06 (1H, d, J = 1.3 Hz, H-16), 2.04 (3H, d, J = 1.3 Hz, H_3-20); δ 148.2 (C-16), 134.3 (C-17), 171.3 (C-18)], a second α-methyl α,β-unsaturated γ-lactone moiety was constructed (Figure 1c). This was supported by the HMBC correlation between a methine proton at δ 8.06 (H-16) and both C-15 and C-17, and also the signal at δ 87.0 (C-15) was consistent with a quaternary carbon next to an oxygen atom. In the HMBC spectrum, the signals at δ 58.2 (C-9) showed HMBC correlations to both H-11 and H-14. Therefore, substructures (a) and (b) were connected by placing C-9 next to the nitrogen atom. In the HMBC spectrum, the quaternary carbon at δ 87.0 (C-15) was correlated to H-5, H-6, H-7, H-13, H-14, H-16, and H-20. These data confirmed C-15 as a bridgehead atom that connected the three substructures together, generating structure **2** as shown. Complete HMBC, DQF-COSY, and NOESY data are given in Supporting Information Table S2.

The relative stereochemistry of **2** (Figure 2) was assigned from the coupling constants and NOESY data. Compound **2** has four chiral centers, and therefore there are 16 possible stereoisomers. All 16 stereoisomers were modeled using the Insight II molecular builder. The cvff force field was used to find the conformation with the lowest energy. Models were excluded if their NOESY-correlated protons

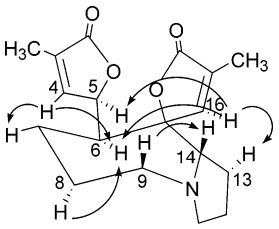


Figure 2. Selected NOESY correlations for compound **2**.

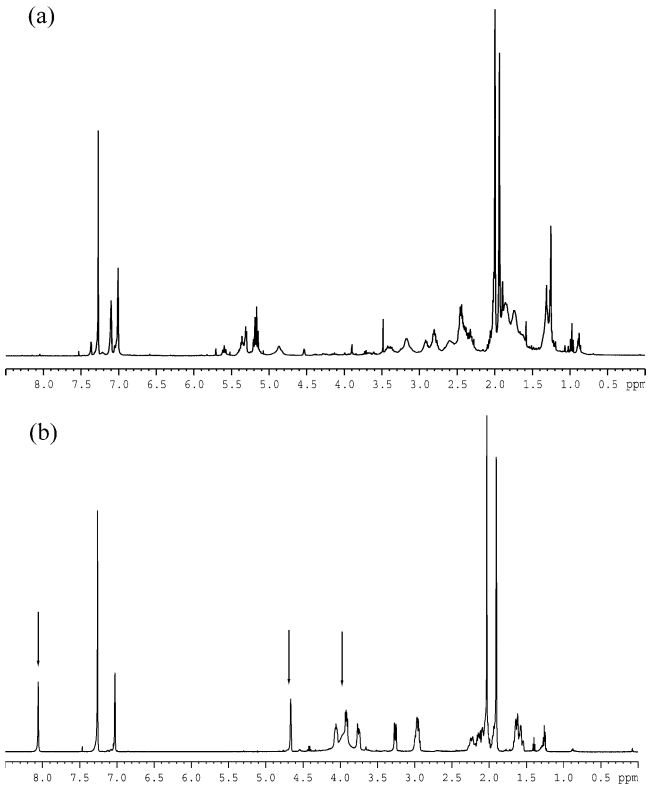


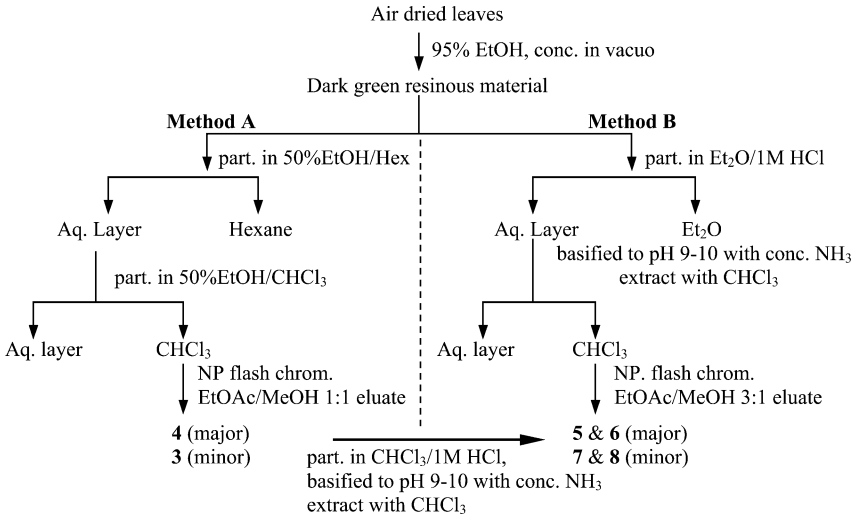
Figure 3. ^1H NMR spectra of alkaloidal extract (a) before and (b) after HPLC purification. Arrows mark the regions showing significant differences.

were separated by >4 Å. Only one model, with the relative stereochemistry of 5*R*, 6*S*, 14*S*, 15*R* and a chair conformation in the seven-membered ring, is consistent with the experimental NOESY data. Distances between protons that show NOESY correlations were in the range 2.6−3.2 Å in the 5*R*, 6*S*, 14*S*, 15*R* Insight model. The lowest energy conformation indicated a dihedral angle of 70° between H5 and H6, which is consistent with the small coupling constant (J = 1.7 Hz) seen in the ^1H spectrum.

The ^1H NMR data indicated that extract compositions had changed during the HPLC purification. Differences in ^1H spectra of the extract before and after HPLC purification yielding compound **2** are shown in Figure 3. Key signals for **2** at δ 8.06, 4.67, 4.06, 3.92, and 3.75 were not observed in the spectrum of the extract before HPLC. Similarly for compound **1**, there was also no evidence for this alkaloid prior to HPLC. Therefore, the isolated alkaloids **1** and **2** were not the "natural products" of *P. amaryllifolius*. This evidence suggested that "natural" pandanus alkaloids are sensitive to the acid conditions used in HPLC to assist in peak resolution. A comparative study of alkaloids isolated from two different extraction methods, a solvent partitioned method and acid−base treatment, was then carried out.

Bulk extraction of a second batch of dried pandanus leaves using 95% EtOH was carried out; half of the crude extract was processed by the solvent partitioned method

Scheme 1. Extraction Methods for (a) Solvent Partitioned and (b) Acid−Base Extraction, Outlining the Isolation of Alkaloids



(method A), while the other half was extracted using acid−base extraction (method B). In the solvent partitioning procedure, acid and base were excluded to minimize the formation of unwanted side reactions that can lead to the formation of artifacts. It was found that the two extraction methods resulted in the isolation of different alkaloids (Scheme 1).

The crude alkaloid extracts obtained from both methods were compared using TLC and NMR. On a TLC plate [SiO_2, solvent system 10% MeOH in $CHCl_3$], method A gave one Dragendorff positive spot with R_f 0.1, while method B gave two spots with R_f 0.7 and 0.2. ^{1}H NMR spectra of crude alkaloids from both methods were also different, as expected from the TLC profile. Two alkaloids were observed in the ^{1}H spectrum of the crude alkaloidal extract from method A, while four alkaloids were observed in the extract from method B.

A mixture of two alkaloids was obtained from the solvent partitioned method (method A): the previously reported pandanamine (**4**)[10] as the major component and another minor alkaloid (**3**). Compound **3** had ^{1}H and ^{13}C spectra that were identical to those of pandanamine, except that the alkene signals at δ 7.43 (H-4) and 5.51 (H-6) appeared at lower field (δ 7.00 (H-4) and 5.14 (H-6) for pandanamine). A significant difference was also observed at δ 134.0 (C-4), which appeared at higher field than that of pandanamine (δ 137.8). These data suggested that **3** and pandanamine (**4**) differed only in the stereochemistry about the C5−C6 double bond. Pandanamine had been determined to have a *Z* configuration in the γ-alkylidene-α-methyl-α,β-unsaturated γ-lactone moiety;[10] therefore, compound **3** is the *E* isomer for pandanamine (6*E*-pandanamine). Other studies on *P. amaryllifolius* alkaloids also showed that an *E* configuration of the γ-alkylidenebutenolide moiety results in lower field proton chemical shifts for H-4 and H-6.[6,9]

Alkaloids from the acid−base extraction (method B, HCl/ether and $NH_4OH/CHCl_3$) were characterized by NMR as a mixture of known tertiary amines, including pandamarilactonines-A and -B (**5**, **6**) (major components) and pandamarilactonines-C and -D (**7**, **8**) (minor components).[8,9] Takayama et al. reported that pandamarilactonine-A exhibited $[\alpha]^{23}_D$ +35 (*c* 4.37, $CHCl_3$) with a 26% enantiomeric excess, while pandamarilactonine-B was isolated as a racemate.[8] Pandamarilactonine-C (the *E* isomer of pandamarilactonine-A) exhibited $[\alpha]^{23}_D$ +26.2 (*c* 0.99, $CHCl_3$), while pandamarilactonine-D (the *E* isomer of pandamarilactonine-B) was a racemate.[9] The $[\alpha]^{23}_D$ value of the mixed pandamarilactonine sample isolated in the present study was +4.0 (*c* 2.56, $CHCl_3$). The acid−base extraction on the second batch of leaves was repeated using H_2SO_4/ether and $NH_4OH/CHCl_3$ and afforded compounds **5**−**8** as reported above. This showed that differences in the acid used during the extraction (HCl vs H_2SO_4) did not affect the type of alkaloids obtained from the acid−base extraction.

Pandamarilactonines were not isolated from the solvent partitioned method, suggesting that they were artifacts formed during the acid−base treatment. The most likely precursors of these alkaloids are the pandanamines, which were isolated from the solvent partitioned method. Pandanamine has been postulated to derive from 4-hydroxy-4-methylglutamic acid[5] and has been isolated from the related species *P. veitchii*.[11]

The pandamarilactonines (**5**−**8**) isolated in this study should be a racemate since the starting compounds, pandanamines (**3** and **4**), are not chiral. The small $[\alpha]^{23}_D$ value of the pandamarilactonines isolated in this study could be attributed to a small amount of impurities in the sample. In a biomimetic synthesis, Takayama et al. have shown that **4** cyclizes to **5** and **6** upon treatment with TFA in CH_3CN.[8] We subjected **3** and **4** isolated from method A to acid−base treatment similar to that in the acid−base extraction procedure. The products of this acid−base treatment were analyzed by NMR (^{1}H, ^{13}C, HSQC, and HMBC) and were found to be the pandamarilactonines **5**−**8**. A likely mechanism for the conversion of pandanamines to pandamarilactonines involves Michael addition of the nitrogen onto the double bond at C-6 followed by protonation at C-15.

Since pandamarilactonines-A and -B (**5** and **6**) were isolated from the crude alkaloidal fraction obtained by the acid−base extraction, it is possible that they are the precursors to compound **2**. Under acidic conditions (e.g., in the presence of TFA), the enol form of **5** or **6** may attack C-6, ultimately leading to the formation of **2** after reprotonation at C-5.

In conclusion, the use of conventional acid−base extraction to isolate pandanus alkaloids should be revised, because it can lead to the formation of artifacts. It is still not clear whether the alkaloids isolated in earlier studies[4−9] are the "natural product" or artifacts formed during the isolation process. It is also possible that *P. amaryllifolius* species have several subspecies or chemotypes, which produce different types of alkaloids.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. HRESIMS was measured on a Finnigan MAT 900 XL double-focusing magnetic sector mass spectrometer. ^{1}H, ^{13}C, HSQC, HMBC, NOESY, and DQF-COSY spectra were recorded on a Bruker DRX 500 MHz spectrometer; the DEPT spectrum was recorded on a Varian Gemini 300 MHz spectrometer. Flash chromatography was carried out using Scharlau silica gel 60 (0.04−0.06 mm). RP-HPLC was carried out using a Vydac C-18 semipreparative column with UV detection at λ 250 nm.

Plant Material. The first batch of fresh leaves of *Pandanus amaryllifolius* was purchased at a traditional market in Jakarta in June 2001. The second batch of leaves was collected in Jakarta in June 2002. The plants were identified at the Bogoriense Herbarium in Bogor, Indonesia. The leaves were air-dried and transported to Australia for subsequent extraction. Voucher specimens (AS012 and AS014) are kept at the IMB, University of Queensland, Brisbane, Australia.

Extraction and Isolation of Compounds 1 and 2. The first batch of dried leaves (180 g) was extracted with 95% EtOH three times and filtered. The combined filtrate was evaporated in vacuo and partitioned between Et_2O and 1 M HCl. The aqueous layer was basified to pH 9−10 with 1 M NaOH and extracted exhaustively with $CHCl_3$ to give a crude alkaloidal fraction. The crude alkaloidal fraction (140 mg) was partitioned by NP flash chromatography using DCM, EtOAc, and MeOH in increasing polarity. The fraction eluting in 100% EtOAc (10 mg) was further purified using RP-HPLC (H_2O/CH_3CN/0.05% TFA, 1% gradient, flow rate 3 mL/min) to afford **2** (3.3 mg). The fraction eluting in EtOAc/MeOH (3:1) (9 mg) was processed similarly to afford **1** (1.8 mg).

Compound 1: colorless, amorphous solid; sample decomposed before $[\alpha]^{24}_D$ measurement was made; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07 (1H, br s, H-16), 7.04 (1H, d, J = 1.3 Hz, H-4), 5.86 (1H, dd, J = 7.8 Hz, H-15), 5.20 (1H, dd, J = 7.8, 7.8 Hz, H-6), 4.01 (1H, ddd, J = 7.3, 4.6 Hz, H-11a), 3.78 (1H, ddd, J = 12.1, 12.1, 4.6 Hz, H-9a), 3.08 (1H, ddd, J = 7.8 Hz, H-14), 2.93 (1H, m, H-9b), 2.51−2.45 (2H, m, H_2-7), 2.33 (1H, m, H-12a), 2.23 (1H, m, H-13a), 2.21 (2H, m, H-8a and H-13b), 2.10 (1H, m, H-12b), 2.00 (3H, br s, H_3-21), 1.96 (1H, m, H-8), 1.95 (3H, br s, H_3-20); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1 (C-18), 170.9 (C-2), 149.5 (C-5), 144.4 (C-16), 137.7 (C-4), 132.9 (C-17), 130.0 (C-3), 110.5 (C-6), 78.5 (C-15), 70.5 (C-14), 54.7 (C-9), 54.1 (C-11), 26.5 (C-13), 24.6 (C-8), 23.2 (C-7), 21.7 (C-12), 10.8 (C-20), 10.5 (C-21); HRESIMS m/z 334.1677 $[M + H]^+$ (calcd for $C_{18}H_{24}NO_5$, 334.1704).

Compound 2: colorless, amorphous solid; $[\alpha]^{24}_D$ −4.35° (c 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (1H, d, J = 1.3 Hz, H-16), 7.03 (1H, dd, J = 3.3, 1.6 Hz, H-4), 4.67 (1H, dd, J = 3.3, 1.7 Hz, H-5), 4.06 (1H, ddd, J = 10.7, 6.3, 4.4 Hz, H-11a), 3.92 (1H, dd, J = 9.5, 5.1 Hz, H-14), 3.75 (1H, m, H-9a), 3.27 (1H, ddd, J = 10.2, 3.0, 1.7 Hz, H-6), 2.95 (1H, m, H-9b), 2.92 (1H, m, H-11b), 2.24 (1H, m, H-8a), 2.14 (1H, m, H-13a), 2.08 (1H, m, H-8b), 2.04 (3H, d, J = 1.3 Hz, H_3-20), 2.03 (1H, m, H-12a), 1.93, (1H, m, H-12b), 1.91 (3H, d, J = 1.6 Hz, H_3-21); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.2 (C, C-2), 171.3 (C, C-18), 148.2 (CH, C-16), 147.0 (CH, C-4), 134.3 (C, C-17), 132.6 (C, C-3), 87.0 (C, C-15), 79.2 (CH, C-5), 69.7 (CH, C-14), 59.0 (CH_2, C-11), 58.2 (CH_2, C-9), 44.6 (CH, C-6), 26.5 (2C, CH_2, C-8 & C-13), 23.3 (CH_2, C-12), 21.6 (CH_2, C-7), 10.7 (CH_3, C-21), 10.6 (CH_3, C-20); HRESIMS m/z 318.1713 $[M + H]^+$ (calcd for $C_{18}H_{24}NO_4$, 318.1704).

Comparative Extraction. The second batch of dried leaves (200 g) was extracted with 95% EtOH three times and filtered. The combined filtrate was evaporated in vacuo, giving dark green resinous material (crude extract), and half of the crude extract was processed using method A and the other using method B. Method A (polarity extraction): the crude extract (400 mg) was redissolved in EtOH (200 mL) and was partitioned with hexane (2 × 300 mL), and water (200 mL) was added to form two layers (aqueous and organic layer). The defatted aqueous layer was extracted with $CHCl_3$ (3 × 200 mL) to give a crude alkaloidal fraction. The crude alkaloidal fraction was chromatographed on a SiO_2 flash column using DCM, EtOAc, and MeOH in increasing polarity. The fraction eluting in EtOAc/MeOH (1:1) afforded a mixture of *Z*- and *E*-pandanamine (**4** and **3**) (40 mg). Method B (acid−base extraction): the crude extract (350 mg) was partitioned between Et_2O and 1 M HCl. The aqueous layer was basified to pH 9−10 with concentrated NH_3 and extracted exhaustively with $CHCl_3$ to give a crude alkaloidal fraction. The crude alkaloidal fraction was chromatographed as in method A. The fraction eluting in 100% EtOAc−EtOAc/MeOH (3:1) afforded a mixture of pandamarilactonines A−D (**5**−**8**) (40 mg).

Compound 3 (6*E*-pandanamine): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 (2H, br s, H-4), 5.51 (2H, dd, J = 8.3, 8.3 Hz, H-6), 2.93 (4H, m, H_2-9), 2.38 (4H, m, H_2-7), 2.0−1.95 (4H, m, H_2-8), 1.96 (6H, br s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8 (C-2), 149.5 (C-5), 134.0 (C-4), 129.6 (C-3), 111.0 (C-6), 47.2 (C-9), 25.4 (C-8), 23.5 (C-7), 10.6 (*C*H_3).

Conversion of 4 and 3 to 5−8. A mixture *Z*- and *E*-pandanamines (**4**, **3**) (20 mg) was dissolved in $CHCl_3$ and extracted with 1 M HCl three times. The combined aqueous layer was basified to pH 9−10 with concentrated NH_3 and extracted three times with $CHCl_3$. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo. The product (white, amorphous solid, 9 mg) was analyzed with NMR (^{1}H, ^{13}C, HSQC, HMBC) and was identified as a mixture of **5**−**8**.

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Supporting Information Available: Table S1, complete NMR data for compound **1** (HMBC, DQF-COSY). Table S2, complete NMR data for compound **2** (HMBC, DQF-COSY, NOESY). This material is available free of charge via the Internet at http://pubs.acs.org.

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