Isolation of Pandamarilactonine-H from the Roots of *Pandanus amaryllifolius* and Synthesis of *epi*-Pandamarilactonine-H

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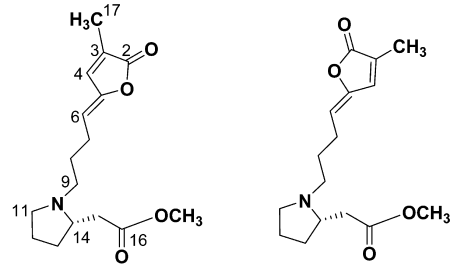
A new alkaloid (**1a**), named pandamarilactonine-H, which possesses a methyl-2-(pyrrolidin-2-yl)acetate function, was isolated from the roots of *Pandanus amaryllifolius.* Eleven known alkaloids were also isolated. Unambiguous assignment of the structure of **1a**, including the absolute configuration, was accomplished by spectroscopic analysis and total synthesis of its enantiomer.

The genus *Pandanus* comprises approximately 700 species that are distributed in tropical and subtropical regions. Many species of this genus are known for their medicinal properties.[1] Phytochemical studies on *Pandanus* species have identified essential oils,[2] lignans, ionones, benzofurans,[3] terpenes,[4] and alkaloids.[5,6] *Pandanus amaryllifolius* Roxb. (Pandanaceae), commonly known as fragrant screw pine, is well studied owing to its importance in folklore medicine and its structurally unique alkaloids. In our continuing search for biologically active alkaloids from the genus *Pandanus*,[6,7] the novel alkaloids from leaves of *P. amaryllifolius* have encouraged us to investigate the alkaloidal constituents in the roots.

The crude alkaloid mixture obtained from a MeOH extract of *P. amaryllifolius* roots was subjected to chromatographic separation and yielded a new alkaloid (**1a**) and the known alkaloids pandamarilactones-1[5a] and -32;[5a] pandamarilactonines-A,[6a] -B,[6a] -C,[6b] -D,[6b] -E,[6f] -F,[6f] -F-*N*-oxide,[6f] and -G;[6f] and dubiusamine-A.[6e] The structure of **1a**, named pandamarilactonine-H, was elucidated on the basis of 1D and 2D NMR and HRMS spectroscopic data and total synthesis. The known alkaloids were identified by comparing their spectroscopic data with those reported in the literature.



Pandamarilactonine-H (**1a**) minor isomer (**1b**)

Pandamarilactonine-H (**1a**) was obtained as an amorphous solid and in optically active form, $[\alpha]^{24}_{D}$ −43 (*c* 0.04, $CHCl_3$). It had the molecular formula $C_{16}H_{23}NO_4$, as revealed by the HRESIMS spectrum (*m/z* 294.1689 $[M + H]^+$, calcd for $C_{16}H_{24}NO_4$, 294.1700). NMR spectra indicated the presence of aliphatic ester (δ_C 172.8, C-16) and lactone (δ_C 171.1, C-2) carbonyls, four sp^2 olefinic carbons, seven sp^3 methylenes, one nitrogen-bearing sp^3 methine (δ_C 61.1, C-14), an allylic methyl (δ_C 10.5, C-17), and a methoxy methyl (δ_C 51.5). A *Z*-configured γ-butylidene-α-methyl-α,β-unsaturated lactone moiety was indicated by NOE correlation

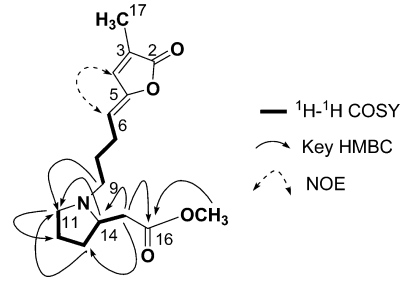


Figure 1. 2D NMR correlations of **1a**.

between the H-4 and H-6 olefinic methines, from the strong UV absorption at 275 nm, and from the characteristic NMR signals {δ_H 6.98 (1H, dd, $J = 1.6$, 0.9 Hz, H-4), 5.15 (1H, dd, $J = 8.0$, 8.0 Hz, H-6), 1.99 (3H, d, $J = 0.9$ Hz, H_3-17); δ_C 171.1 (C-2), 129.1 (C-3), 137.7 (C-4), 148.5 (C-5), 114.1 (C-6), 10.5 (C-17)}. The $^1H-^1H$ COSY spectrum of **1a** showed that the three-carbon methylene fragment (H_2-7/H_2-8/H_2-9) was connected to the olefinic H-6 proton. In the lower segment of **1a**, $^1H-^1H$ COSY correlations were observed from the remainder of the aliphatic methylenes and methine to establish the fragment H_2-11 to H_2-12/H_2-13/H-14/H_2-15. The chemical shifts of C-11 (δ_C 53.6) and the C-14 methine (δ_C 61.1) implied a neighboring nitrogen atom. Thus, a pyrrolidine ring with an additional methylene attached to C-14 was constructed. The remaining ester carbonyl (δ_C 172.8, C-16) and the OCH_3 group (δ_C 51.5) were attached to the C-15 methylene (δ_C 39.5).

Assignment of structure to the lower segment in **1a** was validated using HMBC analysis. The following correlations were observed: H_2-15 to C-13/C-14/C-16; H-14 to C-11; H_2-11 to C-12; H_2-13 to C-11; and the OCH_3 protons to C-16. The observed HMBC correlation of H_2-9 to C-11 led to the gross structure of **1a** as indicated (Figure 1). The ^1H and ^{13}C NMR spectra (Supporting Information) of **1a** also showed minor peaks at δ_H 7.31, 5.60 and δ_C 113.4, 130.2, 133.7, which were attributed to the minor isomer (**1b**) in a 3.6:1 (**1a**/**1b**) ratio, based on ^1H NMR integration. The observed upfield-shifted resonance of C-4 in **1b** (δ_C 133.7) compared to that of **1a** (δ_C 137.7) was attributed to the γ-gauche effect owing to the *E* configuration in the γ-alkylidene-γ-lactone moiety.[6b] Although alkaloid **1a** was isolated as a diastereomeric mixture with **1b**, we were able to synthesize them in the diastereomerically and enantiomerically pure forms using D-proline as the chiral starting material.

To obtain a definite structural assignment, including clarification of the absolute configuration at C-14, the asymmetric total synthesis of **1a** was attempted. The synthetic strategy for formation of **1a** entailed condensation of γ-alkylidene butenolide (**2**) for the upper segment with methyl pyrrolidinylacetate (**3**), which represents the

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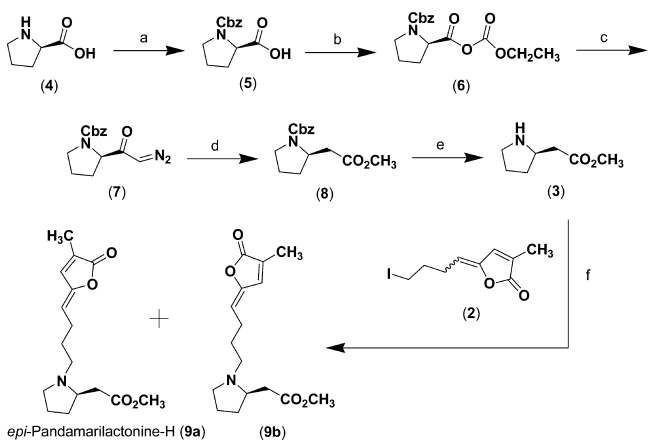
Scheme 1[a]



[a] Reagents and conditions: (a) ref 8, quant.; (b) $ClCOOCH_2CH_3$, Et_3N, THF, −25 °C, 30 min, 71%; (c) $TMSCHN_2$, CH_3CN, 0 °C → rt, 6−19 h, 86%; (d) MeOH, $C_6H_5CO_2Ag$, Et_3N, sonication, 1 h, 83%; (e) H_2 (balloon), 10% Pd/C, MeOH, rt, 1 h, 78%; (f) Ag_2CO_3, CH_3CN, rt, 36 h, 57%.

lower part of **1a**. The synthesis of required compound **3** commenced with the Cbz protection of D-proline (**4**) in quantitative yield.[8] The Cbz-protected-D-proline (**5**) was treated with ethyl chloroformate and Et_3N in THF to afford mixed anhydride **6** in 71% yield. The Arndt−Eistert reaction of **6** employing trimethylsilyldiazomethane ($TMSCHN_2$) in CH_3CN gave the desired α-diazoketone[9] (**7**) in 86% yield. Compound **7** was then subjected to a key homologation reaction step using the Wolff rearrangement. In this process, **7** was initially suspended in MeOH. Then, a solution of silver benzoate in Et_3N was gradually added under sonication. This gave Cbz-protected methyl pyrrolidinylacetate[9a] (**8**) as a colorless oil in 83% yield. The formation of methyl pyrrolidinylacetate[9a,10] (**3**) in 78% yield was accomplished by hydrogenolysis of **8** in 10% Pd/C and MeOH. Condensation of **3** with a 3:2 (*Z*/*E*) mixture of γ-alkylidene butenolide[6b,7b] (**2**) utilizing Ag_2CO_3 in CH_3CN afforded the alkaloidal adducts in 57% combined yield. Careful chromatographic separation furnished synthetically pure *epi*-pandamarilactonine-H (**9a**) {$[\alpha]^{21}_D$ +62 (*c* 0.07, $CHCl_3$)}, having a *Z* configuration, as the major compound, and the synthetically pure compound **9b** diastereomer {$[\alpha]^{22}_D$ +67 (*c* 0.05, $CHCl_3$)}. Both of the synthesized compounds **9a** and **9b** had a C-14*R* configuration. The spectral data (^1H and ^{13}C NMR, HRMS) and chromatographic behavior of **9a** are in excellent agreement with those of the major peaks in the natural product (**1a**), except for the opposite sign of the optical rotation. On the basis of these findings, the absolute configuration of pandamarilactonine-H was elucidated to be C-14*S*, and its structure was conclusively determined as shown in **1a**. Furthermore, the structure of **1b** was also determined by comparing the minor signals observed in the ^1H NMR spectrum of the natural product with those of **9b**. Pandamarilactonine-H (**1a**) is the first *Pandanus* alkaloid having a methyl-2-(pyrrolidin-2-yl)acetate moiety.

Compounds **1a**, **9a**, **9b**, and dubiusamine-B were evaluated for their toxicity on human tumor cell lines A549, HT29, and HCT116. No cytotoxicity was detected for the four compounds (IC_{50} values >5 μg/mL).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO P-1020 polarimeter. UV spectra were recorded on a JASCO V-560 UV−vis spectrophotometer. HRESIMS were recorded on a Thermo Fisher Scientific Exactive or a JEOL AccuTOF-T100LP spectrometer. NMR spectra were recorded on a JEOL JNM A-500, a JEOL JNM A-400, or a JEOL JNM ECP400 spectrometer. The chemical shifts are given in δ (ppm) and coupling constants, in Hz. Kieselgel 60 [Merck, 70−230 mesh (for open column chromatography)], silica gel 60N [Kanto Chemical, 40−50 μm (for flash column chromatography)], and Chromatorex NH (Fuji Silysia Chemical, 100−200 mesh) were used for column chromatography. Medium-pressure liquid chromatography was carried out on a CPS-HS-221-05 silica gel prepacked column (Kusano Kagakukikai).

Plant Material. The whole plant of *Pandanus amaryllifolius* was collected in Nueva Vizcaya, Philippines, in December 2008, and identified by Assistant Professor Rosie Madulid, Department of Biological Sciences, College of Science, University of Santo Tomas. A voucher specimen (USTH-3728) was deposited in the Plant Sciences Herbarium, Research Center for the Natural Sciences, University of Santo Tomas.

Extraction and Isolation. The air-dried, ground roots (523 g) were extracted exhaustively with MeOH (8.6 L) five times and filtered. The combined filtrates were concentrated under reduced pressure to obtain the MeOH extract (116 g). This was dissolved in 1 N HCl and extracted three times with EtOAc. The aqueous layer was basified with Na_2CO_3 (pH 7−8) and extracted exhaustively with 5% MeOH−$CHCl_3$. The combined organic layers were dried with anhydrous $MgSO_4$ and evaporated to obtain the crude base (2.1 g). A portion of the crude base (2 g) was initially separated by silica gel flash column chromatography using a $CHCl_3$/MeOH gradient. The $CHCl_3$ eluate was separated by silica gel flash column chromatography using 50% EtOAc/hexane to yield pandamarilactone-1 (9.1 mg). The 2−5% MeOH/$CHCl_3$ eluate was separated by silica gel flash column chromatography using a $CHCl_3$/EtOH gradient to give four fractions, A1−A4. Fractions A1, A2, and A3 were separated by MPLC (60% EtOAc/hexane or 80% EtOAc/hexane) to afford pandamarilactonine-A (9.9 mg), pandamarilactonine-B (9.6 mg), pandamarilactonine-C (1.1 mg), and pandamarilactonine-D (3.0 mg). A4 was separated by silica gel flash column chromatography (EtOAc → 2% EtOH/$CHCl_3$) to give subfractions B1−B5 and pure pandamarilactone-32 (14.1 mg). Subfraction B1 was purified by amino−silica gel chromatography (50% EtOAc/hexane) to obtain pandamarilactonine-E (4.4 mg). Subfraction B3 was separated by amino−silica gel chromatography (40% EtOAc/hexane) to afford pandamarilactonine-H (**1a**, 3.0 mg). Subfraction B4 was purified by amino−silica gel chromatography to afford pandamarilactonine-G (1.7 mg). Subfraction B5 was purified by amino−silica gel chromatography to afford pandamarilactonine-F (1.3 mg). The 5−10% MeOH/$CHCl_3$ eluate was separated by amino−silica gel chromatography using an EtOAc/hexane gradient to obtain pandamarilactonine-F (2.3 mg), pandamarilactone-32 (1.2 mg), and mixtures of pandamarilactonines-A and -B. The 20−50% MeOH/$CHCl_3$ eluate was separated by amino−silica gel chromatography using an EtOH/$CHCl_3$ gradient to afford dubiusamine-A (44.8 mg). The 50% MeOH/$CHCl_3$ → MeOH eluate was separated by amino−silica gel (10% EtOH/$CHCl_3$) and silica gel (20% MeOH/$CHCl_3$) open column chromatography to afford pandamarilactonine-F-*N*-oxide (1.2 mg).

Pandamarilactonine-H (1a): amorphous solid; $[\alpha]^{24}_D$ −43 (*c* 0.04, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 201 (1.83), 275 (2.45) nm; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98 (1H, dd, *J* = 1.6, 0.9 Hz, H-4), 5.15 (1H, dd, *J* = 8.0, 8.0 Hz, H-6), 3.67 (3H, s, −O*CH*$_3$), 3.12 (1H, m, H-11a), 2.72 (3H, overlapped, H_2-9, H-14), 2.60 (1H, dd, *J* = 14.8, 4.0 Hz, H-15a), 2.40 (2H, m, H_2-7), 2.24 (1H, m, H-15b), 2.15 (1H, m, H-11b), 2.02 (1H, m, H-13a), 1.99 (3H, d, *J* = 0.9 Hz, H_3-17), 1.74 (2H, m, H_2-12), 1.64 (2H, m, H_2-8), 1.55 (1H, m, H-13b); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8 (C=O, C-16), 171.1 (C=O, C-2), 148.5 (C, C-5), 137.7 (CH, C-4), 129.1 (C, C-3), 114.1 (CH, C-6), 61.1 (CH, C-14), 53.9 (CH_2, C-9), 53.6 (CH_2, C-11), 51.5 (CH_3, −O*CH*$_3$), 39.5 (CH_2, C-15), 30.8 (CH_2, C-13), 28.3 (CH_2, C-8), 24.2 (CH_2, C-7), 22.3 (CH_2, C-12), 10.5 (CH_3, C-17); HRESIMS *m*/*z* 294.1689 $[M + H]^+$, calcd for $C_{16}H_{24}NO_4$, 294.1700.

Minor Isomer (1b): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (H-4), 5.60 (H-6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 133.7 (C-4), 130.2 (C-3), 113.4 (C-6).

Preparation of Mixed Anhydride 6. To a stirred solution of **5** (100 mg, 0.402 mmol) in THF (2.0 mL) in an ice−salt bath were added Et_3N (56 μL, 0.402 mmol, 1.0 equiv) and $ClCOOCH_2CH_3$ (38 μL, 0.402 mmol, 1.0 equiv) sequentially. The reaction mixture was stirred mechanically for 30 min and quenched with saturated NH_4Cl. The resulting aqueous layer was extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Title compound **6** was obtained after silica gel flash column chromatography (50% EtOAc/hexane) in 71% yield as a colorless oil (91.6 mg): $[\alpha]^{25}_D$ +52 (*c* 0.19, $CHCl_3$); ^1H NMR (DMSO-

d_6, VT 100, 400 MHz) δ 7.34−7.29 (5H, m, Ph of Cbz), 5.07 (2H, s, CH_2 of Cbz), 4.23 (1H, m, H-2), 3.46 (4H, overlapped, H_2-5, $-OCH_2CH_3$), 1.83−2.12 (4H, m, H_2-3, H_2-4), 1.08 (3H, t, J = 7.0 Hz, $-OCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1 (C, $-CH_2CO_2CO_2-$), 154.0 (C=O of Cbz), 148.6 (C, $-CH_2CO_2CO_2-$), 136.2 (C), 127.8 (CH), 127.9 (CH), 128.4 (CH) [Ph of Cbz], 67.3 (CH_2, $-CO_2CH_2CH_3$), 65.9 (CH_2 of Cbz), 58.7 (CH, C-2), 46.9 (CH_2, C-5), 30.5 (CH_2, C-3), 23.4 (CH_2, C-4), 13.9 (CH_3, $-CO_2CH_2CH_3$); HRESIMS m/z 344.1115 $[M + Na]^+$, calcd for $C_{16}H_{19}NO_6Na$, 344.1110.

Preparation of α-Diazoketone (7). To a stirred solution of **6** (68 mg, 0.212 mmol) in CH_3CN (610 μL) at 0 °C was added $TMSCHN_2$ (2.0 M in hexane, 210 μL, 0.424 mmol, 2.0 equiv). The reaction mixture was stirred mechanically for 6 h at 0 °C and for an additional 19 h at rt. The reaction mixture was quenched with Et_2O and washed successively with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (50% EtOAc/hexane) afforded compound **7** as a colorless oil in 86% yield (50 mg). The spectral data of α-diazoketone (**7**) were in excellent agreement with those in the literature.[9]

Preparation of Cbz-Protected Methyl Pyrrolidinylacetate (8). To a solution of **7** (45 mg, 0.162 mmol) in MeOH (1.6 mL) was added a solution of silver benzoate ($C_6H_5CO_2Ag$, 7.4 mg, 0.0324 mmol, 0.2 equiv) in Et_3N (90 μL, 4 equiv, 0.648 mmol) under sonication. The reaction mixture was sonicated for 1 h, and the MeOH was evaporated under reduced pressure. EtOAc was added, and the resulting organic solution was successively washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (50% EtOAc/hexane) afforded compound **8** in 83% yield as a colorless oil (37 mg). The spectral data of Cbz-protected methyl pyrrolidinylacetate were in excellent agreement with those in the literature.[9a]

Preparation of Methyl Pyrrolidinylacetate (3). To a stirred mixture of **8** (45 mg, 0.162 mmol) in MeOH (3.0 mL) was added 10% Pd/C (11 mg). The resulting mixture was stirred mechanically under a hydrogen atmosphere (balloon) at rt for 1 h, and the heterogeneous mixture was filtered through a pad of Celite (EtOAc). The filtrate was concentrated under reduced pressure to obtain methyl pyrrolidinylacetate (**3**),[9a,10] which was used in the next step without further purification.

Synthesis of 9a and 9b. To a stirred mixture of γ-alkylidene butenolide (**2**, 40 mg, 0.147 mmol, 1.4 equiv) and **3** (15 mg, 0.105 mmol) in CH_3CN (1.0 mL) was added Ag_2CO_3 (50 wt % on Celite, 87 mg, 0.158 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 36 h. The heterogeneous mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. Purification using MPLC (2% EtOH/$CHCl_3$) afforded compounds **9a** (32%) and **9b** (25%) as colorless oils.

***epi*-Pandamarilactonine-H (9a):** colorless oil; $[\alpha]^{21}_D$ +62 (*c* 0.07, $CHCl_3$); ^{1}H and ^{13}C NMR data were identical to those of the natural product **1a**; HRESIMS m/z 294.1729 $[M + H]^+$, calcd for $C_{16}H_{24}NO_4$, 294.1705.

Compound 9b: colorless oil; $[\alpha]^{22}_D$ +67 (*c* 0.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (1H, d, J = 0.8 Hz, H-4), 5.62 (1H, dd, J = 8.6, 8.6 Hz, H-6), 3.67 (3H, s, $-OCH_3$), 3.09 (1H, m, H-11a), 2.72 (2H, overlapped, H-9a, H-14), 2.56 (1H, dd, J = 14.8, 4.0 Hz, H-15a), 2.37 (1H, m, H-7a), 2.26 (3H, overlapped, H-7b, H-9b, H-15b), 2.15 (1H, m, H-11b), 2.02 (3H, br s, H_3-17), 2.01 (1H, m, H-13a), 1.75 (2H, m, H_2-12), 1.65 (2H, m, H_2-8), 1.55 (1H, m, H-13b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1 (C=O, C-16), 171.0 (C=O, C-2), 148.8 (C, C-5), 133.8 (CH, C-4), 130.0 (C, C-3), 113.4 (CH, C-6), 61.1 (CH, C-14), 53.5 (CH_2, C-9), 53.4 (CH_2, C-11), 51.5 (CH_3, $-OCH_3$), 39.5 (CH_2, C-15), 30.8 (CH_2, C-13), 28.7 (CH_2, C-8), 24.2 (CH_2, C-7), 22.3 (CH_2, C-12), 10.8 (CH_3, C-17); HRESIMS m/z 294.1721 $[M + H]^+$, calcd for $C_{16}H_{24}NO_4$, 294.1705.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of pandamarilactonine-H (**1a**), *epi*-pandamarilactonine-H (**9a**), and compound **9b**, and structures of pandamarilactonines-A to -G. This material is available free of charge via the Internet at http://pubs.acs.org.

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