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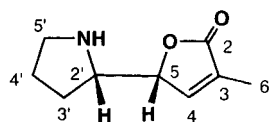
Isolation and Characterization of Two New Alkaloids, Norpandamarilactonine-A and -B, from *Pandanus amaryllifolius* by Spectroscopic and Synthetic Methods

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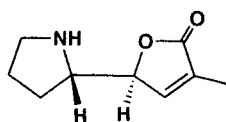
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Two new alkaloids, norpandamarilactonine-A (**1**) and -B (**2**), which have a pyrrolidinyl- α,β -unsaturated γ -lactone moiety as in the known pandamarilactonine alkaloids, were isolated from the leaves of *Pandanus amaryllifolius*. Their structures were determined by spectroscopic analysis and total synthesis.

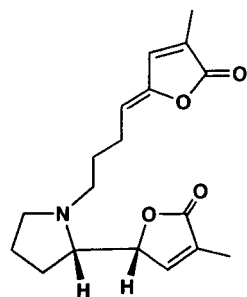
The genus *Pandanus* (Pandanaceae) comprises about 600 species which are widely distributed in tropical and subtropical regions. In a recent pharmacological survey, the hypoglycemic effect of an extract of *P. odoratus* was noted.¹ During our chemical studies on the secondary metabolites in *Pandanus* plants,² we reported the isolation of pandamarilactonines-A (**3**) and -B (**4**), pyrrolidine alkaloids from *P. amaryllifolius*.³ Further investigation of the minor bases in fresh leaves of this plant resulted in the isolation of two additional alkaloids (**1** and **2**), whose structure elucidation by spectroscopic and synthetic methods are described herein.



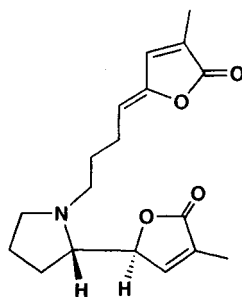
Norpandamarilactonine-A (**1**)



Norpandamarilactonine-B (**2**)



Pandamarilactonine-A (**3**)



Pandamarilactonine-B (**4**)

Compound **1** was obtained as an amorphous powder, $[\alpha]_D^{19} 0^\circ$ (c 0.30, CHCl_3), and high-resolution FABMS analysis established the molecular formula as $\text{C}_9\text{H}_{13}\text{NO}_2$. The presence of an α -methyl- α,β -unsaturated γ -lactone residue was shown by characteristic signals in the ^1H and ^{13}C NMR spectra [δ 7.13 (1H, ddd, $J = 0.8, 1.6, 1.6$ Hz, H-4), 4.73 (1H, ddd, $J = 1.6, 1.9, 6.6$ Hz, H-5), 1.93 (3H); δ 174.3 (C-2), 130.7 (C-3), 147.7 (C-4), 83.8 (C-5), 10.7 (C-6)]. Using the residual four carbons (three methylenes and one methine) and one nitrogen atom, a pyrrolidine ring could be constructed. In the HMBC spectrum, the methine

proton (δ 3.18, 1H, ddd, $J = 6.6, 6.6, 7.4$ Hz, H-2') on the pyrrolidine ring correlated with the sp^2 carbon at C-4 (δ 147.7) in the α,β -unsaturated γ -lactone ring. In addition, the methine proton (δ 4.73) at C-5 (δ 83.8) in the γ -lactone ring had connectivity between C-2' and C-3' in the pyrrolidine ring. All the above findings enabled us to describe the molecular structure of the new alkaloid as **1**, a pyrrolidinyl- α,β -unsaturated γ -lactone skeleton, except for the stereochemistry of the vicinal asymmetric centers at C-5 and C-2'. Because of the lack of a γ -alkylidene- α,β -unsaturated γ -lactone moiety as in the known alkaloids, pandamarilactonines (**3** and **4**), we now name the new alkaloid (**1**) norpandamarilactonine-A.

Alkaloid **2** was also obtained as an amorphous powder, exhibiting $[\alpha]_D^{19} 0^\circ$ (c 0.70, CHCl_3). The UV and mass spectra, as well as the molecular formula obtained by HR-FABMS, were almost identical to those of **1**. The ^1H and ^{13}C NMR spectra were also very similar, indicating that **1** and **2** were diastereomeric at the C-5 and C-2' positions.

To confirm the structures and relative stereochemistry at C-5 and C-2' in the new alkaloids, we planned the total synthesis (Scheme 1). According to the procedure of Martin et al.,⁴ compound **5** was prepared from 2-pyrrolidone and 3-methylfuran-2(5H)-one. The *threo* stereochemistry of the major product (**5**) obtained by vinylogous Mannich coupling reaction has been established by X-ray analysis.⁴ The protecting group on the nitrogen in **5** was removed with TMSI in CH_3CN to give the secondary amine in 94% yield, which was identical with the natural product, norpandamarilactonine-B (**2**), by direct comparison of the chromatographic behavior and high-resolution MS and ^1H and ^{13}C NMR spectra. Therefore, the relative stereochemistry of norpandamarilactonine-A (**1**) was determined to be *erythro*.

In summary, two new diastereomeric alkaloids (**1** and **2**) having a pyrrolidinyl- α,β -unsaturated γ -lactone skeleton were isolated as minor constituents from a tropical medicinal plant, *Pandanus amaryllifolius*. These interesting molecules possessing the substructure of the known alkaloids **3** and **4** were first characterized by spectroscopic analysis and then the structures were confirmed by total synthesis.

Experimental Section

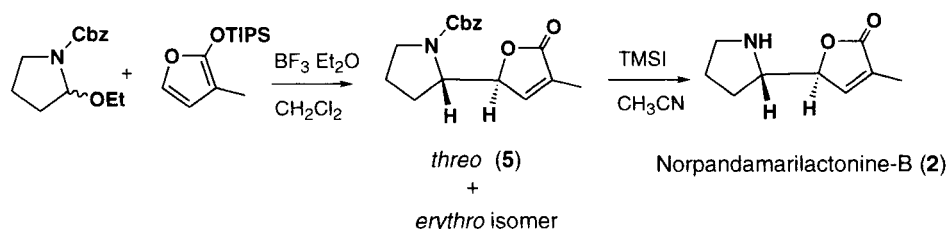
General Experimental Procedures. Optical rotations were measured on a JASCO DIP-140 polarimeter. UV and IR spectra were recorded on Hitachi U-3400 and JASCO FT/IR-230 spectrophotometers, respectively. EIMS and FABMS were

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Scheme 1



recorded on JEOL JMS-AM20 and JEOL JMS-HX110 mass spectrophotometers, respectively. The ^1H and ^{13}C NMR, COSY, HMQC, HMBC, and NOE were recorded on JEOL JNM A-500 and JEOL JNM ECP600 spectrometers. The chemical shifts are given in δ (ppm) and coupling constants in Hz. Kieselgel 60 (Merck, 70–230 and 230–400 meshes) and a silica gel prepacked column (Kusano CPS-HS-221-05) were used for column chromatography.

Plant Material. The fresh leaves of *P. amaryllifolius* were purchased at a flower market in Bangkok (Thailand) and identified by Dr. Kittisak Likhitwitayawuid, Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand. A voucher specimen was deposited at the Herbarium of the Faculty of Pharmaceutical Sciences, Chiba University.

Extraction and Isolation of Alkaloids. Fresh young leaves (8.0 kg) of *P. amaryllifolius* were macerated with EtOH (20 L) three times and filtered. The combined filtrates were concentrated under reduced pressure to give a crude extract (201 g), which was then partitioned between Et₂O and 5% aqueous H₂SO₄. The water-soluble fraction was alkalized with concentrated NH₄OH (pH 10) and exhaustively extracted with CHCl₃. The organic layer was dried over MgSO₄ and evaporated to give a crude alkaloidal fraction (10.03 g). A portion of the crude base (1.63 g) was roughly separated by silica gel flash column chromatography using a CHCl₃–MeOH/CHCl₃ gradient to give seven fractions. The 10% MeOH/CHCl₃ eluate was rechromatographed over SiO₂ using the same solvent to give 6 mg of norpandamarilactonine-A (1) and 33 mg of norpandamarilactonine-B (2).

Norpandamarilactonine-A (1): amorphous powder; $[\alpha]_D^{19}$ 0° (*c* 0.30); UV (MeOH) λ_{max} (log ϵ) 274 (0.44), 252 (0.35), 207 (2.29) nm; IR (neat) ν_{max} 1750 (lactone) cm^{-1} ; ^1H NMR (CDCl₃, 600 MHz) δ 7.13 (1H, ddd, J = 0.8, 1.6 and 1.6 Hz, H-4), 4.73 (1H, ddd, J = 1.6, 1.9 and 6.6 Hz, H-5), 3.18 (1H, ddd, J = 6.6, 6.6 and 7.4 Hz, H-2'), 2.96 (1H, ddd, J = 6.3, 6.3 and 10.4 Hz, H-5'), 2.93 (1H, ddd, J = 6.8, 6.8 and 10.4 Hz, H-5'), 1.93 (3H, s, H₃-6), 1.84–1.92 (1H, m, H-3'), 1.72–1.90 (2H, m, H₂-4'), 1.63 (1H, dddd, J = 6.3, 6.3, 6.6 and 12.9 Hz, H-3'); ^{13}C NMR (CDCl₃, 150 MHz) δ 174.3 (C-2), 147.7 (C-4), 130.7 (C-3), 83.8 (C-5), 60.4 (C-2'), 47.1 (C-5'), 27.9 (C-3'), 25.6 (C-4'), 10.7 (C-6); FABMS (NBA) m/z 168 [M + H]⁺; HRFABMS (NBA) m/z 168.1039 (calcd for C₉H₁₄NO₂, 168.1025).

Norpandamarilactonine-B (2): amorphous powder; $[\alpha]_D^{19}$ 0° (*c* 0.70); UV (MeOH) λ_{max} (log ϵ) 274 (0.36), 253 (0.29), 207 (2.58) nm; IR (neat) ν_{max} 1750 (lactone) cm^{-1} ; ^1H NMR (CDCl₃, 600 MHz) δ 7.02 (1H, ddd, J = 1.4, 1.7 and 3.0 Hz, H-4), 4.79

(1H, dddd, J = 1.6, 1.9, 3.0, and 6.6 Hz, H-5), 3.20 (1H, ddd, J = 6.6, 7.1, and 7.4 Hz, H-2'), 2.98 (1H, ddd, J = 5.8, 7.1 and 12.9 Hz, H-5'), 2.91 (1H, ddd, J = 6.6, 7.7, and 14.3 Hz, H-5'), 1.93 (3H, s, H₃-6), 1.87 (1H, dddd, J = 3.0, 7.4, 10.7, and 15.4 Hz, H-3'), 1.81 (1H, m, H-4'), 1.74 (1H, m, H-4'), 1.56 (1H, dddd, J = 5.2, 6.9, 7.1 and 15.4 Hz, H-3'); ^{13}C NMR (CDCl₃, 150 MHz) δ 174.1 (C-2), 146.6 (C-4), 131.2 (C-3), 84.3 (C-5), 60.2 (C-2'), 46.5 (C-5'), 26.8 (C-3'), 25.1 (C-4'), 10.7 (C-6); FABMS (NBA) m/z 168 [M + H]⁺; HRFABMS (NBA) m/z 168.1030 (calcd for C₉H₁₄NO₂, 168.1025).

Synthesis of Norpandamarilactonine-B (2). To a solution of diastereomerically pure carbamate (5) (30.6 mg, 0.1 mmol), which was prepared according to the procedure by Martin,⁴ in CH₃CN (1 mL), was added TMSI (43 μL , 0.3 mmol) at –10 °C under argon. The reaction mixture was stirred at the same temperature for 15 min and then stirred at 0 °C for 15 min. The reaction mixture was poured into a chilled solution of 1 N HCl, and the whole mixture was extracted with Et₂O. The aqueous layer was basified with 1 N NaOH, and the mixture was extracted with CHCl₃ three times. The combined organic layers were washed with H₂O, dried over MgSO₄, and evaporated to give 2 (16 mg, 94%), which was identical to natural norpandamarilactonine-B by comparison of their chromatographic behaviors, UV, ^1H and ^{13}C NMR, and mass spectra.

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