Structure Characterization, Biomimetic Total Synthesis, and Optical Purity of Two New Pyrrolidine Alkaloids, Pandamarilactonine-A and -B, Isolated from *Pandanus amaryllifolius* Roxb.

Hiromitsu Takayama,*,† Tomotake Ichikawa,† Toshiyuki Kuwajima,† Mariko Kitajima,† Hiroko Seki,‡ Norio Aimi,†,‡ and Maribel G. Nonato*,§

Contribution from the Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan, Chemical Analysis Center of Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan, and Research Center for the Natural Sciences, University of Santo Tomas, Espana, Manila 1008, Philippines

Received March 20, 2000

Abstract: Two new alkaloids, both possessing a pyrrolidinyl α,β-unsaturated γ-lactone residue and a γ-alkylidene α,β-unsaturated γ-lactone residue, were isolated from a tropical medicinal plant, *Pandanus amaryllifolius* Roxb. Their structures were deduced by spectroscopic analysis including the new NMR technique PFG J-HMBC 2D spectroscopy and then confirmed by biomimetic total synthesis. It was found that one diastereoisomer, pandamarilactonine-A (**1**), comprised a mixture enriched with (+)-enantiomer, while another diastereomeric isomer, pandamarilactonine-B (**2**), occurred as a racemate.

Introduction

The genus *Pandanus* belonging to the family Pandanaceae comprises about 600 species which are distributed widely in tropical and subtropical regions. Several *Pandanus* species are recognized as medicinal plants used as a remedy for toothache and rheumatism, and as a diuretic, cardiotonic, etc.[1] Recently, a new structural class of alkaloids, possessing a γ-alkylidene α,β-unsaturated γ-lactone or γ-alkylidene α,β-unsaturated γ-lactam moiety, has been isolated from *Pandanus amaryllifolius*.[2−4] Since the *Pandanus* plants are potentially valuable as candidates for new medicinal resources, we have started chemical studies of *Pandanus* plants.[5] Described herein is the isolation of two new diastereomeric pyrrolidine alkaloids, pandamarilactonine-A (**1**) and -B (**2**), from *P. amaryllifolius* Roxb. native to the Philippines and Thailand, and their structure elucidation using a new NMR technique, viz., PFG J-HMBC 2D analysis. Biomimetic total synthesis of **1** and **2** and analysis of the optical purity of the natural alkaloids are also reported.

Results and Discussion

Isolation and Structure Elucidation of Two New Alkaloids. Two new alkaloids, **1** and **2**, were isolated together with the known compound pandamarilactone-1 (**3**)[3] (Figure 1) by using SiO_2 column chromatography of the alkaloidal fraction obtained by conventional methods from an EtOH extract of the fresh leaves of *P. amaryllifolius*.

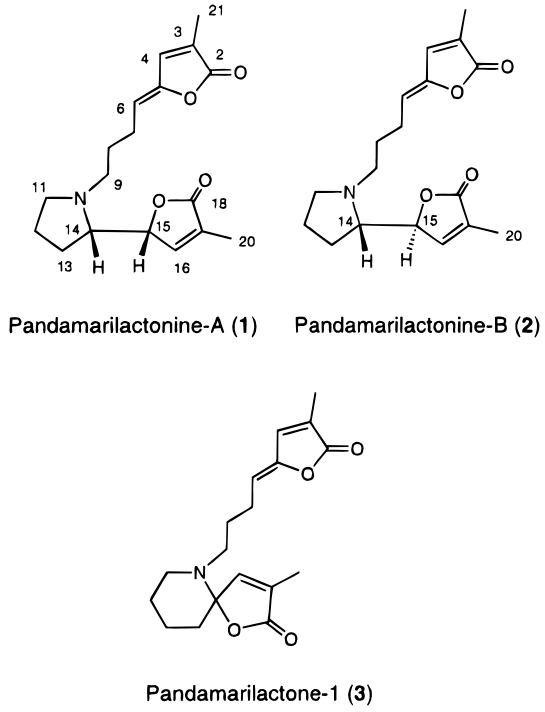

Figure 1.

The new compound **1**, named pandamarilactonine-A, was obtained as an amorphous powder, exhibiting $[\alpha]^{23}_{D}$ +35.0° (*c* 4.37, $CHCl_3$). High-resolution FABMS analysis gave *m*/*z* 318.1721 $[M + H]^+$ and established the molecular formula as $C_{18}H_{23}NO_4$, which indicated **1** to be an isomer of the coexistent alkaloid **3**. The characteristic ^1H and ^{13}C NMR signals {δ 6.99 (1H, d-like, J = 1.5 Hz, H-4), 5.18 (1H, dd, J = 7.9, 7.9 Hz, H-6), 1.99 (3H); δ 171.1 (C-2), 129.1 (C-3), 137.7 (C-4), 148.6

† Faculty of Pharmaceutical Sciences, Chiba University.
‡ Chemical Analysis Center of Chiba University.
§ University of Santo Tomas.

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10.1021/ja0009929 CCC: $19.00
Published on Web 08/22/2000

(C-5), 114.1 (C-6), 10.5 (C-21)} and the UV absorption at 275 nm indicated the presence of a γ-alkylidene-α-methyl α,β-unsaturated γ-lactone moiety. A three-carbon methylene chain was connected with the terminal sp^2 carbon (C-6) of the γ-alkylidene-γ-lactone moiety, which was established by COSY, HMQC, and HMBC spectra. Further, the presence of an α-methyl α,β-unsaturated γ-lactone residue was shown by the characteristic signals in the ^{1}H and ^{13}C NMR spectra {δ 7.09 (1H, dd, J = 1.5, 1.8 Hz, H-16), 4.80 (1H, ddd, J = 1.8, 1.8, 5.5 Hz, H-15), 1.93 (3H); δ 174.3 (C-18), 131.2 (C-17), 147.0 (C-16), 83.4 (C-15), 10.7 (C-20)}. 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 2.83, 1H, m, H-14) on the pyrrolidine ring correlates with the methylene carbon at C-9 (δ 55.0) (the terminal of a three-carbon methylene chain) and the sp^2 carbon at C-16 (δ 147.0) in the α,β-unsaturated γ-lactone ring. In addition, the methine proton (δ 4.80) at C-15 (δ 83.4) in the γ-lactone ring has connectivity between the carbons at C-14 and C-13 in the pyrrolidine ring. In the NOESY spectrum, a clear cross-peak between H-4 and H-6 was observed, demonstrating the (*Z*) configuration in the γ-alkylidene α,β-unsaturated γ-lactone moiety. All the above findings enabled us to compose the molecular structure of the new alkaloid to be the formula **1**, having a novel pyrrolidinyl α,β-unsaturated γ-lactone skeleton, except for the stereochemistry of the vicinal asymmetric center at the C-14 and C-15 positions.

The second new alkaloid (**2**), named pandamarilactonine-B, was also obtained as an amorphous powder, exhibiting $[\alpha]^{23}_D$ 0° (*c* 0.20, $CHCl_3$). The UV and mass spectra, as well as the molecular formula obtained by HR-FABMS (found 318.1704), were completely the same as those of pandamarilactonine-A (**1**). Further, the ^{1}H and ^{13}C NMR spectra were very similar to those of **1**, indicating that new alkaloid **2** is a stereoisomer of compound **1**. As the differential NOE experiment demonstrated the (*Z*) configuration in the γ-alkylidene α,β-unsaturated γ-lactone moiety in **2**, a diastereomeric relation at the C-14 and C-15 positions between **1** and **2** is implied.

Next, we attempted characterization of the relative stereochemistry at C-14 and C-15 in the new alkaloids **1** and **2**. Martin et al. reported that the stereochemistry of the *threo/erythro* diastereomers having the pyrrolidinyl α,β-unsaturated γ-lactone skeleton could be assigned by comparison of the chemical shifts of their ^{13}C and ^{1}H NMR spectra at particular positions.[6] However, this approach was not adaptable to the case of compounds **1** and **2**, because of the indistinct difference in the chemical shifts at the corresponding positions (C-15 and H-14). Then, PFG J-HMBC 2D spectroscopy,[7] which enables the torsion angle between two heteroatoms to be determined, i.e., *H*−C−C−*C*,[8] was applied with a combination of differential NOE experiments to establish the relative stereochemistry in **1** and **2** (Figure 2). Each of the compounds **1** and **2** has the possibility to take three conformations (I, I′, and I″ and II, II′, and II″). From the small coupling constants between H-14 and H-15 (**1**, J = 4.9 Hz; **2**, J = 3.9 Hz), the possibility of conformers I″ and II″ could be excluded. In pandamarilactonine-A, a large coupling constant (5.6 Hz) between H-14 and C-16 and a small coupling constant (3.7 Hz) between H-15 and C-13 were obtained by PFG J-HMBC 2D spectroscopy, indicating their *anti* and *gauche* orientations,[9] respectively, while in the case of pandamarilactonine-B, the small coupling constants, 2.7 Hz ($^3J_{H-14/C-16}$) and 3.3 Hz ($^3J_{H-15/C-13}$), were indicative of the *gauche* relationship of both H-14/C-16 and H-15/C-13. Therefore, conformers I and II corresponded to compounds **1** and **2**, respectively. This analysis was confirmed by differential NOE experiments; specifically, NOEs were observed between H-15 and H-13 and between H-16 and H-13 in compound **1** and between H-15 and H-13 and between H-16 and H-14 in compound **2**. From these data, we propose that pandamarilactonine-A (**1**) has the *erythro* structure taking the conformation I and pandamarilactonine-B (**2**) has the *threo* structure with conformer II.

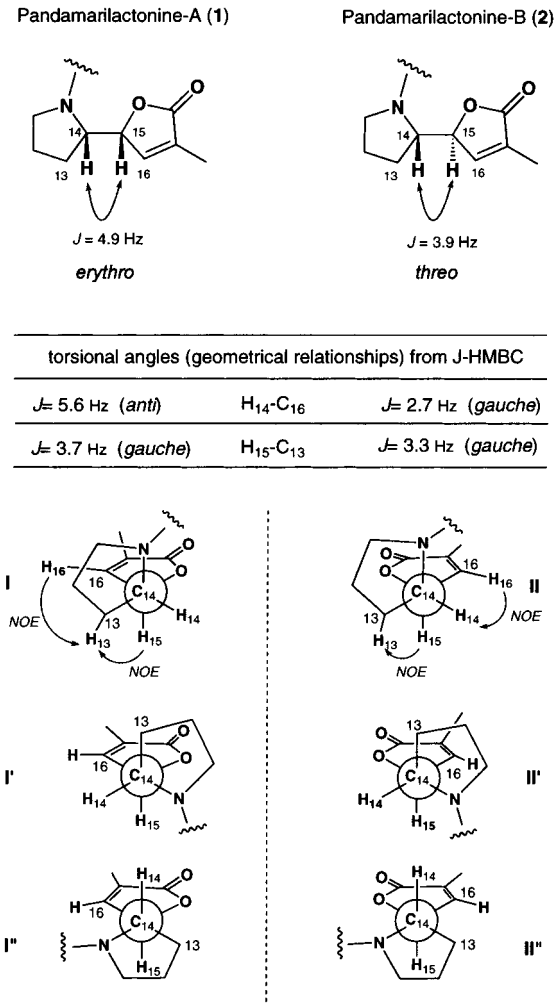

Figure 2.

Biomimetic Total Synthesis of Pandamarilactonine-A and -B. A biosynthetic route to the known *Pandanus* alkaloids, such as pandamarine (**4**)[2] and pandamarilactone-1 (**3**), has been proposed by Garson[2,4] (Figure 3). By condensation of two units of 4-hydroxy-4-methylglutamic acid (**5**),[10] which has been found in a *Pandanus* species,[11] and a C-4−N−C-4 dicarboxylic acid (**6**) probably derived from glutamic acid, an intermediate (**7**) possessing a basic backbone structure would be formed. Through a decarboxylation, cyclization, reduction, and dehydration process, plausible biogenetic intermediates **8** and **9** having a

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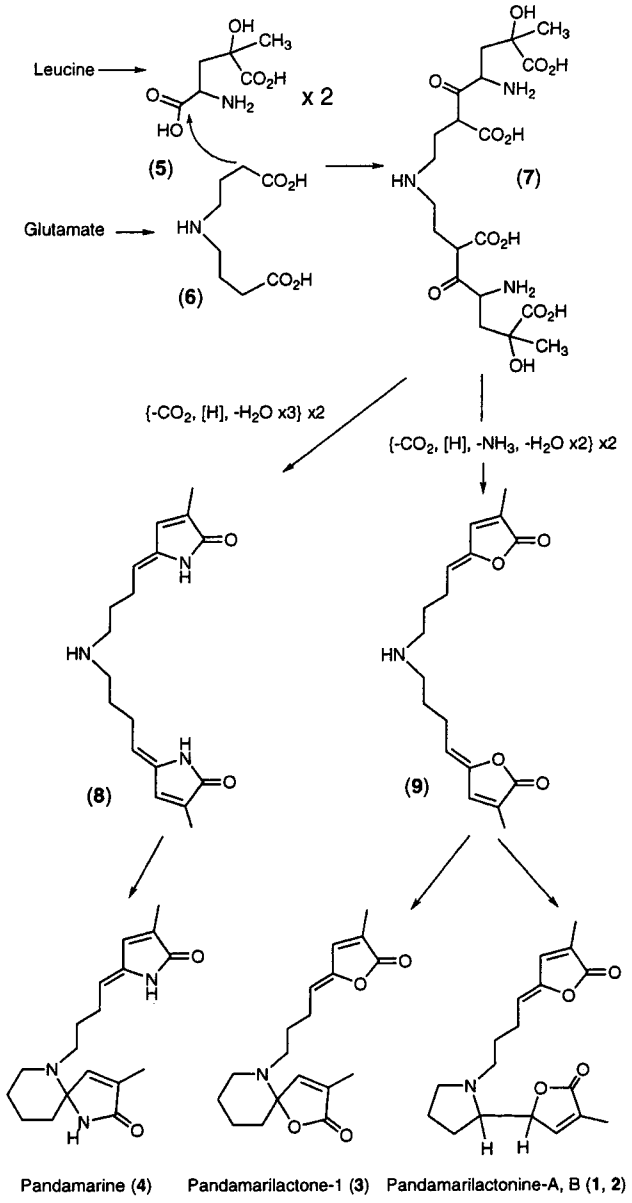

Figure 3. Hypothetical biogenetic route of the *Pandanus* alkaloids.

symmetrical structure would be generated. Successive intramolecular cyclization of the secondary amine to one of the two γ-alkylidene α,β-unsaturated γ-lactones or γ-alkylidene α,β-unsaturated γ-lactams would produce **3** or **4**. The newly isolated alkaloid found in the present study could also be biosynthesized in a divergent way via the common intermediate **9**.

We planned a total synthesis of **1** and **2** by a route which mimics the final stage of the biosynthesis (from **9** to **1**/**2**) proposed above. The key secondary amine derivative **9**, which corresponds to the hypothetical biogenetic intermediate, was prepared as follows (Figure 4). *N*-Dialkylation of benzylamine (**10**) with *O*-tetrahydropyranyl-4-chlorobutanol (**11**) was carried out using potassium carbonate in the presence of a catalytic amount of sodium iodide to yield the tertiary amine **12** in 61% yield. Then, the benzyl group was switched to a β,β,β-trichloroethoxycarbonyl group[12] to give carbamate **13**. After removal of the THP ether in **13**, the free alcohols in **14** were converted to aldehyde **15** in 72% yield by Swern oxidation. The aldol reaction of aldehyde **15** with siloxyfuran using boron

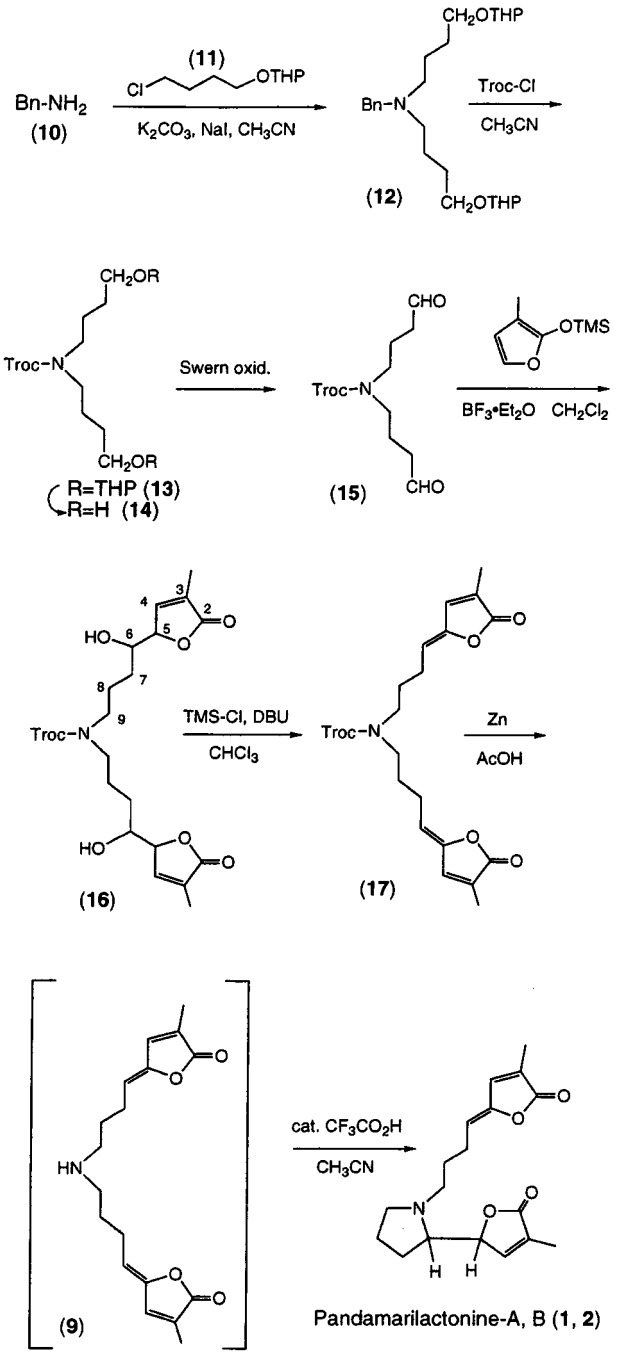

Figure 4.

trifluoride etherate ($BF_3 \cdot Et_2O$)[13] gave a mixture of stereoisomeric adducts **16** in quantitative yield. Next, installation of the *exo* double bond was performed by treatment of the adducts **16** with a combination of TMS−Cl and DBU to give γ-alkylidenebutenolide (**17**) in 41% yield together with the (*Z*,*E*) isomer in 25% yield. Finally, the protecting group on nitrogen in **17** was removed with Zn in AcOH. Because of the lability of amine **9** toward SiO_2 column chromatography, the crude residue obtained by usual workup was directly treated with a catalytic amount of trifluoroacetic acid in CH_3CN. By careful separation of the crude products, pandamarilactonine-A (**1**) and -B (**2**) were obtained in 9% and 9% yields, respectively. They were respectively identical with the natural products by direct comparison of the chromatographic behavior and high-resolution MS and ^1H and ^{13}C NMR spectra. Although the chemical yield

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of the final stage in the present synthesis was not satisfactory, we succeeded in the first and biomimetic total synthesis of the new alkaloids, which provided chemical support for the suggested biogenetic route of **1** and **2** as well as proof for the chemical structures deduced by spectroscopic analysis.

Optical Purity of Natural Pandamarilactonine-A and -B. As described in the isolation section above, pandamarilactonine-A (**1**) exhibited $[\alpha]^{23}_{D}$ +35.0° (*c* 4.37, $CHCl_3$); in contrast, the specific rotation of pandamarilactonine-B (**2**) was almost zero. We were interested in the optical purity of these natural products.[14] With the synthetic racemates in hand, we first examined the resolution of the enantiomers using chiral column chromatography. Synthetic pandamarilactonine-A (**1**) exhibited two peaks at 43.2 and 51.7 min when Chiralcel OB was used, and synthetic pandamarilactonine-B (**2**) showed two peaks at 18.7 and 20.4 min by using Chiralcel OD. Then, natural alkaloids were subjected to chiral HPLC analysis, which established that the natural pandamarilactonine-A (**1**) contained dominantly the (+)-enantiomer over the (−)-enantiomer in a ratio of 63:37, while natural **2** existed as a racemate. On the basis of the biosynthetic proposal and the chemical conversion of **9** to **1** and **2**, it is conceivable that pandamarilactonine-A and pandamarilactonine-B undergo acid-catalyzed interconversion during the isolation process and that pandamarilactonine-B (**2**) is an artifact from pandamarilactonine-A (**1**). To test this hypothesis, the natural alkaloids **1** and **2** were respectively treated with 5% H_2SO_4 under the conditions used in the partitioning of alkaloids and the recovered alkaloids were carefully analyzed with 500 MHz NMR spectroscopy. In the recovered **1** and **2**, the presence of the stereoisomers and/or pandamarilactonine-1 could not be observed. Further, recovered pandamarilactonine-A exhibited same optical purity (63:37) by chiral HPLC analysis, revealing that no racemization has occurred. These experiments demonstrate that pandamarilactonine-A and -B are not interconvertible under the isolation conditions and that pandamarilactonine-B is not an artifact produced during the isolation process.

In summary, two new alkaloids having a pyrrolidinyl α,β-unsaturated γ-lactone moiety and a γ-alkylidene α,β-unsaturated γ-lactone residue were isolated from a tropical medicinal plant, *P. amaryllifolius*. Their structures were first deduced by spectroscopic analysis including the new NMR technique PFG J-HMBC 2D spectroscopy and then confirmed by biomimetic total synthesis. Interestingly, it was found that one of the diastereoisomers, pandamarilactonine-A (**1**) having the *erythro* structure, was comprised of a mixture enriched with the (+)-enantiomer, while another diastereomeric *threo* isomer, pandamarilactonine-B (**2**), occurred as a racemate in nature.

Further investigation of the minor constituents in this plant, development of an efficient synthetic pathway of **1** and **2**, determination of the absolute configuration of (+)-pandamarilactonine-A, and biological evaluation of these alkaloids are in progress in our laboratories.

Experimental Section[15]

Extraction and Isolation of Alkaloids. Fresh young leaves (1.2 kg) of *P. amaryllifolius* purchased at flower market in Bangkok (Thailand) were macerated with ethyl alcohol (6 L) three times, and filtered. The combined filtrate was concentrated under reduced pressure to give a crude extract (105 g), which was then partitioned between Et_2O and 5% aqueous H_2SO_4. The water-soluble fraction was alkalinized with concentrated NH_4OH until pH 10 and exhaustively extracted with $CHCl_3$. The organic layer was dried over magnesium sulfate and evaporated to give a crude alkaloidal fraction (2.56 g). The portion of the crude base (1.10 g) was roughly separated by silica gel flash column chromatography eluted with a $CHCl_3$ to MeOH/$CHCl_3$ gradient to give the 10 fractions. The 2−5% MeOH/$CHCl_3$ eluate was subjected to SiO_2 medium-pressure liquid chromatography using 2% EtOH/$CHCl_3$ to give 95 mg of pandamarilactonine-A (**1**), 10 mg of pandamarilactonine-B (**2**), and 9 mg of pandamarilactone-1 (**3**).

Pandamarilactonine-A (1). An amorphous powder. R_f value 0.5 [SiO_2, solvent system 5% MeOH in $CHCl_3$]. $[\alpha]^{23}_{D}$ +35.0° (*c* 4.37, $CHCl_3$). UV (MeOH): λ_{max} (nm) (log ϵ) 275 (2.43), 232 (sh), 207 (1.82). IR (neat): ν_{max} (cm^{-1}) 1750 (lactone). FABMS (NBA): *m*/*z* 318 $[M + H]^+$. HR-FABMS (NBA): calcd for $C_{18}H_{24}NO_4$ 318.1704, found 318.1721. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (1H, dd, J = 1.5 and 1.8 Hz, H-16), 6.99 (1H, d-like, J = 1.5 Hz, H-4), 5.18 (1H, dd, J = 7.9 and 7.9 Hz, H-6), 4.80 (1H, ddd, J = 1.8, 1.8 and 5.5 Hz, H-15), 3.12 (1H, dd, J = 6.7 and 7.6 Hz, H-11), 2.88 (1H, ddd, J = 4.0, 7.9 and 12.9 Hz, H-9), 2.83 (1H, m, H-14), 2.45 (1H, m, H-9), 2.43 (2H, dd, J = 7.3 and 15.0 Hz, H_2-7), 2.21 (1H, m, H-11), 1.99 (3H, d-like, J = 0.9 Hz, H_3-21), 1.93 (3H, dd, J = 1.5 and 1.8 Hz, H_3-20), 1.70−1.80 (2H, m, H-12 and H-13), 1.59−1.70 (3H, m, H_2-8 and H-13), 1.42 (1H, m, H-12). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.27 (1H, dd, J = 1.5 and 2.9 Hz, H-16), 7.26 (1H, ddd, J = 1.7, 1.7 and 3.2 Hz, H-4), 5.33 (1H, dd, J = 7.8 and 8.1 Hz, H-6), 4.86 (1H, ddq, J = 4.9, 2.9 and 2.0 Hz, H-15), 3.10 (1H, ddd-like, J = 2.0, 7.1 and 8.5 Hz, H-11), 2.90 (1H, ddd, J = 8.1, 8.1 and 11.7 Hz, H-9), 2.85 (1H, ddd, J = 4.9, 4.9 and 9.3 Hz, H-14), 2.44 (1H, ddd, J = 4.9, 6.8 and 11.7 Hz, H-9), 2.38 (2H, ddd, J_1 = J_2 = J_3 = 7.6 Hz, H-7), 2.19 (1H, ddd, J = 6.1, 8.8 and 10.2 Hz, H-11), 1.90 (3H, dd-like, J = 0.5 and 1.5 Hz, H-21), 1.83 (3H, dd, J = 1.5 and 2.0 Hz, H-20), 1.57−1.77 (5H, m, 2 × H-8, H-12, and 2 × H-13), 1.42 (1H, m, H-12). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3 (C-18), 171.1 (C-2), 148.6 (C-5), 147.0 (C-16), 137.7 (C-4), 131.2 (C-17), 129.1 (C-3), 114.1 (C-6), 83.4 (C-15), 65.3 (C-14), 55.0 (C-9), 54.2 (C-11), 28.3 (C-8), 25.7 (C-12), 24.0 (C-7), 23.8 (C-13), 10.7 (C-20), 10.5 (C-21).

Pandamarilactonine-B (2). An amorphous powder. R_f value 0.5 [SiO_2, solvent system 5% MeOH in $CHCl_3$]. $[\alpha]^{23}_{D}$ 0° (*c* 0.20, $CHCl_3$). UV (MeOH): λ_{max} (nm) (log ϵ): 275 (2.49), 232 (sh), 207 (1.72). IR (neat): ν_{max} (cm^{-1}) 1758 (lactone). FABMS (NBA): *m*/*z* 318 $[M + H]^+$. HR-FABMS (NBA): calcd for $C_{18}H_{24}NO_4$ 318.1704, found 318.1704. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (1H, dd, J = 1.5 and 1.7 Hz, H-16), 7.00 (1H, d-like, J = 1.5 Hz, H-4), 5.18 (1H, dd, J = 7.8 and 8.0 Hz, H-6), 4.71 (1H, ddd, J = 1.7, 2.0 and 5.9 Hz, H-15), 3.12 (1H, m, H-11), 2.73 (1H, m, H-9), 2.70 (1H, m, H-14), 2.42−2.48 (2H, m, H-7 and H-9), 2.36 (1H, m, H-7), 2.25 (1H, m, H-11), 1.99 (3H, d-like, J = 0.7 Hz, H_3-21), 1.93 (3H, dd, J = 1.7 and 1.7 Hz, H_3-20), 1.73−1.87 (4H, m, H_2-12 and H_2-13), 1.59−1.67 (2H, m, H_2-8). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.28 (1H, dd-like, J = 1.5 and 2.9 Hz, H-16), 7.26 (1H, ddd, J = 1.5, 1.7 and 3.2 Hz, H-4), 5.32 (1H, dd-like, J = 7.8 and 8.1 Hz, H-6), 4.81 (1H, ddq, J = 3.9, 2.9 and 2.0 Hz, H-15), 3.08 (1H, m, H-11), 2.80 (1H, ddd, J = 8.1, 8.1 and 12.0 Hz, H-9), 2.77 (1H, ddd, J = 3.9, 5.1 and 8.8 Hz, H-14), 2.45 (1H, m, H-9), 2.33 (2H, ddd, J = 7.8, 7.8 and 15.6 Hz, H-7), 2.24 (1H, m, H-11), 1.92 (3H, dd-like, J = 0.7 and 1.5 Hz, H-21), 1.83 (3H, dd-like, J = 1.5 and 2.0 Hz, H-20), 1.59−1.77 (6H, m, 2 × H-8, 2 × H-12, and 2 × H-13). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3 (C-18), 171.1 (C-2), 148.5 (C-5), 147.5 (C-16), 137.7 (C-4), 130.8 (C-17), 129.1 (C-3), 114.1 (C-6), 83.4 (C-15), 66.3 (C-14), 55.8 (C-9), 54.2 (C-11), 28.4 (C-8), 27.1 (C-12), 24.0 (C-7), 24.0 (C-13), 10.8 (C-20), 10.5 (C-21).

Experimental Conditions for PFG J-HMBC 2D Spectroscopy. All NMR experiments were performed at 303 K for solution of ca. 10 mg of alkaloid dissolved in 0.5 mL of acetone-d_6 on a JEOL LA600 spectrometer equipped with a 5 mm NALORAC HX inverse probe. Fifteen J-HMBC 2D spectra were acquired with 16 scans for a 1024 (F2) × 128 (F1) data matrix and with 300 ms of constant time and varying evolution time (Δ) from 10 to 290 ms in 20 ms steps. The HMBC signal intensity is given by a sine function of the evolution time (Δ) and coupling constant (J_{HX}). Therefore, the J value (coupling constant) can be obtained from a least-squares approximation by fitting

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(15) See the Supporting Information for general procedures.

a sine curve to the signal amplitude of the HMBC correlation peak depending on the characteristic $\sin(\pi J_{HX})$ with increasing evolution time (Δ).

Synthesis of Pandamarilactonine-A (1) and -B (2). Zinc dust (50 mg, 0.076 mmol) was added to a solution of γ-alkylidenebutenolides [**17**, (*Z*,*Z*)-form] (25.2 mg, 0.051 mmol) in acetic acid (2 mL), and the mixture was stirred at room temperature under argon atmosphere for 4 h. After the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give a residue. A portion of the residue was roughly purified by SiO_2 flash column chromatography (10%MeOH/$CHCl_3$) to characterize the secondary amine **9**. [^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (2H, d, J = 1.5 Hz, H-4), 5.14 (2H, dd, J = 7.8 and 8.1 Hz, H-6), 2.94 (4H, dd, J = 8.1 and 8.1 Hz), 2.47 (4H, dd, J = 15.3 and 7.3 Hz), 2.08 (4H, m), 2.00 (6H, s, $-CH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.74 (C-2), 149.38 (C-5), 137.61 (C-4), 130.00 (C-3), 110.99 (C-6), 47.32 (C-9), 25.26 (C-8), 23.34 (C-7), 10.56 (-*C*H$_3$). EIMS: *m*/*z* (rel intens) 317 (M^+, 1), 220 (29), 151 (3), 55 (100).] The crude residue obtained by the reaction above was dissolved in CH_3CN (1 mL). After addition of trifluoroacetic acid (2 μL), the reaction mixture was stirred at 80 °C under argon atmosphere for 5 h. The reaction mixture was concentrated under reduced pressure, and dissolved in $CHCl_3$. The $CHCl_3$ solution was poured into saturated aqueous $NaHCO_3$, washed with brine, dried over $MgSO_4$, and evaporated. The residue was separated by SiO_2 MPLC (2% EtOH/$CHCl_3$) to give pandamarilactonine-A (**1**) (1.4 mg, 9%), and -B (**2**) (1.4 mg, 9%). They were respectively identical with the natural products by direct comparison of the chromatographic behavior and high-resolution MS and ^{1}H and ^{13}C NMR spectra.

Chiral HPLC Analysis of Synthetic and Natural Pandamarilactonine-A and B. Pandamarilactonines were respectively analyzed by HPLC using chiral column chromatography (pandamarilactonine-A, Chiralcel OB, Daicel Chemical Industries, Ltd., solvent 40% *i*-PrOH/*n*-hexane, flow rate 0.3 mL/min, column temperature 30 °C; pandamarilactonine-B, Chiralcel OD, Daicel Chemical Industries, Ltd., solvent 20% EtOH/*n*-hexane, flow rate 0.5 mL/min, column temperature 30 °C). The synthetic and natural **1** exhibited two peaks at 43.2 and 51.9 min in ratios of 50:50 and 63:37, respectively. Both the synthetic and natural **2** exhibited two peaks at 18.8 and 20.5 min in a ratio of 50:50, respectively.

Acknowledgment. This work was supported in part by Grants-in-Aid (Nos. 10877349 and 10044325) for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Detailed experimental procedures for the syntheses of **12**−**17** and copies of the ^{1}H and ^{13}C NMR spectra of natural and synthetic pandamarilactonine-A and -B and those of synthetic intermediates **12**−**17** and **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0009929