Isolation and Structure Elucidation of Two New Alkaloids, Pandamarilactonine-C and -D, from *Pandanus amaryllifolius* and Revision of Relative Stereochemistry of Pandamarilactonine-A and -B by Total Synthesis

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Two new pyrrolidine alkaloids, pandamarilactonine-C and -D, were isolated from *Pandanus amaryllifolius*. Based on the total synthesis of pandamarilactonine-C and its related alkaloid, pandamarilactonine-A, the relative stereochemistry of pandamarilactonine-A and -B, which was previously proposed by spectroscopic analysis, was revised.

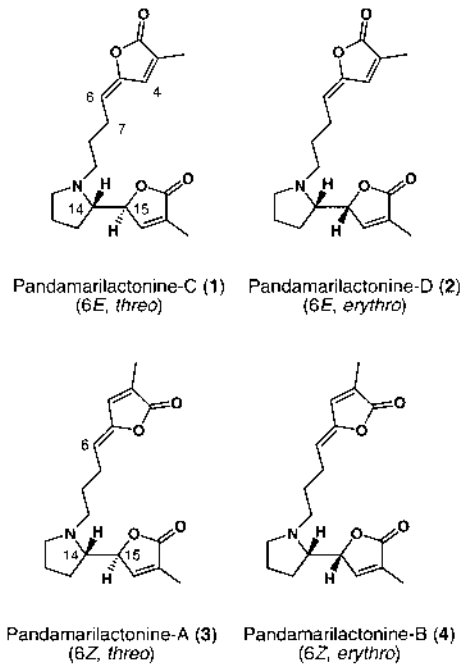
Key words pyrrolidine alkaloid; *Pandanus*; pandamarilactonine; total synthesis; structure elucidation; structure revision

The genus *Pandanus* (Pandanaceae) comprises approximately 600 species that are widely distributed in tropical and subtropical regions. Several *Pandanus* species are used as a remedy for toothache and rheumatism, and as diuretic, cardiotonic, *etc.*[1] In a recent pharmacological screening, the hypoglycemic effect of an extract of *P. odorus* was noted.[2—4] In our continuing search for structurally unique and biologically active *Pandanus* alkaloids, new pyrrolidine alkaloids were found in *P. amaryllifolius* ROXB.[5—7] Further investigation of the minor constituents in the fresh leaves of this plant resulted in the isolation of two new alkaloids, pandamarilactonine-C and -D (**1**, **2**). In this communication, we describe the structure elucidation of these alkaloids as well as the total synthesis of pandamarilactonine-C (**1**) and its related alkaloid, pandamarilactonine-A (**3**), which resulted in the revision of the relative stereochemistry of pandamarilactonine-A and -B (**3**, **4**), which was previously proposed based on the results of spectroscopic analysis.

The crude alkaloid fraction (1.10 g), which was obtained from young leaves of *P. amaryllifolius*,[5] was initially separated by SiO_2 column chromatography using MeOH/$CHCl_3$ gradient, and then the 2—5% MeOH/$CHCl_3$ eluate was subjected to SiO_2 medium pressure liquid chromatography using 2% EtOH/$CHCl_3$ to give 20 mg of pandamarilactonine-C and 4 mg of pandamarilactonine-D.

The two new compounds, pandamarilactonine-C (**1**)[8] and pandamarilactonine-D (**2**),[9] gave respectively *m/z* 318.1691 $[M+H]^+$ and *m/z* 318.1704 $[M+H]^+$ by high-resolution FAB-MS, which established the molecular formulas of the two compounds as $C_{18}H_{23}NO_4$, and indicated that these are isomers of coexisting alkaloids, pandamarilactonine-A and B.[5] The UV, ^{1}H- and ^{13}C-NMR spectra of pandamarilactonine-C and -D were very similar to those of pandamarilactonine-A and B, which comprised γ-butylidene-α-methyl α,β-unsaturated γ-lactone and pyrrolidinyl α,β-unsaturated γ-lactone residues, indicating that these four alkaloids are stereoisomers. Unambiguous assignment of all the carbons and protons in **1**[8] and **2**[9] was realized using ^{1}H–^{1}H correlated spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond correlation (HMBC) spectra. Comparing the ^{13}C-NMR data of **1** and **2** with those of **3** and **4**,[5] a significant difference was observed in the chemical shifts at the C-4 position. The signals of **1** (δ 130.3) and **2** (δ 133.9) appeared in the higher field than those of **3** (δ 137.7) and **4** (δ 137.7), which can be reasonably interpreted in terms of the γ-gauche effect due to the *E* configuration in the γ-alkylidene-γ-lactone moiety of both **1** and **2**. Differential nuclear Overhauser effect (NOE) experiments on **1** and **2**, *i.e.*, observation of a clear peak enhancement from H-4 to H-7, also demonstrated the *E* configuration of the γ-alkylidenebutenolide moiety. All of the above findings enabled us to elucidate the molecular structures of the new alkaloids (**1**, **2**) except for the stereochemistry of the vicinal asymmetric center at the C-14 and C-15 positions.

To confirm the structures and the relative stereochemistry at the C-14 and C-15 positions in the new alkaloids, we attempted the total synthesis of pandamarilactonines. The lower part of the alkaloids, *i.e.*, the pyrrolidinyl α,β-unsaturated γ-lactone residue, was synthesized according to the procedure of Martin *et al.*[10] as follows. Compound (**7**), whose stereochemistry at the vicinal positions was established to be *threo* by X-ray analysis,[10] was prepared by vinylogous Mannich coupling reaction of **5** and **6**. The protecting group on the nitrogen in **7** was removed by treatment with TMSI in CH_3CN to give **8** in 94% yield. The iodide (**13**) corresponding to the upper part of pandamarilactonines was prepared by a three-step operation: i) condensation of the alde-



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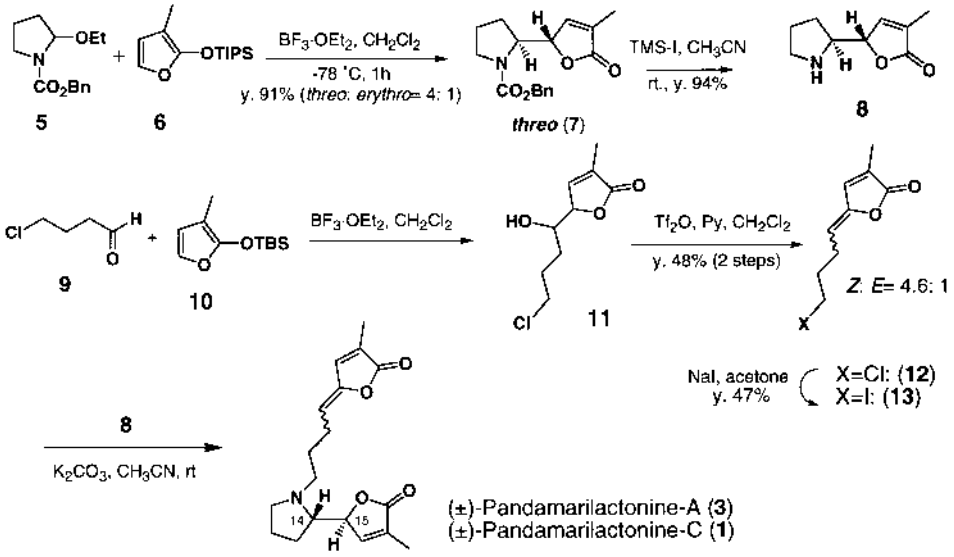

Chart 1. Total Synthesis of (±)-Pandamarilactonine-A and -C

hyde (**9**) with the siloxyfuran (**10**) in the presence of $BF_3 \cdot Et_2O$; ii) dehydration of the resultant aldol adduct (**11**) with trifluoromethanesulfonic anhydride and pyridine[11] (48% overall yield); and iii) halogen exchange of (**12**) with NaI in acetone (47% yield). The thus-obtained C9 unit (**13**) consisted of *Z* and *E* isomers in the ratio of 4.6 : 1, and was then condensed with secondary amine (**8**) in acetonitrile in the presence of K_2CO_3 to give two pandamarilactonines in 33% and 7% yields, both of which possessed the *threo* form at the C-14 and C-15 positions. The major synthetic product having the *Z* configuration was completely identical with natural pandamarilactonine-A and the minor one having the *E* configuration was identical with natural pandamarilactonine-C, respectively, by direct comparison of their chromatographic behavior, as well as their mass, and ^{1}H- and ^{13}C-NMR spectra. Based on the results of this synthetic study, the structures of pandamarilactonine-C, -D, -A, and -B were unambiguously established to be formulas **1** to **4**, respectively. The stereochemistry at the vicinal centers in pandamarilactonine-A and -B was analyzed by spectroscopic methods and the structures having the *erythro*-form for pandamarilactonine-A and the *threo*-form for B have been proposed.[5] However, they should be revised as above.

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8) Pandamarilactonine-C (**1**): An amorphous powder, $[\alpha]_D^{23}$ +26.2° (*c*= 0.99, $CHCl_3$), UV (MeOH) λ_{max} nm (log ε): 275 (4.23), 220 (sh), 201 (3.67). IR (neat) ν_{max} cm^{-1}: 1758 (lactone). FAB-MS (NBA) *m/z*; 318 $[M+H]^+$. HR-FAB-MS (NBA): Calcd for $C_{18}H_{23}NO_4$: 318.1704, Found 318.1691. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.31 (1H, dd, *J*=0.9, 1.5 Hz, H-4), 7.04 (1H, d-like, *J*=1.5 Hz, H-16), 5.64 (1H, dd, *J*=8.2, 8.5 Hz, H-6), 4.80 (1H, ddd, *J*=1.8, 1.8, 5.5 Hz, H-15), 3.12 (1H, dd-like, *J*=6.7, 7.3 Hz, H-11), 2.91 (1H, ddd, *J*=7.9, 8.2, 11.9 Hz, H-9), 2.78 (1H, m, H-14), 2.45 (1H, ddd, *J*=5.8, 7.0, 11.9 Hz, H-9), 2.35 (1H, ddd, *J*=7.0, 8.2, 14.7 Hz, H-7), 2.25 (2H, m, H-7 and H-11), 2.02 (3H, d, *J*=0.9 Hz, H_3-21), 1.94 (3H, d-like, *J*=1.8 Hz, H_3-20), 1.71—1.82 (2H, m, H-12, H-13), 1.62—1.68 (3H, m, H_2-8, H-13), 1.45 (1H, m, H-12). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.2 (C-18), 171.0 (C-2), 148.7 (C-5), 146.7 (C-16), 131.3 (C-17), 130.3 (C-4), 129.1 (C-3), 113.4 (C-6), 83.8 (C-15), 65.6 (C-14), 55.2 (C-9), 54.2 (C-11), 29.1 (C-8), 26.1 (C-12), 24.2 (C-7), 23.8 (C-13), 10.8 (C-20, C-21).
9) Pandamarilactonine-D (2): An amorphous powder, $[\alpha]_D^{25}$ 0° (*c*=0.21, $CHCl_3$), UV (MeOH) λ_{max} nm (log ε): 276 (4.38), 234 (sh), 203 (4.30). IR (neat) ν_{max} cm^{-1}: 1760 (lactone). FAB-MS (NBA) *m/z*; 318 $[M+H]^+$. HR-FAB-MS (NBA): Calcd for $C_{18}H_{23}NO_4$: 318.1704, Found 318.1704. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35 (1H, m, H-4), 6.99 (1H, dd, *J*=1.5, 1.7 Hz, H-16), 5.60 (1H, dd, *J*=8.3, 8.8 Hz, H-6), 4.74 (1H, m, H-15), 3.08 (1H, m, H-11), 2.77 (1H, m, H-9), 2.72 (1H, m, H-14), 2.42 (1H, m, H-9), 2.29 (2H, m, H_2-7), 2.25 (1H, m, H-11), 2.01 (3H, m, H_3-21), 1.94 (3H, dd-like, *J*=1.5, 2.0 Hz, H_3-20), 1.78—1.92 (4H, m, H_2-12, H_2-13), 1.63 (2H, m, H_2-8). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.3 (C-18), 171.0 (C-2), 149.0 (C-5), 147.1 (C-16), 131.0 (C-17), 133.9 (C-4), 130.3 (C-3), 113.3 (C-6), 83.0 (C-15), 65.9 (C-14), 55.1 (C-9), 54.0 (C-11), 28.7 (C-8), 26.3 (C-12), 24.0 (C-7), 23.9 (C-13), 10.8 (C-20), 10.7 (C-21).
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