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Determination of absolute configuration of *Pandanus* alkaloid, pandamarilactonine-A, by first asymmetric total synthesis

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Abstract—The absolute configuration of pandamarilactonine-A, a pyrrolidine alkaloid, was established on the basis of total synthesis starting from L-prolinol. An insight into the mechanism of the low enantiomeric purity of natural pandamarilactonine-A is discussed.

Previously, we have reported the isolation of two new pyrrolidine alkaloids, pandamarilactonine-A (**1**) and -B (**2**), from *Pandanus amaryllifolius*.[1] Their structures were first characterized by spectroscopic analysis and biomimetic total synthesis through a plausible biogenetic intermediate (**3**),[2] and the relative stereochemistry of the vicinal chiral centers at C14 and C15 was elucidated by the total synthesis of racemates **1** and **2**.[3] Interestingly, natural pandamarilactonine-A exhibited $[\alpha]_D^{23}$ +35 (*c* 4.37, $CHCl_3$) with 26% enantiomeric excess, whereas pandamarilactonine-B was isolated as a racemate. To elucidate the absolute configuration of the major enantiomer in pandamarilactonine-A and to examine why pandamarilactonine-A was isolated as a compound possessing low optical purity, we attempted the asymmetric total synthesis of **1** and used it for resolving the issue of concern (Fig. 1).

Initially, L-prolinol (**4**) was converted into aldehyde (**5**, $[\alpha]_D^{26}$ −63.1 (*c* 1.14, MeOH))[4] in two steps, and then the Reformatsky-type condensation with ethyl 2-(bromomethyl)acrylate was carried out. When Zn metal was used, the adducts were obtained in 52% yield, which contained *erythro* (more polar, **6**) and *threo* (less polar, **7**) isomers in the ratio of 4:1, the stereochemistry of which was determined in the later stage, as described below. On the other hand, indium-mediated coupling[5] gave the same adducts in 80% yield, the diastereoselectivity of which was 2:1. The *erythro* isomer (**6**), which had an undesired stereochemistry, was transformed into the *threo* isomer (**7**) by inversion of the secondary alcohol in it. Initially, the intramolecular Mitsunobu reaction was applied to carboxylic acid (**8**) that was prepared by the alkaline hydrolysis of **6**. Treatment of **8** with di-*tert*-butyl azodicarboxylate (DTAD) and PPh_3 in THF at room temperature gave the lactone derivative in quantitative yield, which contained *threo* isomer (**9**) and its *erythro* isomer in the ratio of 7.3:1. The unexpected minor *erythro*-lactone with retention of the configuration of the alcohol was formed via an acyloxyphosphonium ion intermediate.[6] Application of the conventional intermolecular Mitsunobu reaction to ester (**6**) resulted in the recovery of the starting material. For the inversion of the alcohol in **6**, we also attempted the oxidation–reduction sequence. Ketone derivative (**10**) prepared from **6** by oxidation with Dess–Martin periodinane was reduced with $NaBH_4$ in MeOH at −20 °C to afford *threo* (**7**) and *erythro* (**6**) alcohols in the ratio of 2.6:1. The major alcohol **7** thus obtained was treated with trifluoroacetic acid in CH_2Cl_2 to give lactone (**9**) in 90% yield, which was identical with the major product obtained via the intramolecular Mitsunobu reaction described above. Next, the isomerization of the double bond in **9** from *exo* to *endo* position was performed by using Et_3SiH (5 mol%) and tris(triphenylphosphine)rhodium chloride (10 mol%)[7] in refluxing toluene to afford α-methyl butenolide (**11**) in 86% yield. The ^1H and ^{13}C NMR spectra of **11** ($[\alpha]_D^{25}$ −183 (*c* 0.49, $CHCl_3$), 100% ee based on the chiral HPLC analysis) were identical with those of Martin et al.'s racemic

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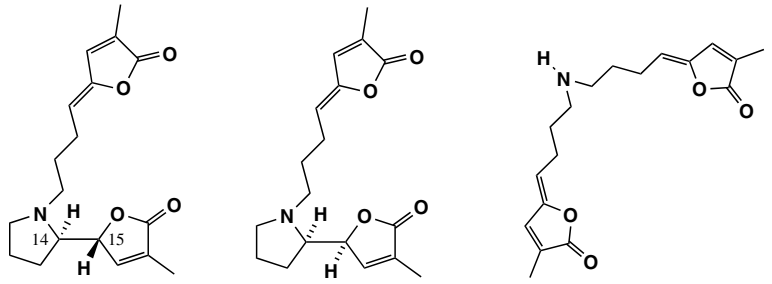
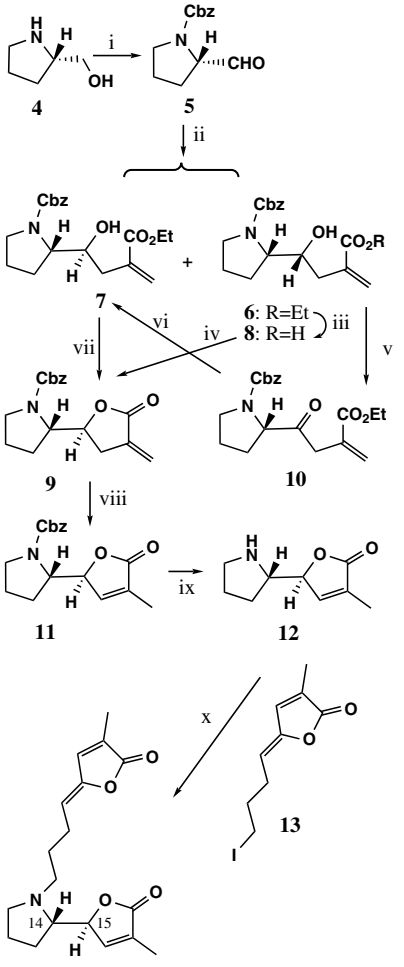


Pandamarilactonine-A (**1**) Pandamarilactonine-B (**2**) Pandanamine (**3**)

Figure 1.

compound,[8] the relative stereochemistry at C14 and C15 of which was established to be *threo* by X-ray analysis. Careful removal of the Cbz group on nitrogen (TMSI in CH_3CN at −15 °C for 30 min) gave secondary amine (**12**) ($[\alpha]_D^{24}$ −49.4 (*c* 1.22, $CHCl_3$))[9] in quantitative yield (Scheme 1).



(–)-Pandamarilactonine-A (**1**)

Scheme 1. Reagents and conditions: (i) Cbz–Cl, K_2CO_3, CH_3CN, then Swern oxidation, 91%; (ii) ethyl 2-(bromomethyl)acrylate, 2 equiv Zn, THF–aq satd NH_4Cl or 1.1 equiv indium, aq EtOH; (iii) LiOH, aq THF, quant; (iv) DTAD, PPh_3, THF, rt; (v) DMP, CH_2Cl_2, rt, quant; (vi) $NaBH_4$, MeOH, −20 °C, 86%; (vii) TFA, CH_2Cl_2, rt, 90%; (viii) 5 mol% Et_3SiH, 10 mol% $Rh(PPh_3)_3Cl$, toluene, reflux, 86%; (ix) TMSI, CH_3CN, −15 °C, quant; (x) Ag_2CO_3, CH_3CN, rt.

The final stage of the total synthesis of **1** is the coupling of optically active amine (**12**) with the C9 unit involving a γ-alkylidene butenolide moiety. Iodide (**13**),[3] which consisted of *Z* and *E* isomers in the ratio of 5:1, was condensed with freshly prepared **12** in CH_3CN in the presence of Ag_2CO_3 at room temperature to furnish the adducts in 66% yield. After repeated column chromatography, pure pandamarilactonine-A (**1**) was obtained in 48% yield. The synthetic compound with 14*S* and 15*S* configurations, whose spectroscopic data, including ^1H and ^{13}C NMR, UV, IR, MS, and HR–MS, were completely identical with those of the natural product, exhibited $[\alpha]_D^{23}$ −94.0 (*c* 0.12, $CHCl_3$). This finding demonstrated that the absolute configuration of the major enantiomer in natural pandamarilactonine-A (**1**) was 14*R* and 15*R*.[10]

As mentioned in the introductory part, pandamarilactonine-A (**1**) was obtained as a compound with 26% enantiomeric excess from nature, whereas pandamarilactonine-B (**2**) was isolated as a racemate. Craik and co-workers have claimed in their recent report[11] that pandamarilactonines isolated from acid–base treatment are artifacts produced during the extraction of pandanamine (**3**). However, the fact that our natural pandamarilactonine-A was optically active, albeit its low enantiomeric excess, led us to consider that **1** is produced enzymatically in the plants, and during the extraction or isolation process, optically active **1** might isomerize to optically inactive **1** and **2** under acidic conditions through the mechanism shown in Figure 2. To examine this hypothetical mechanism, the behavior of pandamarilactonine-A in acidic solution (CD_3OD + 1 mol% CD_3CO_2D) was monitored by ^1H NMR spectroscopy. If the ring-opening/ring-closing process occurred in this solution, the formation of both **1** and **2** having a deuterium at the C15 position would be observed. However, the formation of **2** as well as **1** having a deuterium at C15 was not recognized even after one month, and only the gradual production of **3** was observed. This indicates that pandamarilactonine-B (**2**) was not derived from pandamarilactonine-A (**1**). Taking Craik and co-workers experiments, that is, racemic pandamarilactonines are formed from pandanamine by acid–base treatment, into consideration, we speculate that our

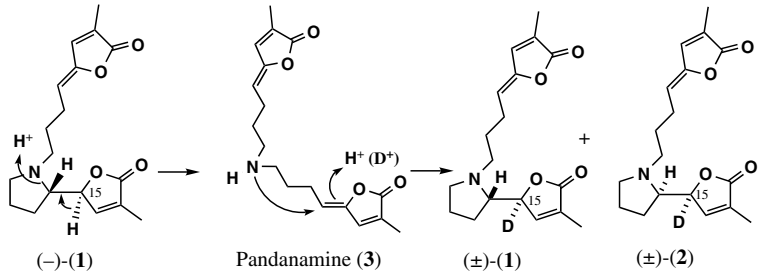


Figure 2. A hypothetical mechanism for isomerization of pandamarilactonine.

natural pandamarilactonine-A consists of enzymatically formed **1** with high optical activity and a racemate formed during the extraction/isolation process, resulting in the compound possessing a low optical purity. By contrast, pandamarilactonine-B is an artifact from pandanamine (**3**), as mentioned in Ref. 11.

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10. The optical purity of synthetic **1** was estimated to be 70% ee based on the specific rotation of the natural **1**. For reference, optically active pandamarilactonine-B (**2**) with 14*S* and 15*R* was also prepared from **6** via the same synthetic sequence as that for **1**. A synthetic intermediate corresponding to norpandamarilactonine-A[12] showed $[\alpha]_D^{24}$ +80.2 (*c* 0.79, $CHCl_3$). Except for the optical rotation, $[\alpha]_D^{24}$ +26.9 (*c* 0.17, $CHCl_3$), the spectroscopic data of synthetic **2** were identical with those of the natural product.[1]
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