Synthetic Studies on *Pandanus* Alkaloids: From Norpandamarilactonines to Pandamarilactonines, a Proof of Their Configurational Instability[‡]

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Keywords: Alkaloids / Total synthesis / Configurational stability

The ethyl carbamate of norpandamarilactonine-A was prepared in an enantiomerically pure form starting from (*S*)-prolinol. Deprotection of the amine functionality rendered both diastereomeric norpandamarilactonines as racemates, which were used as synthetic precursors of pandamarilactonine-A and -B.

Introduction

Pandanus amaryllifolius Roxb. (Pandanaceae), commonly named the screw pine, is a small species of about 50 cm characterized by very sweet smelling leaves. It is cultivated extensively through tropical and subtropical regions and traditionally used as a food flavoring additive and in folk medicine.[2] A tea made from the leaves of this plant is commonly used for strengthening the heart.[3] The hypoglycemic effect of an extract of this plant, under the botanical synonym of *Pandanus odorus*, has also been well established.[4] The two pyrrolidine alkaloids pandamarilactonine-A (**1**) and -B (**2**) (Figure 1) were first isolated from this plant by Takayama and co-workers and their relative stereochemistries at the C-14 and C-15 positions were respectively assigned as *erythro* and *threo*, based on spectroscopic-conformational studies.[5] More recently, these authors isolated from the same source the two remaining diastereomers with *E* configurations of the double bonds, pandamarilactonine-C (**3**) and -D (**4**) and, by correlation with a synthetic precursor, the relative stereochemistries initially proposed for alkaloids **1** and **2** were amended to those shown in Figure 1.[6] Conversely, the *erythro* isomers **2** and **4** isolated from the plant were described as optically inactive, while the *threo* isomers **1** and **3** were reported as dextrorotatory with $[\alpha]_D^{23}$ = +35 (*c* = 4.37, $CHCl_3$)[5] and +26 (*c* = 0.99, $CHCl_3$)[6] respectively, but chiral HPLC analysis of natural pandamarilactonine-A showed a low enantiomeric enrichment (26% *ee*).[5] These data result in a reasonable uncertainty about the configurational stability of these alkaloids.

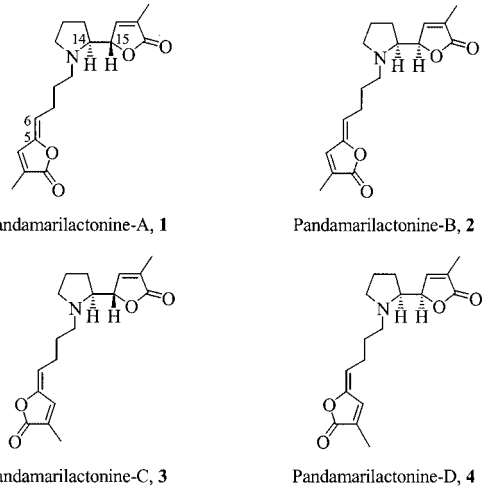

Figure 1. The *Pandanus* alkaloids

Along with their isolation, the first total syntheses of **1** and **2** were described in racemic form, passing through the key symmetrical amine **5** (Figure 2), which was considered

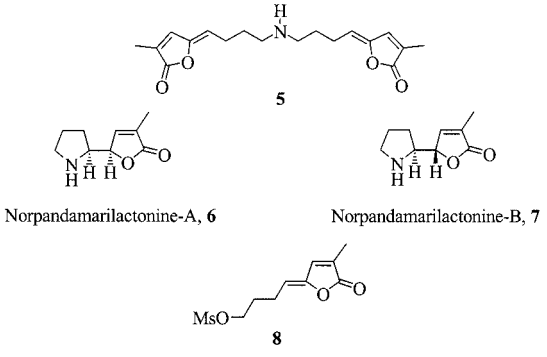

Figure 2. Synthetic precursors of pandamarilactonines

[‡] For preliminary account of this work see ref.[1]

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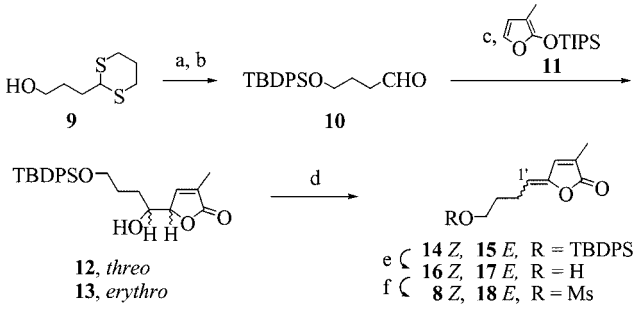
  DOI: 10.1002/ejoc.200300474

as a plausible biogenetic precursor of pandamarilactonines.[5] A reinvestigation of the alkaloidal fraction of the plant led to the isolation of compound **5**, which was named pandamine.[7] Additionally, another pair of diastereoisomeric alkaloids with a closely related structure, norpandamarilactonine-A (**6**) and -B (**7**) were also found in racemic form as minor bases in fresh leaves of the plant and the *threo* isomer **7** was synthesized from 2-pyrrolidone and 3-methyl-2(5*H*)-furanone.[8]

In relation to a project directed at the synthesis of other alkaloids, we were interested in the preparation of the norpandamarilactonine skeleton in enantiomerically pure form. With this compound at our disposal, we attempted its stereoselective conversion into the *Pandanus* alkaloids as a means of testing their configurational stability and, eventually, of establishing the absolute configuration of the major antipode in natural pandamarilactonine-A. Here we present an alternative synthesis of norpandamarilactonines **6** and **7** and their conversion into pandamarilactonines **1** and **2** by alkylation with the suitable partner **8**. Our synthetic studies provide evidence for the configurational instability of these alkaloids.

Results and Discussion

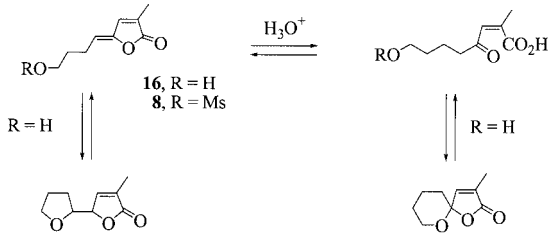
The aldehyde **10** was selected as a suitable precursor of the fragment **8** (Scheme 1). The preparation of compound **10** described in the literature was by monosilylation of 1,4-butanediol and subsequent oxidation of the remaining alcohol moiety.[9] Nevertheless, in our hands, it proved to be advantageous to utilize an alternative preparation of **10** starting from hydroxydithiane **9**[10] which, after silylation and removal of the thioacetal function, furnished the aldehyde **10** in 88% yield. The vinylogous Mukaiyama reaction[11] of **10** with the silyloxyfuran **11**, prepared by the Martin methodology,[12] afforded a 7:1 mixture of the *threo* and *erythro* alcohols **12** and **13** in 82% overall yield. Treatment of a 6:1 mixture of these diastereomeric alcohols with TMSCl/DBU in chloroform gave a mixture of the olefins **14** and **15** in 94% yield after purification by silica gel chromatography. Provided that the elimination follows an anti-



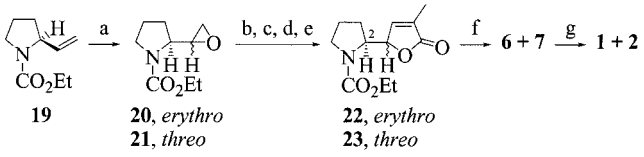
Scheme 1. *Reagents and conditions*: (a) TBDPSCl, Im, DMF, room temp., 96%; (b) $CaCO_3$, MeI, CH_3CN/H_2O, room temp., 92%; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 2 h, 82%; (d) TMSCl, DBU, $CHCl_3$, reflux, 1 h, 94%; (e) Bu_4NF, THF, room temp., 3 h, 86%; (f) MsCl, pyridine, CH_2Cl_2, room temp., overnight, 74%

periplanar E2 type mechanism, the *Z* olefin **14** should be formed stereospecifically from the *threo* alcohol **12** and the *E* olefin **15** from the *erythro* alcohol **13**. Nevertheless, the ^1H NMR spectrum of the isolated mixture displayed two olefinic signals at δ = 5.57 and 5.09, corresponding to 1′-H in an approximately 1:3 ratio, which were respectively assigned to the *E* and *Z* isomers,[5,13] denoting some extent of *Z*/*E* isomerization under the reaction conditions. Pure samples of each of the isomeric olefins **12** and **13** could be isolated by repeated column chromatography, but for synthetic purposes it turned out to be more practical to proceed with the mixture.

Desilylation was accomplished in 86% yield but the free alcohols **16** and **17** showed a low stability and were therefore converted into the sulfonates without intermediate purification. The isomeric sulfonates **8** and **18** were chromatographically separated (74% total yield). Although interconversion between them was not detected, their stability is also quite limited and **8** should be transformed rapidly. Based on ^1H NMR analysis of evolved samples, we suspect that the low stability of both the sulfonates and their hydroxylic precursors is associated with the facile hydrolysis of the lactone and, in the case of the alcohols, other additional evolution pathways such as intramolecular conjugate addition of the free hydroxyl group to the δ-carbonyl position or formation of ketals (Scheme 2).



Scheme 2. Evolution pathways for lactones **8** and **16**



Scheme 3. *Reagents and conditions*: (a) MCPBA, $CHCl_3$, room temp., 24 h, 77%; (b) separation of diastereoisomers; (c) $PhSeCH(CH_3)CO_2H$, LDA (2 equiv.), THF, 0 °C to room temp., 1.5 h; (d) AcOH, THF, reflux, 16 h; (e) H_2O_2, AcOH, 0 °C, 45 min, 61% from **20**; (f) TMSI, $CHCl_3$, reflux, 5 h, 84%; (g) **8**, pyridine, DMF, 60 °C, 3 days, 44%

The synthesis of the pyrrolidine fragment (Scheme 3) was accomplished starting from the carbamate **19** which can be easily prepared from (*S*)-prolinol.[14] Oxidation of **19** with MCPBA furnished the two oxiranes **20** and **21** in 77% total yield and an *erythro*/*threo* ratio of 1.5:1. The oxiranes were separated and the major isomer **20** was converted into the *erythro* α-methyl butenolide **22** by a three step protocol[15] consisting of addition of the dianion of 2-phenylselenopropionic acid[16] to **20**, followed by acid induced lactonization

and oxidation of the selenide function with consequent thermal elimination, with an overall 61% yield.

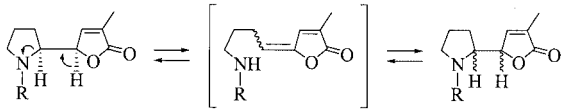
The stereochemical assignments of oxiranes **20** and **21** and the butenolide **22** are based on NMR parameters (Table 1). According to literature data for similar compounds,[12,17] the proton 2-H in *erythro* isomers is upfield shifted compared with the *threo* isomers, while the opposite occurs for the carbon atom C-2. The revised stereochemical assignments of pandamarilactonine-A (**1**) and -B (**2**) are also in agreement with this trend.[6] Due to slow rotation around the N−C bond in the carbamate, a splitting of the NMR signals was observed for the oxiranes at 250 K.

Table 1. Relevant NMR spectroscopic data used to establish the *erythro*/*threo* stereochemistry

Compound	Relative configuration	δ 2-H [ppm]	δ C-2 [ppm]
20[a]	*erythro*	3.59 and 3.48	58.8 and 58.3
21[b]	*threo*	4.25−4.00	55.8 and 55.7
22	*erythro*	3.95	58.9
23[c]	*threo*	4.27	57.9
2	*erythro*	2.70	66.3
1	*threo*	2.83	65.3

[a] Spectra were acquired at 260 K. [b] Spectra were acquired at 250 K. [c] A small amount of **23** was synthesized in order to obtain the corresponding NMR spectroscopic data.

It has been reported that epimerization does not occur when the benzylcarbamate of **7** is deprotected by treatment with TMSI in CH_3CN at room temperature.[6] On the contrary, treatment of the *erythro* butenolide **22** with TMSI in chloroform at reflux resulted in cleavage of the carbamate with concomitant epimerization of the stereogenic center of the lactone moiety, furnishing an approximately 1:1 mixture of the two norpandamarilactonines, which were separated by silica gel chromatography. The first and second eluted diastereomers showed ^{1}H NMR spectra identical to those reported for natural norpandamarilactonine-B (**7**) and A (**6**), respectively. The specific rotation measured for **6** was $[\alpha]_D^{20} = -7$ ($c = 1.5$, $CHCl_3$) and for **7** $[\alpha]_D^{20} = -3$ ($c = 2.6$, $CHCl_3$). We suspected that the reason for such low optical activity values could be that, besides epimerization, racemization had also occurred to some extent. Thus, the configurational instability of these alkaloids was confirmed when a mixture of **6** and **7** was treated with an equimolar amount of freshly prepared mesylate **8** in DMF in the presence of pyridine at 60 °C. Under these conditions, pandamarilactonines **1** and **2** were slowly formed in an approximately 1:1 ratio. After three days, the reaction mixture was treated and purified by flash chromatography over silica gel. The first eluted isomer showed a ^{1}H NMR spectrum identical to that reported for natural pandamarilactonine-B (**2**) while the second matched the spectroscopic data reported for pandamarilactonine-A (**1**).[5] The overall isolated yield was 44%. Analyzed pure samples of each diastereomer exhibited no optical activity. Although it has been described that in acidic media pandamarilactonine-A and -B do not interconvert and that the former does not racemize either[5] in neutral or basic media, a mechanism involving β-elimination-conjugate addition[18] (Scheme 4) may easily cause the configurational instability of these alkaloids.



Scheme 4. A plausible mechanism to explain the configurational instability of the *Pandanus* alkaloids

Conclusion

In conclusion, we have synthesized the ethyl carbamate of the *erythro*-norpandamarilactonine (**6**) in enantiopure form. Its deprotection to the free amine causes epimerization and the conversion of the mixture of epimeric norpandamarilactonines **6** and **7** into pandamarilactonine-A (**1**) and -B (**2**) finally resulting in the racemates. In the synthetic precursors **16/17** and **8/18**, we have also observed a lack of configurational stability of the double bond at position C5−C6 of the alkaloids. Moreover, pandamarilactonine-A isolated from natural sources shows a low 26% *ee* and pandamarilactonine-B is a racemate.[5] Considering all these data together, we believe that the existence in the plant of all the pandamarilactonines which have been isolated in racemic form (-B, -C, and -D) is questionable.

Experimental Section

General Remarks: Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 5−10 Torr. Flash chromatography was performed using Merck silica gel (230−400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-250-WB or AM-400-WB instruments at 250 or 400 MHz and 62.5 or 100 MHz, respectively, in $CDCl_3$. Tetramethylsilane (δ = 0.00 ppm) or $CHCl_3$ (δ = 7.27 ppm) were used as internal standards for ^{1}H and ^{13}C NMR spectra. Mass spectra were performed on a Hewlett−Packard 5985B instrument at 70 eV; only peaks with intensities higher than 20% are reported, unless they belong to molecular ions or to significant fragments.

4-(*tert*-Butyldiphenylsilyloxy)butanal (10): To a solution of alcohol **9** (1.0 g, 5.6 mmol) and imidazole (0.746 g, 11.2 mmol) in DMF (11 mL), was added a solution of *tert*-butylchlorodiphenylsilane (1.55 mL, 5.9 mmol) in DMF (1 mL). The mixture was stirred at room temperature overnight, diluted with 150 mL of diethyl ether and washed with brine (3 × 100 mL). The organic layer was concentrated under reduced pressure yielding a crude material which was purified by flash chromatography (hexanes/diethyl ether, 8:1) to afford 2-[3-(*tert*-butyldiphenylsilyloxy)propyl]-1,3-dithiane (2.24 g, 5.4 mmol, 96% yield). This compound was dissolved in 80% aqueous acetonitrile (20 mL) and treated with $CaCO_3$ (0.535 g, 5.4 mmol) and iodomethane (2.0 mL, 32.3 mmol). The mixture was stirred overnight at room temperature and then diluted

with CH_2Cl_2 (25 mL) and filtered through a short path of silica gel. The solvent was evaporated under reduced pressure to furnish aldehyde **10** (1.62 g, 5.0 mmol, 92% yield) which proved to be unstable and was used for the next reaction without further purification. ^{1}H NMR (250 MHz, ppm): δ = 1.01 (s, 9 H, *t*Bu), 1.88 (m, 2 H, 3-H), 2.57 (td, $J_{2,3}$ = 9.0, $J_{2,1}$ = 1.6 Hz, 2 H, 2-H), 3.67 (t, $J_{4,3}$ = 6.1 Hz, 2 H, 4-H), 7.38 (m, 6 H, Ph), 7.63 (m, 4 H, Ph). ^{13}C NMR (62.5 MHz, ppm): δ = 19.2 (*t*Bu-C), 25.3 (C-3), 26.8 (*t*Bu-CH_3), 40.7 (C-2), 62.9 (C-4), 127.7/129.7/133.6/135.5 (Ph), 202.4 (C-1).

***threo*- (12) and *erythro*-5-[4-(*tert*-Butyldiphenylsilyloxy)-1-hydroxybutyl]-3-methyl-2(5*H*)-furanone (13):** A solution of 3-methyl-2(5*H*)-furanone (620 μL, 7.15 mmol) and triethylamine (1.0 mL, 7.49 mmol) in dry CH_2Cl_2 (8 mL) was cooled to 0 °C and treated with triisopropylsilyl triflate (2.0 mL, 7.49 mmol). The mixture was stirred at room temperature for 2 days and then concentrated under vacuum. The resultant crude material was dissolved in CH_2Cl_2 (60 mL) and aldehyde **10** (2.70 g, 8.28 mmol) was added. The mixture was cooled to −78 °C, treated with boron trifluoride−diethyl ether (1.0 mL, 8.28 mmol) and stirred at this temperature for 3 h. After this time, the reaction mixture was quenched with brine and allowed to warm to room temperature. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2. The organic extracts were combined and concentrated under vacuum. Purification of the resultant crude material by flash chromatography (hexanes/diethyl ether, 2:1) afforded a 7:1 mixture of alcohols **12** and **13** (2.61 g, 6.15 mmol, 82% yield). **12** + **13**: ^{1}H NMR (250 MHz, ppm): δ (*threo* isomer **12**) = 1.03 (s, 9 H, *t*Bu), 1.50−1.83 (m, 4 H, 2′,2′,3′,3′-H), 1.92 (d, *J* = 1.7 Hz, 3 H, CH_3), 2.80 (d, *J* = 4.8 Hz, 1 H, OH), 3.67 (m, 3 H, 1′,4′,4′-H), 4.82 (m, 1 H, 5-H), 7.00 (qn, *J* = 1.7 Hz, 1 H, 4-H), 7.38 (m, 6 H, Ph), 7.63 (m, 4 H, Ph); δ (*erythro* isomer **13**, observable signals) = 3.28 (d, *J* = 4.7 Hz, 1 H, OH), 4.75 (m, 1 H, 5-H), 7.18 (qn, *J* = 1.5 Hz, 1 H, 4-H). ^{13}C NMR (62.5 MHz, ppm): δ (*threo* isomer **12**) = 10.8 (CH_3), 19.2 (*t*Bu-C), 26.8 (*t*Bu-CH_3), 28.4/29.8 (C-2′/C-3′), 63.8 (C-4′), 71.9 (C1′), 83.8 (C-5), 131.3 (C-3), 127.7/129.7133.4/135.5 (Ph), 145.9 (C-4), 173.9 (C-2); δ (*erythro* isomer **13**, observable signals) = 30.8/31.5 (C-2′/C-3′), 64.1 (C-4′), 72.1 (C-1′), 83.4 (C-5), 131.3 (C-3), 146.6 (C-4). EIMS: *m*/*z* = 442 (66) $[M + 18]^+$, 424 (16) $[M]^+$, 346 (100). $C_{25}H_{32}O_4Si$: calcd. C 70.72, H 7.60; found C 70.53, H 7.73.

(*Z*)- (14) and (*E*)-5-[4-(*tert*-Butyldiphenylsilyloxy)-1-butylidene]-3-methyl-2(5*H*)-furanone (15): TMSCl (3.0 mL, 24.2 mmol) was added to a solution of a 7:1 mixture of alcohols **12** and **13** (4.1 g, 9.66 mmol) in dry $CHCl_3$ (60 mL), the mixture was stirred at room temperature for 1 h and then treated with freshly distilled DBU (7.2 mL, 48.3 mmol). The resultant hot solution was allowed to cool to room temperature and stirred for 1 h. It was then diluted with $CHCl_3$ (40 mL), washed with 10% HCl (2 × 40 mL) and brine (40 mL), and concentrated under vacuum to yield an oil which, after purification by flash chromatography (hexanes/diethyl ether, 3:1), afforded a 3:1 mixture of olefins **14** and **15** as an oil (3.71 g, 9.1 mmol, 94% yield). A second chromatographic procedure enabled the separation of the isomers. **14**: ^{1}H NMR (250 MHz, ppm): δ = 1.03 (s, 9 H, *t*Bu-CH_3), 1.70 (qn, *J* = 6.9 Hz, 2 H, 3′,3′-H), 1.96 (d, *J* = 0.6 Hz, 3 H, CH_3), 2.51 (q, *J* = 7.5 Hz, 2 H, 2′-H), 3.67 (t, $J_{4',3'}$ = 6.2 Hz, 2 H, 4′,4′-H), 5.09 (t, $J_{1',2'}$ = 7.9 Hz, 1 H, 1′-H), 6.90 (m, 1 H, 4-H), 7.37 (m, 6 H, Ph), 7.63 (m, 4 H, Ph). ^{13}C NMR (62.5 MHz, ppm): δ = 10.5 (CH_3), 19.2 (*t*Bu-C), 22.8 (C-3′), 26.9 (*t*Bu-CH_3), 32.0 (C-2′), 63.2 (C-4′), 114.2 (C-1′), 129.0 (C-3), 127.6/129.6/133.9/135.6 (Ph), 137.6 (C-4), 148.4 (C-5), 171.1 (C-2). **15**: ^{1}H NMR (250 MHz, ppm): δ = 1.05 (s, 9 H, *t*Bu-CH_3), 1.68 (qn, *J* = 6.6 Hz, 2 H, 3′,3′-H), 1.96 (s, 3 H, CH_3), 2.36 (q, *J* = 7.7 Hz, 2 H, 2′,2′-H), 3.67 (t, $J_{4',3'}$ = 5.9 Hz, 2 H, 4′,4′-H), 5.57 (t, $J_{1',2'}$ = 8.6 Hz, 1 H, 1′-H), 7.25 (m, 1 H, 4-H), 7.37 (m, 6 H, Ph), 7.63 (m, 4 H, Ph). ^{13}C NMR (62.5 MHz, ppm): δ = 10.7 (CH_3), 19.2 (*t*Bu-C), 22.6 (C-3′), 26.9 (*t*Bu-CH_3), 32.3 (C-2′), 62.4 (C-4′), 113.1 (C-1′), 130.1 (C-3), 133.7 (C-4), 127.7/129.7/133.8/135.6 (Ph), 149.0 (C-5), 171.0 (C-2). **14** + **15**: EIMS: *m*/*z* = 269 (9), 199 (100), 139 (48). $C_{25}H_{30}O_3Si$ calcd. C 73.85, H 7.44; found C 73.70, H 7.31.

(*Z*)- (8) and (*E*)-5-(4-Mesyloxy-1-butylidene)-3-methyl-2(5*H*)-furanone (18): A solution of a 3:1 mixture of olefins **14** and **15** (200 mg, 0.49 mmol) in dry THF (2.5 mL) at room temperature was treated with 1.0 M TBAF (590 μL, 0.59 mmol). The mixture was stirred at room temperature for 3 h and then concentrated under vacuum to yield a crude material which, after purification by flash chromatography (hexanes/diethyl ether, 1:1), afforded a 3:1 mixture of two diastereomeric alcohols **16** and **17** (70 mg, 0.42 mmol, 86% yield) as an oil, which was used in the next reaction without further purification: ^{1}H NMR (250 MHz, ppm): δ (major isomer) = 1.72 (m, 2 H, 3′,3′-H), 1.97 (s, 3 H, CH_3), 2.45 (q, *J* = 7.5 Hz, 2 H, 2′-H), 3.66 (m, 2 H, 4′,4′-H), 5.15 (t, $J_{1',2'}$ = 8.0 Hz, 1 H, 1′-H), 6.96 (m, 1 H, 4-H); δ (minor isomer, observable signals) = 1.98 (s, 3 H, CH_3), 2.35 (q, *J* = 7.3 Hz, 2 H, 2′,2′-H), 5.60 (t, $J_{1',2'}$ = 8.0 Hz, 1 H, 1′-H), 7.30 (m, 1 H, 4-H). ^{13}C NMR (62.5 MHz, ppm): δ (major isomer): 10.4 (CH_3), 22.5 (C-3′), 32.8 (C-2′), 61.9 (C-4′), 113.7 (C, 1′), 129.0 (C-3), 137.7 (C-4), 148.6 (C-5), 171.1 (C-2); δ (minor isomer, observable signals) = 10.7 (CH_3), 22.5 (C-3′), 32.1 (C-2′), 61.2 (C-4′), 113.0 (C-1′), 130.2 (C-3), 133.8 (C-4), 149.0 (C-5). EIMS: *m*/*z* = 186 (100) $[M + 18]^+$, 169 (14) $[M + 1]^+$. A solution of a freshly prepared 3:1 mixture of the former alcohols **16** and **17** (90 mg, 0.54 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was treated with freshly distilled pyridine (64 μL, 0.64 mmol) and mesyl chloride (91 μL, 1.2 mmol) and the mixture was stirred overnight. It was then washed with brine (2 mL) and a saturated Na_2CO_3 solution (2 mL) and concentrated under vacuum to yield a mixture of mesylates **8** and **18** which, when purified by flash chromatography (hexanes/ethyl acetate, 3:1), afforded **8** (44 mg, 0.18 mmol, 33% yield) and **18** (54 mg, 0.22 mmol, 41% yield). These sulfonates were unstable even at low temperature and were used in the next reaction without further purification. **8** + **18**: ^{1}H NMR (250 MHz, ppm): δ (major isomer **8**) = 1.92 (m, 2 H, 3′,3′-H), 2.01 (s, 3 H, CH_3), 2.49 (q, *J* = 7.4 Hz, 2 H, 2′,2′-H), 3.01 (s, 3 H, CH_3OSO_2), 4.22 (m, 2 H, 4′,4′-H), 5.11 (t, $J_{1',2'}$ = 8.0 Hz, 1 H, 1′-H), 6.97 (m, 1 H, 4-H); δ (minor isomer **18**, observable signals) = 2.35 (q, *J* = 7.3 Hz, 2 H, 2′,2′-H), 2.99 (s, 3 H, CH_3OSO_2), 5.54 (t, $J_{1',2'}$ = 8.4 Hz, 1 H,1′- H), 7.28 (m, 1 H, 4-H).

Ethyl (2*S*,1′*S*)- (20) and (2*S*,1′*R*)-2-Oxiranylpyrrolidine-1-carboxylate (21): A solution of 55% *m*-CPBA (1.53 g, 4.88 mmol) in chloroform (10 mL) was dried with anhydrous Na_2SO_4, filtered, and added to a solution of **19**[14] (0.550 g, 3.25 mmol) in chloroform (10 mL). The mixture was then diluted with $CHCl_3$ (20 mL) and washed with a saturated $NaHCO_3$ solution (2 × 25 mL) and brine (25 mL). The organic phase concentrated under vacuum yielded an approximately 1.5:1 mixture of **20** and **21** as oil. Separation by flash chromatography (hexanes/ethyl acetate 4:1) afforded pure **20** (0.310 g, 1.68 mmol, 51% yield) and **21** (0.160 g, 0.86 mmol, 26% yield). **20**: $[\alpha]_D^{20}$ = −13 (*c* = 1.3, ethanol). IR (KBr): $\tilde{\nu}$ = 2973, 2931, 2882, 1701, 1546, 1419, 1384, 1342, 1187, 1110 cm^{-1}. ^{1}H NMR (400 MHz, 260 K, ppm): δ = 1.20 (t, *J* = 7.0 Hz) + 1.24 (t, *J* = 7.0 Hz) (3 H, CH_3CH_2O), 1.78−1.97 (m, 4 H, 3,3,4,4-H), 2.67 (m) + 2.78 (m) (1 H, 2′-H), 2.82 (m, 1 H, 2′-H), 2.87 + 2.95 (1 H, 1′-H), 3.25−3.45 (m, 2 H, 5,5-H), 3.48 (m)

+ 3.59 (m) (1 H, 2-H), 4.07 (m, 2 H, CH_3CH_2O). ^{13}C NMR (100 MHz, 250 K, ppm): δ = 14.5 + 14.6 (CH_3CH_2O), 23.0 + 23.8 (C-4), 27.3 + 2 8.6 (C-3), 46.5 + 46.8 (C-5), 47.7 + 48.0 (C-2′), 52.4 + 52.7 (C-1′), 58.3 + 58.8 (C-2), 60.9 + 61.0 (CH_3CH_2O), 155.4 + 155.7 (CO_2N). EIMS: *m*/*z* = 186 (9) $[M + 1]^+$, 185 (1) $[M]^+$, 142 (100), 98 (29), 70 (90) $[C_4H_8N]^+$. $C_9H_{15}NO_3$ calcd. C 58.36, H 8.16, N 7.56 found C 58.27, H 8.24, N, 7.40. **21**: $[\alpha]_D^{20}$ = −42 (*c* = 1.3, ethanol). IR (KBr): ṽ = 2980, 2931, 2882, 1694, 1419, 1384, 1342, 1187, 1110 cm^{-1}. ^1H NMR (400 MHz, 250 K, ppm): δ = 1.21 (t, *J* = 7.1 Hz) + 1.22 (t, *J* = 7.1 Hz) (3 H, CH_3CH_2O), 1.75−2.05 (m, 4 H, 3,3,4,4-H), 2.48 (m, 1 H, 2′-H), 2.68 (t, *J* = 4.4 Hz, 2 H, 2′-H), 3.04 (m, 1 H, 1′-H), 3.22−3.41 (m, 2 H, 5,5-H), 4.00−4.25 (m, 3 H, 2-H, CH_3CH_2O). ^{13}C NMR (100 MHz, 250 K, ppm): δ = 14.6 + 14.7 (CH_3CH_2O), 23.4 + 24.1 (C-4), 28.4 + 28.7 (C-3), 44.2 + 44.4 (C-2′), 46.7 + 46.9 (C-5), 53.8 + 53.9 (C-1′), 55.7 + 55.8 (C-2), 61.0 (CH_3CH_2O), 155.3 + 155.7 (CO_2N). EIMS: *m*/*z* = 185 (1) $[M]^+$, 142 (90), 98 (23), 70 (100) $[C_4H_8N]^+$. $C_9H_{15}NO_3$ calcd. C 58.36, H 8.16, N 7.56 found C 57.96, H 8.24, N, 7.38.

Ethyl (2*S*)-2-[(2*R*)-2,5-Dihydro-4-methyl-5-oxo-2-furyl]pyrrolidine-1-carboxylate (22): A solution of 2-phenylselenopropionic acid (371 mg, 1.62 mmol) in dry THF (2.4 mL) was added to a solution of LDA, prepared from diisopropylamine (460 μL, 3.24 mmol) in dry THF (4 mL) and *n*BuLi 1.6 M in hexane (2.1 mL, 3.24 mmol) at 0 °C. The mixture was heated and stirred at 40 °C for 30 min. After cooling to 0 °C, a solution of oxirane **20** (200 mg, 1.08 mmol) in dry THF (0.5 mL) was added and the reaction mixture was allowed to stand at room temperature for 2 h. The reaction mixture was acidified with glacial acetic acid and heated to reflux overnight. It was then neutralized with a saturated $NaHCO_3$ solution and extracted with diethyl ether (3 × 25 mL). The organic phases were combined, concentrated under vacuum, and the resultant crude material was purified by flash chromatography (hexanes/ethyl acetate, 4:1) affording the corresponding phenylselenolactone (288 mg, 0.72 mmol, 67% yield) as an oil, which was used for the next reaction: ^1H NMR (400 MHz, ppm): δ = 1.17 (m, 3 H, CH_3CH_2O), 1.52 (s) + 1.53 (s) (3 H, CH_3), 1.40−2.38 (m, 6 H, 3,3,4,4,3′,3′-H), 3.15−3.45 (m, 2 H, 5,5-H), 3.83 (m, 1 H, 2-H), 4.04 (m, 2 H, CH_3CH_2O), 4.40−4.70 (m, 1 H, 2′-H), 7.15−7.37 (m, 3 H, Ph), 7.50−7.70 (m, 2 H, Ph).

A cold (0 °C) solution of the previous lactone (950 mg, 2.39 mmol) and glacial acetic acid (270 μL, 4.77 mmol) in dry THF (10 mL) was treated with 30% H_2O_2 (1.35 mL, 11.9 mmol). The mixture was stirred at 0 °C for 45 min, then neutralized with a saturated $NaHCO_3$ solution and extracted with diethyl ether (3 × 25 mL). The combined organic phases were concentrated under vacuum affording an oil which, after purification by flash chromatography (hexanes/ethyl acetate, 3:1), gave **22** (520 mg, 2.8 mmol, 91% yield): $[\alpha]_D^{20}$= −33 (*c* = 0.9, ethanol). IR (KBr): ṽ = 3072, 2988, 2903, 2882, 1764, 1687, 1420, 1384, 1335, 1202, 1110 cm^{-1}. ^1H NMR (400 MHz, ppm): δ = 1.24 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 1.55−2.00 (m, 4 H, 3,3,4,4-H), 1.90 (broad s, 3 H, CH_3), 3.41 (m, 2 H, 5,5-H), 3.95 (m, 1 H, 2-H), 4.12 (m, 2 H, CH_3CH_2O), 5.03 (m) + 5.29 (m) (1 H, 2′-H), 7.01 (m, 1 H, 3′-H). ^{13}C NMR (100 MHz, ppm): δ = 14.6 (CH_3CH_2O), 24.2 (C-4), 24.8 (C-3), 46.6 (C-5), 58.9 (C-2), 61.2 (CH_3CH_2O), 81.0 (C-2′), 130.5 (C-4′), 147.1 (C-3′), 155.4 (CO_2N), 174.2 (C-2′). EIMS: *m*/*z* = 194(2) [M − EtO]$^+$, 142 (95) $[C_4H_7NCO_2Et]^+$. $C_{12}H_{17}NO_4$ calcd. C 60.22, H 7.17, N 5.86 found C 60.24, H 7.09, N, 5.63.

Norpandamarilactonine-A (4) and -B (5): A solution of carbamate **22** (60 mg, 0.25 mmol) in dry chloroform (300 μL) was treated with TMSI (43 μL, 0.30 mmol) and heated to reflux for 3 h. MeOH (4 drops) was added to the cold reaction mixture (room temperature) and it was concentrated under vacuum. The resultant oil was redissolved in CH_2Cl_2 (5 mL) and 10% HCl (0.5 mL) and the phases were separated. The organic layer was concentrated under vacuum, affording a mixture of epimers of the starting carbamate (12 mg, 0.05 mmol). The aqueous layer was brought to pH 9 with 30% NH_4OH and extracted with CH_2Cl_2 (3 × 5 mL). These last organic extracts were combined and concentrated under vacuum affording an approximately 1:1 mixture of the two norpandamarilactonines **6** and **7** (35 mg, 0.21 mmol, 84% yield). Both diastereomers were separated by flash chromatography (hexanes/ethyl acetate, 3:1). The first and second eluted isomers showed ^1H NMR spectra identical to those reported for natural norpandamarilactonine-B (**7**) and -A (**6**), respectively.[8]

Pandamarilactonine-A (1) and -B (2): A solution of a 1:1 mixture of **6** and **7** (101 mg, 0.60 mmol) in dry DMF (1.5 mL) was treated with freshly prepared mesylate **8** (179 mg, 0.73 mmol) and heated to 60 °C for 3 days. The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (15 mL), and washed with 10% HCl (5 mL). The aqueous layer was brought to pH 9 with 30% NH_4OH and extracted with CH_2Cl_2 (3 × 5 mL). These last organic extracts were combined and concentrated under vacuum affording an approximately 1:1 mixture of the two pandamarilactonines **1** and **2** (48 mg, 0.22 mmol, 44% yield based upon consumed norpandamarilactonines) and a mixture of starting norpandamarilactonines (16 mg, 0.10 mmol). Both diastereomers were separated by flash chromatography (hexanes/ethyl acetate, 3:1). The first and second eluted isomers showed ^1H NMR spectra identical to those reported for natural pandamarilactonine-B (**2**) and -A (**1**), respectively.[5]

Acknowledgments

We gratefully acknowledge financial support from the Ministerio de Ciencia y Tecnología (Project BQU2001−2600) and CIRIT (Project 2001SGR 00178).

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Received July 29, 2003

