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Total synthesis of four *Pandanus* alkaloids: pandamarilactonine-A and -B and their chemical precursors norpandamarilactonine-A and -B

Félix Busqué, Pedro de March, Marta Figueredo,* Josep Font and Elena Sanfeliu

Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

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Abstract—Norpandamarilactonine-A and -B are prepared from (*S*)-prolinol and converted into pandamarilactonine-A and -B.

Pandanus amaryllifolius Roxb. (Pandanaceae), commonly named screw pine, is a small species of about 50 cm characterised by very sweet smelling leaves. It is cultivated extensively through tropical and subtropical regions and traditionally used as a food flavouring additive and in folk medicine for strengthening the heart and as a diuretic.[1] The two diastereoisomeric pyrrolidine alkaloids pandamarilactonine-A (**1**) and -B (**2**) (Fig. 1) were recently isolated by Takayama and co-workers from this plant.[2] The isolated *erythro* isomer **1** was dextrorotatory with $[\alpha]_D^{23}=+35$ (*c* 4.37, $CHCl_3$), while the *threo* isomer **2** was optically inactive. Besides their isolation and structural characterisation, the authors described a total synthesis of racemic **1** and **2** passing through the key symmetrical amine **3**, which was considered as a plausible biogenetic precursor of pandamarilactonines. A reinvestigation of the alkaloidal fraction of the plant led to the isolation of compound **3**, which was named pandamine,[3] reinforcing the biogenetic hypothesis. Additionally, another pair of diastereomeric alkaloids with a closely related structure, norpandamarilactonine-A (**4**) and -B (**5**) were also found in racemic form as minor bases in fresh leaves of the plant[4] and the *threo* isomer *rac*-**5** was synthesised from 2-pyrrolidone and 3-methyl-2(5*H*)-furanone, following the protocol developed by Martin et al.[5] Here we present an alternative synthesis of both norpandamarilactonines **4** and **5** and their conversion into pandamarilactonines **1** and **2** by alkylation with the suitable partner **6**.

The preparation of **6** (Scheme 1) started from the hydroxydithiane **7**,[6] which after silylation and removal of the thioacetal function furnished the aldehyde **8** in

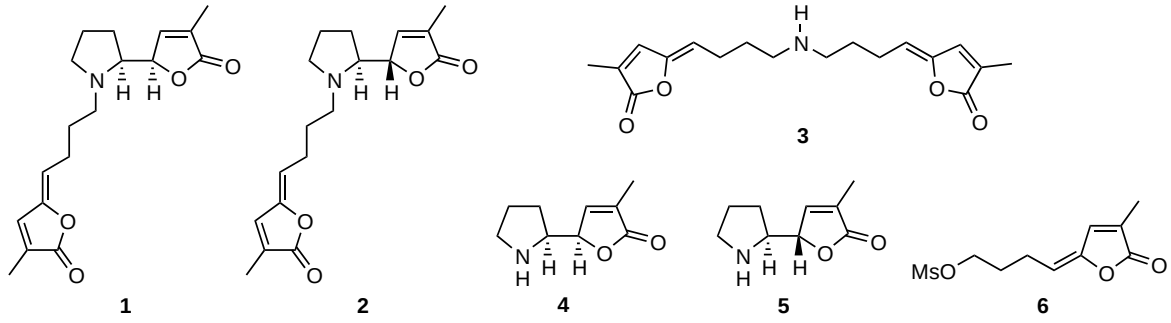

Figure 1.

Keywords: *Pandanus* alkaloids; total synthesis; norpandamarilactonine; pandamarilactonine.
* Corresponding author. Tel.: 34-935811853; fax: 34-935811265; e-mail: marta.figueredo@uab.es

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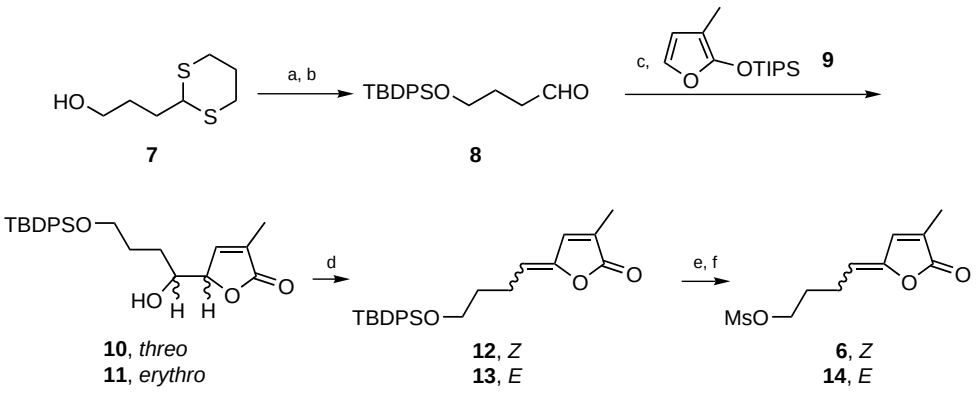
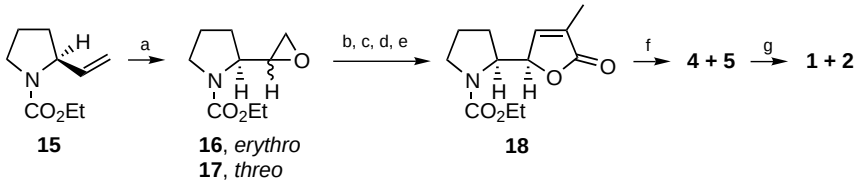


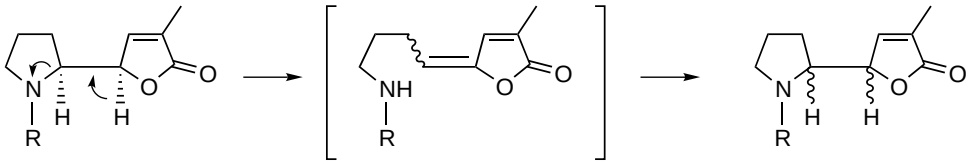
Scheme 1. *Reagents and conditions*: (a) TBDPSCl, Im, DMF, rt, 96%; (b) $CaCO_3$, MeI, CH_3CN–H_2O, rt, 92%; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C, 2 h, 82%; (d) TMSCl, DBU, $CHCl_3$, reflux, 1 h, 94%; (e) Bu_4NF, THF, rt, 3 h, 86%; (f) MsCl, pyr, CH_2Cl_2, rt, overnight, 74%.

88% yield. The vinylogous Mukaiyama reaction[7] of **8** with the silyloxyfuran **9**, prepared by Martin methodology,[5] delivered a 7:1 mixture of the *threo* and *erythro* alcohols **10** and **11** in 82% yield. Treatment of a 6:1 mixture of these diastereomeric alcohols with TMSCl/DBU in refluxing chloroform gave the olefins **12** and **13** in 94% yield after purification by silica gel chromatography. Provided that an antiperiplanar E2 type mechanism is operating during the elimination step, the *Z* olefin **12** should be formed from the *threo* alcohol **10** and the *E* olefin **13** from the *erythro* alcohol **11**, but **12** and **13** were isolated in a ca. 3:1 ratio, denoting some extent of *Z*/*E* isomerisation. The olefins were finally converted by standard procedures into the sulfonates **6** and **14**, which could be chromatographically separated. Although interconversion between the two isomeric sulfonates was not detected, their stability is quite limited due to the easy hydrolysis of the lactone and the sulfonate **6** should be transformed rapidly.

The synthesis of the pyrrolidine fragment (Scheme 2) was accomplished starting from the carbamate **15**, easily prepared from (*S*)-prolinol.[8] Oxidation of **15** with MCPBA produced the two oxiranes **16**, $[\alpha]_D^{20}=-13$ (*c* 1.3, EtOH), and **17**, $[\alpha]_D^{20}=-42$ (*c* 1.3, EtOH), in 77% total yield and *erythro*/*threo* ratio 1.5:1. The oxiranes were separated and the major isomer **16** was converted into the *erythro* α-methyl butenolide **18**, $[\alpha]_D^{20}=-33$ (*c* 0.9, EtOH), by a three-step protocol,[9] consisting in addition to the dianion of 2-phenylselenopropionic acid,[10] followed by acid induced lactonisation and oxidation of the selenide function with consequent thermal elimination, with an overall 61% yield. Cleavage of the carbamate with TMSI in refluxing chloroform took place with concomitant epimerisation of the stereogenic centre of the lactone moiety, furnishing a ca. 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 respectively identical to those reported for natural norpandamarilactonine-B (**5**) and -A (**4**).[4] The specific rotation measured for **4** was $[\alpha]_D^{20}=-7$ (*c* 1.5, $CHCl_3$) and for **5** $[\alpha]_D^{20}=-3$ (*c* 2.6, $CHCl_3$). We suspected that the reason for such low optical activity values could be that racemisation had occurred in some extent. Thus, the configurational instability of these alkaloids was confirmed when a mixture of **4** and **5** was treated with an equimolar amount of freshly prepared mesylate **6** in DMF in the presence of pyridine at 60°C. Under these conditions, pandamarilactonines **1** and **2** were slowly formed in a ca. 1:1 ratio. After 3 days, the reaction mixture was treated and purified by flash chromatography over silica gel. The first eluted isomer showed ^{1}H NMR spectrum identical to that reported for natural pandamarilactonine-B (**2**), while the second matched the spectral data reported for pandamarilactonine-A (**1**).[2] The overall isolated yield was 44%. Analysed 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 racemise either,[2] pandamarilactonine-A isolated from natural sources shows a low 26% e.e. and pandamarilactonine-B is a racemate. In neutral or basic media, a mechanism involving β-elimination–conjugate addition[11] (Scheme 3) may easily cause the configurational instability of these alkaloids.



Scheme 2. *Reagents and conditions*: (a) MCPBA, $CHCl_3$, rt, 24 h, 77%; (b) separation of diastereoisomers; (c) $PhSeCHCH_3CO_2H$, LDA (2 equiv.), THF, 0°C to rt, 1.5 h; (d) AcOH, THF, reflux, 16 h; (e) H_2O_2, AcOH, 0°C, 45 min, 61% from **16**; (f) TMSI, $CHCl_3$, reflux, 5 h, 84%; (g) **6**, pyr, DMF, 60°C, 3 days, 44%.



Scheme 3.

Acknowledgements

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