FIRST TOTAL SYNTHESIS OF THE *PANDANUS* ALKALOIDS, PANDAMARILACTAM-3Y AND -3X

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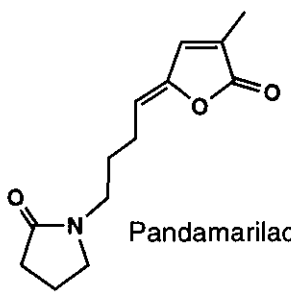
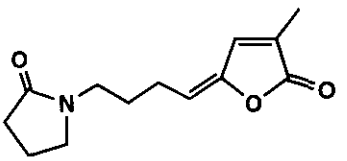
Abstract - Total synthesis of two *Pandanus* alkaloids, pandamarilactam-3y and -3x, having a γ-alkylidenebutenolide moiety, was accomplished via aldol-type condensation/β-elimination expedient.

The genus *Pandanus* belonging to the family Pandanaceae comprises about 500 species which distribute in tropical and subtropical regions. Several *Pandanus* species are recognized as medicinal plants.[1] Recently, a new skeletal type of alkaloids, which features the γ-alkylidene-α,β-unsaturated γ-lactone or γ-alkylidene-α,β-unsaturated γ-lactam moiety in the molecule, has been isolated from *P. amaryllifolius*.[2-4] Since the *Pundanus* plants are potentially valuable as candidates for new medicinal resources, we have started chemical investigation as well as synthetic studies on the constituents of *Pandanus* plants. At the beginning of our synthetic studies toward various *Pandanus* alkaloids, we initiated an efficient synthesis of pandamarilactam-3y (**1**) and -3x (**2**), which are the simplest members among the six congeners known. Described herein is the first total synthesis of **1** and **2**, which features stereoselective construction of the (*Z*)-2-methyl-4-ylidenebutenolide moiety.

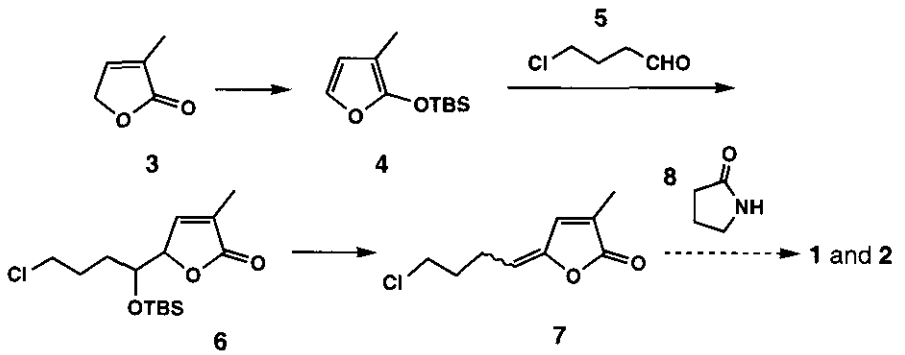


Pandamarilactam-3y (**1**)



Pandamarilactam-3x (**2**)

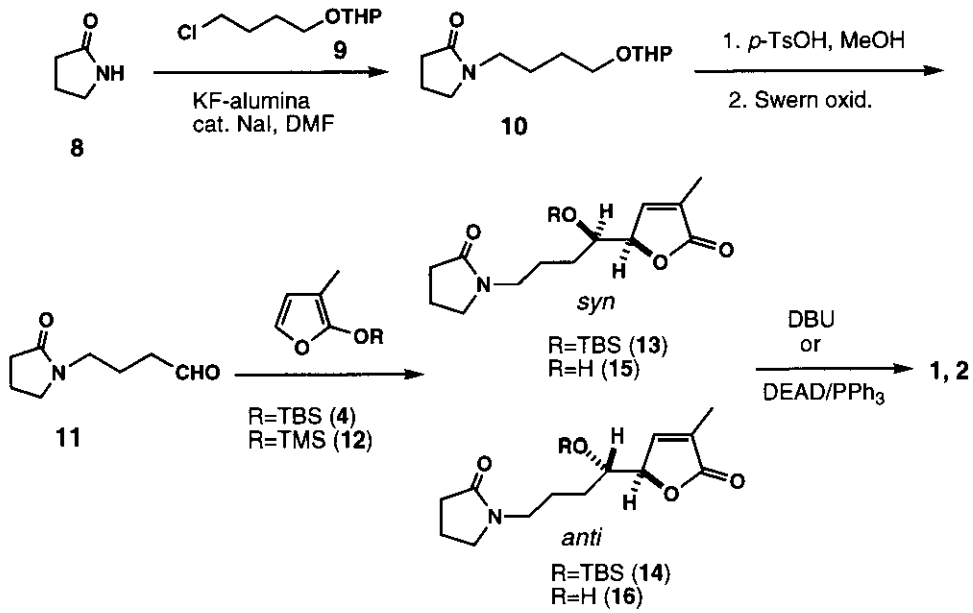
For total synthesis of **1** and **2**, we initially planned the conjunction of 2-pyrrolidinone (**8**) with a butenolide segment (**7**), which is a universal subunit in five *Pandanus* alkaloids. For construction of this substructure, the known 3-methylfuran-2(5H)-one (**3**)[5] was converted to siloxyfuran (**4**) using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and then subjected to aldol-type condensation with 4-chlorobutanal (**5**). By using TBSOTf as a catalyst,[6] a diastereomeric mixture of adducts (**6**) was obtained in 42% yield. Treatment of the mixture of siloxy adducts with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[6] in $CHCl_3$ at 50℃ for 3 h afforded the requisite γ-alkylidenebutenolides (**7**) as a *Z*:*E*-mixture (ratio 77:23) in 78% yield. However, the chlorobutenolides (**7**) were unstable in solution and actually decomposed under the various reaction conditions in attempts to condense with 2-pyrrolidinone.



Scheme 1

For this reason, the synthetic route was changed, in which construction of the γ-alkylidenebutenolide moiety would be conducted in the final step of the synthesis. *N*-Alkylation of 2-pyrrolidinone (**8**) with tetrahydropyranyl (THP) 4-chrolobutanol (**9**) was efficiently carried out using potassium fluoride on alumina[7] in the presence of a catalytic amount of sodium iodide to yield the tertiary amide (**10**) in 76% yield. After removal of the THP ether in **10**, the resultant free alcohol was converted to aldehyde (**11**) in 85% yield by Swern oxidation. The aldol reaction of aldehyde (**11**) with siloxyfuran (**4**) using tetrabutylammonium fluoride (TBAF) (10 mol %) in the presence of TBSOTf gave a mixture of adducts in 37% yield [*syn* (**13**): *anti* (**14**) = 3:7][8] along with the desilylated alcohols (**15** and **16**) (3:7)[8] in 11% yield. When boron trifluoride etherate (BF_3•Et_2O) was employed,[9] the *syn* adduct (**15**)[10] was predominantly[11] (33:1) obtained in 48% yield together with 20% of the recovered starting material (**11**). To improve the chemical yield, the TBS group in **4** was replaced by a trimethylsilyl (TMS) function in anticipation that the aldol condensation would proceed more efficiently. Condensation of aldehyde (**11**) with 2-trimethylsiloxy-3-methylfuran (**12**) in the presence of BF_3•Et_2O gave the adducts as a *syn* (**15**) and *anti* (**16**) mixture (ratio 88:12) in 80% yield. Finally, installation of the *exo*-double bond, *i.e.*, construction of the γ-alkylidenebutenolide moiety, was performed. Treatment of a mixture of the *O*-silylated adduct [(**13** and **14**) (3:7 ratio)] with DBU gave γ-alkylidenebutenolides in 92% yield in a 9:1 ratio of *Z* and *E* mixture. This

result was ascribable to the E1cb mechanism[6,12] favoring the formation of the thermodynamically more stable isomer. Dehydration of the major aldol adduct (**15**) using excess of DEAD/PPh_3[9] resulted in the *anti*-elimination to form exclusively the *Z*-isomer (**1**) in 82% yield. The geometric mixture obtained above by the elimination reaction using DBU could be purified by careful HPLC separation using C18-silica column chromatography with MeCN/H_2O as eluent. The major and minor isomers were respectively identical with the natural products, pandamarilactam-3y (**1**) and -3x (**2**), by comparison of high-resolution MS, ^{1}H- and ^{13}C-NMR data with those in the literature.[4] Synthetic studies of other *Pandanus* alkaloids are currently being made in our laboratory.



Scheme 2

ACKNOWLEDGMENTS

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8 The *syn/anti* ratio of the aldol adducts was determined by ^{1}H-NMR spectra (see ref. 10).

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10 *syn* **15**: ^{1}H-NMR ($CDCl_3$, δ): 7.07 (1H, dq, *J*=3.7, 1.7 Hz), 4.83 (1H, ddd, *J*=7.1, 3.7, 1.7 Hz), 3.79 (1H, m), 3.27 (1H, m), 3.35-3.50 (3H, m), 3.30 (1H, d, *J*=7.0 Hz), 2.40 (2H, dd, *J*=8.6, 7.8 Hz), 2.04 (2H, m), 1.93 (3H, dd, *J*= 1.7, 1.7 Hz), 1.60-1.80 (2H, m), 1.40-1.60 (2H, m). ^{13}C-NMR ($CDCl_3$, δ): 175.5, 174.0, 146.1, 131.2, 84.0, 71.6, 47.3, 42.1, 31.0, 29.1, 23.7, 17.8, 10.7. *anti* **16**: As this compound could not be purified from the mixture of **15** and **16**, the ^{1}H- and ^{13}C-NMR signals of **16** were assigned using the data obtained from the mixture (**15** and **16**). ^{1}H-NMR ($CDCl_3$, δ): 7.23 (1H, dq, *J*=3.7, 1.5 Hz), 4.71 (1H, ddd, *J*=8.1, 3.7, 1.8 Hz), 3.67 (1H, m), 3.82 (1H, d, *J*=6.1 Hz), 1.93 (1H, dd, *J*=1.8, 1.5 Hz). ^{13}C-NMR ($CDCl_3$, δ): 175.8, 174.2, 147.0, 130.7, 83.8, 72.5, 47.4, 42.3, 31.0, 29.6, 23.9, 17.9, 10.7. The *syn/anti* stereochemistry was assigned on the basis of i) mechanistic consideration,[10] and ii) the fact that compound (**15**) gave the *Z*-olefin (**1**) under the E2 elimination condition (DEAD/PPh_3). By desilylation of the aldol adducts [(**13** and **14**) (3:7)] using TBAF, the corresponding alcohols (**15** and **16**) were obtained in the ratio of 3:7, resulting in the demonstration of the relative stereochemistry in **13** and **14**.

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