

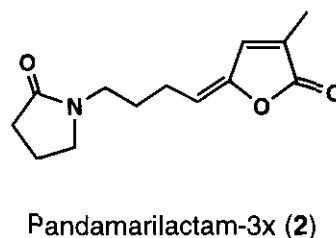
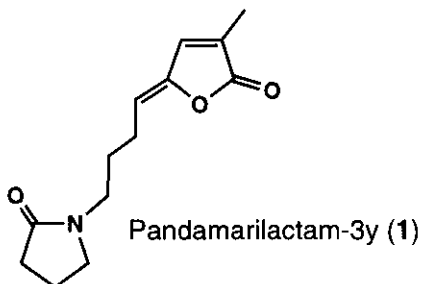
FIRST TOTAL SYNTHESIS OF THE *PANDANUS* ALKALOIDS, PANDAMARILACTAM-3Y AND -3X

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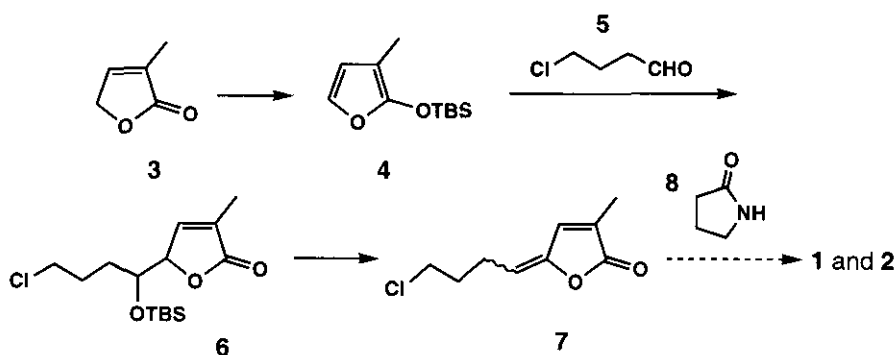
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Abstract - Total synthesis of two *Pandanus* alkaloids, pandamarilactam-3y and -3x, having a γ -alkylidenebutenolide moiety, was accomplished via aldol-type condensation/ β -elimination expedient.

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 *Pandanus* 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.



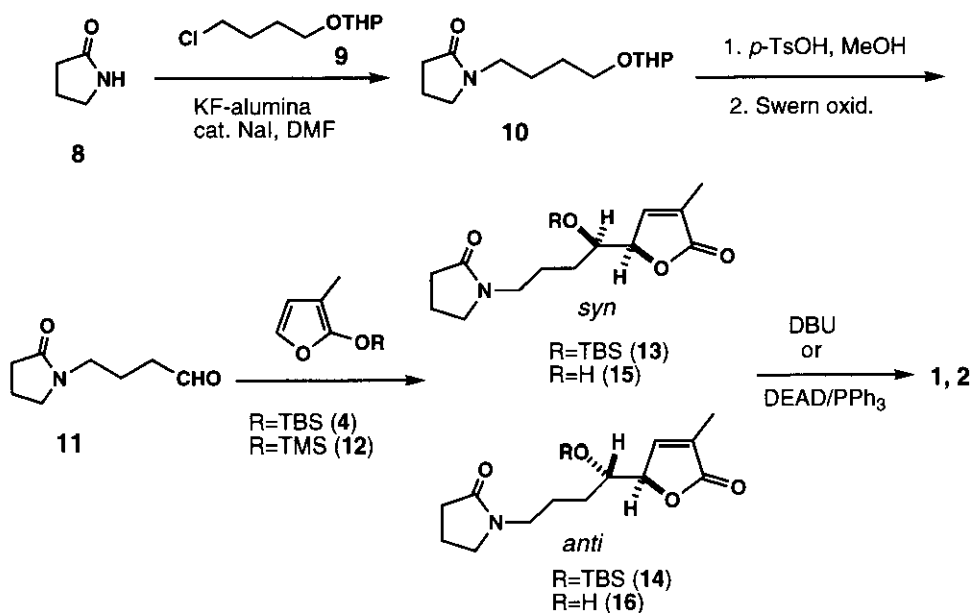
For total synthesis of **1** and **2**, we initially planned the conjunction of 2-pyrrolidinone (**8**) with a butenolide segment (**7**), which is a universal subunit in five *Pandanus* alkaloids. For construction of this substructure, the known 3-methylfuran-2(5H)-one (**3**)⁵ was converted to siloxyfuran (**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 CHCl₃ at 50°C 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-chlorobutanol (**9**) was efficiently carried out using potassium fluoride on alumina⁷ 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 (BF₃·Et₂O) was employed,⁹ the *syn* adduct (**15**)¹⁰ was predominantly¹¹ (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-trimethylsilyloxy-3-methylfuran (**12**) in the presence of BF₃·Et₂O 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/PPh₃⁹ 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/H₂O 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, ¹H- and ¹³C-NMR data with those in the literature.⁴ Synthetic studies of other *Pandanus* alkaloids are currently being made in our laboratory.



Scheme 2

ACKNOWLEDGMENTS

This work was supported in part by Grant-in-Aid (No. 10877349) for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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- 8 The *syn/anti* ratio of the aldol adducts was determined by $^1\text{H-NMR}$ spectra (see ref. 10).
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- 10 *syn* **15**: $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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 $^1\text{H-}$ and $^{13}\text{C-}$ NMR signals of **16** were assigned using the data obtained from the mixture (**15** and **16**). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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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Received, 6th July, 1998