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Novel stereoselective synthesis of enantiopure (+)-*N*-Boc-norpandamarilactonine-A, the intermediate for pandamarilactonines

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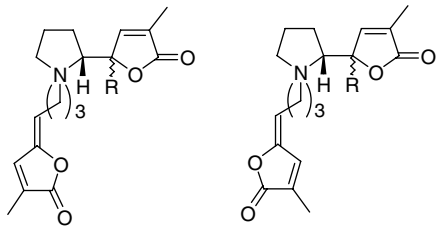
Abstract—A novel synthesis of enantiopure *N*-Boc-norpandamarilactonine-A was established by employing a double ring-closing metathesis of a tetraene derivative, as a key step, where two five-membered rings were constructed in one step. *N*-Boc-Norpandamarilactonine-A was also converted to *ent*-norpandamarilactonine-A, and subsequently to pandamarilactonine-A and B.

The genus *Pandanus* is widely distributed in tropical and subtropical regions, and is used in traditional folk medicine for strengthening the heart and for hypoglycemic purpose.[1] Pandamarilactonine-A **1** and -B **2**, isolated from *Pandanus amaryllifolius* Roxb. (Pandanaceae),[2] are alkaloids having unique structural features with a pyrrolidinyl-α,β-unsaturated γ-lactone moiety (Fig. 1).

Their structures including relative stereochemistries were first proposed on the basis of spectroscopic analyses by Takayama and co-workers.[2] They also isolated from the same plant two diastereoisomeric compounds, pandamarilactonine-C **3** and -D 4[3] (Fig. 1). Moreover,



Pandamarilactonine-A **1** R = α-H Pandamarilactonine-C **3** R = α-H
Pandamarilactonine-B **2** R = β-H Pandamarilactonine-D **4** R = β-H

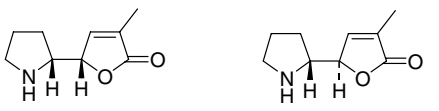
Figure 1. Structures of pandamarilactonines.

norpandamarilactonine-A **5** and -B **6** have been found in the leaves of *P. amaryllifolius* as natural products[4] (Fig. 2).

Very recently, the same group has determined the absolute configuration of pandamarilactonine-A by the total synthesis of its enantiomer.[5] Interestingly, it is known that pandamarilactonine-A comprised a mixture enriched with the (+)-enantiomer, while its diastereomeric pandamarilactonine-B occurred as a racemate, probably due to its instability.

In relation to our synthetic work on biologically active natural products by employing an intramolecular RCM,[6] we are also interested in the synthesis of pandamarilactonine-B **2** via norpandamarilactonine-A **5**, hopefully in optically pure form.[5,7] Our basic strategy for the synthesis of pandamarilactonine-B via norpandamarilactonine-A is outlined in Scheme 1.

The initial plan was to prepare *N*-Boc-pandamarilactonine-A via double cyclization of a tetraene derivative **B** by ring-closing metathesis.[8] This process would



Norpandamarilactonine-A **5** Norpandamarilactonine-B **6**

Figure 2. Structures of norpandamarilactonines.

Keywords: *N*-Boc-pandamarilactonine-A; Double ring-closing metathesis; Pandamarilactonine-A; Pandamarilactonine-B; Ruthenium catalyst.
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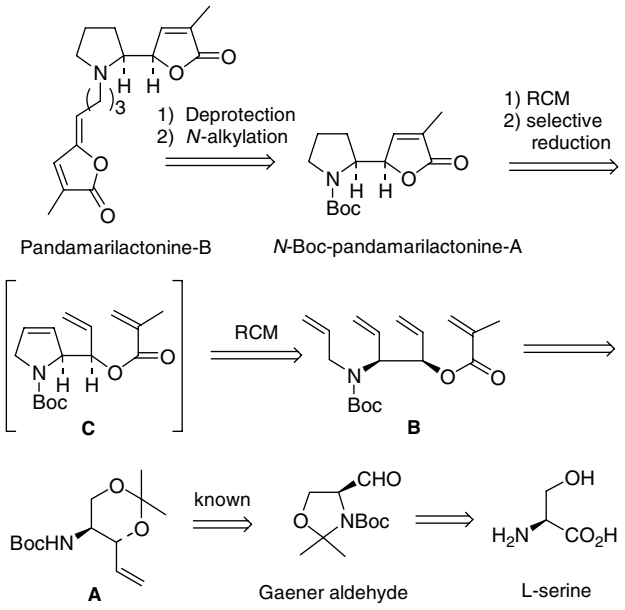


Scheme 1. Retrosynthetic analysis of *ent*-pandamarilactonine-B.

proceed through the formation of a dihydropyrrole **C**, followed by further cyclization of the remaining diene to a butenolide. Such double cyclization of a tetraene derivative constructing two five-membered rings, simultaneously, has been little focused on the synthesis of natural products. Moreover, the stereochemistry presented in a tetraene compound would be intact under the reaction conditions employed, to lead to the desired compound, stereoselectively, in an optically active form. Tetraene derivative **B** would be derived from the known amine **A** by manipulation of the functional groups.

To prepare the requisite substrates for the norpandamarilactonine-A project, we decided to employ a readily available L-serine as the chiral starting material, since the absolute configuration of pandamarilactonine-B had not been determined yet, when we started this synthesis.

L-Serine methyl ester hydrochloride was converted to the known compound **A**,[9] which, on allylation with allyl iodide and NaH in DMF gave *N*-allyl compound **7**.[10] Removal of the acetonide in **7** on treatment with *p*-toluenesulfonic acid gave diol **8**. After selective protection of the primary alcohol of **8** with *tert*-butyldimethylsilyl chloride, the resulting silyl ether **9** was protected as its MOM ether **10**, which was further converted to primary alcohol **11** by treatment with TBAF. It was appreciated that the oxidation of **11** with Dess–Martin periodinane proceeded smoothly to give aldehyde **12**, which, on methylenation with methyltriphenylphosphonium bromide and *n*-BuLi in the usual manner afforded the desired triene **13**, in good yield.

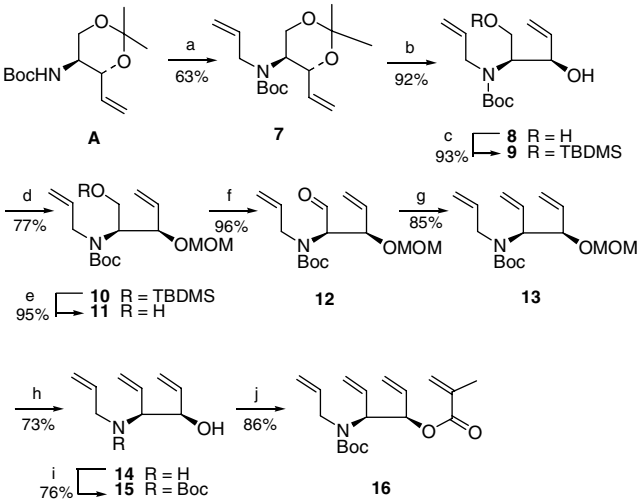
After the two-step manipulation of the protecting groups in **13**, involving removal of the Boc and MOM groups by acid hydrolysis, followed by protection of the resulting amino group of **14** with Boc_2O, the resulting secondary alcohol **15** was esterified with methacrylic acid in the presence of DCC and DMAP to provide the desired tetraene derivative **16** (Scheme 2).

With the requisite tetraene available, a study was made for the best conditions for a double RCM.[11]

First, we attempted a double RCM for **16** using 10 mol % of Grubbs' 2nd-generation ruthenium catalyst[12] in benzene at 80 °C for 20 h; however, the desired compound **17** was isolated in only 2% yield. The major products were found to be mono-cyclized products **18** and **20**, in 25% and 25% yields, respectively (Table 1, entry 1). When this reaction was carried out using 10 mol % of the Hoveyda catalyst[13] in benzene at 80 °C for 20 h, bicyclic tetrahydropyridine derivative **19** was isolated as the major product, in 28% yield, together with the desired compound **17** (6%), pyrrolidine derivative **18** (2%), and tetrahydropyridine derivative **20** (24%) (Table 1, entry 2). Interestingly, a similar reaction of **16** with 10 mol % of the Hoveyda catalyst at 60 °C gave the desired compound **17**, in 73% yield, together with **20** (23%) (Table 1, entry 4). Even with the use of 5 mol % of the Hoveyda catalyst, RCM of **16** in benzene at 60 °C for 20 h furnished butenolide **17**, in 24% yield accompanied with pyrrolidine **18** in 44% yield (Table 1, entry 3). These results obviously indicated that the products ratio depended on the reaction temperature, and butenolide **17** might be the kinetically-controlled product, whereas **19** would be the thermodynamically-controlled product.

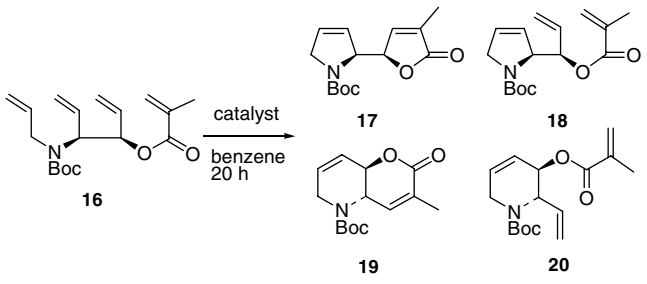
To prove this hypothesis, butenolide **17** was subjected to further RCM in benzene at 80 °C for 20 h in the presence of 10 mol % of the Hoveyda catalyst to give **19** in 82% yield as expected (Scheme 3).

On screening a variety of reaction conditions for RCM of **16**, we found that the use of 10 mol % of the Grela

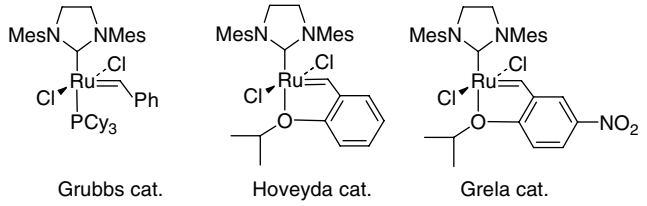


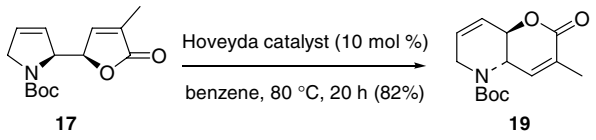
Scheme 2. Reagents and conditions: (a) allyl iodide, NaH, DMF, 0 °C to rt, 2 h; (b) *p*-TsOH, MeOH, rt, 3 h; (c) TBDMSCl, imidazole, DMF, rt, 3 h; (d) MOMCl, $^{i}Pr_2NEt$, DMAP, CH_2Cl_2, 0 °C to rt, 8 h; (e) TBAF, THF, rt, 10 h; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h; (g) $CH_3P^{+}Ph_3Br^{-}$, *n*-BuLi, THF, −78 °C, 8 h; (h) 10% HCl, MeOH, 70 °C, 2 h; (i) Boc_2O, Et_3N, THF, rt, 8 h; (j) methacrylic acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 16 h.

Table 1. RCM for tetraene **16**



Entry	Catalyst (mol %)	Temperature (°C)	Product yield (%)			
			17	18	19	20
1	Grubbs (10)	80	2	25	7	25
2	Hoveyda (10)	80	6	2	28	24
3	Hoveyda (5)	60	24	44	0	22
4	Hoveyda (10)	60	73	3	0	23
5	Grela (10)	rt	14	64	0	22
6	Grela (5)	60	70	5	0	25
7	Grela (10)	60	76	2	0	22



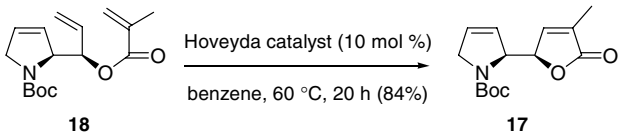


Scheme 3. Conversion of **17**–**19**.

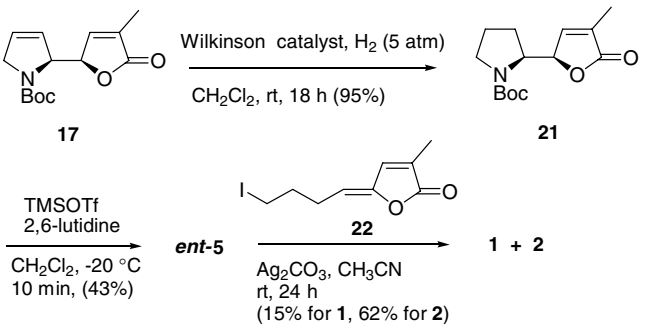
catalyst[14] in benzene at 60 °C for 20 h afforded the desired compound **17**, in 76% yield (Table 1, entry 7). Keeping the reaction temperature at 60 °C, butenolide **17** could be isolated from the reaction mixture even with the use of 5 mol % of the Grela catalyst, in 70% yield (Table 1, entry 6). When this RCM was carried out at room temperature in the presence of 10 mol % of the Grela catalyst for 20 h, mono-cyclized pyrrolidine **18** was isolated as the major product, in 64% yield (Table 1, entry 5). The results obtained for RCM of **16** are summarized in Table 1.

The observed formation of tetrahydropyridine derivative **20** would be rationalized by assuming that the Ru-carbenoid, firstly generated from a reaction of the terminal olefin in the *N*-allyl moiety with ruthenium catalyst, would react with another mono-substituted olefin in the acylated allyl alcohol group, competitively.

Mono-cyclized pyrrolidine **18** could also be converted to **17** by further reaction with 10 mol % of the Hoveyda catalyst in benzene at 60 °C for 20 h, in 84% yield (Scheme 4). The structure of **17** was unambiguously determined by X-ray crystallographic analysis.[15]



Scheme 4. Conversion of **18**–**17**.



Scheme 5. Synthesis of *N*-Boc-norpandamarilactonine-A and its conversion to pandamarilactonines.

Selective reduction of the double bond in the pyrrolidine ring of **17** was successfully achieved by catalytic hydrogenation with the Wilkinson catalyst under 5 atm of hydrogen to afford (+)-*N*-Boc-norpandamarilactonine-A **21**, mp 75–77 °C. $[\alpha]_D$ −51.1 (*c* 1.0, $CHCl_3$), in 95% yield (Scheme 5).

Treatment of **21** with trimethylsilyl triflate provided *ent*-norpandamarilactonine-A ***ent*-5**, $[\alpha]_D$ +55.0 (*c* 0.82, $CHCl_3$) {lit.,[5] +80.2 (*c* 0.79, $CHCl_3$)}, as the sole product, which, however, gradually became a mixture with norpandamarilactonine-B **6**, due to its rapid partial epimerization.[16] Although a similar instability of norpandamarilactonines was already observed in the previous syntheses,[5,7] conversion of ***ent*-5** to pandamarilactonine-B **2** by coupling with iodide **22**,[3] was attempted according to Takayama's procedure,[5] and we could isolate both racemic pandamarilactonine-A and optically active pandamarilactonine-B in 15% and 62% yields, respectively. The spectroscopic data of the synthesized pandamarilactonine-B, $[\alpha]_D$ +13.1 (*c* 0.72, $CHCl_3$), were identical with those provided by Professor Takayama.

In summary, we were able to develop a novel chiral synthesis of (+)-*N*-Boc-norpandamarilactonine-A in an enantiopure form by means of RCM of the tetraene derivative, where the desired bis-five-membered rings were constructed in one step, in high yield. It is noteworthy that the cyclization product ratios depend on the reaction conditions, especially on reaction temperature. The desired bis-five-membered compound **17** is supposed to be a kinetically-controlled product.

Acknowledgements

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norpandamarilactonines and pandamarilactonines. This work was supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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15. Crystal data for **20**: Mp 85–87 °C. $C_{14}H_{19}NO_4$; $M = 265.31$; $D_c = 1.201$ g/cm^3; orthorhombic, space group $P2_12_12_1$; $a = 15.4991\ (15)$, $b = 15.9956\ (14)$, $c = 5.9166\ (7)$; $Z = 4$, $R = 0.0567$, $R_w = 0.0680$.
16. The ^{1}H NMR spectrum of the synthesized *ent*-norpandamarilactonine-A was identical with that of the natural product provided by Prof. Takayama. However, when this compound was allowed to stand at room temperature for 1 h, the presence of a mixture of ***ent*-5** and ***ent*-6** was confirmed in the ^{1} NMR spectrum, in a ratio of ca. 5:2.