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Total Synthesis of Lamellarins D, H, and R and Ningalin B

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ABSTRACT

A concise total synthesis of lamellarins D (7 steps), H (7 steps), and R (5 steps) and ningalin B (5 steps) is achieved starting from the corresponding aldehydes and amines. The synthesis features three oxidative reactions as key steps in a biomimetic manner, involving an AgOAc-mediated oxidative coupling reaction to construct the pyrrole core, a $Pb(OAc)_4$-induced oxidative cyclization to form the lactone, and Kita's oxidation reaction to form the pyrrole−arene C−C bond.

Since the first isolation of lamellarins A−D (Figure 1) by Faulkner and co-workers in 1985,[1] more than 70 different lamellarins and related naturally occurring pyrrole-derived alkaloids have been isolated from diverse marine organisms such as mollusks, ascidians, and sponges. The lamellarins and related pyrrole-derived alkaloids have shown promising biological activities such as antitumor activity, reversal of multidrug resistance (MDR), and HIV-1 integrase inhibition activity.[2] In light of their fascinating novel structures, intriguing biological properties, and the difficulty in obtaining large quantities from natural sources, the lamellarins and related alkaloids have attracted considerable attention from organic and medicinal chemists. Several research groups, notably those of Steglich,[3] Banwell,[4] Iwao,[5] Boger,[6] Ruchirawat,[7] Faulkner,[8] Gupton,[9] Handy,[10] and Álvarez,[11] have reported the total synthesis of lamellarins and related pyrrole-derived alkaloids.[12] These syntheses can be divided into two

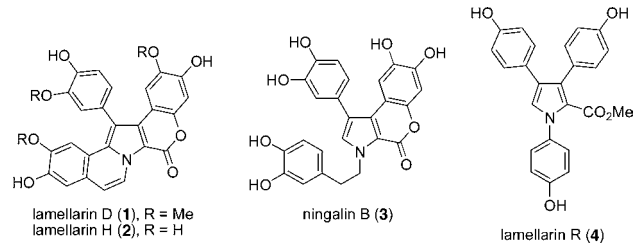

Figure 1. The structures of lamellarins D, H, and R and ningalin B.

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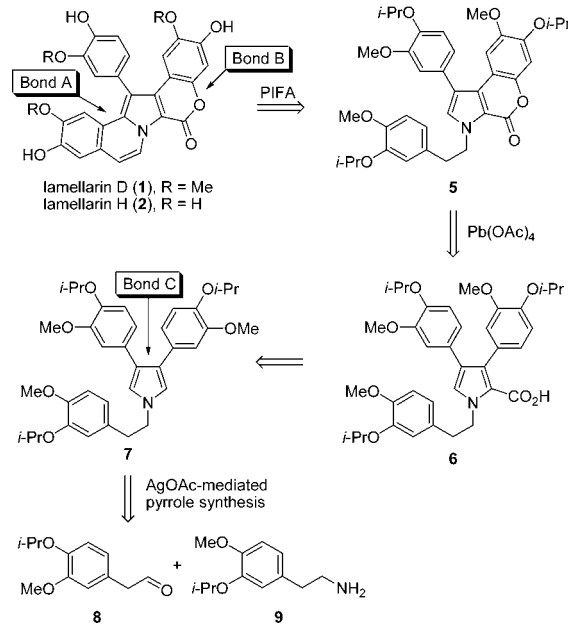
broad categories: one is the formation of the pyrrole core as the key step, and the other is the functionalization of the pre-existing pyrrole.

Recently, we developed a simple and efficient method for the synthesis of 1,3,4-trisubstituted or 3,4-disubstituted pyrroles, especially 3,4-diaryl-substituted derivatives, from simple, readily available aldehydes and amines (anilines) by using an AgOAc-mediated oxidative coupling reaction in a one-pot manner.[13] Herein, we reported a concise total synthesis of lamellarins D, H, and R and ningalin B by using this novel pyrrole synthesis approach as the key step in a biomimetic manner.

From the biosynthesis point of view, the pentacyclic forms of lamellarin D and its siblings are generated from their simpler counterparts (analogues to **7** or **6**) through two consecutive oxidative cyclizations that lead to the formation of bonds A and B as indicated in structure **1** (Scheme 1).[3,4d]

Scheme 1. Retrosynthesis of Lamellarins D and H



Also, the simpler conterparts are generated from DOPA (2-amino-3-(3′,4′-dihydroxyphenyl)propionic acid) metabolic products by oxidative coupling (formation of bond C).[3,14] Therefore, biosynthetically, the skeleton of the lamellarins is formed mainly through oxidative coupling reactions, and the lamellarins proper represent higher oxidation states. Inspired by the lamellarin biosynthesis pathway, our retrosynthetic analysis of **1** and **2** is outlined in Scheme 1. Lamellarins D (**1**) and H (**2**) could be synthesized from **5** by using PIFA oxidation according to Iwao's work.[5b] Lactone **5** was envisioned by $Pb(OAc)_4$-mediated oxidative lactonization of acid **6**.[3a,b] The acid **6** could be formed by the Vilsmeier−Haack reaction of **7**, followed by Lindgren oxidation of the corresponding aldehyde.[15] The key intermediate pyrrole **7** could be obtained from an AgOAc-mediated oxidative coupling reaction from aldehyde **8** and amine **9**.

The synthesis of aldehyde **8** and amine **9** is shown in Scheme 2. Isopropyl protection of the hydroxyl group of the commercially available vanillin afforded **10** in 97% yield. Wittig reaction of *O*-isopropylvanillin (**10**) with the ylide generated from (methoxymethyl)triphenylphosphonium chloride and *t*-BuOK afforded the enol ether **11** in 82% yield as an *E*/*Z* mixture. Acid-catalyzed hydrolysis of **11** provided crude aldehyde **8**, which was used for the pyrrole synthetic step without further purification due to its instability. Amine **9** was prepared from commercially available isovanillin following literature procedures.[3b,5b]

With aldehyde **8** and amine **9** in hand, they were subjected to the crucial AgOAc-mediated oxidative coupling reaction,

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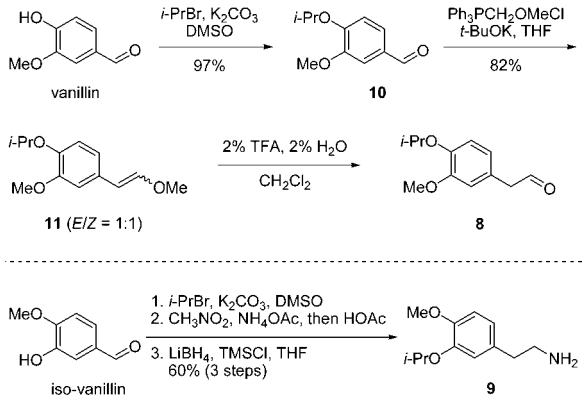
Scheme 2. Synthesis of Aldehyde **8** and Amine **9**

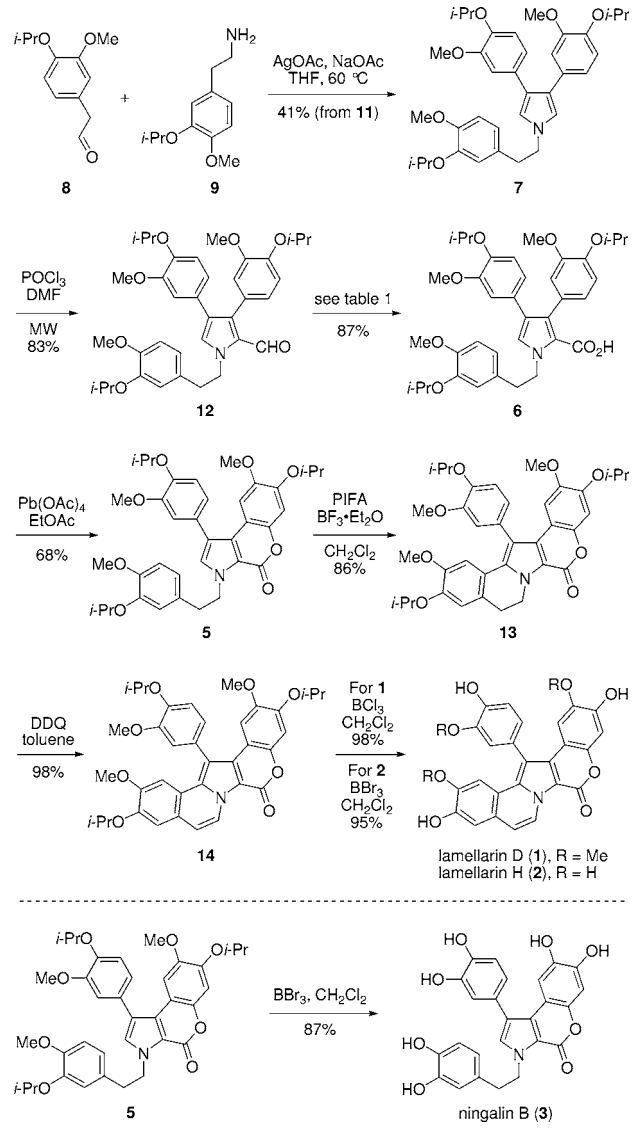


which afforded the desired key intermediate, pyrrole **7**, in 41% yield (two steps from enol ether **11**) (Scheme 3). Vilsmeier−Haack formylation of pyrrole **7** under traditional heating conditions did not yield the desired formylpyrrole **12**, resulting in either no reaction (60 °C) or decomposition of the starting material (at reflux). Gratifyingly, the microwave-accelerated Vilsmeier−Haack reaction provided **12** in 83% yield.[9b]

The stage was now set for the oxidation of the formyl group to the carboxylic group. We soon realized that it was a difficult reaction. After many attempts, we found that Lindgren oxidation could give the desired carboxylic acid **6** in low conversion. Thus, a variety of reaction conditions (mainly the cosolvent and temperature) were examined, and some of the representative results are shown in Table 1. The solvent played an important role in the reaction. When DMSO/H_2O was used as the solvent, no reaction occurred (Table 1, entry 1). When THF/*t*-BuOH/H_2O (4:1:4) was used, the desired carboxylic acid **6** was obtained in 21% yield (29% conversion), accompanied by a substantial amount of 5-chlorinated side product **15** (Table 1, entry 2). We reasoned that the 5-chlorinated product **15** was produced due to the hypochlorite, which was formed in the reaction and was not completely removed by the scavenger 2-methylbut-2-ene from the reaction mixture. Reducing the reaction temperature might decrease the formation of the byproduct **15** (Table 1, entry 3). As anticipated, when the reaction was run at 10 °C, it provided acid **6** as the sole product (Table 1, entry 4) although the conversion was still low. Further optimization of the reaction indicated that the ratio of the cosolvent dramatically affected the conversion of **12**. When THF/*t*-BuOH/H_2O (3:3:1) was used, **12** was completely consummed and converted to the desired carboxylic acid **6** in 87% yield (Table 1, entry 5).

Subsequent reaction of the carboxylic acid **6** with $Pb(OAc)_4$ in refluxing EtOAc furnished the known lactone **5** in 68% yield,[3a,b] which was the key intermediate in Iwao's total synthesis of lamellarin D. According to the protocol reported by Iwao, compound **5** was readily converted to lamellarin D via intramolecular oxidative biaryl coupling of

Scheme 3. Synthesis of Lamellarins D and H and Ningalin B



5 under Kita's conditions,[5b,16] DDQ oxidation, and selective deprotection of the isopropyl group of **14** with BCl_3. Cleavage of both methyl and isopropyl groups in **14** with BBr_3 afforded lamellarin H (**2**) in 95% yield.[8] Alternatively, treatment of **5** with BBr_3 produced ningalin B (**3**) in 87% yield.[3e,4e,6b,12d]

To further demonstrate the utility of this new strategy, we planned to perform the total synthesis of the natural product lamellarin R (**4**), which belonged to a group of simple and nonfused 3,4-diarylpyrrole marine alkaloids. Lamellarin R was first isolated from the southern Australian sponge *Dendrilla cactos* by Capon and co-workers in 1995.[17] Up

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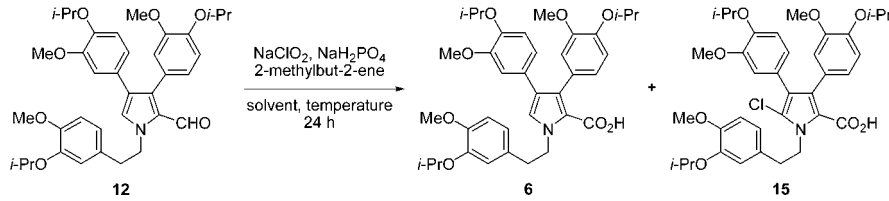
Table 1. Optimization of Lindgren Oxidation of **12**[a]



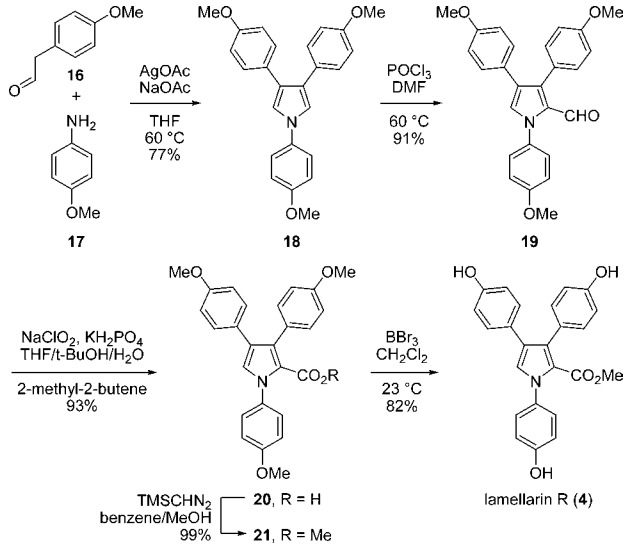
entry	solvent	temp (°C)	convn (%)	ratio (**6**:**15**)[b]	yield % (**6** + **15**)[c]
1[d]	DMSO/H_2O	0 to 25	0		0
2	THF:*t*-BuOH:H_2O (4:1:4)	25	29	3:1	21
3[e]	THF:*t*-BuOH:H_2O (4:1:4)	25 to 10	60	8:1	44
4	THF:*t*-BuOH:H_2O (4:1:4)	10	45	100:0	35
5	THF:*t*-BuOH:H_2O (3:3:1)	10	100	100:0	87

[a] General reaction conditions: concentration 0.02 M in solvent, 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methylbut-2-ene. [b] The ratio of **6** and **15** based on 400 MHz ^1H NMR. [c] Isolated yield. [d] 3.0 equiv of $NaClO_2$, 1.0 equiv of NaH_2PO_4, no 2-methylbut-2-ene was added. [e] According to entry 2, 25 °C for 24 h, followed by the addition of 3.0 equiv of $NaClO_2$, 3.0 equiv of NaH_2PO_4, 8.0 equiv of 2-methylbut-2-ene at 10 °C for 24 h.

to now, only one group has reported the total synthesis of lamellarin R.[5e]

Our total synthesis of lamellarin R commenced with aldehyde **16** and amine **17** (Scheme 4). The oxidative coupling reaction smoothly afforded the pyrrole **18** in 77% yield. Interestingly, unlike compound **7**, traditional Vilsmeier−Haack reaction of **18** smoothly produced formylpyrrole **19** in 91% yield. Lindgren oxidation of **19** under the optimized conditions afforded acid **20** in 93% yield, which was unexpectedly labile and decarboxylated to **18** even upon dissolving in $CDCl_3$ for a short period of time. In addition, when Lindgren oxidation was run in THF:*t*-BuOH:H_2O (4:1:4) at 25 °C, aldehyde **19** was completely consumed and converted to **20** and 5-chlorinated **20** in quantative yield with a ratio of 3 to 1. Treatment of **20** with $TMSCHN_2$ gave methyl ester **21** in 99% yield. Final demethylation of **21** with BBr_3 at room temperature afforded lamellarin R (**4**) in 82% yield.

Scheme 4. Synthesis of Lamellarin R



In summary, we have successfully achieved the total synthesis of lamellarins D (7 steps), H (7 steps), and R (5 steps), and ningalin B (5 steps) from the corresponding aldehydes and amines in a biomimetic manner. The synthesis features three oxidative coupling reactions, involving an AgOAc-mediated oxidative coupling reaction to form the 1,3,4-trisubstituted pyrrole, a $Pb(OAc)_4$-induced oxidative cyclization to form the lactone, and Kita's oxidation reaction to form the pyrrole−arene C−C bond. The evaluation of the biological activity of these important lamellarins and related compounds and their derivatives is in progress in our laboratory and will be reported in due course.

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Supporting Information Available: Full experimental procedures, and ^1H and ^{13}C NMR spectra of compounds **1**−**7**, **9**−**14**, **18**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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