Marine Alkaloid Synthesis

A Highly Efficient Synthesis of Lamellarins K and L by the Michael Addition/Ring-Closure Reaction of Benzyldihydroisoquinoline Derivatives with Ethoxycarbonyl-β-nitrostyrenes**

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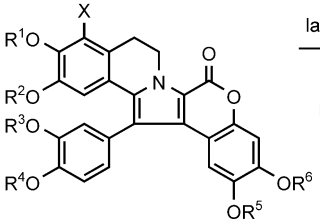
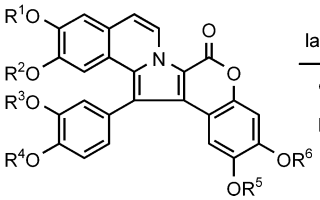
Among the recently discovered marine natural products isolated from the prosobranch mollusc *Lamellaria* sp. and also from the ascidians is a group of 3,4-diarylpyrroloisoquinoline lactone derivatives known as lamellarins, whose structures contain different patterns of polyoxygenated aromatics on their periphery (Scheme 1). Since the first four of these alkaloids were isolated by Faulkner and co-workers in 1985, a total of 35 lamellarins have been identified thus far.[1] Our research group has been particularly interested in lamellarins K (**1a**) and L (**1b**) for their reported biological activities which include cytotoxicity, HIV-1 integrase inhibition, and multidrug-resistance (MDR) reversal.[2,3] A recent biological evaluation by Faulkner and co-workers of lamellarin α (**2a**) and its 20-sulfate and 13,20-disulfate derivatives for inhibition of HIV-1 integrase showed that the presence of sulfate groups on the periphery could greatly influence selectivity in HIV-1 integrase inhibition.[4] It has also been found that lamellarins act as nontoxic inhibitors of acquired MDR. Lamellarin I (**1c**) showed sensitizing effects to doxorubicin in multidrug-resistant P388/Schabel cells at concentrations as low as 0.2 μM and showed full potentiation at a concentration 10-times lower than that of the prototype MDR inhibitor verapamil.[5] Fürstner and co-workers have recently shown that cytotoxicity and MDR reversal of lamellarins can be uncoupled.[6] The exact molecular mechanism of action of lamellarins and their related compounds is currently under extensive investigation.



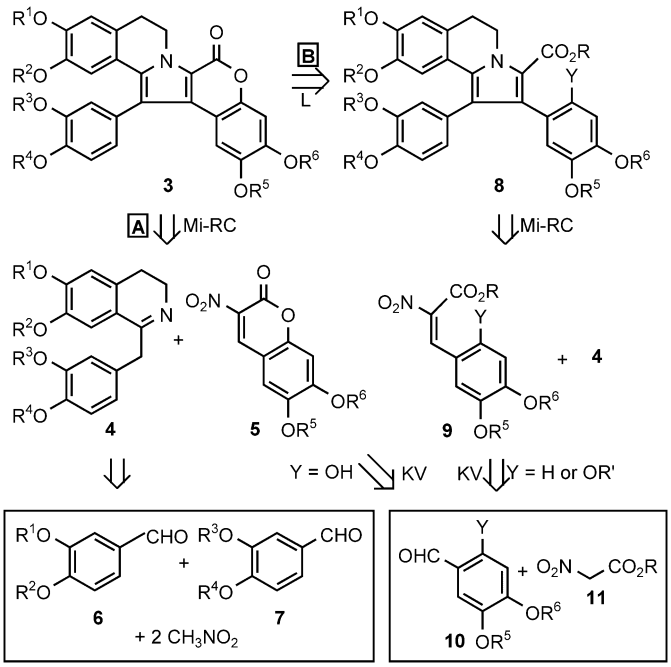
lamellarin	R^1	R^2	R^3	R^4	R^5	R^6	X
K (**1a**)	Me	Me	Me	H	Me	H	OH
L (**1b**)	H	Me	H	Me	Me	H	H
I (**1c**)	Me	Me	Me	Me	Me	H	OMe



lamellarin	R^1	R^2	R^3	R^4	R^5	R^6
α (**2a**)	Me	Me	H	Me	Me	H
N (**2b**)	H	Me	H	Me	Me	H

Scheme 1. Structures of lamellarins K (**1a**), L (**1b**), I (**1c**), α (**2a**), and N (**2b**).

There have been several studies[7] directed toward the total synthesis of lamellarins, notably by the research groups of Steglich,[8] Banwell,[9] Boger,[10] Ishibashi,[11] and ourselves.[12] Previously, we reported two synthetic approaches to the lamellarin skeleton, both of which involved the key condensation of the appropriately substituted benzyldihydroisoquinoline with phenacyl bromide derivatives to form the pyrrole core.[12] We now envisioned that the lamellarin skeleton **3** could arise from condensation of the benzyldihydroisoquinoline **4** with a Michael acceptor, such as **5** or **9**, which essentially would install the lactone or ester group on the 2-position (Scheme 2). This synthetic approach would prove highly convergent since, in a single step, it would form



Scheme 2. Retrosynthetic analysis and strategies for the synthesis of the lamellarin skeleton **3**. L = lactonization, Mi–RC = Michael addition/ring-closure reaction, KV = Knoevenagel reaction.

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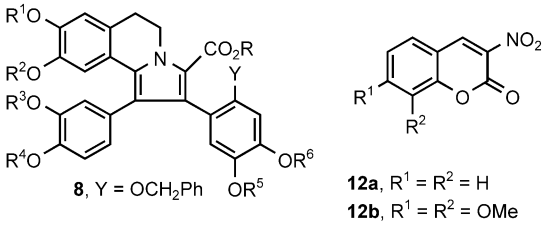
the pyrrole as well as providing the lactone directly or the ester group for subsequent lactonization. Since imines, which exist in equilibrium with their enamines, have been shown to react with β-nitrostyrene to give the corresponding pyrroles,[13] it was expected that Michael addition of an enamine derived from benzyldihydroisoquinoline with a powerful Michael acceptor, such as **5** or **9**, followed by ring closure and aromatization could provide a more direct route to the lamellarin alkaloids than previous methods.

Modeling the Michael addition/ring-closure reaction between simple β-nitrostyrenes and 3,4-dihydropapavarine hydrochloride under basic conditions resulted in complete consumption of both starting materials but gave no desired product. We then examined the use of ester nitrostyrenes in place of the simple nitrostyrenes in a similar Michael addition/ring-closure reaction. The ester nitrostyrenes are more powerful Michael acceptors than the simple nitrostyrenes due to the additional electron-withdrawing effect provided by the ester group; this allows the ester nitrostyrenes to react under milder reaction conditions than those required for the simple nitrostyrenes.

We turned our attention to the coumarin derivatives **12a** and **12b** (Scheme 3) as the ester nitrostyrenes for the reaction under basic conditions (pathway A in Scheme 2). These

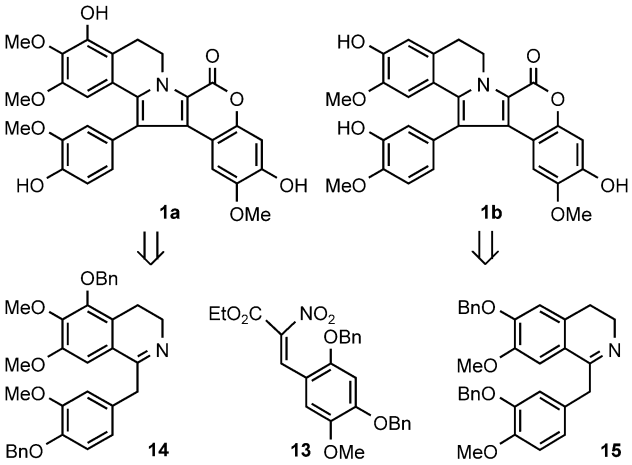


Scheme 3. Structures of intermediate pyrrole ester **8** and nitrocoumarins **12a** and **12b**.

coumarin derivatives offered a significant advantage in that their structures already contained the lactone moiety. We anticipated that, if the reaction occurred with these coumarins, all of the lamellarin skeleton, in particular the pyrrole and lactone moieties, would be successfully installed in one chemical operation. Unfortunately, such a reaction with these coumarins gave the desired lamellarins in only 5–6% yields.

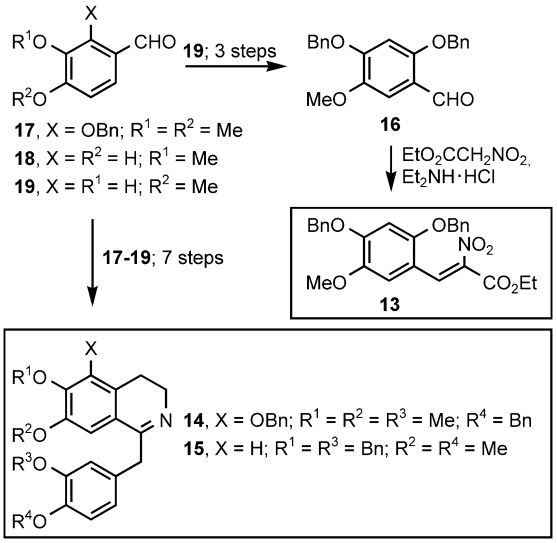
The poor yield resulting from the reaction with nitrocoumarins **12a** and **12b** prompted us to examine the use of acyclic ester nitrostyrenes like **9** (pathway B in Scheme 2). Despite adding one step of lactonization into the synthesis, this alternative synthetic route would probably allow for a more effective preparation of the lamellarin framework. Our required intermediate would then assume the structure of compound **8** (Scheme 3).

From the structure of compound **8**, it was apparent that the desired lactone moiety could be formed by unmasking the benzyloxy-protected phenol by hydrogenolysis and subsequently initiating base-mediated lactonization. Retrosynthetic analysis (Scheme 4) revealed that our target lamellarins K (**1a**) and L (**1b**) would require the same ester nitro-



Scheme 4. Retrosynthetic analysis for the synthesis of lamellarins K (**1a**) and L (**1b**). Bn = benzyl.

styrene, **13**, which could be prepared in 56% overall yield in four steps from **19** including the Knoevenagel condensation of aldehyde **16**[14] with ethyl nitroacetate (Scheme 5). As an alternative to the procedure depicted in Scheme 5, aldehyde

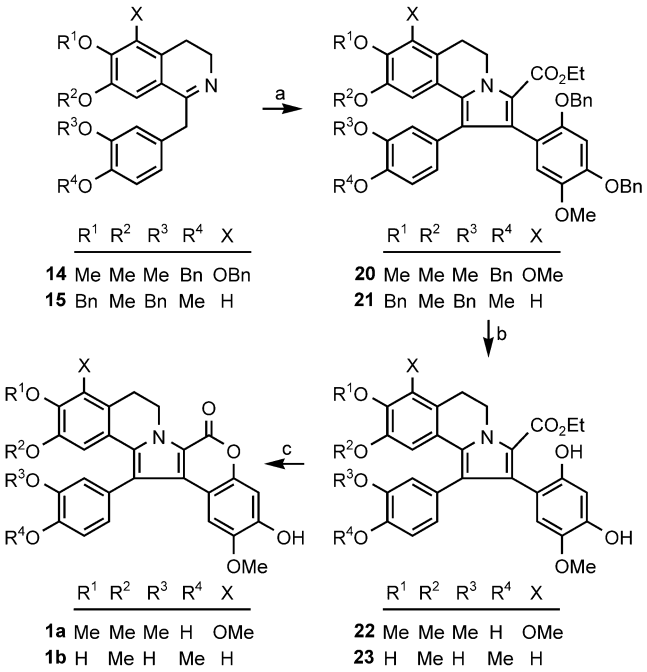


Scheme 5. Synthesis of ester nitrostyrene **13** and benzyldihydroisoquinoline derivatives **14** and **15**.

16 could be prepared in 79% overall yield by selective bisdemethylation of 2,4,5-trimethoxybenzaldehyde with $AlCl_3$[15] followed by benzylation. Synthesis of the substituted benzyldihydroisoquinolines **14** and **15** is well known in the literature[16–24] and both compounds were synthesized in seven steps by Bischler–Napieralski reactions of the appropriate aryl ethylamines and aryl acetic acids, which were readily prepared from three common starting materials, **17**–**19** (Scheme 5).

The Michael addition/ring-closure reaction of the imines **14** and **15** with the ester nitrostyrene **13** proceeded smoothly in refluxing anhydrous acetonitrile in the presence of

$NaHCO_3$ to give the desired pyrroles **20** and **21**, both in 70% yield (Scheme 6). The syntheses were completed by subjecting pyrroles **20** and **21** to hydrogenolysis to give compounds **22** and **23** quantitatively, followed by base-mediated lactonization with sodium hydride in dry THF to produce lamellarin K (**1a**) in 93% yield and lamellarin L (**1b**) in 87% yield over two steps.



Scheme 6. Synthesis of lamellarins K (**1a**) and L (**1b**). a) $NaHCO_3$, **13**, CH_3CN, reflux, 70% (**20**), 70% (**21**); b) H_2, Pd/C, EtOAc; c) NaH, THF, 93% (**1a**, over two steps), 87% (**1b**, over two steps).

In summary, lamellarins K and L were successfully synthesized in three steps from benzyldihydroisoquinolines **14** and **15** with ester nitrostyrene **13** in 65% and 61% overall yields, respectively. The key step was the Michael addition/ring-closure reaction which proceeded in 70% yield for both lamellarins. The basic building blocks for the lamellarins are the simple and easily prepared substituted-benzaldehyde derivatives. Each lamellarin could be analyzed to consist of three such building blocks, two in the benzyldihydroisoquinoline derivative and the other in the ester nitrostyrene. Our convergent synthetic approach offers a significant improvement over others reported thus far in that it allows easy incorporation of all aryl groups on the lamellarin skeleton without the need for complex protecting-group strategies. The benzyl group was chosen as the only necessary hydroxy-protecting group since all of the benzyl groups could be removed in the same step by simple palladium-catalyzed hydrogenolysis. The syntheses of other lamellarins employing this similar approach will be reported in due course.

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