Syntheses of Lamellarins I and K by [3+2] Cycloaddition of a Nitrone to an Alkyne

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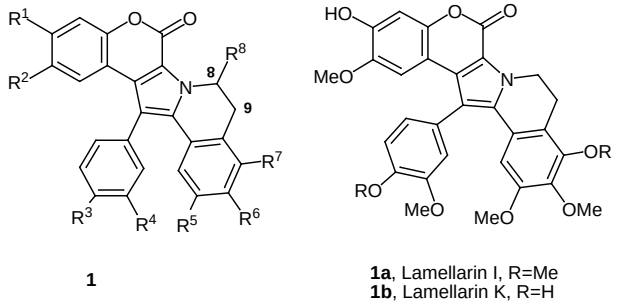
Abstract: Lamellarins I and K were obtained by a new approach based on the 1,3-dipolar cycloaddition of a nitrone to an alkyne. The key cycloaddition yields an isoxazoline which rearranges to afford the central pyrrole ring.

Key words: lamellarins, nitrone-alkyne 1,3-dipolar cycloaddition

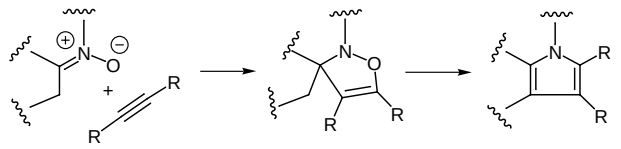
The lamellarin alkaloids are a group of approximately 35 compounds isolated from the marine prosobranch mollusc *Lamellaria* sp., the marine ascidian *Didemnum* sp. and the sponge *Dendrilla cactos*. Most of them have the basic structure **1**, although about a third have a double bond between carbons 8 and 9.[1] The lamellarins have an interesting range of pharmacological activities, including antitumour and anti HIV-1 properties, reversal of multidrug resistance (MDR), and immunomodulatory activity.[1,2] For example, it has been claimed that lamellarins I (**1a**) and K (**1b**) not only exhibit potent cytotoxic activity *in vitro* against multidrug-resistant cell lines, but also reverse their MDR at noncytotoxic concentrations, [2,3] and the results of in vivo tests of lamellarin K are consistent with these claims.[3]



1 **1a**, Lamellarin I, R=Me **1b**, Lamellarin K, R=H

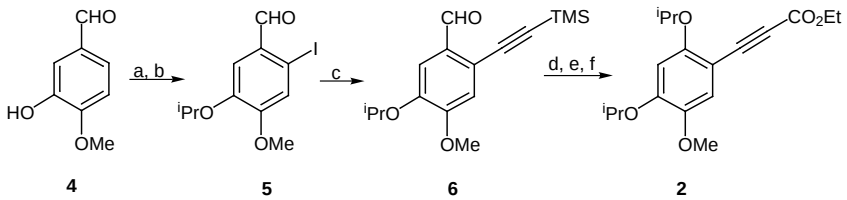
Figure 1

The first synthesis of lamellarins was published by Steglich's group in 1997.[4] Since then, new procedures for the preparation of lamellarins of general structure **1** have been developed by Banwell[5] and Ishibashi.[6] Banwell's synthesis of lamellarin K is particularly interesting because it is convergent, versatile and high-yielding.[5a] The key step in this approach is the formation of the central pyrrole ring by an intramolecular 1,3-dipolar cycloaddition between an azomethine ylide and an alkyne.[5] Here we present a related approach to lamellarins which relies on two known facts: a) nitrones add to alkynes to form isoxazolines,[7] and b) isoxazolines with a R-CH_2- substituent at position 3 can be rearranged to pyrroles[8] (Scheme 1).



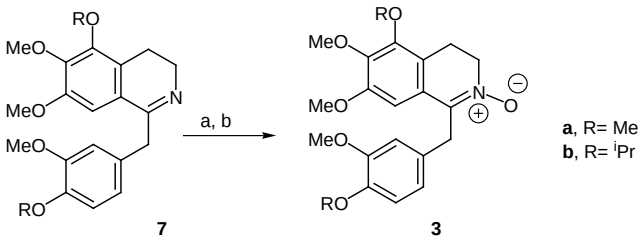
Scheme 1

As synthetic targets we selected lamellarins I and K. Application of our procedure to their synthesis requires preparation of alkyne **2** and nitrones **3**. Alkyne **2** was synthesized from isovanillin (**4**) as shown in Scheme 2. Protection of the hydroxyl group of **4** as an isopropyl ether by treatment with K_2CO_3 and ^iPrBr, followed by treatment with iodine and silver trifluoroacetate, afforded iodide **5**, which upon palladium-catalyzed coupling with trimethylsilylacetylene (TMSA) yielded **6**. Treatment with MCPBA transformed the formyl group of **6** into a hydroxyl group, which was then protected with K_2CO_3 and ^iPrBr as above, with accompanying loss of the TMS group. Finally, deprotonation of the resulting alkyne with LDA

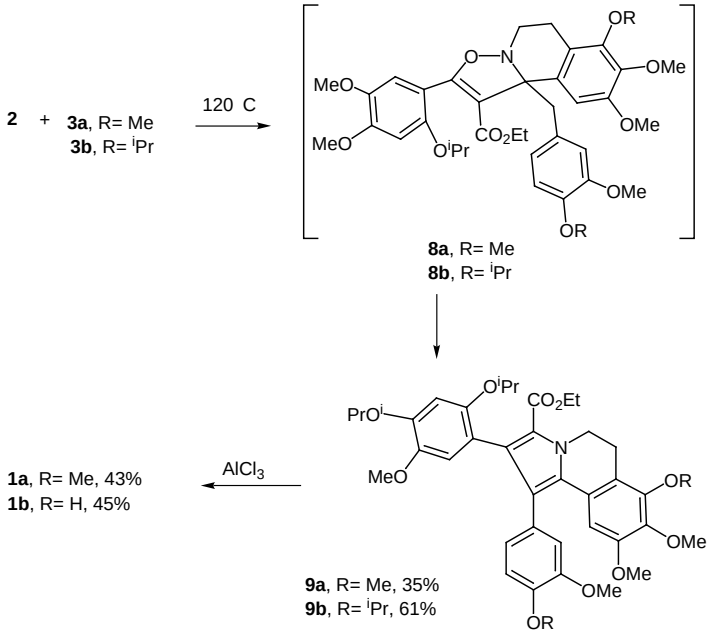


4 **5** **6** **2**

Scheme 2 a) K_2CO_3, 2-bromopropane/DMF, 100 °C, 24 h, 98%; b) I_2, $F_3C\ CO_2\ Ag$, $CHCl_3$, rt, 3 h, 80%; c) TMSA, $PdCl_2(PPh_3)_2$, CuI, Et_3N, dioxane, 45 °C, 3 h, 98%; d) MCPBA, $NaHCO_3$, CH_2Cl_2, rt, 30 min, 73%; e) K_2CO_3, 2-bromopropane/DMF, 100 °C, 24 h, 45%; f) LDA, THF, –78 °C, 15 min; then $ClCO_2Et$, –78 °C→ rt, 94%



Scheme 3 a) $NaBH_4$, MeOH, rt, 1 h, 96-97%; b) H_2O_2, Na_2WO_4, MeOH, rt, 3 h, 45-49%



Scheme 4

and carboxylation with ethyl chloroformate afforded **2** in good yield.

N-Oxides **3** were obtained from dihydroisoquinolines **7**, which were prepared using standard isoquinoline alkaloid procedures.[9] Reduction of the imine double bond of **7** with sodium borohydride, followed by a non-optimized oxidation with sodium tungstate[10] (45-49% yield), afforded N-oxides **3**.

The key cycloaddition step was carried out by heating a mixture of nitrone **3** and alkyne **2** under argon for 18 h at 120 °C in a sealed tube. Under these conditions compounds **9** were obtained in moderate yields.[11] The cycloaddition appears to take place with the expected regiochemistry to form the isoxazoline **8**, which upon heating undergoes rearrangement to the corresponding pyrrole **9**.

Finally, lamellarins I and K were obtained from **9a** and **9b**, respectively, by removal of the isopropyl protecting groups[12] with concomitant acid-catalyzed lactonization.[13]

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(11) Experimental procedure for the cycloaddition. A solution of **3b** (37 mg, 0.08 mmol) and **2** (38 mg, 0.12 mmol) in toluene (1 mL) was heated under argon in a sealed tube for 18 h at 120 °C. Then the solvent was evaporated in vacuo and the residue was chromatographed (silicagel, hexane/ether) to yield **9b** (38 mg, 61% yield) as an oil. Spectroscopic data for **9b**: UV (EtOH), λ_{max}: 304 nm. IR (NaCl), ν: 1694 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 6.73 (m, 2H), 6.61 (s, 1H), 6.50 (s, 1H), 6.40 (m, 2H), 4.50-4.32 (m, 5H), 4.05-3.98 (m, 3H), 3.74 (s, 3H), 3.52 (s, 3H), 3.46 (s, 3H), 3.25 (s, 3H), 3.10-2.90 (m, 2H), 1.26-0.78 (m, 27H) ppm. ^{13}C NMR ($CDCl_3$), 162.2 (C), 151.4 (C), 150.1 (C), 149.5 (C), 148.2 (C), 145.8 (C), 145.7 (C), 144.5 (C), 141.3 (C), 130.0 (C), 129.0 (C), 127.8 (C), 124.0 (C), 123.2 (CH), 122.0 (C), 120.1 (C), 119.8 (C), 119.6 (C), 115.9 (CH), 114.8 (CH), 107.4 (CH), 104.7 (CH), 75.5 (CH), 71.7 (CH), 71.6 (CH), 71.4 (CH), 60.5 (CH_3), 59.7 (CH_2), 56.1 (CH_3), 55.7 (CH_3), 55.1 (CH_3), 42.6 (CH_2), 23.0 (CH_2), 22.7 (CH_3), 22.2 (CH_3), 21.9 (CH_3), 15.2 (CH_3), 13.7 (CH_3) ppm. LRMS, m/z (%):745 (M^+, 34). HRMS, m/z calcd. for $C_{43}H_{55}NO_{10}$ 745.382598, found 745.385468.
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