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Efficient Synthesis of Ningalin C

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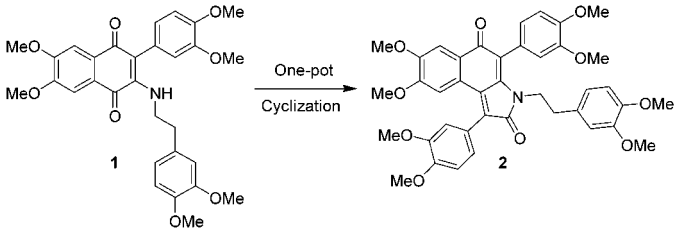
ABSTRACT



A concise and efficient synthesis of the permethyl derivative of the marine alkaloid ningalin C (2) has been accomplished. The key step involves the formation of a pyrrolinone from an aminoquinone in one pot. An efficient route for the synthesis of the key aminoquinone has also been developed.

In 1997, Kang and Fenical[1] reported the isolation of four novel aromatic alkaloids, ningalin A−D (Figure 1), from an unidentified ascidian of the genus *Didemnum*[2] collected in ascidia-rich habitats near Ningaloo Reef region at the northwest cape of western Australia. These ningalin derivatives, as well as lukianols, polycitrins, and lamellarins, appeared to be derived from the condensation of 3,4-dihydroxyphenylalanine (DOPA) in the biosynthetic pathway.[3]

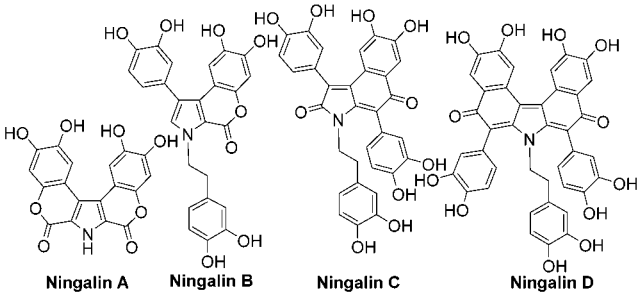


Figure 1. Structures of ningalin A, B, C, and D.

The first total syntheses of ningalin A and B were reported by Boger et al. in 1999, utilizing the application of the versatile heteroaromatic azadiene Diels−Alder reaction.[4] Steglich has recently reported an efficient synthesis of ningalin C using an intramolecular Friedel−Crafts acylation.[5]

In this paper, we report a new and efficient method for the synthesis of ningalin C as a continuation of our synthetic

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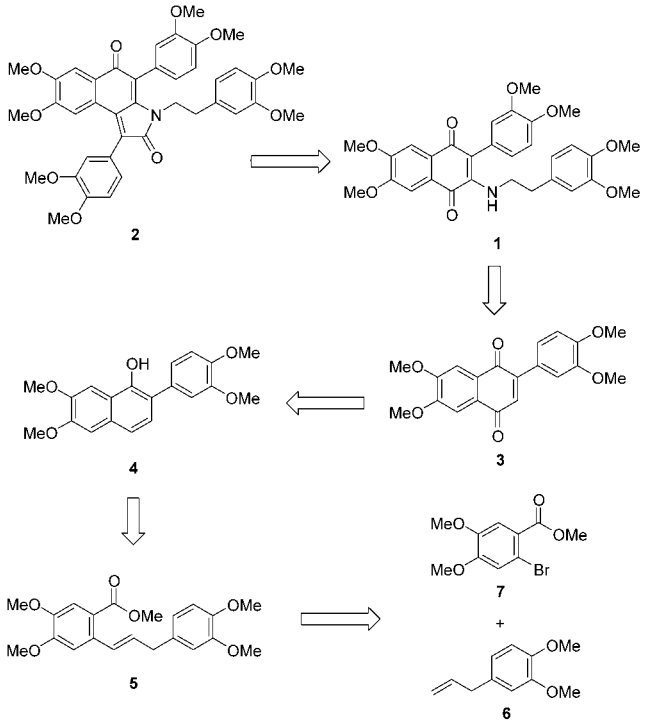
program on lamellarins and other bioactive pyrrole alkaloids.[6] Our retrosynthetic analysis of this compound is outlined in Scheme 1.

Scheme 1

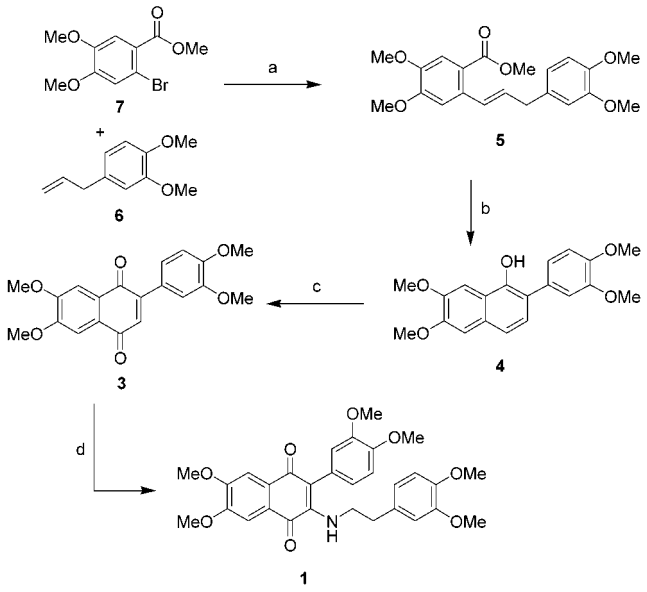


It was planned that the pyrrolinone system of the target ningalin compound **2** could be synthesized from naphthoquinone **1** via addition of the enolate derived from methyl homoveratrate and subsequent lactam bond formation. This aminoquinone could be synthesized by addition of an amine to quinone **3** derived from the oxidation of naphthol derivative **4**. It was expected that an allyl carbanion prepared from **5** would undergo intramolecular acylation to give compound **4**. The alkene **5** could conceivably be prepared by the reaction of eugenol methyl ether **6** with bromo compound **7** via the Heck reaction.[7]

In practice, the palladium-catalyzed coupling reaction[8] between the methyl 2-bromoveratrate **7** and commercially available eugenol methyl ether **6** gave ester **5** in 65% yield. (Scheme 2).

Further cyclization[9] of methyl ester **5** was accomplished by treatment with 2 equiv of lithium diisopropylamide in THF at −78 °C to give naphthol **4** (76%), which has recently been obtained by a different route.[10]

Scheme 2[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, $NaHCO_3$, DMF, reflux, 24 h, 65%; (b) 2 equiv of LDA, THF, −78 °C, 2 h, then rt 2 h, 76%; (c) H_2O_2, I_2, H_2SO_4, MeOH, 62%; (d) homoveratrylamine (**9**), EtOH, rt, 24 h, 80%

Oxidation[11] of naphthol **4** with 30% hydrogen peroxide containing a trace amount of iodine and sulfuric acid in methanol afforded the desired naphthoquinone **3** in 62% yield as a red solid.

On the basis of the synthetic plan proposed in Scheme 1, the key aminoquinone intermediate could be prepared via the nucleophilic addition of amine to naphthoquinone derivative **3**. Indeed, it was found that treatment of naphthoquinone **3** with homoveratrylamine **9** in ethanol[12] at room temperature furnished the homologous amide, aminonaphthoquinone **1**, as a deep red solid in 80% yield (Scheme 2).

Similarly, the aminonaphthoquinone **10** was readily prepared by the addition of homoveratrylamine **9** to commercially available menadione **8** in ethanol at room temperature for 24 h. The aminoquinone derivatives have recently been shown to be versatile intermediates in the synthesis of various natural products.[13]

The construction of the pyrrolinone moiety in the ningalin skeleton was initially investigated using this readily available aminoquinone derivative **10**.

It was reasoned that the presence of the amino group would render the C-1 carbonyl less electrophilic and thus the

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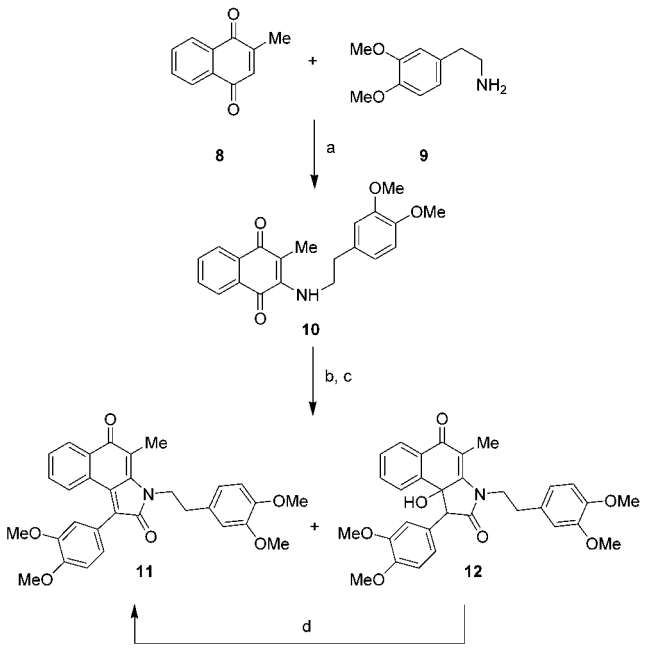
nucleophile would preferentially attack C-4 carbonyl group.[14] This prediction was indeed found to be the case. When aminonaphthoquinone **10** was treated with the carbanion derived from the reaction of methyl homoveratrate and 2 equiv of lithium diisopropylamide in tetrahydrofuran at −78 °C, the desired ningalin C skeleton **11** was obtained (69%) as an orange solid together with hydrated product **12**, isolated as a white solid in 9% yield (Scheme 3). It was gratifying

Scheme 3[a]

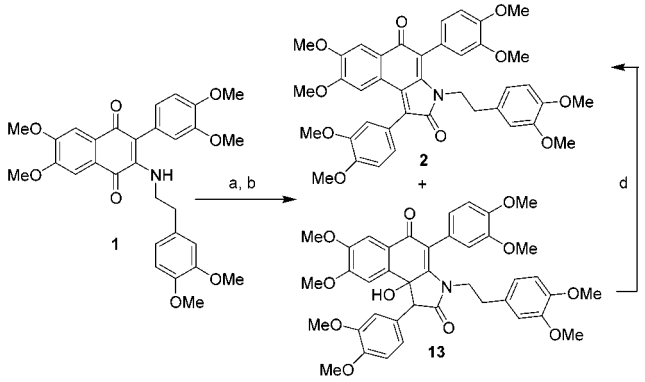


[a] Reagents and conditions: (a) EtOH, rt, 24 h, 82%; (b) 2 equiv of LDA, THF, −78 °C; (c) 1 equiv of methyl homoveratrate, THF, −78 °C, 2 h then rt 2 h, 69%(**11**), 9%(**12**); (d) 2 M HCl, CH_2Cl_2, rt, 5 h

to see that not only was the addition of the anionic species to the right ketone group of compound **10** but also the lactam cyclization took place to generate the ultimate pyrrolinone system in one pot. We were unable to carry out the *intermolecular* amide bond formation by the reaction of aminonaphthoquinone **10** with homoveratroyl chloride in the presence of various bases (Na_2CO_3, K_2CO_3, NaH, Et_3N). This is presumably due to the fact that the lone pair of electrons on nitrogen is not readily available because the nitrogen is part of a vinylogous amide. It was thus concluded that in the key formation of the pyrrolinone the formation of the carbon−carbon bond preceded the *intramolecular* amide bond formation.

With the starting material **1** and an efficient method for the synthesis of pyrrolinones in hand, the synthesis of permethyl ningalin C **2** was then investigated. The reaction of aminoquinone **1** with methyl homoveratrate and 2 equiv of LDA gave the required permethyl ningalin C **2** (73%) and the hydrated compound **13** (15%) in a straightforward manner (Scheme 4). The hydrated compounds **12** and **13**

Scheme 4[a]



[a] Reagents and conditions: (a) 2 equiv of LDA, THF, −78 °C; (b) 1 equiv of methyl homoveratrate, THF, −78 °C, 2 h then rt 2 h, 73% (**2**), 15%(**13**); (d) 2 M HCl, CH_2Cl_2, rt, 5 h.

could be readily dehydrated by treatment with 2 M hydrochloric acid in dichloromethane at room temperature for 5 h to give the ningalin compound **11** and permethyl ningalin C **2** in quantitative yield. Permethyl ningalin C **2** was demethylated[5] by BBr_3 in methylene chloride to give ningalin C in 72% yield. The spectral data (IR, UV, ^{1}H NMR, ^{13}C NMR, MS) of our synthetic ningalin C are in full agreement with the published data for the natural product.[1,5]

In conclusion, our synthetic approach to ningalin C demonstrates the utility of the one-pot reaction for the preparation of the pyrrolinone system, the core moiety of ningalin C. The synthesis of the quinone and aminoquinone also shows great promise for application in the synthesis of related quinone derivatives.

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Supporting Information Available: Detailed experimental procedures and characterization data for new compounds and spectra (IR, UV, ^{1}H NMR, ^{13}C NMR, MS) of the synthetic ningalin C. This material is available free of charge via the Internet at http://pubs.acs.org.

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