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Studies toward the Total Synthesis of Nagelamide K

Biao Jiang,*,†,‡ Jue Wang,† and Zuo-gang Huang‡

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, and Shanghai Advanced Research Institute, Chinese Academy of Sciences, 99 Haike Road, Shanghai 201210, China

jiangb@sioc.ac.cn

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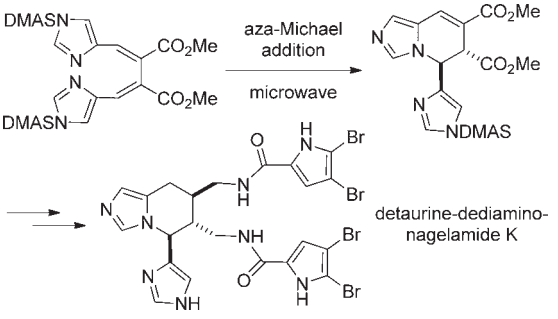
ABSTRACT



A stereocontrolled strategy toward the synthesis of nagelamide K has been developed. The dimeric imidazole acrylate, diimidazolidenesuccinate, was constructed as a synthetic precursor by a Ni-catalyzed coupling reaction; the microwave-promoted intramolecular aza-Michael addition afforded the imidazo[1,5-*a*]pyridine core structure of nagelamide K in high stereoselectivity. A detaurine−dediamino analogue of nagelamide K has been prepared.

Bromopyrrole−imidazole alkaloids are common secondary metabolites from marine sponge families[1] and have attracted great attention from the synthetic community.[2,3] The pyrrole portions could be introduced by acylation with 2-(trichloroacetyl)pyrroles in a chloroform reaction[4] or the Mitsunobu reaction[5] with pyrrolecarboxamides. Various strategies had been developed to introduce the 2-aminoimidazole portion, for example, an elaboration on the imidazole moiety by 2-lithiation and installation of an azide ($-N_3$) or methylthiol (MeS−) group,[6] or via imidazolone,[7] hydantoin,[8] or 2-thiohydantoin[9] precursors or the condensation of a halomethyl ketone with guanidine[10] used in Baran's work.[11] Although significant progress has been made in the development of strategies for the synthesis

† Shanghai Institute of Organic Chemistry.
‡ Shanghai Advanced Research Institute.

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of such compounds, there remains a need for alternative approaches.

For this family of pyrrole–imidazole alkaloids, it is not hard to conceive that all these closely related structures could arise, in a biosynthetic pathway, from one common precursor, oroidin, which was first identified in 1971.[12] The hypotheses of biosynthesis have not only helped in elucidation and chemical rationalization of their structures but also facilitated the design and execution of total synthesis endeavors.[13] Recently, Kobayashi et al. reported the isolation of four dimeric bromopyrrole alkaloids, nagelamides K, L, Q, and R from Okinawan marine sponges.[14] Interestingly, nagelamides K/Q are new dimeric bromopyrrole alkaloids possessing a rare piperidine/pyrolindine central ring and two aminoimidazole moieties with one being tethered with a taurine unit. A plausible biogenetic path to nagelamides K (**1**) and Q (**2**) has been proposed in intramolecular cyclizations from a common intermediate A (Figure 1).[14b]

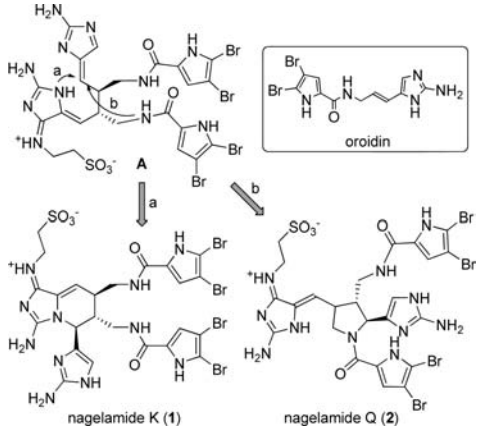
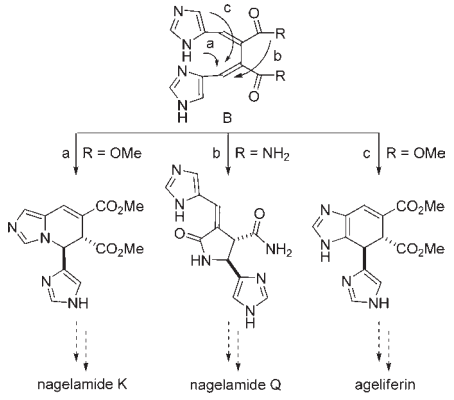


Figure 1. Presumed biogenetic synthesis of nagelamide K, Q.

Since the presumed intermediate A with a variable 2-aminoimidazole fragment was highly dependent on polarity of solvents and pH conditions,[15] we proposed an alternative strategy as shown in Scheme 1, with a dimeric imidazole acrylate intermediate B for intramolecular aza-Michael additions to both nagelamide K (route a) and Q (route b); in addition, the skeleton of ageliferin might also be accessible (route c).

Scheme 1. Proposed Synthetic Strategy for Nagelamides K and Q and Ageliferin



As shown in Figure 2, we chose **3**, a detaurine–dediamino analogue of nagelamide K, as a simplified target for nagelamide K (**1**). In a retrosynthetic analysis, the pyrrolecarboxamides could be introduced via Mitsunobu reactions using pyrrolecarboxamide **5**. The diol **4** was postulated to diester **6**, which servers as the key intemediate, and may arise in an intramolecular aza-Michael addition as designed in Scheme 1 from diimidazolidenesuccinate (**7**), and **7** could be synthesized via dimerization of bromoacrylate **8**. Herein, we report our synthetic work on the basis of this analysis.

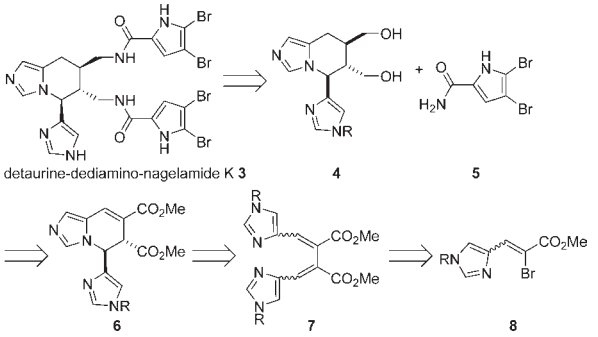


Figure 2. Retrosynthetic analysis.

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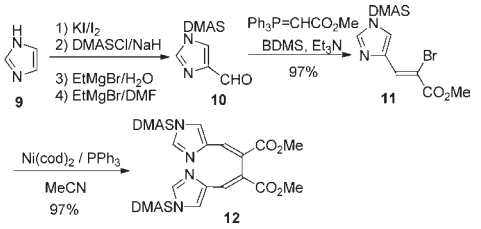
First, the bromination of methyl urocanote to **8** (R = H) with Br_2/Et_3N was attempted, but poor selectivities and low yields were obtained.[16] Then, as shown in Scheme 2, the 4-DMAS-protected imidazole carbaldehyde **10**, prepared from **9** in four steps,[17] was reacted with $Ph_3P{=}CHCO_2Me$ and bromodimethylsulfonium bromide (BDMS) by a method developed in our group[18] to afford the (*Z*)-1-(dimethylsulfamoyl-1*H*-imidazol-4-yl)bromoacrylate **11** in high yield and selectivity. The zerovalent nickel complexes $Ni(cod)_2$-mediated dimeric coupling of **11** produced the product **12** in high yield (97%).[19]

Scheme 2. Synthesis of Diimidazolidenesuccinate **12**



Having the dimeric **12** in hand, we turned to the study of intramolecular aza-Michael additions, and the results are summarized in Table 1. To our delight, the cyclization to compound **13** took place upon simply heating a toluene solution of **12** in the presence of 2 equiv of water at 140 °C, 95% yield and 8/1 selectivity were obtained after 96 h (entry 1), and the *trans*-substituted isomer was determined to predominate. Apparently, the deprotection of one DMAS group occurred during the aza-Michael addition in this transformation. Switching to more polar solvent DMSO, much better trans/cis selectivity (>95/1) was achieved with 53−71% yield after heating at 130 °C for 12−18 h (entries 2 and 3). Using microwave heating, 43% yield was obtained after 15-min irradiation in DMSO at 130 °C, and a remarkable yield of 96% was achived when irradiated at 150 °C without decreasing the stereoselectivity (entries 4 and 5), while microwave heating in toluene did not improve the reaction outcome (entry 6).

As shown in Scheme 3, reduction of **13** with $LiAlH_4$ afforded **14** in 92% yield, and catalytic hydrogenation on Pd/C provided **15** in excellent yield and stereoselectivity. The diol **15** was subjected to a double Mitsunobu reaction[5] with dibromopyrrolehydantoin (**16**, DBPH) and gave intermediate **17**.[20] Exposure of **17** to aqueous NaOH resulted in the hydrolysis of the ureas and liberated the

(16) Direct bromination of methyl urocanote affording (*E*)-bromoacrylate **8** in moderate yield (42%) and (*Z*)-bromoacrylate **8** in 16% yield.

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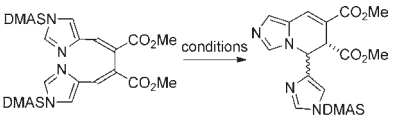
(20) The bishydantoin **17** was easy to hydrolyze so we could not get its perfect ^1H NMR and ^{13}C NMR. After primary purification of **17**, we exposed the mixture to aqueous sodium hydroxide, affording **18** in 73% yield (two steps combined).

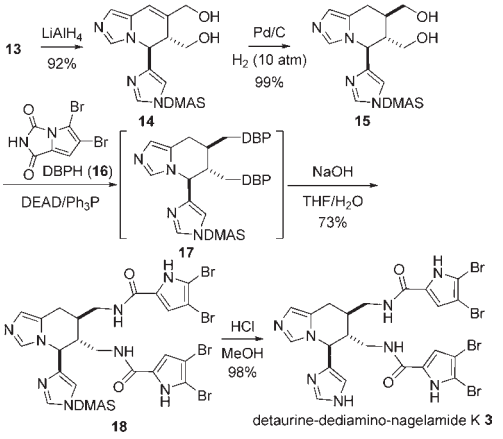
Table 1. Optimization of the Cyclization of **12** to **13**



entry	solvent	condition	temp/°C	time	yield[a] (%)	trans/cis[b]
1	toluene	normal heating	140	96 h	95	8/1
2	DMSO	normal heating	130	18 h	71	>95/1
3	DMSO	normal heating	150	12 h	53	>95/1
4	DMSO	microwave	130	15 min	43	>95/1
5	DMSO	microwave	150	15 min	96	>95/1
6	toluene	microwave	140	30 min	30	9/1

[a] Yield of isolated product. [b] Determined by ^1H NMR.

Scheme 3. Synthesis of Detaurine−Dediaminonagelamide K (**3**)



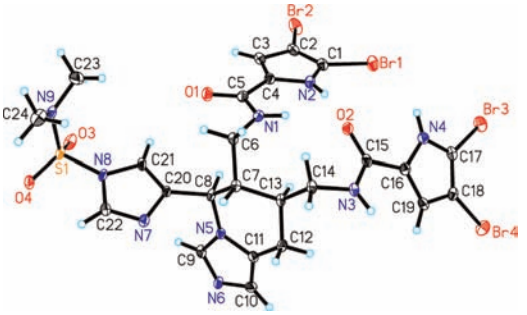


Figure 3. Molecular structrue of the pyrrolecarboxamide **18**.

pyrrolecarboxamide **18** in 73% yield over two steps, and the structure has been confirmed by X-ray analysis (Figure 3).[21] Removal of the DMAS protecting group with methanolic

(21) For X-ray crystal structures of compounds **11**−**15** and **18**, see the Supporting Information.

HCl afforded compound **3** in 98% yield. In this way, the basic skeleton of nagelamide K has been accessed, with two amino and taurine moieties to be introduced.

In summary, a novel method toward the synthesis of nagelamide K has been developed, and the detaurine–dediamino analogue of nagelamide **3** has been prepared efficiently. Noteworthy features of this concise synthesis include (a) a dimeric imidazole acrylate intermediate B via a Ni-catalyzed coupling of α-bromomethyl urocanote, which may serve as a common precursor for nagelamide Q/K and ageliferin; (b) an efficient intramolecular aza-Michael addition to synthesize the rare imidazole–piperidine ring; and (c) generally excellent yields and high selectivities. Studies toward the total synthesis of nagelamide K/Q and ageliferin are now in progress in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data, and CIF files for **11**–**15** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.