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Studies toward the Total Synthesis of Nagelamide K

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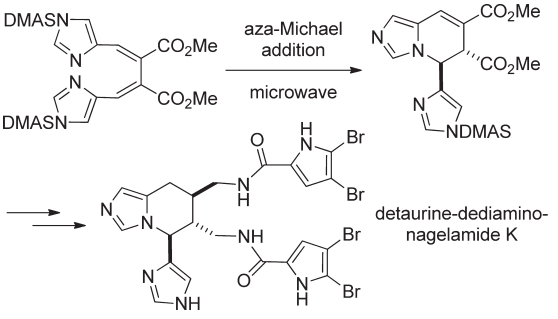
ABSTRACT



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

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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]

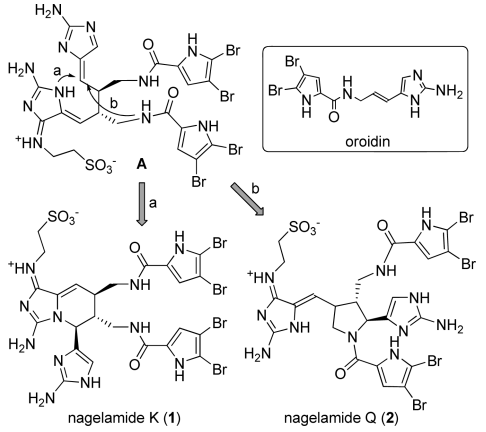
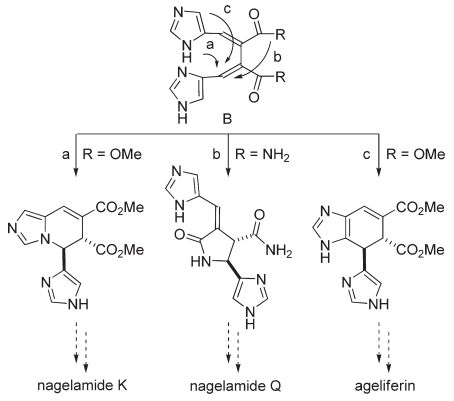


Figure 1. Presumed biogenetic synthesis of nagelamide K, Q.

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.

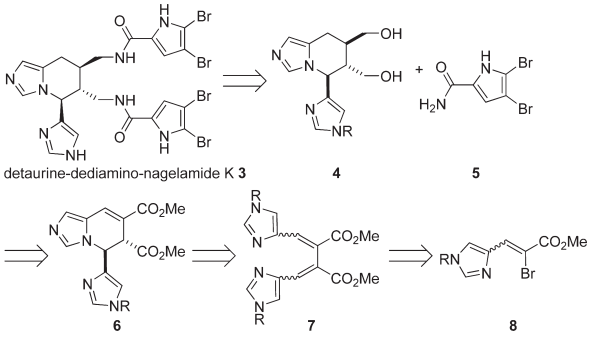


Figure 2. Retrosynthetic analysis.

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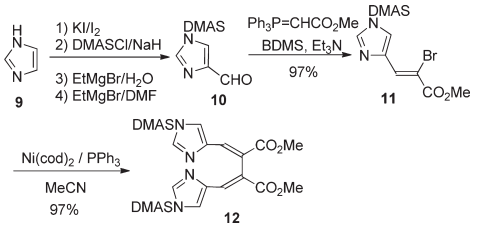
First, the bromination of methyl urocanote to **8** (R = H) with Br_2/Et_3N was attempted, but poor selectivities and low yields were obtained.[16] Then, as shown in Scheme 2, the 4-DMAS-protected imidazole carbaldehyde **10**, prepared from **9** in four steps,[17] was reacted with $Ph_3P{=}CHCO_2Me$ 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]

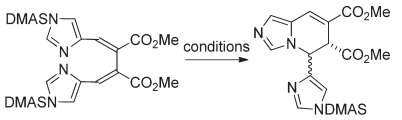
Scheme 2. Synthesis of Diimidazolidenesuccinate **12**



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

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

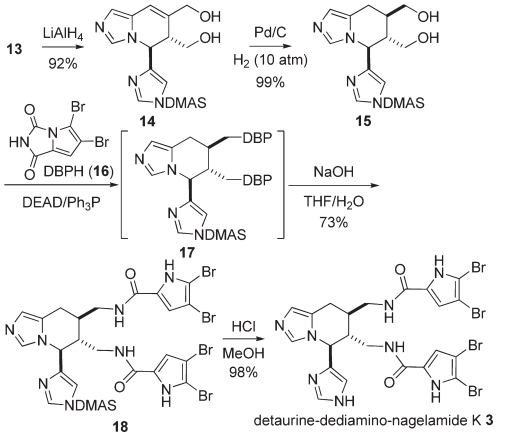


12 13

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**)



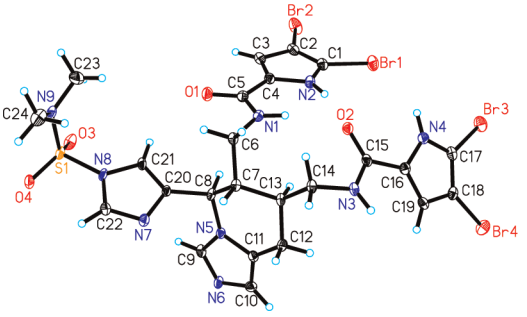


Figure 3. Molecular structrue of the pyrrolecarboxamide **18**.

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

(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).

(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.