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Total Syntheses of Kealiinines A–C

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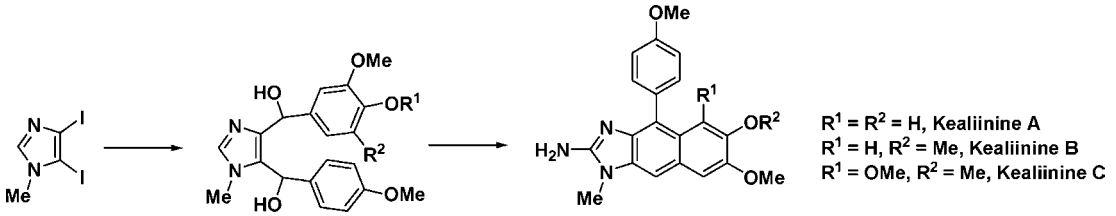
ABSTRACT



Short total syntheses of the *Leucetta*-derived alkaloids, kealiinines A–C, have been accomplished using an intramolecular Friedel–Crafts–dehydration sequence of a bis benzylic diol. The precursor diol was obtained through a series of position-specific Grignard reactions from 1-methyl-4,5-diiodoimidazole. C2-Azidation and hydrogenation of the azide then provided the reported structures of kealiinines A–C. While the ^{1}H NMR data did not completely match for these materials, the HPLC data were consistent with the assigned structure of these alkaloids.

The *Leucetta* alkaloids are a group of approximately 60 2-aminoimidazole alkaloids[1] isolated from sponges of the *Leucetta* and *Clathrina* families.[2−4] Structurally, all of these alkaloids contain at least one oxygenated benzyl group (Figures 1 and 2), e.g., clathridine A (**1**),[5] and in many cases, there are two benzyl groups, e.g., naamidine G (**2**).[6] Within this collection of alkaloids a subgroup **6**–**8** containing a naphthimidazole moiety has been reported that still retains the two benzylic groups,[7−9] but these are now embedded within the heterocyclic framework (Figure 2). Kealiinines A–C (**8a**–**c**)[7] were isolated by the Proksch group in 2004, along with naamine G and naamidine H (**3**); the former are structurally related to the more highly oxygenated kealiiquinone (**6**)[9] and 2-deoxy-2-aminokealiiquinone (**7**).[8]

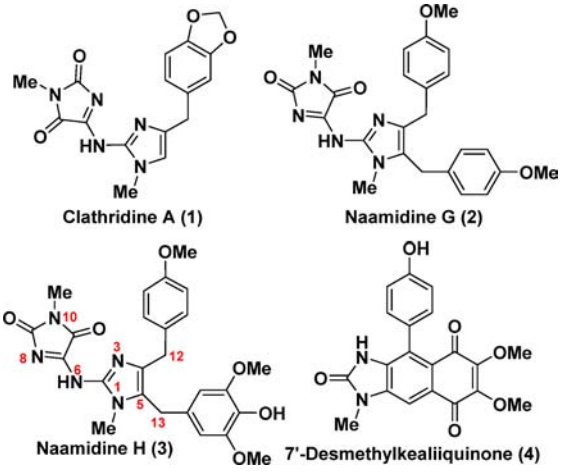


Figure 1. Structures of the *Leucetta* family of alkaloids.

It has been suggested that kealiinine C (**8c**) may serve as a biosynthetic precursor to **6** and **7**,[7] but there is no experimental evidence to support this hypothesis.[10] No bioactivity was reported by Proksch for **8b** and **8c**,[7] presumably

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(10) We have demonstrated the feasibility of such a transformation in the conversion of a kealiinine-type intermediate into kealiiquinone and 2-deoxy-2-aminokealiiquinone.

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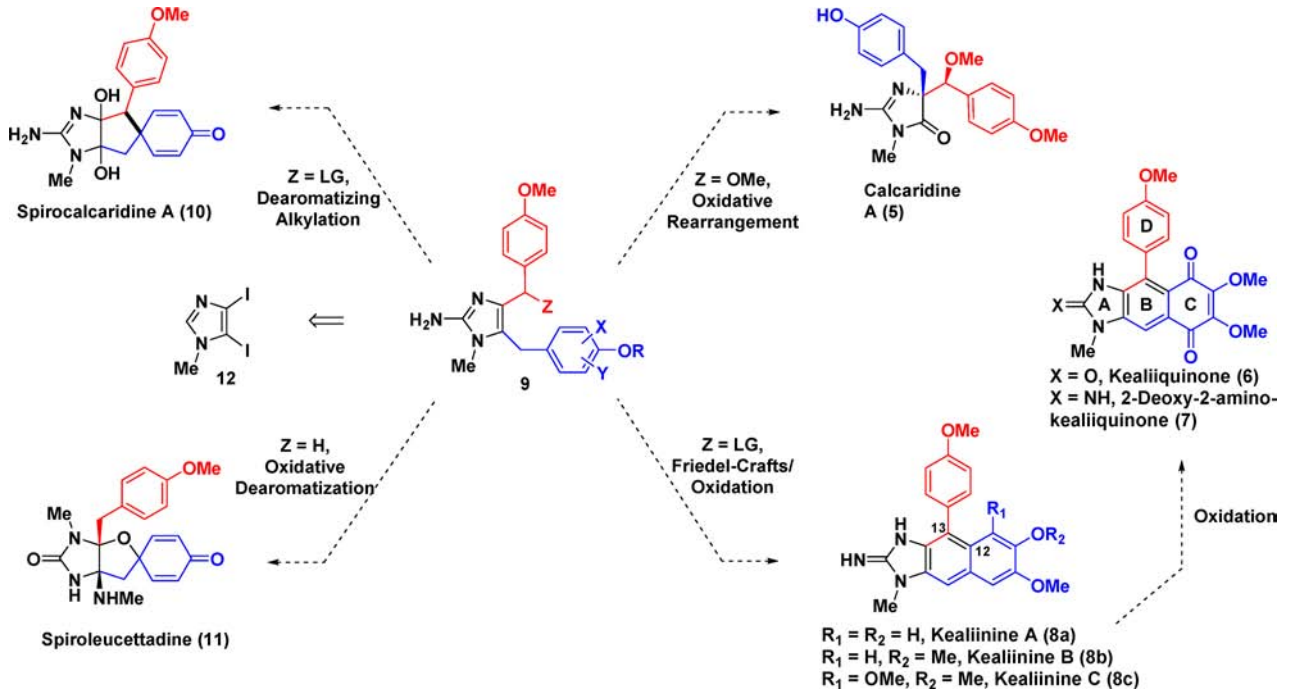

Figure 2. Putative biosynthetic relationships among the *Leucetta* alkaloids.

as a consequence of the modest amounts of material isolated, but kealiinine A (**8a**) was shown to be active in the brine shrimp toxicity assay.[7] To date, only two published synthetic studies toward this subgroup of alkaloids have appeared resulting in a total synthesis of kealiiquinone (**6**)[11] and the non-natural 7′-desmethyl derivative (**4**).[12] Furthermore, since the biological activity of the kealiinines has not been extensively investigated, it would appear that a program directed toward their synthesis is warranted.[13]

Over the past few years, our laboratory has developed several synthetic methods for the total synthesis of 2-aminoimidazole alkaloids using site-selective functionalization of polyhaloimidazoles. Using this strategy, we have reported total syntheses of several *Leucetta* alkaloids including clathridine A (**1**),[14] naamidine G (**2**),[15] naamidine H (**3**),[16] and calcaridine A (**5**).[17] We have more recently turned our attention to members of this class containing a naphthimidazole framework such as kealiinines A−C (**8a**−**c**), kealiiquinone (**6**),[12] and the 2-amino congener **7**. While the details of the biosynthesis of these natural products remain to be elucidated experimentally, hypothetical biosynthetic relationships between both the simple systems and the more highly oxidized derivatives are evident. It is thought that naamine-type systems **9** may serve as precursors for other family members through net oxidative functionalization (Figure 2). Some of these potential relationships are outlined in Figure 2, and while they are purely hypothetical, they have provided a framework for our synthetic programs. Indeed, we have used such a biomimetic strategy en route to calcaridine A (**5**) via **9** (R = X = Y = H, Z = OMe).[17] It has been speculated that the naphthimidazole framework arises from a net oxidative coupling between C12 and C13 (kealiinine numbering) and further oxidation to lead to the natural product. Circumstantial evidence to support this idea can be found in reports of C12-oxygenated naamidine derivatives,[6] but there is no experimental data to confirm this hypothesis. From a synthetic perspective, one can envision that a similar outcome might be obtained through a Friedel−Crafts type of strategy to form the C12−C13 bond followed by dehydration.[11] Such a strategy in principle would provide access to all family members with only C2-amination and deprotection necessary. Oxidation of the C-ring would provide an entry to kealiiquinone and congeners.

In order to establish the viability of the strategy we selected kealiinine C (**8c**) as our first target, thereby avoiding potential regioselectivity issues in the cyclization step forming the naphthimidazole system (Scheme 1). In a forward sense, metalation of **12** with EtMgBr in CH_2Cl_2 provides the 5-imidazolyl Grignard, which upon reaction with the trimethoxybenzaldehyde **13c** results in the

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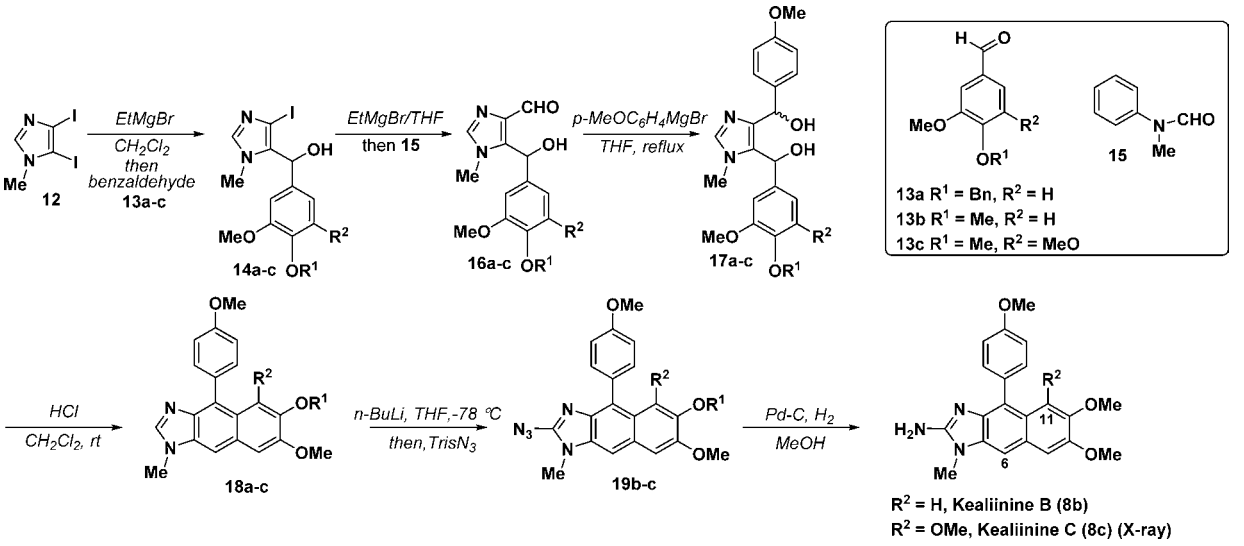
Scheme 1. Assembly of the Benzimidazole Framework (for Yields, See Table 1)



formation of the corresponding alcohol **14c**. Treatment of alcohol **14c** with excess EtMgBr leads to the formation of the 4-imidazolyl Grignard, which reacts with *N*-methyl formanilide (**15**), producing aldehyde **16c**. Treatment of aldehyde **16c** with excess *p*-methoxyphenylmagnesium bromide affords the diol **17c** as an inconsequential diastereomeric mixture in good yield. Attempts to introduce the benzyl moiety directly, i.e., **14c**→**17c** via metalation and reaction with *p*-anisaldehyde, were not successful leading to the two-step sequence described. Gratifyingly, treatment of unpurified **17c** with HCl resulted in an intramolecular Friedel–Crafts cyclization–dehydration sequence to provide the naphthimidazole **18c**, a result that was confirmed by X-ray crystallography. C2-Metalation with *n*-BuLi, followed by exposure to $TrisN_3$, produced the 2-azido compound **19c**. Subsequent treatment with Pd–C/H_2 led to the reduction of the azide to the amine and the completion of the synthesis of the kealiinine C (**8c**).

The ^{1}H NMR spectroscopic data of synthetic kealiinine C in DMSO-d_6 were not in agreement with the data reported for the natural product, and ^{13}C NMR data were not obtained for the natural product.[7] For example, the aromatic proton at C6 on the naphthimidazole framework appeared at δ 7.33 in the synthetic material compared to δ 7.66 in the natural material. Similarly, there were some inconsistencies with the signals due to the methyl substituents. In particular we noted methyl signals at 3.49 (N-Me) and 3.06 ppm (MeO at C11) in the synthetic material, whereas in the naturally occurring material the highest field signal was at 3.40 ppm. We had prepared substantially more material than was isolated from the sponge, and thus we hypothesized that the differences simply may be due to concentration effects. However, while dilution of NMR samples of synthetic material resulted in some minor shift changes ($\Delta\delta \sim 0.05$ ppm), the spectroscopic data were still not in agreement with that reported for the natural product. Attemps to reproduce the

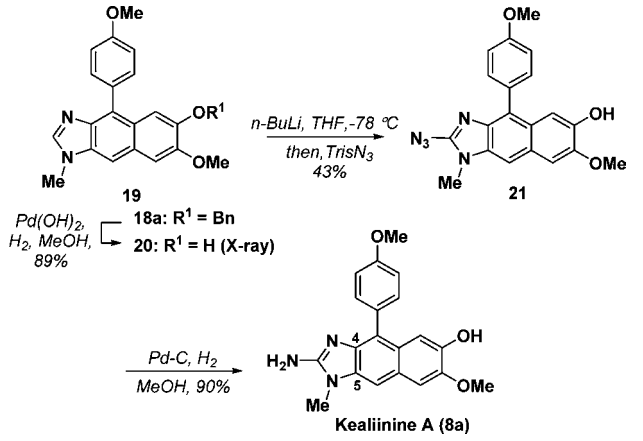
Table 1. Yields for Synthesis of the Kealiinines A–C (**8a**–**c**)

compd	**14** (%)	**16**(%)	**18**(%)	**19**(%)	**8**(%)
a	70	70	65		
b	72	70	70	69	87
c	87	70	65	69[a]	85[a]

[a] Confirmed by X-ray analysis.

"as isolated" sample by the addition of water and/or TFA also failed to cause substantial changes in the chemical shifts. While the connectivity of the naphthimidazole framework and the relative location of the *p*-methoxyphenyl and methyl groups was confirmed through the X-ray analysis of **18c**, it is conceivable that metalation with *n*-BuLi may have occurred at sites other than the imidazole C2. Fortunately, we were able to obtain an X-ray crystal structure of our synthetic final product **8c**, which unequivocally indicated that the required substitution pattern corresponding to the reported structure was obtained. Interestingly, the X-ray structure revealed that we had obtained the amino tautomer, rather than the imino tautomer described for the natural product. While extrapolating from the solid state to the solution phase must be done with caution, one possible explanation for the discrepancy in the spectroscopic data between the isolated natural product and the synthetic material may lie in the extent of the equilibrium. Since only a very small amount of the natural material was isolated, the presence of impurities in the natural sample may substantially influence the position of the tautomeric equilibrium, which in turn may affect the chemical shifts of this material. A related issue with tautomers has been observed with kealiiquinone which was isolated as this enol tautomer,[9] but the synthetic material was prepared as the keto form.[11]

Scheme 2. Completion of Kealiinine A (**8a**)



To partially address this issue, the Proksch lab was kind enough to perform comparative HPLC analysis of our synthetic material with a natural product sample. This analysis showed that the two samples coeluted, suggesting that they were in fact chromatographically identical.[18]

Given that there was some uncertainty in the structure of kealiinine C (**8c**), we decided to prepare the other two family members, kealiinine A (**8a**) and B (**8b**). Their syntheses follow largely the same strategy, simply substituting the appropriate benzaldehyde for **8a** and **8b** providing the targets in seven steps (11% overall yield) and six steps (21% overall yield), respectively, from **12**. In the case of kealiinine A (**8a**), deprotection of the *O*-benzyl group was accomplished prior to C2-azidation and reduction as metalation was more effective with a free phenolic OH (Scheme 2). X-ray crystallographic analysis of **20** unequivocally confirmed the connectivity of the Friedel–Crafts product. Puzzlingly, however, the spectroscopic data for both synthetic materials also did not coincide with the data reported for by the Proksch laboratory. On the other hand the chromatographic properties of the synthetic and natural materials were identical based on HPLC data. In the case of kealiinine A (**8a**), the ^{13}C NMR data were reported, but our data did not appear to match well either. However, the major disagreements are largely confined to carbons assigned to C4 and C5, which are consistent with the hypothesis of the different tautomeric identities of the isolated and synthetic materials.

In summary, we have developed high-yielding, protecting-group-free synthesis of the *Leucetta* alkaloids kealiinine A–C (**8a**–**c**) using sequential and chemoselective halogen–magnesium exchange reactions. Subsequent Friedel–Crafts cyclization and lithiation at C2 with electrophilic trapping leads to introduction of the 2-amino moiety. While the structures of the synthetic materials are secure and their chromatographic properties match the natural materials, the spectroscopic data do not match. One explanation for these observations may be related to the preparation of the amino form rather than the isolated imino forms. Attempts to reproduce the spectroscopic characteristics of the as isolated material through changing the sample concentration and introduction of additives have been unsuccessful.

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Supporting Information Available. Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Tabulated listing of NMR assignments, copies of HSQC, HMBC and ROESY plots, and comparative HPLC traces. CIFs for compounds **8c**, **18c**, and **20**. This information is free of charge from the Internet at http://pubs.acs.org.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) An alternative interpretation of these observations is that the assigned structure is in fact incorrect. To address this possibility, we prepared an isomeric congener through similar chemistry and found that although the NMR data were a better match (but not exact), the chromatographic properties were substantially different from the naturally occurring material.