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Studies towards the *Leucetta*-Derived Alkaloids Spirocalcaridine A and B – Possible Biosynthetic Implications

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An exploration of an abiotic approach to spirocalcaridines A and B is described centered on electrophile-induced dearomatizing spirocyclization of aryl enyne derivatives. Elaboration of the α-iodoenone through an Ullmann-like, copper-catalyzed amidation provided a formamide, which upon treatment with methylamine undergoes a dienol-arene rearrangement to provide the corresponding kealiinine-like framework. This observation suggests a possible biosynthetic links between the spirocalcaridine and naphthimidazole group of *Leucetta* alkaloids.

Introduction

The *Leucetta* family of marine sponges produces a wide variety of secondary metabolites, which includes a growing number of 2-aminoimidazole alkaloids that have recently been reviewed.[1] Many of these imidazole-containing metabolites are biologically active and exhibit, amongst others, anti-cancer and antibiotic activities, but their biological roles in nature have yet to be rigorously defined.[1b] Structurally, these 2-aminoimidazoles fit into five broad subclasses as a function of their substitution patterns and oxidation levels. The simplest systems are characterized by the presence of one benzyl moiety on the 2-aminoimidazole framework, e.g., preclathridine A (**1**); oftentimes there is a closely related congener in which the 2-amino moiety is functionalized with methyl parabanic acid, e.g., clathridine A (**2**).[2] Two groups contain two benzylic moieties; the naamine/naamidine group is substituted with benzyl groups at C4 and C5, e.g. naamidine H (**3**),[3] whereas the isonaamine/isonaamidine group is functionalized at N1 and C4, e.g., isonaamidine E (**4**).[4] The fourth group of *Leucetta* alkaloids contains a naphthimidazole framework, such as that found in the kealiinines, e.g., **5**[5] and kealiiquinones, e.g. **6**[6] and **7**.[7] The final and most recently isolated group of alkaloids that belongs to this family of sponges is the most highly oxygenated and includes calcaridine A (**8**),[8] spirocalcaridines A (**9**) and B (**10**),[8b] and spiroleucettadine (**11**)[9] and spironaamidine (**12**) (Figure 1).[10]

To date, there have been no experimental studies directed towards unraveling the biosynthetic pathways that lead to the formation of these compounds. The lack of experimental support notwithstanding, obvious relationships can be mapped out among the various family members (Figure 2). The parent systems have been hypothesized to be derived from either octapamine (**13**), tyramine (**14**) or *p*-hydroxyphenyl pyruvate (**16**), which leads to **17** and the 4,5- and 1,4-disubstituted systems result from elaboration of this species.[1a] The remaining family members can then be derived from naamine A (**19**) or closely related analogs. For example, calcaridine A (**8**), which contains a 4,4-disubstituted 5-imidazolone fragment, derives from the oxidative rearrangement of naamine derivative.[8a,8c,11] Spirocalcaridines (**9**) and (**10**) can also be traced back to the same general precursor through a dearomatizing alkylation and oxidation of the resulting intermediate. Spiroleucettadine (**11**) and related spironaamidine (**12**) can be envisioned to derive from the corresponding naamine derivative by oxidation of the imidazole 4,5-bond followed by an oxidative dearomatization. The final group of *Leucetta*-derived alkaloids that originate from naamine-type precursors are the kealiinines[5c] and kealiiquinones.[6,7] The former can be derived from an intramolecular Friedel–Crafts-like process followed by oxidation to deliver the kealiinines. Additional oxidation would then permit entry to the kealiiquinones. Our group has taken advantage of these putative relationships to accomplish the total syntheses of calcaridine A,[8a,8c] kealiinines A–C,[5a,5b] kealiiquinone, and 2-deoxy-2-amino-kealiiquinone.[12]

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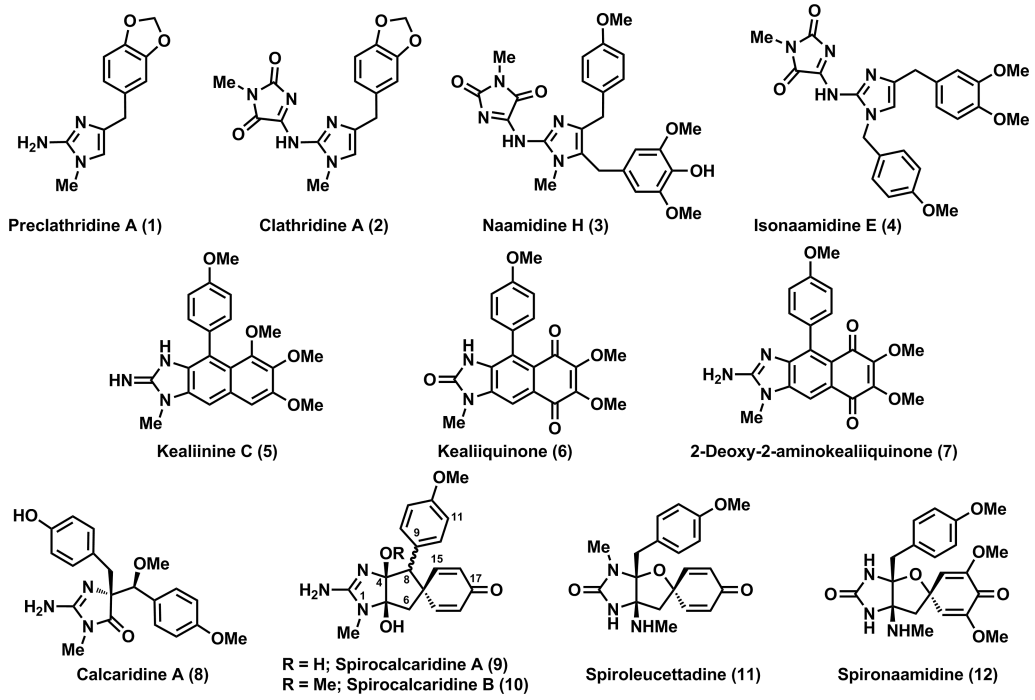


Figure 1. Representative *Leucetta* alkaloids.

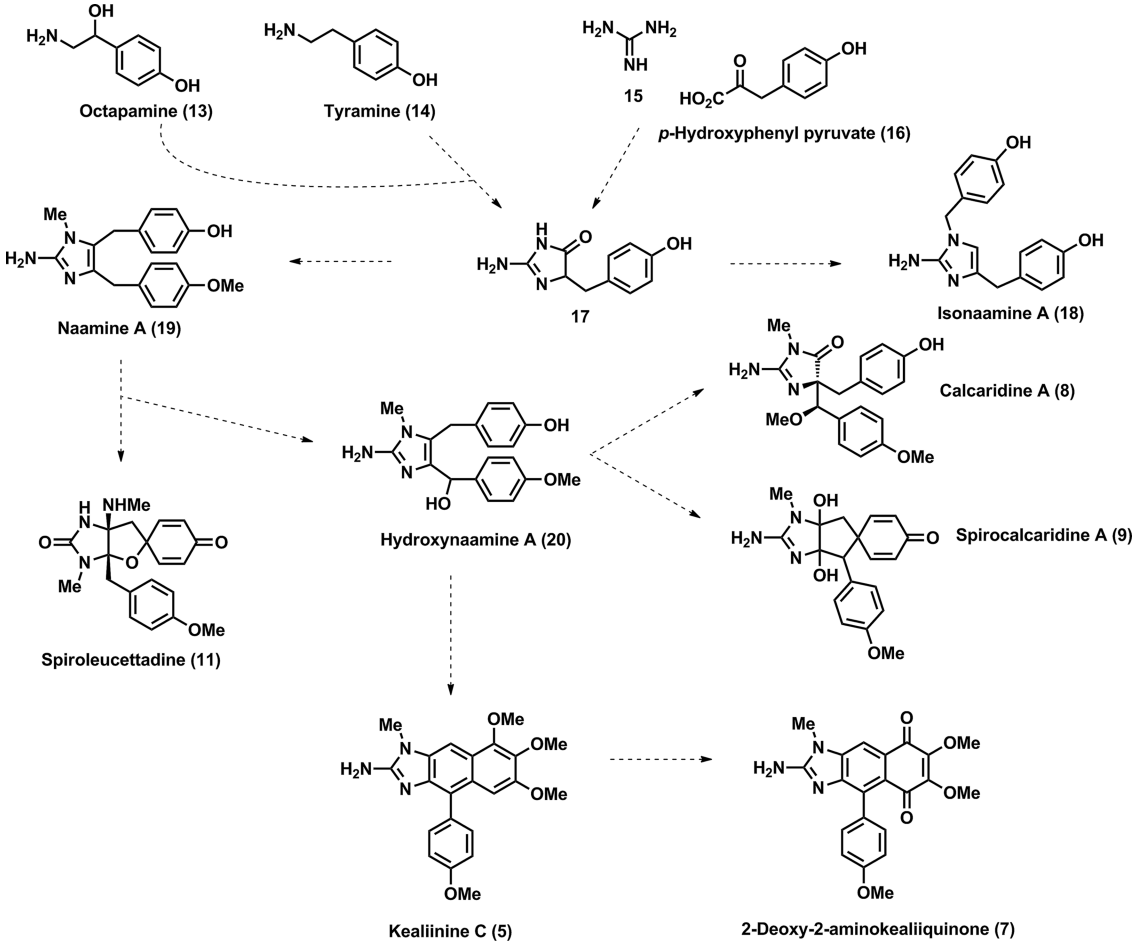


Figure 2. Putative biosynthesis and biosynthetic relationships among the *Leucetta* alkaloids.

Results and Discussion

In our studies towards both the *Leucetta*[13] and the oroidin alkaloids[14] we have adopted a general strategy to elaborate pre-existing imidazoles rather than the de novo construction of the heterocycle and broadly bioinspired approaches to construct the key structural elements contained within the alkaloid framework. Our attempts to execute such a strategy towards the spirocalcaridines have been largely unsuccessful and thus we have pursued an alternative abiotic approach.[15] The general plan depicted in retrosynthetic form centered on the construction of key spirofused framework **23** through an electrophile-induced dearomatizing spirocyclization and then annulation of the imidazole ring (**23**→**22**; Figure 3). Adjustment of the oxidation state of the imidazole, if necessary, would be accomplished based on chemistry developed in our laboratory by using *N*-sulfonyloxaziridines (**21**→**9** or **10**; Figure 3).[11] This strategy was predicated on the availability of **23** through dearomatizing cyclization of aryl ynones, chemistry developed independently by Larock[16] and Li[17], and subsequently developed further by others.

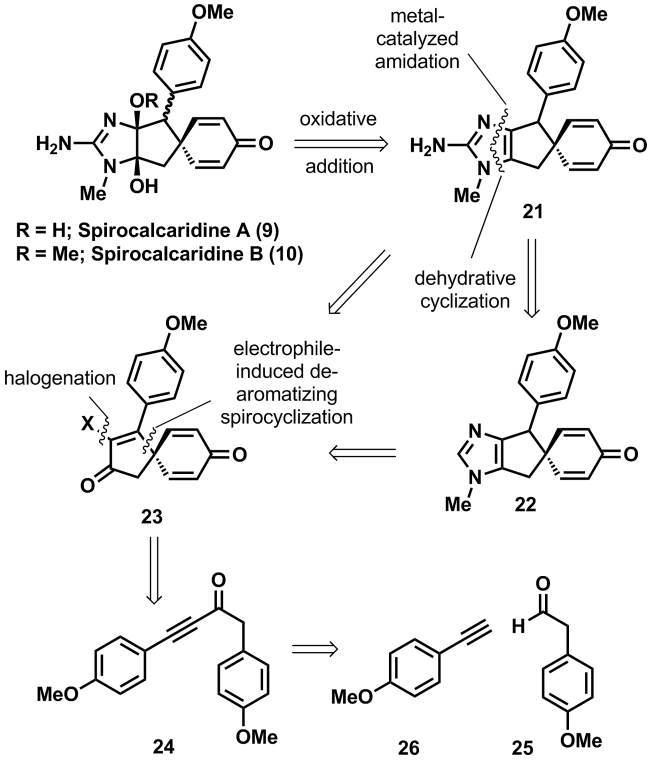
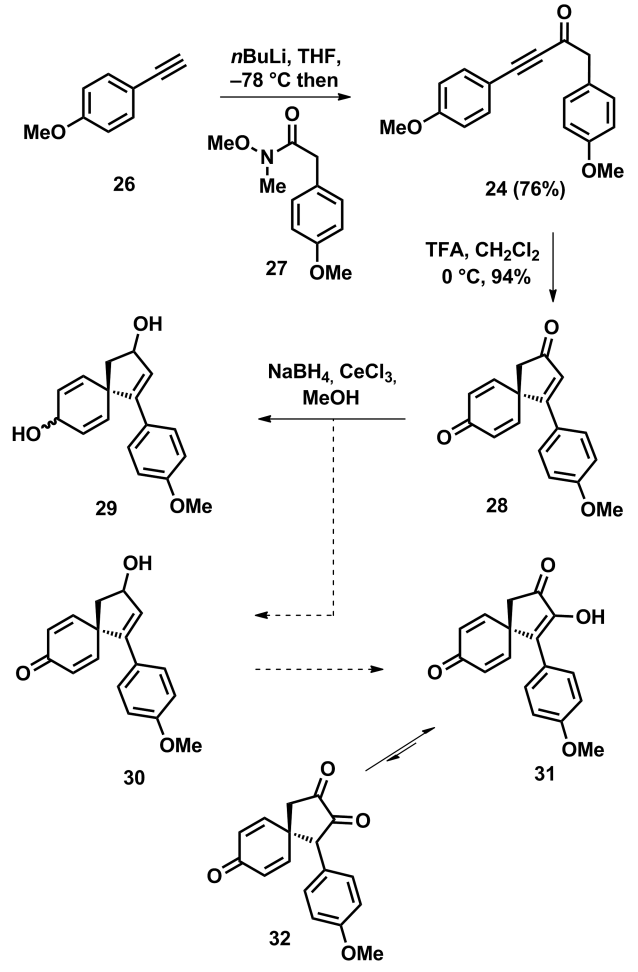


Figure 3. A retrosynthetic analysis of spirocalcaridines A and B.

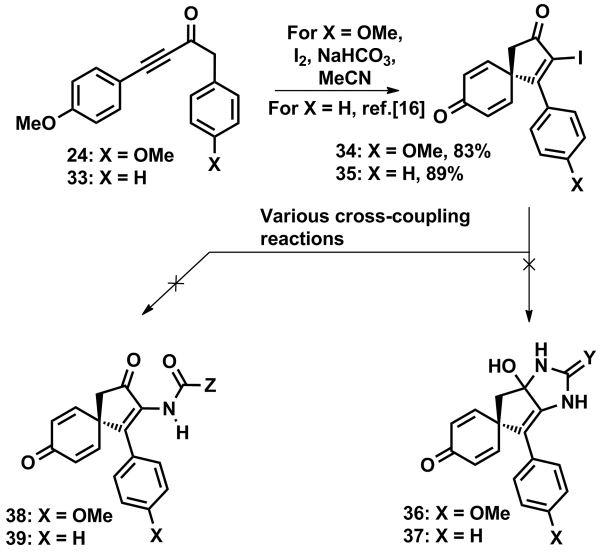
In an initial foray towards these natural product targets, we identified α-diketone **32** as a potentially useful intermediate for further elaboration (Scheme 1). Taylor and coworkers have used a similar strategy in their recently published total synthesis of spirobacillene A.[18] To access this material, spirofused derivative **28** was required, which in turn necessitated ynone **24** as a precursor (Scheme 1). This was accomplished from deprotonation of *p*-ethynylanisole (**26**)[19] with *n*BuLi and by trapping the resulting lithium acetylide with Weinreb amide **27** (Scheme 1).[20] Gratifyingly, ynone **24** delivered spirofused triene dione **28** in 94% yield upon treatment with trifluoroacetic acid (TFA).[18] With the spiro derivative in hand, our plan involved the selective epoxidation of the cyclopentenone followed by isomerization to give the α-diketone.[18] However, attempts to effect selective reduction of cyclopentenone were compromised by competitive reduction of the dienone carbonyl, which resulted in a complex mixture of alcohols and diols.[18] Presumably, the electron rich aryl ring retards the reduction rate of the cyclopentenyl carbonyl and thus competitive reduction of both enones occur. As a result, we directed our attention towards the preparation of derivatives already functionalized at the α-position.



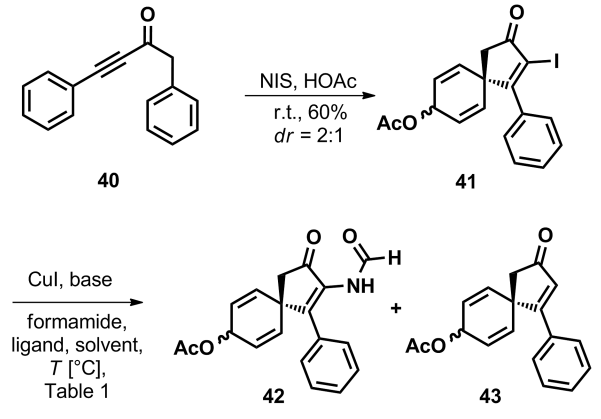
Scheme 1.

Larock has described previously the preparation of α-iodocyclopentenone **35** from the dearomatizing spirocyclization of **33** with *N*-iodosuccinimide (NIS).[16] Similarly, we found that the anisyl-substituted derivative led to related spirocycle **34** under similar conditions (Scheme 2). Brief attempts were made to react these intermediates with either guanidine or urea as means to install the imidazole component, but these experiments were unsuccessful. Similarly, attempts to introduce a nitrogen substituent in place of the iodine through a variety of palladium[21] or copper-cata-

lyzed cross-coupling reactions were unsuccessful (see Scheme 3 for successful implementation of this strategy).[22] Although the failure of the direct installation of the imidazole moiety was not unexpected,[23] given the general robustness of cross-coupling chemistry, we suspected the presence of the cyclohexadienone was the cause of the problems. As a result, we decided to investigate the corresponding dienol derivative, which would not be susceptible to Michael addition reactions.



Scheme 2.



Scheme 3. Dearomatizing spirocyclization.

Initial studies were performed with diphenyl-substituted derivative **40**, because this could be prepared through known procedures from phenylacetylene. Treatment of alkynone **40** with NIS in acetic acid provided spirocyclic enone **41** as a 2:1 mixture of diastereomers (Scheme 3). The stereochemistry of the major diastereomer was not assigned and this mixture was used directly in the next step. Given that the acetoxy-bearing center would eventually be converted into a carbonyl in the synthetic scheme this stereoisomeric mixture was of no consequence. It was our intention to use the iodo moiety as a means to introduce a substituted nitrogen through a cross-coupling strategy. Although several options are available in a general sense, the use of palladium catalysis was likely to be compromised by the presence of the allylic acetate, and thus our efforts were directed towards the use of copper-mediated methods.[22] The Buchwald group has demonstrated that cross-coupling reactions between vinyl iodides and acetamides occurs upon treatment with 5 mol-% CuI, *N*,*N*′-dimethylethylenediamine (DMEDA), Cs_2CO_3 in tetrahydrofuran (THF) at 50–70 °C.[22a] Subjection of iodide **41** to these reaction conditions but with the use of formamide resulted in the formation of coupling product **42** in 50% yield along with 25% of **43** derived from the net reductive deiodination of **41** (Table 1, Entry 1; and Scheme 3).[24] A screen of various solvents (Table 1, Entries 2–5) resulted in no improvement in the cross-coupling yields, although it is of note that in acetonitrile there is an increase in the amount of reduction product **43**. Attempts to improve the yield of cross-coupling product **42** by using stoichiometric quantities of copper and DMEDA were not successful (Table 1, Entry 6); reduction of the reaction temperature with catalytic loadings of CuI still resulted in appreciable reductive deiodination. By changing the base to K_2CO_3 or the copper salt to the bromide has little to no effect on the yield. We also briefly investigated other coupling partners under the best conditions, but found that neither urea nor *N*-methylurea delivered the cross-coupled product and only reductive deiodination was observed.[25]

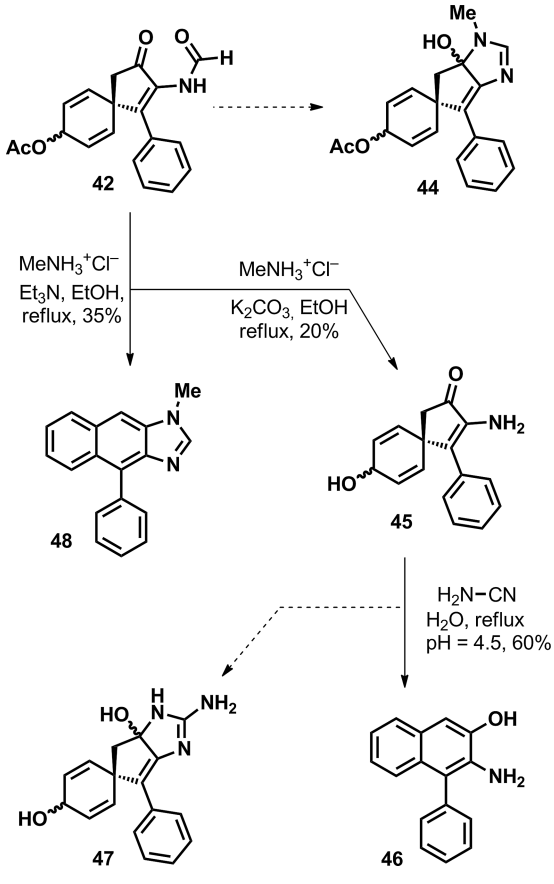
With formamide **42** in hand, we attempted to install the remaining nitrogen atom in the basic alkaloid framework ideally providing **44** (Scheme 4). Initial experiments were conducted with methylamine, because this would provide an avenue for the direct introduction of the methyl group in a site-specific manner to provide **44**. Subsequent regioselective and chemoselective hydration of the carbon-carbon double bond in the cyclopentene would then provide the entire AB-ring system of spirocalcaridine. However, when **42** was treated with methylamine·HCl in the presence of K_2CO_3, hydrolysis of both the acetate and formamide occurred, which provided amino alcohol **45** in low, non-optimized yield. The efficiency notwithstanding, we attempted to convert **45** into corresponding 2-aminoimidazole **47** by treatment with cyanamide, but this resulted in rearrangement of the spirofused system into aminonaphthol derivative **46** rather than the desired 2-aminoimidazole (Scheme 4). A related rearrangement occurred upon treatment of **42** with methylamine·HCl in the presence of Et_3N and EtOH at reflux, which provided aminonaphthol derivative **48**. Notably in this case the product does contain a methyl imidazole moiety, which suggests that it may be possible to annulate **42** under the appropriate circumstances (see below).

Given that both spirocalcaridines A (**9**) and B (**10**) possess a methoxy group on the aryl ring we prepared corresponding substrate **53** by iodine-induced *ipso* cyclization reaction of known alkynone **52**,[26] which delivered **53** in good yield as an almost 1:1 mixture of diastereomers (Scheme 5). It is of note that the reaction temperature has

Table 1. Optimization of the cross-coupling reaction of **41**.

Entry	Solvent	Ligand	Base	Catalyst	Amide	Temp. [°C]	Time [h]	% Yield **42**	% Yield **43**
1	THF	10% DMEDA	1.5 equiv. Cs_2CO_3	5% CuI	formamide	70	22	50	25
2	1,4-dioxane	10% DMEDA	2.0 equiv. Cs_2CO_3	5% CuI	formamide	110	28	n.r.[a]	–
3	toluene	10% DMEDA	1.5 equiv. Cs_2CO_3	5% CuI	formamide	80	24	n.r.[a]	–
4	DMF	10% DMEDA	1.5 equiv. Cs_2CO_3	5% CuI	formamide	70	30	10	–
5	CH_3CN	10% DMEDA	1.5 equiv. Cs_2CO_3	5% CuI	formamide	70	30	45	40
6	THF	2 equiv. DMEDA	2 equiv. Cs_2CO_3	1 equiv. CuI	formamide	80	48	52	30
7	THF	2 equiv. DMEDA	2 equiv. Cs_2CO_3	1 equiv. CuI	formamide	40	10	21	20
8	THF	10% TMEDA	2 equiv. K_2CO_3	5% CuI	formamide	25	12	–	–
9	THF	10% DMEDA	2 equiv. K_2CO_3	5% CuI	formamide	70	15	40	30
10	THF	10% DMEDA	2 equiv. Cs_2CO_3	5% CuBr	formamide	70	15	50	30
11	THF	10% DMEDA	2 equiv. Cs_2CO_3	5% CuI	formamide	70	15	30	–
12	THF	10% TMEDA	2 equiv. Cs_2CO_3	5% CuCN	formamide	70	15	–	–
13	THF	10% DMEDA	2 equiv. Cs_2CO_3	5% CuI	urea	70	15	–	30
14	THF	10% DMEDA	2 equiv. Cs_2CO_3	5% CuI	*N*-methylurea	70	15	–	30

[a] n.r.: no reaction, starting material recovered unreacted.

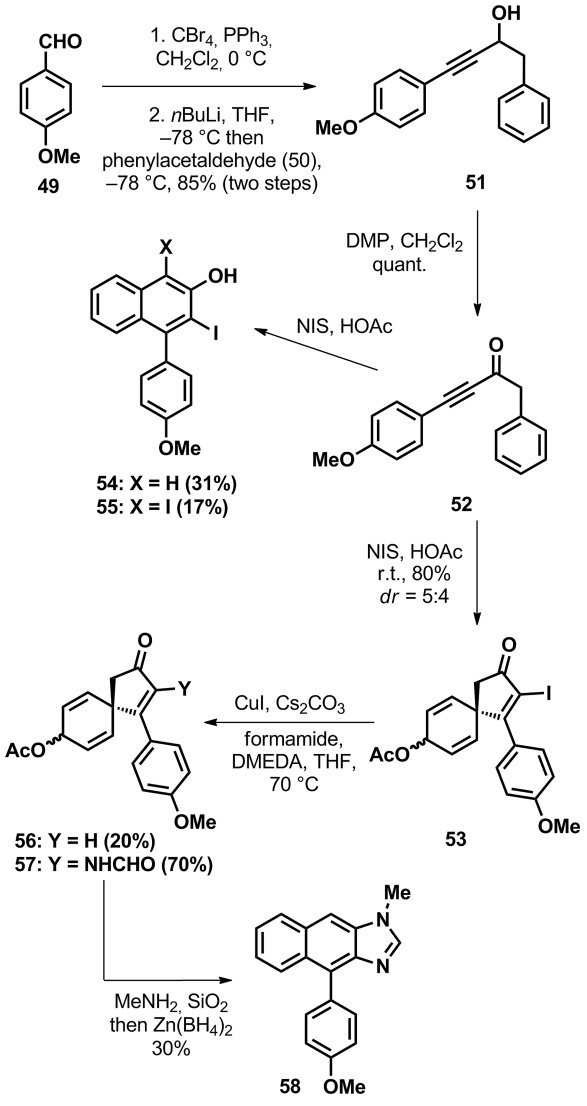


Scheme 4. Attempted annulation of imidazole moiety.

to be controlled very carefully during the addition of NIS, otherwise formation of iodonaphthol **54** and diiodonaphthol **55** are observed. An X-ray structure of **55** unequivocally confirms the location of the iodides in the diiodinated naphthol (Figure 4; Scheme 5).[27] α-Iodoenone **53** was subjected to the cross-coupling chemistry with CuI and formamide to provide corresponding amide **57** in 70% yield along with 20% of reductively deiodinated product **56**. With formamide **57** in hand we explored a slightly different approach in which the oxidation state of the system was adjusted by reducing the C4–C8 double bond (spirocalcaridine numbering). A wide variety of conditions were evaluated, but none of them delivered the reduction product. An alternative strategy involved the formation and reduction of an imine (or iminium species), and an ensuing cyclization would result in the formation of the key framework elements found in spirocalcaridines A and B. However, we found that although an *N*-methylimidazole was formed, the spiro ring system had again undergone rearrangement to form a naphthimidazole framework **58** (Scheme 5).

The tendency of these spiro systems to undergo rearrangement under acidic conditions or in the presence of Lewis acid is not surprising given their close relationship to substrates that participate in the cyclohexadienol-benzene rearrangement. Mechanistically, we assume that the methylamine reacts to form imine **60**, which then undergoes rearrangement to form naphthyl framework **62** after activation by protonation via **61** (Scheme 6). Deprotonation provides **63**, which undergoes tautomerization and dehydrative cyclization to form the imidazole ring and **40**.

This propensity to undergo rearrangement raises the possibility that the spirocalcaridines (and perhaps as yet unidentified congeners) may serve as biosynthetic precursors to the naphthimidazole group of *Leucetta* alkaloids (Scheme 7). As a result the biosynthetic relationships among the more highly functionalized congeners may require some reanalysis. Naamine A (**65**, X = Y = H) or naamine G (**65**, X = Y = MeO) derivatives after *N*-methylation may serve as precursors to spirofused derivative **66** through oxidative-dearomatizing spirocyclization. Subsequent rearrangement by hydrolytic ring opening, and ring-closure of the 2-aminoimidazole to the 2-imidazolone then delivers the two spiroleucettadine congeners **11** and **12**. The 14-functionalized naamine derivative (**65**, Z = OH) may serve as a biosynthetic precursor to calcaridine A (**8**) through *O*-methylation and oxidative rearrangement. It is of note that we have accomplished the latter through the use of an *N*-sulfonyloxaziridine.[11] The same precursor (**65**, Z = OH) upon activation of the hydroxy group may engage in a dearomatizing spirocyclization, which upon dihydrox-



Scheme 5. Attempted iodine-induced *ipso* addition reaction of alkyne **51**. DMP = Dess–Martin periodinane.

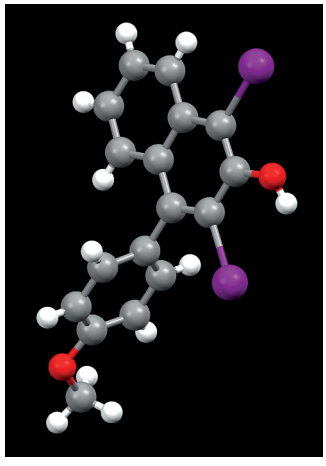
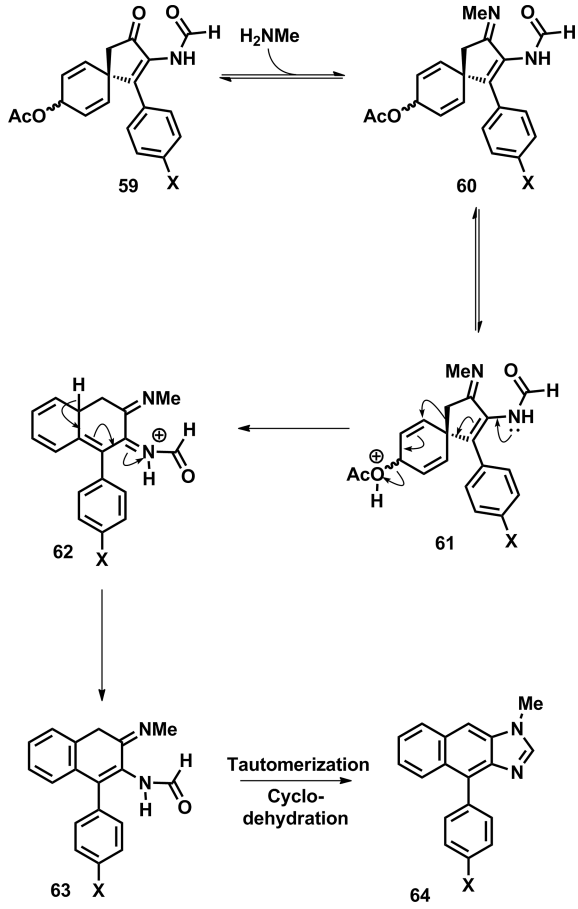


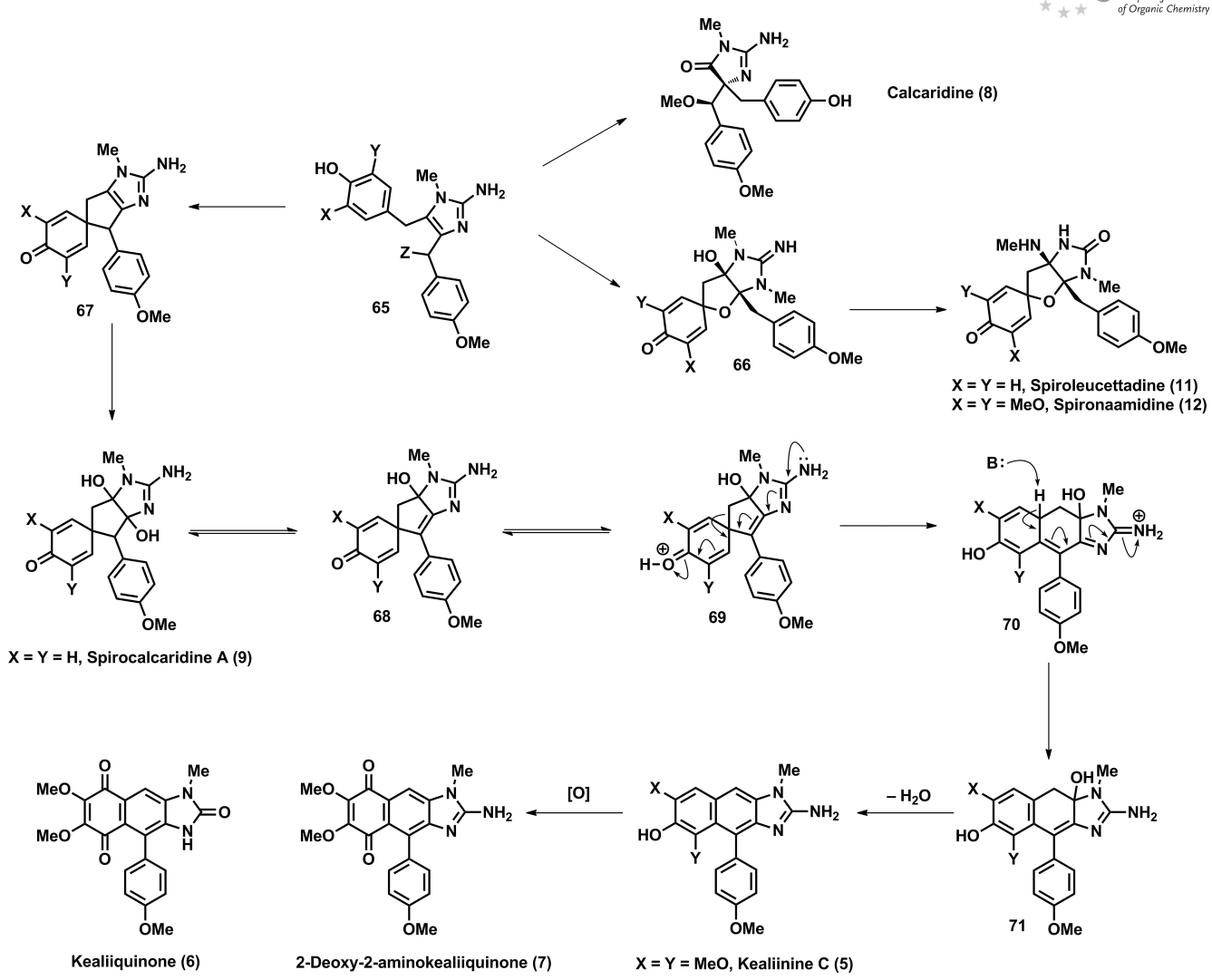
Figure 4. X-ray crystal structure of diiodonaphthol derivative **55**.

ylation would lead to the formation of the spirocalcaridine framework. It has been speculated that derivatives related



Scheme 6. Putative mechanism for the conversion of spirofused system into the naphthimidazole framework.

to **65** (Z = OH) can serve as precursors to the naphthimidazole framework by electrophilic addition (Friedel–Crafts-like) and subsequent oxidation. However, other pathways are feasible, which includes *ipso* addition, followed by rearrangement via an intermediate related to **67** and then oxidation.[5a] Our own studies with this system points to another possibility in which spirocalcaridine (or closely related derivative) may undergo dehydration to **68**; protonation of the carbonyl oxygen primes the system for rearrangement by a dienone-phenol rearrangement (**69**→**70**, Scheme 7). Rearomatization to **71** and a second dehydration delivers the naphthimidazole derivatives, the kealiinines. Alternatively, oxidation of **67** provides same intermediate **68** for the dienone-phenol rearrangement to deliver **70**. Further oxidation of the naphthimidazole provides the naphthoquinone derivatives kealiiquinone and 2-deoxy-2-aminokealiiquinone. We note that we have recently accomplished the total synthesis of both kealiiquinone and 2-aminokealiiquinone through oxidative functionalization of kealiinine derivatives, thus there is a direct synthetic connection between three types of *Leucetta* alkaloids.[12b] When these results and ideas are taken in concert with our previous results, the direct connection between almost all the *Leucetta* alkaloids can be mapped out, specifically the relationship between the naamidine framework and the



Scheme 7. Putative biosynthetic relationship between the naamine, calcaridines and the naphthimidazole group of *Leucetta* alkaloids.

other members can be envisioned. Only the feasibility of the conversion of the naamine to spirocalcaridine framework remains to be demonstrated in the laboratory. This is a challenge that we are presently pursuing. It is important to note that Scheme 7 is purely hypothetical as far as the biosynthesis is concerned and there is no evidence for this sequence in biological systems. Although our experiments do not address the biosynthesis directly, we have a growing body of evidence to suggest that the postulated transformations are feasible. Based on these hypotheses, it raises the possibility of additional family members related to **66**, **67**, and **68** in which X = Y = OMe, and non-symmetrical variants in which either X = H and Y = OMe, or X = OMe and Y = H.

Conclusions

In summary, we have described some exploratory experiments towards the total synthesis of spirocalcaridine A and B, and although these have not been successful owing to dienone-phenol rearrangements, these results provide circumstantial evidence for alternative biosynthetic relationships between the spirofused and naphthimidazole systems. This type of rearrangement has been posited to account for the biosynthesis of several aporphinoid alkaloids.[28] Recent results from our laboratory have demonstrated that oxidation of the kealiinine framework gives rise to the quinone moiety within the kealiiquinone group and thus we have demonstrated experimentally a link between four subfamilies of these aminoimidazole natural products. Although these results do not prove the biogenesis of these *Leucetta* alkaloids, it provides evidence that these pathways are at least feasible.

Experimental Section

General: All chemicals were obtained from commercial vendors and were used as received unless stated otherwise. All reactions were conducted under an atmosphere of dry nitrogen in oven-dried glassware. Solvents were dried by using a Pure-Solv 400 solvent

purification system (Innovative Technology, Inc.), except for dimethylformamide (DMF), which was dried with CaH_2 and then distilled under vacuum. The ^1H NMR spectra were acquired at 500 MHz in $CDCl_3$, unless indicated otherwise, by using residual $CHCl_3$ as a reference. ^{13}C NMR spectra were obtained at 125 MHz in $CDCl_3$, unless otherwise indicated, by using the central absorbance of $CDCl_3$ as an internal standard. In cases in which diastereomers were isolated as inseparable mixtures, ^1H NMR spectroscopic signals for related absorptions are integrated together and the minor isomer signal is underlined. For ^{13}C NMR spectroscopic data, the minor isomer is reported in parentheses. High-resolution mass spectra were obtained at the University of Florida by electrospray ionization (HRMS-ESI) or at the Shimadzu Center for Advanced Analytical Chemistry, University of Texas at Arlington.

1,4-Bis(4-methoxyphenyl)but-3-yn-2-one (24): To a solution of alkyne **26** (3.00 g, 22.7 mmol) in anhydrous THF (20 mL) at –78 °C was added *n*-butyllithium (2.5 M solution in hexane, 10.9 mL, 27.2 mmol). The yellow solution was stirred at –78 °C for 30 min, before adding into a pre-cooled (–78 °C) solution of Weinreb amide **27** (5.22 g, 25.0 mmol) in anhydrous THF (20 mL) by cannula. The mixture was stirred at –78 °C for 1 h, then the cooling bath was removed and the mixture was stirred for another 15 min. The mixture was then cooled to –78 °C and quenched with satd. aq. NH_4Cl (40 mL). Upon warming to room temperature the mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL), dried with Na_2SO_4 and concentrated under vacuum. The obtained crude material was subjected to purification by flash column chromatography (ethyl acetate/hexane = 1:4) to afford desired compound **24** as yellow solid (4.83 g, 76%), m.p. 78–80 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.6 Hz, 2 H), 7.22 (d, J = 8.6 Hz, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 3.84 (s, 2 H), 3.82 (s, 3 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.8, 161.8, 159.0, 135.3, 130.0, 125.6, 114.4, 111.7, 94.1, 87.8, 55.5, 55.4, 51.3 ppm. FTIR (neat): $\tilde{\nu}$ = 2964, 2936, 2899, 2839, 2188, 1667, 1599, 1508, 1462, 1439, 1396, 1297, 1247, 1173, 1068, 1020, 818, 795, 688, 567, 534 cm^{-1}. HRMS (*m*/*z*): calcd. for $C_{18}H_{15}O_3$ $[M - H]^+$ 279.1027; found 279.1020.

4-(4-Methoxyphenyl)spiro[4.5]deca-3,6,9-triene-2,8-dione (28): To a solution of compound **24** (1.00 g, 3.57 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C was added TFA (5.5 mL, 71.35 mmol) and the resulting solution was stirred at 0 °C for 3 h. During this time, the reaction color changed to red wine from light yellow. The volatiles were removed under vacuum, ethyl acetate (150 mL) was added and the organic layer was washed with sat aq. $NaHCO_3$ (100 mL), dried with Na_2SO_4, and concentrated under vacuum. Obtained crude material was purification by flash column chromatography (ethyl acetate/hexane = 3:7) to afford compound **28** as a black solid (0.90 g, 94%), m.p. 70–72 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.6 Hz, 2 H), 6.93 (d, J = 10.3 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 6.60 (s, 1 H), 6.40 (d, J = 10.3 Hz, 2 H), 2.73 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.2, 184.9, 173.2, 162.5, 152.2, 129.8, 129.7, 127.6, 125.5, 114.5, 55.6, 51.1, 46.9 ppm. FTIR (neat): $\tilde{\nu}$ = 3086, 3043, 2936, 2841, 2245, 1737, 1697, 1661, 1583, 1509, 1397, 1308, 1245, 1185, 1041, 1020, 864, 836, 731, 592, 509 cm^{-1}. HRMS (*m*/*z*): calcd. for $C_{17}H_{14}O_3Na$ $[M + Na]^+$ 289.0835; found 289.0824.

4-(4-Methoxyphenyl)-3-iodospiro[4.5]deca-3,6,9-triene-2,8-dione (34): To a solution of compound **24** (1.00 g, 3.57 mmol) in anhydrous acetonitrile (35 mL) at room temperature was added $NaHCO_3$ (0.60 g, 7.13 mmol) followed by iodine (1.81 g, 7.13 mmol). The resulting brown mixture was stirred at room temperature for 30 min. The reaction was quenched with satd. aq. $Na_2S_2O_3$ (100 mL), extracted with ethyl acetate (3 × 100 mL), dried with Na_2SO_4, and concentrated under vacuum. The crude material thus obtained was purified by flash column chromatography (ethyl acetate/hexane = 2.5:7.5) to afford compound **34** as a black solid (1.16 g, 83%), m.p. 133–135 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, J = 10.0 Hz, 2 H), 6.87 (d, J = 10.0 Hz, 2 H), 6.80 (d, J = 10.0 Hz, 2 H), 6.37 (d, J = 10.0 Hz, 2 H), 3.82 (s, 3 H), 2.93 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.3, 184.5, 175.1, 161.5, 149.8, 130.5, 129.2, 126.3, 114.0, 104.3, 55.5, 54.3, 43.7 ppm. FTIR (neat): $\tilde{\nu}$ = 2960, 2919, 2838, 1718, 1693, 1660, 1622, 1601, 1562, 1503, 1415, 1293, 1247, 1178, 1024, 923, 857, 835, 766, 553, 524 cm^{-1}. HRMS (*m*/*z*): calcd. for $C_{17}H_{13}O_3INa$ $[M + Na]^+$ 414.9802; found 414.9804.

2-Iodo-3-oxo-1-phenylspiro[4.5]deca-1,6,9-trien-8-yl Acetate (41): Alkynone **40** (1.35 g, 6.1 mmol) was dissolved in acetic acid (5 mL) followed by the careful addition of NIS (1.65 g, 7.3 mmol) to maintain ambient temperature. After stirring the resulting mixture for 30 min, ethyl acetate was added to it followed by aqueous saturated $NaHCO_3$ to neutralize the reaction mixture. The EtOAc solution was separated and the aqueous layer was extracted with EtOAc two more times. The combined organic layers were dried (Na_2SO_4) and concentrated to provide a crude product, which was separated chromatographically (10% ethyl acetate in hexanes) to provide a ≈ 2:1 mixture of **41** (1.46 g, 60%) as a pale brown oil: ^1H NMR: δ = 7.42–7.35 (m, 3 H), 7.24–7.22 (m, 2 H), 5.95–5.88 (m, 2 H), 5.87–5.81 (m, 2 H), *5.55*, 5.25 (m, 1 H), 2.82, *2.76* (s, 2 H), 2.04, *1.94* (s, 3 H) ppm. ^{13}C NMR: δ = 201.1 (201.0), 180.1 (178.9), 170.5 (170.5), 135.2 (135.0), 132.5 (133.8), 130.0 (129.9), 128.3 (128.0), 127.3 (127.9), 126.3 (125.4), 105.4 (104.8), 63.6 (63.4), 51.8 (51.4), 46.7 (47.6), 21.1 (21.0) ppm. IR (neat): $\tilde{\nu}$ = 3033, 2924, 1721, 1369, 1236, 1016, 928, 739, 698 cm^{-1}. HRMS-ESI (*m*/*z*): calcd. for $C_{18}H_{15}INaO_3$ $[M + Na]^+$ 428.9958; found 428.9926.

2-Formylamino-3-oxo-1-phenylspiro[4.5]deca-1,6,9-trien-8-yl Acetate (42): A 10 mL resealable, thick-walled tube was charged with CuI (20 mg, 0.1 mmol), iodo-ketone **41** (841 mg, 2.1 mmol) and Cs_2CO_3 (1.01 g, 3.1 mmol). The tube was evacuated and back filled with nitrogen and *N*,*N*′-dimethylethylenediamine (0.02 mL, 0.2 mmol), formamide (0.10 mL, 2.5 mmol) and THF (5 mL) were added under nitrogen. The pressure tube was sealed with a Teflon cap, immersed in a preheated oil bath at 70 °C and the reaction mixture was stirred for 48 h, and progress followed by TLC. After the resulting pale blue suspension was allowed to reach room temp., EtOAc was added. The reaction mixture was filtered through a pad of silica (EtOAc). The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (10% ethyl acetate in hexanes) to provide **42** as brown oil (334 mg, 50%). ^1H NMR: δ = *8.88*, 8.83 (d, J = 11.5 Hz, 1 H), 7.39 (s, 3 H), 7.34 (m, 1 H), 7.18 (m, 2 H), 5.95–5.90 (m, 2 H), 5.86–5.80 (m, 2 H), *5.59*, 5.32 (m, 1 H), 2.73, *2.67* (s, 2 H), 2.05, *1.95* (s, 3 H) ppm. ^{13}C NMR: δ = 199.9 (199.8), 170.5, 161.8 (162.0), 154.1 (153.5), 133.3 (134.5),133.9 (133.6), 132.3 (132.5), 129.6 (129.7), 129.1 (128.8), 127.6 (128.1), 126.1 (125.3), 63.6 (63.4), 47.4 (48.2), 46.2 (45.9), 21.2 (21.0) ppm. IR (neat): $\tilde{\nu}$ = 3195, 3023, 2917, 2850, 1667, 1494, 1441, 1221, 1097, 748, 698 cm^{-1}. HRMS (*m*/*z*): calcd. for $C_{19}H_{16}NO_4$ $[M - H]$ 322.1085; found 322.1069.

3-Oxo-1-phenylspiro[4.5]deca-1,6,9-trien-8-yl Acetate (43): From the above reaction a second product **43** (87 mg, 15%) was isolated as a dark brown oil: ^1H NMR: δ = 7.75–7.72 (m, 1 H), 7.54–7.51 (m, 1 H), 7.43–7.32 (m, 3 H), *6.58*, 7.51 (s, 1 H), 6.01–5.93. (m, 4 H), 5.78–5.77 (m, 1 H), 2.67, *2.60* (s, 2 H), *2.13*, 2.11 (s, 3 H) ppm. ^{13}C NMR: δ = 205.8 (205.7), 176.9 (175.8), 170.8 (170.6), 135.4 (135.2), 133.9 (133.4), 131.0 (130.8), 129.9 (129.3), 128.7 (128.5),

128.5 (127.8), 124.4 (124.3), 64.2 (64.0), 51.3 (50.7), 48.5 (47.9), 21.3 (21.3) ppm. IR (neat): $\tilde{\nu}$ = 3022, 1726, 1691, 1590, 1568, 1368, 1229, 1012, 966, 863, 754, 647 cm^{-1}. HRMS: calcd. for $C_{18}H_{16}O_3Na$ [M + Na] 303.0992; found 303.0966.

3-Amino-8-hydroxy-4-phenylspiro[4.5]deca-3,6,9-trien-2-one (45): Methylamine hydrochloride (200 mg, 3.0 mmol) and K_2CO_3 (410 mg, 3.0 mmol) were added to a solution of **42** (192 mg, 0.6 mmol) in ethanol (10 mL) and the mixture was heated at reflux overnight. Water was added to the reaction mixture after evaporating the solvent and the aqueous solution was extracted with EtOAc (2× 10 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated to provide a crude product, which was purified by chromatography on silica gel (EtOAc/hexanes = 2:3) of to isolate **45** (30 mg, 20%) as a light brown solid. ^{1}H NMR: δ = 7.40–7.38 (m, 2 H), 7.35–7.32 (m, 2 H), 7.28–7.27 (m, 1 H), 5.95 (dd, J = 3.2, 10.1 Hz, 2 H), 5.72 (dd, J = 1.8, 10.1 Hz, 2 H), 4.37 (s, 1 H), 8.84 (s, 2 H), 2.58 (s, 2 H) ppm. ^{13}C NMR: δ = 201.6, 140.7, 140.1, 135.0, 134.4, 128.7, 128.6,128.2, 127.5, 61.9, 48.0, 44.9 ppm.

3-Amino-4-phenyl-2-naphthol (46): Aminol **45** (23 mg, 0.1 mmol) was added to a solution of cyanamide (90 mg, 2.1 mmol) in water. This mixture was acidified to pH 4.5 by careful addition of 10% HCl and the resulting mixture was heated at 90 °C for 3 h. After cooling, the resulting mixture was made basic to pH 10 with 20% NaOH and the aqueous layer was extracted with EtOAc (2× 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide **46** (60%) as a brown solid, m.p. 162–164 °C. ^{1}H NMR ([D$_6$]acetone): δ = 7.58–7.53 (m, 3 H), 7.46–7.43 (m, 1 H), 7.34–7.32 (m, 2 H), 7.17 (s, 1 H), 7.10–7.07 (m, 2 H), 7.06–7.03 (m, 1 H),4.25 (br. d, 2 H), 2.85 (br. d, 2 H) ppm. ^{13}C NMR ([D$_3$]methanol): δ = 145.8, 137.5, 133.7, 130.6, 128.9, 128.8, 128.7, 127.2, 125.7, 123.5, 122.7, 122.1, 120.1, 107.6 ppm. HRMS (*m*/*z*): calcd. for $C_{16}H_{12}NO$ [M – H] 234.0924; found 234.0924.

1-Methyl-4-phenyl-1*H*-naphtho[2,3-*d*]imidazole (48): Methylamine hydrochloride (158 mg, 2.4 mmol) and Et_3N (0.13 mL, 0.9 mmol) were added to a solution of **42** (153 mg, 0.5 mmol) in ethanol (5 mL), and the resulting mixture was heated at reflux temperature overnight. Water was added to the reaction mixture after evaporation of the solvent and the aqueous layer was extracted with EtOAc (2× 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide a crude product, which was purified with silica gel (EtOAc/hexanes = 3:2) to produce **48** (43 mg, 35%) as a green solid, m.p. 185–188 °C. ^{1}H NMR: δ = 8.70 (d, J = 10.1 Hz, 1 H), 8.27 (d, J = 9.2 Hz, 1 H), 8.01 (s, 1 H), 7.97 (d, J = 7.8 Hz, 2 H), 7.54 (t, J = 7.8 Hz, 2 H), 7.47 (t, J = 10.1 Hz, 1 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.09 (t, J = 9.2 Hz, 1 H), 7.01 (t, J = 10.1 Hz, 1 H), 4.21 (s, 3 H) ppm. ^{13}C NMR: δ = 155.7, 147.1, 135.7, 135.4, 135.2, 133.9, 129.8, 128.8, 128.0, 126.8, 126.5, 122.7, 121.9, 121.4, 117.1, 33.8 ppm. IR (neat): $\tilde{\nu}$ = 3039, 2918, 2844, 1607, 1592, 1572, 1538, 1495, 1456, 1372, 1261, 1171, 1044, 896, 740 cm^{-1}. HRMS-ESI (*m*/*z*): calcd. for $C_{18}H_{14}N_2$ [M + H]$^+$ 259.1230; found 259.1227. calcd. for $C_{36}H_{29}N_4$ [2M + H]$^+$ 517.2387; found 517.2390.

2-Iodo-1-(4-methoxy-phenyl)-3-oxospiro[4.5]deca-1,6,9-trien-8-yl Acetate (53): Alkynone **52** (530 mg, 2.1 mmol) was dissolved in acetic acid (5 mL) followed by careful addition of NIS (577 mg, 5.5 mmol) to maintain ambient temperature. After stirring the resulting mixture for 15 min, ethyl acetate (75 mL) was added, followed by addition of sufficient satd. aq. $NaHCO_3$ to neutralize the reaction mixture. The organic solution was separated and the aqueous layer was extracted with ethyl acetate (2× 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide a crude product, which was separated chromatographically (20% ethyl acetate in hexanes) to provide a 5:4 mixture of **53** (747 mg, 81%) as a reddish brown oil. ^{1}H NMR: δ = *7.57*, 7.32 (d, J = 8.7 Hz, 2 H), 6.88, 6.87 (d, J = 8.7 Hz, 2 H), *5.95–5.92*, 5.94–5.91 (m, 2 H), 5.86–5.82, *5.85–5.80* (m, 2 H), *5.59*, 5.39 (m, 1 H), *3.82*, 3.82 (s, 3 H), 2.78, *2.71* (s, 2 H), 2.05, *2.01* (s, 3 H) ppm. ^{13}C NMR: δ = 201.1 (200.9), 179.1 (177.6), 170.5 (170.5), 161.1 (160.8), 133.3 (134.3), 129.2 (130.2), 127.3 (127.0), 125.8 (125.0), 113.7 (113.4), 104.2 (103.0), 63.8 (63.5), 55.3, 51.7 (51.3), 47.0 (47.9), 21.2 (21.1) ppm. IR (neat): $\tilde{\nu}$ = 2930, 2837, 1728, 1704, 1603, 1504, 1330, 1226, 1175, 1020, 900, 835, 760 cm^{-1}. HRMS-ESI (*m*/*z*): calcd. for $C_{19}H_{18}IO_4$ [M + H]$^+$ 437.0244; found 437.0243.

3-Iodo-4-(4-methoxyphenyl)naphthalen-2-ol (54) and 1,3-Diiodo-4-(4-methoxyphenyl)naphthalen-2-ol (55): Alkynone **52** (530 mg, 2.1 mmol) was dissolved in acetic acid (5 mL) and NIS (577 mg, 5.5 mmol) was added at once to the reaction at room temp. (the reaction mixture became warm). The resulting mixture was stirred for 15 min before usual workup provided the crude material, which was purified with silica gel (EtOAc/hexanes = 1:9) to give **54** (245 mg, 31%) and **55** (179 mg, 17%).

Characterization data for compound **54**, reddish brown solid, m.p. 139–141 °C. ^{1}H NMR: δ = 7.72 (d, J = 7.8 Hz, 1 H), 7.43 (t, J = 7.8 Hz, 2 H), 7.34 (d, J = 8.7 Hz, 1 H), 7.19 (d, J = 7.8 Hz, 1 H), 7.18 (d, J = 8.7 Hz, 2 H), 7.06 (d, J = 8.7 Hz, 2 H), 5.66 (s, 1 H), 3.92 (s,3 H) ppm. ^{13}C NMR (DEPT 135): δ = 159.4 (C), 151.1 (C), 146.2 (C), 138.9 (C), 134.7 (C), 131.0 (CH), 129.1 (C), 127.5 (CH), 127.2 (CH), 126.7 (CH), 124.4 (CH), 114.0 (CH), 108.9 (CH), 97.7 (C), 55.4 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3478 (br.), 2954, 2833, 1604, 1583, 1510, 1328, 1242, 1213, 1170, 1026, 872, 843, 795, 773, 753 cm^{-1}. HRMS-ESI (*m*/*z*): calcd. for $C_{17}H_{14}IO_2$ [M + H]$^+$ 377.0033; found 377.0046. calcd. for $C_{17}H_{13}INaO_2$ [M + Na]$^+$ 398.9853; found 398.9867.

Characterization data for compound **55**, reddish brown solid, m.p. 104–106 °C. ^{1}H NMR: δ = 8.06 (d, J = 8.7 Hz, 1 H), 7.53 (tt, J = 1.4, 7.8 Hz, 1 H), 7.36 (d, J = 8.2 Hz, 1 H), 7.22 (tt, J = 1.4, 7.8 Hz, 1 H), 7.14 (d, J = 8.7 Hz, 2 H), 7.08 (d, J = 8.7 Hz, 2 H), 6.36 (s, 1 H), 3.92 (s,3 H) ppm. ^{13}C NMR (DEPT 135): δ = 159.5 (C), 151.1 (C), 147.5 (C), 135.5 (C), 134.9 (C), 131.1 (CH), 131.0 (CH), 129.6 (C), 128.9 (CH), 128.5 (CH), 125.1 (CH), 114.1 (CH), 93.5 (C), 83.2 (C), 55.6 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3391 (br.), 3062, 2953, 2840, 1605, 1511, 1486, 1371, 1234, 1171, 1027, 749 cm^{-1}. HRMS-ESI (*m*/*z*): calcd. for $C_{17}H_{13}I_2O_2$ [M + H]$^+$ 502.9005; found 341.1512. calcd. for $C_{17}H_{12}I_2NaO_2$ [M + Na]$^+$ 524.8824; found 363.1328. Observed ion consistent with MW of 340 Da. This structure was confirmed by X-ray crystallography.

2-Formylamino-1-(4-methoxyphenyl)-3-oxospiro[4.5]deca-1,6,9-trien-8-yl Acetate (57): By following the procedure for **42**, CuI (2 mg, 0.01 mmol), iodo-ketone **53** (102 mg, 0.23 mmol) and Cs_2CO_3 (152 mg, 0.50 mmol), *N*,*N*′-dimethylethylenediamine (0.01 mL, 0.02 mmol), formamide (0.02 mL, 0.50 mmol) and THF (2 mL) were heated at reflux for 12 h. The crude product was purified with silica gel (EtOAc/hexanes = 1:1) to isolate a 1:1 mixture of **57** (58 mg, 70%) as light brown oil. ^{1}H NMR: δ = 8.87, *8.83* (two overlapping doublets, 1 H), 7.38, *7.38* (d, J = 8.5 Hz, 1 H), 7.19, *7.19* (d, J = 8.5 Hz, 2 H), 6.89, *6.89* (d, J = 8.5 Hz, 2 H), 5.98–5.90 (m, 2 H), 5.90–5.78 (m, 2 H), 5.64, *5.44* (s, 1 H), 3.81, *3.81* (s, 3 H), 2.69, *2.62* (s, 2 H), 2.06, *2.01* (s, 3 H) ppm. ^{13}C NMR: δ = 199.8 (199.7), 170.6 (170.5), 162.0 (162.3), 160.6 (160.8), 154.4 (153.9), 133.9 (134.8), 133.3 (132.7), 129.1 (129.8), 125.8 (125.7), 124.4 (124.5), 114.6 (114.3), 63.8 (63.6), 55.4 (55.4), 47.6 (48.5), 46.1 (45.7), 21.2 (21.1) ppm. IR (neat): $\tilde{\nu}$ = 3317, 3011, 2965, 2828, 1699, 1662, 1604, 1507, 1384, 1283, 1245, 1175, 1030, 804, 734 cm^{-1}. HRMS-ESI (*m*/*z*): calcd. for $C_{20}H_{20}NO_5$ [M + H]$^+$

354.1341; found 354.1311. calcd. for $C_{20}H_{19}NNaO_5$ $[M + Na]^+$ 376.1161; found 376.1129.

1-(4-Methoxyphenyl)-3-oxospiro[4.5]deca-1,6,9-trien-8-yl Acetate (56): From the above reaction a small amount of reductive dehalogenation product **56** (15 mg, 20%) was isolated as a 1:1 mixture of a dark brown solid, m.p. 92–95 °C. ^{1}H NMR: δ = 7.72, 7.42 (d, J = 8.8 Hz, 2 H), 6.75 (d, J = 8.3 Hz, 4 H), 6.37, 6.34 (s, 1 H), 5.89–5.81 (m, 4 H), 5.74, 5.64 (m, 1 H), 3.70, 3.68 (s, 3 H), 2.49,2.42 (s, 2 H), 2.04,2.00 (s, 3 H) ppm. ^{13}C NMR: δ = 205.6 (205.5), 176.0 (175.2), 170.9 (170.6), 161.9 (161.8), 136.1 (135.5), 130.5 (129.8), 127.7 (127.1), 126.2 (125.9), 124.1 (123.9), 114.2 (114.0), 64.3 (64.1), 55.5, 51.3 (50.8), 48.2 (47.7), 21.3 ppm. IR (neat): $\tilde{\nu}$ = 2841, 1728, 1680, 1600, 1585, 1508, 1238, 1176, 1022, 869, 806, 757 cm^{-1}. HRMS (m/z): calcd. for $C_{19}H_{18}O_4Na$ 333.1097; found 333.1072.

1-Methyl-4-(4-methoxyphenyl)-1*H*-naphth[2,3-*d*]imidazole (58): A solution of methylamine in methanol (8.03 M, 0.05 mL, 0.4 mmol) was added to amide **58** (120 mg, 0.4 mmol) pre-absorbed on silica gel (≈ 1 g). After stirring at room temp. overnight, $Zn(BH_4)_2$ in THF (4.0 M, 0.10 mL, 0.4 mmol) was added to above reaction, and stirred for 2 h. After removing the solvent, crude product was purified with silica gel (EtOAc/hexanes = 1:1) to isolate **59** (30 mg, 30%) as a light brown solid, m.p. 158–160 °C. ^{1}H NMR: δ = 8.07 (d, J = 8.7 Hz, 1 H), 8.00 (d, J = 8.7 Hz, 2 H), 7.79 (s, 1 H), 7.57 (d, J = 8.7 Hz, 2 H), 7.45 (tt, J = 1.4, 7.3 Hz, 1 H), 7.35 (tt, J = 1.4, 7.3 Hz, 1 H), 7.12 (d, J = 8.7 Hz, 2 H), 3.92 (s, 3 H), 3.91 (s, 1 H) ppm. ^{13}C NMR: δ = 159.1, 147.5, 142.5, 134.9, 132.3, 131.1, 129.6, 128.9, 128.3, 127.8, 126.5 124.4, 123.5, 114.0, 104.6, 55.4, 31.2 ppm. IR (neat): $\tilde{\nu}$ = 3054, 2920, 2844, 1667, 1513, 1241, 1174, 1024, 828, 746 cm^{-1}. HRMS (m/z): calcd. for $C_{19}H_{16}ONa$ $[M + Na]^+$ 311.1155; found 311.1137.

X-ray Crystallographic Data: A suitable crystal covered with a layer of hydrocarbon/paratone-N oil was selected and mounted on a Cryo-loop, and immediately placed in the low temperature nitrogen stream. The X-ray intensity data for **55** were measured at 100(2) K on a SMART APEX CCD area detector system equipped with a Oxford Cryosystems 700 series cooler, a graphite monochromator, and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å). Intensity data were processed by using the Saint Plus program. All the calculations for the structure determination were carried out by using the SHELXTL package (version 6.14). Initial atomic positions were located by direct methods by using XS, and the structure of the compound was refined by the least-squares method by using XL. Absorption correction was applied by using SADABS. Hydrogen atoms were placed at calculated positions and refined riding on the corresponding carbons. All non-hydrogen atoms were refined anisotropically.

Supporting Information Copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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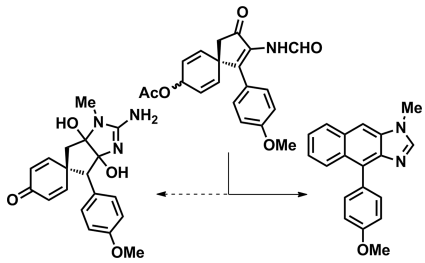
Natural Product Synthesis

A putative approach to the *Leucetta*-derived alkaloids predicated on the elaboration of spirofused cyclohexandienols is described. However, the strategy is compromised by rearrangement of key intermediates into corresponding naphthimidazole derivatives. This latter observation suggests a new hypothesis about the biosynthetic origins of this family of natural products.



Keywords: Synthetic methods / Cross-coupling / Rearrangement / Natural products / Alkaloids / Spiro compounds / Nitrogen heterocycles

