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Aza-[3 + 3] Annulations: A New Unified Strategy in Alkaloid Synthesis

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1. Introduction

Cycloaddition and annulation reactions are among the most powerful methods in organic synthesis because of their ability to afford multiple bond formations with regio- and stereochemical control.^{1,2} Accordingly, these reactions constitute highly convergent strategies for constructing complex carbocycles and heterocycles whether through a concerted, step-wise, or sequential process. Over the last twelve years, we have been developing a formal [3 + 3] cycloaddition³ or *aza*-annulation^{4–9} that involves condensing vinylogous amides¹⁰ with α,β -unsaturated iminium salts [Scheme 1]. This annulation provides a unique approach to bond formation in the synthesis of piperidiny] heterocycles that represent a prevalent structural motif among a diverse array of biologically relevant natural products.^{4–8,11}

Mechanistically, as illustrated in Scheme 2, intermolecular reactions of vinylogous amides **1** with α,β -unsaturated iminium ions **2** involve a tandem Knoevenagel condensation/ 6π -electron electrocyclic ring-closure of 1-azatrienes **3**^{12,13} to give heterocycles **4**.^{14,15} The challenge in this and other related annulations is the regiochemical control,⁵ *head-to-head versus head-to-tail* [i.e., the Hickmott-Stille's *aza*-annulation],¹⁶ which can be unpredictable and lead to complex mixtures.^{4–6,17} However, the use of α,β -unsaturated iminium salts in our annulations has led to *head-to-head* regioselectivity in almost all reactions.⁵ For the intramolecular variant of this reaction,¹⁸ there would not be such regioselectivity issues. We were the first to report an intramolecular version of this *aza*-annulation reaction,⁵ that entails a different mechanistic sequence. Specifically, with vinylogous amides **5**, our intramolecular *aza*-[3 + 3] annulation involves a tandem sequence of *N*-1,4-addition followed by *C*-1,2-addition/ β -elimination to give quinolizidines **7**. Both the inter- and intramolecular annulation pathways represent an attractive sequential or domino transformation¹⁹ and can be considered as a stepwise formal [3 + 3] cycloaddition in which two σ bonds are formed in addition to a new stereogenic center adjacent to the heteroatom.

After establishing the feasibility of the *aza*-[3 + 3] annulation, we developed a highly stereoselective variant of the intermolecular formal [3 + 3] cycloaddition using chiral vinylogous amides **8**, leading to dihydropyridines **10** in high diastereoselectivity [Scheme 3].²⁰ A subsequent, detailed mechanistic study of this stereoselective annulation provided support to it being the first example^{12,13} of stereoselective 6π -electron electrocyclic ring-closure of 1-azatrienes [see **9A**].¹⁴ In an alternative approach toward a stereoselective *aza*-[3 + 3] annulation, we were able to achieve a torquoselective ring-closure of 1-azatrienes containing acyclic chirality at the *C*-terminus [see **13A**] derived from α,β -unsaturated iminium ions **12**

[Scheme 4], thereby representing an unexplored venue for controlling this pericyclic process through 1-azatrienes **13A** that contain an acyclic stereochemical manifold [red arrow].²¹

Additionally, we have focused on identifying an asymmetric version of our *aza*-[3 + 3] annulation using chiral amine salts.²² After screening over 30 chiral amine salts, chiral amine **17** at 25 mol% could provide ~ 70% *ee* for the intramolecular *aza*-[3 + 3] annulation of vinylogous amide **16**. Calculations indicated that *Pro-R* TS-**18a** is more stable relative to the corresponding diastereomeric *Pro-S* TS-**18b** by 1.41 kcal mol⁻¹. This difference can be attributed to the steric repulsion between the diphenylhydroxymethyl substituent on the pyrrolidine ring and the cyclohexenone moiety in *Pro-S* TS-**18b**. It was postulated that the asymmetric intramolecular formal *aza*-[3 + 3] cycloadditions promoted with C1-symmetrical amine catalysts, such as **17**, proceed predominantly through *Pro-R* TS-**18a** giving rise to (*R*)-**18a** as the major enantiomer.

Another major methodological development in this area was the unveiling of an interesting variant of the *carbo*-[3 + 3] annulation²³ that competes with the *aza*-[3 + 3] annulation pathway. We observed that annulations of the piperidine-based exocyclic vinylogous urethanes **19** proceeded through an unexpected *carbo*-[3 + 3] annulation pathway,^{3,24} leading to hexahydroquinolines **22** [Scheme 6]. Mechanistically, it likely involved a tandem C-1,4-addition/Mannich-type cyclization through respective intermediates **20** and **21**. This finding invoked historical perspectives from Prelog's work in 1949²⁵ and Stork's enamine work in the 1950's.²⁶ With the latter case, a distinct contrast could be generalized whereby annulations of α,β -unsaturated carbonyl systems with enamines mostly led to *carbo*-[3 + 3] annulation,²⁴ those with enamines, or vinylogous amides, almost exclusively proceeded down the pathway of an *aza*-[3 + 3] annulation.

Given the distinct six-membered nitrogen heterocyclic motif of many structurally diverse and exciting alkaloids, we recognized that our *aza*-[3 + 3] annulation can be a powerful synthetic strategy in alkaloid synthesis, and that it represents both an attractive and complimentary approach to *aza*-[4 + 2] cycloadditions in constructing piperidines [Figure 1]. While *aza*-[4 + 2] cycloadditions remain a versatile synthetic method, *aza*-dienes and imines employed for *aza*-[4 + 2] cycloadditions are not always the most accessible or the easiest substrates to handle given the problems of isomerization and hydrolysis.^{1,27} Conversely, our *aza*-annulation utilizes more readily accessible and easily handled vinylogous amides and enals. In addition, our *aza*-[3 + 3] annulation can be biosynthetic in nature because it invokes Robinson's double Mannich-type process,²⁸⁻³⁰ which can be categorized as Type-I *aza*-[3 + 3] annulation with ours being Type-II, according to Harriety's classifications.⁷

Despite such potential significance, the synthetic scope of this type of *aza*-[3 + 3] annulation has been insufficiently explored until the last 15 years. An impressive array of *aza*-[3 + 3] annulations, including earlier work, had been accounted for in a collection of reviews in 2005.⁴⁻⁸ Summarized in Figure 2 are selected examples of total syntheses and methodological developments reported recently,³¹ and notably, these examples also include elegant *aza*-[3 + 3] concepts that are not directly related to our *aza*-annulation. In our own efforts, we have been focusing on total syntheses of alkaloids with the most significant development in the last six years being the evolution of the *aza*-[3 + 3] annulation into an attractive, unified strategy for alkaloid synthesis. Our completed total syntheses reflect both the competitive nature of this annulation strategy in the overall synthetic length and its flexibility in accessing structural and stereochemical diversity, and that it has positioned us with a unique perspective in the alkaloid community. Without detracting from known elegant approaches in constructing alkaloids, whether or not documented in this review, we highlight here our complete total synthesis efforts to unequivocally demonstrate that this *aza*-[3 + 3] annulation can serve as a highly useful and powerful strategy in organic synthesis [Figure 3].

2. An Intermolecular Aza-[3 + 3] Annulation

2.1. Aza-spirocycles: Synthesis of 2-*epi*(±)-perhydrohistrionicotoxin

Aza-spirocyclic (–)-histrionicotoxin was isolated from the skin extracts of neotropical tree frog *Dendrobates histrionicus*.³² In addition to its unique aza-spirocenter, (–)-histrionicotoxin and its saturated derivatives have shown potency as noncompetitive blockers of nicotinic receptor-gated channels,³³ thereby making them attractive and popular targets for synthetic chemists. 34:35 As illustrated in Scheme 7, our synthetic efforts featured a highly stereoselective aza-[3 + 3] annulation of α,β -unsaturated iminium salt **26** and *N*-benzyl aminopyrone **25** to generate the requisite aza-spirocenter **24**. An unprecedented decarboxylation of the 2-pyrone ring in **24** followed by hydrogenation afforded the *n*-amyl side chain of 2-*epi*(±)-perhydrohistrionicotoxin.³⁶

We began our total synthesis of the non-naturally occurring 2-*epi*(±)-perhydrohistrionicotoxin by constructing cyclohexylidene α,β -unsaturated iminium salt **26** in seven steps from 2-cyclohexenone [Scheme 8]. To this end, an epoxidation of 2-cyclohexenone **27** followed by alkylation with *n*-butyllithium and subsequent TBS protection afforded ketone **28**. At this stage a Horner-Wadsworth-Emmons reaction proved to be unsuccessful, therefore we utilized a Peterson olefination protocol of **28**, thereby affording the desired homologation. Next, a DIBAL-H reduction followed by Dess-Martin periodinane [DMP] oxidation afforded enal **29**, which upon treatment with equal amounts of piperidine and acetic anhydride heating at 85 °C for 3 hours gave cyclohexylidene α,β -unsaturated iminium salt **26**. At this point, the vinyl iminium salt **26** was poised to undergo an intermolecular aza-[3 + 3] annulation with *N*-benzyl aminopyrone **25**. Thus, **26** and vinylogous amide **25** were heated at 150 °C to afford aza-spirocyclic **24** in 64% yield as a single diastereomer unambiguously assigned using nOe experiments. Next, a quantitative hydrogenation of **24** afforded 2-pyrone **30** [Scheme 9]. By this approach, the three contiguous stereocenters of perhydrohistrionicotoxin were established in a very short sequence, thereby highlighting this novel approach to aza-spirodecane ring systems with high diastereomeric control at the aza-spirocenter.

At this stage, decarboxylations of **30** proved to be a formidable challenge, as a variety of methods were inadequate. We found a solution by employing a unique LAH-mediated decarboxylation protocol, followed by treatment of the crude reaction mixture to 60 *psi* of H₂ in the presence of Pd-C to afford **32** with the desired *n*-amyl side chain in 60% overall yield. Acid-mediated desilylation and subsequent debenzoylation using Pearlman's catalyst generated 2-*epi*(±)-perhydrohistrionicotoxin **23** in 90% yield overall. This completed an eleven-step total synthesis of 2-*epi*(±)-perhydrohistrionicotoxin in 21% overall yield and revealed the pivotal aza-[3 + 3] annulation to be a unique strategy towards aza-spirocycles.

2.2. *Cis*-decahydroquinoline Alkaloids

2.2.a. Synthesis of (–)-4a,8a-diepi-pumiliotoxin C—In the late 1960s, pumiliotoxin C was isolated from the skin secretions of the Central American frog species *Dendrobates pumilio*.³⁷ Possessing an interesting biological profile, pumiliotoxin C has been proven to act as a noncompetitive blocker of acetylcholine receptor channels. Additionally, it inhibits the specific binding of [³H]BTX-B to brain membranes with an IC₅₀ value at 45 μ M.³⁸ Due to its synthetic challenges, notably the *cis*-fused aza-decalin core with three contiguous stereocenters, pumiliotoxin C has been an attractive synthetic target.^{39,40} Retrosynthetically, we envisioned (–)-pumiliotoxin C to arise from an olefination/hydrogenation sequence of *cis*-decahydroquinoline **34**, which would be obtained *via* hydrogenation of the C4a-C8a ring fusion in **35** [Scheme 10].¹⁴ Reductive removal of the chiral auxiliary in cycloadduct **36** would afford **35**. Lastly, dihydropyridine **36** would be obtained *via* a stereoselective aza-[3 + 3] annulation of chiral vinylogous amide **38** and α,β -unsaturated iminium salt **37**.

Our efforts toward (–)-pumiliotoxin C commenced with reacting chiral vinylogous amide **38** with a pre-formed α,β -unsaturated piperidinium acetate salt **37** to afford *aza*-[3 + 3] annulation product **36** in 77% yield with high diastereoselectivity [Scheme 11]. Subsequent hydrogenation of the endocyclic olefin provided chiral vinylogous amide **39** in 94% yield. At this stage, olefination of the carbonyl was then attempted; however, Tebbe's olefination of **39** failed to give any desired product. Instead, cleavage of the TBS group in **39**, followed by hydrogenation using $\text{Pd}(\text{OH})_2$ and NH_4OCHO provided the free amide **40**.

With vinylogous amide **40** in hand, direct hydrogenation of the olefin employing a variety of conditions failed. We speculated that the nitrogen atom required a protecting group to facilitate the hydrogenation. Therefore, protection of the free vinylogous amide in **40** using TFAA, followed by high pressure hydrogenation, afforded a mixture of alcohol **41** and ketone **42** [Scheme 12]. A Dess-Martin periodinane oxidation of the mixture then afforded ketone **42** in 68% yield over two operations as a single diastereomer. The relative stereochemistry based on nOe experiments revealed an *anti* relationship between the C2 and C8a hydrogens. We postulated that the conformation of **40-N-TFA** is favored (Spartan AM1 calculations: a minimum of $2.01 \text{ kcal mol}^{-1}$ over other conformers) as it relieves much of the pseudo $A^{1,2}$ strain between the *N*-trifluoroacetyl group and the *n*-propyl group at C2, thereby resulting in delivery of hydrogen from the bottom face. While this hydrogenation did not afford the desired *syn* C2-C8a relationship required for (–)-pumiliotoxin C, this finding represented a rare and highly stereoselective entry to the *anti* relative stereochemistry at C2 and C8a of *cis*-1-azadecalins.

Ketone **42** was then subjected to a Peterson olefination protocol, since various Wittig-type olefination conditions proved to be inadequate [Scheme 13]. An ensuing acid-mediated elimination and subsequent hydrogenation gave **43** in 43% yield over three operations. We found that the stereoselectivity of the hydrogenation of the exocyclic olefin at C5 ranged from 8:2 to 9:1 in favor of the reduction taking place at the convex face of the *cis*-1-azadecalin. Notably, the major isomer was later assigned based on nOe experiments of **45**. Reductive removal of the trifluoroacetyl group in **43** using NaBH_4 resulted in a mixture of the non-naturally occurring alkaloids 4a,8a-*diepi*-(–)-pumiliotoxin C **45** and 2-*epi*-(+)-pumiliotoxin C **44** as a 8:2 to 9:1 ratio in 25% overall yield. The low isolated yields of **44** and **45** were attributed to the slow rate of removing the TFA group and the reaction not being driven to completion.

2.2.b. Synthesis of (+)-Lepadine F and (+)-Lepadine G—The lepadine family, comprised of eight *cis*-decahydroquinoline alkaloids, was isolated from various sources such as *Clavelina lepadiformis*,^{41a} flatworm *Prostheceraeus villatus*,^{41b} tropical marine tunicate *Didemnum* sp.,^{41c} and Australian great barrier reef ascidian *Aplidium tabascum* [Scheme 14].^{41d} Their biological activity profiles include tyrosine kinase inhibition, cytotoxicity, antiplasmodial and antitrypanosomal properties as well as antimalarial properties,^{41a-d} thereby attracting attention from the synthetic community.^{42–49}

The stereochemical relationships of the lepadines can be categorized into three subsets, as illustrated in Scheme 15. The most challenging aspect would be the 1,3-stereochemical relationship at C2 and C8a, which can be *syn* as in lepadines A-E and H, or *anti* as in F and G. We envisioned that each subset could arise in a stereodivergent manner from a common intermediate **46**, which can be accessed *via* an intermolecular *aza*-[3 + 3] annulation of chiral vinylogous amide **38** and enal **49**. While iminium ion chemistry has served us well, one drawback here was the solubility of iminium salt. Alternatively, we later developed a more operationally simple means of accessing quinolines by a TiCl_4 -initiated *aza*-annulation. We found that while the initial product afforded by a Lewis acid-mediated *aza*-annulation as a 51:49 mixture of **46** and 2-*epi*-**46**, it could be thermally equilibrated to pure **46** through a sequence of pericyclic *aza*-ring opening and ring closure.⁵⁰

Retrosynthetically, (+)-lepadin F **48** was envisioned to materialize from decahydroquinoline **49** through a side chain installation *via* Julia-Kocienski olefination and an esterification utilizing Yamaguchi's protocol [Scheme 16].⁵¹ Homologation of vinylogous amide **46** would afford an α,β -unsaturated ester, which in turn would be hydrogenated to give *cis*-decahydroquinoline **49**. Lastly, dihydropyridine **46** would be derived from a highly diastereoselective *aza*-[3 + 3] of chiral vinylogous amide **38** with α,β -unsaturated iminium species **50**.

We commenced our synthesis of (+)-lepadin F by submitting vinylogous amide **38** and an α,β -unsaturated iminium salt **50** to *aza*-[3 + 3] annulation conditions affording core dihydropyridine **46** in 70% yield with 96:4 diastereoselectivity [Scheme 17]. Osmium tetroxide dihydroxylation of the C3-4 olefin afforded diol **51** in 60–70% yield, and subsequent reductive removal of the C4-OH group in the presence of excess TFA and triethylsilane was performed. The free alcohol was then acylated to give vinylogous amide **52** in 90% yield over two operations.

Our next synthetic challenge was seen during hydrogenation of the endocyclic olefin, for over-reduction of the C5-carbonyl group in **52** was observed in a variety of protocols. We found a solution by homologating acetate **52** *via* a three-step sequence featuring Eschenmoser's episulfide contraction, affording α,β -unsaturated ester **53** exclusively as the *E*-isomer [Scheme 18]. A double hydrogenation was then achieved to afford **49** in 91% yield as a 5:1 mixture of separable diastereomers with respect to the C5 stereochemistry. It is noteworthy that the chiral auxiliary plays two roles: (1) in the establishment of the C2 stereochemistry during the *aza*-[3 + 3] annulation step, and (2) as a steric blocking group setting up three stereocenters in the double hydrogenation of **53**. The chiral auxiliary in **49** was reductively removed, affording a free vinylogous amide which was immediately Boc-protected *in situ*. Subsequent deacylation afforded free alcohol **54** in 77% yield over two operations.

At this stage, we were ready to complete the total synthesis of (+)-lepadin F by installing the side chains. To this end, a two-step sequence of Dess-Martin periodinane oxidation and NaBH₄ reduction was performed to invert the C3-alcohol to its desired stereochemistry [Scheme 19]. This resultant alcohol was then silylated to give silyl ether **55** in 91% yield over three operations. A DIBAL-H reduction of the ester in **55**, and a subsequent DMP oxidation revealed an aldehyde **56** which was poised to undergo a Julia-Kocienski olefination. Thus, utilizing sulfone (*S*)-**57**, installation of the alkyl side chain to core **56** afforded alkene **58** in 90% yield. Next, the alkene was hydrogenated over Pd/C and TBAF-mediated desilylation gave alcohol **59** in nearly quantitative yield over two steps. We then performed an esterification employing Yamaguchi's protocol and (*E*)-oct-2-enoic acid, and subsequent global deprotection afforded (+)-lepadin F in twenty steps with 15.2% overall yield from chiral vinylogous amide **38**.

Our spectroscopic data for (+)-lepadin F matched those reported by Carroll and coworkers⁴¹ for the natural (+)-lepadin F and Blechert's synthetic sample,⁴⁸ thereby allowing us to claim a completed total synthesis. Yet we believed there to be a high margin of error in determining the C5' stereochemistry, since not only was the C5' stereocenter never defined in the isolation report, the C5' stereocenter is acyclic and highly insulated on the side chain. Consequently, we synthesized the C5' epimer of (+)-lepadin F commencing with advanced intermediate aldehyde **56** and sulfone (*R*)-**57** in the requisite Kocienski-modified Julia olefination [Scheme 20].⁵² Spectroscopic comparisons of both ¹H and ¹³C NMR datasets of our synthetic (+)-lepadin F and (+)-5'-*epi*-lepadin F with Carroll's natural (+)-lepadin F enabled us to confirm the correct relative stereochemistry at C5' in (+)-lepadin F as *S*.

Considering that two complex structures differing only at a remote and highly insulated stereocenter could still be differentiated spectroscopically, we were prompted to synthesize (+)-lepadin G and its C5' epimer in an attempt to concisely determine its correct relative stereochemistry. Therefore, total syntheses of both (+)-lepadin G and (+)-5'-*epi*-lepadin G were performed commencing with **ent-38**.⁵² **Ent-55** was quickly accessed by our intermolecular *aza*-[3 + 3] annulation of **ent-38** with the appropriate vinyl iminium salt and further synthetic manipulations in 40% overall yield [Scheme 21].⁵² **Ent-55** was then transformed to **ent-59** (or its C5' epimer in the case of (*S*)-**57**) in 43% yield over thirteen steps.

The synthetic sequence differed from that of (+)-lepadin F in the second-to-last step, whereby installation of a different ester side chain, namely (2*E*,4*E*)-octadienoic acid, under Yamaguchi conditions afforded **60**. An ensuing global deprotection afforded both (+)-lepadin G **61** and (+)-5'-*epi*-lepadin G **62**. As before, spectroscopic comparisons of the NMR datasets of our synthetic (+)-lepadin G and (+)-5'-*epi*-lepadin G with Carroll's natural (+)-lepadin G sample suggested that the correct relative stereochemistry at C5' should be *R* for (+)-lepadin G.

3. An Intramolecular *Aza*-[3 + 3] Annulation

Over the last decade, we have been developing an *aza*-[3 + 3] annulation reaction as a general strategy in alkaloid synthesis.^{4,14,15,18,20–23,52–58} The intramolecular variant of this reaction has proven to be valuable in natural product synthesis. Specifically, the intramolecular *aza*-[3 + 3] annulation of vinylogous amides tethered to a vinyl iminium motif **63** proceed through a tandem sequence of *N*-1,4-addition and *C*-1,2-addition/ β -elimination that can lead to a variety of nitrogen heterocycles [Scheme 22]. As will be discussed, our endeavors into the methodological development of this annulation and concurrent total syntheses have confirmed the pivotal intramolecular *aza*-[3 + 3] annulation to be advantageous in constructing a diverse array of alkaloid natural products **64a–64f**.^{6a,55–58}

3.1. Piperidinyl Heterocycles: Synthesis of (+)-Gephyrotoxin

We recognized an opportunity to showcase our intramolecular annulation of a vinylogous amide tethered to an α,β -unsaturated iminium salt in the formal total synthesis of (+)-gephyrotoxin **65**.^{18b} As illustrated in Scheme 23, we noticed that of the three known total syntheses^{59,60} of ($\pm$)-gephyrotoxin,⁶¹ Kishi's intermediate **66**, a tricyclic heterocycle, could be easily accessed by our intramolecular *aza*-[3 + 3] annulation and would provide a successful employment of this diastereoselective reaction. Our plan was to intercept *aza*-annulation substrate **67** in eight steps from ethyl acetoacetate *via* condensation of **68** with 1,3-cyclohexanedione.

To complete the formal total synthesis, chiral vinylogous amide **69** (or **70**) was submitted to *aza*-[3 + 3] annulation conditions by heating the substrate with piperidinium acetate in an ethyl acetate/ethanol solvent mixture. After two hours, we found that the major isomer **73- β** of our annulation, after hydrogenation, was not Kishi's intermediate, but was the opposite stereoisomer [Scheme 24]. We suspected that the unprotected primary alcohol was distorting the conformation of the transition state, and therefore we explored various silyl protecting groups to provide a substrate that would undergo the annulation with the desired stereochemical outcome.

To that end we found that the reaction of *tert*-butyldiphenylsilyl (TBDPS)-protected alcohol **70** was the most amenable to the desired outcome, providing the diastereomeric cycloadducts after hydrogenation in a ratio of 60:40 for **73- α** /**73- β** . Subsequent desilylation and chromatographic separation of the two diastereomers led to the isolation of tricyclic compound **74- α** , which matched Kishi's intermediate by NMR and optical rotation. Of importance, we observed that the tricyclic cycloadducts from our *aza*-annulations were less stable than

anticipated, and to improve their stability, the crude reaction mixture containing the cycloadduct would be directly submitted to hydrogenation conditions to reduce the endocyclic double bond. This prudent, one-pot protocol provided **73**, and would prove to be an important *modus operandi* for our subsequent endeavors in synthesizing other *aza*-heterocycles. The overall sequence to Kishi's intermediate proved to be concise and demonstrated the synthetic feasibility of this intramolecular formal [3 + 3] cycloaddition reaction in the synthesis of natural products.

3.2. Quinolizidine Heterocycles: Synthesis of (±)-2-Deoxylasubine II

Despite success over the last decade, when using a vinylogous urethane tethered to a vinyl iminium salt **77** [Scheme 25], our annulation strategy had not been advantageous in constructing quinolizidine structural motifs, only providing low yields. This problem was rectified once we found that the role of the counteranion [X⁻] in these iminium salts provided a vital function in the annulation.²² While iminium salts with acetate as the counteranion were wholly inadequate, employing the more reactive trifluoroacetate salt proved to be the solution, thereby rendering a vinylogous urethane deployable in the *aza*-[3 + 3] annulation. Furthermore, we were cognizant of the great potential in exploiting vinylogous urethanes in our formal cycloaddition since the resultant methoxy carbonyl group provides an excellent functional handle, amenable to further chemical transformations or removal.

(±)-2-Deoxylasubine II **75**^{62–67} became our first successful entry in constructing a member of the quinolizidine family of alkaloids by our intramolecular annulation.⁵⁸ Retrosynthetically, the requisite quinolizidine nucleus **76** would be generated by our pivotal *aza*-annulation of substrate **77** [Scheme 25]. We elected to access vinylogous urethane **77** by amine **78**, which could be constructed from propargyl alcohol **79**. A concise end-game strategy would feature a Barton decarboxylation at C3 of vinylogous urethane **76**.

Our efforts commenced with amine **78** prepared in five steps from propargyl alcohol **79** [Scheme 26]. Reaction of amine **78** with alkynoate **80** led to vinylogous urethane **81**. The stereochemistry of the vinylogous urethane **81** was determined to be exclusively *Z*, likely due to favorable internal hydrogen bonding.

At this point, a two-step sequence of TBAF-mediated desilylation and subsequent oxidation gave the *aza*-annulation substrate **82** in 86% yield with a *Z/E* ratio of 3.3:1 for the enal. With the vinylogous urethane tethered to the enal **82** in hand, the more reactive piperidinium trifluoroacetate salt was exploited to trigger the annulation, and *in situ* hydrogenation allowed isolation of the annulation product **76** in 62% yield over two operations [Scheme 27]. To complete the total synthesis, hydrogenation of cycloadduct **76** using Adams' catalyst gave ester **83** in 95% yield as a single diastereomer. Lithium iodide-promoted demethylation of ester **83**, followed by Barton's standard protocol for decarboxylation of the resultant acid, afford (±)-2-deoxylasubine II **75** in 33% overall yield for the sequence.

The key feature of this investigation was the successful construction of a member of the quinolizidine family of alkaloids by using the more reactive piperidinium trifluoroacetate salt to effectively allow a vinylogous urethane to be employed in the *aza*-[3 + 3] annulation.

3.3. A Unified Strategy towards Indoloquinolizidine Heterocycles

An application of the intramolecular *aza*-[3 + 3] annulation as a unified strategy was illustrated by our syntheses of tangutorine^{55a} and deplancheine^{55b} [Scheme 28]. Tangutorine⁶⁸ **84** possesses a novel benz[*f*]indolo[2,3-*a*]quinolizidine skeleton and is related to the well-known monoterpenoid (+)-indole alkaloids such as (+)-deplancheine **91**,⁶⁹ (+)-geissoschizine,⁷⁰ yohimbine and reserpine.^{71–73} Natural products possessing the indoloquinolizidine

substructure are prevalent among alkaloids that are derived biosynthetically from tryptophan. Syntheses^{74–78} of these monoterpene indole alkaloids have often featured the classic Pictet-Spengler cyclization.^{72,73,79–81}

As outlined in Scheme 28, both tangutorine and deplancheine can be accessed from a similar indoloquinolizidine core, in which the indoloquinolizidine CD-ring **85** (or **92**) should be attainable *via* the pivotal intramolecular *aza*-[3 + 3] annulation, depending upon the vinylogous amide (**86** or **93**) requisite for the core structure. Condensation of the free amine **88** with 1,3-diketone **87** for tangutorine, or reaction with 4-methoxy-3-buten-2-one **94** for deplancheine would provide the requisite substrates for the intramolecular *aza*-[3 + 3] annulation. Amino alcohol **88** would be prepared *via* a Heck cross-coupling of a protected 2-bromotryptamine **90** with an appropriate 3-carbon synthon. Notably, implementing a Heck coupling to construct the C2-C3 bond was used in place of the frequently employed Pictet-Spengler cyclization. The preparation of **90** would commence with tryptamine **89**.

3.3.a. Synthesis of (±)-Tangutorine—To prepare *aza*-annulation substrate **96**, tryptamine **89** was di-protected and brominated so that an ensuing Heck coupling would provide ester **95** in 82% yield [Scheme 29]. Further synthetic manipulations, including condensation with 1,3-cyclohexanedione **87** gave a vinylogous amide and oxidation with MnO₂ revealed the enal, thus giving the requisite intramolecular substrate **96**. Under standard intramolecular *aza*-[3 + 3] annulation conditions followed by hydrogenation of the endocyclic olefin, pentacycle **85** was isolated in 56% yield. With this finding, a practical synthetic approach toward tangutorine and other tryptophan-derived monoterpene indole alkaloids was established, and furthermore, the study provided the first example of an *aza*-[3 + 3] annulation where the indole motif was present.

To complete the total synthesis of (±)-tangutorine **84** [Scheme 30], pentacycle **85** was transformed in three operations to keto-pentacycle **97** as a single diastereomer in 61% yield. To append a carbonyl group at C18 of the E-ring, we found that the LHMDs/HMPA/Mander's reagent protocol was inadequate. Instead, pentacycle **97** was refluxed in THF in the presence of NaH and diethyl carbonate to yield β-ketoester **98** regioselectively as a mixture of diastereomers. Further synthetic manipulations were performed to afford the allylic alcohol, thereby concluding the synthesis of (±)-tangutorine **84**.

3.3.b. Synthesis of (±)-Deplancheine—As illustrated in Scheme 31, the synthesis of deplancheine **91** began with an identical approach as tangutorine, with the divergent point being reaction of the free amine with 4-methoxy-3-buten-2-one **94**.

Thus, phthalimido ester **95** was obtained from tryptamine **89** in four steps, including Fukuyama's Heck coupling protocol [Scheme 31]. Of note, It was determined that we could also employ Fu and Littke's^{82,83} conditions of excess methyl acrylate and a 1 : 1 ratio of Pd catalyst and a bulky *t*-Bu₃P ligand for the Heck coupling. To deprotect ester **95**, we exploited Ganem's reductive sequence, whereby slightly more than three equivalents of DIBAL-H cleanly afforded a hydroxyaminal (not shown). Further reduction with NaBH₄ provided an amide intermediate, which upon adding HOAc to the reaction mixture led to free amino alcohol **88**. The formation of vinylogous amide **99** was then effected, using 4-methoxy-3-buten-2-one **94**, giving an overall yield of 26% for the three operations. Notably, vinylogous amide **99** is distinctly manifested as the *Z*-conformer based on ¹H NMR coupling constants in addition to a well-defined peak for the NH suggesting a hydrogen bond between the NH and the carbonyl. After MnO₂ oxidation of **99**, the strategic *aza*-[3 + 3] annulation of vinylogous amide **100** was investigated [Scheme 32].

As in our synthesis of ($\pm$)-tangutorine (*vide supra*), we employed piperidinium acetate salt to afford indoloquinolizidine tetracycle **92** after hydrogenation in 35% yield over three steps. Deprotection of **92** with TFA and CH₂Cl₂ in a 1:1 mixture followed by reduction with NaBH₄ completed the total synthesis of ($\pm$)-deplancheine **91**, and gave a minor isomer which was believed to be the *Z*-isomer of ($\pm$)-deplancheine.

3.3.c. Synthesis of *S*-(-)-Deplancheine and *R*-(+)-Deplancheine—To accomplish the total syntheses of *S*-(-)-**91** and *R*-(+)-**91**, vinylogous amide **100** was subjected to an enantioselective *aza*-[3 + 3] annulation²² using chiral amine salts *S*-**101** or *R*-**101** [Scheme 33]. After hydrogenation, indoloquinolizidine *S*-**92** was found in 46% yield over three steps with an *er* of 80:20 in favor of the *S*-enantiomer. When employing *R*-**101** as the chiral amine salt, *R*-**92** was isolated in 15% yield over three operations with an HPLC ratio of 69:31 in favor of *R*-**92**. Similar chemical modifications, as in the racemic synthesis, were then performed independently to provide *S*-(-)-deplancheine in 42% overall yield and *R*-(+)-deplancheine in 83% overall yield. The syntheses of tangutorine **84** and deplancheine **91** confirmed the *aza*-[3 + 3] annulation to be a practical synthetic approach in constructing tryptophan-derived monoterpenoid indole alkaloids.

3.4. Tricyclic Marine Alkaloids: Cylindricines and Lepadiformines

In the early 1990s, Blackman reported the isolation of (-)-cylindricines A-K84c-e from the marine ascidian *Clavelina cylindrica* collected in Tasmania. Additionally, two structurally related alkaloids, lepadiformine and fascicularin, were isolated from the marine ascidian *Clavelina lepadiformis*^{84f} and *Nephtesis fascicularis*,^{84g} respectively. Given the unique tricyclic structural motif, low natural abundance, and biological activity, an impressive collection of synthetic efforts towards these alkaloids have been published.^{84–91} We envisioned an application of the intramolecular *aza*-[3 + 3] annulation as a unified strategy in the total synthesis of certain tricyclic marine alkaloids, specifically the cylindricine and lepadiformine alkaloid families [Figure 4].^{84a,b,h,i}

As will be discussed, our pivotal intramolecular *aza*-[3 + 3] annulation was remarkably efficient in providing the tricyclic scaffold of (-)-cylindricine C **101** and that of putative (-)-lepadiformine **106** (or: (-)-4-deoxo-2-*epi*-cylindricine C),^{56b,84} yet this route could not be implemented in our synthesis of (-)-lepadiformine **102**. To reconcile this, we devised a unified strategy to synthesize (-)-lepadiformine and (+)-cylindricines C-E (**103–105**) that would utilize an *N*-acyliminium ion/diene cyclization and a Wharton's rearrangement to access a common intermediate.

3.4.a. Synthesis of (-)-Cylindricine C and 2-*epi*-(-)-Cylindricine C—In 2006, we reported the total synthesis of (-)-cylindricine C.⁵⁶ As aforementioned, we intended to utilize an intramolecular *aza*-[3 + 3] annulation strategy that would be amenable for the nitrogen *aza*-heterocyclic motif found in lepadiformine and cylindricines. Retrosynthetically, the key intermediate tricycle **107** leading to the (-)-cylindricines would be accessed *via* a diastereoselective *aza*-[3 + 3] annulation of a chiral vinylogous amide tethered to a vinyl iminium ion **108** [Scheme 34]. Vinylogous amide **108** would be prepared from chiral amine **109**, which can be constructed from vinyl oxazoline **110**. The vinyl oxazoline would be prepared in five steps from *L*-serine,⁹² thereby providing the source of chirality in this work. The end-game strategy in our total synthesis would utilize a sequence featuring an interesting halohydrin formation of the C4-C5 olefin *en route* to the C4-carbonyl.

Our total synthesis commenced with hydroboration of chiral synthon **110** with 9-BBN followed by a Suzuki-Miyaura coupling of the ensuing borane with vinyl triflate **111** to give ester **112** [Scheme 35]. This unsaturated ester was converted to an allyl alcohol in three simple

operations, providing **113** in 61% yield for the four-step sequence. The free hydroxyl group of **113** was capped as the corresponding acetate followed by removal of the Boc group using TFA. At this stage, we had considerable flexibility in the choice of an appropriate vinylogous amide [see R¹, R² of **108** in Scheme 34]. Considering our development of a protocol for reductive ring-opening of α -pyrones,³⁶ we elected to employ bromopyrone **114** for vinylogous amide formation. Therefore, reaction of the free amine with 6-*n*-butyl-4-bromo-2-pyrone **114** led to amino pyrone **115** in 61% yield over three steps. Compound **115** was then converted to enal **116** in 85% yield over two operations.

With the annulation substrate **116** in hand, the vital intramolecular *aza*-[3 + 3] annulation proceeded smoothly by heating with 0.5 equiv of piperidinium acetate as the catalyst for vinyliminium formation. After 12 h, tetracyclic annulation product **117** materialized in 68% yield as a separable 9:1 mixture of diastereomers favoring the desired isomer as shown. Importantly, this isomer possessed the necessary configuration at C10 of the alkaloid.

The remaining goal was to install the ketone at C4, yet this proved to be a formidable challenge. We ultimately found the solution to be an intriguing three-step sequence involving chlorohydrin formation [Scheme 36]. Specifically, reaction of tetracycle **117** with 3.0 equiv NCS in aqueous *t*-BuOH generated chlorohydrin **118** as a single diastereomer in 76% yield (configuration of alcohol not ascertained). TPAP-oxidation and subsequent reductive dechlorination of the tertiary Cl group using Zn and HOAc provided ketone **119** in 65% yield. Significantly, ketone **119** had the correct stereochemistry at C5 of (–)-cylindricine. α -Pyrone **119** was then converted to **120** in an interesting stepwise sequence: (1) hydrogenation provided a partially reduced dihydropyrone; (2) an ensuing sodium cyanoborohydride reduction in the presence of HCl (or HOAc) then gave a reductive decarboxylation product; (3) and subsequent desilylation afforded alcohol **120** in 86% yield over three steps.

At this point, a Stork-Crabtree directed hydrogenation was pursued, yet we obtained the non-naturally occurring (–)-2-*epi*-cylindricine C **121** in 54% yield and **120** was recovered in 35% yield [entry *i* in Scheme 36]. Alternatively, we found that a remote hydroxyl-directed reduction of the vinylogous amide with Na(OAc)BH₃ gave (–)-cylindricine **101** in 83% yield (entry *ii*).

3.4.b. Synthesis of (–)-4-deoxo-2-*epi*-cylindricine C—(–)-4-deoxo-2-*epi*-cylindricine C (or, putative (–)-lepadiformine) was synthesized^{56b} in a three-step sequence commencing with tetracycle **117**. Notably, **117** is the same tetracycle used in (–)-cylindricine C synthesis prior to chlorohydrin formation. *Aza*-tetracycle **117** was hydrogenated over Pd/C to afford a reduced intermediate (not shown) as a single diastereomer in 90% yield [Scheme 37]. This 2-pyrone intermediate was reductively ring-opened utilizing LAH followed by hydrogenation.³⁶ After desilylation with TBAF, the reaction sequence afforded putative (–)-lepadiformine **106** along with a minor isomer, (–)-4-deoxycylindricine C **119**.

While the details are unknown, a possible mechanism for this transformation is illustrated in Scheme 37. After hydrogenation, pyrone **118** is obtained after a 1,6-hydride reduction followed by deconjugative protonation. This intermediate could then lose CO₂ through a retro-Diels-Alder cycloaddition. Subsequent hydrogenation should then be favored from the bottom face of **118**, providing a rationale for the stereochemical outcome at C2.

Encouraged by this facile reductive ring-opening of the pyrone motif, we attempted the synthesis of (–)-lepadiformine. Unfortunately, our efforts in applying the *aza*-[3 + 3] annulation towards (–)-lepadiformine were thwarted. The reason for abandoning this strategy towards (–)-lepadiformine was that after hydrogenating the minor isomer **120** of our *aza*-[3 + 3] annulation, reductive ring opening of **121** gave an inseparable mixture of *epi*-lepadiformines (**122** and **123**) in low yields [Scheme 38]. The 1:1 ratio of diastereomers implied that following

extrusion of CO₂ through a retro-Diels-Alder step, both faces of the resultant amino diene intermediate **124** were equally susceptible to hydrogenation.

3.4.c. Syntheses of (+)-Cylindricines C-E and (-)-Lepadiformine—While developing our intramolecular *aza*-[3 + 3] formal annulation strategy, we became cognizant of a deficiency in all synthetic strategies towards these families of alkaloids: an *N*-acyliminium cyclization approach has been exclusively employed in total syntheses of (-)-lepadiformine **102**^{93,94} and never for any of the cylindricines [Figure 4].^{87,95–98} Specifically, Weinreb^{88a} and Kibayashi^{88b} employed this *N*-acyliminium cyclization to construct the C5-C10 bond in the *aza*-spirocyclic AC-ring of (-)-lepadiformine **102**.⁹⁹ This approach suggested that the desired *cis*-fused 1-*aza*-decalinic AB-ring at C5-C10 in cylindricines **103–105** may not be a product of the *N*-acyliminium cyclization approach, since the reaction provided the desired *trans* relative stereochemistry at C5-C10 of (-)-lepadiformine **102**. We decided to test the validity of this presupposition by pursuing the total syntheses of (+)-cylindricines C-E and (-)-lepadiformine *via* a common intermediate derived from an *N*-acyliminium, or *aza*-Prins, cyclization and a seldom used Wharton's rearrangement.^{84h,i} This common intermediate **125**, we believed, would relate structurally through an epimerization at C5 [Scheme 39].

As illustrated in Scheme 39, *aza*-tricycle **125** would link the synthetic pathways towards (+)-cylindricines C-E **103–105** and (-)-lepadiformine **102**, by either a C5-epimerization *en route* to (+)-cylindricines, or a C4-deoxygenation leading to (-)-lepadiformine. Since our original plan of a tandem Mannich strategy to the *aza*-tricycle was thwarted by many difficulties,^{84h,i} we elected to prepare the vital tricycle **125** from **128** by utilizing an *aza*-Prins type *N*-acyliminium addition followed by Wharton's rearrangement.

Our synthesis commenced with metalating iodide **130**, and addition of the ensuing alkyllithium to the enantiomerically pure (*S*)-lactam **129** provided the ring-opened, Boc-protected amino ketone **128** in 61% yield [Scheme 40]. A formic acid-induced *aza*-Prins cyclization afforded an inseparable diastereomeric mixture of *aza*-spirocycles **131** in which the allyl cation intermediate had been trapped by the formate anion.

Next, a three-step sequence was employed to convert diastereomeric spirocycles **131** to epoxy ketone **132**. This intermediate was subjected to a Wharton rearrangement using 5.0 equiv hydrazine and 0.5 equiv HOAc to yield the desired transposed allyl alcohol **133-trans** in 66% yield as a mixture of inseparable diastereomers. While we observed this *trans*-allyl alcohol in most trials, we found the *cis*-allyl alcohol **133-cis** in 42% yield when using 10 equiv HOAc. This interesting phenomenon observed in Wharton's rearrangement may be associated with the stereochemistry of the epoxide or the amount of HOAc used. Subsequent MnO₂ oxidation of **133-trans** provided spirocycle **134** in 90% yield.

Removal of the Boc group in enone **134** with TFA resulted in a free amine that underwent an *in situ* Michael cyclization to provide the desired *aza*-tricycle **125**, the common intermediate, in 72% yield [Scheme 41]. Additionally, we isolated a second product, which after careful scrutiny, learned that the *aza*-tricycle underwent rapid epimerization at C5 when exposed to silica gel, thereby giving the TBDPS-protected form of (+)-cylindricine C **103** as well as **125** in a 1:1 mixture. It turned out that TBAF-mediated deprotection of the silyl group in *trans*-*azadecalin* **125** concomitantly epimerized C5 of the *aza* tricycle, providing (+)-cylindricine C **103** and importantly verified the link between cylindricines and lepadiformine. Subsequent chemical manipulations then afforded (+)-cylindricines D and E [**104** and **105** in Scheme 42].

To complete the synthesis of (-)-lepadiformine **102**, as illustrated in Scheme 42, a four-step sequence was pursued. The C4-carbonyl of the common tricyclic intermediate **125** was reduced with NaBH₄ and the resultant β-alcohol was converted to the corresponding xanthate. Barton-

McCombie deoxygenation was then performed, and subsequent desilylation afforded (–)-lepadiformine **102** in 57% yield over four operations. Ultimately, we established a unique and potentially biosynthetic link between the cylindricines and lepadiformine, and that the C5-H can be epimerized but possibly only with an *aza*-tricyclic intermediate.

3.5. A Unified Strategy Towards Azaphenalene Alkaloids

As a defensive mechanism, ladybird beetles (*Coccinellidae*) release an orange fluid that contains a mixture of defensive alkaloids, serving to protect them from predators.^{100,101} In the early 1970s, Tursch and coworkers reported the isolation of a family of structurally related azaphenalene alkaloids—namely, myrrhine **136**, hippodamine **142**, convergine **143**, precoccinelline **144** and coccinelline **145**—from the aforementioned fluid secreted by *Coccinellidae*.¹⁰² In 1976, Ayer reported the first total syntheses¹⁰³ of these five azaphenalene alkaloids, and subsequently, other syntheses have been published.^{104,105} With one exception, ^{103a} installation of the equatorial methyl group was performed in the latter stages of the synthesis.

3.5.a. Stereoselective Synthesis of Myrrhine, Hippodamine, Convergine, Precoccinelline and Coccinelline—To advance our quest in demonstrating the utility of our pivotal intramolecular *aza*-[3 + 3] annulation as a unified strategy to access different *N*-heterocyclic manifolds known in naturally occurring alkaloids, we synthesized the family of *Coccinellidae* defensive alkaloids **136** and **142–145** [Figure 5].⁵⁷ Our strategy utilizes a common intermediate, the *aza*-tricyclic core **141**, which is attained via an intramolecular *aza*-[3 + 3] annulation.

We envisioned that the symmetric nature of myrrhine **136**, hippodamine **142** and precoccinelline **144** could be exploited and retrosynthetically could be derived *via* four distinct pathways depending upon the stereochemical outcome of the intramolecular *aza*-[3 + 3] annulation and the location of the methyl substituent [Figure 5].

We considered many approaches, pathways **A–D**, towards these azaphenalene alkaloids. If vinylogous amide **140** undergoes an *aza*-[3 + 3] annulation selectively to favor the *anti* (defined by the angular hydrogen atoms in blue) annulation product **141**, hippodamine **142** and precoccinelline **144** could be rapidly constructed, as **141** would match three of the four stereocenters in **142** and **144** (pathway **A**). However, access to myrrhine **136** would necessitate an epimerization of **141**. A more expeditious synthesis of **136**, as illustrated by pathway **B**, would be to utilize *syn* (defined by the angular hydrogens in red) *aza*-tricycle **135** *via* a *syn*-selective annulation of **140**. In pathway **C**, the carbon tether of vinylogous amide **146** would contain the methyl group of these natural products, and an enantioselective total synthesis of **142** (**136** and **144** are achiral or meso) could be observed if **146** can be made in an optically enriched manner. Lastly, an enone intramolecular *aza*-[3 + 3] annulation of vinylogous amide **139** could be employed to obtain the azaphenalene alkaloids *via* **137** and/or **138**.

With these approaches, we elected to pursue pathways **A** and **B** because it is not trivial to build **146** in an optically enriched manner, and a useful enone version of our pivotal *aza*-[3 + 3] annulation had yet to be developed. Thus, the key common intermediate **141** would be prepared by an *aza*-[3 + 3] annulation of vinylogous urethane **140**, which would be accessed in several steps from *cis*-1,3-disubstituted lactam **149** with glutarimide **147** and bromide **148** as the essential starting points [Scheme 43].

Our synthesis commenced with reductive alkylation of glutarimide **150** with the Grignard reagent generated from bromide **148** [Scheme 44]. The reduction proceeded stereoselectively, affording lactam **149** in 75% yield exclusively as the 1,3-*syn* isomer. To access vinylogous urethane **152**, we elected to employ an Eschenmoser's episulfide contraction. Thus, **149** was

converted to thiol imide **151** in 90% yield over two steps, and was subsequently treated with PPh₃ in the presence of DIPEA in CH₃CN. After 48 h, vinylogous urethane **152** was isolated in 90% yield.

The substrate **140** for the *aza*-[3 + 3] annulation was then prepared in 82% yield over two operations from **152** [Scheme 45]. Treatment of vinylogous urethane **140** with the more reactive piperidinium trifluoroacetate salt provided *aza*-tricycle **141** stereoselectively as a single isomer with *anti* relative stereochemistry in 51% yield. Implementing our one-pot protocol involving *in situ* hydrogenation of the cycloadduct **141**, after the formal cycloaddition, gave **153** in 43% yield over two steps. In this case, Pd(OH)₂/C was chosen as the catalyst due to its lower tendency, relative to Pd/C, to be poisoned by the amine. At this stage, tricycle **153** possesses three of the four stereocenters in hippodamine **142** and precocinelline **144**, and therefore represents the common intermediate upon which stereodivergent conversion of **153** to precocinelline, coccinelline, hippodamine and convergine were accomplished [*vide infra*, Schemes 48 and 49].

To complete the total synthesis of myrrhine **136**, we needed an adequate epimerization of the stereocenter (shown in red) of the common intermediate **141**. As illustrated in Scheme 46, we elected to pursue an aromatization-reduction sequence by treating *aza*-tricycle **141** with DDQ, and the ensuing pyridinium salt **154** was hydrogenated over Adams' catalyst in AcOH to give the all-*syn* *aza*-tricycle **155** in 54% yield for the two-step protocol as a 2:1 mixture of diastereomers with respect to the ester group.

Submitting this 2:1 diastereomeric mixture of **155-ax** and **155-eq** to saponification conditions afforded the equatorial acid **156-eq** as the predominant diastereomer [Scheme 47]. This indicated that the axial isomer underwent significant epimerization to the more stable equatorial acid. Unfortunately, a subsequent Barton's decarboxylation protocol of the diastereomeric mixture provided myrrhine **136** in very low yield with almost complete recovery of the equatorial acid starting material. This outcome implied that the equatorial acid **156-eq** is much less reactive to decarboxylation than the axial acid. Therefore a different protocol was employed.

Revisiting pyridinium salt **154** in Scheme 46, instead of using Adams' catalyst in AcOH we had found conditions to hydrogenate the salt using 14 *psi* H₂ over Pd(OH)₂ in MeOH, that would provide **155** in 44% yield over two steps as a 5:1 mixture of diastereomers. We opted to saponify this diastereomeric mixture of **155-ax** and **155-eq** (5:1 isomeric ratio in favor of **155-ax**) using LiI in EtOAc, providing lithium carboxylate **157-ax** in 73% yield with no epimerization observed [Scheme 47]. Lastly the mixture was acidified and the ensuing acid was submitted to Barton's decarboxylation conditions to give myrrhine **136** in 31% yield over a four-step sequence.

To complete the stereodivergent syntheses of the other members in the *Coccinellidae* family — precocinelline, coccinelline, hippodamine and convergine—we returned to *aza*-tricycle **153**, the common intermediate, as the stereodivergent starting point. To this end, hydrogenation of *aza*-tricycle **153** over Adams' catalyst proceeded in a stereodivergent manner, giving a 2:1 isomeric ratio of **158a** and **158b** [Scheme 48]. Of importance, precocinelline **144** and its *N*-oxide, coccinelline **145**, possess the framework observed in major isomer **158a**, while **158b** resembles hippodamine **142** and convergine **143**. Rather than chromatographically separating the mixture of esters **158a** and **158b**, we elected to resolve the esters *via* alkaline hydrolysis of equatorial ester **158a**. Thus, the crude mixture of esters **158a,b** was treated with aqueous KOH and a simple extraction provided unreacted axial ester **158b** in 36% overall yield.

To isolate acid **159a**, the aqueous phase was acidified, thereby affording **159a** in 49% yield over two operations from **153**. The synthesis of precocinelline **144** was finished by subjecting

acid **159a** to Barton's decarboxylation protocol, providing the desired alkaloid in 43% overall yield [Scheme 49]. An ensuing oxidation with *m*-CPBA afforded coccinelline **145** in an excellent 96% yield.

Unfortunately, the synthesis of hippodamine **142** proved to be a more formidable challenge, whereby preliminary efforts to directly hydrolyze axial ester **158b** as well as epimerization (K_2CO_3 /MeOH and DBU/toluene protocols) of the axial ester group to the more stable equatorial ester **158a** failed. We attributed the unsuccessful hydrolysis attempt to the axial ester **158b** being hindered, thereby rendering it inaccessible. On the other hand, both of the epimerization protocols were inadequate with complete recovery of the starting material. Ultimately, we found conditions that were amenable to epimerize then hydrolyze the ester, thus transforming **158b** to acid **159b**.

Therefore, treatment of ester **158b** with KHMDS at $-78\text{ }^\circ\text{C}$ followed by quenching the reaction mixture with MeOH at $0\text{ }^\circ\text{C}$ gave the desired equatorial ester that was subsequently hydrolyzed with aqueous KOH to afford acid **159b** [Scheme 49]. Hippodamine **142** was then obtained in 43% yield by decarboxylation of **159b**. An ensuing oxidation with *m*-CPBA afforded convergine **143** in 88% yield. This work provided a novel approach to the *Coccinellidae* family and further established the pivotal *aza*-[3 + 3] annulation as a unified strategy to intercept alkaloid families.

4. Concluding Remarks

After accomplishing a diverse array of total syntheses, we believe that the *aza*-[3 + 3] annulation has provided us with a unique perspective in alkaloid synthesis. We recognize that the *aza*-[3 + 3] annulation represents a powerful strategy in organic synthesis that can be both flexible in accessing structural and stereochemical diversity and competitive in overall efficiency.

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Figure 1.
Aza-[3 + 3] Annulation: A Complementary to Aza-[4 + 2].

Figure 2.
Recent Chemistry Related to Aza-[3 + 3] Annulations.

Figure 3.
A Unified Strategy for Alkaloid Synthesis: Completed and Almost Completed Alkaloids to Date.

101: (-)-cylindricine C **103** [R = H]: (+)-cylindricine C**104** [R = Me]: (+)-cylindricine D**105** [R = Ac]: (+)-cylindricine E **102:** (-)-lepadiformine **106:** putative
(-)-lepadiformine

Figure 4.
Cylindricines and Lepadiformines.

Figure 5.
Potential Routes toward the Azaphenylene Alkaloids.

Scheme 1.
An Aza-[3 + 3] Annulation.

intermol aza-[3 + 3] **Regioselectivity**

head-to-head
carbonyl groups
aligned

versus

head-to-tail
carbonyl groups
unaligned

intramol aza-[3 + 3]

Scheme 2.
A Mechanistic Overview.

Scheme 3.
 Aza-Annulations with Chiral Vinylogous Amides.

Scheme 4.
Aza-Annulations with Chiral Iminium Ions.

Scheme 5.
Asymmetric Intramolecular Aza-[3 + 3].

Scheme 6.
An Unexpected Carbo-[3 + 3] Annulation.

Scheme 7.
Retrosynthetic Analysis of **23**.

Scheme 8.
Aza-[3 + 3] of **25** and **26**.

Scheme 9.
Synthesis of 2-epi-(±)-perhydrohistrionicotoxin.

Scheme 10.
Retrosynthetic Analysis of (-)-Pumiliotoxin C.

Scheme 11.
Stereoselective Aza-[3 + 3] of **37** and **38**.

Scheme 12.
Hydrogenation of **40-N-TFA**.

Scheme 13.
 Synthesis of 4a,8a-*diepi*-(-)-pumiliotoxin C.

Scheme 14.
The Lepadin Family of Alkaloids.

Scheme 15.
 A Stereodivergent Approach to the Lepadins.

Scheme 16.
Retrosynthetic Analysis of (+)-Lepadine F.

Scheme 17.
 Aza-[3 + 3] Annulation of **28** and **50**.

Scheme 18.
Double Hydrogenation of Ester **53**.

Scheme 19.
Total Synthesis of (+)-Lepadin F.

Scheme 20.
Total Synthesis of (+)-5'-epi-lepadin F.

Scheme 21.
Synthesis of (+)-Lepadine G and C5' Epimer.

Scheme 22.
An Intramolecular Aza-[3 + 3] Annulation.

Scheme 23.
Retrosynthetic Analysis of (+)-Gephyrotoxin.

Scheme 24.
Formal Synthesis of (+)-Gephyrotoxin.

Scheme 25.
Retrosynthetic Analysis of 2-Deoxylasubine II.

Scheme 26.
Synthesis of Annulation Substrate **82**.

Reagents and conditions: (i): $(\text{COCl})_2$, cat. DMF, 0 °C-rt; (ii) 2-mercaptopyridine-1-oxide sodium salt, DMAP, 0 °C-rt; (iii) *t*-BuSH, *hν*, tungsten lamp, 2 h.

Scheme 27.
Synthesis of (±)-2-deoxylasubine II.

Scheme 28.
Retrosynthetic Analysis of Tangutorine and Deplancheine.

Scheme 29.
Synthesis of Pentacycle **85** via Aza-[3 + 3].

Scheme 30.
Synthesis of $(\pm)$ -Tangutorine.

Scheme 31.
Synthesis of Vinylogous Amide **99**.

Scheme 32.
Synthesis of (±)-Deplancheine.

Scheme 33.
Synthesis of S- and R-Deplancheine.

Scheme 34.
Retrosynthetic Analysis of **101**.

Scheme 35.
 Synthesis of Tetracycline **117**.

entry	reagents and conditions	yields of 101 ^a	of 121 ^a
<i>i</i>	50 <i>psi</i> H_2 , 10% Pd/C, EtOAc 1.0 equiv $\text{Ir}[\text{cod}(\text{PCy}_3)\text{py}]\text{PF}_6$, rt, 48 h	0	54
<i>ii</i>	$\text{Na}(\text{OAc})_3\text{BH}$, cat. HOAc, CDCl_3 , rt, 21 h, reflux, 40 min	83	0
(a) isolated yields			

Scheme 36.
 Synthesis of (-)-Cylandricine C **101**.

Scheme 37.
 Synthesis of Putative (-)-Lepadiformine **106**.

Scheme 38.
 Attempt at (-)-Lepadiformine **102**.

Scheme 39.
Retrosynthetic Analysis of (+)-Cylindricines C-E and (-)-Lepadiformine.

Scheme 40.
 Synthesis of Spirocycle **134**.

Scheme 41.
Synthesis of (+)-Cylindricine C.

Scheme 42.
Synthesis of **102**, **104** and **105**.

Scheme 43.
Retrosynthetic Analysis of **141**.

Scheme 44.
Synthesis of Annulation Precursor **152**.

Scheme 45.
 Synthesis of Key Aza-Tricycle **153**.

Scheme 46.
Hydrogenation of Pyridinium Salt **154**.

Scheme 47.
Completing the Synthesis of Myrrhine.

Scheme 48.
Stereodivergent Hydrogenation of **153**.

Scheme 49.
Total Syntheses of **142**, **143**, **144** and **145**.