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Cyclic enaminones. Part II: Applications as versatile intermediates in alkaloid synthesis

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Among many other strategies, the enaminone approach is an important strategy to construct and diversify the azacyclic core in various alkaloids syntheses. In this brief review we discuss the application of cyclic enaminones as building blocks, as well as potential intermediates in the total synthesis of selected alkaloids.

1. Introduction

Cyclic enaminones[1] in which the nitrogen atom is embedded in the ring are versatile intermediates in the synthesis of a variety of *N*-containing natural products. In addition to providing the nitrogen atom needed in a segment of the molecule as a tertiary amine, they also offer many options to functionalize the enone portion in order to systematically build up required appendages for further elaboration. The term enaminone refers to a generic β-amino-α,β-unsaturated carbonyl compound such as a ketone or an ester for example. Commonly used enaminones as intermediates in the total synthesis of azacyclic natural products are represented by the three structural variants featuring acyclic, exocyclic and endocyclic motifs as shown in Figure 1.

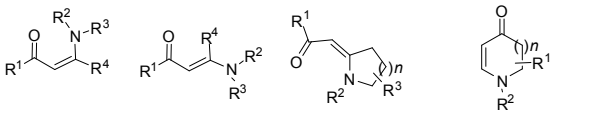

Figure 1: Enaminone structures.

An endocyclic enaminone is formally related to a 2,3-dihydro-4-pyridone.[2] The different methods for the enantioselective synthesis of functionalized cyclic enaminones were reviewed in Part 1 of this series.[3] Their inherent structure lends itself to a variety of reactions that provide functionalized azacyclic compounds that are often enantiomerically pure or highly enriched. A summary of such transformations is shown in Figure 2.

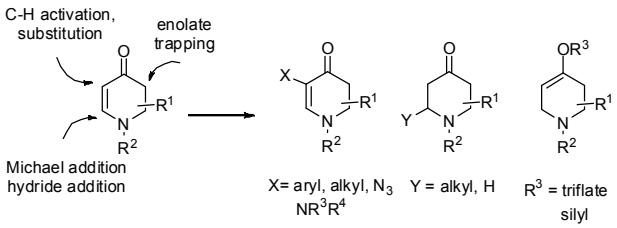

Figure 2: Representative reactions with a cyclic enaminone.

Of particular synthetic utility is the Michael acceptor character of an enaminone which allows the introduction of carbon substituents.[4] Hydride reduction with a bulky reagent such as L-Selectride and trapping the enolate leads to enolsilanes[5] and enoltriflates.[6] Pd-catalyzed C-H insertion of a functional group at the α- or β-position of the enaminone gives access to α-or β-substituted congeners including alkyl, aryl and nitrogen bearing groups.[7]

In this brief review, we shall discuss the utilization of chiral non-racemic cyclic enaminones harboring exocyclic and

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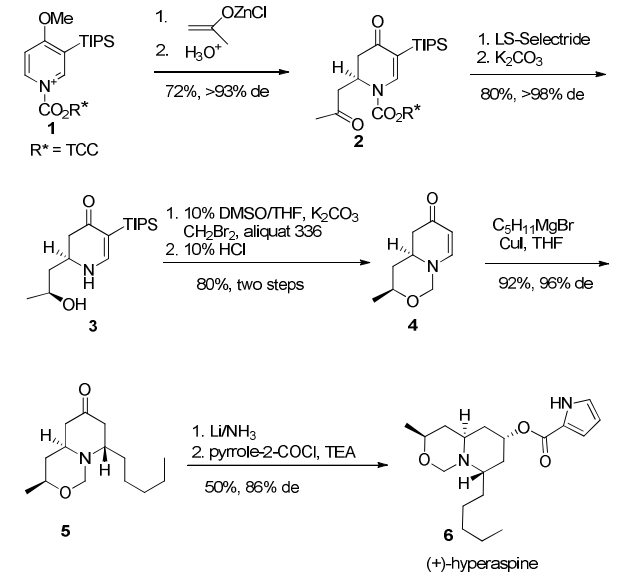
endocyclic double bonds (i.e. 2,3-dihydro-4-pyridones) as chiral synthons (chirons) toward the total synthesis of selected naturally occurring alkaloids.

2. Total synthesis of selected alkaloids using cyclic enaminones from pyridinium salts

2.1. (+)-Hyperaspine

(+)-Hyperaspine, a new type of ladybird alkaloid was isolated by Braekman and co-workers[8] in 2001 from the European Coccinellidae *Hyperaspis campestris*. Its structure was assigned by NMR and mass spectroscopic analysis, although the absolute stereochemistry was not assigned. To date, no biological activity has been reported for hyperaspine. Its skeleton is biosynthetically related to members of the piperidine, homotropane and perhydroazaphenalene alkaloids already isolated from these beetles.[8] The presence of a novel 3-oxaquinolizidine ring system in hyperaspine instigated much interest toward its total synthesis. [9]

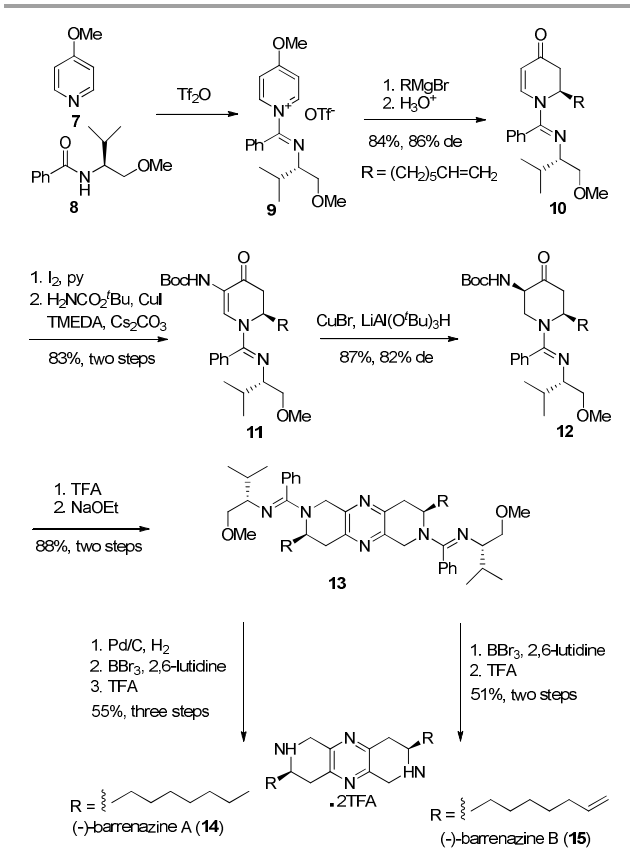


Scheme 1. Comins' synthesis of (+)-hyperaspine.

A concise synthesis of (+)-hyperaspine was reported by Comins and Sahn[10] in 2005, utilizing previously developed methodology[11] (Scheme 1). The key step involved a nucleophilic zinc enolate addition to a chiral pyridinium salt, prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine and (+)-*trans*-2-(α-cumyl)cyclohexyl chloroformate (TCC-chloroformate). Subsequent steps involved highly diastereoselective reduction of an acyclic ketone, followed by acetal protection using aliquat 336 as a phase transfer catalyst. The stereochemistry of the newly formed hydroxyl center was assigned by a NOESY experiment. TIPS deprotection of enaminone **3,** followed by copper mediated conjugate addition provided the 3-oxaquinolizidine **5** in 96% de and excellent yield. Finally, dissolving metal reduction and *in situ* acylation using pyrrole 2-carbonyl chloride led to the intended target in 86% de over 6 steps and 21% overall yield.[11]

2.2. (-)-Barrenazine A & B

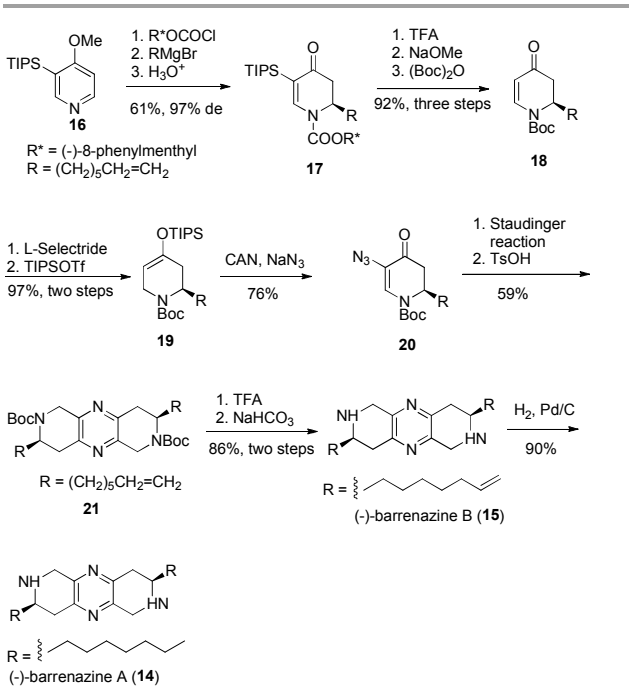
In 2003, Kashman and co-workers[12] isolated two novel compounds, barrenazine A and B from an unidentified tunicate collected at Barren Islands (Ban de l'Albatros), North-West of Madagascar. The structures of the two alkaloids were elucidated by interpretation of mass, COSY, HMQC, HMBC, NOESY, and ^{15}N-HMBC data. Barrenazine A exhibits weak cytotoxicity against LOVO-DOX colon carcinoma (with a GI_{50} value of 0.9 g/mL). It has an unprecedented heterocyclic skeleton, namely 1,3,4,6,8,9-hexahydrodipyridino[3,4-*b*:3',4'-*e*]pyrazine.



Scheme 2: Charette's synthesis of (-)-barrenazine A and B.

In 2006, Focken and Charette[13] reported the first total synthesis of (-)-barrenazine A and B starting with 4-methoxypyridine (Scheme 2). Treatment with *N*-benzoyl-*O*-methyl-L-valinol in the presence of triflic anhydride led to the chiral pyridinium salt **9** which was subjected to a diastereoselective Grignard addition followed by acid

hydrolysis to afford **10** with 86% de and good yield. Subsequent steps involved a chemoselective iodination followed by a Buchwald Cu-catalyzed C-N cross-coupling[14] using *tert*-butyl carbamate and diastereoselective 1,4-hydride addition to give compound **12** in 82% de. Boc deprotection followed by base-mediated cyclization-aromatization afforded the tricyclic hexahydropyridinopyrazine **13**. Finally, hydrogenation of **13** followed by cleavage of the chiral auxiliary gave barrenazine A. Similarly, treatment with BBr_3 and 2,6-lutidine afforded barrenazine B. Both natural products were isolated as the TFA salt. The synthesis of (-)-barrenazine A and B was accomplished in 30% (8 steps) and 28% (7 steps) overall yield, respectively, from 4-methoxypyridine.

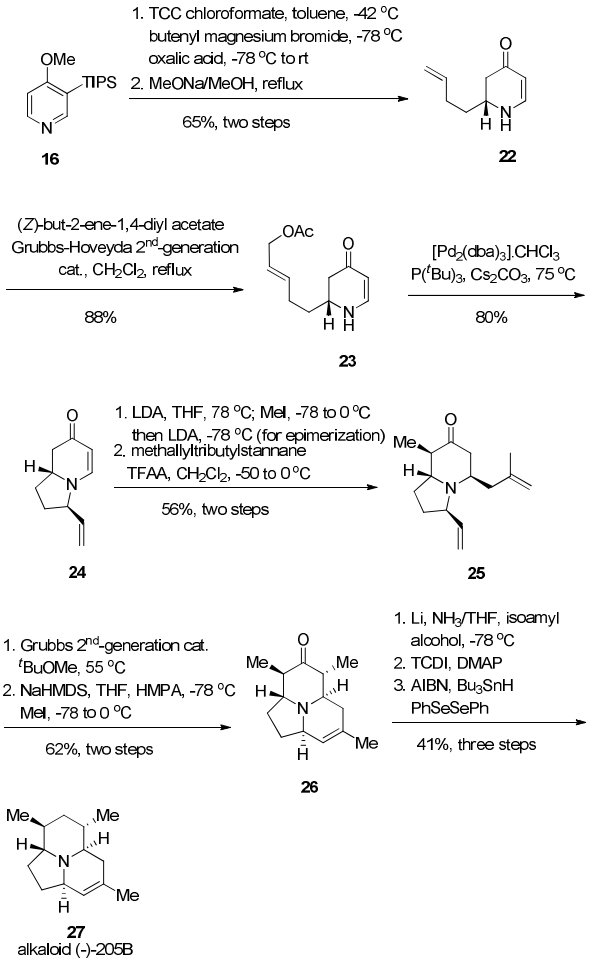


Scheme 3: Sarandeses' and Sestelo's synthesis of (-)-barrenazine A and B.

A second synthesis of (-)-barrenazines A and B was reported by Sarandeses, Sestelo and co-workers in 2007[15] (Scheme 3). A key strategy involved diastereoselective Grignard addition to an (-)-8-phenylmenthyl pyridinium salt, generated *in situ* from the 4-methoxy-3-(triisopropylsilyl)pyridine and (-)-8-phenylmenthyl carbamate to give **17** with 97% de. Subsequent steps involved acid promoted TIPS deprotection, cleavage of the chiral auxiliary and Boc protection to give enaminone **18**. Trapping an enolate from 1,4 reduction of **18** as silyl enol ether, followed by free-radical azidation led to **20**. Staudinger reduction and an acid-promoted cyclization afforded the intended *N*-Boc tricyclic octahydrodipyridopyrazine **21**. Boc deprotection of **21**, followed by basification gave (-)-barrenazine B (**15**), which was further converted to (-)-barrenazine A (**14**) upon hydrogenation. The enantioselective synthesis of (-)-barrenazine A and B was accomplished in 9 steps (19% overall yield) and 8 steps (21% overall yield), respectively.

2.3. Alkaloid (-)-205B

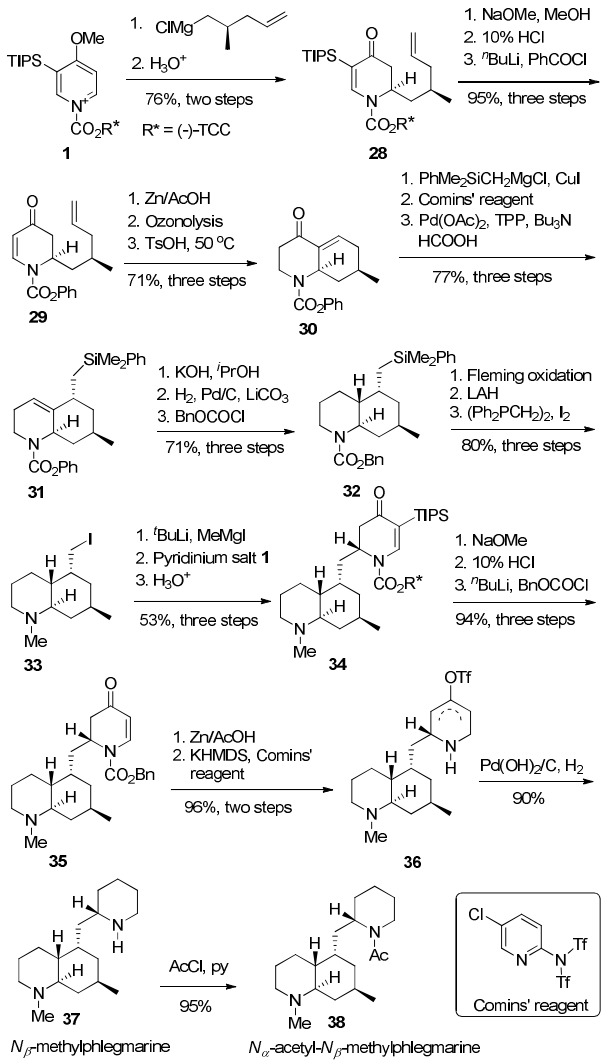
The tricyclic indolizidine alkaloid (-)-205B was isolated by Daly and co-workers[16] in 1987 from skin extracts of the neotropical poisonous frog *Dendrobates pumillo*, and its structure was proposed by NMR and mass spectrometric analysis.[17] The enantiomer of the alkaloid displays selective inhibitory activity at the α7-nicotinic acetylcholine receptor.



Scheme 4: Comins' synthesis of alkaloid (-)-205B.

In 2011, Tsukanov and Comins[18] reported a concise synthesis of (-)-205B starting with 4-methoxy-3-triisopropyl pyridine (Scheme 4). The key reaction involved the diastereoselective addition of butenylmagnesium bromide to a *N*-(+)-*trans*-2-(α-cumyl)cyclohexyl pyridinium salt followed by acidic and basic hydrolysis to provide enantiopure dihydropyridone **22**. Subsequent steps involved olefin cross-

metathesis using the Grubbs-Hoveyda 2nd generation catalyst to give **23** which was subjected to a Tsuji-Trost intramolecular allylic amination[19] to afford **24** in 70% yield. A highly stereoselective methylation of the ketone enolate of **24**, followed by stereoselective carbonyl activated conjugate addition of methallyltributylstannane led to **25**. Ring closing metathesis[20] using the Grubbs 2nd generation catalyst, followed by a second enolate methylation afforded the intended tricycle **26**. Finally deoxygenation of **26** was achieved in three additional steps in 41% yield, to provide alkaloid (-)-205B. The synthesis was accomplished in 11 steps with an overall yield of 8%.[21] The successful Pd-catalyzed allylic amination with the enamine nitrogen atom under stereochemical control and the intramolecular Grubbs 2nd generation catalyzed ring closing metathesis are added highlights of the synthesis (Scheme 4).

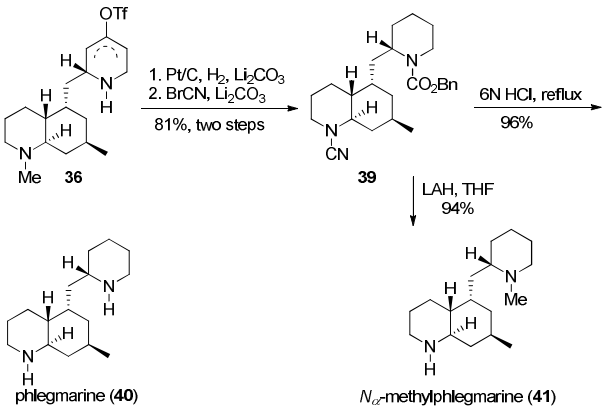


Scheme 5: Comins' synthesis of N_β-methylphlegmarine and N_α-acetyl-N_β-methylphlegmarine.

2.4. Phlegmarines

In 1987, Braekman and co-workers[22] isolated the phlegmarines, a $C_{16}N_2$ skeletal group of *Lycopodium* alkalolids, from *L. clavatum* var. *borbonicum*, *L. phlegmaria*, and *L. cernuum*. The four phlegmarines differ only by their nitrogen atom substituents. The biosynthesis of these alkaloids has been proposed by the Braekman group. In 1981 MacLean and co-workers[23] determined the relative stereochemistry of all five stereogenic centers of phlegmarines. In 1999, the absolute streochemisty of these alkaloids was established by the Comins group through the asymmetric total synthesis of (-)-N_α-acetyl-N_β-methylphlegmarine.[24]

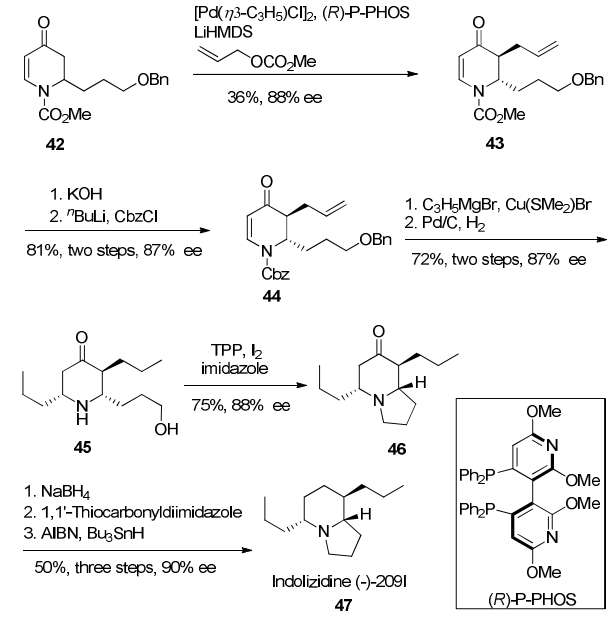
In 2010, the Comins group[25] reported the asymmetric total synthesis of all four phlegmarine alkaloids (Scheme 5). The key reaction involved addition of (*R*)-5-chloro-4-methylpentenyl Grignard to a chiral *N*-acylpyridinium salt, prepared *in situ* from 4-methoxy-3-(triisopropylsilyl) pyridine, followed by acid hydrolysis and recrystallization to provide enaminone **28** in enantiomerically pure form. A three-step deprotection-protection protocol provided enaminone **29**. Subsequent steps involved conjugate reduction, oxidative cleavage of the olefin followed by a TsOH-mediated intramolecular aldol reaction to provide the bicyclic ketone **30**. A face-selective copper mediated conjugate addition of (dimethylphenylsilyl)methylmagnesium chloride to enone **30**, followed by trapping the enolate with the Comins' reagent and reduction of the enol triflate under Cacchi's conditions[26] provided the alkene **31** in good yield. Cleavage of the phenylcarbamate and a *trans*-selective hydrogenation installed the fourth stereocentre. Fleming oxidation of **32**, followed by reduction with LAH and iodination provided the azabicyle **33**. Conversion of **33** to the corresponding Grignard reagent followed by a second addition to the chiral pyridinium salt proceeded with moderate yield, affording the intermediate **34**. That the five streocenters were correctly introduced was determined by single-crystal X-ray analysis. Deprotection-protection provided enaminone **35**, the key intermediate, in excellent yield. Subsequent steps involved conjugate reduction with Zn/acetic acid, followed by trapping the enolate with Comins' reagent and hydrogenation to provide the intended target alkaloid N_β-methylphlegmarine (**37**), which upon acetylation provided N_α-acetyl-N_β-methylphlegmarine (**38)** (Scheme 5). A selective hydrogenation of **36** with platinum on carbon followed by treatment with cyanogen bromide led to cyanamide **39** in excellent yield (Scheme 6). Hydrolysis of **39** under acidic condition provided phlegmarine (**40**). On the other hand, lithium aluminumhydride reduction of **39** afforded N_α-methylphlegmarine (**41**). The use of the chiral pyridiniumm salt in two separate steps in this synthesis leading to high enantioselectivity is noteworthy.



Scheme 6: Comins' synthesis of phlegmarine and N_α-methylphlegmarine.

3. Total synthesis of selected alkaloids using cyclic enaminones *via* kinetic resolution

3.1. Alkaloid (-)-209I



Scheme 7: Ding and Hou's synthesis of alkaloid (-)-209I.

Indolizidine alkaloid (-)-209I was found in poisonous frogs of certain genera of the *Dendrobatidae, Mantellinae,* and *Myobatrachidae* family and isolated by Daly and co-workers.[27] Structures or tentative structures of members of these alkaloids were based on mass and infrared spectroscopy and in some cases NMR spectroscopy. Rassat, Daly and co-workers[28] first synthesized (-)-209I confirming the tentative structural assignments of this natural alkaloid and permitting the elucidation of the absolute stereochemistry. Several groups have accomplished the synthesis of indolizidine (-)-209I.[29]

In 2014, Hou, Ding and co-workers[30] reported an enantioselective synthesis of alkaloid 209I based on a catalytic asymmetric strategy (Scheme 7). The key reaction involved kinetic resolution of racemic 2,3-dihydro-4-pyridone **42** using (*R*)-P-PHOS as ligand *via* a palladium-catalyzed asymmetric allylic alkylation strategy,[31] to give **43** in 88% ee. Subsequent steps involved an exchange of the carbamate group and a highly diastereoselective copper-mediated conjugate addition, catalytic hydrogenation, conversion of the alcohol to the iodide and *in situ* cyclization to afford the bicyclic indolizidine **46** in 54% yield over four steps. Reduction of the ketone function to the alcohol and a radical-mediated Barton deoxygenation[32] afforded alkaloid 209I in 24% overall yield starting with racemic 2,3-dihydro-4-pyridone **42** in an 8-step process.

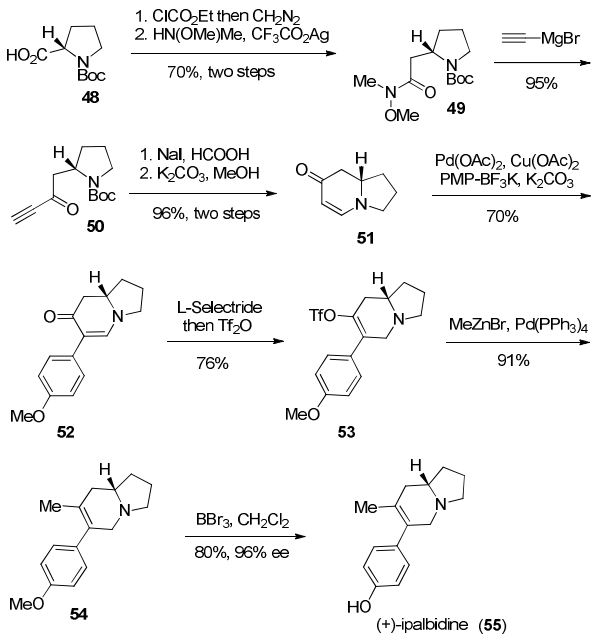
4. Total synthesis of selected alkaloids using cyclic enaminones derived from amino acids

4.1 (+)-Ipalbidine

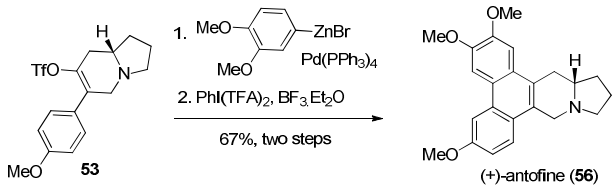
(+)-Ipalbidine, a hexahydroindolizine alkaloid, was isolated by Heacock and co-workers[33] in 1969 from the seeds of *Ipomoea alba L*. (family: Convolvulaceae). The structure of this alkaloid was assigned by mass spectrometric and NMR spectroscopic analysis. Ipalbidine is a non-addictive analgesic and oxygen free-radical scavenger.[34] It shows potent inhibitory activity against respiratory burst of leukocytes.[34] After its first synthesis in 1970 by Govindachari,[35o] several syntheses of racemic and enantiopure ipalbidine were reported.[35]

In 2010, the Georg group[35c] reported a concise total synthesis of (+)-ipalbidine starting from L-proline (Scheme 8). The key reactions involved synthesis of a bicyclic enaminone from an ynone and a Pd mediated direct cross-coupling reaction. The synthesis commenced with commercially available Boc-L-proline **48**, which was converted to ynone **50** *via* an Arndt-Eistert reaction, followed by treatment of the Weinreb amide with ethynylmagenesium bromide. Using a one-pot two-step protocol, ynone **50** was converted to the bicyclic enaminone **51** in 96% ee. Partial loss of enantiomeric excess occurred, due to a retro-Michael process, which was promoted by both acidic and basic conditions and found to be particularly problematic for β–homoproline derivatives. The following steps involved, a Pd-mediated direct cross-coupling reaction with *p*-methoxyphenyl trifluoroborate, a 1,4-conjugate hydride addition and *in situ* trapping of the resulting enolate as an *O*-Tf ether to give compound **53** in 53% yield over three steps. A typical Negishi cross-coupling reaction[36] with MeZnBr, followed by *O*-methyl deprotection afforded the

intended target (+)-ipalbidine **55** in 8 steps with an overall yield of 26%.



Scheme 8: Georg's synthesis of (+)-ipalbidine.

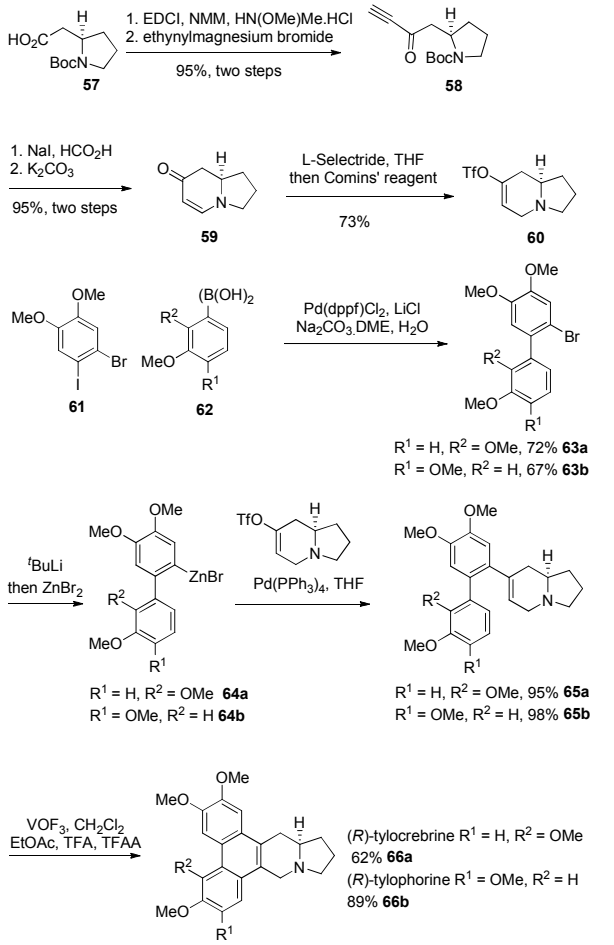


Scheme 9. Georg's synthesis of (+)-antofine.

4.2 (+)-Antofine

In 1989, the phenanthroindolizidine alkaloid (-)-antofine was isolated from *Vincetoxinrm nigrwn* L. Moench (Asclepiadaceae), a plant growing in localized areas of the Balearic Islands (Spain), by Capo and Saa.[37] (-)-Antofine has been previously isolated from *Cynuncbum vincetoxicum* and *Antitoxicum funebre*.[38] It exhibits low nanomolar activity against drug-sensitive KB-3-1 and multidrug-resistant KB-V1 cancer cell lines, comparable to that of clinically employed cytotoxic drugs.[39] It has pronounced DNA and RNA binding affinities.[40] (-)-Antofine exhibits inhibitory activity on cell proliferation by arresting the G2/M phase of the cell cycle.[41] Several total syntheses of racemic antofine, and its (-) and (+) enantiomers were reported in last 40 years.[42]

In 2010, the Georg group[35c] reported a concise synthesis of the antipode of natural (-)-antofine, along with ipalbidine starting with Boc-L-proline. The synthesis of (+)-antofine (**56**) was achieved in two consecutive steps from common bicyclic intermediate **53**, used for the ipalbidine synthesis. Successive steps involved, a Negishi cross-coupling with 3,4-dimethoxyphenylzinc bromide followed by a $PhI(TFA)_2$ mediated biaryl coupling. The synthesis of (+)-antofine was accomplished in 8 steps with an overall yield of 24% from commercially available Boc-L-proline (Scheme 9).



Scheme 10: Georg's synthesis of (*R*)-tylophorine and tylocrebrine.

4.3. (*R*)-Tylophorine and Tylocrebrine

Tylophora indica, belongs to the family Asclepiadaceae, whose extracts have long been used in Ayurvedic medicine for the treatment of various diseases such as bronchitis, rheumatism, and dysentery.[43] Phenanthroindolizidine alkaloid tylophorine, was first isolated in 1935 from the perennial climbing plant *Tylophora indica* (*T. asthmatica*) commonly available in the southern and eastern part of India.[44] The structural elucidation of these alkaloids was undertaken by Govindachari and co-workers[45] in 1951 by chemical degradation. Tylophorine exhibits cancer cell growth

inhibition[46], anti-inflammatory[47], antiameobicidal[48] and antiviral activity.[49] It also exerts anti-angiogenesis effects *via* the VEGFR2 signaling pathway.[50]

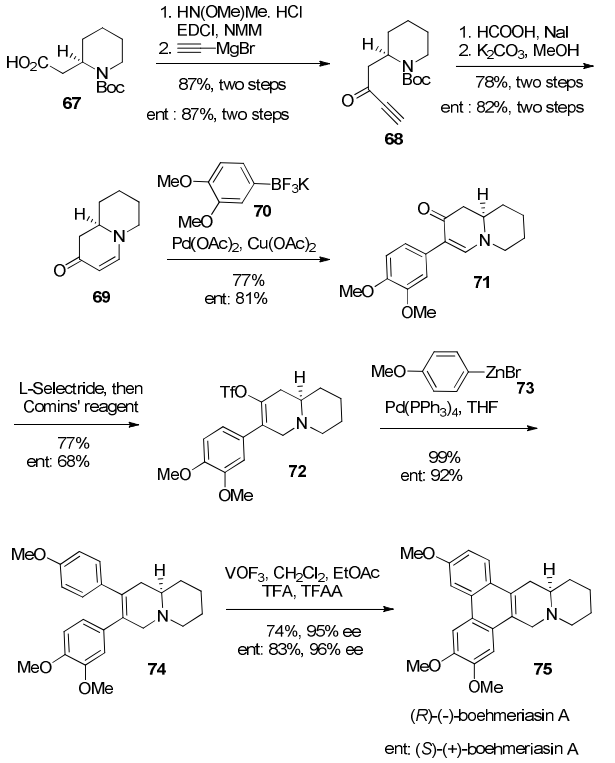
In 1962, Gellert and Govindachari[51] isolated (*R*)-tylocrebrine from *Tylophora crebriflora* (family *Asclepiadaceae*) available in northern Queensland. The structure of tylocrebrine was assigned by analytical and spectroscopic evidence methods and finally confirmed by its synthesis as the racemate. Although this phenanthroindolizidine alkaloid exhibits antileukemic activity,[52] further clinical trials were stopped due to its profound side-effects on the central nervous system.[53] A number of total syntheses have been reported in literature.[54]

In 2011, Georg and co-workers[54f] synthesized (*R*)-tylophorine and (*R*)-tylocrebrine from enaminone **59** available from Boc-L-proline in four steps (Scheme 10). 1,4-Conjugate reduction and trapping the enolate as *O*-Tf afforded **60**. Successive steps involved a Negishi cross-coupling reaction[36] between **60** and biaryl-zinc bromides **64a-b**, generated in situ from the corresponding bromides **63a-b** to give **65a** and **65b**. Oxidative cross-coupling using VOF_3, afforded (*R*)-tylophorine (**66a**) and (*R*)-tylocrebrine (**66b**) in good yield and high optical purity in 8 steps from Boc-L-homo-proline. This concise synthetic strategy of tylocrebrine not only solves the regioselectivity problem but allows late stage diversification. The regioselectivity problem can be addressed when the aryl rings of the indolizidine scaffold are substituted unsymmetrically.

4.4. (-) and (+)-Boehmeriasin A

The phenanthroquinolizidine alkaloid boehmeriasin A was isolated in crystalline form from *Boehmeria siamensis* by a bioassay-guided fractionation by Zhang and co-workers[55] in 2003. The structure was elucidated by mass and NMR spectroscopic analysis. Boehmeriasin A shows potent cytotoxic activity against lung, colon, breast, prostate, kidney and leukemia cell lines with GI_{50} values between 0.2 to 100 ng/mL. Boehmeriasin A also shows potent inhibitory activity against breast cancer cell line MDA-MB-231.[56] The total synthesis of boehmeriasin A was previously reported by Wang[57a,b] and Couture.[57c]

In 2011, Leighty and Georg[58] reported enantioselective concise syntheses of natural and unnatural boehmeriasin A starting from enantiopure (*R*)-homopipecolic acid (Scheme 11). The key steps involved a one-pot, two-step protocol to generate the quinolizidine core and a C-H functionalization reaction between tetrahydroquinolizidinones and an aryltrifluoroborate. Synthetic steps followed a previously established protocol involving the conversion of (*R*)-homopipecolic acid **67** to the corresponding Weinreb amide, followed by addition of ethynylmagnesium bromide to give ynone **68**. In successive steps, ynone **68** was converted to the bicyclic enaminone **69**, which was subjected to a Pd-mediated direct cross-coupling reaction with an aryltrifluoroborate, affording enaminone **71** in good yield. 1,4-Conjugate reduction followed by trapping with Comins' reagent gave enol triflate **72**. A Negishi cross-coupling reaction[36] furnished the advanced intermediate **74**. Finally, VOF_3 mediated oxidative biaryl coupling afforded the natural (-)-boehmeriasin A. The Georg group also synthesized (+)-boehmeriasin A from (*S*)-homopipecolic acid and upon comparing the biological activity, it was found that (-)-boehmeriasin A is more potent than its antipode in all of the cancer cell lines.



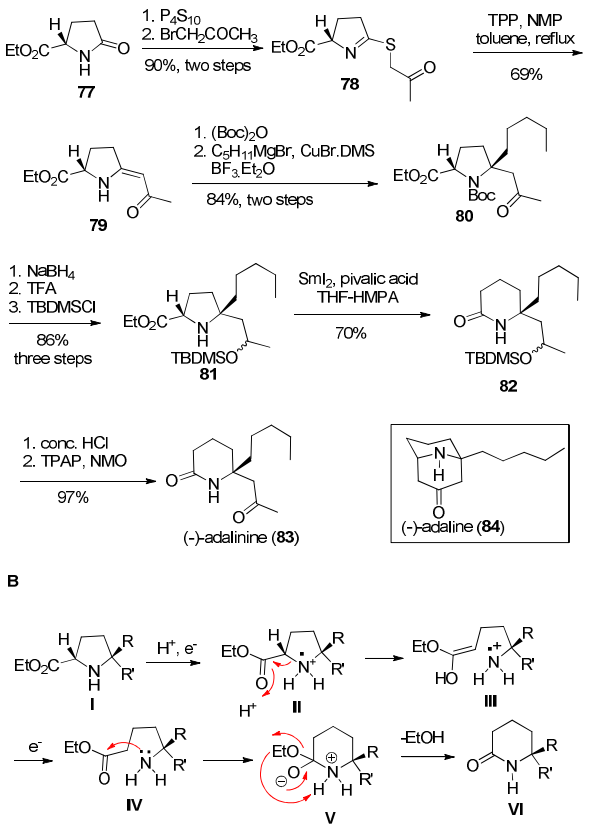
Scheme 11: Georg's synthesis of (-) and (+)- boehmeriasin.

4.5. (-)-Adalinine

In 1995, Lognay and co-workers[59] isolated the piperidine alkaloid (-)-adalinine (**83**), along with (-)-adaline (**84**) from the European two-spotted ladybird beetle, *Adalia bipunctata* (Scheme 12). The presence of this alkaloid was found in every life cycle stages of *Adalia bipunctata*. The structure of adalinine was proposed by mass spectrometric and NMR analysis after only 3.1 mg of the alkaloid was isolated from 545 adult specimens. To date no biological activity has been reported with this piperidine alkaloid. In 2001, Breakman, Daloze and co-workers carried out biosynthetic studies of adaline and adalinine,[60] and reported that the latter is biosynthetically derived from adaline *via* a retro Mannich reaction, followed by hydrolysis and oxidation. Few syntheses of this alkaloid have been reported in the literature.[61]

In 2000, Honda and co-workers[62] reported a concise, enantiospecific synthesis of (-)-adalinine, starting from (-)-(*S*)-pyroglutamic acid (Scheme 12). The key reaction involved a

samarium iodide, mediated C-N bond cleavage reaction of *α*-amino acids.[63] Treatment of the thiolactam, derived from ethyl (*S*)-pyroglutamate **77**, with bromoacetone and subsequent desulfurization of the thioether **78** provided enaminone **79** in good yield. Subsequent reactions involving carbamate protection, 1,4-conjugate addition, afforded keto ester **80** in 84% yield. In three successive steps keto ester **80** was converted to **81**, which upon treatment with SmI_2 in (7:1) THF-HMPA, underwent a smooth C-N bond cleavage and *in situ* cyclization to afford *δ*-lactam **82** in good yield. Finally desilylation and subsequent oxidation of the resulting alcohol provided (-)-adalinine. The synthesis was accomplished in 11 linear steps in 31% overall yield. Two single electron ring expansions from **81** to the lactam **82** is a noteworthy step.



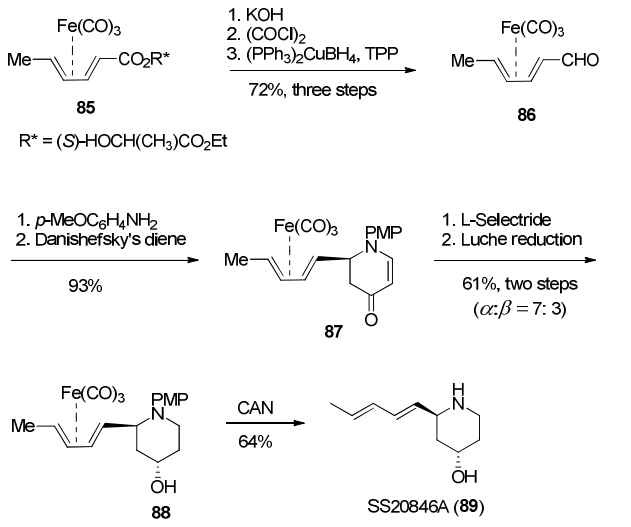
Scheme 12: Honda's synthesis of (-)-adalinine.

5. Total synthesis of selected alkaloids using cyclic enaminones *via* hetero Diels-Alder reactions

5.1. Synthesis of alkaloid SS20846A

Alkaloid SS20846A was first isolated form *Streptomycis sp*. S20846A by Komoto and co-workers in 1986.[64] In 1991, Hammann and co-workers[65] isolated the same alkaloid from *Streptomyces luteogriseus* (strain FH-S 1307), from a soil sample collected in Kypcerissia, Greece. The structure and relative stereochemistry of this piperidine alkaloid were established by mass spectrometry and NMR spectroscopic analysis. It exhibits antibacterial and anticonvulsant properties. More interestingly, the enantiomeric SS20846A shows remarkable DNA binding properties.[66]

In 1994, Iwata and Takemoto[67] reported the first total synthesis of SS20846A (Scheme 13). The key reaction involved a $LiClO_4$-catalyzed cycloaddition reaction of an imine derived from a chiral 1-azatriene iron-tricarbonyl complex, with Danishefsky's diene,[68] affording enaminone **87** in 95% de. The subsequent steps involved 1,4-conjugate hydride addition, followed by a Luche reduction of the keto functionality, which led to a 7:3 ratio of *α* and β separable diastereomeric mixtures **88** in 61% yield. Finally, simultaneous deprotection of the iron-tricarbonyl and PMP group afforded the target natural product **89**. The synthesis was accomplished in 6 steps form the known optically active 1-azatriene iron-tricarbonyl complex **85** in 26% overall yield. Other syntheses of the alkaloid SS20846A have also been reported in literature.[69]

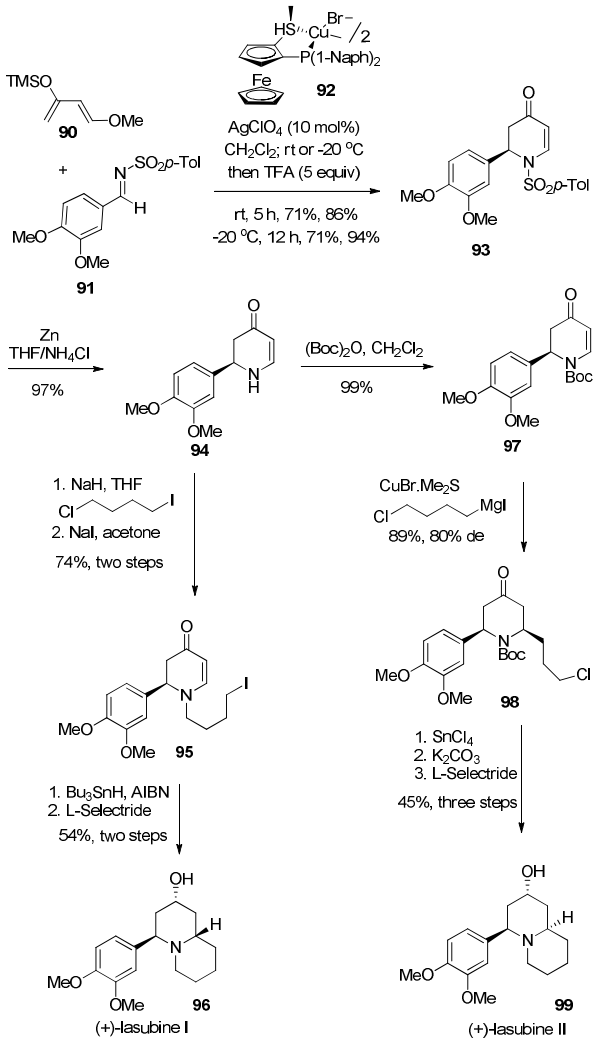


Scheme 13: Iwata's synthesis of alkaloid SS20846A.

5.2. Lasubin I and II

In 1978, Fuji and co-workers[70] isolated lasubines I and II from the leaves extract of *Lythraceae subcostata,* collected at Amami-ohshima Island. The structures of these two quinolizidine alkaloids were elucidated by mass spectrometry and NMR spectroscopic analysis. The relative stereochemistry of lasubin I was further confirmed by Schwarting,[71] following its total synthesis. Lasubines I and II differ only in the configuration at C-10. Several total syntheses have been reported in past few years. [72-74] (See also section **6.2**, **7.1**)

In 2007, Carretero and co-workers[74a] reported a stereodivergent and highly stereoselective synthesis of (+)-lasubines I and II, from the same *N*-tosyl-2,3-dihydro-4-pyridone intermediate (Scheme 14). The key reaction involved a hetero Diels-Alder reaction of an aromatic tosyl imine and Danishefsky's diene in the presence of a ferrocene catalyst and $AgClO_4$, affording the dihydropyridone **93** in good yield and 91% ee. The subsequent steps involved formation of *N*-functionalized iodo-derivative **95**, radical mediated face selective conjugate addition and diastereoselective reduction of the ketone, affording lasubine I (**96**). The synthesis of lasubine I was accomplished in 6 steps in 28% overall yield.

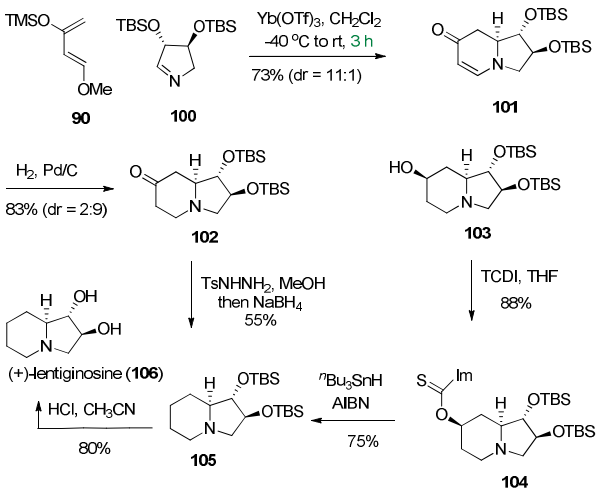


Scheme 14: Carretero's synthesis of (+)-lasubine I and II.

For the synthesis of lasubine II, a copper mediated conjugate addition of a Grignard reagent to **97** afforded piperidone **98** in 80% de. Lewis acid-assisted carbamate deprotection followed by base-induced ring closing, provided the entire carbon skeleton. Finally diastereoselective reduction of the ketone afforded lasubine II (**99**) in 45% yield over three steps. The synthesis was accomplished in 7 steps in 31% overall yield.

5.3 (+)-Lentiginosine

In 1990, Elbein and co-workers[75] isolated the dihydroxyindolizidine alkaloid, (+)-lentiginosine, from the leaves of *Astragalus lentiginosus* and its structure was assigned by mass spectrometry and NMR spectroscopic analysis. The Elbein group also proposed a biosynthetic pathway for this alkaloid, thereby assigning a tentative stereochemistry. Since its discovery, the absolute configuration of natural lentiginosine has been found to be a matter of dispute.[76] Lentiginosine is a reasonably good and selective inhibitor of the fungal α-glucosidase, amyloglucosidase (Ki = 1 X 10^5 M). According to Macchi and Brandi et al., *ent*-lentiginosine is found to be more potent in some tumor cell lines compared to the natural one.[77] Several total syntheses of both enantiomers have been reported, mostly to validate new methodologies.[78]



Scheme 15: Yang's synthesis of (+)-lentiginosine.

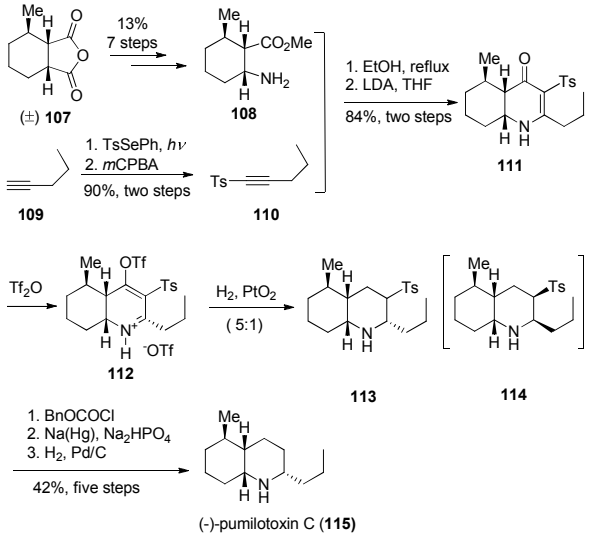
In 2012, Shao and Yang[79] reported a synthetic route to (+)-lentiginosine utilizing an aza Diels-Alder strategy (Scheme 15). The key step involved a $Yb(OTf)_3$ mediated aza-Diels-Alder reaction of an optically active cyclic imine **100** with Danishefsky's diene **90**, which provided the bicyclic enaminone **101** in 83% de. Starting with the major isomer, subsequent steps involved hydrogenation followed by a free radical mediated deoxygenation and TBS deprotection, to afford (+)-lentiginosine **106** in good yield. Alternatively **105** could be obtained from **102** via $NaBH_4$ reduction of the corresponding Ts-hydrazone. Due to its biological importance, the Yang group also synthesized *ent*-lentiginosine using the same strategy. The

synthesis was accomplished in 5 steps starting from the known cyclic imine precursor **100**.

6. Total synthesis of selected alkaloids using cyclic enaminones *via* conjugate addition-cyclization

6.1 Pumilotoxin C

In 1969, Daly and co-workers[80] isolated pumilotoxin C as a crystalline hydrochloride from the skin extract of *Dendrobates pumilo*, a strikingly colored Panamanian frog. The structure and relative configuration of pumilotoxin C was established by X-ray analysis. Later in 1977, the absolute stereochemistry of naturally occurring (-)-pumilotoxin C was established by the Daly group.[81] Pumilotoxin is a potent reversible blocker of the nicotinic acetylcholine receptor channel.[82] The biosynthetic origin of this alkaloid is not well established.[83h] Due to its pharmacological importance and limited availability, several enantioselective syntheses of this natural product have been reported in the literature.[83a]

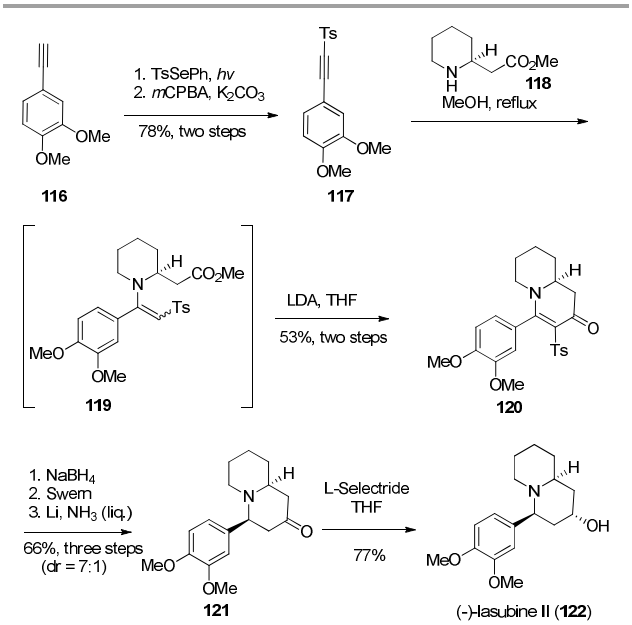


Scheme 16: Back's synthesis of (-)-pumilotoxin C.

In 1998, Back and Nakajima[84] reported an enantioselective synthesis of (-)-pumilotoxin C from a chiral amino ester and an acetylenic sulfone, acting as an alkene dipole equivalent (Scheme 16). The key sequence involved, conjugate addition of β-amino ester **108** (derived form **107** *via* enzymatic resolution) to an acetylenic sulfone **110**, followed by LDA mediated intramolecular cyclization *via* formation of a sulfone-stabilized vinyl carbanion, to afford bicyclic enaminone **111** in moderate yield. Subsequent reactions involved enol triflate formation, followed by hydrogenation, to provide an inseparable diastereomeric mixture of **113** and separable **114** as a single diastereomer. Finally, the azabicycle **113** was converted to pumilotoxin C in three consecutive steps. The synthesis was completed in 14 steps from racemic **107**. (See also section **8.2**)

6.2 (-)-Lasubine II

In 2002, Back and co-workers[73] reported the synthesis of natural (-)-lasubine II (Scheme 17). The key reactions involved a Michael-type addition of amino ester **118** to acetylenic sulfone **117**, followed by treatment of the crude product **119** with LDA, to afford bicyclic enaminone **120** in moderate yield. Successive steps involved reduction of the enone, followed by oxidation and tosyl deprotection, to provide a 7:1 separable mixture of diastereomers. Finally stereoselective reduction of ketone **121** afforded lasubine II. The synthesis was accomplished in 6 steps with 23% overall yield starting from the readily available methyl ester of (*R*)-homopipecolic ester **118**. (See also section **5.2**, **7.1**)



Scheme 17: Back's synthesis of (-)-lasubine II.

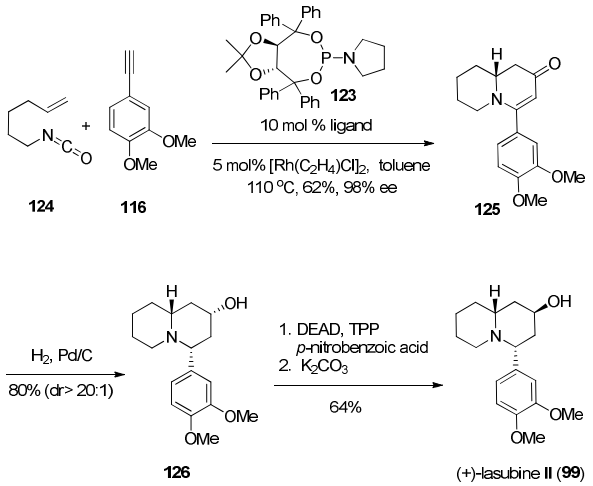
7. Total synthesis of selected alkaloids using cyclic enaminones *via* cycloaddition reactions

7.1. (+)-Lasubine II

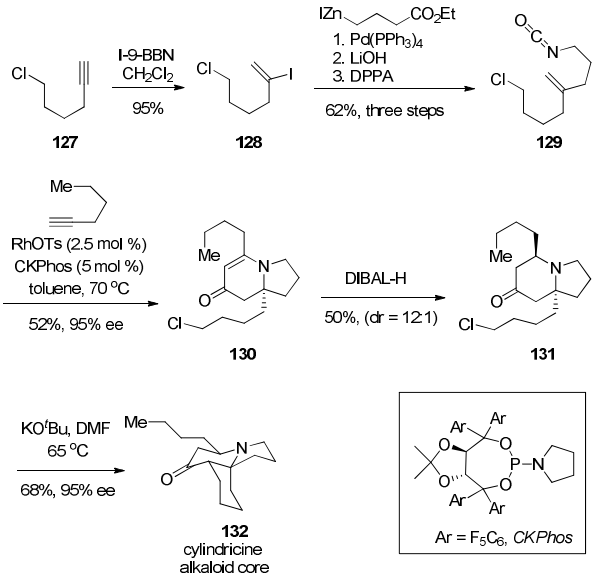
In 2006, Rovis and coworkers[85] developed an efficient regio- and enantioselective rhodium-catalyzed [2+2+2] cycloaddition reaction of alkenyl isocyanates with terminal alkynes, to give bicyclic enaminones. To establish the efficiency of this methodology, Rovis and co-workers[74b] reported an enantioselective total synthesis of (+)-lasubine II (Scheme 18).

The key reaction involved a [2+2+2] cycloaddition reaction of 4-ethynyl-1,2-dimethoxybenzene (**116**) and 6-isocyanatohex-1-ene **124** in the presence of catalytic

$[Rh(C_2H_4)_2Cl]_2$ and a chiral phosphoramidite ligand (**123**), to give **125** in 98% ee and moderate yield (See Part I for mechanistic details). The subsequent steps involved diastereoselective hydrogenation of the enaminone **125,** followed by Mitsunobu reaction, to give (+)-lasubine II (**99**). The synthesis was accomplished in three consecutive steps from known starting material **124** with an overall yield of 32%. Compared to other reported syntheses,[72-74] the Rovis route exemplifies the highest level of practicality toward the synthesis of lasubine II. (See also section **5.2**, **6.2**)



Scheme 18: Rovis' synthesis of (+)-lasubine II.



Scheme 19: Rovis' synthesis of the cylindricine alkaloid core.

7.2 Cylindricine alkaloid core

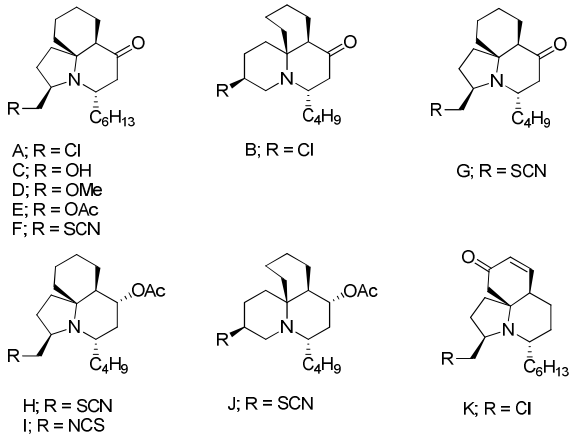


Figure 3. Cyclindricine A-K.

During the period 1993 to 1995, Blackman and co-workers[86] isolated cylindricines A- K from the ascidian *Clavelina cylindrical*, collected in Tasmania. The structures of cylindricine A and B were established by NMR and single crystal X-ray analysis. The structures of cylindricines C-K were established by mass spectrometry and NMR analysis (Figure 3). Although many alkaloids isolated from this family exhibit a broad range of pharmacological activity, no biological activities were reported for cylindricines A-K. Due to the novelty of the structure, several syntheses of cyclindricine C have been reported. [87] (See also section **8.3**, **8.4**)

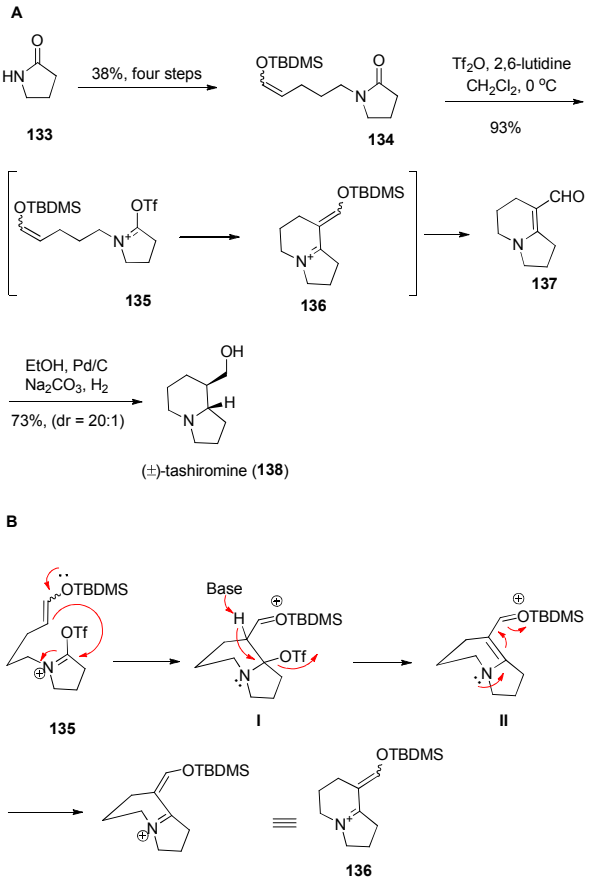
In 2013, Dalton and Rovis[88] reported a catalytic asymmetric method for the synthesis of bicyclic enaminone **130**, possessing an aza-quaternary stereocentre. To demonstrate the synthetic potential of this method, they pursued a strategy towards the synthesis of the cyclindricine core structure (Scheme 19). The key reaction involved Rh(I)CKphos catalyzed [2+2+2] cycloaddition of 1,1-disubstituted alkenyl isocyanate **129** with an aliphatic alkyne moiety to provide enaminone **130**, in moderate yield and 95% ee (See Part I for mechanistic details). The alkenyl isocyante **129** was synthesized in four consecutive steps from the commercially available aliphatic-alkyne **127**. The successive steps involved a diastereoselective hydride addition, followed by a base-promoted cyclization to afford the tricyclic cylindricine core in 7 steps and 11% overall yield.

8. Total synthesis of selected alkaloids using functionalized enaminone intermediates

8.1 (±)-Tashiromine

In 1990, Ohmiya and co-workers[89] isolated tashiromine from the stems of the leguminous plant *Maackia tashiroi*. The structure and relative stereochemistry were

assigned by mass spectrometric and NMR spectroscopic analysis and confirmed by comparison of the spectral data with those of the diasteromers of 5-hydroxymethyl indolizidine obtained synthetically. A biosynthetic pathway and biological activity of this compound have not yet been reported. Due to their structural simplicity, several total syntheses have been reported in the literature.[90]

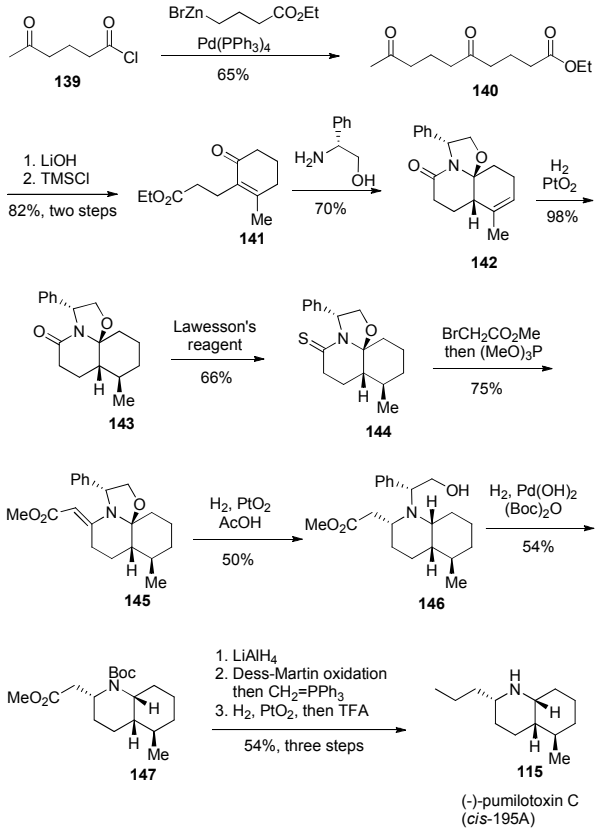


Scheme 20: Bélanger's synthesis of (±)-tashiromine.

In 2006, Bélanger and co-workers[90i] reported a concise synthesis of racemic tashiromine (**138**) (Scheme 20A). The key step involved *6-endo* cyclization of a TBDMS enol ether onto the activated butyrolactam **135**, affording the bicyclic enaminal **137** in excellent yield. A plausible mechanism proceeding through an *6-endo* cyclization is shown in Scheme 20B. Pd(0) catalyzed high pressure hydrogenation of **137** provided a 20:1 mixture of racemic tashiromine **138** in 6 steps with a global yield of 26%.

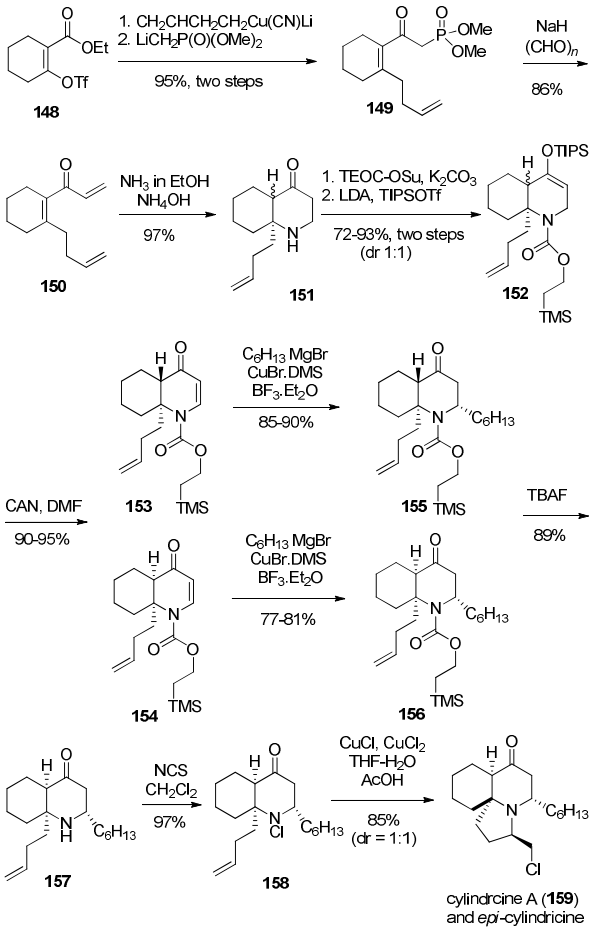
8.2 (-)-Pumilotoxin C

In 2010, Amat, Bosch and co-workers[83a] reported a biomimetic construction of the hydroquinoline ring system of the amphibian alkaloid (-)-pumilotoxin C (Scheme 21). The key reaction involved an enantioselective synthesis of **142** from 1,5-polycarbonyl compound **140**, using (*R*)-phenylglycinol as a latent chiral form of nitrogen with an overall yield of 37%. Subsequent steps involved face selective hydrogenation to **143**, thiolactam formation, and an Eschenmoser sulfide contraction reaction[91] of **144**, to give enamino ester **145** in 49% yield over three steps. PtO_2 mediated hydrogenation under acidic conditions, led to a stereoselective reduction of the vinylogus urethane double bond and reductive cleavage of the oxazolidine C-O bond to give **146**. A subsequent debenzylation using Pearlman's catalyst and an *in situ* carbamate protection afforded compound **147** in 54% yield over two steps. Lastly, conversion of ester **147** into pumilotoxin C was accomplished in three consecutive steps in 54% yield. The synthesis of (-)-pumilotoxin C was accomplished in 5% overall yield over 12 steps. The use of (*R*)-phenylglycinol as a source of nitrogen and as a latent chiral auxiliary is noteworthy. (See also section **6.1**)



Scheme 21: Amat and Bosch's synthesis of (-)-pumilotoxin C.

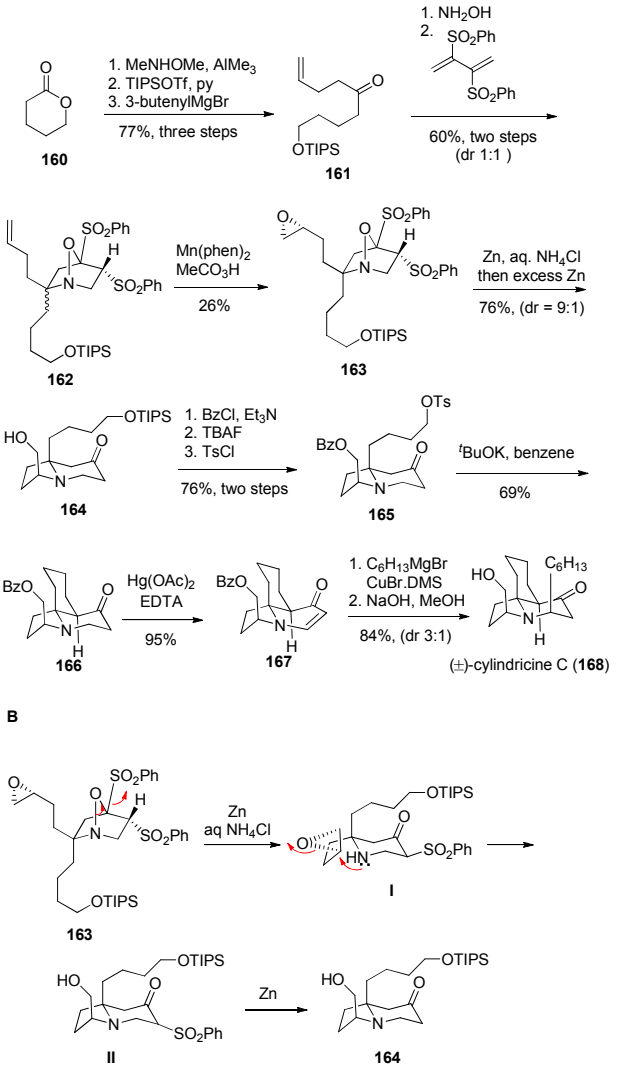
8.3. (±)-Cylindricines A and B



Scheme 22: Heathcock's synthesis of (±)-cylindricine A.

In 1999, Heathcock and Liu[92] reported the first total synthesis of racemic cyclindricines A and B. (See also section **7.2**, **8.4**) A conjugate Lipshutz cuprate addition-elimination reaction, followed by addition of the lithium anion of dimethyl methylphosphonate provided the desired ketophosphonate **149** in 95% yield over two steps (Scheme 22). The consecutive steps involved Horner-Emmons reaction[93] with paraformaldehyde, followed by a double-Michael addition of ammonia to the dienone **150,** affording a 1:1 diastereomeric mixture of bicyclic amine **151** now harboring an angular 1-butenyl group in 83% yield over two steps. A ceric ammonium nitrate oxidation[94] of **152** led to the enaminones **153** and **154** in excellent yield, which could be separated. Treatment of each diastereomer with a mixed organocuprate, afforded the azabicyclics **155** and **156** respectively in excellent yield and high stereoselectivity. A fluoride-mediated carbamate deprotection as well as an epimerization of **155** and **156** provided compound **157** in 89% yield. Several trials of electrophilic amine addition to the terminal alkene failed to provide the desired tricyclic product. Finally NCS mediated *N*-chloramine formation followed by treatment with copper (I) and copper (II) salts in aqueous acetic/THF afforded the tricyclic product **158** in 85 % yield as a ~1:1 separable mixture of cylindricine A (**159**) and *epi*-cyclindricine A. Lastly, cyclindricine A was converted to the natural mixture of cylindricines A and B in C_6D_6 *via* an aziridinium ion intermediate. The noteworthy transformations involved double Michael addition of ammonia to the dienone **150** and the D. A. Evans oxidation[94] of enol ether **152** to the corresponding enaminones **153** and **154**.

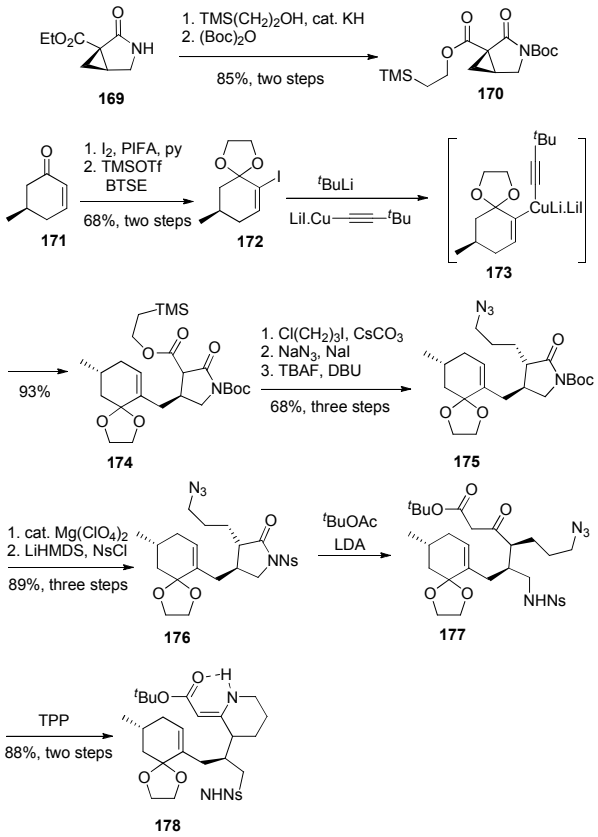
8.4. (±)-Cylindricine C



Scheme 23: Padwa's synthesis of (±)-cylindricine C.

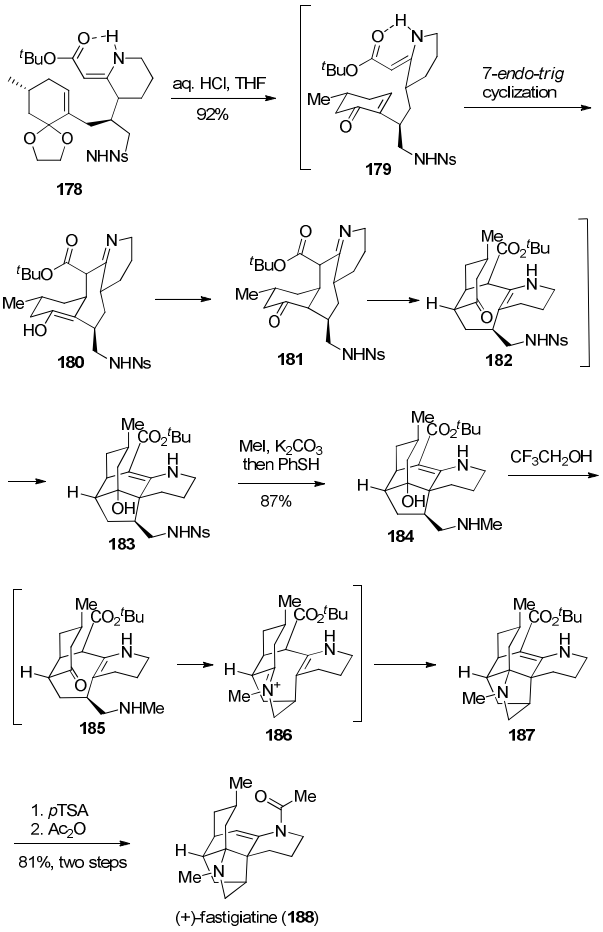
In 2008, Padwa and co-workers[87c] reported a concise stereocontrolled synthesis of racemic cylindricine C (Scheme 23A). (See also section **7.2**, **8.3**) The TIPS protected ketone **161** was synthesized from *δ*-valerolactone in three consecutive steps in 77% overall yield. In successive steps, ketone **161** was converted to the oxime, followed by treatment with bis(phenylsulfonyl)diene to provid the dipolar cycloaddition cascade product **162** in excellent yield. Subsequent steps involved a Stack epoxidation[95] to **163**, followed by a zinc mediated reductive-cyclization cascade to give the bicyclic ketone **164** in 80% de. The reductive-cyclization cascade involved an incision of the *N-O* bond in **163** followed by spontaneous ejection of phenyl sulfenic acid and a rapid intramolecular indolizidine ring formation *via* epoxide ring opening (Scheme 23B). In a series of functional group transformations **164** was converted to the tosylate **165**, which upon treatment with *t*-BuOK in benzene afforded tricyclic amine **166** in 69% yield. Treatment with $Hg(OAc)_2$ led to the enaminone **167** which underwent a 1,4-conjugate addition using a modified Donohoe procedure.[96] Alkaline saponification led to racemic cyclindricine C in 14 steps with an overall yield of 4%. The strategy to use a [2+3]-dipolar cycloaddition reaction to generate a piperidine harboring the eventual carbonyl group in the target is to be noted.

8.5. (+)-Fastigiatine



Scheme 24: Shair's synthesis of intermediates toward (+)-fastigiatine.

In 1986, MacLean, Lock and co-workers[97] first isolated fastigiatine as a minor component of the alkaloids of *Lycopodium fastigiatum*. The structure and relative configuration were determined by X-ray analysis of the free base. The unique pentacyclic ring system of fastigiatine was not observed previously in the *Lycopodium* family. A biosynthetic pathway has been proposed for this alkaloid but to date no biological activity is known.



Scheme 25: Shair's synthesis of (+)-fastigiatine.

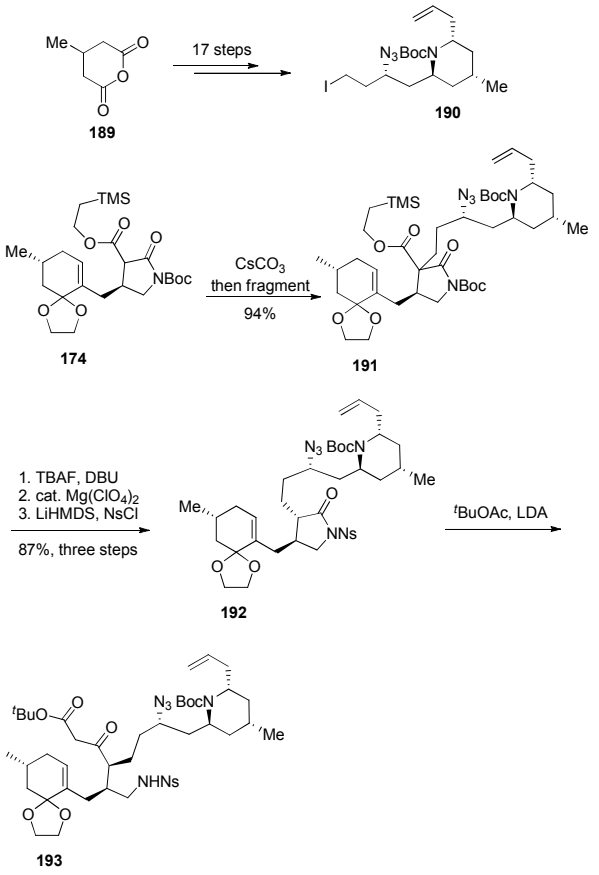
In 2010, Shair and co-workers[98] reported the first total synthesis of (+)-fastigiatine (Schemes 24 & 25). The noteworthy transformations involved a convergent fragment coupling *via* a nucleophilic cyclopropane ring opening, diastereoselective [3+3]-cycloaddition and a transannular Mannich reaction to construct the natural product core.

The first key reaction commenced with coupling of enantiomerically pure fragments cyclopropane unit in **170** and vinyl iodide **172**, derived from the known synthetic intermediates **169** and **171** respectively. The electrophilic cyclopropane **170** underwent a nucleophilic ring opening in presence of mixed organocuprate **173** with an excellent yield of 93%. The subsequent reactions involved an alkylation with 1-chloro-3-iodopropane, displacement with NaN_3, fluoride mediated silylester cleavage and concomitant decarboxylation followed by an *in situ* base-catalyzed epimerization, afforded azide **175** in 68% yield over three steps. $Mg(ClO_4)_2$ mediated Boc deprotection of **175**, followed by nosyl protection of the amine afforded **176** in excellent yield. Addition of the lithium enolate of *tert*-butyl acetate to **176,** followed by Staudinger reduction of azide **177** provided enaminone **178** as a 3:2 mixture of epimers. The enaminoester **178** was found to be an important intermediate for cascade ring-closing and opening reactions to provide the intended pentacyclic motif of fasigiatine. When compound **178** was directly exposed to aqueous HCl, it underwent a series of unique transformations involving dioxalane cleavage, enamine-mediated conjugate addition (**179** to **180**), enol tautomerization to ketone **181** and an enamine-mediated aldol cyclization of **182** to give **183** in 92% yield (Scheme 25). *N*-methylation followed by nosyl deprotection afforded enamino ester **184** which upon heating with degassed 2,2,2-trifuluoroethanol, yielded pentacycle **187**, *via* a retro-aldol, iminium ion formation and a biomimetic transannular Mannich reaction. Finally, acid-mediated decarboxylation of **187**, followed by *N*-acetylation furnished (+)-fastigiatine **188**. The total synthesis of (+)-fastigiatine was accomplished in 15 steps with 30% overall yield from known cyclopropane **169**. Many noteworthy reactions used in this highly stereocontrolled total synthesis of a complex tetracyclic alkaloid, taking advantage of cascade reactions in a biomimetic fashion are highlights to be commended (Scheme 24-25).

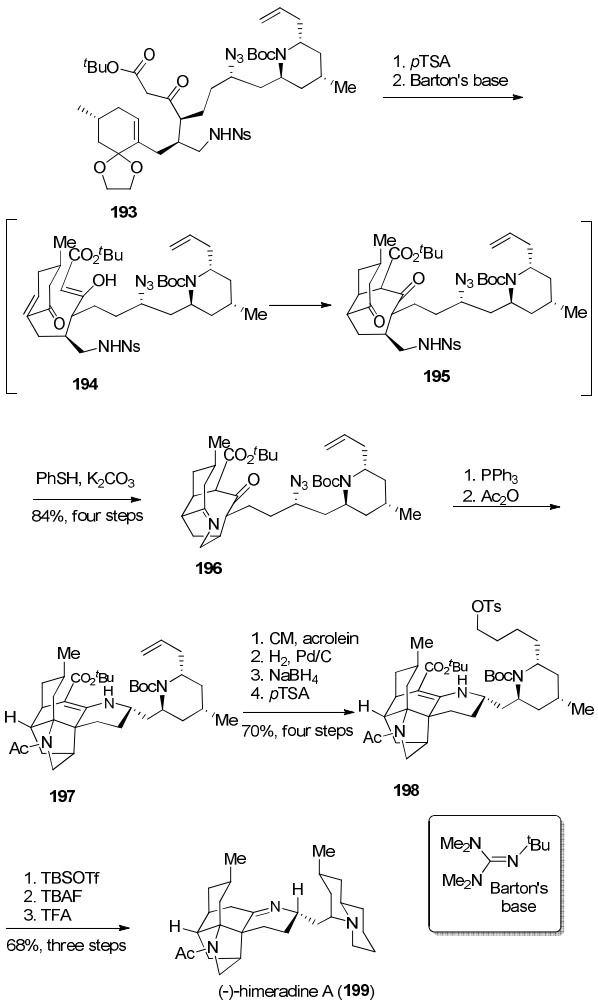
8.6. (-)-Himeradine A

In 2003, the Kobayashi group[99] isolated a novel *Lycopodium* alkaloid himeradine A from the club moss *L. chinense.* The structure and relative stereochemistry were elucidated by NMR and mass spectroscopic analysis. Himeradine A consists of two domains, a fastigiatine-type skeleton and a quinolizidine moiety. The stereochemical relationship between the two domains was not unambiguously determined and appeared to be assigned based on the assumption that the pelletierine units utilized to form the two domains have the same stereochemical origin. Himeradine A exhibits in vitro cytotoxicity against murine lymphoma L1210 cells (IC_{50}, 10 µg/mL). The same group also proposed a biosynthetic pathway for this complex alkaloid.

In 2011, Callett and Carter[100] reported a short synthesis of eastern quinolizidine domain of himeradine A. In 2014, Shair and Liau reported the first total synthesis of the proposed structure of himeradine A[98] (Scheme 26 & 27). Here we highlight the most relevant synthetic steps for this synthesis. Enantiomerically pure fragment **190** was synthesized in 17 steps from 3-methylglutaric anhydride **189**. The successive steps involved a fluoride mediated desilylation of **174**, concomitant decarboxylation and two-step protective group deprotection-protection sequences to provide compound **192** in 87% yield over three steps. Addition of the lithium enolate of *tert*-butylacetate to **192** led to **193**. The key biomimetic cascade sequence involved dioxolane cleavage to **194**, followed by a Barton's base induced 7-*endo*-*trig* intramolecular cyclization to **195**, cleavage of *N*-Ns protection group, and finally formation of the imine **196** (Scheme 27). The three-step two-pot sequence afforded imine **196** in 84% yield. Next, Staudinger reduction of **196** resulted in formation of the corresponding enaminoester, which underwent the key biomimetic transannular Mannich reaction to afford the intended hexacycle **197** after *N*-acetylation. In a sequence of steps compound **197** was converted to the tosylate **198** then to himeradine A (**199**). The total synthesis of the complex seven-membered (-)-himeradine A was accomplished in 33 steps (Scheme 26-27).



Scheme 26: Shair's synthesis of intermediates toward (-)-himeradine A.



Scheme 27: Shair's synthesis of (-)-himeradine A.

Conclusion

In part one, of this two part review on cyclic enaminones, we presented methods toward the stereocontrolled synthesis of substituted 2,3-dihydro-4-pyridones harboring one or more stereogenic centers in enantiopure or enantioenriched form. In this second part, we have shown how chiral non-racemic substituted cyclic enaminones in general, and 2,3-dihydro-4-pyridones in particular were utilized as versatile intermediates toward the total synthesis of a variety of naturally occurring alkaloids. These comprise monocyclic and polycyclic compounds containing one or more nitrogen atoms with a number of alkyl and aryl substituents on stereogenic carbons. Methods enabling highly diastereoselective alkylation of pyridinium salts have produced a variety of 2-substituted-4-dihydropyridones which were used as a template to further elaborate more complex molecules. Starting with amino acids such as proline and pipecolic acid allowed the stereocontrolled synthesis of a variety of indolizidines and quinolizidines as core units which were further functionalized toward phenanthroindolizidine and related alkaloids. The methods developed toward 2-substituted dihydropyridones using hetero Diels-Alder cycloadditions and conjugate additions were nicely exploited toward the total synthesis of piperidine, indolizidine, quinolizidine and isoquinolizidine alkaloids. Substituted enaminones generated in the course of a multistep process have been exploited for their reactivity and utility as advanced intermediates. With the versatile methods available to prepare chiral non-racemic enaminones, the core structures of many alkaloids, similar to the ones highlighted in this review, will be efficiently constructed and further elaborated toward biologically relevant azacyclic compounds.

Notes and references

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