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Recent advances in the synthesis of azaphenalene alkaloids. First enantioselective approaches

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ABSTRACT

The azaphenalene alkaloids are biosynthesised and segregated by diverse insects of the Coccinellidae family (ladybirds) and are believed to play an important role in the defensive mechanism against their natural predators. The particular unique framework of these alkaloids, along with their potential in the field of biological pest control, has led to several research groups to develop synthetic sequences to prepare these compounds. The main purpose of the present review is providing an update of the more recent synthetic progress towards these alkaloids, including the pioneer enantioselective approaches to the chiral congeners.

INTRODUCTION

The Coccinellidae family is comprised of more than 5000 species worldwide of small coleopteran insects, commonly named ladybugs, ladybirds or lady beetles.¹ Due to their voracious appetite for aphids and other harvest-damaging insects, some coccinellids have played an important role in biological pest control.² The main defence mechanism of coccinellids against their natural predators (such as birds and ants) is reflex bleeding, consisting in the secretion of an orange fluid (haemolymph) when they feel attacked.³ The strong smell and bitter taste of this fluid is associated with the presence of specific alkaloids.^{1,4} Among them, the most characteristic are the azaphenalenes, which confer the bitter taste to these insects.⁵ Up to now, nine different monomeric alkaloids with perhydro-9b-azaphenalene skeleton have been isolated (Figure 1), which differ in their relative stereochemistry, the oxidation state of the nitrogen atom and the presence and location of a carbon-carbon double bond. In addition, several “dimeric” alkaloids containing at least one perhydro-9b-azaphenalene unit have also been discovered.⁶ Precoccinelline (and its *N*-oxide, coccinelline) and myrrhine are *meso* compounds. In the rest of this family members the reflection symmetry is broken either by the presence of an endocyclic double bond (hippocasine, its *N*-oxide, propyleine and isopropyleine) or because of the *trans* position of protons H-3a and H-9a (hippodamine and convergine). Propyleine and isopropyleine are in equilibrium and have not been independently isolated. Besides their application for mimicking the effect of ladybirds in crops, it has been also described that some azaphenalene alkaloids are non-competitive antagonists for nicotinic acetylcholine receptor⁷ and some derivatives are potent receptor antagonists of the neurotransmitter serotonin.⁸ All the azaphenalene alkaloids were isolated and characterized during the 1970's. The corresponding studies, along with the early syntheses, were comprehensively reviewed by King and Meinwald in 1996 in an article dealing with the “defensive chemistry of coccinellids”.⁴ The main purpose of the present review is providing an update of the more recent synthetic progress towards

these alkaloids, which includes the pioneer enantioselective approaches to the chiral congeners.

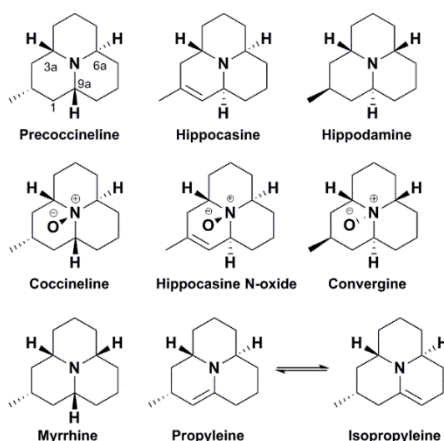
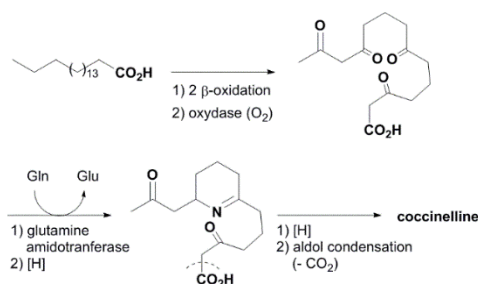


Figure 1. Monomeric azaphenalene alkaloids.

2. Biogenetic studies

On the basis of some experiments performed with ^{14}C -labelled sodium acetate, it was initially proposed that coccinelline was biogenetically derived from a β -polyketoacid produced by linear combination of seven acetate units,⁹ but subsequent studies from the same laboratory with $^3\text{H}_3$ -labelled stearic acid led to the formulation of the more plausible hypothesis depicted in Scheme 1.¹⁰



Scheme 1. Biogenetic hypothesis for coccinelline.¹⁰

3. Synthesis

3.1. Chronology

Probably attracted by the peculiar structure and apparent exclusiveness of their origin, along with their potential application in pest control, immediately after their isolation from various ladybird species, several groups undertook synthetic studies, which culminated in the total synthesis of all the known monomeric azaphenalene alkaloids, allowing to confirm their structure and relative stereochemical assignment. The plot displayed in Figure 2 shows the chronological evolution of the synthetic publications from 1976 to 2018. Analysis of this plot reveals that, after the early syntheses, there was essentially a lack of new contributions, while, in the last years, the interest for these

compounds has resurfaced. All the alkaloids presenting a free amine functionality have been efficiently converted into the corresponding *N*-oxides and, hence, a unique synthetic sequence allows the preparation of each couple precoccinelline/coccinelline, hippocasine/hippocasine *N*-oxide and hippodamine/converine. On the other hand, the selective preparation of propyleine or isopropyleine is not possible since, as already mentioned, these two enamines are in equilibrium. Some of the works included in the plot describe an improvement or an alternative preparation of an intermediate previously transformed into a targeted alkaloid. Up to 2010, all the reported syntheses ended up with achiral or racemic products and, only more recently, some enantioselective approaches have been described. Moreover, the syntheses of three “dimeric” azaphenalene alkaloids have been also disclosed.

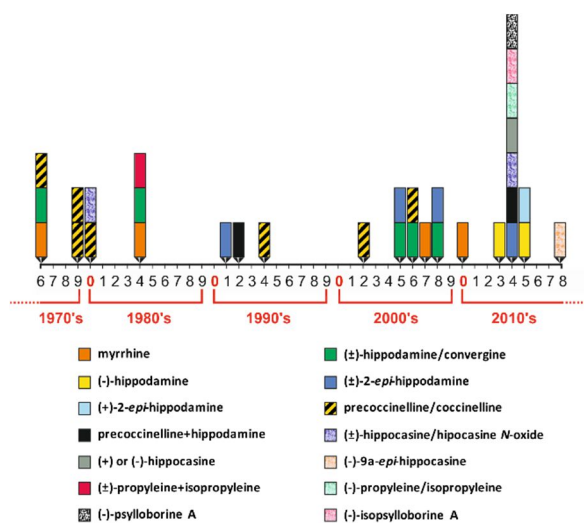


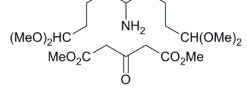
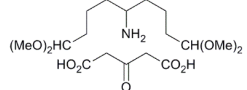

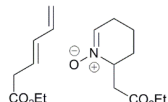



Figure 2. Chronology of the synthesis of azaphenalene alkaloids described until 2018.

3.2. Early approaches to achiral and racemic alkaloids

As stated before, the early syntheses of azaphenalene alkaloids were covered in a previous review⁴ and will not be discussed here in detail. However, in order to provide a quick overview of these initial approaches, a summarized compilation is shown in Table 1, where the key precursors, total number of steps, global yields and corresponding literature references are supplied. Most of these syntheses started from symmetric substrates (entries 1-5) and, in some cases, by splitting of the sequence, a common intermediate was derived to different alkaloids (entries 1 and 5). The total number of steps from commercially available materials was in the range 8 to 15 and the highest global yield among the early total syntheses was 21% and corresponds to the last reported within this group (entry 7). The formal synthesis of the couple precoccinelline/coccinelline (entry 4) is merely an improvement of one of the steps in a previous synthesis (entry 3). All the final products were either *meso* forms or racemates, even in the case where the starting material was homochiral (entry 7).

Table 1. Synthesis of azaphenalene alkaloids published till 1994

Entry	Key precursors	Alkaloid (steps, yield)	Author (year) ^{reference}
1		(±)-Hippodamine (8, 0.9%) ^a Myrrhine (8, 1.3%)	Ayer <i>et al.</i> (1976) ¹¹
2		Precoccinelline (8, ~1%)	Ayer and Furuichi (1976) ¹²
3 ^b		Coccinelline (11, 5.7%)	Stevens and Lee (1979) ¹³
4 ^{b,c}		Coccinelline (11, 10.7%)	Langlois <i>et al.</i> (1992) ¹⁴
5 ^d	 + BH ₃	Precoccinelline (12, 5.7%) Myrrhine (15, 2.2%) (±)-Hippodamine (15, 6.3%) (±)-Hippocasine (14, 3.8%) (±)-Propyleine (11, 3.9%)	Mueller <i>et al.</i> (1979-84) ¹⁵
6		(±)-2 <i>epi</i> -Hippodamine (12, 8.4%) ^a	Adams <i>et al.</i> (1991) ¹⁶
7		Precoccinelline (10, 21%)	Royer <i>et al.</i> (1994) ¹⁷

^a One of the steps lacked reproducibility. The yield indicated is that of the best run.

^b The amino bisacetal was prepared in 6 steps from dimethyl malonate and acrolein.

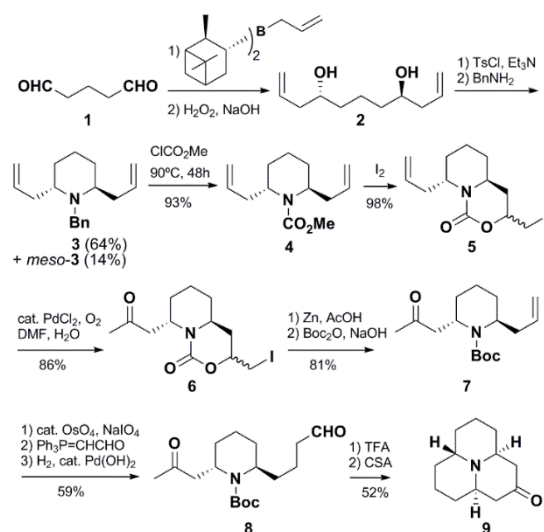
^c This was a formal synthesis, which improved one of the steps in ref. 13.

^d Some discrepancies were observed between the reported yield of a same step, depending on the publication.

3.3. Recent approaches to achiral and racemic alkaloids

In 2002, Takahata and collaborators disclosed a new methodology to prepare ketone **9**,¹⁸ a key intermediate in the previous syntheses of precoccinelline of Ayer and Furuichi,¹² Stevens and Lee¹³ and Mueller *et al.*,^{15a,d} which preparation had been later on improved by Langlois *et al.*¹⁴ and Royer *et al.*¹⁷ The synthetic sequence (Scheme 2) was initiated by treatment of glutaraldehyde, **1**, with *B*-allyldiisopinocampheylborane, followed by oxidation with hydrogen peroxide in basic medium to furnish diol **2**. Aminocyclization of the corresponding ditosylates with benzylamine gave a mixture of the *trans*- and *cis*-2,6-diallylpiperidines, **3**, in 64% and 14% yield, respectively, for the three steps. An exchange of *N*-protecting groups from benzyl to carbamate, followed by iodocarbamation produced oxazinone **5**, which was oxidized under Wacker conditions to ketone **6**. A two-step treatment consisting of reduction of the oxazolidinone and then *N*-protection as the Boc derivative furnished the allylpiperidine **7** in 81% yield. Oxidative cleavage of **7** and subsequent Wittig olefination provided an α,β -unsaturated aldehyde, which was reduced to the dicarbonyl compound **8** in 59% yield for the three steps. Ketoaldehyde **8** was treated with TFA in order to liberate the amine and submit it to an intramolecular Mannich-type cyclization leading to the tricyclic ketone **9**, precursor of precoccinelline. Overall, this preparation of **9** required 14 steps from glutaraldehyde and the

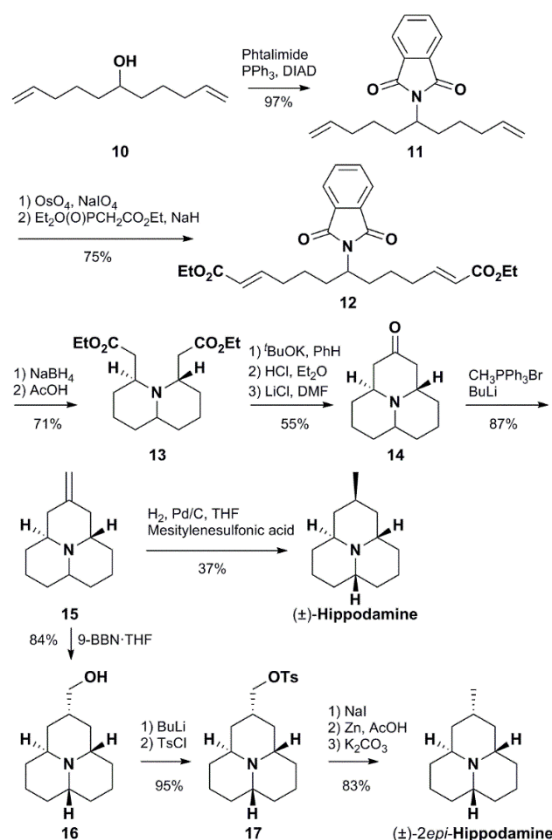
global yield was 12.5%. Its best preceding synthesis required 8 steps from commercially available materials with around 28% total yield.¹⁷



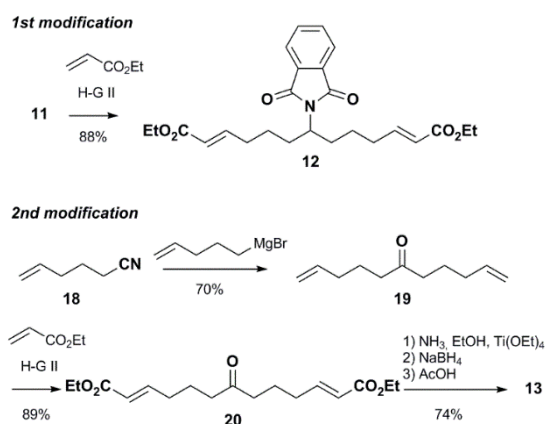
Scheme 2. New synthetic pathway to ketone **9** by Takahata *et al.*¹⁸

In 2004, Stockman and co-workers described a new synthesis of (\pm)-hippodamine, through a two-directional strategy starting from the known symmetric alcohol **10** (Scheme 3).¹⁹ Mitsunobu substitution of the alcohol by phthalimide furnished diene **11** in 97% yield. Homologation of **11** to diester **12** was best accomplished by osmium tetroxide catalysed oxidative cleavage followed by a double Horner-Wadsworth-Emmons (HWE) olefination. After extensive experimentation, the conditions of the planned key step consisting of a tandem *N*-deprotection/intramolecular double conjugate addition were conveniently adjusted to obtain the bicyclic amine **13** in good yield. To be effective, the next Dieckmann condensation required azeotropic removal of EtOH. Subsequent deethoxycarbonylation yielded ketone **14**, which was olefinated to **15**. The hydrogenation of alkene **15** was attempted in the presence of different additives and it was found that mesitylenesulfonic acid gave the best stereoselectivity. The synthesis of (\pm)-hippodamine was accomplished in 9% overall yield. On the other hand, stereoselective hydroboration of **15** with 9-BBN furnished alcohol **16**, which was converted to the corresponding iodide. Without isolation, this last intermediate was reduced with zinc delivering (\pm)-2*epi*-hippodamine, in 16% overall yield.

In 2008, a publication from the same laboratory described the introduction of some changes in the sequence to improve the synthesis (Scheme 4).²⁰ The first modification concerned the oxidative cleavage of **11**. This reaction produced large amounts of toxic osmium waste and, besides, the instability of the subsequent dialdehyde forced its immediate elaboration through the HWE reaction. As an alternative to convert diene **11** to diester **12**, a double cross-metathesis with ethyl acrylate using Hoveyda-Grubbs second generation catalyst (H-G II) was accomplished in 88% yield and, hence, it was more efficient than the previous transformation. The second modification intended avoiding the use of the phthalimide protecting group and was achieved by developing a new tandem reductive amination/double intramolecular Michael addition on the previously known ketone **20**. With this variation the original 44% overall yield of the key bicyclic intermediate **13** from commercially available compounds was increased to 46%.



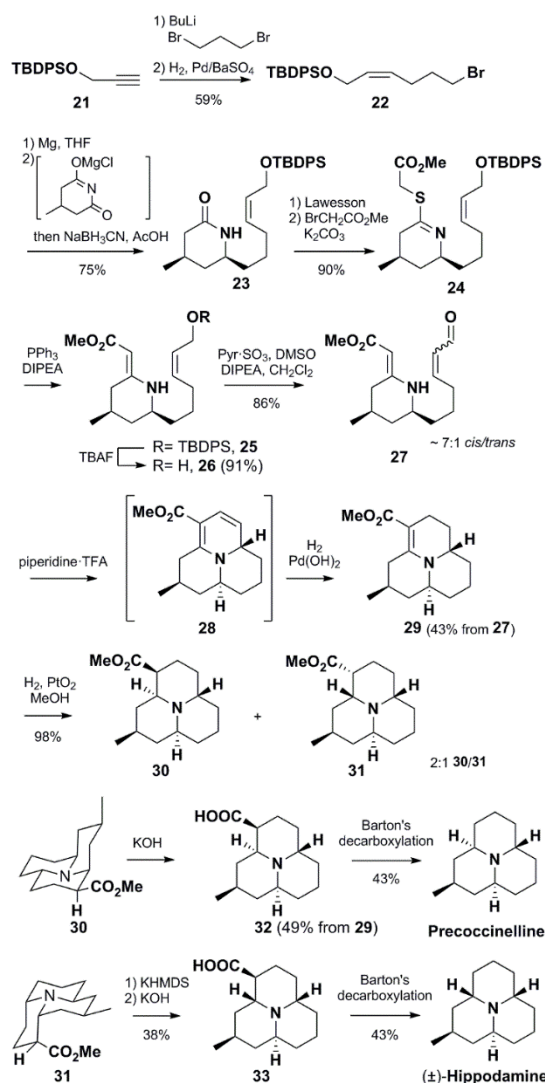
Scheme 3. Synthesis of (±)-hippodamine and (±)-2epi-hippodamine by Stockman *et al.*¹⁹



Scheme 4. Improvements on the synthesis of (±)-hippodamine and (±)-2epi-hippodamine by Stockman *et al.*²⁰

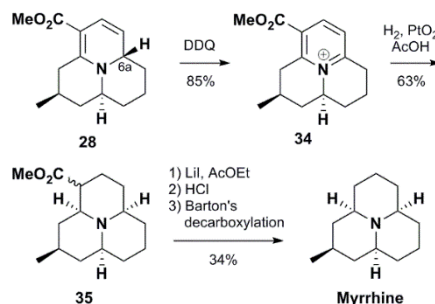
In 2006, Hsung and Gerasyuto described a stereodivergent synthesis of precoccinelline and hippodamine (and their *N*-oxides) using an *aza*-[3+3] annulation strategy (Scheme 5).²¹ The synthetic route started with the alkylation of alkyne **21** with 1,3-dibromopropane, followed by chemoselective hydrogenation that furnished alkene **22**. Reductive alkylation of 4-methyl glutarimide with the magnesium reagent derived from **22** provided lactam **23** as a *cis* isomer. This lactam was efficiently converted into the tioether **24** by treatment with Lawesson's reagent and consecutive alkylation with α -bromo methyl acetate. Eschenmoser sulphide contraction led

to the vinylogous urethane **25**, which was desilylated by treatment with TBAF. Oxidation of the allylic alcohol **26** furnished aldehyde **27** as an approximately 7:1 mixture of the *cis* and *trans* isomers. The crucial *aza*-[3+3] annulation was accomplished by treatment of **27** with piperidinium trifluoroacetate in 51% yield with *anti* relative configuration at the ring junction. Due to its low stability, the intermediate diene **28** was directly subjected to Pd(OH)₂ catalysed chemoselective hydrogenation in a one-pot protocol that delivered the α,β -unsaturated ester **29** in 43% yield. A second hydrogenation using Adams catalyst afforded **30** and **31** in a 2:1 ratio, which correlate with precoccinelline and hippodamine, respectively. The two isomers were resolved by selective alkaline hydrolysis of the equatorial ester **30**, since the axial isomer **31** was unreactive towards aqueous KOH. Decarboxylation of **32** using Barton's methodology²² led to precoccinelline. The synthesis of hippodamine required an additional step to convert ester **31** into its equatorial epimer. The yield of the sequence from **21** to the common intermediate **29** was 13.4%. Unfortunately, the last steps did not work very efficiently, furnishing the target alkaloids coccinelline and hippodamine in 2.8% and 2.2%, respectively, namely 5% overall.



Scheme 5. Synthesis of precoccinelline and (±)-hippodamine by Hsung and Gerasyuto.²¹

One year later, the same research group published an article describing the synthesis of myrrhine by alternative elaboration of the intermediate **28** (Scheme 6).²³ This endeavour required the epimerisation of C-6a, which was achieved by aromatization of the dihydropyridine ring through oxidation with dichlorodicyanoquinone (DDQ), followed by stereoselective reduction of the pyridinium salt **34**. The catalytic hydrogenation, best performed with Adams catalyst in AcOH, was concomitant with epimerisation of the α -ester stereogenic centre. This epimerisation was not synthetically inconsequential because the successive decarboxylation of the equatorial carboxylic acid did not work well.

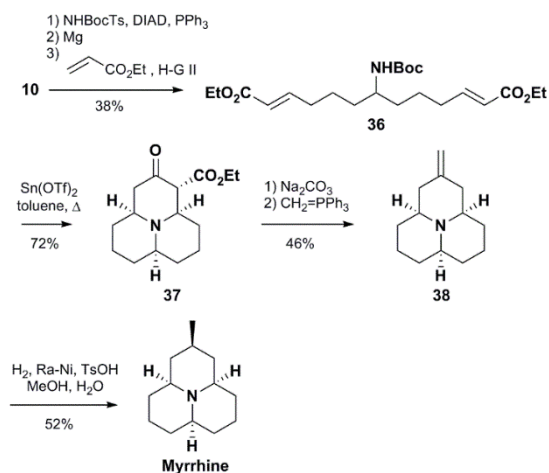


Scheme 6. Synthesis of myrrhine by Hsung and Gerasyuto.²³

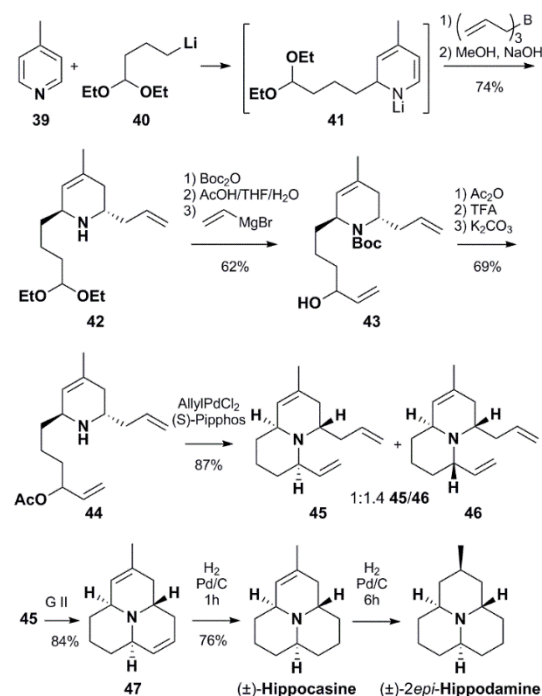
In 2010, Spring and co-workers published a new synthesis of myrrhine (Scheme 6).²⁴ Their starting material and strategy were identical to those in the previous work of the Stockmann group, but they developed a methodological alternative, which allowed to construct the tricyclic framework from an acyclic precursor in a single operation. The appropriate substrate **36**, analogous to **12**, was prepared from alcohol **10** in a similar manner. Their main challenge was to find a Lewis acid able to deprotect the nitrogen atom and promote the double conjugate addition and Dieckman cyclisation cascade. This objective was accomplished by the use of 0.5 equivalents of tin(II) triflate, delivering ketoester **37** in 72% yield, with the relative configuration of myrrhine at the ring junctions, in contrast with the relative stereochemistry of intermediate diester **13** of the Stockmann sequence. According to the authors explanation, based on some experimental results, when using $\text{Sn}(\text{OTf})_2$ in catalytic amounts the enolate formed after the first conjugate addition undergoes a Dieckmann condensation before the second conjugate addition. The synthesis of myrrhine from ketoester **37** was completed through three additional steps, including ester hydrolysis/decarboxylation, Wittig olefination and catalytic hydrogenation under acidic conditions to direct the facial selectivity. The synthesis of myrrhine was thus completed in 7 steps and 6.5% total yield.

In 2014, Kuznetsov and collaborators described the synthesis of (\pm)-hippocasin, second after the early approach of Mueller,^{15d} starting from 4-picoline, **39**, (Scheme 8).²⁵ Their strategy encompasses a one-pot nucleophilic alkylation/allyl boration, an intramolecular allylic amination and a ring-closing metathesis (RCM) reaction. The organolithium nucleophile **40** was generated by reaction of $t\text{BuLi}$ with the iodide precursor, prepared in two steps and 63% yield from commercially available materials. Sequential incorporation of 4-picoline and triallylborane to an ethereal solution of **40** resulted in the formation of the 2,6-*trans* tetrahydropyridine **42** in 74% yield. Protection of the nitrogen, followed by acetal hydrolysis and then addition of vinylmagnesium bromide, delivered the allylic alcohol **43** as a unique isomer, provided that the reaction was run at -90°C . Acylation of alcohol **43** and removal of the Boc group led to the free

amine **44**, which by palladium promoted cyclisation was converted into the azabicyclic isomers **45** and **46** with low diastereoselectivity. The relative configuration of hippocasine correlates with that of the minor isomer **45**, but complementary assays with other palladium or iridium catalysts did not improved these results. After separation, diene **45** was treated with Grubbs second generation catalyst (G II) to furnish the tricyclic amine **47**. Partial hydrogenation of **47** afforded (\pm)-hippocasine. The overall yield was 7.4%. Longer reaction times produced exhaustive hydrogenation, affording (\pm)-2*epi*-hippodamine, although the yield of this transformation was not indicated.



Scheme 7. Synthesis of myrrhine by Spring *et al.*²⁴

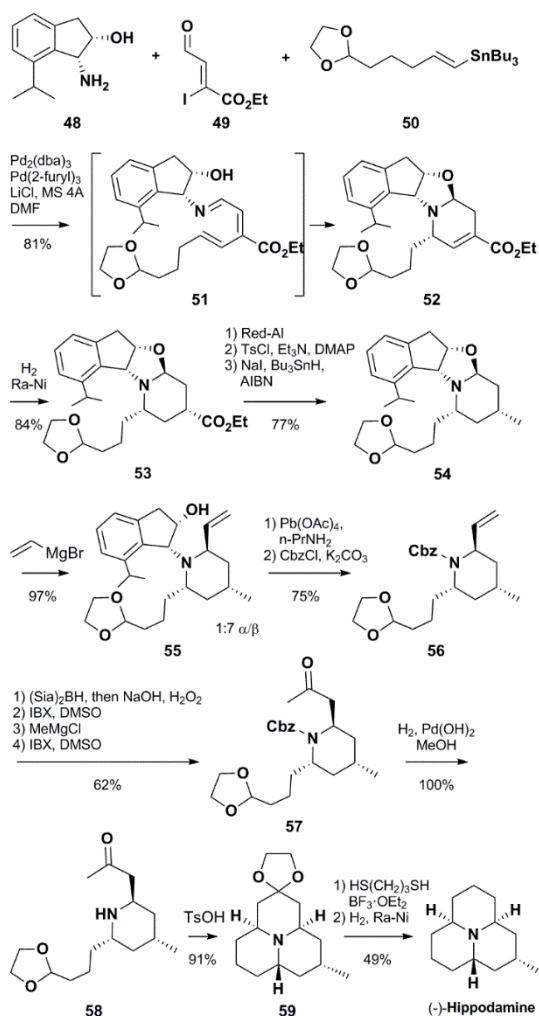


Scheme 8. Synthesis of (\pm)-hippocasine by Kuznetsov *et al.*²⁵

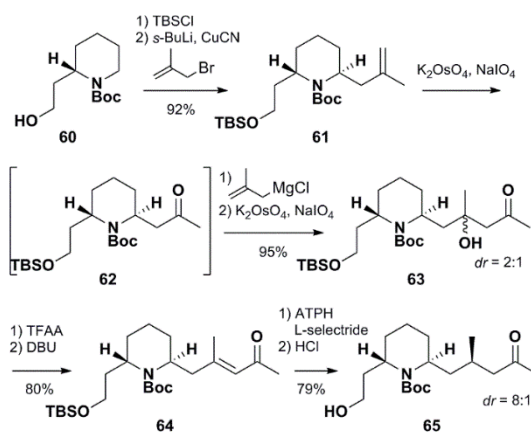
3.4. Enantioselective approaches

The first enantioselective synthesis of an azaphenalene alkaloid was developed by Katsumura and co-workers in 2013 (Scheme 9).²⁶ They devised a target-oriented strategy addressed to hippodamine which relied on an asymmetric azaelectrocyclisation reaction. This methodology furnished oxazolidine **52** from amino-alcohol **48**,^{27c} vinylstannane **49** and (Z)-2-iodo-4-oxobuenoate, **50**, in a one-pot operation, as a single stereoisomer, in 81% yield. The starting materials **49** and **50** (readily available from commercial precursors)^{27a,b} provided the appropriate carbon framework, while the amino-alcohol **48** provided the nitrogen atom and acted as sacrificial chiral auxiliary. Chemo- and stereoselective hydrogenation of the α,β -unsaturated ester **52**, followed by a three-step conversion of the ester into a methyl group, delivered compound **54** in a quite efficient fashion. The subsequent nucleophilic vinylation led to a 1:7 mixture of diastereoisomers **55**, the relative configuration of the major one correlating with hippodamine. The observed diastereoselectivity was attributed to the directing effect of the alkoxide coordinated to the Grignard reagent in the intermediate iminium ion, whose indanol moiety is orientated to the opposite face of α -alkyl chain. Oxidative removal of the indanol moiety and then protection of the amine with Cbz allowed the separation of the minor isomer, furnishing pure **56** in good yield. A sequence of four conventional reactions converted the vinyl substituent into a methyl ketone (**57**), which was next involved in the intramolecular Mannich reaction leading to the tricycle **59**. Finally, deoxygenation of the acetal was accomplished via dithioacetalisation-desulphuration, as in Ayer's synthesis of racemic hippodamine.¹¹ The synthetic hippodamine was levorotatory with a measured $[\alpha]_D$ value of -1.2 (c 1.1, CHCl₃) and had the same absolute configuration as the alkaloid extracted from the insects. The optical activity of natural hippodamine had not been described before, but its absolute configuration was established through X-ray analysis of convergine hydrochloride, which showed optical activity values very small and strongly solvent dependent, even with changes of the sign.²⁸ The overall yield of (-)-hippodamine from **48**, **49** and **50** was 10.3%.

In 2014, Snyder and collaborators published an article describing the second enantioselective approach to azaphenalene alkaloids, making use of a chiral pool strategy.²⁹ They accomplished the total or formal syntheses of several monomeric alkaloids from the common intermediate **65**, which contains the complete carbon skeleton of the targets (Scheme 10). The synthesis started with the commercially available amino-alcohol **60** encompassing a key stereogenic centre that was intended to induce diastereoselectivity in the sequential transformations. Although the authors developed two alternative routes to convert **60** into compound **65**, only the most practical of them is displayed in Scheme 10. After protection of the alcohol in **60** as the *tert*-butyldimethylsilyl ether, a copper-mediated allylation provided alkene **61**. Oxidative cleavage of the olefin in **61** led to ketone **62** that, without isolation, was submitted to a second nucleophilic allylation and then another oxidative cleavage to produce hydroxyketone **63** as a synthetically inconsequent 2:1 mixture of diastereoisomers in good total yield. This mixture was dehydrated to enone **64** by trifluoroacetate formation and DBU-promoted elimination. The preparation of **65** was concluded by stereoselective reduction of enone **64** with aluminium tris(2,6-diphenylphenoxide) (ATPH) in combination with L-selectride, followed by acid promoted desilylation, in 79% yield for the two steps and with a diastereoisomeric ratio of 8:1.



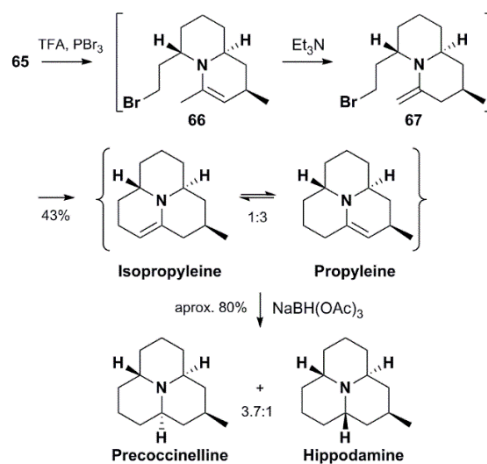
Scheme 9. First enantioselective synthesis of hippodamine by Katsumura *et al.*²⁶



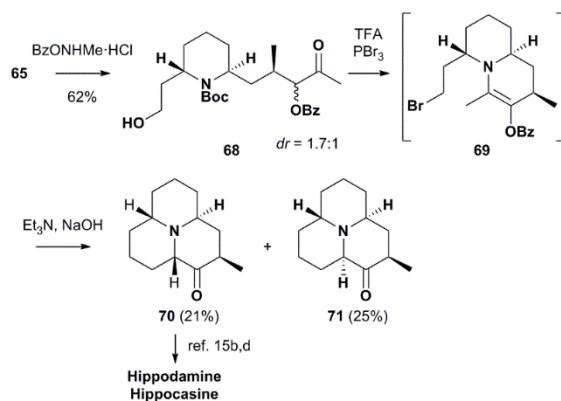
Scheme 10. Synthesis of the key common intermediate **65** by Snyder *et al.*²⁹

The conversion of intermediate **65** in propylene/isopropylene was effected in a one-pot protocol (Scheme 11). Treatment of alcohol **65** with TFA and PBr_3 led to bromide **66**, bearing an enamine in a strategic position, which in the presence of Et_3N isomerized to the unstable enamine **67** that rapidly evolved by intramolecular alkylation to the equilibrium mixture of

isopropyleine and propyleine (1:3) in 43% overall yield. The negative optical rotation value of this mixture, $[\alpha]_D -271.7$ (c 1.1, CHCl_3), allowed to establish the absolute configuration of the natural occurring material, which was reported to be levorotatory too.³⁰ Reduction of the propyleine/isopropyleine mixture with $\text{NaBH}(\text{OAc})_3$ produced precoccinelline and hippodamine in a 3.7:1 ratio and a total yield close to 80% that was not precisely determined due to the difficulties associated with the isolation of these compounds, which are highly volatile.^{1,20} Alternatively, α -carbonyl oxidation of **65** with $\text{BzONHMe}\cdot\text{HCl}$ (Scheme 12), followed by an analogous sequence of steps as above, provided a new access to ketone **70**, an intermediate in the previous synthesis of hippodamine and hippocasine by Mueller.^{15b,d} The cyclisation of the intermediate enamine **69** presented very low stereoselectivity, furnishing an approximately 1:1 mixture of two epimers, which were chromatographically separated. Reexposure of the undesired ketone **71** to base led to a nearly equimolecular mixture of the two ketones, which seem to present similar stabilities.



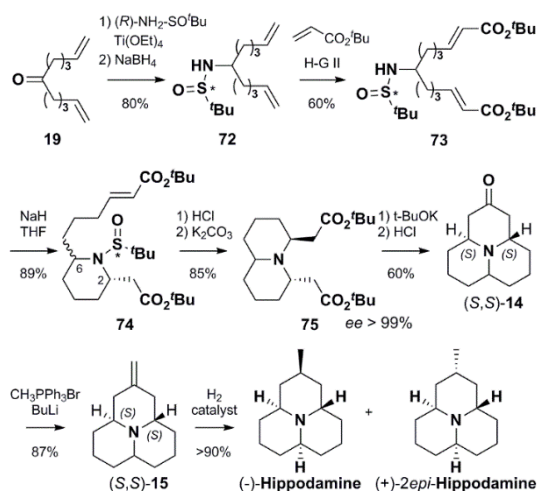
Scheme 11. Enantioselective synthesis of propyleine/ isopropyleine and precoccinelline+hippodamine by Snyder *et al.*²⁹



Scheme 12. Enantioselective synthesis of ketone **70** (formal synthesis of hippodamine and hippocasine) by Snyder *et al.*²⁹

In 2015, Fustero and co-workers developed the first asymmetric synthesis of (+)-2*epi*-hippodamine and the third of (-)-hippodamine.³¹ They employed a chiral *N*-sulfinyl amine both

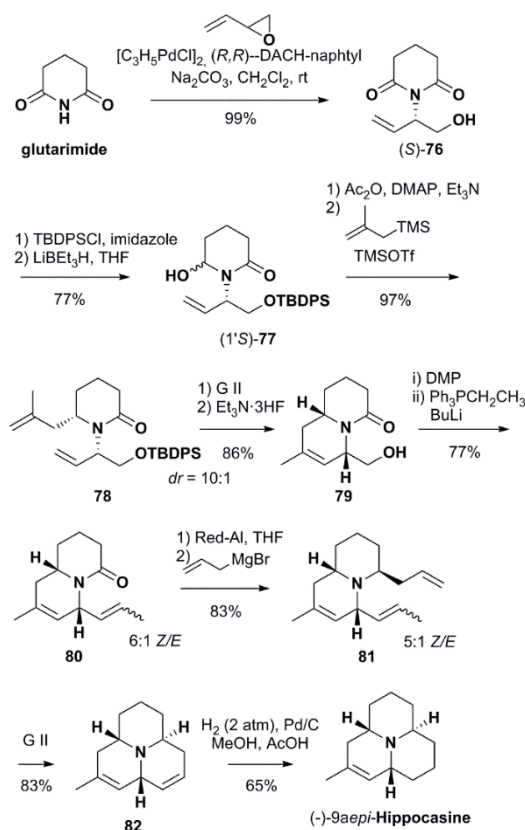
as a chiral inducer and nucleophilic nitrogen source (Scheme 13) and applied the strategy reported by Stockman for the synthesis of the same alkaloids in racemic form (Scheme 3).¹⁹ The starting material was the readily available symmetric ketone **19** (see Scheme 4). Its condensation with (*R*)-*N*-*tert*-butanesulfonamide, followed by treatment with sodium borohydride, led to the reductive amination product **72** bearing the chiral auxiliary. A double cross-metathesis with ethyl acrylate furnished diester **73**. This substrate was submitted to a desymmetrisation process by means of an intramolecular *aza*-Michael reaction that originated the first ring of the alkaloid. Although this transformation produced a mixture of three isomers, 95% of the product presented *S* configuration at C-2 and the *cis/trans* relative geometry C2/C-6 is synthetically inconsequential. Thus, after the second intramolecular *aza*-Michael reaction, due to its inherent C-2 symmetry, both isomers deliver the same bicyclic product **75**. The preparation of the last intermediate (*S,S*)-**15** was completed to a standard protocol including, Dieckmann condensation, decarboxylation and Wittig methylenation. Catalytic hydrogenation of alkene (*S,S*)-**15** produced mixtures of (-)-hippodamine, [α]_D -1.5 (c 1.0, CHCl₃), and (+)-2*epi*-hippodamine, [α]_D +8.5 (c 1.0, CHCl₃), in good yield and variable proportions depending on the catalyst.



Scheme 13. Enantioselective synthesis of (-)-hippodamine and (+)-2*epi*-hippodamine by Fustero *et al.*³¹

In our laboratory, we developed a new strategy for the stereoselective synthesis of azaphenalene alkaloids starting from the chiral material **76**, readily available in either enantiomeric form through the palladium-catalysed asymmetric allylic alkylation of glutarimide in the presence of the DACH-naphtyl Trost ligand³² (Scheme 14). Our strategy relied on an iterative methodology encompassing two nucleophilic allylations and two RCM processes. The starting acylaminal (1'*S*)-**77**, easily prepared from glutarimide in two steps and 90% yield,^{32a} was acetylated and, without isolation of the intermediate acetate, trimethyl(2-methylallyl)silane and a catalytic amount of TMSOTf were added, resulting in the formation of diene **78** in 97% yield and 10:1 diastereoisomeric ratio. A first RCM reaction provided, after desilylation, alcohol **79** as a pure isomer in 86% yield for the two steps. The relative configuration of **79** was established by X-ray diffraction analysis. Oxidation of alcohol **79** by treatment with Dess–Martin periodinane (DMP) furnished the corresponding aldehyde, which slowly decomposed to unidentified products, and, hence, was immediately submitted to the next alkenylation step. This transformation was better

accomplished through a Wittig ethylenation that provided a synthetically inconsequential mixture of *Z/E* isomers. The next endeavour was the reduction of the lactam to hemiaminal, in order to generate an iminium ion suitable for the second nucleophilic allylation. After extensive experimentation, it was found that a one-pot protocol consisting of reduction with Red-Al, followed by addition of allylmagnesium bromide, delivered triene **81** in 83% yield. A second RCM reaction then furnished diene **82**, which was amenable for partial or total hydrogenation. Although its full characterization data were not described, compound **82** had been previously prepared as a racemate and converted into the *meso* alkaloids precocinelline and coccinelline.^{12,15a} Our synthetic efforts were therefore devoted to the partial hydrogenation that should provide a chiral alkaloid. This transformation was successfully accomplished by treatment of **82** with hydrogen (2 atm) in the presence of Pd/C and acetic acid in methanol as the solvent for 48 h. The first synthesis of (-)-9*aepi*-hippocasine, [α] -0.71 (*c* 0.27, CHCl₃), was completed in 11 steps from glutarimide and 26% total yield. The low specific rotation is in agreement with the values observed for related azaphenalene alkaloids.²⁸



Scheme 14. Enantioselective synthesis of (-)-9*aepi*-hippocasine by Figueredo *et al.*³²

3.5. “Dimeric” alkaloids

As anticipated above, several alkaloids isolated from the same natural sources present a more complicated structural framework, where at least one half is an azaphenalene unit (Figure 3). In exochomine and chilacorines A and B, the azaphenalene moiety correlates with hippodamine, and the other half is a pyrroloquinolizinone attached through

different linkages. Psylloborine A and isopsylloborine A present truly dimeric azaphenalene structures and are tautomeric enamines.

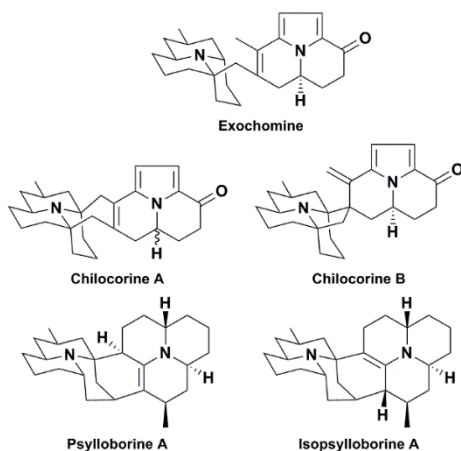
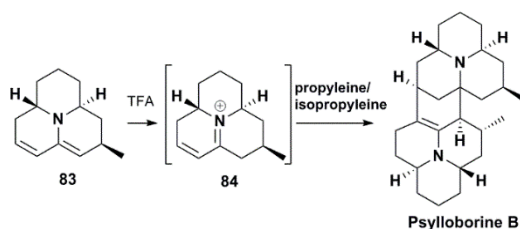


Figure 3. “Dimeric” azaphenalene alkaloids.

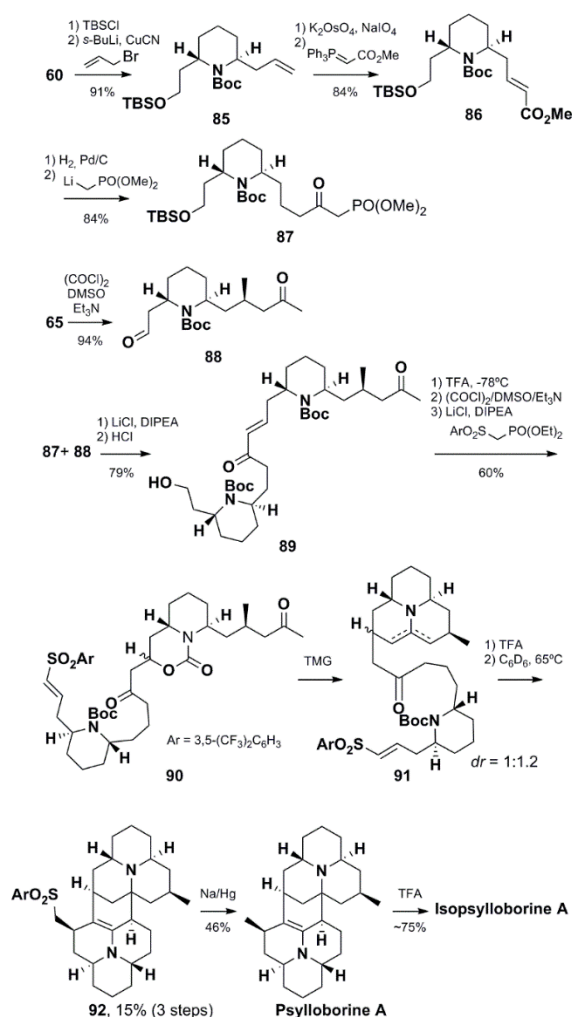
Up to date, there are only two publications concerning synthetic efforts toward these “dimeric congeners” and both come from the group of Snyder. Initially, the synthesis of psylloborine A and isopsylloborine A was attempted by direct dimerization of two azaphenalene units derived from propyleine/isopropyleine (Scheme 15).²⁹ However, these efforts resulted in the formation of a non-natural regioisomer that was named as psylloborine B.



Scheme 15. Synthesis of psylloborine B by Snyder *et al.*²⁹

In view that the putative natural monomeric precursors afforded only a non-natural analogue, an “intramolecular dimerization” strategy was devised (Scheme 16). The starting material **60** was the same as for the monomeric alkaloids. The alcohol was protected and then allylated following the same methodology as above (Scheme 10). In the present sequence, the oxidative cleavage of **85** led to an aldehyde, which, without isolation, was treated with methyl (triphenylphosphoranylidene)acetate furnishing the α,β -unsaturated ester **86**. Ester **86** was converted into the phosphonate **87** in a one-pot protocol, including catalytic hydrogenation, followed by condensation with dimethyl methylphosphonate. In a parallel sequence, aldehyde **88** was prepared by oxidation of the previously prepared key intermediate **65** (see Scheme 10). The reaction between phosphonate **87** and aldehyde **88** assembled the two halves of the target. The carbamate protecting groups in the resulting enone **89** were differentiated, taking advantage of

neighbouring group participation, upon treatment with TFA at -78°C , transforming one of them into a base-labile carbamate through cyclisation onto the enone and leaving intact the other one.

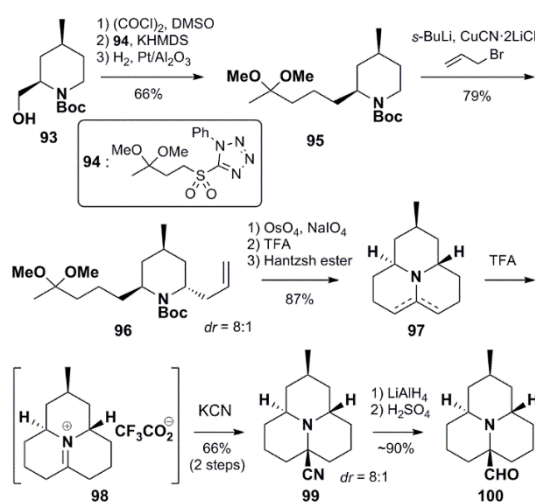


Scheme 16. Synthesis of psylloborine A and isopsylloborine A by Snyder *et al.*²⁹

The synthesis of the key intermediate **90** was then completed through oxidation of the alcohol to the corresponding aldehyde and subsequent one-carbon homologation by reaction with a sulphonyl phosphonate. Treatment of **90** with 1,1,3,3-tetramethylguanidine (TMG) triggered a cascade sequence involving carbamate cleavage, enone regeneration, condensation, enamine equilibration to the exocyclic isomer and a terminating Michael addition. The resulting product **91** was obtained as a mixture of two diastereoisomers embodying the first azaphenalene moiety, which presented low stability and was carried forward immediately to a second cascade of events. To this end, **91** was treated with TFA to remove the remaining Boc group and then the free amine was heated to promote condensation, Michael closure and a terminating Mannich reaction. This second cascade sequence delivered the expected heptacyclic product **92** in 15% yield for the three steps (first cascade, Boc removal, second cascade). Finally, reaction of **92** with Na/Hg amalgam transformed it into psylloborine A

in 46% yield. This alkaloid could be converted into isopsylloborine A by TFA treatment, but repeated attempts to purify the crude material were unsuccessful due to its instability, and had to be characterised as such.

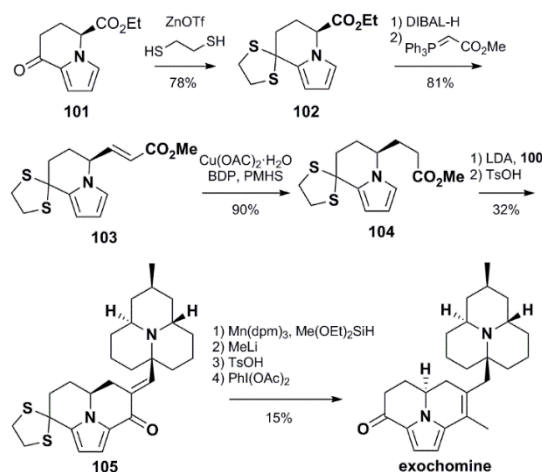
The total synthesis of exochomine was published in 2016.³³ Conversely to the later alkaloids, the two moieties of exochomine present different skeletal framework and hence were prepared through unrelated synthetic routes. The starting material for the azaphanalene moiety (Scheme 17) was the known *N*-protected alcohol **93**.³⁴ When alcohol **93** was submitted to Swern oxidation, followed by Julia-Kocienski olefination and then catalytic hydrogenation, the elongated ketal **95** was produced in 66% overall yield. A Cu(I)-promoted allylation of **95** furnished alkene **96**, along with its *cis* diastereoisomer, which could not be separated. Oxidative cleavage of the double bond in **96** produced the corresponding aldehyde, concomitant with partial deprotection of the ketone. The crude product was then treated with TFA, effecting Boc deprotection and condensation of the free amine with the ketone (and/or remaining ketal) to form an enamine, which reacted with the aldehyde furnishing the expected tricyclic, α,β -unsaturated iminium ion, which was reduced *in situ* with Hantzsch ester to produce, after acid treatment, the salt **98**. Addition of KCN to **98** delivered nitrile **99** as a mixture of two isomers. Despite the individual steps from **96** to **99** were monitored through ¹H-NMR analysis, the involved intermediates were not isolated and the sequence was carried forward with crude reaction products. Reduction of the mixture of nitriles **99** with LiAlH₄ and then treatment with concentrated H₂SO₄ led to the isolation of aldehyde **100** as a single isomer in good yield.



Scheme 17. Synthesis of the azaphenalene moiety of exochomine by Snyder *et al.*²⁹

The synthesis of the pyrroloquinolizine moiety (Scheme 18) started from ketone **101**, which was prepared from ethyl L-glutamate, according to a previous literature reference.³⁵ The carbonyl group in **101** was protected as the dithiolane and then ester **102** was homologated to **103** by reduction to the aldehyde followed by Wittig olefination. The carbon-carbon double bond was reduced by *in situ* formed copper hydride and the resulting ester **104** was coupled with the aldehyde **100** by means of an aldol reaction. Without isolation of the aldol product, an acid-promoted, intramolecular Friedel-Crafts reaction furnished ketone **105** with the “dimeric” skeleton of the targeted alkaloid. The overall transformation of **104** to **105** was accomplished in

32% yield. The remaining steps to exochomine included: regioselective reduction of the enone, nucleophilic methylation, dehydration and cleavage of the dithiolane to deprotect the masked carbonyl group.



Scheme 18. Preparation of the pyrroloquinolizinone moiety and completion of the synthesis of exochomine by Snyder *et al.*³³

CONCLUSIONS

The peculiar structure and putative application in pest control of azaphenalene alkaloids make these compounds attractive targets for synthetic chemists. The early syntheses were mainly motivated by the corroboration of their structural assignment and the investigation of the biogenetic pathways. Then, there was essentially a lack of new contributions on the field, but, in the last years, the interest in these alkaloids has resurfaced, giving rise to several new, imaginative synthetic strategies. Moreover, among the recent reports, the first enantioselective approaches to the chiral congeners have been published, as well as pioneer syntheses of some “dimeric” members of the family. However, there is still a lot of room for improvement, particularly in terms of efficiency and stereoselectivity, while the total synthesis of some “dimeric” azaphenalene alkaloids remains undisclosed.

Acknowledgements

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