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Synthetic Approaches towards Alkaloids Bearing α -Tertiary Amines

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REVIEW

Synthetic Approaches towards Alkaloids Bearing α -Tertiary Amines

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Alkaloids account for some of the most beautiful and biologically active natural products. Although they are usually classified along biosynthetic criteria, they can also be categorized according to certain structural motifs. Amongst these, the α -tertiary amine (ATA), *i.e.* a tetrasubstituted carbon atom surrounded by three carbons and one nitrogen, is particularly interesting. A limited number of methods have been described to access this functional group and fewer still are commonly used in synthesis. Herein, we review some approaches to asymmetrically access ATAs and provide an overview of alkaloid total syntheses where those have been employed.

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1 Introduction

Alkaloids have played an important role in the development of synthetic organic chemistry, pharmacology and medicine. Once considered to be metabolic waste products, they are now known to benefit their producers in various ways, e.g. as antimicrobials, antifeedants or as mediators of ecologically beneficial interactions.¹ Though a limited number of amino acids are involved in their biosynthesis, alkaloids exhibit enormous structural variability, which is often increased through the incorporation of terpenoid and polyketide components and late-stage oxidative transformations.² Reflecting their structural diversity and relatively weak basicity, alkaloids interact with a large variety of biological targets and have found many uses in human medicine.^{3,4} In addition, they have provided inspiration for countless synthetic drugs that borrow structural motifs from their natural counterparts.

The α -tertiary amine (ATA) stands out among the structural features frequently found in alkaloids.⁵⁻⁸ For the purposes of this review and in keeping with the literature, we define an ATA as a nitrogen atom bound to a sp^3 -hybridized carbon that bears three additional carbon-carbon bonds. The nitrogen itself can be sp^3 -hybridized as part of a primary, secondary and tertiary amine. Broadening our definition, it can also be sp^2 - or sp -hybridized, e.g. in an amide or isonitrile. The tetrasubstituted carbon from which the C,N-bond branches out is often stereogenic, which makes ATAs particularly interesting from a synthetic point of view. Our definition puts emphasis on this particular C,N-bond and avoids the confusion that is often associated with the term 'quaternary stereocenter', which, strictly speaking, refers only to a carbon atom surrounded by four other carbons.

Figure 1 shows some alkaloids and drugs with alkaloid-like properties that illustrate our definition and demonstrate that the nitrogen in ATAs (highlighted in red) can be substituted to

various degrees. Memantine and huperzine A contain primary ATAs, whereas ketamine, MK-801 and histrionicotoxin 283A (HTX 283A) feature secondary ATAs, and lycopodine is representative of molecules containing a tertiary ATA. 2,2,6,6-Tetramethylpiperidine (TMP) and the alkaloid porantherine are examples for molecules featuring a twofold ATA. The dimeric alkaloid stephacidin B contains no fewer than four ATAs. Notably, the α -carbons are stereogenic in the majority of these compounds.

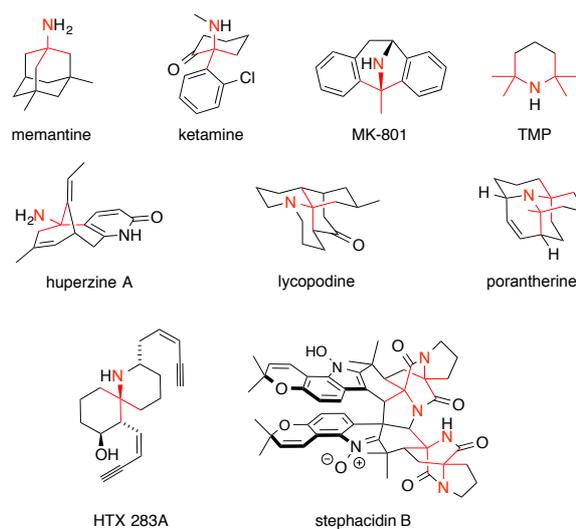


Fig. 1 Alkaloids and synthetic molecules that contain the ATA motif.

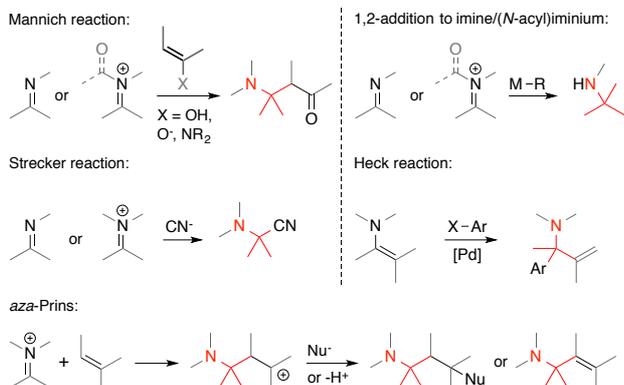
In this review, we wish to provide a brief survey of synthetic methods used to install the ATA motif and discuss their application in the total synthesis of alkaloids. The syntheses included here have been selected based on their historical significance, the intriguing structure of their target molecule, and the elegance and efficiency of the method used. The order of their presentation is somewhat arbitrary, mixing biosynthetic and taxonomic categories (such as *Lycopodium* alkaloids), with purely structural ones (such as quinolizidine alkaloids). Generally, we have aimed to proceed from simpler target molecules to more complex ones. While our review is by no means comprehensive, we hope to feature the most instructive examples for the establishment of ATAs and thus provide inspiration and valuable lessons for future work. We also hope that this review will benefit the design of synthetic pathways toward drugs and synthetic building blocks that contain α -tertiary amines.

2 Methods used for the installation of α -tertiary amines

Many approaches toward the installation of ATAs have been developed but only a relatively small subset of these has proven popular in alkaloid total synthesis. Here, we provide a brief survey of these methods, discussing them in general terms. We classify them according to the bond that is formed in the key step and the electronic nature of the nitrogen and carbon, respectively. However, it should be noted that not all of the syntheses discussed in this review fall into this simplified organizational scheme.

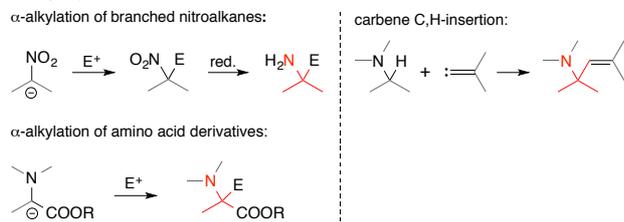
a) A C,C-bond is formed in the step that generates the ATA.

The α -carbon is electrophilic. Some of the most commonly encountered methods involve the addition of carbon nucleophiles to activated imines and iminium ions (Scheme 1). They include Mannich reactions, Strecker reactions, Aza-Prins reactions and the 1,2-addition of organometallic reagents to C,N-double bonds. *N*-Acyliminium ions are particularly powerful electrophiles in reactions of this type. A variant of the Heck olefination that involves enamines also falls into this category.



Scheme 1 C,C-bond formation involving electrophilic α -carbons.

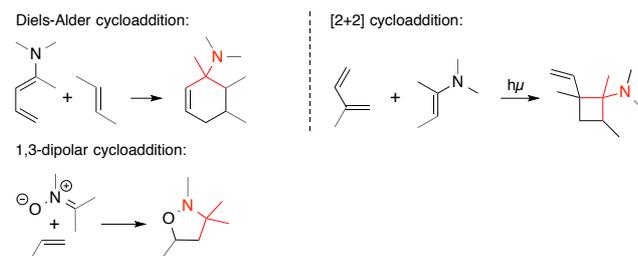
The α -carbon is nucleophilic. In an Umpolung of the above situation, the α -carbon can also serve as a nucleophile (Scheme 2). For instance, the alkylation of branched nitroalkanes or of deprotonated amino acid derivatives can be used to establish ATAs. Insertions of carbons into nucleophilic C,H-bonds next to a C,N-bond are a member of this general category as well.



Scheme 2 C,C-bond formation involving nucleophilic α -carbons.

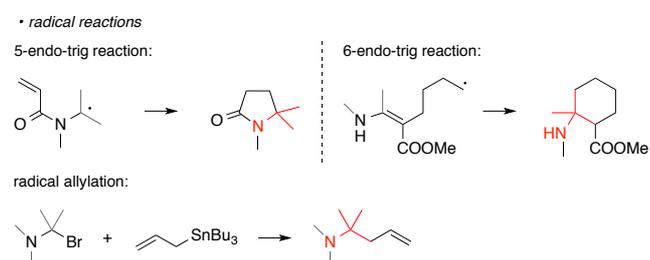
Pericyclic reactions. Pericyclic reactions that form a C,C-bond in the key step have occasionally been employed to form ATAs (Scheme 3). They include Diels-Alder cycloadditions involving

1-aminodienes or 2-azadienes, as well as certain amino dienophiles, [2+2]-cycloadditions, and 1,3-dipolar cycloadditions involving nitrones and azomethine imines.



Scheme 3 C,C-bond formation involving pericyclic reactions.

Radical reactions. Radical reactions establishing ATAs are relatively rare, but not unprecedented (Scheme 4). 5-*Endo*-trig and 6-*endo*-trig cyclizations as well as radical transfer allylations belong to this category.

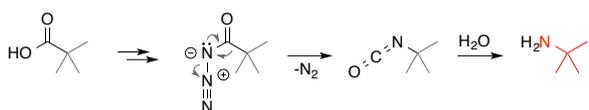


Scheme 4 C,C-bond formation *via* radical reactions.

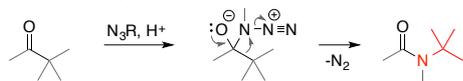
b) A C,N-bond is formed in the step that generates the ATA.

The nitrogen is electrophilic. Rearrangements that involve electron-deficient nitrogen atoms are often encountered in the formation of ATAs (Scheme 5).

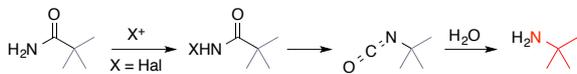
Curtius rearrangement:



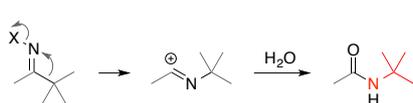
Schmidt rearrangement:



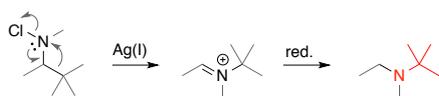
Hofmann rearrangement:



Beckmann rearrangement:



Stieglitz rearrangement:



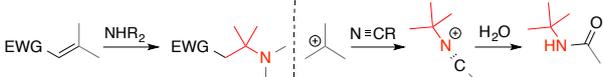
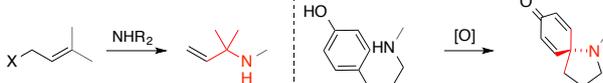
Nitrene C,H-insertion:

**Scheme 5** C,N-bond formation involving electrophilic nitrogens.

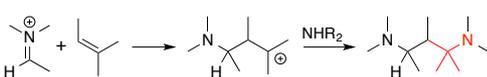
They include the Curtius, Schmidt, Hofmann, Beckmann and Stieglitz rearrangements.⁵ Often, these reactions can be classified as 1,2-sigmatropic rearrangements. Related nucleophilic substitutions involving *N*-haloamines have been used as well. An electron-deficient nitrogen atom also plays a role in the insertion of nitrenes into C,H-bonds.

- *The nitrogen is nucleophilic.* The formation of ATAs through nucleophilic additions or substitutions involving nitrogen is fairly common (Scheme 6). The classical Michael addition falls into this category, as do S_N2' reactions and haloaminations. For obvious reasons, S_N2 reactions are rare and mostly confined to intramolecular cases. Carbocations that react with nucleophilic nitrogen occur in the aza-Prins reaction and the Ritter reaction. Oxidative dearomatizations have also been used in a few cases to establish ATAs.

1,4-addition (Michael addition):

 S_N2' reaction:

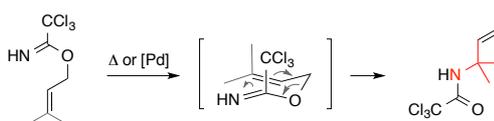
aza-Prins:

**Scheme 6** C,N-bond formation involving nucleophilic nitrogens. EWG = electron-withdrawing group.

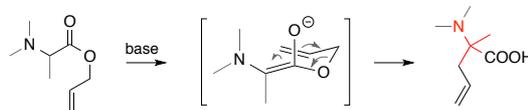
- *Pericyclic reactions.* Pericyclic reactions in which a C,N-bond is formed provide powerful means to establish ATAs (Scheme 7). Overman, Kazmaier-Claisen and 3,3-sigmatropic rearrangements of allylic isocyanides belong to this category.

Divinyl cyclopropane rearrangements have also been used to establish ATAs.⁵

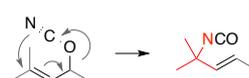
Overman rearrangement:



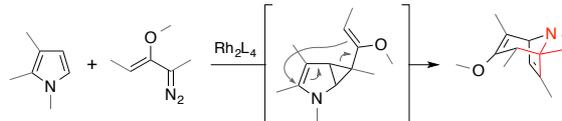
Kazmaier-Claisen rearrangement:



Allylic cyanate to isocyanate rearrangement:



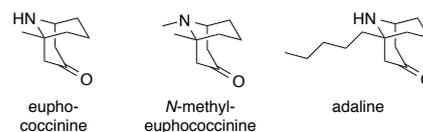
Cyclopropyl-accelerated Cope rearrangement:

**Scheme 7** A C,N-bond formation involving pericyclic reactions.

Many more methods have emerged in recent years that can be used to create ATAs, such as reactions proceeding *via* C,H-activation⁹ and hydroaminations.¹⁰ Since they have not yet been employed in the total synthesis of alkaloids, they are not featured in this review. Other methods, such as the Mannich reaction, Curtius rearrangement and Michael reaction, have proven to be so popular in the total synthesis of alkaloids that we cannot include all instances where they have been employed in this review.

3 Homotropane Alkaloids

One of the first applications of Mannich reactions in the construction of ATAs occurred during the synthesis of certain homotropane alkaloids. Three representatives, euphococcinine, *N*-methyl euphococcinine and adaline, feature an ATA in the bridgehead position of a bicyclic framework (Figure 2). These simple natural products are excreted by lady beetles (coccinellids) when threatened.^{11,12}

**Fig. 2** Representative ATA-containing homotropane alkaloids.

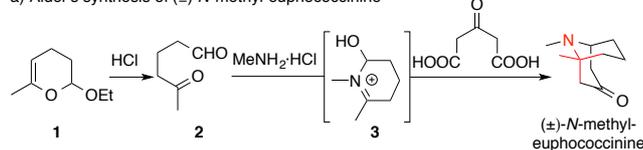
In 1959, Alder synthesized *N*-methyl-euphococcinine using a protocol analogous to the famous tropinone syntheses of Robinson^{13,14} and Schöpf¹⁵ (Scheme 8a).¹⁶ Dehydropyran **1** was converted into ketoaldehyde **2**, which was then transformed into *N*-methyl-euphococcinine in a one-pot process (*via* iminium-intermediate **3**).¹⁷⁻¹⁹ A similar strategy was later adopted to synthesize the structurally related alkaloid adaline.²⁰

Throughout the years, this biomimetic Mannich strategy was adopted in other syntheses of euphococcinine and adaline.²¹⁻²³ Alternative approaches involved a 1,3-dipolar cycloaddition,²⁴ addition to an *N*-acyliminium ion,²⁵ Michael addition^{26,27} and

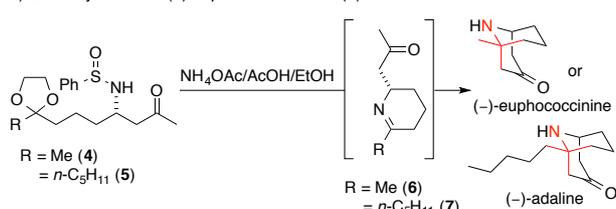
allylic rearrangement of a cyanate to an isocyanate.^{28, 29}

In 2010, Davis published a biomimetic synthesis of (-)-euphococcinine and (-)-adaline in enantiopure form (Scheme 8b).³⁰ The key steps of these syntheses involved the stereoselective formation of piperidine **6** and **7** from the enantiomerically pure *N*-sulfinyl aminoketones **4** and **5**, respectively.³¹ An ensuing intramolecular Mannich reaction afforded the azabicyclononane natural products.

a) Alder's synthesis of (±)-*N*-methyl-euphococcinine



b) Davis' synthesis of (-)-euphococcinine and (-)-adaline



Scheme 8 Homotropane alkaloid syntheses by Alder (1959) and Davis (2010). Ac = acetyl.

4 Histrionicotoxins

In 1971, Daly isolated six different alkaloids, termed histrionicotoxins (HTXs), from skin extracts of the Colombian poison arrow frog *Dendrobates histrionicus* (Figure 3).^{32, 33} They all contain a unique spirocyclic piperidine core and differ mostly in the length and the degree of saturation of the two side chains. Several histrionicotoxins were identified as inhibitors of nicotinic acetylcholine receptors,³⁴⁻³⁸ which, together with their attractive structures, prompted significant attention from the synthetic community.³⁹ The low natural abundance of these alkaloids and the fact that the frogs do not secrete HTXs in captivity made an efficient synthetic approach all the more desirable.

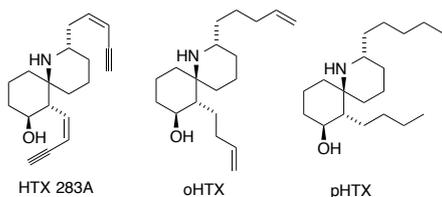


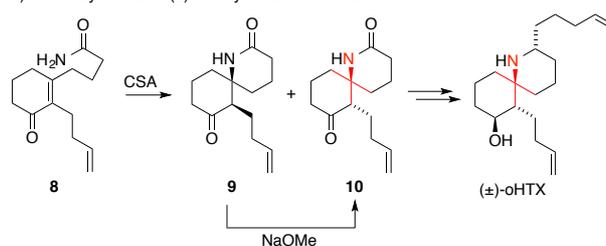
Fig. 3 The major members of the histrionicotoxin family.

The first total synthesis of histrionicotoxin alkaloids was reported by Kishi in 1975 (Scheme 9a).⁴⁰⁻⁴² His synthesis of octahydrohistrionicotoxin (oHTX) utilized an intramolecular acid-catalyzed aza-Michael addition to set the ATA. Amide **8** was converted to a 2:1 mixture of epimeric spiroketolactams **9** and **10**. It was possible to transform **9** into the desired diastereoisomer **10** upon treatment with sodium methoxide.

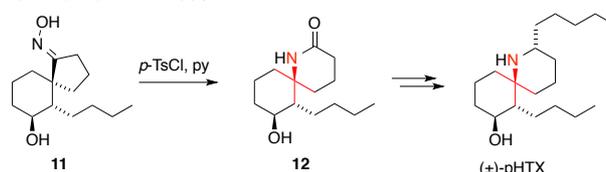
In the same year, Corey reported the first racemic synthesis of perhydrohistrionicotoxin (pHTX), a synthetic HTX derivative (Scheme 9b).⁴³ For the installation of the ATA, Corey used a Beckmann rearrangement that expanded spirocyclic oxime **11** to spirocyclic amide **12**. Several other groups subsequently

employed related ring expansion strategies.⁴⁴⁻⁴⁸

a) Kishi's synthesis of (±)-octahydrohistrionicotoxin



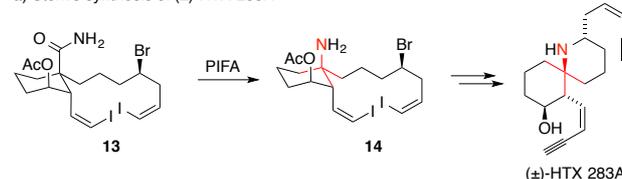
b) Corey's synthesis of (±)-pHTX



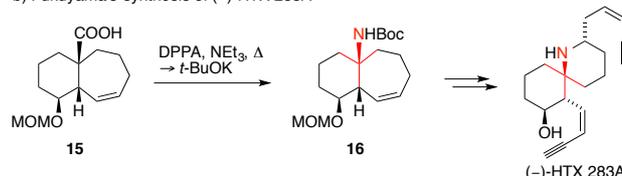
Scheme 9 Early synthetic approaches to HTXs by Kishi (1975) and Corey (1975). CSA = camphorsulfonic acid, HTX = histrionicotoxin, *p*-TsCl = *para*-toluenesulfonyl chloride.

Stork reported a synthesis of HTX 283A using a Hofmann rearrangement to set the ATA (Scheme 10a).⁴⁹ During this transformation, amide **13** was oxidized with bis(trifluoroacetoxy)iodobenzene to promote the alkyl migration, giving amine **14** after decarboxylation. More recently, Fukuyama reported an asymmetric synthesis of HTX 283A (Scheme 10b).^{50, 51} The key carboxylic acid **15** underwent a stereospecific Curtius rearrangement to yield bicyclo[5.4.0]undecane **16** which could be converted into HTX 283A.

a) Stork's synthesis of (±)-HTX 283A



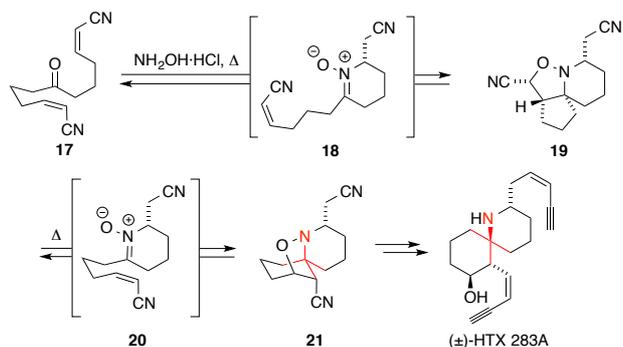
b) Fukuyama's synthesis of (-)-HTX 283A



Scheme 10 HTX 283A syntheses by Stork (1990) and Fukuyama (2011). HTX = histrionicotoxin, Ac = acetyl, Boc = *tert*-butyloxycarbonyl, *t*-Bu = *tert*-butyl, DPPA = diphenylphosphoryl azide, MOM = methoxymethyl, PIFA = (bis(trifluoroacetoxy)iodo)benzene.

A particularly short and efficient synthesis of racemic HTX 283A was reported in 2006 by Stockman and Fuchs (Scheme 11).⁵² In their approach, the key intermediate **21** was formed from the symmetric ketodinitrile **17** using a cascade reaction. Ketone **17** was condensed with hydroxylamine yielding nitron **18** after intramolecular Michael addition. Subsequent intramolecular [3+2] cycloaddition afforded isoxazolidine **19**. Following its isolation, **19** was converted to its more stable regioisomer **21** through a retro-[3+2]/[3+2] cycloaddition process (*via* intermediate **20**). This so-called 'Holmes dinitrile' (**21**) had been previously converted into HTX 283A.^{53, 54}

Stockman and Fuchs' synthesis of (±)-HTX 283A



Scheme 11 HTX 283A synthesis by Stockman and Fuchs (2006). HTX = histrionicotoxin.

Additional strategies to set the ATA in the histrionicotoxins involved Michael reactions,^{41, 55, 56} Tsuji-Trost amination,^{57, 58} iodoetherification,⁵⁹⁻⁶¹ oxidative dearomatizations,⁶² Henry reactions,⁶³ diastereoselective aziridation,⁶⁴ 1,2-carbon migration of hydroxyimines,⁶⁵ [2,3]-sigmatropic rearrangements,⁶⁶ [3,3]-sigmatropic rearrangements (Kazmaier-Claisen rearrangement)⁶⁷ and [2+2]-cycloadditions.^{68, 69}

5 Lycopodium Alkaloids

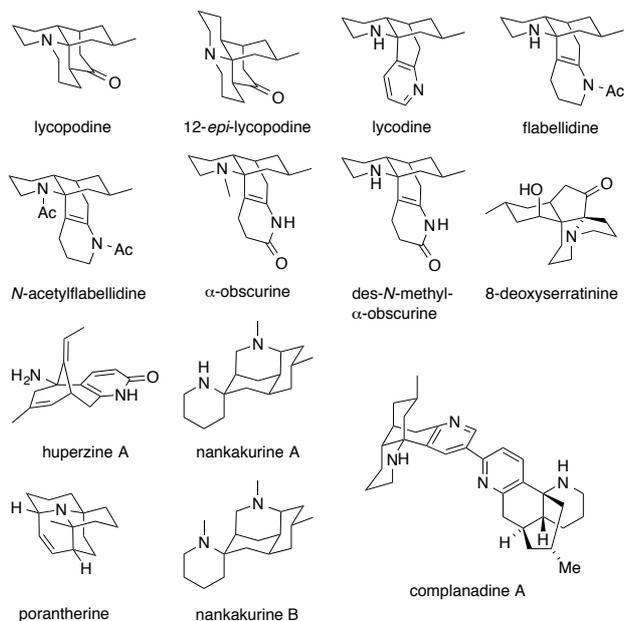
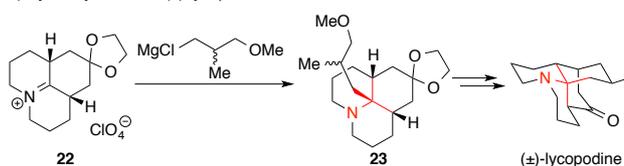


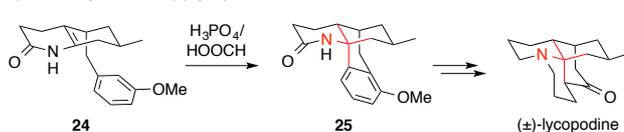
Fig. 4 Representative *Lycopodium* alkaloids.

The genus *Lycopodium* comprises more than 200 species of moss-like plants that have been used in traditional Chinese medicine for centuries.⁷⁰ They have yielded a variety of ATA-containing alkaloids, most of which are featured in Fig. 4. Lycopodine, the first member of the family described in the literature,⁷¹ has proven to be a particularly attractive target for chemical synthesis. In 1968, only seven years after its structural elucidation, Stork⁷² and Ayer^{73, 74} simultaneously published the first syntheses of this natural product. Ayer established the ATA using an intermolecular addition of a racemic Grignard reagent to tricyclic, C_v-symmetric iminium ion **22** to obtain **23** (Scheme 12a).

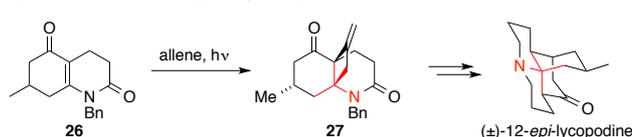
a) Ayer's synthesis of (±)-lycopodine



b) Stork's synthesis of (±)-lycopodine



c) Wiesner's synthesis of (±)-12-epi-lycopodine

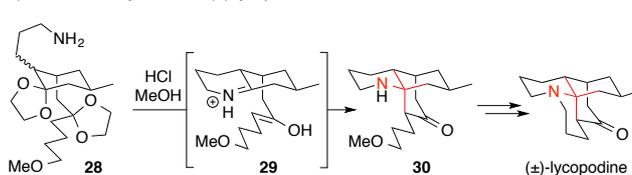


Scheme 12 Representative lycopodium syntheses by Ayer (1968), Stork (1968) and Wiesner (1967). Bn = benzyl.

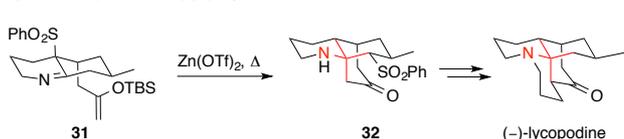
Stork's synthesis involved a Pictet-Spengler type reaction, furnishing tetracyclic amide **25** (**24** → **25**, Scheme 12b). A similar cyclization approach was also utilized almost 30 years later in Padwa's asymmetric synthesis of lycopodine (not shown).⁷⁵ Wiesner published a synthesis of 12-*epi*-lycopodine and annotinine using an innovative photochemical strategy (Scheme 12c).⁷⁶⁻⁷⁹ This work involved the conversion of vinylogous imide **26** into *exo*-methylene cyclobutane **27** via a photochemical [2+2]-cycloaddition of allene.

Heathcock established one of the most elegant and influential routes to lycopodine in 1982 (Scheme 13a).⁸⁰⁻⁸² In a remarkable sequence, intermediate **28** underwent deprotection, condensation and intramolecular Mannich reaction to yield secondary amine **30**, presumably via iminium ion **29**. The installation of the α-tertiary amine and the formation of two out of four rings thus occurred in a single step, mimicking the proposed biosynthesis of this natural product. Subsequent optimization led to the shortest synthesis of lycopodine to date, consisting of only eight steps.⁸² Using a similar sequence, lycodine and lycodoline were prepared as well.⁸²

a) Heathcock's synthesis of (±)-lycopodine



b) Carter's synthesis of (-)-lycopodine



Scheme 13 Lycopodium syntheses by Heathcock (1982) and Carter (2008). OTf = trifluoromethanesulfonate, TBS = *tert*-butyldimethylsilyl.

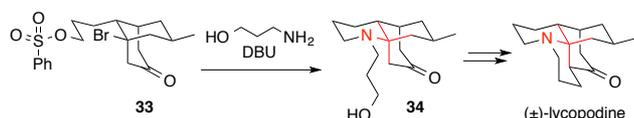
Variations of Heathcock's strategy have been used in other synthetic approaches toward *Lycopodium* alkaloids, e.g. in

syntheses of clavolonine by Evans (2005)⁸⁴ and Fujioka (2011).⁸³ One drawback of intramolecular Mannich reactions, however, is the need to simultaneously form an iminium ion and an enol. Thus, long reaction times of up to 18 days were needed.⁸²

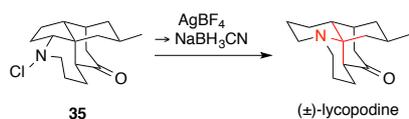
5 Recently, this problem was solved in an elegant way by Carter (Scheme 13b).^{85, 86} Using an aza-Wittig approach, Carter was able to prepare and isolate the TBS-enol ether imine **31**. Treatment of **31** with zinc triflate furnished the ATA and concomitantly resulted in the rearrangement of the sulfinyl residue yielding lycopodine precursor **32**.

In 1985, Kraus published a route towards lycopodine that was based on the formation of a bridgehead olefin (Scheme 14a).⁸⁷ Tertiary alkyl bromide **33** was treated with DBU and 3-amino-1-propanol to install amino ketone **34**, which could be further transformed into the natural product in two additional steps using Heathcock's protocol. An equally unusual approach was reported by Grieco, who employed a Stieglitz rearrangement (Scheme 14b).⁸⁸ To effect the reaction, *N*-chloroamine **35** was treated with silver tetrafluoroborate followed by cyanoborohydride. Many other syntheses of lycopodine have been accomplished utilizing different strategies, such as Michael additions, for the assembly of the ATA.⁸⁹⁻⁹¹

a) Kraus' synthesis of (±)-lycopodine



b) Grieco's synthesis of (±)-lycopodine

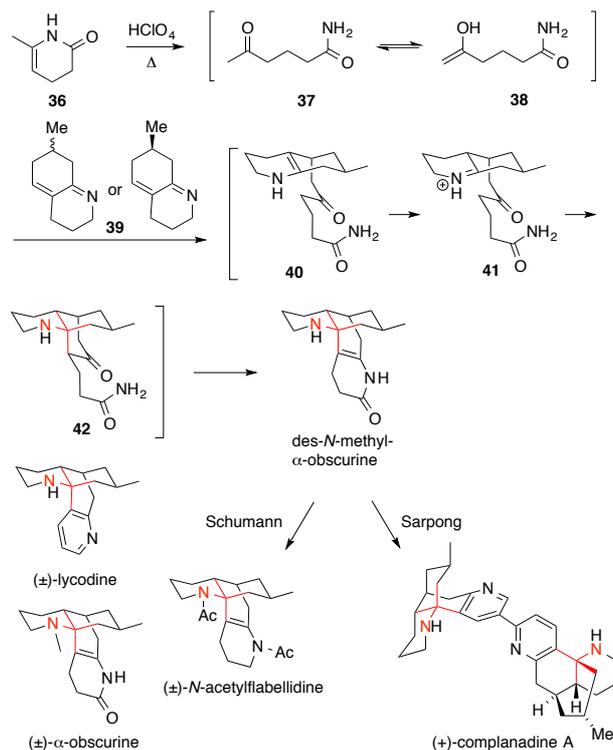


Scheme 14 Lycopodine syntheses by Kraus (1985) and Grieco (1998).
25 DBU = 1,8-diazabicyclo[5.4.0]undec-7-en.

Members of the lycopodine class of natural products feature an ATA and a pyridine or pyridone moiety. The parent compound, lycopodine,⁹² was first isolated from *L. annotinum* in 1958.⁹³ Apart from the Heathcock synthesis mentioned above,⁸² several additional syntheses of lycopodine have been achieved to date.⁹⁴⁻⁹⁷

Schumann used a classical Mannich strategy to access racemic lycopodine, α -obscurine and *N*-acetylflabellidine (Scheme 15).⁹⁸⁻¹⁰⁰

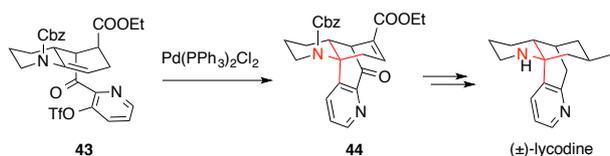
Schumann's syntheses of (±)-lycopodine, (±)- α -obscurine, (±)-*N*-acetylflabellidine and Sarpong's synthesis of (+)-complanadine A



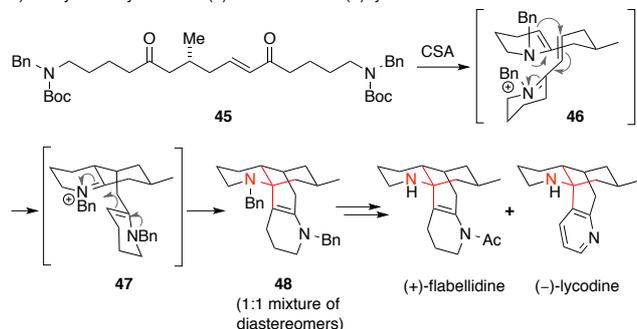
Scheme 15 Synthesis of various *Lycopodium* alkaloids by Schumann
35 (1982) and Sarpong (2010). Ac = acetyl.

The mechanism of the key double Mannich reaction cascade was further explored almost 30 years later by Sarpong.⁹⁴ He used the same cascade as an opening sequence in an asymmetric synthesis of enantiomerically pure (+)-complanadine A, a lycopodine dimer,
40 which was shown to enhance expression of nerve growth factor in human cells.¹⁰¹ It was found that cyclic enamide **36** opens to ketone **37** or enol **38** under acidic conditions, which adds to the unsaturated bicyclic imine **39**. Protonation of the resulting enamine **40** triggers a second, intramolecular Mannich reaction to
45 afford tricyclic **42** via the iminium ion **41**. Finally, an intramolecular enamide formation furnished tetracyclic des-*N*-methyl- α -obscurine, containing the entire lycopodine framework. In an unusual approach, Tsukano and Hiram applied an intramolecular palladium-mediated Heck reaction between
50 encarbamate and pyridine triflate **43** to form the ATA, which yielded lycopodine precursor **44** (Scheme 16a).⁹⁵

a) Tsukano's and Hiram's synthesis of (±)-lycodine



b) Takayama's synthesis of (+)-flabellidine and (-)-lycodine

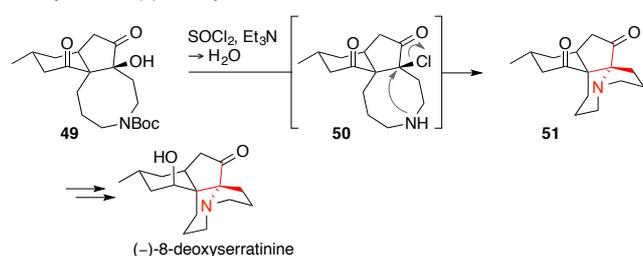


Scheme 16 Syntheses of various *Lycopodium* alkaloids by Tsukano (2010) and Takayama (2014). Cbz = carboxybenzyl, CSA = camphorsulfonic acid, Boc = *tert*-butyloxycarbonyl, Bn = benzyl, OTf = trifluoromethanesulfonate.

Recently, another very short synthesis of (-)-lycodine as well as the closely related (+)-flabellidine was accomplished by Takayama (Scheme 16b).⁹⁷ Starting from a linear precursor **45**, he was able to assemble the whole tetracyclic skeleton **48** of both alkaloids in a cascade reaction involving a double condensation (**45**→**46**), a conjugate addition (**46**→**47**) followed by a Mannich reaction (**47**→**48**). In addition, Shair published an approach towards several members of the 7-membered-ring-containing *Lycopodium* alkaloids using a transannular Mannich reaction (not shown).^{102, 103}

One of the rare cases of a S_N2 reaction in ATA formation can be found in Lei's recent synthesis of (-)-8-deoxyserratinine (Scheme 17).¹⁰⁴ Tertiary alcohol **49** was converted into chloride **50**, which was attacked intramolecularly by the free secondary amine (**50**→**51**). In 2014, Lei extended his strategy to a synthesis of the oxidised congener (-)-serratinine.¹⁰⁵ Other approaches towards 8-deoxyserratinine and related alkaloids include a Schmidt rearrangement and an intramolecular epoxide opening.¹⁰⁶⁻¹⁰⁸

Lei's synthesis of (-)-8-deoxyserratinine



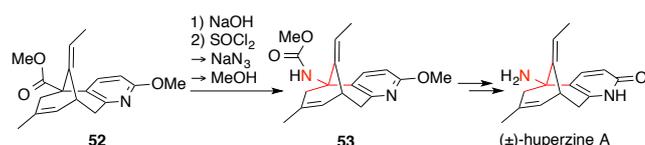
Scheme 17 Lei's synthesis of (-)-8-deoxyserratinine (2014). Boc = *tert*-butyloxycarbonyl.

In contrast to the multiple strategies used for the installation of ATAs in the *Lycopodium* alkaloids mentioned above, the methods used to access the medicinally important acetylcholine esterase inhibitor huperzine A are less diverse. Since the ATA in huperzine A is primary, it can be efficiently installed using a

Curtius rearrangement. Indeed, synthetic efforts towards huperzine A were almost exclusively focused on carboxylic acid precursors, such as **52**.¹⁰⁹⁻¹¹⁶

The first synthesis of huperzine A was published by Kozikowski in 1989 (Scheme 18).¹⁰⁹ First, they completed the core **52** wherein the primary amine is replaced by a methyl ester. After saponification, Curtius rearrangement (**52**→**53**) followed by double deprotection provided racemic huperzine A. In the following years, many huperzine A syntheses and several semi-syntheses were published.^{117, 118} All of them featured a racemic or enantiomerically pure carboxylic acid derivative of precursor **53**, keeping the Curtius rearrangement as the key step for the formation of the ATA.¹⁰⁹⁻¹¹⁶ These efforts culminated in the recently published large-scale asymmetric synthesis of huperzine A.¹¹⁹

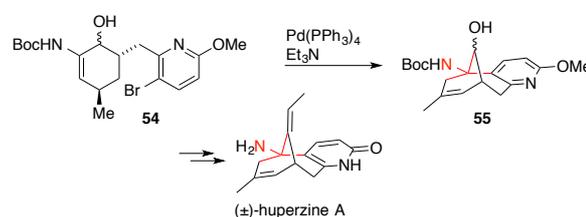
Kozikowski's synthesis of (±)-huperzine A



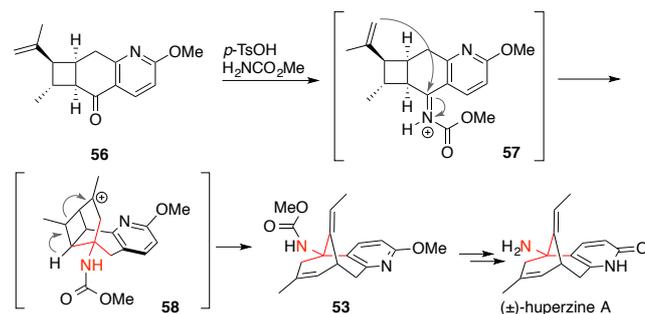
Scheme 18 Huperzine A synthesis by Kozikowski (1989).

A few groups, however, have been able to avoid Curtius rearrangements in the synthesis of huperzine A. Sun and Lin accessed the alkaloid using an intramolecular Heck reaction (**54**→**55**) (Scheme 19a),¹²⁰ whereas the White group performed an elegant tandem intramolecular aza-Prins cyclization/cyclobutane fragmentation (**56**→**53**) to set the ATA in **53** (Scheme 19b).¹²¹

a) Sun's and Lin's synthesis of huperzine A



b) White's synthesis of (±)-huperzine A

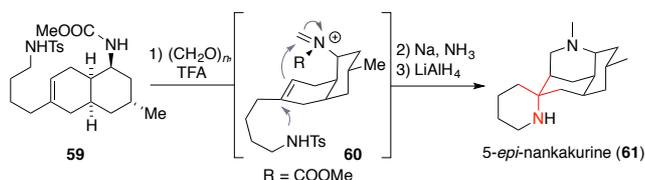


Scheme 19 Huperzine A syntheses by Sun/Lin (2012) and White (2013). Boc = *tert*-butyloxycarbonyl, *p*-TsCl = *para*-toluenesulfonic acid.

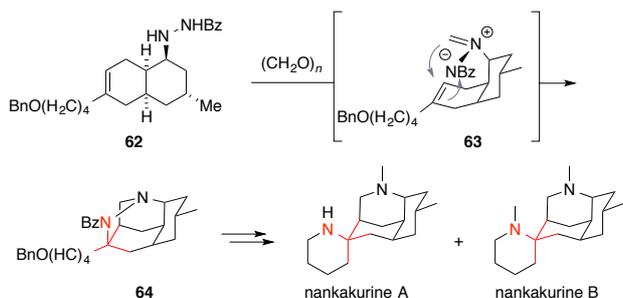
Two *Lycopodium* alkaloids recently isolated from *Lycopodium hamiltonii*, viz. the nankakurines A and B, have attracted broad interest in the synthetic community (Fig. 4).^{122, 123} So far, two syntheses of these natural products have been reported. In 2008, Overman published an enantioselective synthesis of the

misassigned original structure of nankakurine A (**61**) (Scheme 20a) followed by the syntheses of the reassigned structures of nankakurine A and B in 2010 (Scheme 20b).^{124, 125}

a) Overman's synthesis of misassigned nankakurine A (**61**)



b) Overman's synthesis of (+)-nankakurines A and B



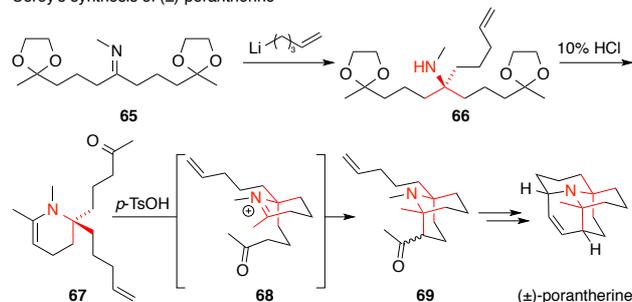
Scheme 20 Overman's syntheses of misassigned nankakurine A (2008) and revised nankakurines A and B (2010). Bn = benzyl, Bz = benzoyl, TFA = trifluoroacetic acid, Ts = *para*-toluenesulfonyl.

In the case of 5-*epi*-nankakurine (**61**), an aza-Prins reaction (**59**→**60**) was used, which allowed for the direct formation of both piperidine rings in **61** in one step starting from bicycle **59**.¹²⁴ This strategy, however could not be applied for the formation of actual nankakurine A. Its synthesis was accomplished utilizing an intramolecular 1,3-dipolar cycloaddition of an azomethine imine **63**, formed *in situ* via condensation of **62** with formaldehyde. This reaction provided access to tetracyclic pyrazolidine **64**, which, after SmI_2 mediated *N,N*-bond cleavage, gave rise to nankakurines A and B.¹²⁵ Two years later, Waters reported a racemic synthesis of nankakurines A and B using a Grignard addition to an iminium species derived from luciduline, which is easily accessible by total synthesis (not shown).¹²⁶

Porantherine, the major alkaloid of the poisonous woody shrub *Poranthera corymbosa*, is structurally similar to the *Lycopodium* alkaloids, although not a member of the family (Fig. 4).^{127, 128}

Possessing two tertiary carbons attached to the same amine (twofold ATA), porantherine is a considerable synthetic challenge that has been met only twice thus far.^{129, 130} Both syntheses are racemic and based on similar strategies for the assembly of the ATA motif, namely an addition to a ketimine followed by Mannich reaction. Corey published his synthesis of the natural product in 1974 (Scheme 21),¹²⁹ only three years after its isolation. The first ATA was installed through addition of an organolithium compound to imine **65** to form **66**, which then cyclized to the corresponding enamine **67** upon treatment with acid. The formation of the second ATA center through an intramolecular Mannich addition (*via* iminium ion **68**) furnished ketone **69**, which was eventually converted to the natural product.

Corey's synthesis of (±)-porantherine



Scheme 21 Porantherine synthesis by Corey (1974). *p*-TsOH = *para*-toluenesulfonic acid.

A second synthesis of porantherine, published by Stevens in 1987, involved the addition of two alkyl lithium compounds to an iminoether (not shown).¹³⁰

6 Hasubanan Alkaloids

The hasubanan alkaloids, isolated from various plant sources, are structurally related to the better-known morphine alkaloids but feature a pyrrolidine ring instead of a piperidine ring. They are comprised of over 40 family members, all of which share the same aza-propellane skeleton (Fig. 5).¹³¹

Although the physiological effects of the hasubanans are of limited significance, their beautiful structures stimulated numerous synthetic studies and several total syntheses have been reported to date.¹³²⁻¹⁴⁶

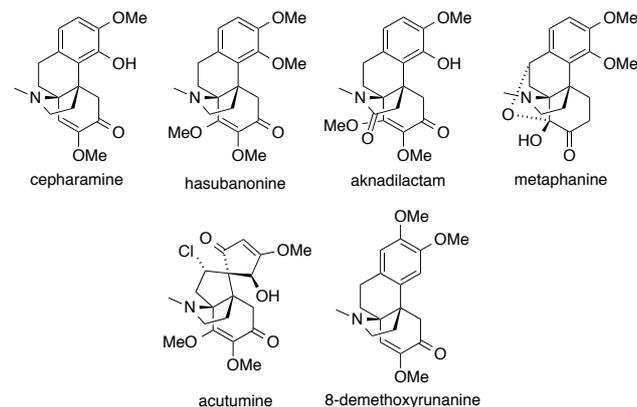


Fig. 5 Representative hasubanan alkaloids.

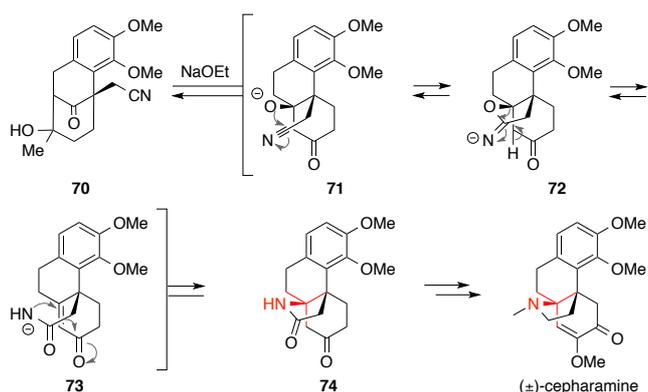
The first successful syntheses of (±)-cepharamine,^{132, 135} (±)-hasubanone,^{134, 137} (±)-aknadilactam¹³⁴ and (±)-metaphanine^{136, 138} were published by Inubushi in the 1970s (Scheme 22a). Starting from tricyclic β-tetralone **70**, the ATA was set *via* a cascade reaction involving an aza-Michael addition (**71**→**74**).

Almost 30 years later, Schultz prepared (+)-cepharamine using a Hofmann-type rearrangement to introduce the ATA (not shown).¹³⁹

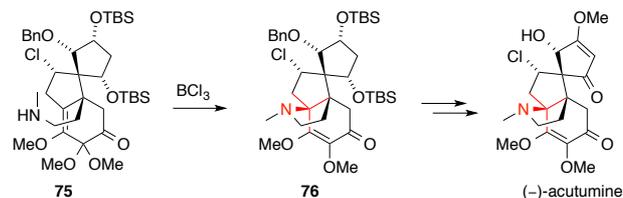
Recent years have seen revived interest in hasubanans. An elegant method for the installation of the ATA was developed by Castle, who closed the pyrrolidine ring of isohasubanone through a $\text{S}_{\text{N}}2'$ -reaction.^{140, 147} Subsequently, this strategy was adapted to access (-)-acutumine (Scheme 22b).¹⁴² To this end, amine **75** was exposed to a Lewis acid to generate an allylic cation that was intercepted by the appended secondary amine. The resulting

ATA-containing pyrrolidine **76** was then converted into (–)-acutumine.

a) Inubushi's synthesis of (±)-cepharamine



b) Castle's synthesis of (–)-acutumine

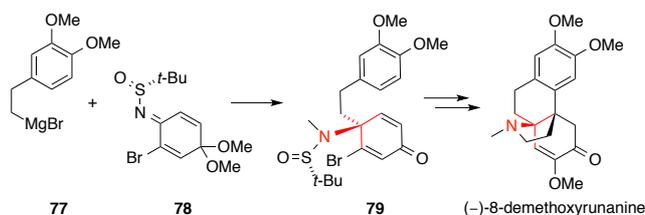


Scheme 22 Synthesis of hasubanan alkaloids by Inubushi (1969) and Castle (2009). Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

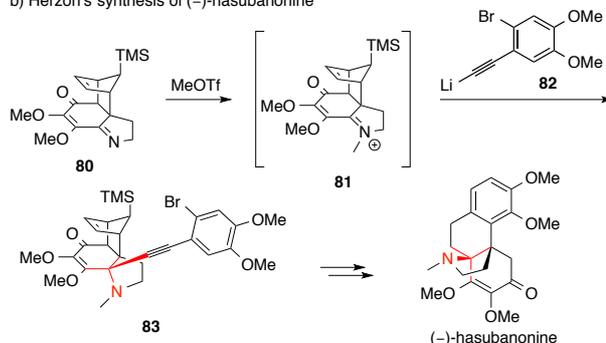
In contrast to this approach, which sets the ATA at a relatively late stage in the synthesis, Reisman installed it at the beginning (Scheme 23a).¹⁴⁴ Reaction of the chiral *N*-*tert*-butanesulfinimine **78** with phenethyl Grignard **77** provided sulfonamide **79** with a high degree of diastereoselectivity. Subsequently, **79** was converted into a series of hasubanan alkaloids such as (–)-8-demethoxyrunanine.

The first enantioselective synthesis of hasubanonine was published by Herzon (Scheme 23b).¹⁴³ Methylation of iminoquinone Diels-Alder adduct **80** (**80**→**81**), followed by addition of alkynyl lithium **82** gave amine **83**, which was eventually transformed into optically pure (–)-hasubanonine. This strategy proved to be versatile, as many more hasubanan alkaloids, including (–)-runanine, (–)-delavayine, (+)-periglaucine B and (–)-acutumine, could be accessed by variation of the alkynyl species.^{143, 145, 146}

a) Reisman's synthesis of (–)-8-demethoxyrunanine



b) Herzon's synthesis of (–)-hasubanonine



Scheme 23 Synthesis of hasubanan alkaloids by Reisman (2011) and Herzon (2011). *t*-Bu = *tert*-butyl, TMS = trimethylsilyl, OTf = trifluoromethanesulfonate.

7 Stemona Alkaloids

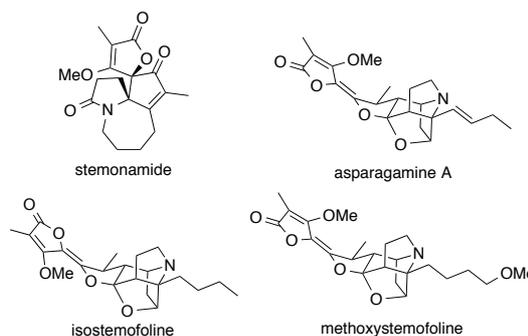


Fig. 6 Representative *Stemona* alkaloids.

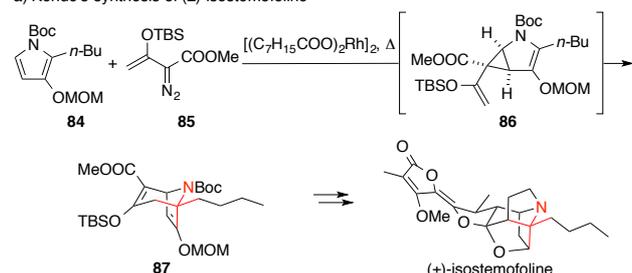
Plants belonging to the family *Stemonaceae*, which are mostly found in Southeast Asia, have been used for centuries as insecticides and for the treatment of respiratory diseases.¹⁴⁸⁻¹⁵⁰ Phytochemical investigations led to the isolation of a variety of natural products known as *Stemona* alkaloids (Fig. 6).^{151, 152} These polycyclic natural products possess highly complex structures weaving together pyrrolidines and butenolides, often through *spiro* fusions that contain ATAs.

The structural beauty of these molecules generated considerable interest in the synthetic community and stimulated the development of new synthetic methods for the installation of ATAs.^{151, 152} The strategies employed range from classical additions to imines,^{153, 154} to radical cyclization cascades,^{155, 156} radical allylations,¹⁵⁷ semipinacol-Schmidt cascades,^{158, 159} Schmidt reactions,¹⁶⁰ aza-Cope-Mannich reactions,¹⁶¹ cyclopropane-Cope rearrangements¹⁶² and catalytic 1,3-dipolar cycloadditions.¹⁶³

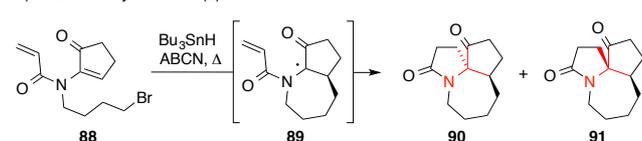
The first synthesis of a *Stemona* alkaloid, *viz.* isostemofoline, was published by Kende in 1999 and employed a highly unusual and elegant approach.¹⁶² The ATA was formed *via* rhodium-catalyzed

reaction of pyrrole **84** with vinyl diazoester **85**. The resultant divinyl cyclopropane **86** underwent Cope rearrangement *in situ* to afford bicycle **87**, which was then used as a key intermediate in the further assembly of the natural product (Scheme 24a).

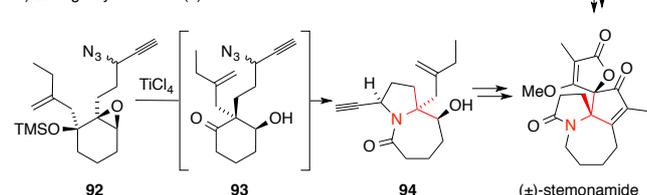
a) Kende's synthesis of (±)-isostemonifoline



b) Ishibashi's synthesis of (±)-stemonamide



c) Zhang's synthesis of (±)-stemonamide



Scheme 24 Syntheses of *Stemona* alkaloids by Kende (1999), Ishibashi (2008) and Zhang (2011). ABCN = 1,1'-azobiscyclohexarbonitrile, Boc = *tert*-butyloxycarbonyl, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

10 More recently, two synthetic approaches aimed at members of the stemonamine group were published. Ishibashi developed an entry to racemic stemonamide and isostemonamide as well as their reduced derivatives stemonamine and isostemonamine, based on a radical cascade as the key step for the formation of the ATA

15 (Scheme 24b).^{155, 156} Treatment of the achiral precursor **88** with tributyltin hydride and 1,1'-azobiscyclohexarbonitrile (ABCN) at elevated temperatures effected a 7-*endo-trig* cyclization that likely yielded radical **89** as the proposed intermediate, which in turn underwent an unusual 5-*endo-trig* cyclization providing

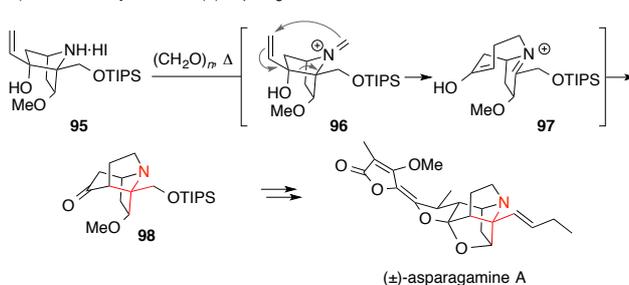
20 access to a separable mixture of isomers **90** and **91**. Further transformations of these tricyclic compounds furnished stemonamide and some of its congeners.

An alternative approach to stemonamide and related *Stemona* alkaloids was published by Zhang (Scheme 24c).¹⁵⁹ Based on his

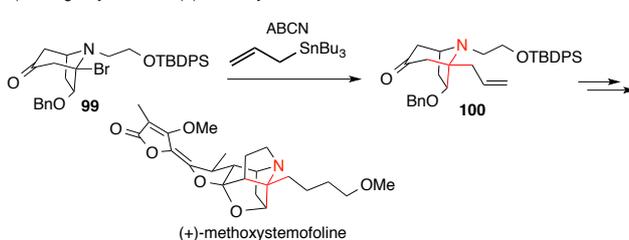
25 systematic studies on the reactivity of α -hydroxy epoxides such as **92**,¹⁶⁴ he developed a powerful cascade that combines a semipinacol rearrangement with an Aubé-Schmidt reaction (**92**→**94**). The resulting amide **94** was obtained as a 5:1 mixture of diastereomers, reflecting the diastereomeric mixture of

30 propargylic azides employed as substrates. Using this strategy and variations thereof, Zhang was able to synthesize stemonamide and three additional *Stemona* alkaloids, *viz.* maistemonine, stemonamine, and isomaistemonine.¹⁵⁸⁻¹⁶⁰

a) Overman's synthesis of (±)-asparagamine A



b) Huang's synthesis of (+)-methoxystemofoline



Scheme 25 Syntheses of *Stemona* alkaloids by Overman (2003) and Huang (2015). ABCN = 1,1'-azobiscyclohexarbonitrile, Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl.

The only synthesis of asparagamine A, an unsaturated derivative of stemonamide, was achieved by Overman in 2003.¹⁶¹ He

40 installed the ATA using his signature aza-Cope-Mannich cascade (Scheme 25a). The synthesis of a precursor molecule suitable for this transformation commenced with a Diels-Alder reaction, forming an ATA that later took part in the rearrangement. Treatment of **95** with excess paraformaldehyde at elevated

45 temperatures generated iminium ion **96**, which underwent the aza-Cope-Mannich sequence to afford the ATA of asparagamine A (**98**, *via* intermediate **97**). More recently, a radical allylation (**99**→**100**) was utilized by Huang to set the ATA in (+)-methoxystemofoline at an early stage of the synthesis (Scheme

50 25b).¹⁵⁷

8 Indole Alkaloids

Indole alkaloids are a structurally and biosynthetically heterogeneous class of natural products characterized by an indole nucleus or derivative thereof. Several of them, albeit not the best

55 known ones, contain ATAs (Fig. 7).

Kopsine, the first member of the so-called *Kopsia* alkaloids, was isolated as early as 1890,¹⁶⁵ but it took several decades before its complex structure, and those of its congeners, could be elucidated.¹⁶⁶⁻¹⁷³ All members of this family possess an ATA

60 incorporated in a bicyclo[2.2.2]octane system. Thus, the kopsanes seem predestined for Diels-Alder reactions, and few syntheses fail to employ a [4+2]-cycloaddition strategy.¹⁷⁴⁻¹⁷⁶ The routes used can be divided into two main categories: a) intermolecular Diels-Alder reactions¹⁷⁷⁻¹⁸⁰ and b) intramolecular Diels-Alder

65 reactions.¹⁸¹⁻¹⁸⁵

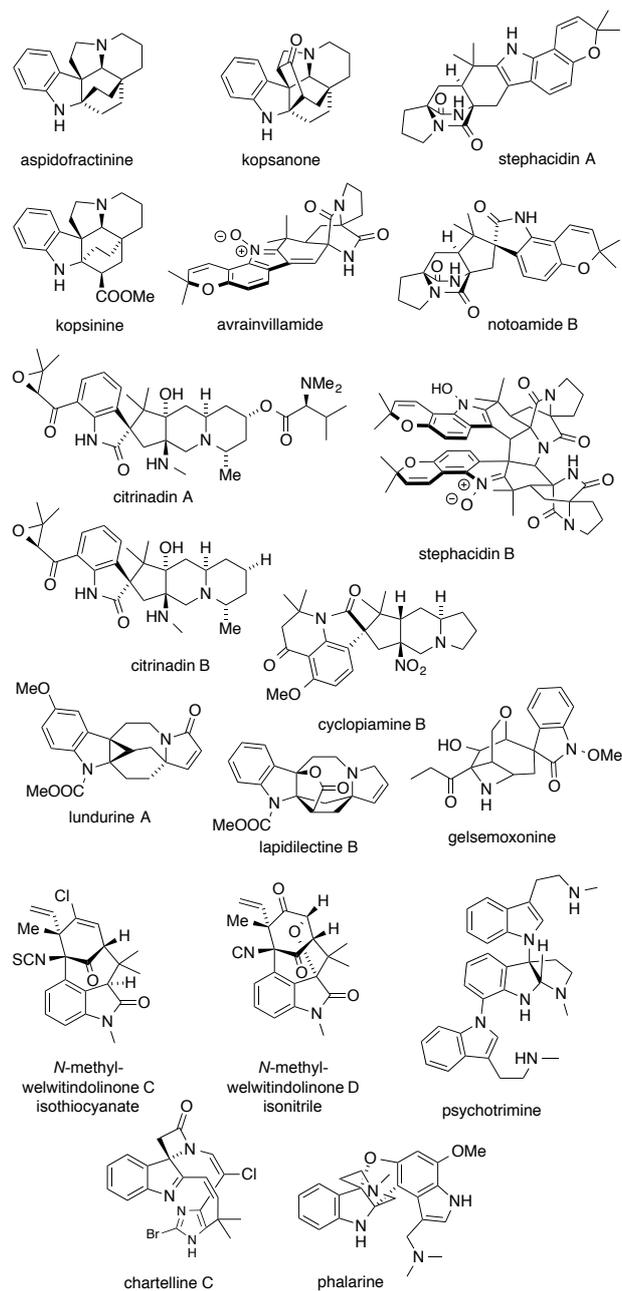


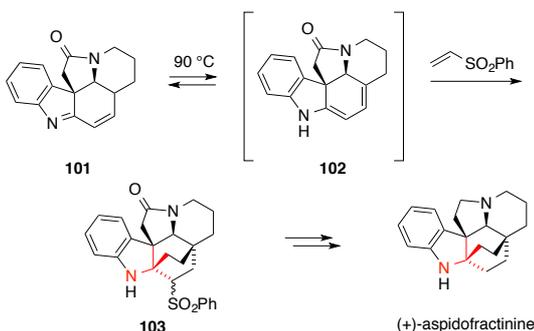
Fig. 7 Indole alkaloids featuring ATAs.

The very first synthesis of (±)-aspidofractinine, completed in 1976, introduced an intermolecular Diels-Alder reaction to set the ATA using nitroethylene as a dienophile (not shown).¹⁷⁷ Over time, phenyl vinyl sulfone emerged as a more practical dienophile^{178, 179} and in 2009 the first enantioselective synthesis of (+)-aspidofractinine was reported by Spino using this reagent (Scheme 26a).¹⁸⁰ In this case, imine **101** thermally isomerized to diene **102**, which then underwent cycloaddition from the sterically more accessible convex side to afford sulfone **103**.

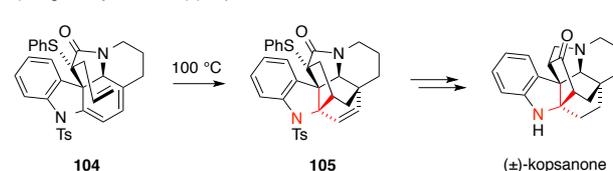
The first successful intramolecular Diels-Alder approach to (±)-kopsanone and (±)-10,22-dioxokopsane was reported in 1983 by Magnus (Scheme 26b).^{181, 182} They synthesized sulfide **104** as a suitable precursor, with the dienophile placed in the concave position. The cycloaddition reaction proceeded at 100 °C and provided intermediate **105**, which was transformed into (±)-

kopsanone in a few steps. Using a similar strategy, other indole alkaloids, (±)-kopsijasmine and (±)-kopsine, were prepared as racemates,^{184, 185} as well as (–)-kopsinilam and (–)-kopsinine in enantiomerically pure form.¹⁸³

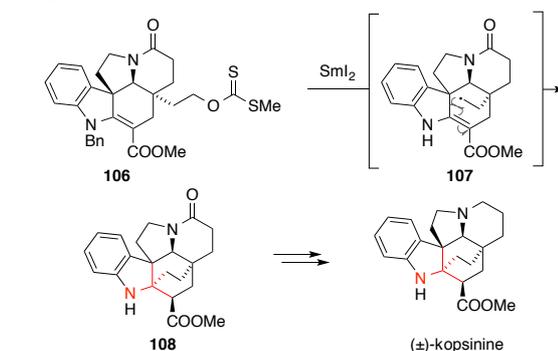
a) Spino's synthesis of (+)-aspidofractinine



b) Magnus' synthesis of (±)-kopsanone



c) Boger's synthesis of (±)-kopsinine



Scheme 26 *Kopsia* alkaloid syntheses by Spino (2009), Magnus (1983) and Boger (2013). Bn = benzyl, Ts = *p*-toluenesulfonyl.

In a recent example for an alternative approach by Boger, a powerful radical transannular cyclization was applied to install the ATA of kopsinine (Scheme 26c).¹⁷⁶ Upon treatment of xanthate **106** with Sml₂, ATA **108** was formed as a single diastereomer. Presumably, a primary radical intermediate **107** is formed, which undergoes a radical cyclization followed by reduction and diastereoselective protonation of the ester enolate.

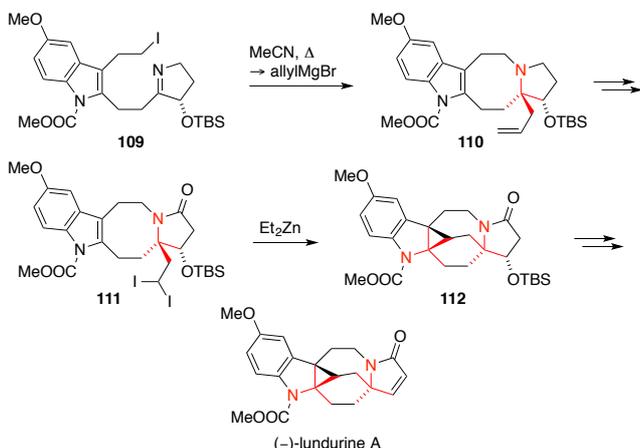
Lapidilectine B and lundurine A are two structurally related *Kopsia* alkaloids that contain two ATAs. Although not originating from the same organism, they show a similar scaffold with a bridged 8-membered ring fused to an indoline on one side and a 5-membered ring on the other. Lapidilectine A was isolated by Awang from the leaves of the tree *Kopsia lapidilecta* in 1992.^{186, 187} Lundurines A-D were isolated from the Malaysian tree *Kopsia tenuis*,¹⁸⁸ and shown to be effective at bypassing multidrug resistance in vincristine-resistant KB cells.¹⁸⁹

Qin accomplished the first enantioselective synthesis of (–)-lundurine A in 2014 (Scheme 27a).¹⁹⁰ The first ATA was established *via* the addition of allylmagnesium bromide to an

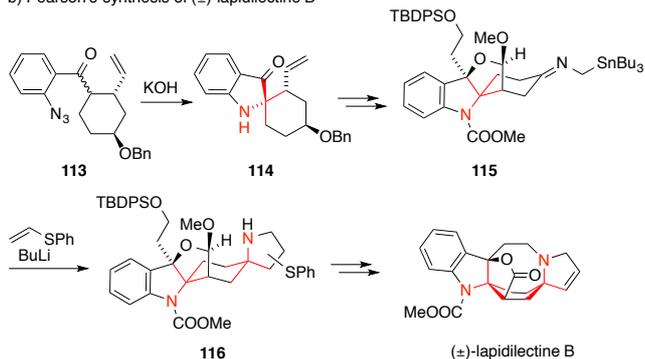
iminium ion generated by *in situ* alkylation of imine **109** to form tetracycle **110**. In order to establish the two fully substituted stereocenters on the indoline of **112**, Qin resorted to an unusual intramolecular Simmons-Smith cyclopropanation of diiodide **111**.

Two other racemic syntheses of lundurine A and B have been reported by Nishida.¹⁹¹⁻¹⁹³ He employed a Curtius rearrangement and a 1,2-addition to an iminium ion for lundurine B¹⁹³ and a Tsuji-Trost amination and an indoxyl bisalkylation for the synthesis of lundurine A (not shown).^{191, 192}

a) Qin's synthesis of (-)-lundurine A



b) Pearson's synthesis of (±)-lapidilectine B



Scheme 27 Syntheses of *Kopsia* alkaloids by Qin (2014) and Pearson (2001). Bn = Benzyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

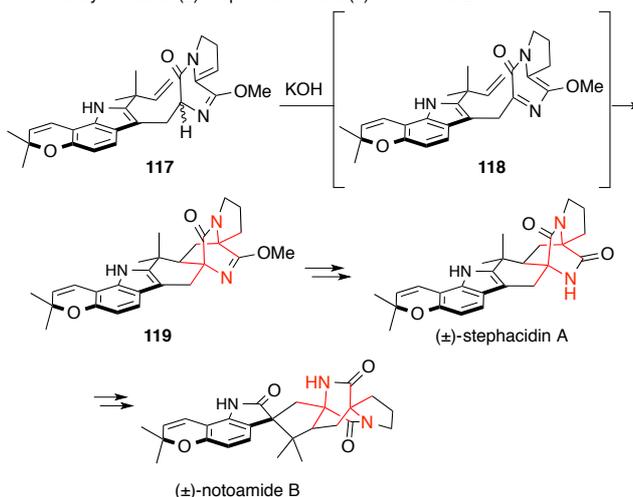
In 2001, Pearson employed a Smalley cyclization of aryl ketone azide **113** to furnish the spiroindoxyl **114** (Scheme 27b).^{194, 195} In the final steps of his lapidilectine B synthesis, he then used his trademark azaallyl anion [3+2]-cycloaddition to establish the pyrrolidine ring (**115**→**116**) as an inconsequential mixture of regioisomers.

The cycloaddition approach has not been limited to the kopsane alkaloids. Other indole alkaloids, such as stephacidin A and the notoamides, which bear two ATAs, were prepared by a presumably biomimetic [4+2]-cycloaddition.

Williams synthesized stephacidin A and notoamide B starting from imidate **117**, which underwent base-mediated isomerization to **118** followed by intramolecular Diels-Alder reaction to afford diazabicyclo[2.2.2]octane **119** (Scheme 28).¹⁹⁶ This remarkable reaction sets both ATAs in a single step. Later that year, stephacidin B was accessed *via* avrainvillamide using the same

strategy.¹⁹⁷

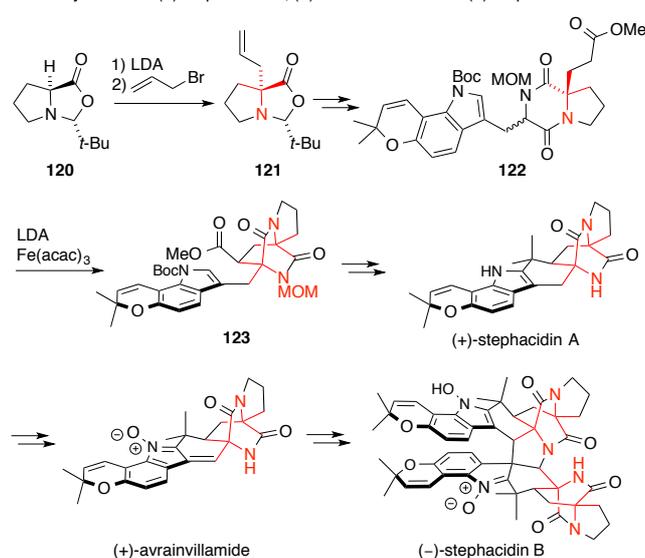
Williams' synthesis of (±)-stephacidin A and (±)-notoamide B



Scheme 28 Synthesis of prenylated indole alkaloids by Williams (2007).

In 2005, Baran used the α -alkylation of proline derivative **120** with complete chirality transfer, a method developed by Seebach,¹⁹⁸ to set the first ATA of stephacidin A in **121** (Scheme 29).¹⁹⁹ The second ATA present in **123** was installed by an intramolecular, stereocontrolled oxidative enolate coupling starting from diketopiperazine **122**. Baran was then able to convert stephacidin A into avrainvillamide and stephacidin B following a biosynthetic proposal.²⁰⁰

Baran' synthesis of (+)-stephacidin A, (+)-avrainvillamide and (-)-stephacidin B

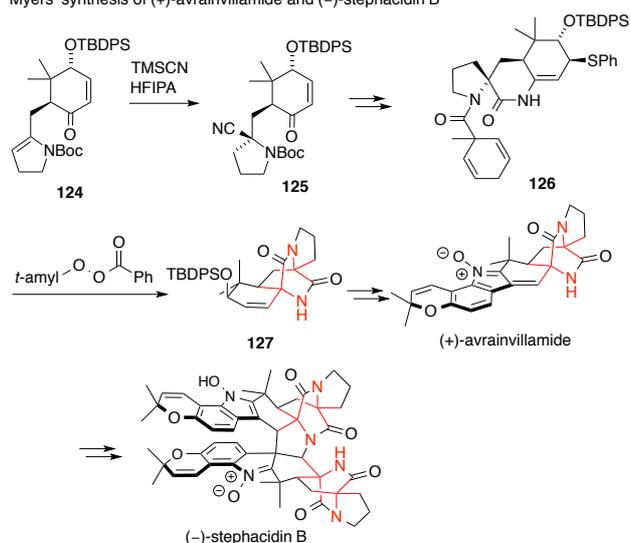


Scheme 29 Synthesis of prenylated indole alkaloids by Baran (2005). acac = acetylacetonate, Boc = *tert*-butyloxycarbonyl, *t*-Bu = *tert*-Butyl, LDA = Lithiumdiisopropylamide.

A second synthesis of avrainvillamide and stephacidin B was accomplished concurrently by Myers (Scheme 30). In this case, the first ATA was installed by a Strecker-type addition of TMS cyanide to enamine **124** to form the *N*-Boc amino nitrile **125**.²⁰¹ The second ATA was then set by a very unusual radical transfer cyclization. Abstraction of a hydrogen atom in **126**, followed by loss of toluene, generates an aminoacyl radical which attacks the

enamide double bond and ejects a phenylthiyl radical to form the diketopiperazine **127**.

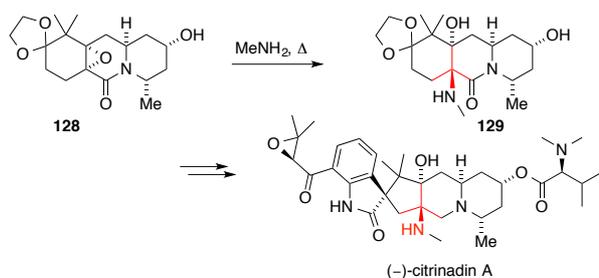
Myers' synthesis of (+)-avrainvillamide and (-)-stephacidin B



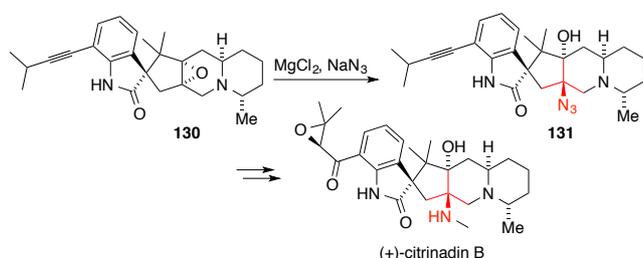
Scheme 30 Synthesis of prenylated indole alkaloids by Myers (2005). *t*-amyl = *tert*-amyl (2-methylbutyl), Boc = *tert*-butyloxycarbonyl, HFIPA = 1,1,1,3,3,3-hexafluoroisopropyl acrylate, TBDPS = *tert*-butyldiphenylsilyl, TMSCN = trimethylsilyl cyanide.

Several members of a related family of prenylated spirooxindole alkaloids, namely cyclopiamine, citrinadin A and citrinadin B, also feature an asymmetric ATA.²⁰²⁻²⁰⁴ In 2013, Martin and Wood reported the first syntheses of citrinadin A and B.^{205, 206} In the case of citrinadin A, epoxide **128** was heated in the presence of methylamine to provide 1,2-amino alcohol **129** (Scheme 31a).²⁰⁵ Wood's approach employed an azide-mediated opening of epoxide **130** to establish the ATA in **131** (Scheme 31b).²⁰⁶ Both reactions are rare examples where an ATA has been set through a S_N2 reaction.

a) Martin's synthesis of (-)-citrinadin A



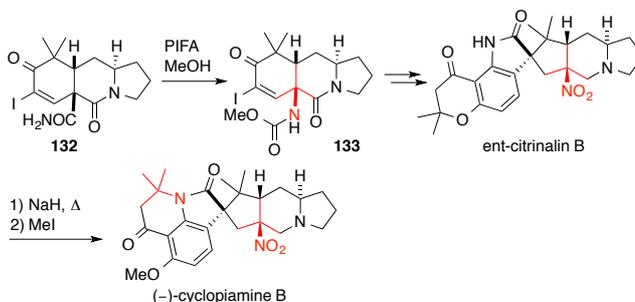
b) Wood's synthesis of (+)-citrinadin B



Scheme 31 Syntheses of prenylated indole alkaloids by Martin (2013) and Wood (2013).

More recently, Sarpong published his entry to the prenylated indole alkaloids cyclopiamine B and *ent*-citrinalin B (Scheme 32). The first ATA was set *via* a Hofmann rearrangement (**132**→**133**).²⁰⁷ The second, not asymmetric, ATA center was established by treating *ent*-citrinalin B with sodium hydride to effect the rearrangement of the chromanone to the tetrahydroquinolone moiety present in cyclopiamine *via* *retro*-Michael/Michael addition. Using a similar approach, he was then able to synthesize the structurally related alkaloids stephacidin A and notoamide B.²⁰⁸

Sarpong's synthesis of (-)-cyclopiamine B

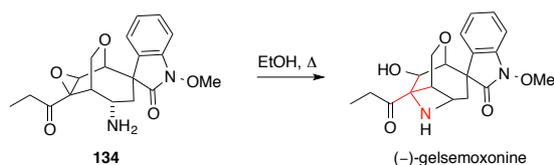


Scheme 32 Synthesis of *ent*-citrinalin B and (-)-cyclopiamine B by Sarpong (2015). PIFA = (Bis(trifluoroacetoxy)iodo)benzene.

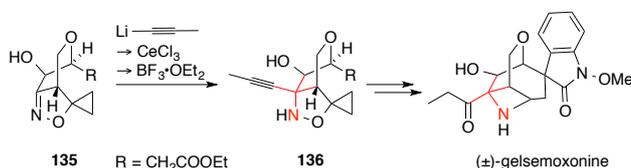
Two alkaloids closely related to notoamide B, marcfortine B and *35* C, were synthesized by Trost using a Michael addition and a radical cyclization to set the two ATAs (not shown).^{209, 210}

Gelsemoxonine is an indole alkaloid with an ATA that is part of an azetidine, a rare structural motif. It is also a member of the *Gelsemium* spirooxindole family, a large alkaloid family with highly compact, strained and complex structures, which have attracted considerable synthetic activity.²¹¹⁻²¹³ In 2011, Fukuyama accomplished a total synthesis of gelsemoxonine that employed an intramolecular epoxide opening of **134** to install the ATA (Scheme 33a).²¹⁴ Recently, Carreira published an elegant entry to gelsemoxonine, setting the ATA **136** *via* a diastereoselective propynyllithium addition to isoxazoline **135** (Scheme 33b).²¹⁵

a) Fukuyama's synthesis of (-)-gelsemoxonine



b) Carreira's synthesis of (±)-gelsemoxonine



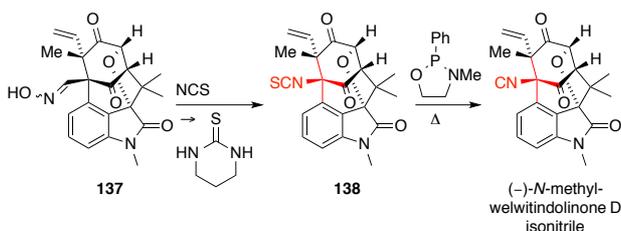
Scheme 33 Syntheses of gelsemoxonine by Fukuyama (2011) and Carreira (2013). Boc = *tert*-butyloxycarbonyl.

50 The welwitindolinones are another class of indole alkaloids with an ATA that is not part of the indole-derived moiety itself. The first welwitindolinone natural products (Fig. 7) were isolated by Moore in 1994 from the cyanobacteria *Hapalosiphom welwitschii*

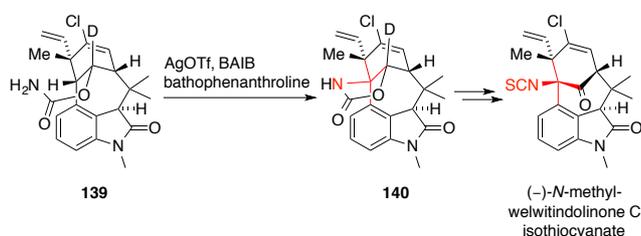
and *Westiella intracta*.²¹⁶ All welwitindolinones known so far feature a [4.3.1] bicyclic framework, which, in some cases, contains a modified ATA that bears an isothiocyanate or isonitrile functional group.^{217, 218}

Being a considerable challenge for total synthesis, the welwitindolinones have become popular targets.²¹⁹ The first total synthesis of *N*-methylwelwitindolinone D isonitrile was accomplished by Rawal in 2011²²⁰⁻²²² using Kim's oxime rearrangement to install the isothiocyanide (**137**→**138**, Scheme 34a).^{223, 224} Desulfuration of **138** then gave the naturally occurring isonitrile. Martin completed a synthesis that intercepts Rawal's synthesis in 2012.²²⁵

a) Rawal's synthesis of (–)-*N*-methylwelwitindolinone D isonitrile



b) Garg's synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate



Scheme 34 Syntheses of welwitindolinones by Rawal (2011) and Garg (2011). BAIB = (diacetoxyiodo)benzene, NCS = *N*-chlorosuccinimide, OTf = trifluoro-methanesulfonate, Ph = phenyl.

Garg's total synthesis of *N*-methylwelwitindolinone C isothiocyanate used an intramolecular Ag-mediated nitrene C,H-insertion of amide **139** as the critical step, which furnished carbamate **140** (Scheme 34b).^{226, 227} To improve the regioselectivity and yield of this late stage transformation, the authors beautifully exploited the deuterium kinetic isotope effect.²²⁸

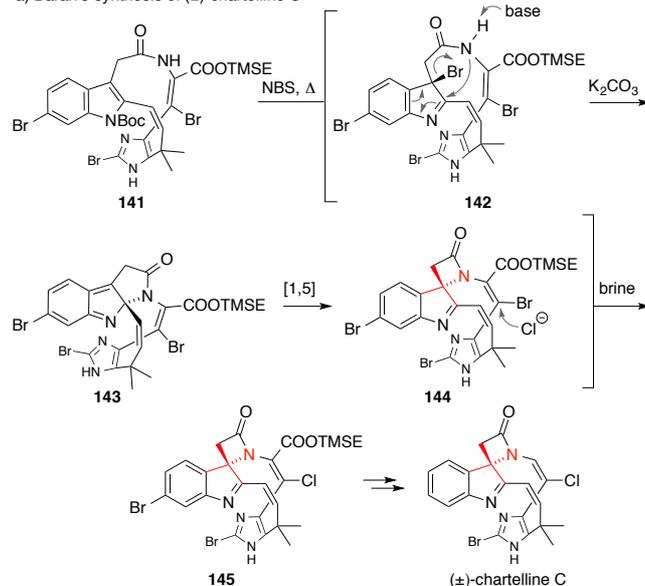
Both Rawal and Garg were able to subsequently synthesize several members of the welwitindolinone family by varying their initial strategies.^{222, 228-230} In addition, Hatakeyama recently accomplished another synthesis of (–)-*N*-methylwelwitindolinone C isothiocyanate using an endgame similar to Rawal's.²³¹

Two examples of reactions which have been specifically developed to set an ATA, both explored by the Baran laboratory, are shown in Scheme 35.

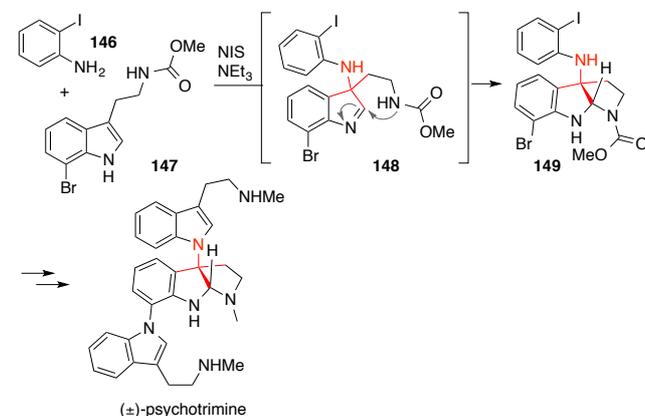
In the synthesis of chartelline C, the ATA was set *via* a cascade reaction initiated by the bromination of indole **141** at 185 °C resulting in **142** (Scheme 35a). Amide attack furnished intermediate **143**, which then rearranged in a 1,5-shift to give the ring contracted spiro-β-lactam **144**.^{232, 233} For the synthesis of psychotrimine, a coupling of indole **147** with 2-iodoaniline (**146**) was developed to yield **148**, which then underwent further cyclization to give **149** (Scheme 35b).²³⁴ This method was also used for the syntheses of psychotetramine,²³⁵ kapakahine B and

kapakahine F.^{236, 237}

a) Baran's synthesis of (±)-chartelline C



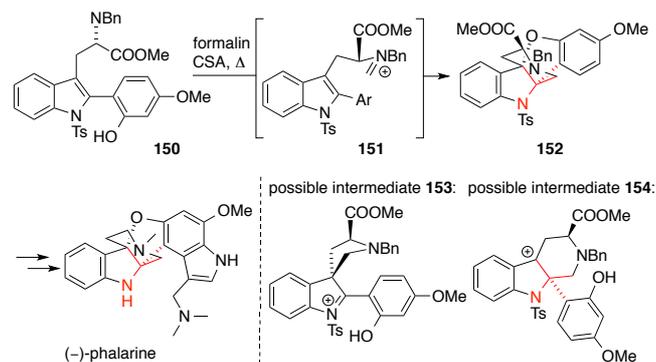
b) Baran's synthesis of (±)-psychotrimine



Scheme 35 Baran's syntheses of chartelline C (2006) and psychotrimine (2008). Bn = benzyl, Boc = *tert*-butyloxycarbonyl, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide, TMSE = 2-(trimethylsilyl)ethyl.

Another interesting way to install an ATA in a structurally complex indole alkaloid was published by Danishefsky (Scheme 36).²³⁸ In his synthesis of the furanobisindole alkaloid phalarine, amino acid derivative **150** was treated with formaldehyde and acid to set the ATA in a diastereoselective fashion (**150**→**152**). It is not clear, however, whether this reaction proceeds *via* a 1,2-Wagner-Meerwein shift (possible intermediate **153**) or a Pictet-Spengler reaction (possible intermediate **154**) starting from iminium intermediate **151**.

Danishefsky's synthesis of (-)-phalarine



Scheme 36 Danishefsky's synthesis of phalarine (2010). Bn = Benzyl, CSA = camphorsulfonic acid.

9 Cephalotaxines

Due to their interesting chemical structure and antileukemic activities, the cephalotaxines, isolated from the Japanese plum yew (*Cephalotaxus harringtonii*), have emerged as popular targets for natural product synthesis (Fig. 8).²³⁹

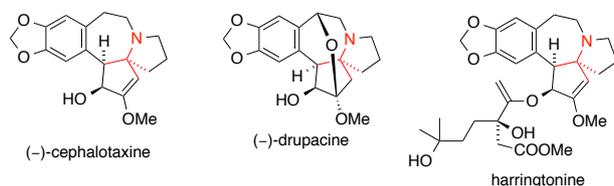
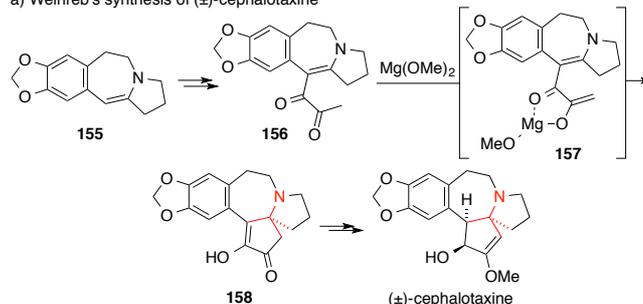
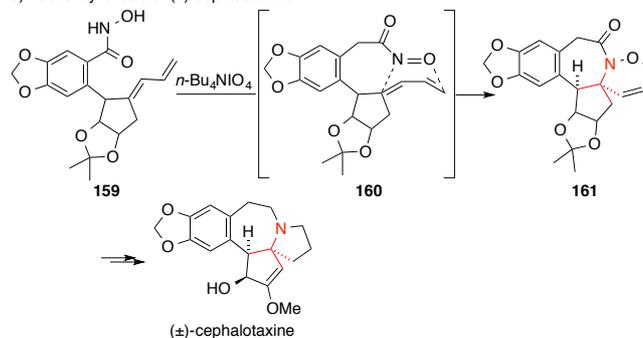


Fig. 8 Cephalotaxines

The first synthesis of cephalotaxine itself was reported by Weinreb²⁴⁰ in 1972 (Scheme 37a). Conversion of enamine **155** into diketone **156** set the stage for a Lewis-acid catalyzed cyclization to yield tertiary amine **158** (via intermediate **157**). Weinreb was able to synthesize cephalotaxine in six additional steps with an overall yield of 20%, setting a high bar for the following syntheses.

a) Weinreb's synthesis of (\pm)-cephalotaxineb) Fuchs' synthesis of (\pm)-cephalotaxine

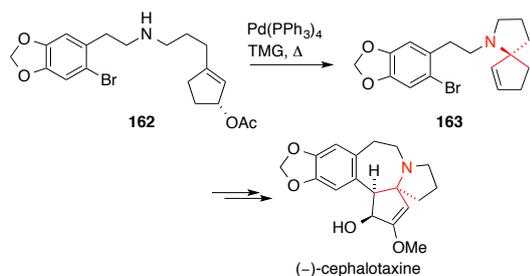
Scheme 37 Syntheses of Cephalotaxine by Weinreb (1972) and Fuchs (1988).

In 1988, Fuchs utilized an intramolecular [4+2] nitroso-Diels-Alder cycloaddition to assemble the benzazepine **161** from hydroxamic acid **159** (via intermediate **160**, Scheme 37b).²⁴¹

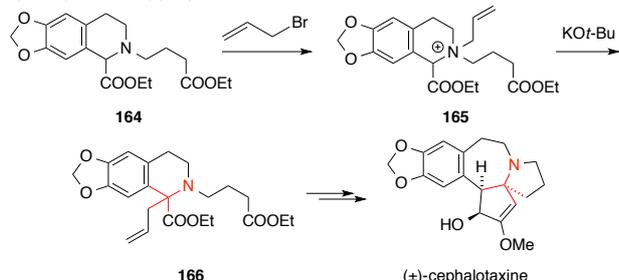
Tietze published a formal asymmetric synthesis of (-)-cephalotaxine in 1999 that is based on palladium catalysis (Scheme 38a).²⁴² A Tsuji-Trost allylation on secondary amine **162** established the ATA and afforded **163** which was converted into cephalotaxine via a subsequent Heck reaction. A similar Tsuji-Trost allylation was used by Stoltz in 2007 in his synthesis of drupacine and cephalotaxine.²⁴³

A [2,3]-sigmatropic rearrangement was utilized by Li to convert quaternary ammonium ion **165** to the α -tertiary amino ester **166** (**164**→**166**, Scheme 38b).²⁴⁴

a) Tietze's synthesis of (-)-cephalotaxine



b) Li's synthesis of (±)-cephalotaxine

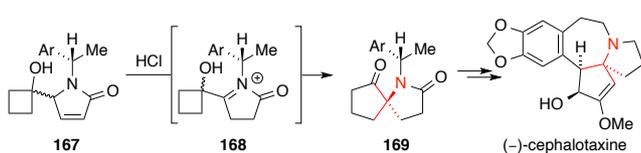


Scheme 38 Syntheses of Cephalotaxine by Tietze (1999) and Li (2003). Ac = acetyl, TMG = 1,1,3,3-tetramethylguanidine.

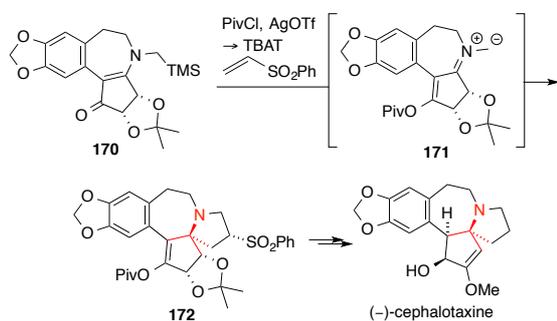
A rather unusual approach for the asymmetric synthesis of (-)-cephalotaxine was pursued by Royer, who introduced the ATA on key intermediate **169** via semipinacol rearrangement of chiral α -hydroxyiminium **168**. The latter was generated by acid-catalyzed isomerization and protonation of pyrrolinone **167** (Scheme 39a).²⁴⁵

Another synthesis was developed by Gin, who transformed vinyligous amide **170** into azomethine ylide **171** which then underwent 1,3-dipolar cycloaddition with phenyl vinyl sulfone to yield **172** (Scheme 39b).^{246, 247} The unexpected yet advantageous stereochemical outcome of this cycloaddition was confirmed by X-ray analysis.

a) Royer's synthesis of (-)-cephalotaxine



b) Gin's synthesis of (-)-cephalotaxine



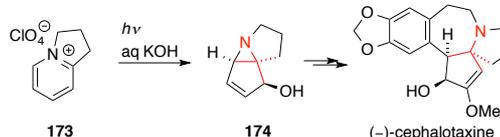
Scheme 39 Syntheses of cephalotaxines by Royer (2004) and Gin (2006). Ar = aryl, OTf = trifluoromethanesulfonate, Piv = pivaloyl, TBAT = tetrabutylammonium difluorotriphenyl-silicate.

In 2006, Mariano used a photochemical cyclization of a bicyclic pyridinium ion **173** to afford aziridine **174**, which was then transformed into the natural product (Scheme 40a).²⁴⁸ Hayes' synthetic route towards (-)-cephalotaxine made use of an alkylidene carbene 1,5 C,H-insertion starting from ketone **175** to furnish spiro[4.4]azanonane **177**, which corresponds to the skeleton of cephalotaxine (**175**→**177**, Scheme 40b).²⁴⁹

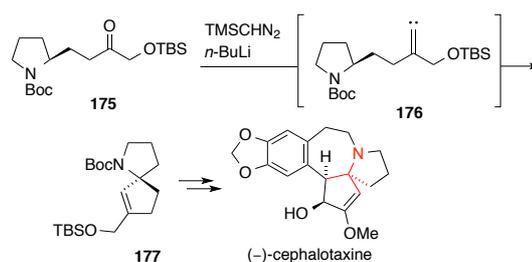
Ishibashi chose a radical cyclization approach to synthesize cephalotaxine (Scheme 40c).²⁵⁰ Treatment of aryl iodide **178** with tributyltin hydride and a radical initiator resulted in a 7-endo cyclization followed by a 5-endo cyclization that, after hydrogen transfer, yielded **179**. Additional functional group manipulations allowed them to intercept an intermediate that had previously been used to synthesize (-)-cephalotaxine.²⁵¹

A host of other methods have been used for the installation of the ATA in cephalotaxines.²³⁹ These include alkylation,^{252, 253} Claisen rearrangement,²⁵⁴ Michael addition,^{255, 256} Schmidt reaction,²⁵⁷ addition to an imine,²⁵⁸ transannular cyclization²⁵⁹ and oxidative rearrangement.²⁵¹

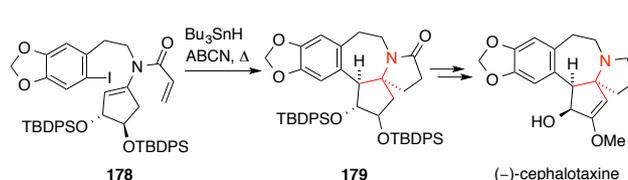
a) Mariano's formal synthesis of (-)-cephalotaxine



b) Hayes' formal synthesis of (-)-cephalotaxine



c) Ishibashi's synthesis of (-)-cephalotaxine



Scheme 40 Syntheses of cephalotaxine by Mariano (2006), Hayes (2008) and Ishibashi (2008). ABCN = 1,1'-azobis(cyclo-hexanecarbonitrile), Boc = *tert*-Butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

10 Erythrina Alkaloids

Erythrina alkaloids were discovered at the end of the 19th century, when extracts of *Erythrina* trees were found to possess curare-like neuromuscular activities.²⁶⁰ Due to their biological activities and interesting structures, several total syntheses of these natural products have been carried out and many creative ways to install ATAs have been developed in this context.²⁶¹

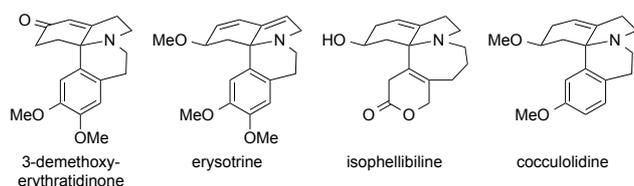
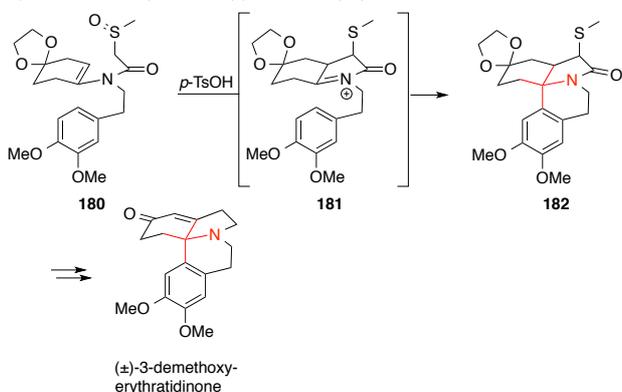


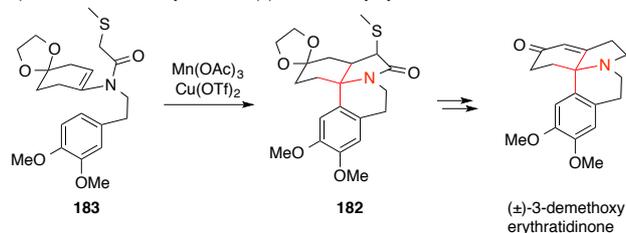
Fig. 9 Representative *Erythrina* alkaloids.

In 1990, the group of Ishibashi published the synthesis of (\pm)-3-demethoxyerythratidinone using an intramolecular Pummerer-like rearrangement of the enamine **180**, setting the stage for a Pictet-Spengler-type reaction (**181** \rightarrow **182**) to furnish the ATA (Scheme 41a).²⁶² Thirteen years later, the same group published an oxidative radical cyclization starting from enamine **183** to obtain the skeleton of 3-demethoxyerythratidinone **182** (Scheme 41b).²⁶³ Tsuda's approach featured an intermolecular photochemical [2+2]-cyclization to install the ATA, starting from bicycle **184** and diene **185** (Scheme 41c). In the following steps, a ring expansion of the four-membered ring in **186** furnished the six-membered ring by a formal 1,3-migration of a vinylcycobutane, affording the scaffold of erysotrine.²⁶⁴

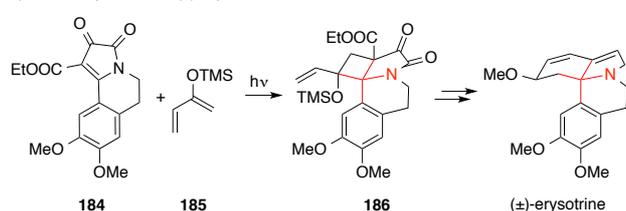
a) Ishibashi's first synthesis of (\pm)-3-demethoxyerythratidinone



b) Ishibashi's second synthesis of (\pm)-3-demethoxyerythratidinone



c) Tsuda's synthesis of (\pm)-erysotrine



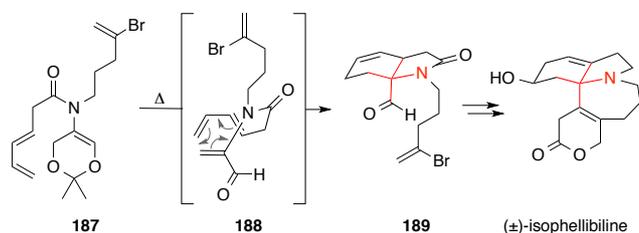
Scheme 41 Syntheses of *Erythrina* alkaloids by Ishibashi (1990 and 2003) and Tsuda (1992). Ac = acetyl, OTf = trifluoromethanesulfonate, TMS = trimethylsilyl, *p*-TsOH = *para*-toluenesulfonic acid.

Funk accomplished the synthesis of isophellibiline *via* an approach that relies on pericyclic reactions (Scheme 42a).²⁶⁵ Heating of dioxine **187** resulted in retro-Diels-Alder reaction to

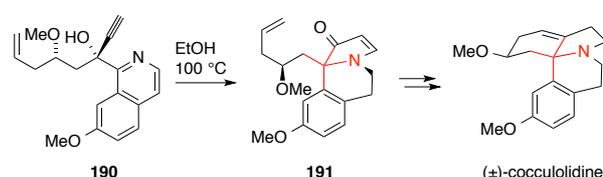
afford dehydroalanine derivative **188**, which then underwent intramolecular [4+2]-cycloaddition to yield lactam **189**. The latter

was converted into isophellibinine in a few steps. Recently, Sarpong developed a new methodology to furnish ATAs and applied it to the synthesis of cocculolidine (Scheme 42b).²⁶⁶ Propargylic alcohol **190** underwent cycloisomerization upon heating to form benz[*g*]indolizinone **191** which was then

a) Funk's synthesis of (\pm)-isophellibiline



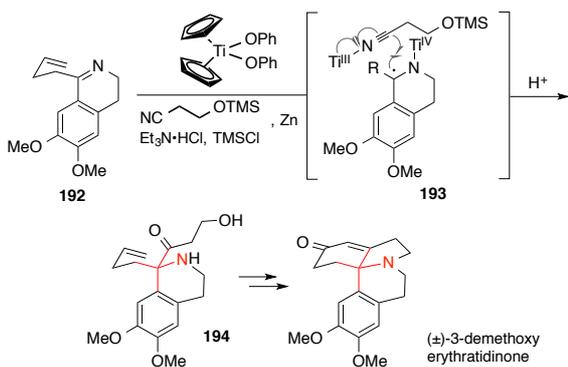
b) Sarpong's synthesis of (\pm)-cocculolidine



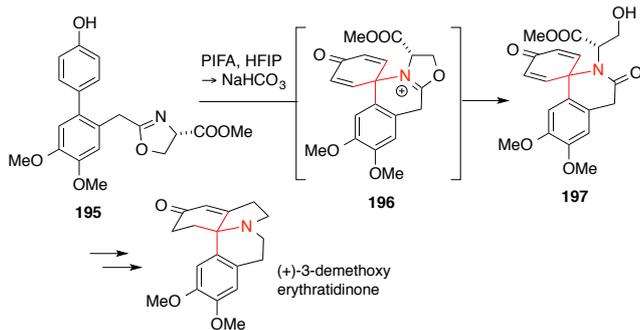
Scheme 42 Syntheses of *Erythrina* alkaloids by Funk (2012) and Sarpong (2013). HFIP = hexafluoroisopropanol, PIFA = bis(trifluoroacetoxy)iodobenzene, TMS = trimethylsilyl.

A short and elegant synthesis of 3-demethoxyerythratidinone was accomplished by Streuff in 2015 (Scheme 43a). He used a titanium(III)-catalyzed reductive Umpolung (**192** \rightarrow **194**) to assemble the 1,1-disubstituted tetrahydroisoquinoline core of the *Erythrina* alkaloids.²⁶⁷ In the same year, Ciufolini set the same ATA *via* an oxidative dearomatizative cyclization of an oxazoline **195**, yielding spiro-piperidine **197** presumably *via* intermediate **196** (Scheme 43b).^{268, 269}

a) Streuff's synthesis of (±)-3-demethoxyerythradinone



b) Ciufolini's synthesis of (+)-3-demethoxyerythradinone



Scheme 43 Syntheses of *Erythrina* alkaloids by Streuff (2015) and Ciufolini (2015). HFIP = hexafluoroisopropanol, PIFA = bis(trifluoroacetoxy)-iodobenzene, TMS = trimethylsilyl.

5

Other methods used to install the ATA in *Erythrina* alkaloids include 1,2-addition of organometallic reagents to sulfinimines or iminium ions,²⁷⁰⁻²⁷² Schmidt reaction,²⁷³ Diels-Alder reactions,²⁷⁴ Michael addition,²⁷⁵ *N*-acyliminium Pictet-Spengler reaction,²⁷⁶⁻²⁷⁸ Heck reaction.²⁷⁹

11 Indolizidine and Quinolizidine Alkaloids

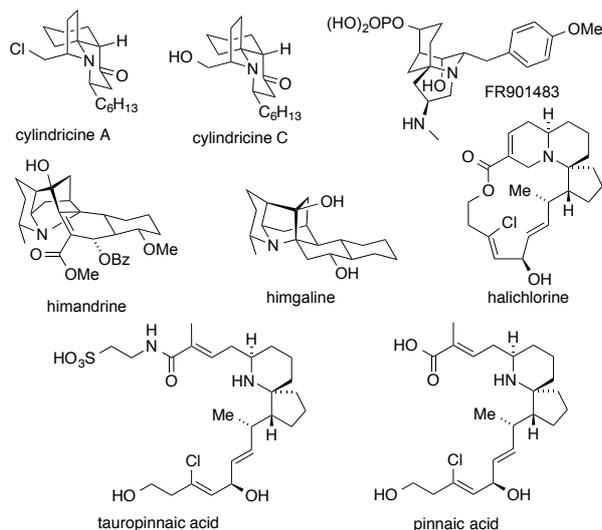


Fig. 10 Selection of quinolizidine alkaloids, including halichlorine and the closely related alkaloids tauropinnaic acid and pinnaic acid.

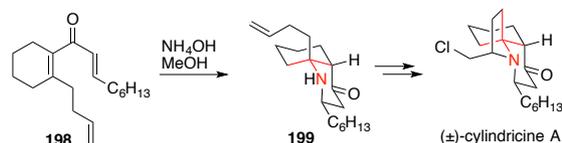
15 A range of alkaloids that belong to the indolizidine and

quinolizidine structural class feature an ATA in their carbon skeleton.²⁸⁰ They include natural products as diverse as the cylindricines,^{280, 281} FR901483,²⁸² himandrines, lepadiformines²⁸³ and halichlorine²⁸⁴ (Fig. 10).

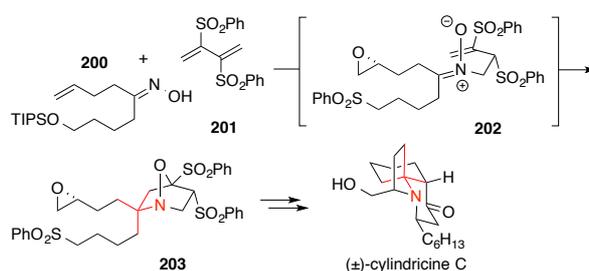
20 The first synthesis of cylindricine alkaloids (*viz.* cylindricine A, D and E) was accomplished by Snider utilizing a double Michael addition of ammonia to divinylketone **198** which gave the ATA **199**, a direct precursor of cylindricine A (Scheme 32a).²⁸⁵ Variations of this approach have been used several times in the

25 synthesis of cylindricines.²⁸⁶

a) Snider's synthesis of (±)-cylindricine A



b) Padwa's synthesis of (±)-cylindricine C



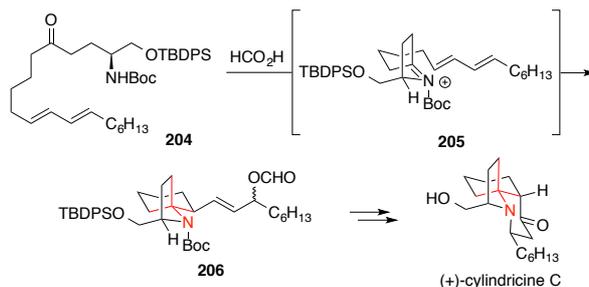
Scheme 44 Synthesis of cylindricines by Snider (1997) and Padwa (2003). Boc = *tert*-butyloxycarbonyl, TBDPS = *tert*-butyldiphenyl-silyl.

In 2003, Padwa published a synthesis featuring a Michael addition/dipolar cycloaddition cascade between butadiene **201** and oxime **200** to form **203** *via* intermediate **202** (Scheme 32b).²⁸⁷

The Hsung synthesis of enantiomerically pure cylindricine C relies on a nucleophilic attack of a diene on *N*-acyliminium ion **205** starting from ketone **204** (Scheme 45).^{288, 289} This vinylogous

35 aza-Prins approach was based on a synthesis published by Kibayashi in 2005.²⁹⁰

Hsung's synthesis of (+)-cylindricine C



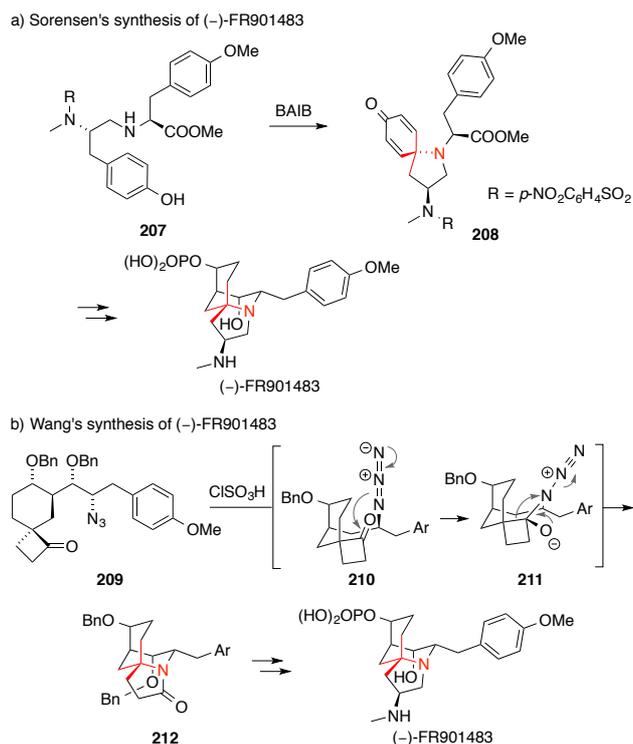
Scheme 45 Synthesis of cylindricine C by Hsung (2004). Boc = *tert*-butyloxycarbonyl, TBDPS = *tert*-butyldiphenyl-silyl.

40 Additional strategies to synthesize the ATA in cylindricine alkaloids involve mainly Michael additions,^{286, 291, 292} Grignard additions to an imine,²⁹³ a cycloaddition of an alkyne to a pyrrole derivative,²⁹⁴ and carboazidation.²⁹⁵

FR901483, an alkaloid isolated from the fermentation broth of a

45 *Cladobotryum* species with an intricate tricyclic structure,²⁸² proved to be an equally popular synthetic target. A biomimetic approach was employed by Sorensen in his enantioselective

synthesis (Scheme 46a).²⁹⁶



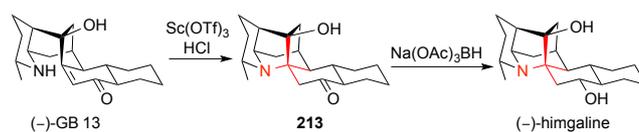
Scheme 46 Syntheses of FR901483 by Sorensen (2000) and Wang (2012). Ar = aryl, BAIB = (diacetoxyiodo)benzene, Bn = benzyl, TBDPS = *tert*-butyldiphenylsilyl.

The oxidative azaspiroannulation of amine **207** promoted by (diacetoxyiodo)benzene resulted in the formation of spiroamine **208**, an intermediate on the way to the natural product. The same year, Ciufolini set the ATA *via* a closely related oxidative spiroannulation (not shown, for an example of the methodology see Scheme 43b).²⁹⁷

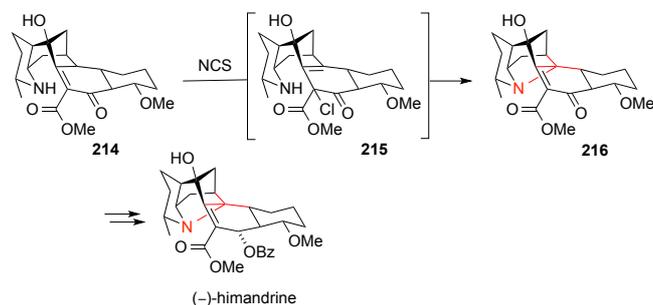
An alternative to this strategy was found by Wang.²⁹⁸ In this case, an Aubé-Schmidt reaction of azide **209** provided access to lactam **212**, featuring the ATA of FR901483 (**209**→**212**, Scheme 46b).²⁹⁷ Additional synthetic strategies to the ATA in FR901483 include a triple Michael addition,²⁹⁹ a one-pot bisalkylation,^{300, 301} an aza-Cope rearrangement/Mannich cyclization^{302, 303} and an oxidative dearomatization.²⁹⁷

The members of the galbulimima alkaloid family, such as himgaline and himandrine, also possess an ATA-containing quinolizidine core (Figure 10). Exploring a biosynthetic hypothesis, Chackalamannil used an intramolecular Michael addition to convert GB 13 to himgaline *via* ketone **213** (Scheme 47a).^{304, 305} In an interesting variation of this approach, Movassaghi converted enone **214** *via* its α -chloroester **215** to hexacyclic amine **216**, which could then be transformed into himandrine. (Scheme 47b).³⁰⁴

a) Chackalamannil's synthesis of (-)-himgaline



b) Movassaghi's synthesis of (-)-himandrine

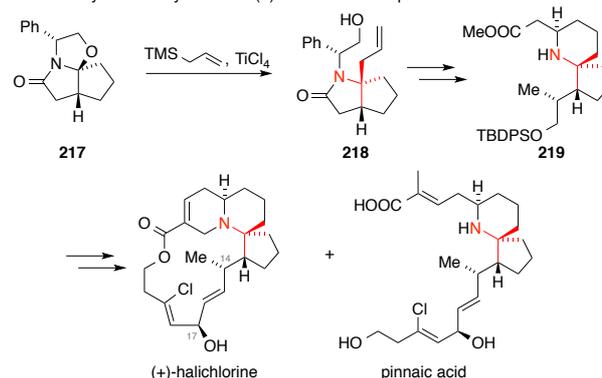


Scheme 47 Synthesis of galbulimima alkaloids by Chackalamannil (2009) and Movassaghi (2009). Ac = acetyl, Bz = benzoyl, NCS = *N*-chlorosuccinimide, OTf = trifluoromethanesulfonate.

In 1996, Uemura disclosed a small series of unusual marine alkaloids featuring ATAs. One of these compounds, halichlorine, was isolated from the marine sponge *Halichondria okadai* and was found to selectively inhibit the induction of vascular cell adhesion molecule-1 (VCAM-1).³⁰⁶ Pinnaic acid and tauropinnaic acid were recovered from bivalve *Pinna muricata*.^{307,308} All three molecules present a challenging 6-aza-spiro[4.5]decane core containing the ATA. The latter two lack a quinolizidine moiety, but are included in this chapter due to their close structural relationship.

Danishefsky and Trauner were the first to report the synthesis of (+)-halichlorine in 1999³⁰⁹ followed by a synthesis of pinnaic acid in 2001 (Scheme 48).^{310, 311} They used Meyers' lactam **217** as a chiral precursor, which was combined with allyltrimethylsilane in a Sakurai reaction to install the ATA in **218**. Intermediate **219** could be diversified to reach both halichlorine and pinnaic acid. These syntheses established the absolute configuration of halichlorine and confirmed the stereochemistry at C-14 and C-17 of pinnaic acid.

Danishefsky-Trauner synthesis of (+)-halichlorine and pinnaic acid

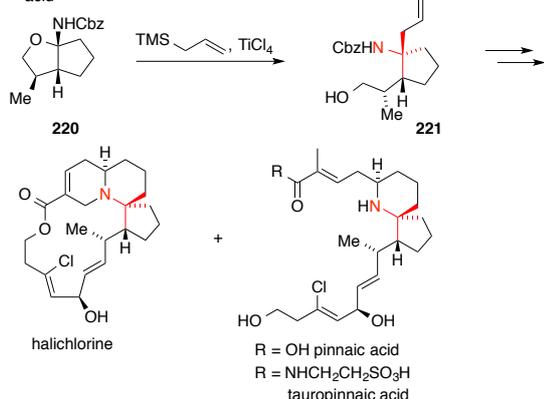


Scheme 48 Synthesis of halichlorine and pinnaic acid by Danishefsky (1999). TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

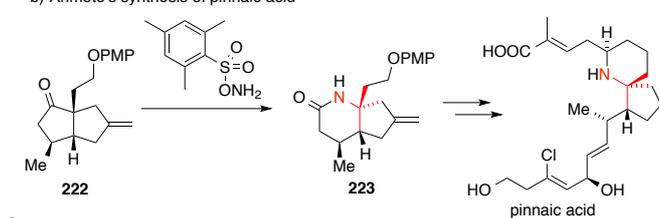
A related approach employing a different type of *N*-acyl iminium ion was used by Heathcock in 2004 for the synthesis of halichlorine, pinnaic acid and tauropinnaic acid (Scheme 49a).³¹²

Treatment of carbamate acetal **220** with allyl trimethylsilane and titanium tetrachloride furnished ATA-bearing carbamate **221** with a high degree of stereoselectivity. This key intermediate could be transformed into all three natural products.

a) Heathcock's synthesis of (±)-halichlorine, (±)-pinnaic acid and (±)-tauropinnaic acid



b) Arimoto's synthesis of pinnaic acid



Scheme 49 Syntheses of halichlorine, pinnaic acid and tauropinnaic acid by Heathcock (2004) and Arimoto (2007). Cbz = benzyloxycarbonyl, PMP = *p*-methoxyphenyl, TMS = trimethylsilyl.

In 2007, Arimoto reported his version of an asymmetric synthesis of pinnaic acid using a Beckmann rearrangement to install the ATA (Scheme 49b).³¹³ The enantiomerically pure bicyclic ketone **222** was treated with a bulky hydroxylamine reagent to afford the desired lactam **223**, which was then converted into the natural product.

12 Lactacystine and Salinosporamide

In 1991, Omura isolated the unusual natural product lactacystin from *Streptomyces sp.* OM-6519 and identified it as a proteasome inhibitor (Fig. 11).^{314, 315} A structurally related β -lactone, salinosporamide A, which shows similar biological activity, was subsequently isolated from a marine bacterium, *Salinispora tropica*.³¹⁶

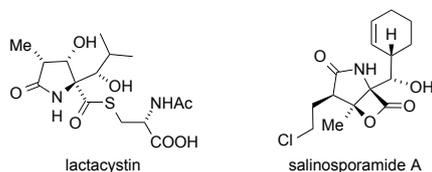


Fig. 11 Lactacystin and salinosporamide A.

Both compounds possess a densely functionalized γ -lactam core with three contiguous stereocenters, one of which is of the ATA type. Their significant biological activity has stimulated a large number of total syntheses,³¹⁷ and a variety of methods for the installation of the ATA motif have been applied.³¹⁸⁻³⁴⁵

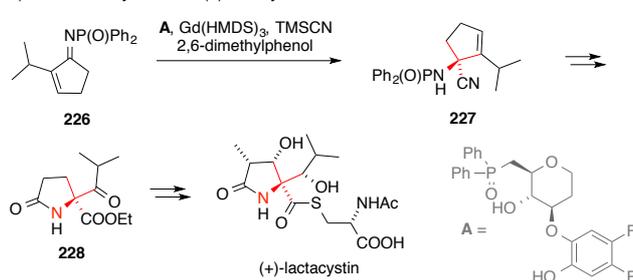
In pioneering work, Corey reported five total syntheses of lactacystin between 1992 and 1998.^{318-320, 326, 327} The Corey group showed that the ATA can be installed using an aldol addition of α -amino acid derivative **224** (via intermediate **225**, Scheme 50a). Other groups also contributed to this field in the 1990s.^{321-325, 328}

In most cases, the strategy applied for the installation of the ATA motif involved an alkylation or aldol reaction of an α -amino acid derivative.^{318-322, 324, 326-328} By contrast, Shibasaki introduced the ATA with a catalytic enantioselective Strecker reaction (Scheme 50b).^{317, 334} In this work, phosphinoylimine **226** was converted to aminonitrile **227** using a gadolinium catalyst and the chiral ligand **A**.

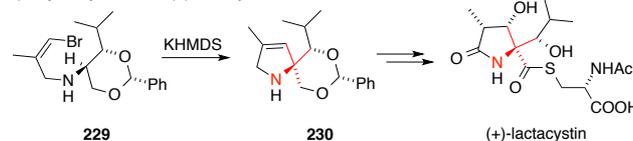
a) Corey's synthesis of (+)-lactacystin



b) Shibasaki's synthesis of (+)-lactacystin



c) Hayes' synthesis of (+)-lactacystin

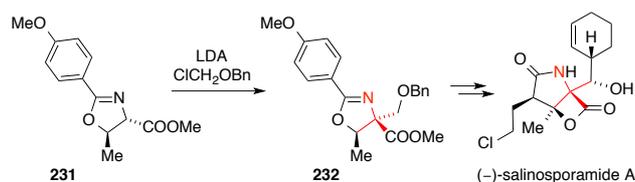


Scheme 50 Syntheses of lactacystin by Corey (1992), Shibasaki (2006) and Hayes (2008). Ac = acetyl, DBU = 1,8-diazabicyclo-undec-7-ene, HMDS = bis(trimethylsilyl)amine, PMB = paramethoxybenzyl, TMS = trimethylsilyl.

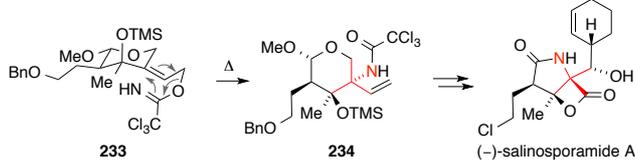
Another unusual approach was taken by Wardrop³⁴⁶ in his formal synthesis and Hayes³³⁸ in his total synthesis of lactacystin (Scheme 50c). Both groups explored an intramolecular carbene insertion into a C,H-bond to form the five-membered heterocyclic core. Hayes converted the enantiomerically pure vinyl bromide **229** to the corresponding vinylidene carbene, which underwent cyclization to afford **230** in high yield.

The first synthesis of salinosporamide was reported by Corey in 2004.^{330, 331} In this case, the ATA was installed by alkylation of threonine-derived oxazoline **231** with chloromethyl benzyl ether (via intermediate **232**, Scheme 51a).

a) Corey's synthesis of (-)-salinosporamide A

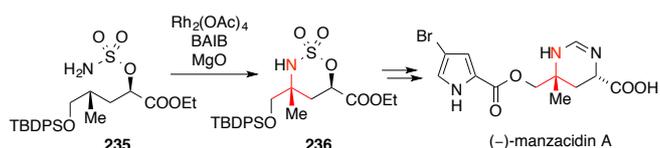


b) Sato's synthesis of (-)-salinosporamide A

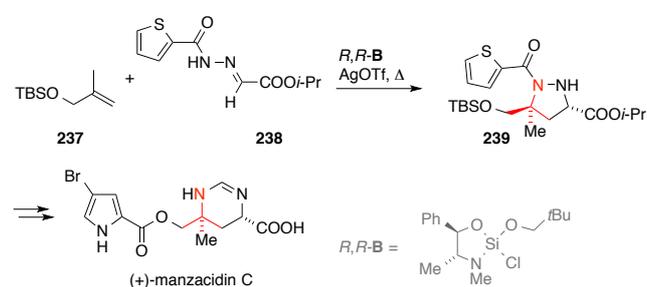


Scheme 51 Syntheses of salinosporamide A by Corey (2004) and Sato (2011). Bn = Benzyl, LDA = lithium diisopropylamide, TMS = trimethylsilyl.

a) Du Bois' synthesis of (-)-manzacidin A



b) Leighton's synthesis of (+)-manzacidin C



Scheme 52 Syntheses of manzacidins by DuBois (2002) and Leighton (2008). Ac = acetyl, BAIB = (diacetoxyiodo)benzene, OTf = trifluoromethanesulfonate, *i*-Pr = *iso*-propyl, TBDPS = *tert*-butyldiphenylsilyl.

5 A more recent synthesis of salinosporamide A published by Sato and Chid uses a stereoselective Overman rearrangement to install the ATA (Scheme 51b).³⁴³ Heating of the highly functionalized trichloroacetimidate **233** provided trichloroacetamide **234** as a key intermediate.

10 Other syntheses of salinosporamide and lactacystine used different strategies for the formation of the ATA, such as intramolecular aldol reactions,^{336, 337} intramolecular acylations,³³² acid catalyzed cyclizations of malonates,^{335, 339} indium-catalyzed Conia-ene reactions³⁴¹, C,H-alkynylation³⁴⁷ and enzymatic desymmetrizations of prochiral ATAs.³⁴⁰

13 Manzacidins

The manzacidins, a small family of bromopyrrole alkaloids, have attracted considerable attention from the synthetic community despite, or maybe because of their relatively simple structures.

20 Manzacidins A-C (Figure 12) were first isolated from the Okinawan sponge *Hymeniacidon* sp. by Kobayashi in 1991,³⁴⁸ followed by the isolation of manzacidin D from the 'living fossil' sponge *Astrosclera willeyana*³⁴⁹ and *N*-methylmanzacidin C from *Axinella brevistyla*.³⁵⁰

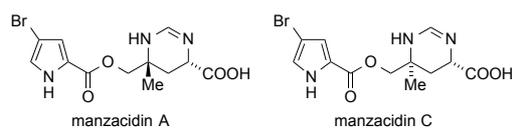
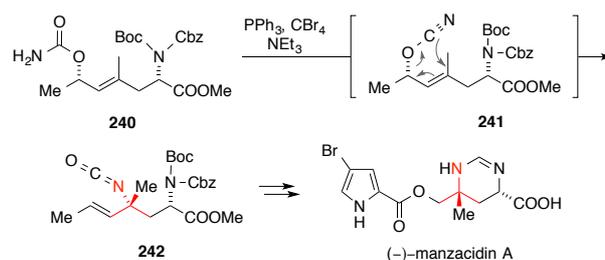


Fig. 12 manzacidin A and C.

In 2000, Ohfuné reported the synthesis of manzacidins A and C *via* a Strecker reaction and assigned the absolute configuration of these natural products (not shown).³⁵¹ In 2002, DuBois synthesized manzacidin C using an elegant oxidative C,H-insertion that involved sulfamate **235** (*via* intermediate **236**, Scheme 52a).³⁵² One year later, he used a similar strategy to set the ATA in tetrodotoxin (see chapter 14, scheme 54c).³⁵³

Ichikawa's synthesis of (-)-manzacidin A



Scheme 53 Synthesis of manzacidin A by Ichikawa (2012). Boc = *tert*-butyloxycarbonyl, Cbz = carboxybenzyl.

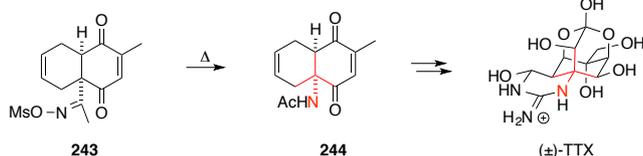
Several other synthetic approaches toward these molecules have
60 been reported. These strategies for the installation of the ATA moiety involve diastereoselective nitrene insertion,³⁵² 1,3-dipolar cycloaddition,^{356, 357} Hofmann rearrangement,³⁵⁸ diastereoselective iodocyclization,^{359, 360} Grignard addition to an imine³⁶¹ and a variety of other methods.³⁶²⁻³⁶⁶ Indeed,
65 Manzacidins remain targets of great interest for synthetic chemists. In 2015, Inoue published a synthesis of manzacidin A

using a radical-based decarbonylative coupling (not shown).³⁶⁷ Recently the relative stereochemistry of manzacidin B, which possesses an additional stereocenter, was revised using total synthesis.^{362, 363, 365}

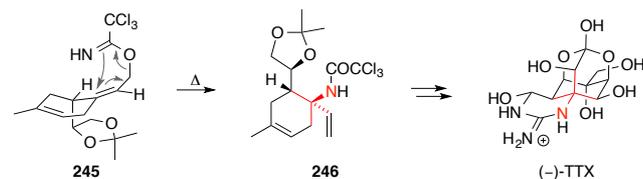
14 Tetrodotoxin

Tetrodotoxin (TTX) was first isolated from the *Fugu* puffer fish in 1909.^{368, 369} Its structure was independently reported by Hirata-Goto,³⁷⁰ Tsuda³⁷¹ and Woodward³⁷² in the 1960s. Their assignment was confirmed by X-ray crystallography, which also established the absolute configuration of the molecule.^{373, 374} TTX features a highly functionalized heteroadamantane framework that contains an *ortho*-acid and is fused to a cyclic guanidinium moiety *via* an ATA motif. The molecule is an extremely powerful and selective blocker of voltage-gated sodium channels and is widely used as a research tool in neuroscience.³⁷⁵⁻³⁷⁹ Due to its intriguing structure and bioactivity, attempts to synthesize TTX have been made from an early stage and activity in this field has recently increased significantly.³⁸⁰

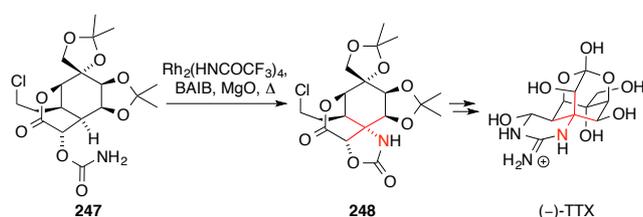
a) Kishi's synthesis of (±)-TTX



b) Isobe's synthesis of (-)-TTX



c) DuBois' synthesis of (-)-TTX



Scheme 54 Syntheses of tetrodotoxin (TTX) by Kishi (1972), Isobe (2003) and DuBois (2003). Ac = acetyl, BAIB = (diacetoxyiodo)benzene, Ms = methanesulfonyl, Ph = phenyl.

The first total synthesis of TTX was accomplished by Kishi in 1972 (Scheme 54a).³⁸¹⁻³⁸⁴ In his approach, the ATA was formed using a Beckmann rearrangement of oxime **243**, which was synthesized using a regioselective Diels-Alder reaction. The resulting key intermediate **244** was converted into TTX using a series of stereoselective redox transformations, ring cleavage and the installation of the cyclic guanidine with newly developed methodology. Although the Kishi synthesis was not enantioselective, it still stands as one of the strategically most elegant approaches to a natural product featuring an ATA motif. After a 30 year lull, Isobe published the first enantioselective synthesis of TTX wherein the ATA motif was installed with a

stereoselective Overman rearrangement (Scheme 54b).³⁸⁵⁻³⁸⁷ To this end, an allylic alcohol was converted to trichloroacetimidate **245**, which underwent rearrangement to yield trichloroacetamide **246**. Compound **246** bears all the carbon atoms of TTX and could

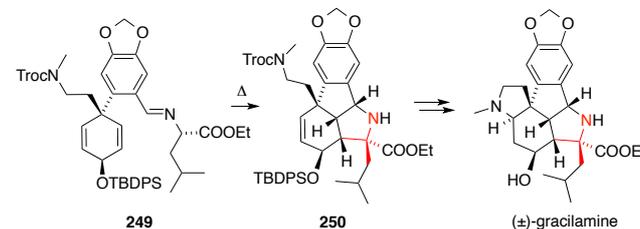
be converted into the natural product in a series of steps. Shortly thereafter, DuBois developed an enantioselective approach to TTX that involved his signature nitrene insertion chemistry (Scheme 54c).³⁵³ Exposure of the key intermediate, carbamate **247**, to a hypervalent iodine reagent and magnesium oxide in the presence of a rhodium catalyst led to the formation of oxazolidinone **248**, which bears the ATA motif. Insertion into other possible C,H-bonds was largely avoided through careful engineering of the substrate.

15 Miscellaneous Alkaloids

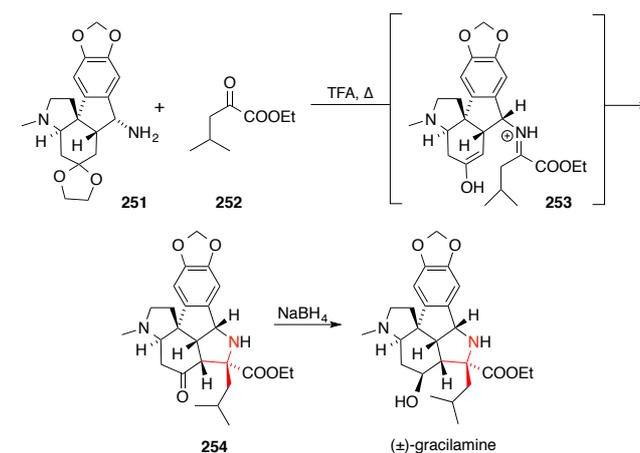
ATA's occur in many other alkaloids that cannot easily be categorized along the biosynthetic and structural lines shown above. An example is gracilamine, which was isolated in 2005 by Ünver and Kaya from the Amaryllidaceae species *Galanthus gracilis*.³⁸⁸ In 2012, the first synthesis of gracilamine was disclosed by Ma (Scheme 55a).³⁸⁹ It relies on a potentially biomimetic, stereoselective and intramolecular [3+2] cycloaddition, transforming **249** into the highly functionalized pyrrolidine **250**.

In a recent synthesis, Gao set the ATA *via* an intramolecular Mannich annulation (Scheme 55b).³⁹⁰ First, α -ketoester **252** was condensed with amine **251**. The resulting iminium ion **253** then underwent a diastereoselective Mannich reaction to furnish the hexacyclic scaffold **254** of gracilamine.

a) Ma's synthesis of (±)-gracilamine



b) Gao's synthesis of (±)-gracilamine



Scheme 55 Syntheses of gracilamine by Ma (2012) and Gao (2014). TBDPS = *tert*-butyldiphenylsilyl, Troc = 2,2,2-trichloroethoxycarbonyl, TFA = trifluoroacetic acid.

The amathaspiramides A-F are a family of marine alkaloids isolated from the bryozoan *Amathia wilsoni* in 1999 (Fig.13).³⁹¹ They feature an unusual spirocyclic core consisting of a pyrrolidine fused to a pyrrolidinone moiety.³⁹¹

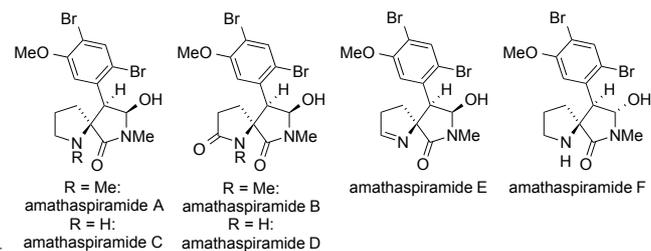
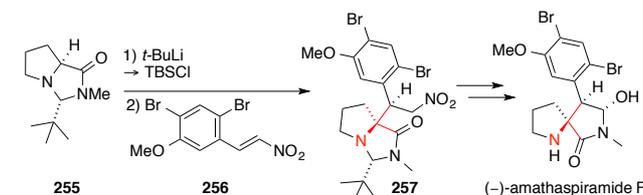


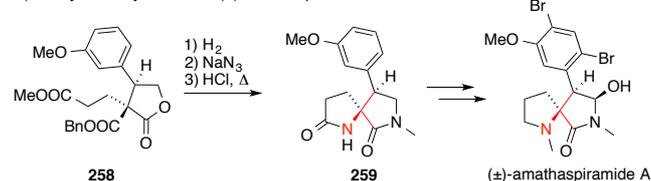
Fig. 13 The amathaspiramides A-F.

The first total synthesis of a member of this family, *viz.* amathaspiramide F, was disclosed by Trauner in 2002 (Scheme 41a).³⁹² In this work, the proline-derived *N,N*-acetal **255** was converted to the corresponding silyl ketene acetal, which underwent a diastereoselective Michael addition to the nitro olefin **256**, establishing the ATA of **257**. Subsequently, Ohfuné published his approach to amathaspiramide F which utilizes an enolate Claisen rearrangement for the same purpose (not shown).³⁹³

a) Trauner's synthesis of (-)-amathaspiramide F

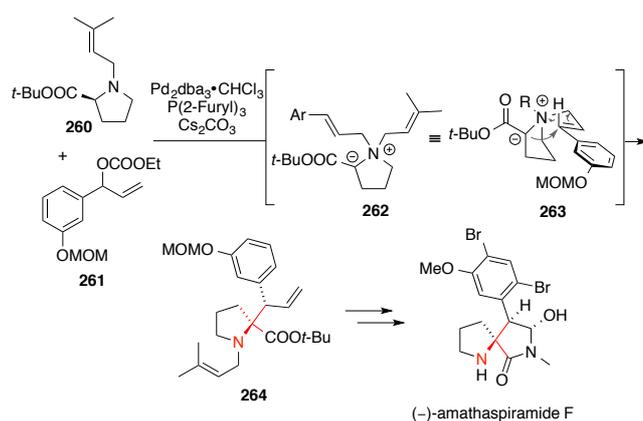


b) Fukuyama's syntheses of (±)-amathaspiramides

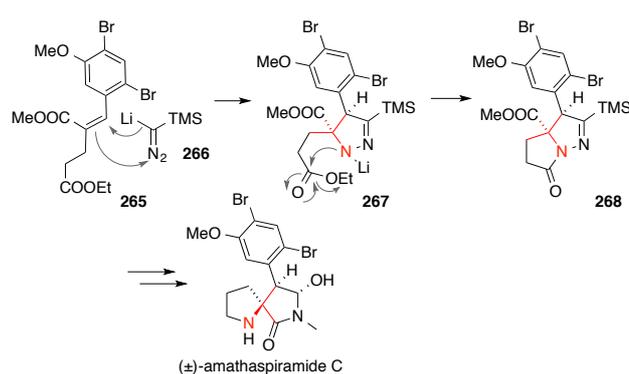


Scheme 56 Syntheses of amathaspiramides by Trauner (2002) and Fukuyama (2012). Bn = benzyl, *t*-Bu = *tert*-butyl, TBS = *tert*-butyldimethylsilyl.

a) Tambar's synthesis of (-)-amathaspiramide F



b) Lee's synthesis of (±)-amathaspiramide C



Scheme 57 Syntheses of amathaspiramides by Tambar (2013) and Lee (2015). Bn = benzyl, *t*-Bu = *tert*-butyl, dba = dibenzylideneacetone, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

More recently, Lee used a formal [3+2] cycloaddition between lithium(trimethylsilyl)diazomethane **266** and α,β -unsaturated ester **265** to set the ATA in amathaspiramide C (*via* intermediate **267**, Scheme 41d).³⁹⁶ The N,N-bond in pyrazoline **268** was cleaved by treatment with *p*-TsoH and additional transformations led to the total synthesis of amathaspiramide C and the formal synthesis of all the other amathaspiramides.

16 Conclusions

Herein, we have provided a survey of syntheses that feature the installation of an α -tertiary amine (ATA) as a common thread. This structural motif is widespread amongst alkaloids and has physicochemical consequences, such as increased lipophilicity and chromatographic mobility that distinguishes its bearers from other basic amines. Since ATAs also occur in drug candidates and building blocks for functional materials, our review is intended to provide a useful reference for medicinal chemists and colleagues active in the material sciences. It may also provide a baseline for the development of additional and hopefully more efficient methods for the synthesis of target molecules containing α -tertiary amines.

17 Acknowledgements

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