Synthetic approaches towards alkaloids bearing \(\alpha\)-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 \(\alpha\)-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.

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. 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. 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. In addition, they have provided inspiration for countless synthetic drugs that borrow structural motifs from their natural counterparts.

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The \(\alpha\)-tertiary amine (ATA) stands out among the structural features frequently found in alkaloids. For the purposes of
this review and in keeping with the literature, we define an ATA as a nitrogen atom bound to a sp³-hybridized carbon that bears three additional carbon–carbon bonds. The nitrogen itself can be sp³-hybridized as part of a primary, secondary and tertiary amine. Broadening our definition, it can also be sp²- 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.

Fig. 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 histrionotoxin 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 ste- phacidin B contains no fewer than four ATAs. Notably, the ν-carbons are stereogenic in the majority of these compounds.

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

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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 \( \alpha \)-tertiary amines.

2 Methods used for the installation of \( \alpha \)-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.

2.1 A C,C-bond is formed in the step that generates the ATA

- **The \( \alpha \)-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.
- **The \( \alpha \)-carbon is nucleophilic.** In an Umpolung of the above situation, the \( \alpha \)-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.
- **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.
- **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.

2.2 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). They include the Curtius, Schmidt, Hofmann, Beckmann and Stieglitz rearrangements. Often, these reactions can be classified as [1,2] sigmatropic rearrangements.
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 a nucleophilic nitrogen occur in the aza-Prins reaction and the Ritter reaction. Oxidative dearymatizations have also been used in a few cases to establish ATAs.

- 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.  

Many more methods have emerged in recent years that can be used to create ATAs, such as reactions proceeding via C,H-activation and hydroaminations. 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 euphococcine and adaline, feature an ATA in the bridgehead position of a bicyclic framework (Fig. 2). These simple natural products are excreted by lady beetles (coccinellids) when threatened.  

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

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

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

**Scheme 7**  C,N-bond formation involving pericyclic reactions.
In 1959, Alder synthesized N-methyl-euphococcinine using a protocol analogous to the famous tropinone syntheses of Robinson\textsuperscript{13,14} and Schöpf\textsuperscript{45} (Scheme 8a).\textsuperscript{20,21} Dehydroprypane 1 was converted into ketoaldehyde 2, which was then transformed into N-methyl-euphococcinine in a one-pot process [via iminium-intermediate 3].\textsuperscript{17–19} A similar strategy was later adopted to synthesize the structurally related alkaloid adaline.\textsuperscript{31}

Throughout the years, this biomimetic Mannich strategy was adopted in other syntheses of euphococcinine and adaline.\textsuperscript{21–23} Alternative approaches involved a 1,3-dipolar cycloaddition,\textsuperscript{24} addition to an N-acyliminium ion,\textsuperscript{25} Michael addition,\textsuperscript{26,27} and allylic rearrangement of a cytanate to an isocyanate.\textsuperscript{28,29}

In 2010, Davis published a biomimetic synthesis of (−)-euphococcinine and (−)-adaline in enantiopure form (Scheme 8b).\textsuperscript{20} The key steps of these syntheses involved the stereoselective formation of piperideine 6 and 7 from the enantiomerically pure N-sulfinyl aminoketones 4 and 5, respectively.\textsuperscript{40} An ensuing intramolecular Mannich reaction afforded the azabicyclononane natural products.

4 Histrionicotoxins

In 1971, Daly isolated six different alkaloids, termed histrionicotoxins (HTXs), from skin extracts of the Colombian poison arrow frog \textit{Dendrobates histrionicus} (Fig. 3).\textsuperscript{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 nictinic acetylcholine receptors,\textsuperscript{14–38} which, together with their attractive structures, prompted significant attention from the synthetic community.\textsuperscript{29} 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.

The first total synthesis of histrionicotoxin alkaloids was reported by Kishi in 1975 (Scheme 9a).\textsuperscript{40–42} His synthesis of octahydrohistrionicotinocin (oHTX) utilized an intramolecular acid-catalyzedaza-Michael addition to set the ATA. Amide 8 was converted to a 2 : 1 mixture of epimeric spiroketalactams 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 perhydrohistrionicotininocin (pHTX), a synthetic HTX derivative (Scheme 9b).\textsuperscript{44} 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.\textsuperscript{40–48}

Stork reported a synthesis of HTX 283A using a Hofmann rearrangement to set the ATA (Scheme 10a).\textsuperscript{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).\textsuperscript{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 particularly short and efficient synthesis of racemic HTX 283A was reported in 2006 by Stockman and Fuchs (Scheme 11). 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 nitrone 18 via 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.

Additional strategies to set the ATA in the histrionicotoxins involved Michael reactions, Tsuji–Trost amination, iodoetherification, oxidative dearomatizations, Henry reactions, diastereoselective aziridination, 1,2-carbon migration of hydroximines, [2,3] sigmatropic rearrangements, [3,3] sigmatropic rearrangements (Kazmaier–Claisen rearrangement) and [2+2] cycloadditions.

5 Lycopodium alkaloids

The genus Lycopodium comprises more than 200 species of moss-like plants that have been used in traditional Chinese medicine for centuries. They have yielded a variety of ATA-containing alkaloids, some of which are featured in Fig. 4. Lycopodine, the first member of the family described in the literature, has proven to be a particularly attractive target for chemical synthesis. In 1968, only seven years after its structural elucidation, Stork and Ayer simultaneously published the first syntheses of this natural product. Ayer established the ATA using an intermolecular addition of a racemic Grignard reagent to tricyclic, C₄-symmetric iminium ion 22 to obtain 23 (Scheme 12a).

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). Wiesner published a synthesis of 12-epi-lycopodine and annotinine using an innovative photochemical strategy (Scheme 12c). This work involved the conversion of vinyllogous 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). 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.\textsuperscript{82} Using a similar sequence, lycodine and lycodoline were prepared as well.\textsuperscript{82}

Variations of Heathcock’s strategy have been used in other synthetic approaches toward \textit{Lycopodium} alkaloids, e.g. in syntheses of clavolonine by Evans (2005)\textsuperscript{84} and Fujioka (2011).\textsuperscript{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.\textsuperscript{82} Recently, this problem was solved in an elegant way by Carter (Scheme 13b).\textsuperscript{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).\textsuperscript{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).\textsuperscript{88} To effect the reaction, \textit{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.\textsuperscript{89–91}

Members of the lycodine class of natural products feature an ATA and a pyridine or pyridone moiety. The parent compound, lycodine,\textsuperscript{92} was first isolated from \textit{L. annotinum} in 1958.\textsuperscript{93} Apart from the ATA, one of the most common motifs in \textit{Lycopodium} alkaloids is the \textit{N}-acetylumbellidine moiety. Schumann and Sarpong have published a number of syntheses of these structures (Scheme 15).\textsuperscript{94–96}

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\textbf{Scheme 12}  Representative lycopodine syntheses by Ayer (1968), Stork (1968) and Wiesner (1967). Bn = benzyl.


\textbf{Scheme 14}  Lycopodine syntheses by Kraus (1985) and Grieco (1998). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

from the Heathcock synthesis mentioned above, several additional syntheses of lycodine have been achieved to date. Schumann used a classical Mannich strategy to access racemic lycodine, α-obscurine and N-acetyl α-bellidine (Scheme 15). The mechanism of the key double Mannich reaction cascade was further explored almost 30 years later by Sarpong. He used the same cascade as an opening sequence in an asymmetric synthesis of enantiomerically pure (+)-complanadine A, a lyco-
dine dimer, which was shown to enhance expression of nerve growth factor in human cells. It was found that cyclic enam-
ide opens to ketone or enol under acidic conditions, which adds to the unsaturated bicyclic imine. Protonation of the resulting enamine triggers a second, intramolecular Mannich reaction to a fford tricycle via the iminium ion. Finally, an intramolecular enamide formation furnished tetra-
cyclic des-N-methyl-α-obscurine, containing the entire lycodine framework.

In an unusual approach, Tsukano and Hirama applied an intramolecular palladium-mediated Heck reaction between enecarbamate and pyridine triflate to form the ATA, which yielded lycodine precursor (Scheme 16a). Recently, another very short synthesis of (-)-lycodine as well as the closely related (+)-flabellidine was accomplished by Takayama (Scheme 16b). Starting from a linear precursor, he was able to assemble the whole tetracyclic skeleton of both alkaloids in a cascade reaction involving a double condensation, a conjugate addition followed by a Mannich reaction. In addition, Shair published an approach towards several members of the 7-membered-ring-containing Lycopodium alkaloids using a trans-annular Mannich reaction (not shown).

One of the rare cases of a SN2 reaction in ATA formation can be found in Lei’s recent synthesis of (-)-8-deoxyserratinine (Scheme 17). Tertiary alcohol was converted into chloride, which was attacked intramolecularly by the free secondary amine. Other approaches towards 8-deoxyserratinine and related alkaloids include a Schmidt rearrangement and an intramolecular epoxide opening.

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 $\text{52}_{2}$.$^{109}-116$

The first synthesis of huperzine A was published by Kozi-kowski in 1989 (Scheme 18).$^{109}$ First, he completed the core $\text{52}$ wherein the primary amine is replaced by a methyl ester. After saponification, Curtius rearrangement ($\text{52} \rightarrow \text{53}$) 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 $\text{53}$, 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.$^{119}$

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 ($\text{54} \rightarrow \text{55}$) (Scheme 19a).$^{120}$ Whereas the White group performed an elegant tandem intramolecular aza-Prins cyclization/cyclobutane fragmentation ($\text{56} \rightarrow \text{53}$) to set the ATA in $\text{53}$ (Scheme 19b).$^{121}$

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 ($\text{61}$) (Scheme 20a) followed by the syntheses of the reassigned structures of nankakurine A and B in 2010 (Scheme 20b).$^{124,125}$

In the case of 5-epi-nankakurine ($\text{61}$), an aza-Prins reaction ($\text{59} \rightarrow \text{60}$) was used, which allowed for the direct formation of both piperidine rings in $\text{61}$ in one step starting from bicyclic $\text{59}$. 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 $\text{63}$, formed in situ via condensation of $\text{62}$ with formaldehyde. This reaction provided access to tetracyclic pyrazolidine $\text{64}$, which, after $\text{SmI}_{2}$ 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 $\text{65}$ to form $\text{66}$, which then cyclized to the corresponding enamine $\text{67}$ upon treatment with acid. The formation of the second ATA center through an intramolecular Mannich addition (via iminium ion $\text{68}$) furnished ketone $\text{69}$, which was eventually converted to the natural product.

A second synthesis of porantherine, published by Stevens in 1987, involved the addition of two alkyllithium 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 less significance compared to the related morphine alkaloids, their beautiful structures stimulated numerous synthetic studies and several total syntheses have been reported to date.\textsuperscript{132–146}

The first successful syntheses of (±)-cepharamine,\textsuperscript{132,135} (±)-hasubanonine,\textsuperscript{134,137} (±)-aknadilactam\textsuperscript{134} and (±)-metaphanine\textsuperscript{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 \rightarrow 74).

Almost 30 years later, Schultz prepared (+)-cepharamine using a Hofmann-type rearrangement to introduce the ATA (not shown).\textsuperscript{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 isohasubanonine through a SN\textsubscript{2}0-reaction.\textsuperscript{140,147} Subsequently, this strategy was adapted to access (−)-acutumine (Scheme 22b).

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).\textsuperscript{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).\textsuperscript{143} Methylation of iminoquinone Diels–Alder adduct 80 (80 \rightarrow 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.\textsuperscript{143,145,146}

### 7 Stemona alkaloids

Plants belonging to the family \textit{Stemonaceae}, which are mostly found in Southeast Asia, have been used for centuries as insecticides and for the treatment of respiratory diseases.\textsuperscript{148–150} Phytochemical investigations led to the isolation of a variety of natural products known as \textit{Stemona} alkaloids (Fig. 6).\textsuperscript{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.\textsuperscript{151,152} The strategies employed range from classical additions to imines,\textsuperscript{153,154} to radical cyclization cascades,\textsuperscript{155,156} radical allylations,\textsuperscript{157} semipinacol-Schmidt cascades,\textsuperscript{158,159} Schmidt reactions,\textsuperscript{160} aza-Cope–Mannich reactions,\textsuperscript{161} cyclopropane-Cope rearrangements\textsuperscript{162} and catalytic 1,3-dipolar cycloadditions.\textsuperscript{163}

The first synthesis of a Stemona alkaloid, viz. isostemofoline, was published by Kende in 1999 and employed a highly unusual and elegant approach.\textsuperscript{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).

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 (Scheme 24b).\textsuperscript{155,156} Treatment of the achiral precursor 88 with tributyltin hydride and 1,1\textsubscript{0}-azo-bis(cyclohexanecarbonitrile) (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 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).\textsuperscript{159} Based on his systematic studies on the reactivity of \(\alpha\)-hydroxy epoxides such as 92,\textsuperscript{164} he developed a powerful cascade that combines a semipinacol rearrangement with an Aubé–Schmidt reaction (92 \rightleftharpoons 94). The resulting amide 94 was obtained as a 5 : 1 mixture of diastereomers, reflecting the diastereomeric mixture of propargyl azides employed as substrates. Using this strategy and variations thereof, Zhang was able to synthesize stemonamide and three additional Stemona alkaloids, viz. maistemo-nine, stemonamine, and isomaistemonine.\textsuperscript{158–160}

The only synthesis of asparagamine A, an unsaturated derivative of stemonamide, was achieved by Overman in 2003.\textsuperscript{163} He installed the ATA using his signature aza-Cope–Mannich cascade (Scheme 25a). The synthesis of a precursor molecule

\textbf{Scheme 24} Syntheses of Stemona alkaloids by Kende (1999), Ishibashi (2008) and Zhang (2011). ABCN = 1,1\textsubscript{0}-azobis(cyclohexanecarbonitrile), Boc = tert-butyloxycarbonyl, MOM = methoxymethyl, TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl.

\textbf{Scheme 25} Syntheses of Stemona alkaloids by Overman (2003) and Huang (2015). ABCN = 1,1\textsubscript{0}-azobis(cyclohexanecarbonitrile), Bn = benzyl, TBDPS = tert-butylidiphenylsilyl, TIPS = trisopropylsilyl.
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 temperatures generated iminium ion 96, which underwent theaza-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 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 known ones, contain ATAs (Fig. 7).

Kopsine, the first member of the so-called Kopsia alkaloids, was isolated as early as 1890,160 but it took several decades before its complex structure, and those of its congeners, could be elucidated.166–172 All members of this family possess an ATA 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 reactions.181–185

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 dienophile178,179 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.185

In a recent example for an alternative approach by Boger, a powerful radical transannular cyclization was applied to the ATA of kopsinine (Scheme 26c).178 Upon treatment of xanthate 106 with SmI2, 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 indole 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 alklylation 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 didecide
Two other racemic syntheses of lundurine A and B have been reported by Nishida.\textsuperscript{191–193} He employed a Curtius rearrangement and a 1,2-addition to an iminium ion for lundurine B\textsuperscript{193} and a Tsuji–Trost amination and an indoxyl bisalkylation for the synthesis of lundurine A (not shown).\textsuperscript{191,192}

In 2001, Pearson employed a Smalley cyclization of aryl ketone azide\textsuperscript{113} to furnish the spiroindoxyl\textsuperscript{114} (Scheme 27b).\textsuperscript{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 (\textsuperscript{115} \rightarrow \textsuperscript{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\textsuperscript{117}, which underwent base-mediated isomerization to \textsuperscript{118} followed by intramolecular Diels–Alder reaction to afford diazabicyclo[2.2.2]octane\textsuperscript{119} (Scheme 28).\textsuperscript{196} This remarkable reaction sets both ATAs in a single step. Later that year, stephacidin B was accessed via avrainvillamide using the same strategy.\textsuperscript{197}

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

A second synthesis of avrainvillamide and stephacidin B was accomplished concurrently by Myers (Scheme 30).\textsuperscript{201} In this case, the first ATA was installed by a Strecker-type addition of TMS cyanide to enamine\textsuperscript{124} to form the N-Boc amino nitrile\textsuperscript{125}. The second ATA was then set by a very unusual radical transfer cyclization. Abstraction of a hydrogen atom in \textsuperscript{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.\textsuperscript{127}

Several members of a related family of prenylated spirooxindole alkaloids, namely cyclopiamine, citrinadin A and citrinadin B, also feature an asymmetric ATA.\textsuperscript{202–204} In 2013, Martin and Wood reported the first syntheses of citrinadin A and B.\textsuperscript{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). Wood's approach employed an azide-mediated opening of epoxide 130 to establish the ATA in 131 (Scheme 31b). Both reactions are rare examples where an ATA has been set through a SN2 reaction.

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). 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.

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

Gelsemoxonine is an indole alkaloid with an ATA that is part of a 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. In 2011, Fukuyama accomplished a total synthesis of gelsemoxonine that employed an intramolecular epoxide opening of 134 to install the ATA (Scheme 33a). Recently, Carreira published an elegant entry to gelsemoxonine, setting the ATA 136 via a diastereoselective propynyllithium addition to isoxazoline 135 (Scheme 33b). 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 Hapalosiphon welwitschii and Westiella intracta. 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.

Being a considerable challenge for total synthesis, the welwitindolinones have become popular targets. The first total synthesis of N-methylwelwitindolinone D isonitrile was accomplished by Rawal in 2011 using Kim’s oxime rearrangement to install the isothiocyanide (137 → 138, Scheme 34a). Desulfuration of 138 then gave the naturally occurring isonitrile. Martin completed a synthesis that intercepts Rawal’s synthesis in 2012.

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

Both Rawal and Garg were able to subsequently synthesize several members of the welwitindolinone family by varying their initial strategies. In addition, Hatakeyama recently accomplished another synthesis of (−)-N-methylwelwitindolinone C isothiocyanate using an endgame similar to Rawal’s.

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. For the synthesis of psychotrimine, a coupling of indole 147 with 2-idoaniline (146) was developed to yield 148, which then underwent further cyclization to give 149 (Scheme 35b). This method was also used for the syntheses of psychotetramine, kapakahine B and kapakahine F.

Another interesting way to install an ATA in a structurally complex indole alkaloid was published by Danishefsky (Scheme 36). 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...
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).\(^{239}\)

The first synthesis of cephalotaxine itself was reported by Weinreb in 1972 (Scheme 37a).\(^{240}\) 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.

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.

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**Scheme 36** Danishefsky’s synthesis of phalarine (2010). Bn = benzyl, CSA = camphorsulfonic acid.

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

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Fig. 8 Representative cephalotaxines.
A Tsuji–Trost allylation on secondary amine established the ATA and afforded 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.

A [2,3] sigmatropic rearrangement was utilized by Li to convert quaternary ammonium ion to the α-tertiary aminoester (Scheme 38b).

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

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

In 2006, Mariano used a photochemical cyclization of a bicyclic pyridinium ion to afford aziridine, which was then transformed into the natural product (Scheme 40a).

Hayes’ synthetic route towards (-)-cephalotaxine made use of an alkylidene carbene insertion starting from ketone to furnish spiro[4.4]azanonane, which corresponds to the skeleton of cephalotaxine (Scheme 40b).

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

A host of other methods have been used for the installation of the ATA in cephalotaxines. These include alkylation, Claisen rearrangement, Michael addition, Schmidt
reaction,\textsuperscript{257} addition to an imine,\textsuperscript{258} transannular cyclization\textsuperscript{259} and oxidative rearrangement.\textsuperscript{251}

10 Erythrina alkaloids

Erythrina alkaloids were discovered at the end of the 19\textsuperscript{th} century, when extracts of Erythrina trees were found to possess curare-like neuromuscular activities.\textsuperscript{260} Due to their biological activities and interesting structures (Fig. 9), several total syntheses of these natural products have been carried out and many creative ways to install ATAs have been developed in this context.\textsuperscript{261}

In 1990, the group of Ishibashi published the synthesis of (±)-3-demethoxyerythratidinone using an intramolecular Pummerer-like rearrangement of the enamine 180, setting the stage for a Pictet–Spengler-type reaction (181 → 182) to furnish the ATA (Scheme 41a).\textsuperscript{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).\textsuperscript{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 vinylcyclobutane, affording the scaffold of erysotrine.\textsuperscript{264}

Funk accomplished the synthesis of isophellibiline via an approach that relies on pericyclic reactions (Scheme 42a).\textsuperscript{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 isophellibilin in a few steps.

Recently, Sarpong developed a new methodology to furnish ATAs and applied it to the synthesis of cocculidine (Scheme 42b).\textsuperscript{266} Propargylic alcohol 190 underwent cycloisomerization upon heating to form benz[a]indolizinone 191 which was then transformed to cocculidine in two additional steps.

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 → 194) to assemble the 1,1-disubstituted tetrahydroisoquinoline core of the Erythrina alkaloids.\textsuperscript{267} In the same year, Ciufolini set the same ATA via an oxidative dearomatizing cyclization of an oxazoline 195, yielding spiroperipederine 197 presumably via intermediate 196 (Scheme 43b).\textsuperscript{268,269}

Fig. 9 Representative Erythrina alkaloids.
Other methods used to install the ATA in *Erythrina* alkaloids include 1,2-addition of organometallic reagents to sulfinimines or iminium ions, Schmidt reaction, Diels–Alder reactions, Michael addition, N-acyliminium Pictet–Spengler reaction and Heck reaction.

### 11 Indolizidine and quinolizidine alkaloids

A range of alkaloids that belong to the indolizidine and quinolizidine structural class feature an ATA in their carbon skeleton. They include natural products as diverse as the cylindricines, FR901483, himadrines, lepadiformines and halichlorine (Fig. 10).

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 which gave the ATA 199, a direct precursor of cylindricine A (Scheme 44a). Variations of this approach have been used several times in the synthesis of cylindricines.

In 2003, Padwa published a synthesis featuring a Michael addition/dipolar cycloaddition cascade between butadiene and oxime to form via intermediate 202 (Scheme 44b). The Hsung synthesis of enantiomerically pure cylindricine C relies on a nucleophilic attack of a diene on *N*-acyliminium ion starting from ketone 204 (Scheme 45).

This vinylogous aza-Prins approach was based on a synthesis published by Kibayashi in 2005.

Additional strategies to synthesize the ATA in cylindricine alkaloids involve mainly Michael additions, Grignard additions to an imine, a cycloaddition of an alkyne to a pyrrole derivative, and carboazidation.

FR901483, an alkaloid isolated from the fermentation broth of a *Cladobotryum* species with an intricate tricyclic structure, proved to be an equally popular synthetic target. A biomimetic approach was employed by Sorensen in his enantioselective synthesis (Scheme 46a).

The oxidative azaspiroannulation of amine promoted by *(diacetoxyiodo)benzene resulted in the formation of spiroamine 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).

An alternative to this strategy was found by Wang. In this case, an Aubé–Schmidt reaction of azide provided access to lactam 212, featuring the ATA of FR901483 (209 → 212, Scheme 46b). Additional synthetic strategies to set the ATA in FR901483 include a triple Michael addition, a one-pot bisalkylation, anaza-Cope rearrangement/Mannich cyclization and an oxidative deaeromatization.

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

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). Pinnaic acid and tauropinnaic acid were recovered from bivalve *Pinna muricata*. 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 1999 followed by a synthesis of pinnaic acid in 2001 (Scheme 48). They used Meyers’ lactam as a chiral precursor, which was combined with allyltrimethylsilane in a Sakurai reaction to install the ATA in Intermediate 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.

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

In 2007, Arimoto reported his version of an asymmetric synthesis of pinnaic acid using a Beckmann rearrangement to install the ATA (Scheme 49b). The enantiomerically pure bicyclic ketone was treated with a bulky hydroxylamine.

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


**Scheme 47** Synthesis of galbulimima alkaloids by Chackalamannil (2009) and Movassaghi (2009). Ac = acetyl, Bz = benzoyl, NCS = N-chlorosuccinimide, OTf = trifluoromethanesulfonate.
reagent to afford the desired lactam 223, which was then converted into the natural product.

12 Lactacyciste and salinosporamide

In 1991, Omura isolated the unusual natural product lactacyciste from Streptomyces sp. OM-6519 and identified it as a proteasome inhibitor (Fig. 11). A structurally related β-lactone, salinosporamide A, which shows similar biological activity, was subsequently isolated from a marine bacterium, Salinispora tropica. 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, and a variety of methods for the installation of the ATA motif have been applied.

In pioneering work, Corey reported five total syntheses of lactacyciste between 1992 and 1998. The Corey group showed that the ATA can be installed using an aldol addition of ω-aminic acid derivative via intermediate 225, Scheme 50a. Other groups also contributed to this field in the 1990s. In most cases, the strategy applied for the installation of the ATA motif involved an alkylation or aldol reaction of an ω-aminic acid derivative. By contrast, Shibasaki introduced the ATA with a catalytic enantioselective Streeker reaction (Scheme 50b). In this work, phosphinoxyline 226 was converted to aminonitrile 227 using a gadolinium catalyst and the chiral ligand A.

Another unusual approach was taken by Wardrop in his formal synthesis and Hayes in his total synthesis of lactacyciste (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...
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. Manzacidins A–C (Fig. 12) were first isolated from the Okinawan sponge Hymeniacidon sp. by Kobayashi in 1991, followed by the isolation of manzacidin D from the ‘living fossil’ sponge Astrosclera willeyana and N-methylmanzacidin C from Axinella brevistyla.

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

Leighton accomplished the synthesis of manzacidin C employing their asymmetric silane-promoted [3+2] cycloaddition methodology (Scheme 52b). Exposure of alkene 237 and hydrazine 238 to chiral silane R,R-B gave pyrazoline 239, thus setting both stereocenters of the target molecule, including the ATA, in a single step. Intermediate 239 was subsequently converted to manzacidin C via reductive N,N-bond cleavage.

A more recent formal synthesis of manzacidins A and C, published by Ichikawa, features a rare allyl cyanate/iminocarbonate rearrangement as the key step (Scheme 53). To this end, he synthesized carbamate 240, which was converted to allyl cyanate 241 by in situ dehydration. The subsequent rearrangement with chirality transfer gave isocyanate 242, which was then transformed into manzacidin A. The synthesis of manzacidin C was accomplished analogously from a diastereoisomer of carbamate 240.

Several other synthetic approaches toward these molecules have been reported. These strategies for the installation of the ATA moiety involve diastereoselective nitrene insertion, 1,3-dipolar cycloaddition, Hofmann rearrangement, diastereoselective iodocyclization, Grignard addition to an imine and a variety of other methods. Indeed, manzacidines remain targets of great interest for synthetic chemists. In 2015, Inoue published a synthesis of manzacidin A using a radical-based decarboxylative coupling (not shown). Recently the relative stereochemistry of manzacidin B, which possesses an additional stereocenter, was revised using total synthesis.
14 Tetrodotoxin

Tetrodotoxin (TTX) was first isolated from the Fugu puffer fish in 1909. Its structure was independently reported by Hirata–Goto, Tsuda and Woodward in the 1960s. Its assignment was confirmed by X-ray crystallography, which also established the absolute configuration of the molecule. 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. 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.

The first total synthesis of TTX was accomplished by Kishi in 1972 (Scheme 54a). 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). To this end, an allylic alcohol was converted to trichloroacetimide 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). 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*. In 2012, the first synthesis of gracilamine was disclosed by Ma (Scheme 55a). 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). 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.

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

The first total synthesis of a member of this family, viz. amathaspiramide F, was disclosed by Trauner in 2002 (Scheme 56a). 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, Ohfune published his approach to amathaspiramide F which utilizes an enolate Claisen rearrangement for the same purpose (not shown).

In 2012, Fukuyama reported the asymmetric synthesis of the entire amathaspiramide family (Scheme 56b). In their work,
the benzyl ester 258 bearing a quaternary stereocenter was first deprotected and the resulting acid converted to the corresponding amine via Curtius rearrangement. After hydrolysis of the resulting isocyanate, the intermediate amino ester underwent cyclization to afford the pyrrolidinone 259, which could be converted into all members of the family.

In Tambar’s asymmetric synthesis of amathaspiramide F, proline derivative 260 underwent a palladium-catalyzed allylic substitution of carbonate 261 to yield an intermediary quaternary ammonium ion 262, which, after deprotonation, engaged in a stereoselective [2,3] Stevens rearrangement via 263 (Scheme 57a). The resulting ATA-containing pyrrolidine 264 was converted into amathaspiramide F.

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 57b).

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.

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

Fig. 13 The amathaspiramides A–F.


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.

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18 Notes and references


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